**Supplementary Materials**

**Supplementary Table 1. Keywords for psychosis, childhood adversities, and mediation/moderation**

|  |  |
| --- | --- |
| **Factor** | **Search terms used** |
| **Psychosis** | psychosis OR schizophrenia OR psychotic OR hallucination OR delusion OR  “prodrom\*” OR “prodrom\* symptom\*” OR “ultra-high risk” OR “high risk” OR “attenuated psycho\*” OR “subclinical symptom\*” OR  “psychosis continuum” OR “attenuated symptom\*” OR “subclinical psychosis” OR “at-risk-mental-state” OR “psychotic symptom\*” OR  “psychotic experience\*” OR paranoia OR “psychotic-like” OR “first episode of psychosis” OR  “first-episode psychosis” OR FEP OR “chronic psychosis” |
| **Childhood adversity** | “child\* trauma” OR “child\* advers\*” OR “child\* maltreat\*” OR “child\* abuse” OR “physical abuse” OR  “sexual abuse” OR molest\* OR “child\* neglect” OR “child\* stressful life event\*” OR separat\* OR “child\* loss” OR “negligent treatment” OR  death OR violen\* OR institution\* OR exploitat\* OR “authority care” OR punishment OR injur\* OR divorce OR abandon OR foster OR adopt |
| **Mediation and moderation** | interact\* OR synerg\* OR pathway OR moderat\* OR mediat\* OR confound\* OR “gene x environment interaction” OR “environment x environment interaction” OR GxE OR GE |

**Supplementary Table 2. Keywords for mediating/moderating risk factors**

|  |  |
| --- | --- |
| **Factor** | **Search terms used** |
| **Genes** | gen\* OR polymorphism OR “famil\* risk” OR “proxy genetic risk” OR SNP\* OR “single candidate gene” OR CNV OR GWAS OR “polygenic score” OR PRS |
| **Obstetric complications** | “obstetric complication” OR “pregnancy complication” OR “birth complication” |
| **Cannabis** | cannabi\* OR marijuana OR hash OR THC |
| **Other substances** | stimulant OR cocaine OR amphetamine OR alcohol OR tobacco OR substance OR drug OR methamphetamines |
| **Later life events, daily life stressors** | “life event\*” OR “life hassle\*” OR “stress sensitivity” OR “daily life stress” OR “adult advers\*” OR “social advers\*” OR “lifetime trauma” OR “traumatic event” |
| **Broader social risk factors** | “social defeat” OR migrat\* OR urban\* OR stigma\* OR “social support” OR “social network” OR friend\* OR  disadvantage OR “social exclusion” OR loneliness OR discrimination OR minority OR “social comparison” |
| **Attachment and parental bonding** | attachment OR “parental bonding” OR “maternal stress” OR “parenting stress” |
| **Non-psychotic symptoms** | depress\* OR anxiety OR worry OR sleep OR insomnia OR mood OR “emotional liability” OR  “emotional instability” OR disphor\* OR “mood instability” OR psychopathol\* OR “psychiatric symptoms” OR “non-psychotic symptoms” OR  dissociat\* OR depersonalization OR depersonalisation OR derealization OR derealisation OR PTSD OR “post-traumatic stress disorder” OR “acute stress disorder” |
| **Self-image and self-esteem** | “self esteem” OR “self-esteem” OR “self concept” OR “self-concept” OR “self image” OR “self-image” OR “sense of coherence” OR “beliefs about the self” OR “core beliefs” |
| **Cognitive bias and social cognition** | “cognitive bias\*” OR “reasoning bias\*” OR “thinking style” OR attribution\* OR “self confirm\*” OR “locus of control” OR LOC OR  “jumping to conclusions” OR JTC OR “confirm\* bias” OR “belief flexibility” OR “cognitive flexibility” OR “theory of mind” OR  “reflective function” OR mentalising OR mentalizing OR mentalisation OR mentalization |

**Supplementary Table 3. Quality assessment tool**

|  |  |
| --- | --- |
| **Items** | **Quality score** |
| **A. Selection Bias** | |
| 1. Are the individuals selected to participate in the study likely to be representative of the target population? |  |
| * There was a non-random selection process or the sampling method was not reported. | 0 |
| * The sample was made up of either incident cases or randomly sampled controls, or there were no control subjects. | 1 |
| * In case-control/cohort studies, the sample was made up of incident cases and randomly sampled controls. In general population studies, the entire sample was randomly selected. | 2 |
| 1. What percentage of selected individuals agreed to participate? |  |
| * Less than 50% of participants, or not reported or not applicable. | 0 |
| * 50-69% of participants. | 1 |
| * 70-100% of participants. | 2 |
| 1. What is the sample size?  * Less than 50 subjects in each group | 0 |
| * At least 50 subjects in each group | 1 |
| * At least 100 cases and controls or sample size calculation indicating adequate statistical power. | 2 |
| **B. Measurement of exposure – Childhood adversity** |  |
| 1. What was the quality of the childhood adversity measurement tool? |  |
| * Self-report checklist | 0 |
| * Interviewer administered checklist | 1 |
| * Semi-structured interview or documented evidence (forensic report/medical examination/social services’ records) | 2 |
| 1. Did the measure assess different types of childhood trauma? |  |
| * No distinction was made between different types of trauma, or not reported. | 0 |
| * There was an assessment of different types of trauma but they were not explored separately in the analysis. | 1 |
| * There was an assessment of different types of trauma and they were analysed separately. | 2 |
| **C. Measurement of the other exposure** |  |
| (6) For gene-environment interaction (GxE) studies: how was the genetic exposure assessed? |  |
| * Proxy (family history) | 0 |
| * Molecular (Genotype, polymorphism, polygenic score…) | 1 |
| (7) For gene-environment interaction (GxE) studies only, what was the quality of the genetic data used: |  |
| * No information about the quality of collection of genetic data or unstandardized measure used | 0 |
| * Standardized assessment of family history used | 1 |
| * Specific information about the collection, storage and analysis of DNA. Hardy-Weinberger equilibrium tested | 2 |
| (8) For Environment-Environment interaction (ExE): how was the other environmental exposure(s) mainly assessed? |  |
| * Self- report checklist/questionnaire | 0 |
| * Interview/ test | 1 |
| **D. Measurement of outcome – Psychotic symptoms** | |
| (9) How were psychotic symptoms measured? |  |
| * Clinician-only diagnosis or brief self-report checklist/1-2 items only or unstandardised measure. | 0 |
| * Structured assessment by trained research worker or standardised self-report measure for psychotic-like experiences | 1 |
| * Structured assessment by clinician | 2 |
| **E. Assessment of the interaction** |  |
| (10) Were descriptive statistics provided showing the distribution of the main exposures? |  |
| * No | 0 |
| * Yes | 1 |
| (11) How was the relationship between childhood trauma and the other factor assessed? |  |
| * Correlation/association study | 0 |
| * Main effects and mediation, moderation or interaction term but not formally tested (for path analysis estimate and account for measurement error terms was done) | 1 |
| * Main effects and mediation, moderation or interaction were formally tested (for path analysis an estimate and account for measurement error terms was done) | 2 |
| (12) Was gene-environment (GE) or environment-environment (EE) correlation also tested and reported? |  |
| * No | 0 |
| * Yes | 1 |
| **F. Confounding** | |
| (13) Was there an assessment of confounding and consideration in the analysis? |  |
| * No adjustment for confounders | 0 |
| * Adjustment for basic demographics e.g. age, gender, ethnicity, socioeconomic status | 1 |
| * Potential confounders were measured and adjusted for in the analysis e.g. adjustment of basic demographics and other risk factors such as urbanicity, drug/alcohol use, IQ. For GxE studies analyses adjusted for population stratification. | 2 |

**Supplementary Table 4. Quality assessment of interaction and moderation studies by type of exposure and population (methodologically robust studies in bold)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year, study** | **Selection bias** | **Participation rate** | **Sample size** | **Quality of information on child adversity** | **Specificity of information on child adversity** | **Definition of genetic exposure** | **Quality of information on genetic exposure** | **Quality of information on environment al or psychological exposures** | **Quality of information on the outcome** | **Reporting of descriptive results** | **Assessment of the relationship between exposures** | **Assessment of rGE or rEE** | **Alternative explanations** | **Total** |
| **GENETIC RISK FACTORS** | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | |
| Alemany et al., 2011 | 0 | 0 | 2 | 0 | 2 | 1 | 2 | NA | 1 | 0 | 2 | 0 | 2 | 12 |
| Alemany et al., 2014 | 0 | 0 | 2 | 0 | 0 | 1 | 2 | 0 | 1 | 1 | 2 | 0 | 2 | 11 |
| Collip et al., 2013  EFPT | 2 | 0 | 2 | 0 | 1 | 1 | 2 | NA | 1 | 1 | 2 | 0 | 2 | 14 |
| Collip et al., 2013 Replication sample | 1 | 0 | 2 | 0 | 1 | 1 | 2 | NA | 1 | 1 | 2 | 0 | 2 | 13 |
| Kramer et al., 2012  EFTP and Flemish twin register | 2 | 2 | 2 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 2 | 1 | 1 | 14 |
| de Castro-Catala et al., 2016  General population | 0 | 0 | 2 | 0 | 2 | 1 | 1 | NA | 1 | 1 | 2 | 0 | 1 | 11 |
| de Castro-Catala et al., 2016  EFPT | 2 | 0 | 2 | 0 | 1 | 1 | 1 | NA | 1 | 1 | 2 | 0 | 1 | 12 |
| Alemany et al., 2016 | 0 | 0 | 2 | 0 | 1 | 1 | 2 | NA | 1 | 0 | 2 | 0 | 2 | 11 |
| de Castro-Catala et al., 2017 | 0 | 0 | 2 | 0 | 1 | 1 | 2 | NA | 1 | 1 | 2 | 0 | 1 | 11 |
| Vinkers et al., 2013  Cannabis Quest | 0 | 0 | 2 | 0 | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 1 | 1 | 12 |
| **Vinkers et al., 2013**  **GROUP** | **2** | **2** | **2** | **0** | **1** | **1** | **2** | **1** | **1** | **1** | **2** | **0** | **1** | **16** |
| **Paksarian, Eaton, Mortensen, Merikangas, & Pedersen, 2015** | **2** | **2** | **2** | **2** | **0** | **0** | **1** | NA | **2** | **0** | **2** | **0** | **2** | **15** |
| **Ramsay et al., 2013**  **CT and ABD studies** | **0** | **1** | **2** | **2** | **1** | **1** | **2** | NA | **2** | **1** | **2** | **0** | **2** | **16** |
| Wigman et al., 2012 | **2** | **2** | **2** | **2** | **2** | **0** | **1** | NA | **2** | **1** | **2** | **1** | **1** | **18** |
| Wicks, Hjern, & Dalman, 2010 | 0 | 2 | 2 | 0 | 1 | 0 | 1 | NA | 1 | 1 | 2 | 1 | 1 | 12 |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Green et al., 2014  ASBR | 0 | 0 | 2 | 0 | 2 | 1 | 2 | NA | 1 | 1 | 2 | 1 | 0 | 12 |
| Green et al., 2015  ASBR | 0 | 0 | 2 | 0 | 1 | 1 | 2 | NA | 1 | 1 | 2 | 0 | 0 | 10 |
| McCarthy-Jones et al., 2014 ASBR | 0 | 0 | 2 | 0 | 2 | 1 | 2 | NA | 1 | 0 | 2 | 0 | 2 | 12 |
| Bi et al., 2018 | 0 | 0 | 2 | 0 | 2 | 1 | 0 | NA | 0 | 1 | 2 | 1 | 1 | 10 |
| De Pradier, Gorwood, Beaufils, Adès, & Dubertret, 2010 | 0 | 0 | 1 | 1 | 0 | 1 | 2 | NA | 2 | 1 | 2 | 0 | 1 | 11 |
| Debost et al., 2017 | **2** | **2** | **2** | **2** | **0** | **1** | **2** | **NA** | **2** | **1** | **2** | **0** | **2** | **18** |
| Gallagher & Jones, 2016 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | NA | 2 | 1 | 1 | 0 | 0 | 8 |
| Koga et al., 2017 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | NA | 2 | 1 | 2 | 0 | 2 | 11 |
| Mihaljevic et al., 2017 | 0 | 0 | 1 | 0 | 1 | 1 | 2 | NA | 1 | 1 | 2 | 0 | 2 | 11 |
| Savitz, Van Merwe, Newman, Stein, & Ramesar, 2010 | 0 | 0 | 2 | 0 | 1 | 1 | 2 | NA | 1 | 1 | 2 | 1 | 2 | 13 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| **Ajnakina et al., 2014**  **GAP** | **1** | **2** | **2** | **1** | **2** | **1** | **1** | **0** | **2** | **1** | **2** | **1** | **2** | **18** |
| **Trotta et al., 2015**  **GAP** | **1** | **0** | **2** | **1** | **2** | **0** | **1** | NA | **2** | **1** | **2** | **1** | **2** | **15** |
| **Trotta et al., 2016**  **GAP** | **1** | **0** | **1** | **1** | **2** | **1** | **2** | NA | **2** | **1** | **2** | **1** | **2** | **16** |
| **Trotta et al., 2018**  **GAP** | **1** | **0** | **2** | **1** | **1** | **1** | **2** | NA | **2** | **0** | **2** | **1** | **2** | **15** |
| Cristóbal-Narváez et al., 2017 | 0 | 0 | 1 | 0 | 1 | 1 | 2 | NA | 1 | 0 | 2 | 0 | 0 | 8 |
| **Fisher et al., 2014** | **2** | **1** | **2** | **1** | **0** | **0** | **1** | NA | **2** | **1** | **2** | **1** | **2** | **15** |
| Ierago et al., 2010 | 0 | 2 | 1 | 1 | 0 | 0 | 0 | NA | 1 | 1 | 2 | 1 | 1 | 10 |
| McGregor et al., 2018 | 0 | 0 | 2 | 0 | 1 | 1 | 2 | NA | 1 | 0 | 2 | 0 | 2 | 11 |
| Veling, Counotte, Pot-Kolder, van Os, & van der Gaag, 2016 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 2 | 0 | 2 | 8 |
| **SUBSTANCE USE** | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | |
| **Houston, Murphy, Adamson, Stringer, & Shevlin, 2008**  **NCS** | **2** | **2** | **2** | **1** | **0** | NA | NA | **1** | **2** | **1** | **2** | **0** | **2** | **15** |
| Murphy, Houston, Shevlin, & Adamson, 2013  NCS-R | 2 | 0 | 2 | 1 | 0 | NA | NA | 1 | 1 | 1 | 2 | 0 | 2 | 12 |
| Harley et al., 2010  CT | 1 | 1 | 1 | 2 | 1 | NA | NA | 1 | 2 | 1 | 1 | 1 | 0 | 12 |
| Houston, Murphy, Shevlin, & Adamson, 2011  APMS | 2 | 1 | 2 | 0 | 0 | NA | NA | 0 | 2 | 1 | 2 | 0 | 2 | 12 |
| Konings et al., 2012  GNPP | 2 | 0 | 2 | 0 | 0 | NA | NA | 0 | 1 | 1 | 2 | 1 | 2 | 11 |
| **Konings et al., 2012**  **NEMESIS-1** | **2** | **1** | **2** | **1** | **1** | NA | NA | **1** | **2** | **1** | **2** | **1** | **2** | **16** |
| **Morgan, Reininghaus, Reichenberg, et al., 2014**  **SELCoH** | **2** | **2** | **2** | **1** | **1** | NA | NA | **1** | **1** | **1** | **2** | **1** | **2** | **16** |
| Vinkers et al., 2013  Cannabis Quest | 0 | 0 | 2 | 0 | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 1 | 1 | 12 |
| **Vinkers et al., 2013**  **GROUP** | **2** | **2** | **2** | **0** | **1** | **1** | **2** | **1** | **1** | **1** | **2** | **0** | **1** | **16** |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Baudin et al., 2016 | 0 | 0 | 2 | 0 | 1 | NA | NA | 1 | 2 | 1 | 2 | 1 | 1 | 11 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| **Ajnakina et al., 2014**  **GAP** | **1** | **2** | **2** | **1** | **2** | **1** | **1** | **0** | **2** | **1** | **2** | **1** | **2** | **18** |
| **Sideli et al., 2018**  **GAP** | **1** | **0** | **2** | **1** | **2** | NA | NA | **0** | **2** | **1** | **2** | **1** | **1** | **13** |
| **STRESSFUL LIFE EVENTS AND SOCIAL RISK FACTORS** | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | |
| **Honings et al., 2017**  **NEMESIS-2** | **2** | **2** | **2** | **1** | **1** | NA | NA | **0** | **2** | **1** | **2** | **1** | **2** | **16** |
| **Lataster, Myin-Germeys, Lieb, Wittchen, & van Os, 2012** | **2** | **2** | **2** | **1** | **1** | NA | NA | **1** | **2** | **1** | **2** | **1** | **2** | **17** |
| **Morgan, Reininghaus, Reichenberg, et al., 2014**  **SELCoH** | **2** | **2** | **2** | **1** | **1** | NA | NA | **1** | **1** | **1** | **2** | **1** | **2** | **16** |
| **Newbury et al., 2018**  **E-Risk** | **2** | **2** | **2** | **2** | **0** | NA | NA | **0** | **2** | **1** | **2** | **1** | **2** | **16** |
| **Ouellet-Morin et al., 2015**  **E-Risk** | **2** | **2** | **2** | **0** | **0** | NA | NA | **1** | **1** | **1** | **2** | **1** | **2** | **14** |
| **Räikkönen et al., 2011**  **Helsinki Birth Cohort study** | **2** | **0** | **2** | **2** | **0** | NA | NA | **1** | **2** | **1** | **2** | **1** | **1** | **14** |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Akün, Durak Batigün, Devrimci Özgüven, & Baskak, 2018 | 0 | 0 | 1 | 0 | 2 | NA | NA | 1 | 1 | 1 | 2 | 1 | 0 | 9 |
| Begemann, Stotijn, Schutte, Heringa, & Sommer, 2017 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 2 | 1 | 2 | 1 | 0 | 9 |
| Frissen et al., 2015  GROUP | 2 | 0 | 2 | 0 | 1 | NA | NA | 1 | 1 | 1 | 2 | 1 | 1 | 12 |
| Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2011 | 0 | 0 | 0 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 0 | 1 | 6 |
| Mansueto & Faravelli 2017 | 2 | 0 | 1 | 1 | 2 | NA | NA | 1 | 0 | 0 | 2 | 1 | 2 | 12 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| **Gayer-Anderson et al., 2015**  **AESOP** | **2** | **0** | **2** | **1** | **2** | NA | NA | **0** | **1** | **1** | **2** | **0** | **2** | **13** |
| **Morgan, Reininghaus, Fearon, et al., 2014**  **AESOP** | **2** | **0** | **2** | **1** | **2** | NA | NA | **1** | **1** | **1** | **2** | **1** | **2** | **15** |
| **PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL MECHANISMS** | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | |
| Goodall, Rush, Grünwald, Darling, & Tiliopoulos, 2015 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 10 |
| Nam, Hilimire, Schiffman, & DeVylder, 2016 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 10 |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| **Mansueto et al., 2019**  **GROUP** | **1** | **0** | **2** | **0** | **2** | **NA** | **NA** | **1** | **1** | **1** | **2** | **1** | **2** | **13** |

rGE: gene-environment correlation; rEE environment-environment correlation; FEP: first-episode of psychosis; NA not applicable**Supplementary Table 5. Quality assessment of mediation studies by type of exposure and population (methodologically robust studies in bold)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year, study** | **Selection bias** | **Participation rate** | **Sample size** | **Quality of information on child adversity** | **Specificity of information on child adversity** | **Definition of genetic exposure** | **Quality of information on genetic exposure** | **Quality of information on environmental or psychological exposures** | **Quality of information on the outcome** | **Reporting of descriptive results** | **Assessment of the relationship between exposures** | **Assessment of rGE or rEE** | **Alternative explanations** | **Total** |
| **GENETIC RISK FACTORS** | | | | | | | | | | | | | | |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Goldstone, Farhall, & Ong, 2011 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 8 |
| Goldstone, Farhall, & Ong, 2012 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 0 | 9 |
| **SUBSTANCE USE** | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | |
| **van Nierop et al., 2014**  **NEMESIS-2** | **2** | **0** | **2** | **2** | **1** | NA | NA | **1** | **2** | **1** | **2** | **1** | **2** | **16** |
| Whitfield, Dube, Felitti, & Anda, 2005  ACE | 2 | 1 | 2 | 0 | 1 | NA | NA | 0 | 0 | 1 | 1 | 1 | 1 | 10 |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Etain et al., 2017 | 0 | 0 | 2 | 0 | 2 | NA | NA | 1 | 2 | 0 | 1 | 0 | 0 | 8 |
| Goldstone et al., 2011 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 8 |
| Goldstone et al., 2012 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 0 | 9 |
| **STRESSFUL LIFE EVENTS AND SOCIAL RISK FACTORS** | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | |
| Boyda, McFeeters, & Shevlin, 2015  APMS | 2 | 1 | 2 | 0 | 0 | NA | NA | 0 | 1 | 0 | 2 | 1 | 0 | 9 |
| Boyda & McFeeters 2015  APMS | 2 | 1 | 2 | 0 | 2 | NA | NA | 0 | 1 | 0 | 2 | 1 | 1 | 12 |
| **Shevlin, McElroy, & Murphy, 2015**  **APMS** | **2** | **1** | **2** | **0** | **2** | NA | NA | **0** | **2** | **0** | **2** | **1** | **2** | **14** |
| Goldstone et al., 2011 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 8 |
| Goldstone et al., 2012 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 0 | 9 |
| **Bhavsar et al., 2019**  **SELCoH** | **2** | **2** | **2** | **1** | **1** | NA | NA | **1** | **1** | **1** | **2** | **1** | **2** | **16** |
| **van Nierop et al., 2014**  **NEMESIS-2** | **2** | **0** | **2** | **2** | **1** | NA | NA | **1** | **2** | **1** | **2** | **1** | **2** | **16** |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Goldstone et al., 2011 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 8 |
| Goldstone et al., 2012 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 0 | 9 |
| Seo & Choi, 2018 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 0 | 2 | 1 | 1 | 8 |
| Steenkamp, Weijers, Gerrmann, Eurelings-Bontekoe, & Selten, 2019 | 0 | 0 | 1 | 2 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 9 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| **Morgan, Reininghaus, Fearon, et al., 2014**  **AESOP** | **2** | **0** | **2** | **1** | **2** | NA | NA | **1** | **1** | **1** | **2** | **1** | **2** | **15** |
| **PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL MECHANISMS** | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | |
| Marwaha, Broome, Bebbington, Kuipers, & Freeman, 2014  APMS | 2 | 1 | 2 | 0 | 0 | NA | NA | 0 | 1 | 0 | 2 | 1 | 0 | 9 |
| Marwaha & Bebbington 2015  APMS | 2 | 1 | 2 | 0 | 0 | NA | NA | 1 | 2 | 0 | 2 | 1 | 0 | 11 |
| **McCarthy-Jones 2018**  **APMS** | **2** | **1** | **2** | **0** | **2** | NA | NA | **0** | **1** | **1** | **2** | **0** | **2** | **13** |
| **Janssen et al., 2005**  **NEMESIS** | **2** | **1** | **2** | **1** | **1** | NA | NA | **1** | **2** | **1** | **2** | **1** | **1** | **15** |
| **van Nierop et al., 2014**  **NEMESIS-2** | **2** | **0** | **2** | **2** | **1** | NA | NA | **1** | **2** | **1** | **2** | **1** | **2** | **16** |
| **Sitko, Bentall, Shevlin, O’Sullivan, & Sellwood, 2014**  **NCS** | **2** | **2** | **2** | **1** | **2** | NA | NA | **1** | **1** | **0** | **2** | **1** | **1** | **15** |
| Berenbaum, Thompson, Milanak, Boden, & Bredemeier, 2003 | 0 | 0 | 1 | 1 | 2 | NA | NA | 0 | 1 | 1 | 1 | 0 | 7 | 7 |
| Berenbaum, Thompson, Milanak, Boden, & Bredemeier, 2008 | 1 | 0 | 2 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 12 |
| Bortolon, Seillé, & Raffard, 2017 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 0 | 2 | 1 | 2 | 10 |
| Bortolon & Raffard, 2018 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 2 | 10 |
| Bellido-Zanin et al., 2018 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 9 |
| Boyda, McFeeters, Dhingra, & Rhoden, 2018 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 2 | 11 |
| Cole, Newman-Taylor, & Kennedy, 2016 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 8 |
| Fisher et al., 2013  ALSPAC | 2 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 0 | 2 | 1 | 2 | 11 |
| Fisher, Appiah-Kusi, & Grant, 2012 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 0 | 2 | 1 | 2 | 10 |
| Gawęda, Göritz, & Moritz, 2019 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 10 |
| Gibson, Reeves, Cooper, Olino, & Ellman, 2018 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 2 | 11 |
| Goodall et al., 2015 | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 10 |
| Lincoln, Marin, & Jaya, 2017 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 8 |
| Mętel et al.,2018 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 8 |
| Murphy, Murphy, & Shevlin, 2015 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 8 |
| Perona-Garcelán et al., 2014 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 0 | 2 | 1 | 0 | 7 |
| Powers, Thomas, Ressler, & Bradley, 2011 | 0 | 0 | 2 | 2 | 2 | NA | NA | 1 | 1 | 1 | 1 | 1 | 0 | 11 |
| Rössler, Ajdacic-Gross, Rodgers, Haker, & Müller, 2016 | 2 | 1 | 2 | 0 | 2 | NA | NA | 0 | 1 | 1 | 1 | 1 | 1 | 12 |
| Sheinbaum, Kwapil, & Barrantes-Vidal, 2014 | 0 | 2 | 2 | 0 | 2 | NA | NA | 0 | 1 | 0 | 2 | 1 | 1 | 11 |
| **Sheinbaum et al., 2015** | **0** | **0** | **2** | **2** | **2** | NA | NA | **1** | **1** | **1** | **2** | **1** | **1** | **13** |
| Udachina & Bentall 2014 | 0 | 0 | 2 | 0 | 0 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 7 |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Goldstone et al., 2011 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 8 |
| Goldstone et al., 2012 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 2 | 1 | 0 | 9 |
| van Dam et al., 2014  GROUP | 2 | 0 | 1 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 10 |
| Isvoranu et al., 2017  GROUP | 1 | 0 | 2 | 0 | 2 | NA | NA | 1 | 1 | 1 | 2 | 0 | 0 | 10 |
| **Mansueto et al., 2019**  **GROUP** | **1** | **0** | **2** | **0** | **2** | **NA** | **NA** | **1** | **1** | **1** | **2** | **1** | **2** | **13** |
| Weijers et al., 2018 | 0 | 0 | 1 | 2 | 2 | NA | NA | 1 | 1 | 0 | 2 | 1 | 0 | 10 |
| Baryshnikov et al., 2018 | 1 | 0 | 2 | 0 | 1 | NA | NA | 0 | 2 | 0 | 2 | 1 | 1 | 10 |
| Chatziioannidis et al., 2019 | 0 | 0 | 1 | 1 | 1 | NA | NA | 1 | 2 | 1 | 2 | 1 | 1 | 11 |
| Choi et al., 2015 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 8 |
| Choi 2017 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 9 |
| Hardy et al., 2016 | 0 | 2 | 2 | 0 | 2 | NA | NA | 0 | 1 | 0 | 2 | 1 | 0 | 10 |
| Muenzenmaier et al., 2015  PSI-FIELDS | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 0 | 2 | 0 | 1 | 7 |
| Ostefjells et al., 2017  TOP | 0 | 0 | 2 | 0 | 2 | NA | NA | 0 | 2 | 1 | 2 | 1 | 1 | 11 |
| Pearce et al., 2017 | 0 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 9 |
| Perona-Garcelán et al., 2012 | 0 | 0 | 1 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 7 |
| Pilton et al., 2016 | 0 | 2 | 1 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 10 |
| Schalinski et al., 2017 | 0 | 0 | 1 | 1 | 2 | NA | NA | 1 | 2 | 0 | 2 | 1 | 1 | 11 |
| Sengutta, Gawęda, Moritz, & Karow, 2019 | 1 | 0 | 2 | 0 | 1 | NA | NA | 0 | 1 | 1 | 2 | 1 | 1 | 10 |
| Varese, Barkus, & Bentall, 2012 | 0 | 0 | 0 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 1 | 0 | 7 |
| Vogel et al., 2011 | 0 | 1 | 0 | 0 | 2 | NA | NA | 1 | 1 | 1 | 2 | 1 | 1 | 10 |
| Wickham & Bentall, 2016 | 0 | 0 | 1 | 0 | 2 | NA | NA | 0 | 1 | 1 | 2 | 0 | 2 | 9 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | |
| Peach, Alvarez Jimenez, Cropper, Sun, & Bendall, 2019 | 0 | 0 | 1 | 0 | 1 | NA | NA | 0 | 2 | 1 | 2 | 1 | 1 | 9 |
| Sun et al., 2018 | 0 | 0 | 1 | 0 | 1 | NA | NA | 1 | 2 | 1 | 2 | 1 | 0 | 9 |
| Appiah-Kusi et al., 2017 | 0 | 0 | 0 | 0 | 2 | NA | NA | 0 | 2 | 0 | 2 | 1 | 2 | 9 |
| Evans, Reid, Preston, Palmier-Claus, & Sellwood, 2015 | 0 | 0 | 0 | 0 | 2 | NA | NA | 0 | 1 | 0 | 2 | 1 | 1 | 7 |
| **Morgan, Reininghaus, Fearon, et al., 2014**  **AESOP** | **2** | **0** | **2** | **1** | **2** | NA | NA | **1** | **1** | **1** | **2** | **1** | **2** | **15** |
| Thompson et al., 2016  PACE | 0 | 0 | 2 | 0 | 0 | NA | NA | 1 | 1 | 0 | 2 | 1 | 0 | 7 |
| **Walker, Cudeck, Mednick, & Schulsinger 1981**  **Danish high-risk project** | **0** | **2** | **2** | **2** | **2** | **0** | **1** | **1** | **2** | **0** | **1** | **1** | **1** | **16** |

rGE: gene-environment correlation; rEE environment-environment correlation; FEP: first-episode of psychosis; NA not applicable

**Supplementary Table 6. Summary of the findings of interaction and moderation studies by type of exposure and population (methodologically robust studies in bold)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors, year, study name, country** | **Sample** | **Type of childhood adversity** | **Measure of childhood adversity** | **Other exposures** | **Measure of other exposures** | **Outcome definition and measure** | **Confounders** | **Main findings** | **Quality score** |
| **GENETIC RISK FACTORS** | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | |
| Alemany et al., 2011  SPAIN | *N* = 533 | Childhood emotional, physical, and sexual abuse (*n* = 136, 25.5%), and physical and emotional neglect (*n* = 172, 32.2%) | CTQ (Bernstein et al., 1994) | *BDNF rs6265*: *Val/Val* (*n* = 282) vs. *Met* carriers (*n* = 188) |  | Frequency of PLEs (at least one positive PLEs ‘often or almost always’ *n* = 217, 40.7%; at least one negative PLEs ‘often or almost always’ *n* = 254, 47.6%)  CAPE (Konings, Bak, Hanssen, Van Os, & Krabbendam, 2006) | Sex, age, cannabis use, schizotypal personality, and anxiety | Child abuse x *BDNF- Vale66Met* increased the frequency of positive PLEs: *Met*-carriers exposed to child abuse were more likely to develop positive PLEs compared to *Val/Val* (*β* = 0.27, SE = 0.10, p = 0.004). No GxE was found with childhood neglect (*β* = 70.09, *SE* = 0.05, *p* = 0.110) | 12 |
| Alemany et al., 2014  SPAIN | *N =* 533 | Childhood emotional, physical, and sexual abuse (*n* = 136, 25.5%) | CTQ (Bernstein et al., 1994) | Lifetime cannabis use (more than one, *n* = 155, 29.1%)  *COMT rs4680: Val/Val* (*n* = 127, 30.3%) vs. *Val/Met*: (*n =* 201, 48.0% vs. *Met/Met* (*n =* 91, 21.7%) | Single question interview | Frequency of PLEs (at least one positive PLEs ‘often or almost always’ *n* = 217, 40.7%; at least one negative PLEs ‘often or almost always’ *n* = 254, 47.6%)  CAPE (Konings et al., 2006) | Sex, age, cannabis use, schizotypal personality, and anxiety | Neither the abuse x cannabis interaction nor the abuse x *COMT* interaction showed an effect on PLEs.  A three-way interaction was found on positive PLEs: in individuals exposed to both childhood abuse and cannabis use, positive PLEs were related to the number of *Val* alleles, while in those exposed only to childhood abuse, PLEs were related to number of *Met* alleles (*β* = 0.30, *SE* = 0.11, *95% CI*: 0.51, 0.09, *p* = 0.006).  No interaction was found to have an effect on negative PLEs | 11 |
| Collip et al., 2013  East Flanders Prospective Twin Survey (EFPT), BELGIUM  Replication sample, NETHERLANDS | EFPT: *N* = 621  Replication sample:  *N* = 272 patients with DSM-IV non affective psychosis,  *N* = 258 unaffected siblings  *N* = 227 healthy controls | Emotional, physical, and sexual abuse, and physical, and emotional neglect (EFPT: *mean =*1.7, *SD =* 0.6; replication sample: controls: *mean =* 1.4, *SD* = 0.4; siblings: *mean =* 1.5, *SD* = 0.4; cases: *mean =* 1.7, *SD* = 0.6) | CTQ (Bernstein et al., 1994) | *FKBP5* SNPs  EFPT: *rs9296158*, *rs4713916*, *rs1043805*, and *rs1360780*  Replication sample: *rs9296158*, *rs4713916*,  *rs992105*, and  *rs3800373* |  | EFPT: PLEs (*mean =* 1.18, *range* 1–4.1) assessed using the CAPE (Konings et al., 2006)  Replication sample: Positive schizotypy (controls: *mean =* 0.50, *range*: 0 –2.14; siblings: *mean =* 0.60, *range*: 0–2.57) assessed using the SIS-R (Kendler, Lieberman, & Walsh, 1989)  Psychotic symptoms (*mean =* 1.67, *range*:1–4.60) assessed using the BPRS (Overall & Gorham, 1962) | EFTP: age, Sex, depression, and stressful life events  Replication sample: age, Sex, and depression | EFPT: Interaction between childhood adversity and *FKBP5* was found for the following SNPs: *rs9296158* (*b* = 0.33, *95% CI*: 0.09, 0.57, *p* = 0.007, risk allele *A*), rs1043805 (*b* = 0.66, *95% CI*: 0.31, 1.01, *p* < 0.001, risk allele *A*), and *rs1360780* (*b* = 0.31, *95% CI*: 0.10, 0.51, *p* = 0.004, risk allele *T*).  Replication sample: in the sibling group childhood adversity interacted only with *rs4713916* (*F* = 5.25, *p* = 0.02, risk allele *A*) and *rs992105* (*F* = 4.23, *p* = 0.04, risk allele *C*) in increasing schizotypy. Furthermore, in the case group, an interaction between childhood adversity and *rs9296158* was found (*F* = 4.55, *p* = 0.03, risk allele *A*). No interaction was found in the control group | EFPT: 14  Replication sample: 13 |
| Kramer et al., 2012  East Flanders Prospective Twin Survey (EFPT)  Flemish Twin Register  BELGIUM | *N =* 621  Participants were assessed at five points (mean interval T0- T1: 132 days; T1-T2: 91 days, T2-T3: 116 days, T3-T4 91 days) | Emotional, physical, and sexual abuse, and physical and emotional neglect (*mean =* 1.7, *SD* = 0.6) | 21-item version of the CTQ (Bernstein et al., 1994) without the four most explicit items concerning sexual and physical abuse | MDD (current MDD: *n* = 23, lifetime: *n* = 87)  Genetic liability to depression (total co-twin with MDD (i.e., having a MZ or a DZ sister affected by MDD): *n* = 90)  Depressive symptoms  Stress sensitivity, defined as experience of negative affects in response to minor daily events | SCID-I (First, Spitzer, Gibbon, & Williams, 1996) administered at T0-T4  Depression subscale of the SCL-90-R (Derogatis 1977) at T0-T4  ESM at T0 | Psychotic symptoms assessed using the SCID-I (First et al., 1996) delusion and hallucination items (follow-up *range score*: 0–4, *median* = 0), and the psychoticism and paranoia SCL-90-R subscales (Derogatis 1977) (follow-up *range score*: 1–3.1, *median* = 1.2) at T0-T4  Psychotic trait liability assessed using the CAPE (Konings et al., 2006) (follow-up *range score*: 1–1.9, *median* = 1.1) at T0, T2, and T4 | Baseline psychotic symptoms or psychotic trait liability | No rGE was found between childhood adversity and genetic liability for depression (DZ twins: *β* = 0.05, *p* = 0.68; MZ twins: *β* = -0.04, *p* = 0.75). The effect of child adversity on follow-up psychotic symptoms and psychotic trait liability, was greater in MZ co-twins of cases with MDD compared to those with no co-twins affected (SCL-90: *β* = 0.45, *χ²* = 23.7, *p* <0.01; CAPE: *β* = 0.30, *χ²* = 6.0, *p* = 0.01) but no difference were found between DZ co-twins and no co-twins. The above interaction was not found on SCID psychotic symptoms.  Furthermore, the child adversity x genetic liability interaction became non-significant when depressive symptoms (but not daily life stress) were included in the model (SCL-90: *β* = 0.09, *χ²* = 1.4, *p* = 0.24; CAPE: *β* = 0.12, *χ²* = 1.1, *p* = 0.30) | 14 |
| de Castro-Catala et al., 2016  General population undergraduate and technical  school students, SPAIN  East Flanders Prospective Twin Survey (EFPT), BELGIUM | General population: *N* = 808  EFPT: *N* = 621 | Emotional, physical, and sexual abuse, and physical and emotional neglect (General population: *mean =* 32.95, *SD* = 8.76; EFPT: *mean =* 34.89, *SD* = 11.98) | CTQ (Bernstein et al., 1994)  In the EFPT a 21-item CTQ version without the four most explicit items concerning sexual and physical abuse | *BDNF Val66Met*  *BDNF Val/Val* (General population: *n* = 501; EFPT: *n* = 302) vs. *Met* carriers (General population: *n* = 298; EFPT: *n* = 171) |  | Positive (General population: *mean =* 8.04, *SD* = 4.88; EFPT: *mean =* 3.60, *SD* = 3.54)  and negative PLEs (General population: *mean =* 9.15, *SD =* 5.26; EFPT: *mean =* 7.08, *SD =* 5.07)  CAPE (Konings et al., 2006) | Sex, age | In the general population sample, *BDNF* x overall childhood adversity (*B* = -0.08, *SE* = 0.04, *95% CI*: - 0.16, -0.01, *p* = 0.036) and *BDNF* x neglect (*B* = -0.15, *SE* = 0.07, *95% CI*: -0.28, -0.01, *p* = 0.033) showed an effect on positive PLEs. The effect of childhood adversity was much stronger among males and among those with *Val/Val* genotype.  In the EFPT, the *BDNF* x childhood adversity interaction showed an effect on positive (*B* = 0.05, *SE*= 0.03, 95% CI: 0.001, 0.1, *p* = 0.045) and negative PLEs (*B* = 0.13, *SE*= 0.04, *95% CI*: 0.06, 0.21, *p* = 0.001). In this sample, including only female participants, *Met* carriers exposed to childhood adversity were at greater risk for PLEs | General population: 11  EFPT: 12 |
| Alemany et al., 2016  SPAIN | Discovery  Sample: *N* = 437  Replication  Sample: *N* = 305 | Childhood emotional, physical, and sexual abuse | CTQ (Bernstein et al., 1994) | *FKBP5* *rs1360780* SNP: *CC* (discovery sample: *n* = 191; replication sample: *n* = 140) vs. *CT* (discovery sample: *n* = 198; replication sample: *n* = 127) vs. TT (discovery sample: *n* = 48; replication sample: *n* = 38) |  | Frequency of positive and negative PLEs  CAPE (Konings et al., 2006) | Sex, age, schizotypy, cannabis use , and, only in the discovery sample, trait anxiety | Child abuse interacted with *FKBP* in predicting positive PLEs both in the discovery (*β* = 0.21, *SE*= 0.06, *p* =0.001, *η²* = 0.019, *χ²*= 11.8, *p* = 0.001) and the replication sample (*β* = 0.53, *SE*= 0.08, *p* < 0.001, *η²* = 0.066, *χ²* = 24.7, *p* < 0.001). *T –* homozygote individuals exposed to childhood abuse showed higher risk for PLEs, compared to *C* – homozygote | 11 |
| de Castro-Catala et al., 2017  SPAIN | *N* = 808 | Emotional, physical, and sexual abuse, and physical and emotional neglect (General population sample: *mean =* 32.95, *SD* = 8.76) | CTQ (Bernstein et al., 1994) | *FKBP5* SNPs:  Block 1 haplotypes: r*s3800373*, r*s9296158*, and *rs1360780* (*CAT* carriers: *n* = 400, 50.38%; *non-CAT* carriers: *n* = 394, 49.62%)  Block 2 haplotypes: *rs9470080* and *rs4713916* (*TA* carriers: *n* = 401, 51, 54%; *non-TA* carriers: *n* = 377, 48.46%) |  | Positive (*mean =* 8.04, *SD* = 4.88) and negative PLEs (*mean =* 9.15, *SD* = 5.26)  CAPE (Konings et al., 2006) | Sex, age, and cohort membership (undergraduate vs. technical school) | No interaction was found between childhood adversity and either block 1 or block 2 haplotypes on PLEs | 11 |
| **Vinkers et al., 2013**  **Cannabis Quest (discovery sample)**  **Genetic Risk and Outcome of Psychosis (GROUP) study (replication sample)**  **NETHERLANDS and BELGIUM** | **Cannabis Quest: *N* = 918**  **GROUP: *N =* 339** | **Emotional, physical, and sexual abuse, and physical and emotional neglect (Cannabis Quest: *mean =* 1.40, *range*: 1.00–4.26; GROUP: *mean =* 1.33, *range*: 1.0–2.95)** | **CTQ-SF (Bernstein et al., 2003)** | **Past year cannabis use (Cannabis Quest: >3 euro/week: *n* = 303, 33%; GROUP: none: *n* = 292, 86%; less than weekly: *n* = 27, 8%; weekly: *n* = 14, 4%; daily: *n* = 7, 2%)**  ***COMT***  ***Val/Val* (Cannabis Quest: *n* = 20, 2%; GROUP: *n* = 24, 7%), *Met/Val* (Cannabis Quest: *n* = 50, 5%; GROUP: *n* = 49, 14%), *Met/Met* (Cannabis Quest: *n* = 30, 3%; GROUP: *n* = 27, 8%)** | **Past year cannabis use was assessed in Quest using an online survey and in GROUP using the CIDI (World Health Organization, 1990)** | **Positive, negative, and depressive PLEs (Cannabis Quest: *mean =* 0.61, *range*: 0.02–2.48; GROUP: *mean =* 0.38, *range*: 0.0–1.29)**  **CAPE (Konings et al., 2006)** | **Sex, age, ethnicity and, in the GROUP study, also family relatedness** | **After adjusting for the main effect of the three exposures, childhood adversity interacted with *COMT* genotype (Cannabis Quest: *β* = -0.47, *p* = 0.019; GROUP: *β* =-0.15, *p* = 0.010).**  **Moreover, only in the Cannabis Quest sample a Cannabis x adversity x COMT- Val158 Met interaction was found (*β*= 0.29, *p* = 0.006), with *Val/Val* genotype related to greater risk for negative and depressive symptoms of psychosis** | **Cannabis Quest: 12**  **GROUP: 16** |
| **Paksarian et al., 2015**  **DENMARK** | ***N =* 985,058** | **Maternal separation, paternal separation and separation from both parents before age of 15 (proportion of any separation ranging from 2.82 to 25.31%)** | **Danish CRS (Pedersen, Gøtzsche, Møller, & Mortensen, 2006)** | **Parental history of psychiatric disorders (approximated maternal history *n* = 60,709, 6.16%; approximated paternal history *n* = 54,095, 5.49%)** | **Danish CRS (Pedersen et al., 2006)** | **Narrow schizophrenia defined as ICD-8 code 295 (excluding 295.79) or ICD-10 (World Health Organization, 1992) code F20 (*n* = 6,469)**  **and broad schizophrenia defined as ICD-8 codes 295, 297 and 298.39, or ICD-10 (World Health Organization, 1992) codes F20–F29 (*n* = 11,464)**  **Danish Psychiatric Central Register** | **Sex, age, birth period, calendar year of follow-up, history of mental disorders in siblings, urbanicity at birth and parental age** | **Interaction between psychiatric parental history and parental separation on broad schizophrenia was found across all 15 age bands (*LR* test ranging from 14.99, *p* = 0.002 (age 1) to 30.06, *p* < 0.001 (age 15))** | **15** |
| **Ramsay et al., 2013**  **Adolescent Brain Development (ABD) study**  **Challenging Times (CT) study**  **IRELAND** | ***N* = 237** | **Sexual and physical abuse and witnessing parental violence before the age of 11-13 (ABD study) or 12-15 (CT study)(*n* = 21)** | **K-SADS (Kaufman et al., 1997)** | ***COMT rs4680* and *BDNF rs6265* SNPs**  ***COMT Val/Val* (*n* = 65) vs. *Val/Met* and *Met/Met* (*n* = 161)**  ***BDNF Val/Val* (*n* = 152) vs. *Val/Met* and *Met/Met* (*n* = 70)** |  | **Diagnosis of psychotic experience according to DSM-IV (*n* = 37)**  **K-SADS (Kaufman et al., 1997)** | **Sex, education, and cannabis use** | **The *BDNF-Val66Met* x childhood adversity interaction was not related to psychotic experiences (*adj. OR* = 1.07, *95% CI*: 0.08, 14.92, *p* = 0.958). The *COMT Val158Met* x adversity interaction showed only a trend for significance (*adj. OR =* 17.16, *95% CI*: 0.86, 344.25, *p* = 0.063)** | **16** |
| Wigman et al., 2012  TRacking  Adolescents’ Individual Lives Survey (TRAILS)  NETHERLANDS | *N* = 2,230 | Moving, hospitalization, sickness or death, parental divorce, being at least 3 months away from home, violence, gossip, bullying, or sexual harassment before age of 16 (*mean =* 5.43, *SD =* 2.1) | Ad hoc questionnaire | Parental general psychopathology (*n* = 974, 45%)  Parental psychotic psychopathology (*n* = 87, 4%) | Brief TRAILS Family  History Interview (Ormel et al., 2005) | PLEs (*mean =* 25.56, *SD =* 4.4) assessed using the positive subscale of the CAPE (Konings et al., 2006)  Developmental trajectories of psychotic experience (low: *n* = 1804; decreasing: *n* = 204, increasing: *n* = 163; persistent: *n* = 41) were identifies using a modified version of the YSR (Achenbach 1991) | Sex | rGE between childhood adversity and parental general and psychotic psychopathology was found (*rho* = 0.25, *p* < 0.001). No additive interaction was found between childhood adversity and parental general and psychotic psychopathology on PLEs, as well as on developmental trajectories of psychotic experience | 12 |
| **Wicks et al., 2010**  **SWEDEN** | ***N* = 13,163 adoptees**  ***N* = 2.9 million Swedish-born persons (non-adoptees)** | **Adoptive parental unemployment (adoptee: 2%; Swedish born: 5.6%), single-parent household (adoptee: 3.2%; Swedish born: 9.9%), living**  **in rented house when the participants were 1–5 years old** | **Swedish Population and Housing Census** | **Parental history**  **of psychosis (adoptee: *n* = 898, Swedish born: *n* = 2.9 million)** | **National Patient Register** | **Non-affective psychosis (adoptees: *n* = 230; Swedish born; *n* = 24,768)**  **National Patient Register** | **Sex, age, and the other two socioeconomic indicators** | **Additive interaction between genetic liability and parental unemployment was marginally significant both in the adoptee (*synergy index* = 3.19, *95% CI*: 1.01, 10.07) and the Swedish born sample (*synergy index* = 1.18, *95% CI*: 1.03, 1.36), while the interactions between genetic liability and single-parenthood was significant only in the Swedish born sample (*synergy index* (adoptee) = 2.63, *95% CI*: 0.97, 7.11; *synergy index* (Swedish born) = 1.22, *95% CI*: 1.08, 1.3).**  **In both samples, interaction between parental history for psychosis and rented housing was not significant (*synergy index* (adoptee) = 1.16, *95% CI:* 0.61, 2.23; *synergy index* (Swedish born) = 0.09, *95% CI*: 0.98, 1.20)** | **18** |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | |
| Green et al., 2014  Australian Schizophrenia Research Bank (ASBR)  AUSTRALIA | *N* = 429 patients with ICD-10 schizophrenia (*n =* 360) or schizoaffective disorder (*n* = 69)  *N* = 652 healthy controls | Child sexual, physical, and emotional abuse, and neglect (cases: *mean =* 6.25, *SD* = 4.87; controls: *mean =* 2.85, *SD* = 3.19) | CAQ (Rosenman & Rodgers, 2004) | *COMT rs4680*: *Val/Val* (cases: *n =* 109, 25.4%; controls: *n* = 56, 23.8%) vs. *Val/Met* (*n* = 224, 52.2%; *n* = 105, 44.7%) vs. *Met/Met* (*n* = 96, 22.4%; *n =* 74, 31.5%) |  | Positive and negative symptoms of schizophrenia  DIP (Castle et al., 2006) | None | Both childhood adversities and *rs4680* *COMT* were associated with schizophrenic spectrum disorders. For positive symptoms, there was an effect of physical abuse (*B =* 3.673, *p* = 0.011) and an additive interaction between *COMT* and physical neglect (*B =* - 3.685, *p* = 0.015).  For negative symptoms, there were significant effects of *COMT* (*B =* 1.106, *p <* 0.001), emotional neglect (*B =* 2.656, *p <* 0.001), and their additive interaction (*B =* - 2.176, *p <* 0.001). Specifically, *Met* homozygote individuals exposed to child adversities showed more symptoms than unexposed | 12 |
| Green et al., 2015  Australian Schizophrenia Research Bank (ASBR)  AUSTRALIA | *N =* 444 patients with ICD-10 schizophrenia  *N =* 292 healthy controls | Childhood physical, emotional, and sexual abuse, and emotional neglect (cases: *n =* 315/ 419, 69.4%; controls: *n =* 220/498, 44.2%) | CAQ (Rosenman & Rodgers, 2004) | *FKBP5* polymorphisms: *rs1360780* (*TT* vs. *TC* vs.*CC*), *rs9470080* (*AA* vs. *AG* vs. *GG*), *rs4713902* (*GG* vs. *AG* vs. *AA*), *rs9394309* (*CC* vs. *TC* vs. *TT*) |  | Severity of positive (*mean =* 9.64, *SD =* 4.01) and negative (*mean =* 19.44, *SD =* 14.60) symptoms  DIP (Castle et al., 2006) and SCAN (World Health Organization, 1992) | Sex, age | Neither child abuse and neglect nor *FKBP5* polymorphisms had a main effect on positive and negative symptoms. No GxE was observed | 10 |
| McCarthy-Jones et al., 2014  Australian Schizophrenia Research Bank (ASBR)  AUSTRALIA | *N =* 333 patients with ICD-10 schizophrenia | Child sexual (*n =* 25, 7.51%), physical (*n =* 82, 24.62%), and emotional abuse (*n =* 129, 38.74%), and neglect (*n =* 53, 15.92%) | CAQ (Rosenman & Rodgers, 2004) | *FOXP2* SNPs: *rs1456031* (*CC* vs. *CT* vs. *TT*), *rs2396753* (*AA* vs. *CC* vs. *AC*),  *rs2253478* (*AG* vs. *AA* vs. *GG*) |  | Lifetime history of auditory verbal hallucinations (*n =* 211, 63%), delusion and negative symptoms  DIP (Castle et al., 2006) | Sex, age, education, non-verbal auditory hallucinations, poverty, and parental divorce | Only *rs1456031* and emotional abuse showed an effect on AVH.  Interaction between *FOXP2* and sexual abuse was not entered in the model due to the large *SE*. There was evidence of interaction between emotional abuse and *FOXP2* *rs1456031*, with greater symptoms for *CC* genotype exposed to emotional abuse and for *TT* genotype unexposed to abuse | 12 |
| Bi et al., 2018  CHINA | *N =* 201 patients with ICD-10 schizophrenia (*n =* 59 FEP patients) | Childhood emotional (*n =* 24, 11.9%), physical (*n =* 39, 19.4%), and sexual abuse (*n =* 47, 23.4%), and physical (*n =* 53, 26.4%) and emotional neglect (*n =*148, 73.6%) | CTQ-SF (Bernstein et al., 2003) | *BDNF*  *Val/Val* (*n =* 34, 17%), *Met/Val* (*n =*105, 52%), and *Met/Met* (*n =*62, 31%) |  | Positive, negative, manic, depressive, and cognitive symptoms  PANSS (Kay, Flszbein, & Opfer, 1987) | None | No rGE was found. A GxE interaction was found on manic symptoms (particularly with physical neglect), but neither on positive nor negative symptoms | 10 |
| De Pradier et al., 2010  FRANCE | *N =* 137 bipolar outpatients with (*n =* 74) and without (*n =* 63) lifetime psychotic symptoms | Childhood sexual abuse (individuals with psychosis: *n =* 11, 15%; without psychosis: *n =* 7, 11%) | THQ (Green 1996) | *5-HTTLPR* polymorphisms: *ss* (with psychosis: *n =* 19, 26%; without psychosis: *n =* 11 17%) vs. *sl* (*n =* 39, 53%; *n =* 26, 41%) vs. *ll* (*n =* 16, 22%; *n =* 26, 41%) |  | Psychotic symptoms  DIGS (Nurnberger et al., 2014) | Cannabis use | The *s* allele showed an effect on lifetime psychotic symptoms, but the interaction between child abuse and the *s* genotype was not significant (*Wald* test = 0.027, *p* = 0.870) | 11 |
| **Debost et al., 2017**  **DENMARK** | ***N =* 1,699 patients with schizophrenia**  ***N =* 1,681 matched controls** | **Parental chronic somatic disease (cases: *n =* 373, 22.1%; controls: *n =* 288, 17.1%), parental loss (cases: *n =* 77, 4.5%; controls: *n =* 50, 3.0%, maltreatment or abuse before age of 15 (cases: *n =* 7, 0.4%; controls: *n =*.2, 0.1%)** | **Danish**  **CRS (Pedersen et al., 2006)**  **Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987)** | ***COMT Val158Met*:**  ***Met/Met* (cases: *n =* 521, 30.7%; controls: *n =* 493, 29.3%) vs. *Val/Met* (cases: *n =* 831, 48.9%; controls: *n =* 819, 48.7%) vs.**  ***Val/Val* (cases: *n =* 347, 20.4%; controls: *n =*. 369, 22.0%)**  ***MTHFR C677T*:**  ***C/C* (cases: *n =* 839, 49.4%; controls: *n =* 829, 49.3%) vs. *C/T* (cases: *n =*704, 41.4%; controls: *n =* 724, 43.1%) vs. *T/T* (cases: *n =* 156, 9.2%; controls: *n =*. 128, 7.6%)** |  | **Diagnosis of ICD-8 or ICD-10 schizophrenia**  **Danish Psychiatric Central Register** | **Sex, age, month of birth, parental history of mental disorders, and PRS** | **No interaction between childhood adversities and *COMT Val/Val* (*adj. IRR p* = 0.12) and *MHTHFR T/T* was found (*adj. IRR p* = 0.06). Furthermore, the three-way *COMT* x *MTHFR* x childhood adversities interaction was not significant (*adj. IRR* p = 0.06)** | **18** |
| Gallagher & Jones, 2016  USA | *N =* 642 patients with DSM-III schizophrenic disorders | Childhood physical and emotional abuse | Unstandardised interview (Social Service Assessment interviews) | Family history for schizophrenic and mood disorders | Unstandardised interview (Social Service Assessment interviews) | Positive and negative psychotic symptoms  SANS (Andreasen 1983), SAPS (Andreasen 1984), and PANSS (Kay et al., 1987) | None | A three-way interaction between family history, abuse, and symptoms was found only for emotional abuse (*G* = 0.445, *p* = 0.035) | 8 |
| Koga et al., 2017  CANADA | *N =* 84 patients with chronic schizophrenia | Childhood emotional, physical, and sexual abuse, and physical and emotional neglect (treatment resistant: *mean =* 43.03, *SD =* 12.75; non-resistant: *mean =* 39.63, *SD =*13.82) | CTQ (Bernstein et al., 1994) | 1,178,234 autosomal SNPs |  | Treatment resistant schizophrenia according to APA criteria (Lehman et al., 2004) (*n =* 31, 36.9%)  SCID-I (First et al., 1996) | Population stratification, suicide attempts | No interaction between childhood adversity and GWAS was found on treatment-resistant schizophrenia. The top SNP was *rs12344695* on chromosome 9 (*OR* = 1.15, *p* =1.15 × 10­4) | 11 |
| Mihaljevic et al., 2017  EU-GEI  SERBIA | *N =* 52 patients with schizophrenia  *N =* 55 healthy siblings  *N =* 51 healthy controls | Childhood emotional, physical, and sexual abuse, and physical and emotional neglect (cases: *mean =* 1.43, *SD =* 0.41; siblings: *mean =* 1.29, *SD =* 0.27; controls: *mean =* 1.20, *SD =* 0.25) | CTQ (Bernstein et al., 1994) | *FKBP5* SNPs: *rs9295158*, *rs3800373*, *rs9740080*, *rs737054*, *rs6926133*, *rs9380529*, *rs9394314*, *rs2766533*, and  *rs12200498* |  | MINI (Lecrubier et al., 1997) | Sex, age, depression | A main effect of *FKBP5* risk alleles (*A* allele of *rs9296158* and *T* allele of *rs3800373*) and *AGTC* “risk” haplotype combination (*rs9296158*, *rs3800373*, *rs9470080* and *rs737054*) on schizophrenia was found.  No GxE interaction was found | 11 |
| Savitz et al., 2010  FRANCE | *N =* 222 participants from 44 families with Bipolar disorders (*n =* 45 with DSM-IV bipolar I, *n =* 18 with bipolar II disorder, *n =* 74 with single episode or recurrent unipolar depression, *n=* 2 with schizophrenia, and *n* = 20 with other diagnoses) | Childhood emotional, physical, and sexual abuse, and physical and emotional neglect | CTQ (Bernstein et al., 1994) | *COMT Val158Met*, *DRD4 48 bp VNTR*, *DRD2 Taq 1A*, *DAT1*, *(SL6A3) 3’VNTR*, *MAOA Promoter*, and *VNTR* |  | Schizotypy  STA (Claridge & Broks, 1984) | Sex, age, ethnicity, depression, and mania | Childhood adversities and *COMT Val158Met* showed no main effect on schizotypy, and no rGE was found between them. There was an interaction between *COMT* genotype and total CTQ score (Effect = 0.08, *SE* = 0.04, *F* =4.58, *p* = 0.034), with higher scores of schizotypy in the *Val* –homozygote individuals who were exposed to child adversity. No interaction was found between child adversity and *DRD2* (*F* = 0.03, *p* = 0.865), *DRD4* (*F* = 0.00, *p* = 0.976), *SLC6A3* (*F* = 1.28, *p* = 0.259) and *MAOA* (*F* = 0.44, *p* = 0.507) | 13 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | |
| **Ajnakina et al., 2014**  **Genetic And Psychosis (GAP) study**  **ENGLAND** | ***N =* 291 patients with ICD-10 FEP**  ***N =* 218 healthy controls** | **Parental separation (cases: *n =* 153, 55.4%; controls: *n =* 79, 36.4%), physical (cases: *n =* 63, 22.7%; controls: *n =* 34, 15.7%) and sexual abuse (cases: *n =* 42, 15.0%; controls: *n =* 25, 11.5%) before age of 17** | **CECA-Q (Bifulco, Bernazzani, Moran, & Jacobs, 2005)** | **Lifetime cannabis use, frequency of cannabis use, and type of cannabis used**  ***FKBP5* *rs1360780* polymorphisms:**  ***CC* (cases: *n =* 118, 40.5%; controls: *n =* 96, 44.0%); *CT* (cases: n 130, 44.7%; controls: *n =* 98, 45.0%); *TT* (cases: *n =* 43, 14.8%; controls: *n =* 24, 11.0%)** | **CEQ (Barkus, Stirling, Hopkins, & Lewis, 2006) and CEQmv (Di Forti et al., 2009)** | **Diagnosis of ICD-10 non-organic psychotic disorders**  **SCAN (World Health Organization, 1992)** | **Sex, age, and genetic ancestry.**  **Interaction between genes and child adversities were adjusted also for lifetime cannabis use, frequency of cannabis use, and type of cannabis used** | **Parental separation was associated with psychosis and, marginally, with genotype (*χ²*= 6.13, *p* = 0.05), with exclusive effect in the case group, suggesting GxE (cases: *χ²*= 6.9, *p* = 0.03; controls: *χ²*= 1.06, *p* = 0.59). The multiplicative interaction between parental separation, cannabis, and *FKBP5* showed an effect only at trend level (*adj. OR* = 0.31, *95% CI*: 0.09; 1.04, *p* = 0.06)** | **18** |
| **Trotta et al., 2015**  **Genetic And Psychosis (GAP) study**  **ENGLAND** | ***N =* 224 patients with ICD-10 FEP**  ***N =* 256 healthy controls** | **Parental separation (cases: *n =* 158, 56.0%; controls: *n =* 90, 35.3%) and loss (cases: *n =* 33, 11.7%; controls: *n =* 16, 6.3%), physical (cases: *n =* 65, 22.8%; controls: *n =* 39, 15.3%) and sexual abuse (cases: *n =* 41, 14.4%; controls: *n =* 28, 11.0%) before age of 17** | **CECA-Q (Bifulco et al., 2005)** | **Family (cases: *n =* 94, 42.0%; controls: *n =* 70, 28.0%) and parental history (cases: *n =* 65, 29.5%; controls: *n =* 49, 20.8%) of mental disorders and family (cases: *n =* 38, 17.3%; controls: *n =* 12, 5.1%) and parental history (cases: *n =* 28, 12.8%; controls: *n =* 8, 3.4%) of psychosis** | **FIGS (NIMH Genetics Initiative, 1992)** | **Diagnosis of ICD-10 psychotic disorders**  **SCAN (World Health Organization, 1992)** | **Sex, age, ethnicity, and education** | **Parental separation was the only adversity associated with psychosis. However, no GxE was found between separation and family mental illnesses (*ICR* = - 3.18, *95% CI:* -6.33, 0.04, *p* = 0.047) or parental mental illnesses (*ICR* = -3.50, *95% CI:* –6.60, 0.40, p=0.027). And the same was true for the other adversities. Furthermore, no evidence of rGE was found.** | **15** |
| **Trotta et al., 2016**  **Genetic And Psychosis (GAP) study**  **ENGLAND** | ***N =* 285 patients with ICD-10 FEP**  ***N =* 256 healthy controls** | **Parental separation and loss, physical and sexual abuse, being taken in institutional care and multiple family arrangement before age of 17 (cases: *n =* 82, 28.8%; controls: *n =* 130, 50.8%)** | **CECA-Q (Bifulco et al., 2005)** | **Polygenic risk score** |  | **Diagnosis of ICD-10 psychotic disorders**  **SCAN (World Health Organization, 1992)** | **Population stratification, sex, age, and education** | **No rGE was found. No additive interaction between PRS and childhood adversities (*adj. B =* -0.20, *SE*= 0.41, *p* = 0.632)** | **16** |
| **Trotta et al., 2018**  **Genetic And Psychosis (GAP) study**  **ENGLAND** | ***N =* 285 patients with ICD-10 FEP**  ***N =* 256 healthy controls** | **Parental separation and loss, physical and sexual abuse, being taken in institutional care and multiple family arrangement before age of 17** | **CECA-Q (Bifulco et al., 2005)** | ***COMT Val158Met*, *AKT1* *rs2494732*, and *DRD2 rs1076560* polymorphisms** |  | **Diagnosis of ICD-10 psychotic disorders**  **SCAN (World Health Organization, 1992)** | **Population stratification, sex, age, ethnicity, and education** | **Childhood adversity was associated with case status, but none of the three polymorphisms was. No evidence of rGE was found.**  **No additive interaction was found either for *COMT Val158Met* (*adj. RD* = -0.03, *95% CI*: -0.09, -0.04), or *AKT1 rs2494732* (*adj. RD* = -0.05, *95% CI*: -0.13, - 0.03), or *DRD2 rs1076560* (*adj. RD* = - 0.05, *95% CI*: -0.18, 0.07)** | **15** |
| Cristóbal-Narváez et al., 2017  SPAIN | *N =* 96 patients with early psychosis (*n =* 60 ARMS and *n =* 36 FEP)  *N =* 242 healthy controls | Emotional, physical, and sexual abuse, and physical and emotional neglect | CTQ (Bernstein et al., 1994) | 10 SNPs within the *COMT*, *BDNF*, *OXTR*, *FKBP5*, and *RGS4* genes clustered as:  1. carriers of at least one risk haplotype  2. carriers of one risk haplotype and one protective haplotype  3.carriers of at least one protective haplotype |  | PLEs assessed using ESM  Early psychosis ascertained with the CAARMS (Yung et al., 2005) and the SCID-I (First et al., 1996) | None | Childhood adversity interacted with *FKBP5* (*B =* 0.009, *SE* = 0.003, *p* = 0.007) and *RGS4* risk haplotypes (*B =* 0.009, *SE* = 0.004, *p* = 0.008) in the whole sample, with a greater effect in the clinical sample (genes x adversity x group interaction) | 8 |
| **Fisher et al., 2014**  **Aetiology and Ethnicity of Schizophrenia and**  **Other Psychoses (AESOP) study**  **ENGLAND** | ***N =* 172 patients with ICD-10 FEP**  ***N =* 246 healthy controls** | **Maternal physical abuse (cases: *n =* 22; controls: *n =* 9)** | **CECA-Q (Bifulco et al., 2005)** | **Family and parental history of psychosis, depression, or mania (cases: *n =* 54, 31.4%; controls: *n =* 32, 13.0%)** | **FIGS (NIMH Genetics Initiative, 1992)** | **Diagnosis of ICD-10 psychotic disorders**  **SCAN (World Health Organization, 1992)** | **Sex, age, ethnicity, study centre, and higher paternal social class** | **Evidence of rGE between maternal physical abuse and family and parental psychosis was found. Furthermore, no interaction was found between maternal physical abuse and either family (*ICR* = 3.51, *95% CI*: -16.16, 23.18, *p* = 0.726) or parental (*ICR* = 1.98, *95% CI*: -19.48, 23.43, *p* = 0.857) history of mental diseases** | **15** |
| Ierago et al., 2010  PALAU | *N =* 184 teenagers at moderate or high genetic risk for schizophrenia | Adoption (*n =* 47, 26%) | Unstandardized interview | Genetic risk for schizophrenia (at genetic higher risk: *n =* 53, 29%; at high risk: *n =* 68, 37%; at moderate risk: *n =* 63, 35%) | Unstandardized interview | KSADS-PL (Kaufman et al., 1997) | Age | Genetic risk status was not related to psychotic symptoms, while adoption status was. There was a rGE between the two (*χ²* = 8.823, *p <* 0.05) but no multiplicative interaction was found (*β* = 0.014, *p* = 0.893) | 10 |
| McGregor et al., 2018  SOUTH AFRICA | *N =* 103 patients with FEP | Childhood emotional, physical, and sexual abuse, and physical and emotional neglect | CTQ (Bernstein et al., 1994) | *MMP9* variants: *rs1304027*, *rs3918242*, *rs3918249*, *rs3918256*, and *rs3918270* |  | Positive, negative, and total psychotic symptoms at the 12-month follow-up  PANSS (Kay et al., 1987) | Sex, age, proportion ancestry, and baseline PANSS scores | No *MMP9* SNPs interacted with childhood adversity on psychotic symptoms, but a trend towards significance was found for four SNPs (*rs3918242*, *rs17576*, *rs2236416*, and *rs2250889*) | 11 |
| Veling et al., 2016  NETHERLANDS | *N =* 55 patients with FEP  *N =*20 individuals at UHR for psychosis  *N =* 42 siblings  *N =* 53 healthy controls | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (FEP patients and UHR individuals: *n =* 43, 71.6%; siblings and controls: *n =* 17, 28.3%) | CTQ-SF (Bernstein et al., 2003) | Psychosis liability: high liability (i.e. FEP patients and UHR individuals), low liability (i.e. siblings and controls) |  | Paranoid thoughts about socially stressful experiences in a virtual environment (exposed to childhood adversities: *mean =* 19.73, *SD =* 7.8; unexposed: *mean =* 17.45, SD 7.39)  SSPS (Freeman et al., 2007) | Sex, age, number of stressors, psychosis liability | No interaction between childhood adversity and psychosis liability on paranoia was found | 8 |
| **SUBSTANCE USE** | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | |
| **Houston et al., 2008**  **National Comorbidity**  **Survey (NCS)**  **USA** | ***N =* 5,877** | **Sexual molestation and rape before 16 years of age (*n =* 543, 9.2%)** | **PTSD module of the CIDI (World Health Organization, 1990)** | **Any cannabis use before 16 years of age (*n =* 643, 10.9%)** | **Medication and Drugs module of the CIDI (World Health Organization, 1990)** | **Diagnosis of non-affective psychosis according to DSM-III-R criteria (*n =* 42)**  **SCID-I (First et al., 1996)** | **Sex, age, lifetime depression, urbanicity, ethnicity, years in education, employment status, and living arrangement** | **Evidence of both additive (*RD* = 0.025, *95% CI*: 0.021, 0.030, *p <* 0.001) and multiplicative interaction (*χ²*= 100.43, *p <* 0.001) between cannabis and sexual abuse was found** | **15** |
| Murphy et al., 2013  National Comorbidity  Survey-Replication  (NCS-R)  USA | *N =* 2,355 | Sexual assault (*n =* 274, 8.3%) and rape (*n =* 192, 5.8%) before 16 years of age | Posttraumatic Stress Disorder module of the modified version of the CIDI 3.0 (Kessler, 1994) | Lifetime cannabis use (*n =* 1,120, 41.2%) | Substance use module of the CIDI 3.0 (Kessler, 1994) | Cumulative score of adult psychotic symptoms (paranoia: *n =* 26, 0.8%; communication from strange forces: *n =* 24, 0.8%; mind controls: *n =* 6, 0.1%; thought insertion: *n =* 13, 0.4%; auditory hallucinations: *n =* 123, 4.0%; visual hallucinations: *n =* 174, 6.3%)  Psychosis module of the CIDI 3.0(Kessler, 1994) | Sex, age, ethnicity, education, income, pre-trauma psychotic experience, and pre-trauma other pathologies (ADHD, conduct disorder, oppositional defiant disorder, separation anxiety disorder, social phobia, specific phobia, intermittent explosive disorder) | Childhood rape was associated with increased risk for psychotic symptoms (β= 0.30, SE= 0.04, *B =* 0.16, *p <* 0.05), while sexual assault and cannabis use were not. Multiplicative interaction between cannabis use and sexual assault was significant only when substance misuse preceded sexual abuse (*β* = 0.40, *SE* = 0.17, *B =* 0.05, *p <* 0.05), but not the other way around.  Pre-trauma social phobia and pre-trauma psychotic symptoms increased the risk for psychosis, but accounted neither for the effect of rape nor for the cannabis x rape interaction | 12 |
| Harley et al., 2010  Challenging times (CT) study  IRELAND | *N =* 211 | Child physical or sexual abuse, or witnessing domestic violence before the age of 12-15 (*n =* 24, 11.3%) | K-SADS (Kaufman et al., 1997) | Lifetime cannabis use (*n =* 18, 8.5%) | Substance misuse module of the K-SADS (Kaufman et al., 1997) | Diagnosis of psychotic symptoms according to DSM-IV (*n =* 14, 6.6%)  Psychosis section of the K-SADS (Kaufman et al., 1997) | None | rEE was found between childhood adversities and cannabis use (*OR* = 4.86, *95% CI*: 1.63, 14.51, *p* = 0.005). Additive interaction between cannabis and childhood adversities was found (*OR* = 20.9, *95% CI*: 2.3,173.5) | 12 |
| Houston et al., 2011  Adult Psychiatric Morbidity Survey (APMS)  ENGLAND | *N =* 7,403 | Uncomfortable sexual talk (*n =* 758), touching (*n =* 618) and non-consensual intercourse (*n =* 141) before 16 years of age | Ad hoc questionnaire (Domestic violence and abuse questionnaire) | Lifetime cannabis use (*n =* 1,699) | Ad hoc questionnaire | Diagnosis of psychotic disorders according to ICD-10 (definitive psychosis *n =* 29)  PSQ (Bebbington & Nayani, 1995) and SCAN (World Health Organization, 1992) | Sex, age, education, ethnicity, employment status, depression, and alcohol abuse | Non-consensual sexual intercourse was related with psychosis controlling for the effect of cannabis use (*adj. OR =* 6.10, *95% CI:* 1.46, 25.44). Evidence of non- consensual intercourse x cannabis interaction was found (*adj. OR =* 15.47, *95% CI:* 1.03, 229.68) | 12 |
| **Konings et al., 2012**  **The Greek National Perinatal Study (GNPP), GREECE**  **The Netherlands Mental Health Survey and Incidence**  **Study (NEMESIS-1), NETHERLANDS** | **GNPP: *N =* 1,636**  **NEMESIS-1: *N =* 4,842** | **GNPP: physical punishment before age of 9 (sometimes: *n =* 940, 58%; often: *n =* 196, 12%).**  **NEMESIS-1: emotional, psychological, physical or sexual abuse before 16 years of age (range 0-3, moderate to severe maltreatment: *n =* 412, 8.5%)** | **GNPP: ad hoc questionnaire filled in by parents**  **NEMESIS-1: ad hoc semi-structured interview** | **Lifetime cannabis use (GNPP: *n =* 96, 6%; NEMESIS-1: *n =* 462, 9.5%)** | **GNPP: ad hoc questionnaire filled in by participants**  **NEMESIS-1: CIDI-L section on substance use (Smeets, 1993)** | **GNPP: frequency of lifetime psychotic symptoms at age 19 assessed using the CAPE (Konings et al., 2006)**  **NEMESIS-1: any lifetime psychotic symptom assessed using the Psychosis section of the CIDI-L (Smeets, 1993)** | **GNPP: sex, urbanicity, other drug use**  **NEMESIS: sex, urbanicity, other drug use, age, ethnicity, single marital status, discrimination, and unemployment** | **Child abuse increased risk for psychotic symptoms in cannabis users (GNPP: *F*= 4.18, *p* = 0.016; NEMESIS-1: *χ2*= 8.08, *p* = 0.04). Only in NEMESIS-1 evidence of rEE was found (*OR* = 1.57, *95% CI:* 1.33,1.86, *p <* 0.001)** | **GNPP: 11**  **NEMESIS-1: 16** |
| **Morgan, Reininghaus, Reichenberg, et al., 2014**  **South East London Community**  **Health Study (SELCoH)**  **ENGLAND** | ***N =* 1,680** | **Childhood physical (*n =* 402, 22.7%) or sexual abuse (*n =* 79, 5.2%)** | **Ad hoc interview** | **Lifetime and past year cannabis use** | **Ad hoc interview** | **Lifetime psychotic experiences (*n =* 315, 17.9%)**  **PSQ (Bebbington & Nayani, 1995)** | **Sex, age, ethnicity, education, social class** | **Evidence of rEE between child abuse and cannabis use was found. Additive interaction with past year cannabis was not significant (*ICR* = 2.40, *95% CI:* -0.17, 4.97, *p* = 0.07)** | **16** |
| **Vinkers et al., 2013**  **Cannabis Quest (discovery sample)**  **Genetic Risk and Outcome of Psychosis (GROUP) study (replication sample)**  **NETHERLANDS and BELGIUM** | **Cannabis Quest: *N =* 918**  **GROUP: *N =* 339** | **Emotional, physical, and sexual abuse, and physical and emotional neglect (Cannabis Quest: *mean =* 1.40, range 1.00–4.26; GROUP: *mean =* 1.33, *range*: 1.0–2.95)** | **CTQ-SF (Bernstein et al., 2003)** | **Past year cannabis use (Cannabis Quest: >3 euro/week: *n =* 303, 33%; GROUP: none: *n =* 292, 86%; less than weekly: *n =* 27, 8%; weekly: *n =* 14, 4%; daily: *n =* 7, 2%)** | **Past year cannabis use was assessed in Quest using an online survey and in GROUP using the CIDI (World Health Organization, 1990)** | **Positive, negative and depressive PLEs (Cannabis Quest: *mean =* 0.61, *range:* 0.02–2.48; GROUP: *mean =* 0.38, *range*: 0.0–1.29)**  **CAPE (Konings et al., 2006)** | **Sex, age, ethnicity and, in the GROUP study, also family relatedness** | **rEE between cannabis and childhood adversities was found only in the Quest sample (*p <* 0.001). In both samples no interaction was found between childhood adversity and cannabis use.** | **Cannabis Quest: 12**  **GROUP: 16** |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | |
| Baudin et al., 2016  Fondamental Advanced Centre of Expertise — Schizophrenia (FACE SCZ)  FRANCE | *N =* 366 patients with DSM-IV schizophrenia | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (*mean =* 41.55, *SD =* 10.91) | CTQ-SF (Bernstein et al., 2003) | Lifetime cannabis use disorders (*n =* 99, 27.05%) | SCID-I for DSM-IV (First et al., 1996) | Positive (*mean =* 16.26, *SD =* 6.65), negative (*mean =* 22.42, *SD =* 8.33), disorganized (*mean =* 24.66, *SD =* 8.28), disphoric (*mean =* 18.09, *SD =* 6.08), and manic symptoms (*mean =* 14.88, *SD =* 4.87)  PANSS (Kay et al., 1987) | Sex, age | rEE was found between childhood adversities and cannabis use disorders. No multiplicative interaction was found on psychotic symptoms | 11 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | |
| **Ajnakina et al., 2014**  **Genetic And Psychosis (GAP) study**  **ENGLAND** | ***N =* 291 patients with ICD-10 FEP**  ***N =* 218 healthy controls** | **Parental separation (cases: *n =* 153, 55.4%; controls: *n =* 79, 36.4%), physical (cases: *n =* 63, 22.7%; controls: *n =* 34, 15.7%) and sexual abuse (cases: *n =* 42, 15.0%; controls: *n =* 25, 11.5%) before age of 17** | **CECA-Q (Bifulco et al., 2005)** | **Lifetime cannabis use, frequency of cannabis use, and type of cannabis used** | **CEQ (Barkus et al., 2006) and CEQmv (Di Forti et al., 2009)** | **Diagnosis of ICD-10 non-organic psychotic disorders**  **SCAN (World Health Organization, 1992)** | **Sex, age, and genetic ancestry.** | **No EXE was found between any of the childhood adversities and any of the cannabis measures.** | **18** |
| **Sideli et al., 2018**  **Genetic And Psychosis (GAP) study**  **ENGLAND** | ***N =* 231 patients with FEP**  ***N =* 214 healthy controls** | **Severe sexual abuse or severe physical abuse before 16 years of age (cases: *n =* 65; controls: *n =* 33)** | **CECA-Q (Bifulco et al., 2005)** | **Lifetime cannabis use (cases: *n =* 161; controls: *n =* 124), frequency of cannabis use, and type of cannabis used** | **CEQ (Barkus et al., 2006) and CEQmv (Di Forti et al., 2009)** | **Diagnosis of ICD-10 non-organic psychotic disorders**  **OPCRIT (McGuffin, Farmer, & Harvey, 1991)** | **Sex, ethnicity, education, and family history of mental disorders** | **Neither rEE nor additive interaction between childhood adversity and lifetime cannabis use (ICR= 1.46, *95% CI:* -0.54, 3.46, p 0.152) were found. The specific effect of type and frequency of cannabis use could not be tested due to small frequencies, but there was a suggestion that EE interaction was mainly driven by low potency and low frequency cannabis** | **13** |
| **STRESSFUL LIFE EVENTS AND SOCIAL RISK FACTORS** | | | | | | | | | |
| **GENERAL POPULATION SAMPLE** | | | | | | | | | |
| Honings et al., 2017  The Netherlands Mental Health Survey and Incidence  Study 2 (NEMESIS-2),  NETHERLANDS | *N =* 6,359 | Emotional neglect, bullying, psychological, physical, or sexual abuse before age of 16 (*n =* 2138, 34.4%) | Ad hoc interview | Physical, psychological and sexual adult victimization (after age of 16; *n =* 1,940, 33.2%) | Ad hoc interview | Psychotic experiences (*n =* 340, 5.3%)  SCID-I for DSM-IV (First et al., 1996) | Sex, age, low socio-economic status, past criminal activity and substance use disorders | rEE was found between childhood and adult victimization (*adj. OR =* 3.15, *95% CI:* 1.87, 5.30, *p <* 0.01). There was no evidence of ExE on psychotic experiences (*adj. OR =* 0.95, *95% CI:* 0.48,1.90, p = 0.89) | 16 |
| **Lataster et al., 2012**  **Early Developmental Stages of Psychopathology**  **Study (EDSP)** | ***N =* 3,021** | **Childhood physical and sexual abuse, parental separation or death, exposure to war, kidnap, imprisonment, natural catastrophe (*n =* 605, 35.1%)** | **CIDI (World Health Organization, 1990)** | **Recent life events (>10 life events: *n =* 433, 25.1%)** | **MEL (Maier-Diewald et al., 1983)**  **CIDI (World Health Organization, 1990)** | **Psychotic symptoms (*n =* 170, 9.9%)**  **CIDI (World Health Organization, 1990)** | **Sex, age, cannabis use, urbanicity** | **rEE between early and recent events was found. Additive interaction was found between childhood adversity and being exposed to more than 10 recent adversities (Wald test *χ²*= 4.59, *p* = 0.032), while for fewer life events the interaction was not significant** | **17** |
| **Morgan, Reininghaus, Reichenberg, et al., 2014**  **South East London Community**  **Health Study (SELCoH)**  **ENGLAND** | ***N =* 1,680** | **Childhood physical (*n =* 402, 22.7%) or sexual abuse (*n =* 79, 5.2%)** | **Ad hoc interview** | **Cumulative exposure to past year or lifetime life event (*range*: 0–9)** | **Ad hoc interview** | **Lifetime psychotic experiences (*n =* 315, 17.9%)**  **PSQ (Bebbington & Nayani, 1995)** | **Sex, age, ethnicity, education, social class** | **Evidence of rEE between child abuse and stressful events. Additive interaction was found between any child abuse and lifetime exposure to life events (*ICR* = 0.21, *95% CI:* 0.05, 0.38, *p* = 0.01), with a stronger interaction with past year life events (ICR= 0.56, *95% CI:* 0.08, 1.05, p = 0.02).** | **16** |
| **Newbury et al., 2018**  **Environmental Risk (E-Risk) Longitudinal Twin Study**  **ENGLAND & WALES** | ***N =* 2,063** | **Personal experiences of violent crime victimization before age of 18 (*n =* 398, 19.3%)** | **JVQ-R2 (Finkelhor, Hamby, Turner, & Ormod, 2011)** | **Neighbourhood social adversity (neighbourhood characterized by both low social cohesion and high neighbourhood disorder, *n =* 772, 35.9%)** | **Ad hoc interview (Odgers et al., 2009)** | **Any psychotic symptom (*n =* 59, 2.9%)**  **PQ-B (Loewy, Pearson, Vinogradov, Bearden, & Cannon, 2011) and ad hoc interview (Polanczyk et al., 2010)** | **Family psychiatric history, family SES, maternal psychotic symptoms, adolescent alcohol and cannabis dependence, childhood psychotic symptoms, and neighbourhood -level deprivation** | **Evidence of rEE between exposure to violent crime and neighbourhood social adversity was found. The cumulative risk associated with violent crime victimisation and neighbourhood social adversity was greater than the risk related to either type of events (*adj. OR =* 4.86, *95% CI:* = 3.28, 7.20, p < 0.001), but the ExE interaction was not significant (*ICR* = 1.81, *95% CI:* = -0.03, 3.65, *p* = 0.054)** | **16** |
| **Ouellet-Morin et al., 2015**  **Environmental Risk (E-Risk) Longitudinal Twin Study**  **ENGLAND & WALES** | ***N =* 1,052** | **Emotional, physical, and sexual abuse and emotional and physical neglect (*n =* 235, 24.9%)** | **CTQ-SF (Bernstein et al., 2003)** | **Intimate partner violence (*n =* 389, 39.8%)** | **CTS-R (Straus, 1990)** | **Any psychotic symptom (*n =* 45, 4.7%) in context of DSM-IV depressive disorder (*n =* 94, 9.8%)**  **DIS (Robins, Cottler, & Buckolz, 1996) and PSQ (Bebbington & Nayani, 1995)** | **Socio-economic deprivation (composite index of family income, education, and social class), young motherhood, substance abuse, and antisocial personality** | **Evidence of rEE between child abuse and partner violence was found. The cumulative risk associated with childhood maltreatment and partner violence was greater than the risk related to either type of events (*adj. OR =* 0.31, *95% CI:* 0.16, 0.62)** | **14** |
| **Räikkönen et al., 2011**  **Helsinki Birth**  **Cohort Study**  **FINLAND** | ***N =* 12,747** | **Separation from parents (*n =* 1,719)** | **Finnish National Archives’ register** | **Socio-economic status (SES)** | **Finnish National Archives’ register** | **ICD-10 non-affective psychoses (*n =* 311)**  **Finnish**  **Hospital Discharge and Causes of Death Registers** | **Sex, year of birth** | **rEE was found between parental separation and low SES (*p <*0.001).**  **Neither parental separation, nor low SES was associated to psychotic disorders. The parental separation x low SES interaction was not significant (*adj. HR* = 1.05, *95% CI:* 0.69, 1.61, *p* = 0.81), but separated children were at higher risk for psychosis if belonging from an upper SES (adj. HR= 2.64, *95% CI:* 1.13, 6.13, p = 0.025)** | **14** |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | |
| Akün et al., 2018  TURKEY | *N =* 53 patients with schizophrenia | Maternal and paternal acceptance- rejection in childhood (warmth/ affection, hostility/ aggression, indifference/ neglect, undifferentiated rejection, and control) | Adult PARQ/C (Rohner, 2005) | Socio-economic status (SES) (low *n =*12, middle *n =* 29, high *n =* 12) | Monthly income level | Diagnosis of schizophrenia according to ICD-10  Positive symptoms assessed using the SAPS (Andreasen 1984) | None | Evidence of rEE between maternal acceptance- rejection and SES was found. Positive symptoms correlated only with maternal neglect (*r*= 0.28, *p* = 0.041).  The two-way maternal neglect x SES interaction was not significant, but the three-way maternal neglect x SES x gender was (*β* = -2.57, *p <* 0.009), suggesting that only female patients exposed to both maternal neglect and low SES had greater positive symptoms | 9 |
| Begemann et al., 2017  NETHERLANDS | *N =*103 patients with psychotic disorders  *N =*134 individuals with PLEs  *N =* 125 healthy controls | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (cases: *mean =* 46.67, *SD =* 20.05; individuals with PLEs: *mean =* 45.20, *SD =*15.45; controls: *mean =* 35.43, *SD =* 8.18) | CTQ-SF (Bernstein et al., 2003) | Adult stressful events (cases: *mean =* 5.05, *SD =* 3.01; individuals with PLEs: *mean =* 5.65, *SD =* 3.13; controls: *mean =* 3.74, *SD =* 2.59) | LSC-R (Wolfe, Kimerling, Brown, Chrestman, & Levin, 1996) | Psychotic disorder and any PLEs  CASH (Andreasen, Flaum, & Arndt, 1992) | None | rEE was found between childhood adversities and late life events. No ExE interaction was found either on case status (vs. controls, *OR* = 1.05, *95% CI:* 0.84, 1.30, *p* = 0.667; vs. PLEs, OR= 1.10, *95% CI:* 0.91, 1.33, *p =* 0.314) or presence of PLEs (vs. controls *OR* = 0.95, *95% CI:* 0.78, 1.17, *p* = 0.635) | 9 |
| Frissen et al., 2015  Genetic Risk and Outcome in Psychosis (GROUP)  NETHERLANDS, BELGIUM | *N =*1,119 patients with a non-affective psychotic disorder  *N =* 589 healthy controls | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (cases: *mean =*1.6, *SD =* 0.5; controls: *mean =* 1.3, *SD =* 0.4). | CTQ-SF (Bernstein et al., 2003) | Urbanicity exposure between 0 and 14 years of age (cases: *mean =* 2.7, *SD =* 1.6; controls: *mean =* 2.6, *SD =* 1.6) | Netherlands and Belgium Statistics record | Diagnosis of DSM-IV-TR non-affective psychotic disorder  CASH (Andreasen et al., 1992) and SCAN (World Health Organization, 1992) | Sex, age | No rEE was found between childhood urbanicity and childhood adversities. The childhood adversities x urbanicity interaction was significant (*χ2*= 7.06, *p* = 0.01), with increasing odds ratios for higher levels of childhood urbanicity in a roughly linear way (from *OR* = 2.76, *95% CI:* 1.71, 4.46, *p <* 0.001 for urbanicity 1, to *OR* = 5.66, *95% CI:* 2.87, 11.6, *p <* 0.001 for urbanicity 4). However, after imputation of CTQ missing data, the adversities x urbanicity interaction was not significant (*χ2* =3.58, *p* = 0.06) | 12 |
| Lardinois et al., 2011  NETHERLANDS, BELGIUM | *N =* 50 patients with non-affective psychotic disorder | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (*mean =* 40.7, *SD =* 11.4) | CTQ-SF (Bernstein et al., 2003) | Daily life event-related stress (*mean =* -1.39, *SD =* 1.68) and activity-related stress (*mean =* 2.55, *SD =* 1.20) | ESM | Psychotic symptoms  ESM | Sex, age | Interactions between childhood adversities and daily life event-related stress (*β* = 0.06, *SE*= 0.02, *p <* 0.001) and between childhood adversities and activity-related stress (*β* = 0.11, *SE*= 0.05, *p <* 0.001) on psychosis were found | 6 |
| Mansueto & Faravelli 2017  PSI-FIELDS  ITALY | *N =* 78 patients with non-affective psychosis, delusional disorder, schizoaffective, or bipolar disorders with psychotic features (*n =* 4 FEP)  *N =* 156 healthy controls | Childhood abuse, neglect, or separation/ loss | CECA-Q (Bifulco et al., 2005)  Ad hoc interview (Pallanti et al., 2008) | Family conflicts, loss of job/financial problem, bereavement, health problems, or recent abuse in the prior year | Ad hoc interview (Faravelli & Ambonetti, 2004) | Clinical diagnosis according to Jablensky et al. (2009) criteria | Sex, age, family history for mental disorders, substance abuse | The risk for psychosis in those exposed to both childhood and recent life events (*adj. OR =* 15.28, *95% CI:* 4.50, 51.03) was much greater than those of the exposed either to childhood adversity alone (OR= 5.27, *95% CI:* 1.55, 17.92) or to recent event alone (*OR* = 8.82, *95% CI:* 2.70, 28.79) | 11 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | |
| **Gayer-Anderson et al., 2015**  **Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study**  **ENGLAND** | ***N =* 202 patient with FEP**  ***N =* 266 healthy controls** | **Severe sexual and physical abuse before 16 years of age (vs. non-severe or none)** | **CECA-Q (Bifulco et al., 2005)** | **Ideal and perceived levels of practical (cases: *mean =* 9.92, *SD =* 2.36; controls: *mean =* 10.83, *SD =* 2.02) and emotional support (cases: *mean =* 10.61, SD 2.57; controls: *mean =* 11.48, *SD =* 1.93)**  **Number of significant others (6-7 significant others (SO): cases: *n =* 68, 33.6%; controls: *n =* 109, 41%)**  **Discrepancy score between ideal and perceived support** | **SOS (Power, Champion, & Aris, 1988)** | **ICD-10 diagnosis of psychotic disorders (*n =* 202)**  **SCAN (World Health Organization, 1992)** | **Sex, age ethnicity, education, current employment, parental history of mental illness, study centre** | **The impact of physical abuse on odds of psychosis was modified by number of significant others, with higher risk for those with poor social network (5 or more SO: *adj. OR =* 0.99, *95% CI:* 0.42, 2.36; less than 5 SO: *adj. OR =* 3.24, *95% CI:* 1.42, 7.38, LR test *χ2* = 3.90, *p* = 0.048)** | **13** |
| **Morgan, Reininghaus, Fearon, et al., 2014**  **Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study**  **ENGLAND** | ***N =* 390 patients with FEP**  ***N =* 391 healthy controls** | **Parental separation (cases: *n =* 160, 41%; controls: *n =* 80, 20.4%) or death (cases: *n =* 30, 7.7%; controls: *n =* 14, 3.6%) before age of 16** | **MRC Socio demographic Schedule (Mallett 1997)** | **Adult disadvantage (five indicators (i.e., unemployment, living alone, no relationship and limited social network, renting house): cases: *n =* 39, 10.1%; controls *n =* 4, 1%)**  **No education (cases: *n =* 24, 32%; controls: *n =* 71, 18.3%)** | **MRC Socio demographic Schedule (Mallett, 1997)**  **RSES (Rosenberg, 1989)** | **ICD-10 diagnosis of psychotic disorders (*n =* 390)**  **SCAN (World Health Organization, 1992)** | **Sex, age, ethnicity, study centre, and parental history of psychosis.** | **Additive interaction was found between early separation and adult disadvantage (*ICR* = 4.30, *95% CI:* 0.66, 7.94, *p* = 0.021), but not between early separation and no education** | **15** |
| **PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL MECHANISMS** | | | | | | | | | |
| **GENERAL POPULATION SAMPLE** | | | | | | | | | |
| Goodall et al., 2015  ENGLAND | *N =* 283 | Emotional (*mean =* 9.42, *SD =* 4.86), physical (*mean =* 6.74, *SD =* 3.39), and sexual abuse (*mean =* 6.23, *SD =* 3.79), and physical (*mean =* 7.25, *SD =* 2.88) and emotional neglect (*mean =* 9.96, *SD =* 4.72) | CTQ (Bernstein et al., 1994) | Attachment anxiety (*mean =* 3.35, *SD =* 1.22) and avoidance (*mean =* 3.02, *SD =* 1.14) | ECR-R (Fraley, Heffernan, Vicary, & Brumbaugh, 2011) | Schizotypy (*mean =* 8.98, *SD =* 5.07)  SPQ-B (Raine & Benishay, 1995) | Age | Attachment anxiety and avoidance correlated with all child adversities but physical abuse. Adjusting for the other adversities, only emotional abuse showed an effect on schizotypy.  No interaction was found between emotional abuse and attachment anxiety (*β* = -0.02, *95% CI:* -0.10, 0.10) and avoidance (*β* = -0.14, *95% CI:* -0.15, 0.07) | 10 |
| Nam et al., 2016  USA | *N =* 799 | Childhood sexual abuse (*n =* 57, 7.1%) | Ad hoc questionnaire | Depression (*mean =* 9.03, *SD =* 10.57)  Bullying (*n =* 171, 21.4%) | CES-D (Radloff 1977) | PLEs severity and distress (*mean =* 19.14, *SD =*10.57)  PQ-B (Loewy et al., 2011) | Sex, ethnicity | Sexual abuse was associated with depression. The sexual abuse x depression interaction was not significant (*B =* -0.116, *SE* = 0.183, *p* > 0.05). A three-way interaction abuse x bullying x depression showed an effect on PLEs (*B =* 1.045, *SE*= 0.258, *p <* 0.001) | 10 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | |
| **Mansueto et al., 2019**  **Genetic Risk and Outcome of Psychosis (GROUP) study**  **NETHERLANDS** | ***N =* 1,119 patients with non-affective psychotic disorder** | **Childhood neglect (*mean =* 1.86, *SD =* 0.63) and abuse (*mean =* 1.43, *SD =* 0.52)** | **CTQ-SF (Bernstein et al., 2003)** | **Mentalizing abilities (*mean =* 17.71, *SD =* 2.73)** | **Hinting Task (Corcoran et al., 1995)** | **Positive (*mean =* 13.62, *SD =* 6.58), negative (*mean =* 14.19, *SD =* 6.19), disorganization (*mean =* 16.16, *SD =* 6.29), excitement (*mean =* 11.70, *SD =* 3.89), and emotional distress symptoms (*mean =* 15.49, *SD =* 5.63)**  **PANSS (Kay et al., 1987)** | **Sex, age, and cannabis use** | **Mentalizing abilities did not moderate the effect of either childhood neglect or abuse on psychotic symptoms** | **13** |

**Supplementary Table 7. Summary of the findings of mediation studies by type of exposure and population (methodologically robust studies in bold)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors, year, study name, country** | | | **Sample** | | | **Type of childhood adversity** | | **Measure of childhood adversity** | **Other exposures** | **Measure of other exposures** | **Outcome definition and measure** | | **Confounders** | | **Main findings** | **Quality score** |
| **GENETIC RISK FACTORS** | | | | | | | | | | | | | | | | |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | | | |
| Goldstone et al., 2011  AUSTRALIA | | | | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | Childhood physical, emotional, and sexual abuse | | Modified version of the ETI-SR (Bremner, Bolus, & Mayer, 2007) | Family history for psychosis  Life hassles  Experiential avoidance  Early cannabis use, before age of 20  Recent methamphetamines use, after age of 20 | Ad hoc questionnaire  Survey of Recent Life Experiences (Kohn & Macdonald, 1992)  AAQ-II (Bond et al., 2011)  Ad hoc questionnaire | Delusional ideation (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  PDI (Peters, Joseph, & Garety, 1999) | | None | | No mediation via family history was found neither in the general population nor in the clinical sample | 8 |
| Goldstone et al., 2012  AUSTRALIA | | | | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | Childhood physical (controls: *mean =* 1.63, *SD =* 1.54; cases: *mean =* 2.61, *SD =* 1.55), emotional (controls: *mean =* 1.38, *SD =* 1.38; cases: *mean =* 2.77, *SD =* 1.76), and sexual abuse (controls: *n =* 13, 10%; cases: *n =* 25, 25%) | | Modified version of the ETI-SR (Bremner et al., 2007) | Family history for psychosis (controls: *n =* 28, 21%; cases: *n =* 39, 39%)  Life hassles (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, SD 14.24)  Experiential avoidance (controls: *mean =* 51.62, *SD =* 10.79; cases: *mean =* 41.62, *SD =* 13.68)  Early cannabis use, before age of 20 (daily: controls: *n =* 11, 8%; cases: *n =* 27, 27%; weekly: controls: *n =* 19, 14%; cases: *n =* 19, 19%)  Recent methamphetamines use, after age of 20 (daily: controls: *n =* 1, 1%; cases: *n =* 9, 9%; weekly/ monthly: controls: *n =* 5, 14%; cases: *n =* 18, 18%)  Metacognitive beliefs (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, *SD =* 14.24) | Ad hoc questionnaire  Survey of Recent Life Experiences(Kohn & Macdonald, 1992)  Ad hoc questionnaire  MCQ (Wells & Cartwright-Hatton 2004) | Hallucination experiences (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  LSHS-R (Bentall & Slade, 1985) | | None | | No mediation via family history was found neither in the general population nor in the clinical sample | 8 |
| **SUBSTANCE USE** | | | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLES** | | | | | | | | | | | | | | | | |
| **van Nierop et al., 2014**  **The Netherlands Mental Health Survey and Incidence**  **Study 2 (NEMESIS-2)**  **NETHERLANDS** | | | | ***N =* 6,646** | | **Emotional neglect, bullying, psychological, physical, or sexual abuse before age 16 years of age (cumulative score: controls: *mean =* 1.4, *SD =* 2.9; EPP: *mean =* 3.9, *SD =* 4.75; PD: *mean =* 5.8, *SD =* 4.8)** | | **Ad hoc interview** | **Frequency of lifetime cannabis use (controls: *mean =* 0.4, *SD =* 1.0; EPP: *mean =* 0.7, *SD =* 1.6; PD: *mean =* 1.2, *SD =* 2.0)** | **CIDI 3.0 (Kessler, 1994)** | **Severity of psychotic experiences in individuals with lifetime psychotic symptoms (EPP: *n =* 384; PD: *n =* 43)**  **Ad hoc interview**  **SCID-I for DSM-IV(First et al., 1996)** | | **Sex, age** | | **Childhood adversity predicted cannabis use (*β* =0.13, *p <* 0.001). Cannabis use did not show any mediation effect** | **16** |
| Whitfield et al., 2005  Adverse Childhood Experiences (ACE)  USA | | | | *N =* 17,337 | | Childhood physical, emotional, and sexual abuse; parental separation or death; substance abuse or mental illness in household; incarcerated household (*n =* 11,096, 64%) | | Ad hoc questionnaire | Alcohol or substance misuse (*n =* 3,970, 22.9%) | Ad hoc questionnaire | Hallucinations (*n =* 347, 2%)  Ad hoc questionnaire | | Sex, age, ethnicity, and education | | A graded relationship between number of childhood adversities and risk for hallucinations was found. The effect of childhood adversity was slightly reduced by including substance misuse in the model, suggesting partial mediation | 10 |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | | | |
| Goldstone et al., 2011  AUSTRALIA | | | | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | Childhood physical, emotional, and sexual abuse | | Modified version of the ETI-SR (Bremner, Bolus, & Mayer, 2007) | Family history for psychosis  Life hassles  Experiential avoidance  Early cannabis use, before age of 20  Recent methamphetamines use, after age of 20 | Ad hoc questionnaire  Survey of Recent Life Experiences (Kohn & Macdonald, 1992)  AAQ-II (Bond et al., 2011)  Ad hoc questionnaire | Delusional ideation (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  PDI (Peters, Joseph, & Garety, 1999) | | None | | No mediation via substance use was found neither in the general population nor in the clinical sample | 8 |
| Goldstone et al., 2012  AUSTRALIA | | | | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | Childhood physical (controls: *mean =* 1.63, *SD =* 1.54; cases: *mean =* 2.61, *SD =* 1.55), emotional (controls: *mean =* 1.38, *SD =* 1.38; cases: *mean =* 2.77, *SD =* 1.76), and sexual abuse (controls: *n =* 13, 10%; cases: *n =* 25, 25%) | | Modified version of the ETI-SR (Bremner et al., 2007) | Family history for psychosis (controls: *n =* 28, 21%; cases: *n =* 39, 39%)  Life hassles (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, SD 14.24)  Experiential avoidance (controls: *mean =* 51.62, *SD =* 10.79; cases: *mean =* 41.62, *SD =* 13.68)  Early cannabis use, before age of 20 (daily: controls: *n =* 11, 8%; cases: *n =* 27, 27%; weekly: controls: *n =* 19, 14%; cases: *n =* 19, 19%)  Recent methamphetamines use, after age of 20 (daily: controls: *n =* 1, 1%; cases: *n =* 9, 9%; weekly/ monthly: controls: *n =* 5, 14%; cases: *n =* 18, 18%)  Metacognitive beliefs (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, *SD =* 14.24) | Ad hoc questionnaire  Survey of Recent Life Experiences(Kohn & Macdonald, 1992)  Ad hoc questionnaire  MCQ (Wells & Cartwright-Hatton 2004) | Hallucination experiences (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  LSHS-R (Bentall & Slade, 1985) | | None | | No mediation via substance use was found neither in the general population nor in the clinical sample | 8 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | | | |
| Etain et al., 2017  FRANCE | | | *N =* 270 patients with bipolar disorder | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (*mean =* 41.8, *SD =* 11.67) | | | CTQ (Bernstein et al., 1994) | Lifetime cannabis or alcohol misuse | DIGS (Nurnberger et al., 2014) | Lifetime psychotic symptoms assessed with the DIGS (Nurnberger et al., 2014)  Lifetime paranoia (*mean =* 6.51, *SD =* 4.06) assessed with the PDI (Peters et al., 1999) | None | | | There was a direct effect of emotional abuse (*β* = 0.19, *p* = 0.003) and cannabis misuse (*β* = 0.18, *p* = 0.003) on paranoia but no indirect path was found. Neither a direct nor an indirect path between childhood adversity and psychotic symptoms were found | 8 |
| **STRESSFUL LIFE EVENTS AND SOCIAL RISK FACTORS** | | | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLE** | | | | | | | | | | | | | | | | |
| Boyda et al., 2015  Adult Psychiatric Morbidity Survey (APMS)  ENGLAND | | | | *N =* 7,403 | | Sexual abuse before 16 years of age (sexual touching and intercourse, *n =* 618) | | Ad hoc questionnaire (Domestic violence and abuse questionnaire) | Loneliness | Single item from Social Functioning Questionnaire (Tyrer et al., 2005) | Any psychotic symptoms in the past year (mania: *n =* 50; thought insertion: *n =* 69; paranoia: *n =* 136; strange experiences: *n =* 234, hallucinations: *n =* 321)  PSQ (Bebbington & Nayani, 1995) | | None | | Childhood sexual abuse showed an effect on loneliness (*adj. OR =* 1.45, *95% CI:* 0.10, 0.64), which in turn was related to thought insertion (*adj. OR =* 3.81, *95% CI:* 0.73, 1.94), paranoia (*adj. OR =* 2.85, *95% CI:* 0.58, 1.52), strange experiences (*adj. OR =* 2.61, *95% CI:* 0.63, 1.29), and hallucinations (*adj. OR =* 2.48, *95% CI:* 0.25, 1.57). However, child abuse had no effect on any psychotic symptoms, therefore the mediation model was not assessed | 9 |
| Boyda & McFeeters 2015  Adult Psychiatric Morbidity Survey (APMS)  ENGLAND | | | | *N =*7,403 | | Physical (*n =* 345, 4.7%) and sexual abuse (sexual touching and intercourse: *n =* 617, 8.4%), physical (*n =* 238, 3.2%), emotional neglect (*n =* 900, 12.2%), parental separation (*n =* 825, 12.1%), and domestic violence (*n =* 230, 3.3%) before 16 years of age | | Ad hoc questionnaire (Domestic violence and abuse questionnaire) | Loneliness  Social engagement  Involvement in recreational activities | Single item from Social Functioning Questionnaire  Ad hoc questionnaire  Ad hoc questionnaire | Presence of PLEs in the past year  PSQ (Bebbington & Nayani, 1995) | | Sex, age, education, ethnicity, low socio-economic status, mood disorders, and drug dependence | | Loneliness mediated the effect of both sexual abuse (*β* = 0.312, *SE*= 0.10, *95% CI:* 0.102, 0.522, *p <* 0.001) and emotional neglect (*β* = 0.636, SE= 0.15, *95% CI:* 0.339, 0.932, *p <* 0.001) on PLEs | 12 |
| **Shevlin et al., 2015**  **Adult Psychiatric Morbidity Survey (APMS)**  **ENGLAND** | | | | ***N =* 7,403** | | **Physical abuse (*n =* 254, 3.4%), sexual touching and intercourse, (*n =* 561, 7.6%), or both (*n =* 97, 1.3%) before 16 years of age** | | **Ad hoc questionnaire (Domestic violence and abuse questionnaire)** | **Loneliness (*mean =* 1.64, *SD =* 0.90)** | **Single item from the Social Functioning Questionnaire (Tyrer et al., 2005)** | **Diagnosis of psychotic disorders according to ICD-10 (definite psychosis *n =* 23).**  **PSQ (Bebbington & Nayani, 1995) and SCAN (World Health Organization, 1992)** | | **Sex, age, education, ethnicity, cannabis use, and adult victimization** | | **Loneliness partially mediated the effect of combined physical and sexual abuse on psychosis (*OR* = 3.81 *95% CI:* 1.07, 13.61; indirect effect: *β* = 0.722, *SE* = 0.24, *p* < 0.001)** | **14** |
| **Bhavsar et al., 2019**  **South East London Community**  **Health Study (SELCoH)**  **ENGLAND** | | | | ***N =* 1,698** | | **Childhood physical or sexual abuse (*n =* 429)** | | **Ad hoc interview** | **Cumulative exposure to past year violent (range 0–4) and non-violent life event (0–3)** | **Ad hoc interview** | **Lifetime psychotic experiences (*n =* 306, 17.9%)**  **PSQ (Bebbington & Nayani, 1995)** | | **Sex, age ethnicity, education, social class** | | **Childhood abuse showed both a direct (*adj. OR =* 1.58, *95% CI:* 1.19, 2.1) and indirect effect via life events (*adj. OR =* 1.51, *95% CI:* 1.32, 1.72). Partial mediation explained 47% of the total effect (33% via violent life events)** | **16** |
| **van Nierop et al., 2014**  **The Netherlands Mental Health Survey and Incidence**  **Study 2 (NEMESIS-2)**  **NETHERLANDS** | | | | ***N =* 6,646** | | **Emotional neglect, bullying, psychological, physical, or sexual abuse before age 16 years of age (cumulative score: controls: *mean =* 1.4, *SD =* 2.9; EPP: *mean =* 3.9, *SD =* 4.75; PD: *mean =* 5.8, *SD =* 4.8)** | | **Ad hoc interview** | **Social defeat (controls: *mean =* 0.8, *SD =* 1.8; EPP: *mean =* 2.0, *SD =* 2.6; PD: *mean =* 4.3, *SD =* 2.9)**  **Affect dysregulation (controls: *mean* = 2.7, *SD*= 5.3; EPP: mean= 6.5, *SD* = 7.3; PD: *mean* = 12.4, *SD* =7.4)** | **CIDI 3.0 (Kessler, 1994)** | **Severity of psychotic experiences in individuals with lifetime psychotic symptoms (EPP: *n =* 384; PD: *n =* 43)**  **Ad hoc interview**  **SCID-I for DSM-IV (First et al., 1996)** | | **Sex, age, and cannabis use** | | **Childhood adversity predicted social defeat (*β* = 0.33, *p <* 0.001) and affective dysregulation (*β* = 0.30, *p* < 0.001). Social defeat mediated 86.6% of the effect of childhood adversity on psychotic experiences in individuals with psychotic disorders (indirect effect: *β* = 0.04, *p* = 0.004).**  **Social defeat and affect dysregulation together mediated 80.4% of the effect of childhood adversity on psychotic experiences in individuals with EPP. Specifically, social defeat alone mediated 30.7% of the effect (*β* = 0.03, *p* = 0.081), while the remaining 49.7% was mediated by social defeat via affective dysregulation (*β* = 0.04, *p* = 0.002).** | **16** |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | | | |
| Goldstone et al., 2011  AUSTRALIA | | | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | Childhood physical, emotional, and sexual abuse | | | Modified version of the ETI-SR (Bremner, Bolus, & Mayer, 2007) | Family history for psychosis  Life hassles  Experiential avoidance  Early cannabis use, before age of 20  Recent methamphetamines use, after age of 20 | Ad hoc questionnaire  Survey of Recent Life Experiences (Kohn & Macdonald, 1992)  AAQ-II (Bond et al., 2011)  Ad hoc questionnaire | Delusional ideation (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  PDI (Peters, Joseph, & Garety, 1999) | None | | | In the non- clinical sample, a pathway from emotional trauma on delusions via life hassles and emotional abuse. Together with the other relevant paths, the model explained 26% of the variance (*χ2* = 19.20, *p* = 0.12, *RMSEA* = 0.06, *TLI* = 0.94). In the clinical sample, all types of abuse were related to delusions, but only sexual abuse adequately fit the model. Replication of the model in the clinical sample explained 37% of the variance (*χ2*= 14.65, *p* = 0.33, *RMSEA* = 0.04, *TLI* = 0.97) | 8 |
| Goldstone et al., 2012  AUSTRALIA | | | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | Childhood physical (controls: *mean =* 1.63, *SD =* 1.54; cases: *mean =* 2.61, *SD =* 1.55), emotional (controls: *mean =* 1.38, *SD =* 1.38; cases: *mean =* 2.77, *SD =* 1.76), and sexual abuse (controls: *n =* 13, 10%; cases: *n =* 25, 25%) | | | Modified version of the ETI-SR (Bremner et al., 2007) | Family history for psychosis (controls: *n =* 28, 21%; cases: *n =* 39, 39%)  Life hassles (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, SD 14.24)  Experiential avoidance (controls: *mean =* 51.62, *SD =* 10.79; cases: *mean =* 41.62, *SD =* 13.68)  Early cannabis use, before age of 20 (daily: controls: *n =* 11, 8%; cases: *n =* 27, 27%; weekly: controls: *n =* 19, 14%; cases: *n =* 19, 19%)  Recent methamphetamines use, after age of 20 (daily: controls: *n =* 1, 1%; cases: *n =* 9, 9%; weekly/ monthly: controls: *n =* 5, 14%; cases: *n =* 18, 18%)  Metacognitive beliefs (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, *SD =* 14.24) | Ad hoc questionnaire  Survey of Recent Life Experiences(Kohn & Macdonald, 1992)  Ad hoc questionnaire  MCQ (Wells & Cartwright-Hatton 2004) | Hallucination experiences (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  LSHS-R (Bentall & Slade, 1985) | None | | | In the general population, emotional abuse showed an indirect effect on hallucinations, via life hassles and metacognition. Along with other relevant paths, the model predicted 28% of the variance (*χ2*= 11.70, *p* = 0.11, *RMSEA* = 0.07, *TLI* = 0.95). The model was replicated in the clinical sample, where emotional abuse was replaced by sexual abuse (*χ2*= 10.39, *p* = 0.17, *RMSEA* = 0.07, *TLI* = 0.93, 24% of the variance explained). | 9 |
| Seo & Choi, 2018  REPUBLIC OF KOREA | | | *N =* 199 patients with non-psychotic disorders | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect | | | CTQ-SF (Bernstein et al., 1994) | Social defeat | Defeat Scale (Gilbert & Allan, 1998) | Paranoid ideation  Restructured Clinical Scale 6 of the MMPI-2 (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989) | Sex, age | | | Social defeat was related to all types of childhood adversity. Childhood adversity had both a direct effect on paranoia (*β* = 0.41, *p <* 0.001) and an indirect effect via social defeat (*β* = 0.46, *p <* 0.001), which, in turn, was related to paranoia (*β* = 0.27, *p <* 0.001) | 8 |
| Steenkamp et al., 2019  NETHERLANDS | | | *N =* 90 patients with non-affective psychotic disorders | | Childhood emotional, physical, and sexual abuse, and parental conflict (*mean =* 2.01, *SD =* 2.24) | | | CECA (Bifulco et al., 1994) | Loneliness (*mean =* 2.36, *SD =* 1.59) | ESM | Positive symptoms (*mean =* 1.82, *SD =* 0.99)  ESM | None | | | Loneliness was associated with childhood adversity. Loneliness fully mediated the effect of childhood adversity on psychosis (direct effect: −0.01, *95% CI*: −0.11, 0.09, *p* = 0.824; indirect effect: 0.08, *95% CI*: 0.02, 0.13, *p* = 0.005) | 9 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | | | |
| **Morgan, Reininghaus, Fearon, et al., 2014**  **Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study**  **ENGLAND** | | | | ***N =* 390 patients with FEP**  ***N =* 391 healthy controls** | | **Parental separation (cases: *n =* 160, 41%; controls: *n =* 80, 20.4%) or death (cases: *n =* 30, 7.7%; controls: *n =* 14, 3.6%) before age of 16** | | **MRC Socio demographic Schedule (Mallett 1997)** | **Adult disadvantage (i.e., unemployment, living alone, no relationship and limited social network, renting house) (five indicators: cases: *n =* 39, 10.1%; controls *n =* 4, 1%)**  **No education (cases: *n =* 24, 32%; controls: *n =* 71, 18.3%)** | **MRC Socio demographic Schedule (Mallett 1997)** | **ICD-10 diagnosis of psychotic disorders (*n =* 390)**  **SCAN (World Health Organization, 1992)** | | **Sex, age, ethnicity, study centre, and parental history of psychosis.** | | **Adult social disadvantages (indirect effect: *adj. OR =* 1.16, *95% CI:* 0.99, 1.37), no qualification (*adj. OR =* 2.38, *95% CI:* 1.34, 4.20), and both (*adj. OR =* 1.57, *95% CI:* 1.20, 2.06) mediated the effect of parental separation on case status, accounting all together for 75% of the variance.** | **15** |
| **PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL MECHANISMS** | | | | | | | | | | | | | | | | |
| **GENERAL POPULATION SAMPLE** | | | | | | | | | | | | | | | | |
| Marwaha et al., 2014  Adult Psychiatric Morbidity Survey (APMS)  ENGLAND | *N =* 7,403 | | | | | Sexual touching or rape before 16 years of age | | Ad hoc questionnaire (domestic violence and abuse questionnaire) | Mood instability | Single item from the DSM-IV Borderline Personality Disorder section of the SCID-II (First, Spitzer, Gibbon, & Williams, 1994) | Symptoms of paranoia or auditory hallucination, diagnosis of probable psychotic disorder according to ICD-10  PSQ (Bebbington & Nayani, 1995) and SCAN (World Health Organization, 1992) | | None | | Mood instability mediated 34.6% of the total effect of child sexual abuse on psychosis (*OR* = 2.30, *z* = 4.54, *p <* 0.001), 34.5% of the effect on paranoia (*OR* = 1.63, *z* = 5.63, *p <* 0.001) and 25.3% of the effect on auditory hallucinations (*OR* = 1.41, *z* = 4.90, *p <* 0.001) | 9 |
| Marwaha & Bebbington, 2015  Adult Psychiatric Morbidity Survey (APMS)  ENGLAND | *N =* 7,403 | | | | | Uncomfortable sexual talk (*n =* 762, 10.3%), touching (*n =* 642, 8.2%), and non-consensual sexual intercourse (*n =* 144, 1.9%) before 16 years of age | | Ad hoc questionnaire (Domestic violence and abuse questionnaire) | Current anxiety (range 1-8) and depression (range 1-9) symptoms | CIS-R (Lewis, Pelosi, Araya, & Dunn, 1992) | Diagnosis of psychotic disorders according to ICD-10 (probable psychosis: *n =* 43)  PSQ (Bebbington & Nayani, 1995) and SCAN (World Health Organization, 1992) | | None | | Anxiety and depression symptoms mediated 38.5% of the effect of childhood sexual intercourse (indirect effect *adj. OR =* 2.41, *95% CI:* 1.61, 3.61) and 38.2% of the effect of contact sexual abuse (*adj. OR =* 1.60, *95% CI:* 1.32,1.94) on psychosis | 11 |
| **McCarthy-Jones 2018**  **Adult Psychiatric Morbidity Survey (APMS)**  **ENGLAND** | ***N =* 7,403** | | | | | **Penetrative sexual abuse (*n =* 126, 2.2%) and physical abuse (*n =* 207, 3.6%)** | | **Ad hoc questionnaire (Domestic violence and abuse questionnaire)** | **Anxiety (*mean =* 0.86, *SD* = 1.56)**  **Depression (*mean =* 0.63, *SD* = 1.49)**  **Obsessions (*mean =* 0.16, SD 0.66) and compulsions (*mean =* 0.11, *SD* = 0.56)**  **PTSD (*mean =* 0.50, *SD* = 1.43)** | **CIS-R (Lewis et al., 1992)**  **Trauma Screening Questionnaire (Brewin et al., 2002)** | **AVH (*n =* 49, 0.8%)**  **PSQ (Bebbington & Nayani, 1995)** | | **Sex, age, ethnicity, education, IQ, childhood physical abuse, and depression** | | **No effect of physical abuse on AVH was found. Sexual abuse had both a direct effect (*adj. OR =* 5.81, *95% CI:* 2.53, 13.33) on AVH and indirect effects via PTSD symptoms (*adj. OR =* 1.11, *95% CI:* 1.00, 1.29) and compulsions (*adj. OR =* 1.10, *95% CI:* 1.01, 1.28). No mediation via depression was found when anxiety was included as covariate** | **13** |
| **Janssen et al., 2005**  **The Netherlands Mental Health Survey and Incidence**  **Study (NEMESIS)**  **NETHERLANDS** | ***N =* 4,045** | | | | | **Emotional, psychological, physical or sexual abuse before 16 years of age (*n =* 369, 10%)** | | **Ad hoc semi-structured interview (Janssen et al., 2004)** | **T0 mother’s and father’s care (range: 0–36) and overprotection (range 0–36)** | **PBI (Parker, Tupling & Brown, 1979)** | **Any T2 psychotic symptom (broad psychosis, *n =* 38) and pathology-level psychotic symptoms (narrow psychosis: *n* = 10)**  **BPRS (Overall & Gorham, 1962)** | | **For broad psychosis: age and any drug use;**  **for narrow psychosis: age, any drug use and any baseline DSM-III-R diagnosis** | | **Childhood adversity was associated with parental care and overprotection. The effect of lower care on broad (*adj. OR =* 1.36, *95% CI:* 0.87, 2.12) and narrow psychosis (*adj. OR =* 1.59, *95% CI:* 0.54, 4.62) became non-significant when childhood adversity was included in the model (broad: *OR* =**  **3.40, *95% CI*: 1.53, 7.56; narrow: *OR* = 8.50, *95% CI*: 1.85, 39.02)** | **15** |
| **van Nierop et al., 2014**  **The Netherlands Mental Health Survey and Incidence**  **Study 2 (NEMESIS-2)**  **NETHERLANDS** | ***N =* 6,646** | | | | | **Emotional neglect, bullying, psychological, physical, or sexual abuse before age 16 years of age (cumulative score: controls: *mean =* 1.4, *SD =* 2.9; EPP: *mean =* 3.9, *SD =* 4.75; PD: *mean =* 5.8, *SD =* 4.8)** | | **Ad hoc interview** | **Social defeat (controls: *mean =* 0.8, *SD =* 1.8; EPP: *mean =* 2.0, *SD =* 2.6; PD: *mean =* 4.3, *SD =* 2.9)**  **Affect dysregulation (controls: *mean* = 2.7, *SD*= 5.3; EPP: mean= 6.5, *SD* = 7.3; PD: *mean* = 12.4, *SD* =7.4)** | **CIDI 3.0 (Kessler, 1994)** | **Severity of psychotic experiences in individuals with lifetime psychotic symptoms (EPP: *n =* 384; PD: *n =* 43)**  **Ad hoc interview**  **SCID-I for DSM-IV(First et al., 1996)** | | **Sex, age, and cannabis use** | | **Childhood adversity predicted social defeat (*β* = 0.33, *p <* 0.001) and affective dysregulation (*β* =0.30, *p* < 0.001). Social defeat mediated 86.6% of the effect of childhood adversity on severity of psychotic experiences in individuals with psychotic disorders (indirect effect: *β* = 0.04, *p* = 0.004).**  **Social defeat and affect dysregulation together mediated 80.4% of the effect of childhood adversity on severity of psychotic experiences in individuals with EPP. Specifically, social defeat alone mediated 30.7% of the effect on psychosis (*β* = 0.03, p = 0.081), while the remaining 49.7% was mediated by social defeat via affective dysregulation (*β* = 0.04, p = 0.002).** | **16** |
| **Sitko et al., 2014**  **National Comorbidity**  **Survey (NCS)**  **USA** | ***N =* 5,877** | | | | | **Witnessing injury or killing (*n =* 519, 8.8%), rape (*n =* 148, 2.5%), sexual molestation (*n =* 371, 6.3%), physical assault (*n* = 178, 3.0%), physical abuse (*n* = 246, 4.2%), neglect (*n* = 164, 2.8%), and being held or threatened with a weapon (*n* = 236, 4.0%) before age of 16** | | **Life events history module of the UM-CIDI (Wittchen & Kessler, 1994)** | **Current attachment stile: secure, avoidant or anxious (*range:* 0 - 4)**  **Severity of lifetime major depression (*range*: 0 - 9)** | **AAQ (Hazan & Shaver, 1987)**  **Sadness module of the UM - CIDI (Wittchen & Kessler, 1994)** | **Lifetime paranoia (*range*: 0-3) and hallucinations (*range*: 0-4)**  **Belief and experience module of the UM-CIDI (Wittchen & Kessler, 1994)** | | **Sex, age** | | **Effect of neglect on paranoia was mediated by anxious and avoidant attachment (*β* = 0.047, *95% CI:* 0.010, 0.252). Effect of being held or threaten with a weapon on paranoia was partially mediated by avoidant attachment (*β* = 0.083, *95% CI:* 0.101, 0.257).**  **Indirect effect of rape on paranoia (*β* = 0.020, *95% CI:* 0.053, 0.15) and hallucinations (*β* = 0.088, *95% CI:* 0.171, 0.523) was mediated by anxious attachment. Depression decreased the mediating effect of attachment insecurity on the relationship between childhood abuse and paranoia and hallucinations** | **15** |
| Berenbaum et al., 2003  USA | *N =* 75 | | | | | Childhood physical (*mean =* 1.9, *SD =* 1.0), emotional (*mean =* 2.4, *SD =* 1.0), and sexual abuse (*mean =* 1.7, *SD =* 1.1), and physical (*mean =* 1.6, *SD =* 0.6) and emotional neglect (*mean =* 2.4, *SD =* 1.1) | | CTQ (Bernstein et al., 1994) | PTSD (*mean =* 10.4, *SD =* 13.1)  Depression (*mean =* 10.4, *SD =* 10.3)  Dissociation (*mean =* 347.5, *SD =* 268.2)  Difficulty identifying feelings (*mean =* 14.0, *SD =* 6.5) | PTDS diagnostic scale (Foa, Cashman, Jaycox, & Perry, 1997)  BDI (Beck et al., 1961)  DES (Bernstein & Putnam, 1986)  TAS**–**20 (Bagby, Parker, & Taylor, 1994) | Schizotypal personality disorders  SPQ (Raine, 1991) (*mean =* 3.5, *SD =* 4.0)  SIDP IV (Pfohl, Blum, & Zimmerman, 1995) (*mean =* 24.9, *SD =* 14.2) | | None | | Childhood adversity correlated with PTSD, depression, dissociation, and difficulty in identifying feelings.  Psychological symptoms (PTSD, depression, dissociation, and difficulty in identifying feelings) partially mediated the effect of childhood neglect on schizotypal personality disorder | 7 |
| Berenbaum et al., 2008  USA | *N =* 303 | | | | | Emotional, physical, and sexual abuse, and physical neglect | | Ad hoc questionnaire | PTSD symptoms  Pathological  absorption and dissociation | Modified version of the FH-RDoC (Andreasen et al., 1977)  CAPS (Blake et al., 1995)  Imagination subscale of the  DPS (Harrison & Watson, 1992)  Absorption subscale of the CES (Goldberg, 1999)  SCID-D(Steinberg, 1993)  DES-T (Waller & Ross, 1997) | Schizotypal traits  Schizotypal module of the PDI-IV (Widiger, Mangine, Corbitt, Ellis, & Thomas, 1995) | | None | | Childhood adversity correlated with current and lifetime PTSD, as well as with absorption and dissociation.  In both genders, evidence of partial mediation between child adversities and schizotypy was found for current PTSD (men: Sobel test’s *z* = 2.39, *p <* 0.05; women: z= 2.62, *p <* 0.01) and for absorption/ dissociation (men: Sobel test’s *z* = 2.29, *p <* 0.05; women; z= 2.96, *p <* 0.01). By contrast, only among women, lifetime PTSD partially mediated the effect of child adversities on schizotypy (Sobel test’s *z* = 2.43, *p <* 0.05) | 12 |
| Bortolon et al., 2017  FRANCE | *N =* 425 | | | | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect | | CTQ (Bernstein et al., 1994) | Early maladaptive schemas (EMS)  Dissociation | SQ-SF (Young, 1998)  DES (Bernstein & Putnam, 1986) | Auditory hallucinations proneness  LSHS-R (Bentall & Slade, 1985) | | Sex, age, anxiety, and depression | | Physical, emotional, and sexual abuse showed both direct and indirect effect on hallucination proneness (physical abuse: *B =* 0.108, *p <* 0.001; emotional abuse: *B =* 0.168, p <0.001; sexual abuse: *B =* 0.036, p = 0.010). Indirect paths included: physical abuse via dissociation; sexual and emotional abuse via schema of subjugation and vulnerability and via dissociation; emotional abuse via schema of abandonment | 10 |
| Bortolon et al., 2018  FRANCE | *N =* 425 | | | | | Childhood physical (*mean =* 12.20, SD = 4.27) emotional (*mean =* 30.19, SD = 11.55), and sexual abuse (*mean =* 9.00, SD = 5.88), and physical (*mean =* 17.97, SD = 8.52) and emotional neglect (*mean =* 45.11, SD = 16.35) | | CTQ (Bernstein et al., 1994) | Dissociation (*mean =* 25.83, SD = 19.43) | DES (Bernstein & Putnam, 1986) | Visual hallucinations proneness (n = 87, 21.6%)  LSHS-R (Bentall & Slade, 1985) | | Sex, age, auditory hallucination proneness, anxiety, and depression | | The effect of childhood adversity on hallucination proneness (*β* = 0.107, *p* = 0.02) was no longer significant when dissociation was entered in the model (*β* = 0.008, *p* = 0.870), suggesting complete mediation | 10 |
| Bellido-Zanin et al., 2018  SPAIN | *N =* 495 | | | | | Memories of familiar threat and subordination (*mean =* 28, *SD =* 10.61) | | ELES (Gilbert, Cheung, Grandfield, Campey, & Irons, 2003) | Dissociative experiences (*mean =* 11.95, *SD =* 10.27) | DES-II (Carlson & Putnan, 1993) | Hallucination proneness assessed using the LSHS-R (Bentall & Slade, 1985; *mean =* 16.13, *SD =* 3.81)  Ideas of reference assessed using the REF (Lenzenweger, Bennett, & Lilenfeld, 1997; *mean =* 4.42, *SD =* 4.14) | | Hallucination proneness and ideas of reference | | Dissociative experiences correlated with hallucination proneness and ideas of reference.  Dissociation fully mediated the effect of childhood adversity on hallucinations (indirect effect: *β* = 0.15, *p <*0.001, *R2* = 0.29) and partially mediated the effect on ideas of reference (direct effect: *β* = 0.13, *p <*0.01; indirect effect: *β* = 0.16, *p <*0.001, *R2* = 0.30) | 9 |
| Boyda et al., 2018  ENGLAND | *N =* 302 | | | | | Childhood physical (*mean =* 1.17, *SD =* 1.33), emotional (*mean =* 1.24, *SD =* 1.09), and sexual abuse (*mean =* 0.76, *SD =* 1.3), physical neglect (*mean =* 2.12, *SD =* 1.52), poor relationship with parents (*mean =* 3.89, *SD =* 1.89), witnessing interpersonal violence (*mean =* 2.57, *SD =* 2.36), and dysfunctional family environment (*mean =* 0.89, *SD =* 0.91) | | ACE-IQ (WHO, 2018) | Early maladaptive schemas (emotional inhibition: *mean =* 1.25, *SD =* 1.26; defectiveness: *mean =* 1.39, *SD =* 1.40; dependency: *mean =* 0.64, *SD =* 0.90; and enmeshment: *mean =* 0.55, *SD =* 0.81) | SQ-SF (Young, 1998) | PLEs (*mean =* 23.28, *SD =* 18.93)  CAPE (Konings et al., 2006) | | Sex, age, ethnicity, urbanicity, socio-economic status, and substance use | | Defectiveness, dependency, and enmeshed schemas were positively associated with PLEs, as well as with emotional and sexual abuse. Poor relationship with parents was related with defectiveness schema.  Defectiveness mediated the effect of poor relationship with parents on PLEs (*β* = 0.046, *p <* 0.05). Both dependency and enmeshed schemas mediated the effect of emotional (dependency: *β* = 0.083; enmeshed: *β* = 0.063, *p <* 0.05) and sexual abuse (dependency: *β* = 0.073; enmeshed: *β* = 0.043, *p <* 0.05) | 11 |
| Cole et al., 2016  ENGLAND | *N =* 200 | | | | | Childhood physical (*mean =* 1.36, *SD =* 0.67), emotional (*mean =* 0.98, *SD =* 0.76), and sexual abuse (*mean =* 0.07, *SD =* 0.24), and neglect (*mean =* 0.78, SD 0.69) | | CATS (Sanders & Becker-Lausen, 1995) | Dissociative experiences (*mean =* 16.17, *SD =* 13.85) | DES-II (Carlson & Putnman 1993) | Hallucination proneness and delusion  LSHS-R (Bentall & Slade, 1985) and PDI (Peters et al., 1999) | | None | | Dissociation partially mediated the effect of childhood adversity on hallucinations (indirect effect: *B =* 3.94, *95% CI:* 2.15, 6.37, *p <* 0.05) and delusions (*B =* 10.75, *95% CI:* 5.87, 17.56, *p <* 0.05). Specifically absorption (*B =* 3.45, *95% CI:* 2.00, 5.47, *p <* 0.05) mediated hallucinations, and amnesia (*B =* -3.68, *95% CI:* -9.46, -0.03, *p <* 0.05) and absorption (*B* = 7.18, *95% CI:* 2.87, 13.33, *p <* 0.05) mediated delusions | 8 |
| Fisher et al., 2013  Avon Longitudinal  Study of Parents and Children (ALSPAC)  ENGLAND | *N =* 6,692 | | | | | Maternal harsh parenting (hitting and hostility) before age of 7 (mild: *n =* 2,476, 37.0%; moderate: *n =* 663, 9.9%; severe: *n =* 281, 4.2%) | | Ad hoc questionnaire for domestic violence and physical abuse | Locus of control (LoC)  Self esteem  Anxiety and depression symptoms | NSIE (Nowicki & Strickland, 1973)  Harter’s Self Perception Profile for Children (Harter, 1985)  DAWBA (Goodman, Ford, Richards, Gatward, & Meltzer, 2000)  SMFQ (Angold et al., 1995) | Any suspected or definite psychotic symptoms (broad definition: *n =* 756, 11.3%; narrow definition: *n =* 314, 4.7%)  PLIK SI interview (Horwood et al., 2008) | | Sex, ethnicity, birth weight, family history of schizophrenia, depression or suicide, IQ, and general family adversity | | LoC, self-esteem, and anxiety and depressive symptoms fully mediated the effect of maternal harsh parenting on broadly (indirect effect *adj. OR =* 1.04, *95% CI:* 1.02, 1.05) and narrowly defined psychosis (indirect effect *adj. OR =* 1.04, *95% CI:* 1.02, 1.07).  Depression mediated 60% (broad psychosis) and 94% (narrow psychosis) of the effect of child abuse, while anxiety respectively mediated 16% and 21%, external LoC 36 and 47%, and self-esteem 33 and 97% | 11 |
| Fisher et al., 2012  ENGLAND | *N =* 212 | | | | | Emotional (*n =* 55, 25.7%), physical (*n =* 45, 21.0%) and sexual abuse (*n =* 24, 11.2%), and emotional (*n =* 40, 18.7%) and physical neglect (*n =* 58, 27.1%) prior to 17 years of age | | CTQ (Bernstein et al., 1994) | Current depression  Current anxiety  Negative schematic beliefs of the self and the other | BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)  BAI (Beck & Steer, 1993)  BCSS (Fowler et al., 2006) | Paranoia in the past year (*n =* 71, 33.2%)  PSQ (Bebbington & Nayani, 1995) | | Sex, age, ethnicity, and psychiatric disorders in first-degree | | Among childhood adversities, only emotional and physical abuse were related to paranoia.  Depression, anxiety, and negative schemas accounted for 45% of the effect of emotional abuse on paranoia (indirect total effect: *adj. OR =* 1.13, *95% CI:* 1.04, 1.27) with the strongest mediation for anxiety.  By contrast, mediators explained only 26% of the effect of physical abuse on paranoia, with non-significant indirect pathways via anxiety and negative self-schemas (indirect total effect: *adj. OR =* 1.07, *95% CI:* 0.98, 1.19) | 10 |
| Gawęda et al.,2019  POLAND, GERMANY | N = 649 | | | | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (*mean =* 36.88, *SD* = 11.58) | | CTQ (Bernstein et al., 1994) | Basic self-disturbances (*mean =* 15.96; *SD* = 5.96)  Aberrant salience (*mean =* 2.26; *SD* = 2.03) | IPASE (Cicero, Neis, Klaunig, & Trask, 2017)  ASI (Cicero, Kerns, & McCarthy, 2010) | PLEs (*mean =* 2.17, *SD =* 2.38)  PQ-16 (Ising et al., 2012) | | Sex | | The direct effect of childhood adversity on PLEs became not significant when aberrant salience and self-disturbances were included in the model (direct effect: *β* = 0.05, *p* ns, *t* = 1.55, *p* = 0.12, 44.45% variance explained).  The mediating effect was stronger for childhood neglect than for childhood abuse, with evidence of full mediation for childhood neglect (direct effect: *β* = 0.01, *p* ns) and complimentary mediation for childhood abuse (direct effect: *β* = 0.10, *p* < 0.01) | 10 |
| Gibson et al., 2018  USA | *N =* 945 | | | | | Emotional, physical, and sexual abuse, and physical and emotional neglect (*mean =* 0.62, *SD =* 1.07) | | CTQ-SF (Bernstein et al., 2003) | Negative schema of the self (*mean =* 2.84, *SD =* 3.88) and the other (*mean =* 6.83, *SD =* 5.38)    Perceived stress (*mean =* 25.22, *SD =* 8.14)  LoC (*mean =* 2.43, *SD =* 3.56)  Dissociation (*mean =* 2.28, *SD =* 1.23) | BCSS (Fowler et al., 2006)  PSS (Cohen, Kamarck, & Mermelstein, 1983)  Rotter I-E Scale (Rotter, 1966)  DES (Bernstein & Putnam, 1986) | PLEs (*mean =* 9.92, *SD =* 7.69)  PQ (Loewy, Bearden, Johnson, Raine, & Cannon, 2005) | | Depression, generalized anxiety, and substance use | | All five potential mediators mediated the effect childhood adversity on PLEs. The findings were fully replicated when the predictor was specified as abuse-only and neglect- only.  After controlling for depressive, anxiety, and substance misuse, the only mediator was dissociation (*B =* 0.02, *95% CI:* 0.0090, 0.0338) | 11 |
| Goodall et al., 2015  ENGLAND | *N =* 283 | | | | | Emotional (*mean =* 9.42, *SD =* 4.86), physical (*mean =* 6.74, *SD =* 3.39), and sexual abuse (*mean =* 6.23, *SD =* 3.79), and physical (*mean =* 7.25, *SD =* 2.88) and emotional neglect (*mean =* 9.96, *SD =* 4.72) | | CTQ (Bernstein et al., 1994) | Attachment anxiety (*mean =* 3.35, *SD =* 1.22) and avoidance (*mean =* 3.02, *SD =* 1.14) | ECR-R (Fraley et al., 2011) | Schizotypy (*mean =* 8.98, *SD =* 5.07)  SPQ-B (Raine & Benishay, 1995) | | Age | | Attachment anxiety and avoidance correlated with all childhood adversities but physical abuse. Adjusting for the other adversities, only emotional abuse showed an effect on schizotypy.  The effect of emotional abuse was partially mediated by attachment anxiety (13%; *B =* 0.06, *SE* = 0.02, *95% CI:* 0.02, 0.11) and avoidance (8%; *B =* 0.04, *SE* = 0.02, *95% CI:* 0.01, 0.08) | 10 |
| Lincoln et al., 2017  GERMANY, INDONESIA, USA | *N =* 562 | | | | | Emotional, physical, psychological or sexual trauma before 16 years of age (*n =* 338, 60.1%) | | Ad hoc semi-structured interview (Janssen et al., 2004) | Emotion regulation | ERSQ (Berking et al., 2008) | Frequency of positive PLEs and related distress  CAPE (Konings et al., 2006) | | None | | Emotion regulation was related with childhood abuse. The path from childhood adversity to PLEs frequency was not significant. | 8 |
| Mętel et al., 2018  POLAND | *N =* 2,684 | | | | | Childhood emotional, and sexual abuse, bullying and neglect (CECA-Q: *mean =* 1.85, *SD =* 1.47) | | CECA-Q(Bifulco et al., 2005)  TEC (Nijenhuis et al., 2002) | Depression (*mean =* 9.40, *SD =* 3.67)  Cognitive biases (*mean =* 27.15, *SD =* 8.63) | CES-D (Radloff, 1977)  DACOBS-18 (Gawęda et al., 2018) | PLEs (*mean =* 21.83, *SD =* 5.51)  PQ-16 (Ising et al., 2012) | | None | | Both depression and cognitive biases were associated with PLEs.  Childhood adversity showed both a direct effect on PLEs (*β* = 0.33, *p <* 0.001) and several complimentary indirect effects. Indirect effect were mediated by depression (*β* *(CA-depression)* = 0.15, *p <* 0.001, *β* *(depression-PLEs)* = 0.32, *p <* 0.001), cognitive biases (*β (CA-cognitive biases)* = 0.30, *p <* 0.001*, β (cognitive biases-PLEs)* = 0.27, *p <* 0.001), and cognitive biases via depression (*β (CA- cognitive biases)* = 0.30, *p <* 0.001, *β (cognitive biases- depression)* = 0.29, *p <* 0.001, *β (depression- PLEs)* = 0.32, *p <* 0.001) | 8 |
| Murphy et al., 2015  IRELAND | *N =* 785 | | | | | Memories of familiar threat and subordination (*mean =* 31.30, *SD =* 10.28) | | ELES (Gilbert et al., 2003) | Negative self-comparisons (*mean =* 65.73, *SD =* 16.90)  Trauma- related beliefs (*mean =* 89.73, *SD =* 36.80) | SCS (Allan & Gilbert, 1995)  PTCI (Foa, Tolin, Ehlers, Clark, & Orsillo, 1999) | PLEs (*mean =* 9.62, *SD =* 3.61)  APSS (Kelleher, Harley, Murtagh, & Cannon, 2011) | | None | | Early life experiences were related with all potential mediators. Evidence of indirect effect was found, via post-traumatic beliefs (*β* = 0.021, *SE* = 0.01, *p <* 0.001).  Analyses indicated that peer victimization was a mediator of  this effect and that loneliness moderated this mediated | 8 |
| Perona-Garcelán et al., 2014  SPAIN | *N =* 318 | | | | | Childhood adversity before 15 years of age (at least one: *n =* 143, 45%; mean number of adversities = 1.62, *SD =* 1.03) | | TQ (Davidson, Hughes, & Blazer, 1990) | Absorption  Depersonalization  Mindful approach to distressing thoughts and images | TAS (Tellegen & Atkinson, 1974)  CDS (Sierra & Berrios, 2000)  SMQ (Chadwick et al., 2008) | High hallucination proneness (i.e., more than one SD from the sample mean, *n =* 55; low: *n =* 28)  LSHS-R (Bentall & Slade, 1985) | | None | | Childhood adversity correlated with absorption and depersonalization but not with mindfulness. The direct effect of childhood adversity was not significant. Absorption (*B =* 0.38, p < 0.01, *95% CI:* 0.17, 0.65) and depersonalization (*B* = 0.16, *p <* 0.01, *95% CI:* 0.03, 0.40) had an indirect effect explaining 51% of the variance | 7 |
| Powers et al., 2011  USA | *N =* 541 (*n =* 57, 10.6% with psychotic disorders) | | | | | Emotional, physical, and sexual abuse (*n =* 161, 29.8%) | | CTQ-SF (Bernstein et al., 2003)  ETI (Bremner, Vermetten, & Mazure, 2000) | PTSD (current: *n =* 89, 16.5; lifetime: *n =* 133, 24.6%) | CAPS (Blake et al., 1995) | Schizotypal personality disorder  SNAP (Clark 1993) | | None | | Childhood emotional abuse correlated with PTSD severity. The effect of emotional abuse on schizotypal personality disorder was reduced after controlling for PTSD symptoms (*β* = 0.12, *p* < 0.05), suggesting a partial mediation (Sobel’s test *z* = 3.45, *p* < 0.001) | 11 |
| Rössler et al., 2016  SWITZERLAND | *N =* 820 | | | | | Emotional, physical, and sexual abuse, and physical and emotional neglect (unaffected by subclinical psychotic experiences (SPEs): *mean =* 32.09, *SD =* 8.59; anomalous perceptions: *mean =*33.00, *SD =* 6.84; odd beliefs and behaviour: *mean =* 39.34, *SD =* 12.23; combined anomalous perceptions and odd beliefs and behaviour: *mean =* 38.63, *SD =* 15.05) | | CTQ-SF (Bernstein et al., 2003) | Stress sensitivity (unaffected: *mean =* −0.35, *SD =* 0.72; anomalous perceptions: *mean =* 0.07, *SD =* 0.69; odd beliefs and behaviour: *mean =* 0.65, *SD =* 0.83; combined: *mean =* 0.89, *SD =* 0.76) | Average z scores of the PSS (Cohen et al., 1983), the PANAS-N (Watson, Clark, & Tellegen, 1988) and the SSCS (Schulz, Schlotz, & Becker, 2004) | Pattern of subclinical psychotic experiences (SPE, unaffected: *n =* 403; anomalous perceptions: *n =* 74; odd beliefs and behaviour: *n =* 145; combined: *n =* 41)  SIAPA (Bunney et al., 1999), SPQ-B (Raine & Benishay, 1995), PARA (Freeman et al., 2005), SCL-90 (Derogatis LR et al., 1973) | | Education | | The effect of childhood adversity on SPE was mediated by stress sensitivity (anomalous perceptions: *B =* 0.20, *p <* 0.001, *adj. OR =* 1.22, *95% CI:* 1.10, 1.34; odd beliefs and behaviour: *B =* 0.40, *p <* 0.001, *adj. OR =* 1.49, *95% CI:* 1.29, 1.70; combined: *B =* 0.50, *p <* 0.001, *adj. OR =*1.65, *95% CI:* 1.34, 1.95) | 12 |
| Sheinbaum et al., 2014  SPAIN | *N =* 546 | | | | | Childhood physical, emotional and sexual abuse, and physical and emotional neglect | | CTQ (Bernstein et al., 1994) | Attachment style (secure vs. fearful vs. preoccupied vs. dismissing) | RQ (Hazan & Shaver, 2004) | PLEs, suspiciousness, and positive and negative schizotypy  Positive symptoms subscale of the CAPE (Konings et al., 2006)  Suspiciousness subscale of the SPQ (Raine 1991)  WSS (Kwapil, Barrantes-Vidal, & Silvia, 2008) | | None | | Fearful attachment mediated the effect of childhood adversity on PLEs (indirect effect: *B =* 0.063, *SE* = 0.034, *p <* 0.05), suspiciousness (indirect effect: *B =* 0.056, *SE* = 0.023, *p <* 0.05), positive schizotypy (indirect effect: *B =* 0.010, *SE* = 0.006, *p <* 0.05), and negative schizotypy (indirect effect: *B =* 0.019, *SE* = 0.009, *p <* 0.05) | 11 |
| **Sheinbaum et al., 2015**  **SPAIN** | ***N =* 214** | | | | | **Parental antipathy (*mean =*1.57, *SD =* 0.91) and role reversal (*mean =* 1.59, *SD =* 0.87)** | | **CECA (Bifulco, Brown, & Harris, 1994)** | **Attachment insecurity (enmeshed: *n =* 12, 5.6%; fearful: *n =* 34, 15.9%; angry-dismissive: *n =* 14, 6.5%; withdrawn: *n =* 31, 14.5%)** | **ASI (Bifulco, Moran, Ball, & Lillie, 2002)** | **Positive (*mean =* 1.21, *SD =* 2.69) and negative subclinical symptoms (*mean =*1.51, *SD =* 2.39)**  **CAARMS (Yung et al., 2005)** | | **Depressive symptoms** | | **Angry-dismissive attachment partially mediated the effect of parental antipathy on positive symptoms (*Raw Parameter Estimate* = 0.126, *SE* = 0.076, *p <* 0.05)** | **13** |
| Udachina & Bentall, 2014  UK | *N =* 302 | | | | | Emotional invalidation (punishment: *mean =* 2.71, *SD =* 0.96; minimization: *mean =*3.67, *SD =* 0.92; distress: *mean =* 3.22, *SD =* 0.96) | | SES (Krause, Mendelson, & Lynch, 2003) | Experiential avoidance (*mean =* 3.43, *SD =* 1.10) | AAQ-II (Bond et al., 2011) | Paranoia assessed using the PIQ (McKay, Langdon, & Coltheart, 2006; *mean =* 0.84, *SD =* 0.73) and the PaDS (Melo, Corcoran, Shryane, & Bentall, 2009; *mean =* 1.50, *SD =* 0.95) | | General parental style, negative self-esteem, attachment security | | Emotional invalidation predicted higher levels of experiential avoidance (*standardized coefficient* = 0.20, *p <* 0.001), which in turn predicted paranoia (*standardized coefficient* = 0.45, *p <* 0.001). | 7 |
| **NON - FIRST-EPISODE PSYCHOSIS (FEP), MIXED, OR UNSPECIFIED CLINICAL SAMPLES** | | | | | | | | | | | | | | | | |
| Goldstone et al., 2011  AUSTRALIA | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | | | | Childhood physical, emotional, and sexual abuse | | Modified version of the ETI-SR (Bremner, Bolus, & Mayer, 2007) | Family history for psychosis  Life hassles  Experiential avoidance  Early cannabis use, before age of 20  Recent methamphetamines use, after age of 20 | Ad hoc questionnaire  Survey of Recent Life Experiences (Kohn & Macdonald, 1992)  AAQ-II (Bond et al., 2011)  Ad hoc questionnaire | Delusional ideation (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  PDI (Peters, Joseph, & Garety, 1999) | | None | | No mediation via experiential avoidance was found. | 8 |
| Goldstone et al., 2012  AUSTRALIA | *N =* 133 controls from the general population  *N =* 100 patients with psychosis | | | | | Childhood physical (controls: *mean =* 1.63, *SD =* 1.54; cases: *mean =* 2.61, *SD =* 1.55), emotional (controls: *mean =* 1.38, *SD =* 1.38; cases: *mean =* 2.77, *SD =* 1.76), and sexual abuse (controls: *n =* 13, 10%; cases: *n =* 25, 25%) | | Modified version of the ETI-SR (Bremner et al., 2007) | Family history for psychosis (controls: *n =* 28, 21%; cases: *n =* 39, 39%)  Life hassles (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, SD 14.24)  Experiential avoidance (controls: *mean =* 51.62, *SD =* 10.79; cases: *mean =* 41.62, *SD =* 13.68)  Early cannabis use, before age of 20 (daily: controls: *n =* 11, 8%; cases: *n =* 27, 27%; weekly: controls: *n =* 19, 14%; cases: *n =* 19, 19%)  Recent methamphetamines use, after age of 20 (daily: controls: *n =* 1, 1%; cases: *n =* 9, 9%; weekly/ monthly: controls: *n =* 5, 14%; cases: *n =* 18, 18%)  Metacognitive beliefs (controls: *mean =* 88.13, *SD =* 20.21; cases: *mean =* 25.06, *SD =* 14.24) | Ad hoc questionnaire  Survey of Recent Life Experiences(Kohn & Macdonald, 1992)  Ad hoc questionnaire  MCQ (Wells & Cartwright-Hatton 2004) | Hallucination experiences (controls: *mean =* 27.21, *SD =* 19.87; cases: *mean =* 54.27, *SD =* 38.46)  LSHS-R (Bentall & Slade, 1985) | | None | | In the general population, emotional abuse showed an indirect effect on hallucinations, via life hassles and metacognition. Along with other relevant paths, the model predicted 28% of the variance (χ2= 11.70, p = 0.11, RMSEA= 0.07, TLI= 0.95). The model was replicated in the clinical sample, where emotional abuse was replaced by sexual abuse (χ2= 10.39, p = 0.17, RMSEA= 0.07, TLI= 0.93, 24% of the variance explained). | 9 |
| van Dam et al., 2014  Genetic Risk and Outcome in Psychosis (GROUP)  NETHERLANDS, BELGIUM | *N =*131 patients with psychotic disorder  *N =*123 siblings  *N =*72 healthy controls | | | | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (cases: *n =* 89, 67.9%; siblings: *n =* 53, 43.1%; controls: *n =* 27, 37.5%) | | CTQ-SF (Bernstein et al., 2003) | Attachment avoidance and anxiety (cases: *n =* 89, 67.9%; siblings: *n =* 57, 46.3%; controls: *n =* 18, 25%) | PAM (Berry et al., 2006) | Positive and negative psychotic symptoms and  PLEs  SAPS (Andreasen 1984), SANS (Andreasen 1983) and CAPE (Konings et al., 2006) | | Sex, age | | Childhood abuse was not related with PLEs in the control group. rEE was found between childhood adversity and attachment anxiety and avoidance across the three groups.  In the sibling group, attachment insecurity partially mediated the effect of childhood adversity on positive symptoms (avoidance: *β* = 0.201, *p* = 0.040; anxiety: *β* = 0.197, *p* = 0.047) and negative symptoms (avoidance: *β* = 0.29, *p* = 0.001; anxiety: *β* = 0.430, *p <* 0.001). In the case group, a mediating effect of attachment anxiety was found on negative symptoms (*β* = 0.209, *p* = 0.017) | 10 |
| Isvoranu et al., 2017  Genetic Risk and Outcome in Psychosis (GROUP)  NETHERLANDS, BELGIUM | *N =* 552 patients with psychotic disorders | | | | | Childhood physical (*n =* 88, 16%), emotional (*n =* 144, 26%), and sexual abuse (*n =* 138, 25%), and physical (*n =* 144, 26%) and emotional neglect (*n =* 436, 79%) | | CTQ-SF (Bernstein et al., 2003) | Specific positive, negative, or general psychopathology symptoms | PANSS (Kay et al., 1987) | Positive (*mean =* 12.50, *SD =* 5.29) and negative (*mean =* 13.26, *SD =* 5.60)  PANSS (Kay et al., 1987) | | None | | No direct connectivity between childhood adversities and psychotic symptoms accounting for general psychopathology. Sexual abuse was linked to most negative psychotic symptoms via physical neglect and motor retardation, and to delusions, hallucinations, and paranoia via emotional abuse and anxiety. Physical neglect was linked via motor retardation to most negative symptoms. Physical abuse was associated with positive symptoms through 3 pathways: 1) via somatic and unusual thought concern to delusions and hallucinations; 2) via poor impulse control to manic symptoms and conceptual disorganization; 3) to paranoia via emotional abuse and anxiety | 10 |
| **Mansueto et al., 2019**  **Genetic Risk and Outcome of Psychosis (GROUP) study**  **NETHERLANDS** | ***N =* 1, 119 patients with non-affective psychotic disorders** | | | | | **Childhood neglect (*mean =* 1.86, *SD =* 0.63) and abuse (*mean =* 1.43, *SD =* 0.52)** | | **CTQ-SF (Bernstein et al., 2003)** | **Mentalizing abilities (*mean =*17.71, *SD =* 2.73)** | **Hinting Task (Corcoran, Mercer, & Frith, 1995)** | **Positive (*mean =* 13.62, *SD =* 6.58), negative (*mean =* 14.19, *SD =* 6.19), disorganization (*mean =* 16.16, *SD =* 6.29), excitement (*mean =* 11.70, *SD =* 3.89), and emotional distress (*mean =* 15.49, *SD =* 5.63)**  **PANSS (Kay et al.,1987)** | | **Sex, age, and cannabis use** | | **Mentalizing abilities were negatively associated with childhood neglect (but not abuse) and with psychotic symptoms.**  **Mentalization partially mediated the effect of childhood neglect on negative symptoms (total effect: 1.01, *95% CI:* 0.27, 0.75; indirect effect: 0.17, *95% CI*: 0.02, 0.40; *adj. R2* = 0.07, *p <* 0.001), disorganization (total effect: 1.29, *95% CI*: 0.46, 1.95; indirect effect: 0.23, *95% CI*: 0.03, 0.49; *adj. R2* = 0.11, *p <* 0.001); and excitement (total effect: 0.76, *95% CI*: 0.32, 1.21; indirect effect: 0.05, *95% CI*: 0.009, 0.14; *adj. R2* = 0.55, *p <* 0.001).**  **When the analyses were run separately for men and women, the mediation was only evident in the men sample** | **13** |
| Weijers et al., 2018  NETHERLANDS | *N =* 90 patients with non-affective psychosis | | | | | Physical, psychological, and sexual abuse, and parental conflict (*mean =* 8.7, *SD =* 10.3) | | CECA (Bifulco et al., 1994) | Mentalization | Hinting Task (Corcoran et al., 1995) | Positive and negative symptoms  PANSS (Kay et al., 1987) | | None | | Childhood adversity was related to mentalization impairment. An effect of childhood adversity on negative symptoms was found, with evidence of partial mediation (*B =* 0.07, *p* = 0.039) via mentalization. Mentalization was not associated with positive symptoms | 10 |
| Baryshnikov et al., 2018  FINLAND | *N =* 183 patients with ICD-10 unipolar depression  *N =* 99 patients with bipolar disorder | | | | | Physical, emotional and sexual abuse, and emotional and physical neglect | | TADS (Patterson, Skeate, & Birchwood, 2002) | Cognitive, behavioural, interpersonal, and affective symptoms of borderline personality disorder (BPD) symptoms | MSI (Zanarini et al., 2003) | Positive PLEs  CAPE (Konings et al., 2006) | | Sex, age | | Childhood adversity was associated with BPD symptoms.  The effect of childhood adversity was fully mediated by BPD cognitive symptoms (*B* = 0.11, *95% CI:* 0.05, 0.11). Within cognitive symptoms, dissociative symptoms mediated 43% of the variance (*95% CI:* 25, 74), identity disturbance 40% (*95% CI:* 30, 73), and distrustfulness 18% (*95% CI:* 12, 50) | 10 |
| Chatziioannidis et al., 2019  GREECE | *N =*63 patients with schizophrenia spectrum disorder  *N =*61 matched controls | | | | | Childhood physical, and sexual abuse, and parental antipathy and neglect (cases: *n =* 42, 66.7%; controls: *n =* 9, 14.8%) | | CTQ-SF (Bernstein et al., 2003) | Attachment avoidance (cases: media*n =* 3.22, range= 4.6; controls: media*n =* 2.33, range 5.2) and anxiety (cases: media*n =* 3.88, range= 5.3; controls: media*n =* 2.17, range= 3.9) | ECR-R (Fraley et al., 2011) | Positive, negative, excitement, depression and cognitive factors, and index of hallucinations (*mean =*89.84, *SD =* 16.88)  PANSS (Kay et al., 1987) | | Education | | Childhood adversity (specifically, maternal antipathy) and attachment anxiety were associated with hallucinations.  Childhood adversity predicted attachment anxiety (*B =* 0.91, *p <*0.001), which in turn predicted PANSS total score (*B =* 1.36, *p <*0.001). A direct effect of childhood adversity was also observed (*B =* 1.70, *p* = 0.008) | 11 |
| Choi et al., 2015  REPUBLIC OF KOREA | *N =* 126 patients with psychotic disorders | | | | | Childhood physical (*mean =* 10.73, *SD =* 5.46), emotional (*mean =*10.44, *SD =* 5.08), and sexual abuse (*mean =* 7.86, *SD =* 3.76) | | CTQ (Bernstein et al., 1994) | PTSD symptoms (*mean =* 55.34, *SD =* 24.75) | IES-R (Horowitz, Wilner, & Alvarez, 1979) | Lifetime psychotic symptoms  Psychoticism subscale of the PSY-5 Factor Scale of the MMPI-2 (Butcher et al., 1989) | | None | | All childhood adversities were related to PTSD. Childhood adversity showed an effect on both psychotic (*β* = 0.30, *p <* 0.01) and PTSD symptoms (*β* = 0.33, *p <* 0.01). PTSD partially mediated the effect of childhood adversity on psychotic symptoms (*χ2* = 3.15, *p* = 0.533; *CFI* = 1.00; *NFI* = 0.98; *RMSEA* < 0.001; *90% CI*: 0.000, 0.121) | 8 |
| Choi 2017  REPUBLIC OF KOREA | *N =* 199 patients with non-psychotic disorders | | | | | Childhood physical (*mean* = 10.09, *SD* = 5.19), emotional (*mean* = 9.85, *SD* = 4.94), and sexual abuse (*mean* = 6.93, *SD* = 3.27), and physical (*mean* = 9.78, *SD* = 4.08) and emotional neglect (*mean* = 13.38, *SD* = 5.35) | | CTQ-SF (Bernstein et al., 1994) | PTSD symptoms (*mean =* 58.29, *SD =* 22.42)  Dissociation (*mean* = 14.83, *SD* = 7.43) | IES-R (Horowitz et al., 1979)  Modified PDEQ (Marshall, Orlando, Jaycox, Foy, & Belzberg, 2002) | Paranoid ideation (*mean =* 54.31, *SD =* 12.46) and aberrant experiences (*mean =* 54.21, *SD =*13.14)  Restructured Clinical Scale 6 OF THE MMPI-2 (Butcher et al., 1989) | | Sex, age | | PTSD and dissociation correlated with most childhood adversities. Childhood adversity had both a direct effect on paranoia (*β* = 0.38, p *<* 0.001) and an indirect effect via PTSD symptoms (*β* = 0.13, *95% CI:* 0.06 - 0.22). Evidence of partial mediation was found also on aberrant experiences, with both a direct (*β* = 0.28, *p* < 0.001) and an indirect effect of childhood adversity via dissociation (*β* = 0.13, *95% CI:* 0.02, 0.23) | 9 |
| Hardy et al., 2016  ENGLAND | *N =* 228 patients with non-affective psychosis | | | | | Childhood physical (*n =* 50, 21.9%), emotional (*n =* 72, 31.6), and sexual abuse (*n =* 50, 21.9%) | | THQ (Green 1996) | PTSD symptoms  Depression  Negative-self and negative-other scales | SRS- PTSD (Carlier, Lamberts, Van Uchelen, & Gersons, 1998)  BDI-II (Beck, Steer, Ball, & Ranieri, 1996)  BCSS (Fowler et al., 2006) | Auditory hallucinations, persecutory delusions, and delusions of reference  SAPS (Andreasen 1984) | | None | | Childhood sexual abuse was associated with PTSD numbing and avoidance, and PTSD hyperarousal. Physical and emotional abuse were associated with negative-other beliefs. PTSD avoidance and numbing (indirect effect: *B =* 1.475, *SE* = 0.188, *p* = 0.038), and PTSD hyperarousal (indirect effect: *B =* 1.439, *SE* = 0.184, *p* = 0.048) fully mediated the effect of sexual abuse on hallucinations. No mediation via PTSD intrusive memory, negative beliefs, and depression was found. Negative-other beliefs partially mediated the effect of emotional abuse on persecutory delusions (*B* = 0.359, *SE* = 0.136, *p* = 0.024) | 10 |
| Muenzenmaier et al., 2015  USA | *N =* 184 patients with schizophrenia, schizoaffective, bipolar, and major depressive disorders, and other unspecified disorders | | | | | Physical (*n =* 181, 75.4%), sexual (*n =* 179, 26.2%), and emotional (*n =* 177, 51.4%) abuse, parental substance abuse (*n =* 183, 47.0%), parental mental illness (*n =* 181, 29.3%), witnessing violence (*n =* 177, 36.6%), and arrest of family member (*n =* 176, 36.4%) before age of 16 | | History of Physical and Sexual Abuse Questionnaire (Meyer, Muenzenmaier, Cancienne, & Struening, 1996)  Ad hoc questionnaire (Muenzenmaier et al., 2014) | Dissociative experiences | DES-T (Waller & Ross, 1997) | Lifetime delusions (*n =* 125, 70.2%) and hallucinations (*n =* 104, 64.2%)  SCID-I (First et al., 1996) | | Sex, age, education, marital status, ethnicity, diagnosis, and treatment | | Dissociative experiences partially mediated the effect of childhood adversity on delusion (*adj. IRR* = 1.14, *95% CI:* 1.00, 1.30, *p <* 0.05; 30% reduction) and hallucinations (*adj. IRR* = 1.09, *95% CI:* 0.92, 1.30, p> 0.05, 47% reduction) | 7 |
| Ostefjells et al., 2017  Thematically Organised Psychosis (TOP)  NORWAY | *N =* 261 patients with DSM-IV psychotic (*n =* 163, 62.5%) or bipolar disorders (*n =* 98, 37.5%) | | | | | Childhood emotional abuse (*n =* 60, 28%) | | CTQ-SF (Bernstein et al., 2003) | Metacognitive negative beliefs about the uncontrollability and danger of thoughts (MCQ-UD; *mean =* 13.8, *SD =* 5.0)  Depression and anxiety symptoms (*mean =* 2.52, *SD =* 1.0) | MCQ (Wells & Cartwright-Hatton, 2004)  PANSS (Kay et al., 1987) | Positive psychotic symptoms (*mean =* 1.92, *SD =* 1.0)  PANSS (Kay et al., 1987) | | Sex, main diagnosis, duration of treatment | | Emotional abuse was related to metacognitive negative beliefs (*rho* = 0.37, *p <* 0.001). Emotional abuse showed both a direct effect on positive symptoms and an indirect effect via metacognitive negative beliefs and anxiety and depression symptoms (3.22 x 0.08 x 0.18, *95% CI:* 0.02, 0.10). The mediation model explained a greater variance than the direct model (*R2* = 0.29, *p <* 0.001 vs. *R2*= 0.03, *p* = 0.02) | 11 |
| Pearce et al., 2017  ENGLAND | *N =* 131 patients seeking professional help for self-reported PLEs | | | | | Childhood emotional, physical, and sexual abuse (*mean =* 14.22, *SD =* 4.43) | | Brief Betrayal Trauma Survey (Goldberg & Freyd, 2006) | Dissociative experiences (*mean =* 85.21, *SD =* 33.04)  Insecure attachment style (fearful: *mean =* 4.82, *SD =* 1.82; preoccupied: *mean =* 3.01, *SD =* 1.97; dismissing: *mean =* 3.42, *SD =* 1.97) | DES-II (Carlson & Putnam, 1993)  RQ | PLEs (paranoia: *mean =* 10.92, *SD =* 2.86; hearing voices: *mean =* 4.67, *SD =* 1.88)  CAPE (Konings et al., 2006) | | Paranoia and hearing voices | | Fearful attachment (but not preoccupied or dismissing) and dissociation were associated with childhood adversity.  Accounting for the effect of fearful attachment, dissociation fully mediated the effect of childhood adversity on hearing voices (*B =* 0.09, *95% CI*: 0.03, 0.17). Both dissociation (*B =* 17, *95% CI*: 0.07, 0.30) and fearful attachment (*B =* 0.05, *95% CI:* 0.01, 0.12) fully mediated the effect of childhood adversity on paranoia | 9 |
| Perona-Garcelán et al., 2012  SPAIN | *N =*71 patients with DSM-IV psychotic disorders | | | | | Sexual and physical abuse, death of a relative/ friend, near- drowning experiences, assault, and accident before 15 years of age (*n =* 32, 45.1%; *mean =* 2.59, *SD =* 1.72) | | TQ (Davidson et al., 1990) | Dissociative experiences (*mean =* 18.70, *SD =* 13.42) | DES-II (Carlson & Putnman 1993) | Severity of hallucinations (*mean =* 2.58, *SD =* 1.94) and delusions (*mean =* 3.18, *SD =* 1.74)  PANSS(Kay et al., 1987) | | None | | Childhood adversity was related to dissociative experiences. Dissociation mediated the effect of childhood adversity on hallucination (indirect effect: *B =* 0.21, *95% CI:* 0.09, 0.38, *p <* 0.01) but not on delusion (*B =* 0.07, *95% CI:* 0.00, 0.21, p > 0.05). Specifically, the mediating effect of dissociation was attributable to the depersonalisation DES factor (*B =* 0.19, *95% CI:* 0.05, 0.39, *p* <0.05) | 7 |
| Pilton et al., 2016  ENGLAND | *N =* 55 patients with schizophrenia (*n =* 44, 80%) or schizoaffective disorder (*n =* 6, 10.9%) | | | | | Childhood physical (*mean =* 0.936, *SD =* 0.243), emotional (*mean =* 10.40, *SD =* 7.35), and sexual abuse (*mean =* 0.924, *SD =* 0.276), and physical (*mean =* 9.04, *SD =* 5.04) and emotional neglect (*mean =* 11.87, *SD =* 5.75) | | CTQ (Bernstein et al., 1994) | Attachment avoidance (*mean =* 18.29, *SD =* 6.53) and anxiety (*mean =* 20.36, *SD =* 4.51) | PAM (Berry et al., 2006) | Auditory hallucinations (*mean =* 27.78, *SD =* 6.80)  PSYRATS-AH (Haddock, McCarron, Tarrier, & Faragher, 1999) | | None | | Sexual abuse, emotional abuse and physical neglect were related to anxious attachment. Anxious attachment fully mediated the effect of sexual abuse, (indirect effect: 0.138, *p* = 0.018) emotional abuse (indirect effect: 0.138, *p* = 0.018), and physical neglect (indirect effect: 0.156, *p* = 0.046) on hallucinations. No direct effect was found | 10 |
| Schalinski et al., 2017  GERMANY | *N =*180 patients with psychotic disorders | | | | | Childhood trauma (*mean =* 3.0, *SD =* 2.8) | | LEC (Gray, Litz, Hsu, & Lombardo, 2004) | Dissociative symptoms | Shutdown Dissociation Scale (Schalinski, Schauer, & Elbert, 2015) | Positive and negative psychotic symptoms  PANSS (Kay et al., 1987) | | Sex, age | | Childhood trauma was related to dissociative experiences. Dissociation fully mediated the effect of trauma on positive symptoms (indirect effect: 0.07, *p* = 0.032), accounting for 25.9% of the total effect. No direct effect of childhood trauma was found. No mediation effect was found for specific types of adversities. | 11 |
| Sengutta et al., 2019  GERMANY | *N =* 200 patients with non- psychotic disorder (*n =* 167 with depressive disorders, *n =*51 with anxiety disorders) | | | | | Childhood emotional, physical, and sexual abuse, emotional and physical neglect, parental separation, violence against the mother, substance abuse or dependence, mental illness and/or imprisonment of a member of the household (*mean =* 3.02, *SD =* 2.40) | | ACE (Schäfer, Wingenfeld, ACE-D, & Spitzer, 2014). | Borderline personality disorders (BPD) features (*mean =* 40.21, *SD =* 21.28)  Depressive symptoms (*mean =* 16.23, *SD =* 5.41)  Anxiety symptoms (*mean =* 12.15, *SD =* 4.80) | BSL-23 (Bohus et al., 2009)  PHQ-9 (Kroenke, Spitzer, & Williams, 2001)  GAD-7 (Spitzer et al., 2006) | PLEs (*mean =* 6.43, *SD =* 3.61)  PQ-16 (Ising et al., 2012) | | Sex | | All potential mediators were associated with childhood adversity.  The effect of childhood adversity on PLEs (*β* = 0.30, *p <* 0.001) was reduced to a non-significant effect by BPD features, with evidence of full mediation (Sobel’s test *z* = 4.47, *p <* 0.001).  Depression (*β =* 0.22, *p* < 0.001; *z* = 3.00; *p* < 0.01) and anxiety (*β* = 0.22, *p <* 0.001, *z* = 2.74; *p <* 0.01) partially mediated the effect of childhood adversity | 10 |
| Varese et al., 2012  WALES | *N =* 45 patients with schizophrenic spectrum disorder with and without hallucinations  *N =* 20 healthy controls | | | | | Child sexual, psychological and physical abuse, and neglect | | CATS (Sanders & Becker-Lausen, 1995) | Dissociative experiences | DES (Bernstein & Putnam, 1986) | Lifetime history of hallucinations and hallucination proneness  SCI-PANSS (Opler, Kay, Lindenmayer, & Fiszbein, 1992) and LSHS-R (Bentall & Slade, 1985) | | None | | Childhood adversity was related to dissociative experiences. Dissociation mediated the effect of childhood adversity on hallucination both in the aggregated sample (indirect effect: *B =* 0.12, *95% CI:* 0.06, 0.19) and in the patient-only group (indirect effect: *B =* 0.1, *95% CI:* 0.06, 0.17). The same was replicated, specifically, for child abuse. Only in the aggregated sample, dissociation mediated the effect of neglect and emotional abuse on hallucination-proneness | 7 |
| Vogel et al., 2011  GERMANY | *N =* 25 patients with schizophrenia  *N =* 35 outpatients with non-psychotic disorders | | | | | Physical, emotional and sexual abuse and emotional and physical neglect (cases: *mean =* 38.36, *SD =* 16.93; controls: *mean =* 39.00, *SD =* 8.68 ; history of any childhood trauma: cases n = 4, controls n = 2) | | CTQ (Bernstein et al., 1994) | Depression (cases: *mean =* 25.72, *SD =* 9.28; controls: *mean =* 26.14, *SD =* 8.89)  PTSD symptoms (cases: *mean =* 10.48, *SD =* 11.66; controls: *mean =* 13.34, *SD =* 13.85)  Dissociative symptoms (cases: *mean =* 13.52, *SD =* 7.84; controls: *mean =* 15.46, *SD =* 6.59) | MADRS (Montgomery & Asberg, 1979)  PTDS (Foa et al., 1997)  AMDP-Dis (Freyberger & Moller, 2004) | Positive and negative psychotic symptoms  SAPS (Andreasen 1984) and SANS (Andreasen 1983) | | Sex, age, positive and negative psychotic symptoms | | In the overall sample, history of any childhood trauma was not related with any of potential mediators. History of any childhood trauma showed a non-significant protective effect on negative symptoms (*B =* -2.83, *SE* = 1.42, *p* = 0.05) that was slightly modified (*B =* -3.33, *SE* = 1.62, *p* = 0.04) when dissociation was entered in the model | 10 |
| Wickham & Bentall, 2016  ENGLAND | *N =* 72 patients with schizophrenic spectrum disorder  *N =* 72 comparison controls | | | | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect | | CTQ-SF (Bernstein et al., 1994) | General and personal belief in just world (BJW) | General Beliefs in a Just World Scale (Dalbert, Montada, & Schmitt, 1987)  Personal Belief in a Just World Scale (Dalbert, 1999) | Current paranoia and hallucinatory experiences  PANSS (Kay et al., 1987) | | Sex, age, and co-occurrence between symptoms | | Controlling for co-occurrence between symptoms, emotional neglect predicted paranoia and sexual abuse predicted hallucinations. Emotional neglect showed both a direct and indirect effect on paranoia via personal BJW (*B =* 0.032, *SE* = 0.02, *95% CI:* 0.00, 0.08). Sexual abuse showed only a direct effect on hallucinations (*B =* 0.08, *SE* = 0.04, *p* < 0.05). | 9 |
| **FIRST-EPISODE PSYCHOSIS (FEP) OR ULTRA HIGH RISK OR GENETIC HIGH RISK CLINICAL SAMPLES** | | | | | | | | | | | | | | | | |
| Peach et al., 2019  AUSTRALIA | | *N =* 66 patients with DSM-IV FEP | | | | | Childhood emotional, physical, and sexual abuse, and physical and emotional neglect (*n =* 35, 53%) | CTQ-SF (Bernstein et al., 2003) | PTSD intrusions (*mean =* 5.58, *SD =* 8.36)  Trauma - related beliefs (*mean =* 113.42, *SD =* 49.04) | CAPS (Blake et al., 1995)  PTCI (Foa et al., 1999) | Positive (*mean =* 11.73, *SD =* 4.02) and negative symptoms (*mean =* 11.61, *SD =* 4.40)  Delusions (*mean =* 3.94, *SD =* 2.05) and hallucinations (*mean =* 2.23, *SD =* 1.63)  PANSS (Kay et al., 1987) | | | Hallucinations, delusions, and PTSD avoidance | Both PTSD intrusions and trauma - related beliefs correlated with childhood adversity.  In a simple regression model, both PTSD - intrusions (*β* = 0.01, *95% CI:* 0.003, 0.034) and trauma - related beliefs (*β* = 0.01, *95% CI:* 0.001, 0.027) mediated the effect of childhood adversity on hallucinations. The same was replicated for delusions (*β* = 0.02, *95% CI:* 0.006, 0.044; *β* = 0.02, *95% CI:* 0.012, 0.041).  In a multiple regression model, the only predictor of hallucination severity was PTSD - intrusions (*β* = 0.53, *p* = 0.01, 9% of the variance explained). Both PTSD - intrusions and trauma - related beliefs predicted delusions severity (*β* = 0.67, *p <* 0.01, *β* = 0.34, *p <* 0.01, 17% of the variance explained) | 10 |
| Sun et al., 2018  AUSTRALIA | | *N =* 66 patients with DSM-IV FEP | | | | | Childhood emotional, physical, and sexual abuse, and physical and emotional neglect (*n =* 35, 53%) | CTQ-SF (Bernstein et al., 2003) | Self - rated dissociative experiences (*mean =* 25, *SD =* 16.41) and clinician - rated dissociative symptoms (*mean =* 7.24, *SD =* 2.70) | DES-II (Carlson & Putnman 1993)  SCID-D (Steinberg, 1993) | Positive (*mean =* 11.73, *SD =* 4.02) and negative symptoms (*mean =* 11.61, *SD =* 4.40)  Delusions (*mean =* 3.94, *SD =* 2.05) and hallucinations (*mean =* 2.23, *SD =* 1.63)  PANSS (Kay et al., 1987) | | | None | Childhood adversity correlated with dissociation (*rho* = 0.54, *p <* 0.001). Clinician -rated dissociation mediated the effect of childhood trauma on delusions (*β* = 0.02, *95% CI:* 0.01, 0.04) and self - rated dissociation mediated the effect on hallucinations (*β* = 0.01, *95% CI:* 0.003, 0.03). No effect was found on negative symptoms | 9 |
| Appiah-Kusi et al., 2017  ENGLAND | | *N =* 30 UHR individuals  *N =* 38 controls | | | | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (UHR: *mean =* 51.83, *SD =* 18.51; controls: *mean =* 36.03, *SD =* 10.54) | CTQ (Bernstein et al., 1994) | Cognitive schema of self and the other | BCSS (Fowler et al., 2006) | Paranoia and UHR status  PTS (Green et al., 2008) | | | Depression, anxiety, and smoking cannabis more than once a month | Emotional neglect was associated with both negative self-schema and negative schema about the others. There was an indirect effect of emotional neglect via negative self-schema on UHR status (*B =* 0.045, *95% CI:* 0.004 0.159) and on paranoia ideation (*B =* 0.988, *95% CI:* 0.323, 1.895). Partial mediation explained respectively 14.7% and 42.2% f the variance | 9 |
| Evans et al., 2015  ENGLAND | | *N =* 29 patients with FEP  *N =* 31 healthy controls | | | | | Childhood physical, emotional, and sexual abuse, and physical and emotional neglect (cases: *median =* 38, *IQR* = 16.50; controls: *median =* 28, *IQR* = 9) | CTQ (Bernstein et al., 1994) | Self-concept clarity  Dissociative experiences | SCCS (Campbell et al., 1996)  DES-II (Carlson & Putnman 1993) | Psychotic symptoms  PANSS (Kay et al., 1987) | | | Age, employment status | Dissociation mediated the effect of physical neglect on psychosis (indirect effect: *B =* -0.101, *95% CI:* 0.002, 0.0365, *p <* 0.05). Self-concept clarity mediated the effect of emotional (*B =* 0.144, *95% CI:* 0.025, 0.404, *p <* 0.05) and physical abuse (*B =* 0.195, *95% CI:* 0.006, 0.647, *p <* 0.05), emotional (*B =* 0.130, *95% CI:* 0.029, 0.379, *p <* 0.05) and physical neglect (*B =* 0.210, *95% CI:* 0.035, 0.573, *p <* 0.05), and total childhood adversity (*B =* 0.057, *95% CI:* 0.012, 0.148, p < 0.05) on psychosis | 7 |
| **Morgan, Reininghaus, Fearon, et al., 2014**  **Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study**  **ENGLAND** | | ***N =* 390 patients with FEP**  ***N =* 391 healthy controls** | | | | | **Parental separation (cases: *n =* 160, 41%; controls: *n =* 80, 20.4%) or death (cases: *n =* 30, 7.7%; controls: *n =* 14, 3.6%) before age of 16** | **MRC Socio demographic Schedule (Mallett, 1997)** | **Self-esteem (cases: mean 36.2, SD 7.8; controls: mean 39.2, SD 7.6)** | **RSES (Rosenberg, 1989)** | **ICD-10 diagnosis of psychotic disorders (*n =* 390)**  **SCAN (World Health Organization, 1992)** | | | **Sex, age, ethnicity, study centre, and parental history of psychosis.** | **Self-esteem did not mediate the effect of parental separation on psychosis** | **15** |
| Thompson et al., 2016  PACE  AUSTRALIA | | *N =* 416 individuals at UHR for psychosis | | | | | Childhood and adolescent sexual abuse | CTQ (Bernstein et al., 1994) | Depression, anxiety, mood swing, lability, and mania | HAM-A (Hamilton, 1959)  HAM-D (Hamilton, 1960)  CASH (Andreasen et al., 1992) | Transition to psychosis  BPRS (Overall & Gorham, 1962) and CASH (Andreasen et al., 1992) | | | None | Sexual abuse was related to transition to psychosis in most of the mediation models but none of the proposed mediators was statistically significant (Indirect effect: HAM-A: *OR* = 1.00, *p* = 0.934; HAM-D: *OR* = 1.00, *p* = 0.687; CAARMS - mood: *OR* = 1.00, *p* = 0.919; CAARMS - anxiety: *OR* = 1.00, *p* = 0.509; CAARMS - dissociation: *OR* = 0.99, *p* = 0.358; CAARMS mood swings: *OR* = 1.00, *p* = 0.730; CAARMS - mania: *OR* = 1.01, *p* = 0.438) | 7 |
| **Walker et al., 1981**  **Danish high-risk project**  **DENMARK** | | ***N =* 207 individuals at CHR for schizophrenia (*n =* 15 affected with schizophrenia)** | | | | | **Parental separation before age of 10** | **Ad hoc interview (Schulsinger, 1976) and Danish population register** | **Being under institutional care before age of 10** | **Ad hoc interview (Schulsinger, 1976) and Danish population register** | **Paranoia/ autistic traits, thought disorders, hebephrenic traits, and borderline delusions or hallucinations**  **CAPPS (Endicott & Spitzer, 1972) and PSE (Wing & Cooper, 1974)** | | | **None** | **Among males, maternal separation was directly related with lower levels of hebephrenic traits. Maternal separation was related to institutional care in both genders, but paternal separation only in males. Furthermore, only among males there was a significant path from parental separation to institutional care to thought disorders (*path coefficient* = 0.80, *p <* 0.01), hebephrenic traits (*path coefficient* = 0.55, *p <* 0.01), and borderline delusions or hallucinations (*path coefficient* = 0.55, *p <* 0.01). No relation was found with paranoia/autistic traits** | **16** |

Note: when not reported in the manuscript, frequencies were calculated from percentages

**Supplementary Table 8: Relationship between findings of robust interaction and moderation studies and sample size, sample type, and outcome**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **NON-SIGNIFICANT INTERACTION** | | | | **SIGNIFICANT INTERACTION** | | | |
| ***Author, year*** | ***N*** | ***Sample*** | ***Outcome*** | ***Author, year*** | ***N*** | ***Sample*** | ***Outcome*** |
| **GENETIC RISK FACTORS** | | | | | | | |
| Ramsay et al., 2013 | *N =* 237 | General population | Disorder (psychosis) | Paksarian et al., 2015 | *N =*985,058 | General population | Disorder (schizophrenia) |
| Debost et al., 2017 | *N =* 1,699 cases  *N =* 1,681 controls | General population | Disorder (schizophrenia) | Wicks et al., 2010 | *N =* 13,163 adoptees  *N =* 2.9 million non-adoptee | General population | Disorder (non-affective psychosis) |
| Ajnakina et al., 2014 | *N =* 291 cases  *N =* 218 healthy controls | FEP/UHR/Genetic HR | Disorder (non-organic psychosis) | Vinkers et al., 2013 | *N =*339 | General population | PLEs |
| Trotta et al., 2015 | *N =* 224 cases  *N =* 256 controls | FEP/UHR/Genetic HR | Disorder (psychosis) |  |  |  |  |
| Trotta et al., 2016 | *N =* 285 cases  *N =* 256 controls | FEP/UHR/Genetic HR | Disorder (psychosis) |  |  |  |  |
| Trotta et al., 2018 | *N =* 285 cases  *N =* 256 controls | FEP/UHR/Genetic HR | Disorder (psychosis) |  |  |  |  |
| Fisher et al., 2014 | *N =* 172 cases  *N =* 246 controls | FEP/UHR/Genetic HR | Disorder (psychosis) |  |  |  |  |
| **SUBSTANCE USE** | | | | | | | |
| Morgan, Reininghaus, Reichenberg, et al., 2014 | *N =* 1,680 | General population |  | Houston et al., 2008 | *N =* 5,877 | General population | Disorder (non-affective psychosis) |
| Vinkers et al., 2013 | *N =* 339 | General population | PLEs | Konings et al., 2012 | *N =* 4,842 | General population | Symptoms |
| Ajnakina et al., 2014 | *N =* 291 cases  *N =* 218 controls | FEP/UHR/Genetic HR | Disorder (non-organic psychosis) |  |  |  |  |
| Sideli et al., 2018 | *N =* 231 cases  *N =* 214 controls | FEP/UHR/Genetic HR | Disorder (non-organic psychosis) |  |  |  |  |
| **STRESSFUL LIFE EVENTS AND SOCIAL RISK FACTORS** | | | | | | | |
| Räikkönen et al., 2011 | *N =* 12,747 | General population | Disorder (non-organic psychosis) | Lataster et al., 2012 | *N =* 3,021 | General population | Symptoms |
| Newbury et al., 2018 | *N =* 2,063 | General population | Symptoms | Morgan, Reininghaus, Reichenberg, et al., 2014 | *N =* 1,680 | General population | PLEs |
|  |  |  |  | Ouellet-Morin et al., 2015 | *N =* 1,052 | General population | Symptom |
|  |  |  |  | Gayer-Anderson et al., 2015 | *N =* 202 FEP  *N =* 266 healthy controls | FEP/UHR/Genetic HR | Disorder (psychosis) |
|  |  |  |  | Morgan, Reininghaus, Fearon, et al., 2014 | *N =* 390 FEP  *N =* 391 healthy controls | FEP/UHR/Genetic HR | Disorder (psychosis) |
|  | | | | | | | |
| Mansueto et al., 2019 | *N =* 1,119 cases | Non – FEP, mixed, or unspecified | Symptoms |  |  |  |  |

Significant interaction: p < .05

**Supplementary Table 9: Relationship between evidence of robust mediation and sample size, sample type, and outcome**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NON-SIGNIFICANT MEDIATION** | | | | **SIGNIFICANT MEDIATION** | | | | |
| ***Author, year*** | ***N*** | ***Sample*** | ***Outcome*** | ***Author, year*** | | ***N*** | ***Sample*** | ***Outcome*** |
| **SUBSTANCE USE** | | | | | | | | |
|  | | | | | | | | |
| van Nierop et al., 2014 | *N =* 6,646 | General population | Symptom |  |  | |  |  |
| **STRESSFUL LIFE EVENTS AND SOCIAL RISK FACTORS** | | | | | | | | |
|  |  |  |  | van Nierop et al., 2014 | *N =* 6,646 | | General population | Symptom |
|  |  |  |  | Bhavsar et al., 2019 | *N =* 1,698 | | General population | PLE |
|  |  |  |  | Shevlin et al., 2015 | *N =* 7,403 | | General population | Symptom |
|  |  |  |  | Morgan, Reininghaus, Fearon, et al., 2014 | *N =* 390 cases  *N =* 391 controls | | FEP/UHR/Genetic HR | Disorder (psychosis) |
| **PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL MECHANISMS** | | | | | | | | |
| Morgan, Reininghaus, Fearon, et al., 2014 | *N =* 390 cases  *N =* 391 controls | FEP/UHR/Genetic HR | Disorder (psychosis) | Janssen et al., 2005 | *N =* 4,045 | | General population | Symptom |
|  |  |  |  | van Nierop et al., 2014 | *N =* 6,646 | | General population | Symptom |
|  |  |  |  | McCarthy-Jones 2018 | *N =* 7,403 | | General population | Symptom |
|  |  |  |  | Sheinbaum et al., 2015 | *N =* 214 | | General population | PLEs |
|  |  |  |  | Sitko et al., 2014 | *N =* 5,877 | | General population | Symptom |
|  |  |  |  | Mansueto et al., 2019 | *N =* 1,119 cases | | Non – FEP, mixed, or unspecified | Symptoms |
|  |  |  |  | Walker et al., 1981 | *N =* 207 | | FEP/UHR/Genetic HR | PLEs |

Significant mediation: p < .05

**Abbreviations**

**General abbreviations:** ADHD: Attention Deficit Hyperactivity Disorder; Adj: adjusted; APA: American Psychiatric Association; AVH: Auditory Verbal Hallucinations; BDNF: Brain Derived Neurotrophic Factor; CHR: Clinical High Risk; CI: Confidence Interval; Coeff: Regression coefficient; COMT: Catechol O-methyltransferase; DAT: Dopamine Active Transporter; DRD: Dopamine Receptor D; DSM: Diagnostic and Statistical Manual of mental disorders; DZ: Dizygotic; EPP: Extended Psychosis Phenotype; ESM: Experience Sampling Method; ExE: Environment by Environment interaction; FEP: First Episode of Psychosis; FES: First Episode of Schizophrenia; FKBP5: Binding protein 5; GxE: Gene by Environment interaction; GWAS: Genome -ide Association Study; ICD: International Classification of Disease; ICR: Interaction Contrast Ratio; IQ: Intellectual Quotient; IQR: Inter-quartile range; LGB: Lesbian, Gay, Bisexual; LoC: Locus of Control; LR: Likelihood Ratio; MAEs: Momentary Anomalous Experience; MAOA: Monoamine oxidase- A; MDD: Major Depressive Disorder; MMP9: matrix metallopeptidase 9; MRC: Medical Research Council;MTHFR: methylenetetrahydrofolate reductase; MZ: Monozygotic; NA: Negative Affect; OR: Odds ratio; PD: Psychotic Disorder; PLEs: Psychosis-Like Experiences; PRS: polygenic risk score; PTSD: Post-Traumatic Stress Disorder; RD: Risk Difference; rEE: Environment-Environment correlation; rGE: Gene-Environment correlation; RMSEA: Root Mean Square Error of Approximation; SD: Standard Deviation; SE: Standard Error; SES: Socio-economic status; SNP: single-nucleotide polymorphism; TLI: Tucker –. Lewis Index; UHR: Ultra-High Risk; Unadj: unadjusted; VNTR: Variable Number Tandem Repeat.

# Measurement instruments: AAQ: Adult Attachment Questionnaire; AAQ-II: Acceptance and Action Questionnaire-II; ACE-IQ: Adverse Childhood Experiences International Questionnaire; ADL: Activity of Daily living; Adult PARQ/C: Adult Parental Acceptance-Rejection Questionnaire /Control; AMDP-Dis: Dissociation module of the Arbeitsgemeinschaft Methodik und Dokumentation in der Psychiatrie; APSS: Adolescent Psychotic-like Symptom Screener; ASI: Attachment Style Interview; BAI: Beck Anxiety Inventory; BCSS: Brief Core Schema Scales; BDI: Beck Depression Inventory; BPRS: Brief Psychiatric Rating Scale; Brief TRAILS Family History Interview; BSL-23: Borderline Symptom List; CAARMS: Comprehensive Assessment of At-Risk Mental States; CAPE: Community Assessment of Psychic Experiences; CAPS: Clinician Administered PTSD Scale; CAPPS: Current and Past Psychopathology Scale; CAQ: Childhood Adversity Questionnaire; CASH: Comprehensive Assessment of Symptoms and History Interview; CATS: Child Abuse and Trauma Scale; CDS: Cambridge Depersonalization Scale; CECA: Childhood Experience of Care and Abuse; CECA-Q: Childhood Experience of Care and Abuse Questionnaire; CEQ: Cannabis Experiences Questionnaire; CEQmv: Cannabis Experiences Questionnaire modified version; CES: Curious Experiences Survey; CES-D: Center for Epidemiologic Studies Depression scale; CIDI: Composite International Diagnostic Interview; CIS-R: Clinical Interview Schedule – Revised; CRS: Danish Civil Registration System; CTQ: Childhood Trauma Questionnaire; CTQ-SF: Childhood Trauma Questionnaire – short form; CTS-R: Conflict Tactics Scale-Form R; DACOBS-18: Davos Assessment of Cognitive Biases Scale; DAWBA: Development and Well-being Assessment; DCFS: Devaluation of Consumers Families Scale; DCS: Devaluation of Consumers Scale; DES: Dissociative Experiences Scale; DIGS: Diagnostic Interview for Genetic Study; DIP: Diagnostic Interview for Psychosis; DIS: Diagnostic Interview Schedule; DPS: Dissociative Processes Scale; ECR-R: Experiences in Close Relationships Questionnaire – Revised; ELES: Early Life Experiences Scale; ERSQ: Emotion Regulation Skills Questionnaire; ETI: Early Trauma Inventory; ETI-SR: Early Trauma Inventory- Self Report; FH-RDoC: Family History Research Diagnostic Criteria; FIGS: Family Interview for Genetic Studies; GAD-7: Generalized Anxiety Disorder questionnaire; GAF: Global Assessment of Functioning; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; IES-R: Impact of Event Scale-Revised; IPASE: Inventory of Psychotic-like Anomalous Self-Experiences; JVQ: Juvenile Victimization Questionnaire; K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children; LEC: Life Events Checklist; LSC-R: Life Stressor Checklist; LSHS-R: Launay-Slade Hallucination Scale-Revised; MADRS: Montgomery–Åsberg Depression Rating Scale; MCQ: Metacognitions Questionnaire; MEL: Munich Interview for the Assessment of Life Events and Conditions; MINI: Mini International Neuropsychiatric Interview; MMPI-2: Minnesota Multiphasic Personality Inventory-2; MSI-BPD: McLean Screening Instrument for Borderline Personality Disorder; NSIE: Nowicki-Strickland Internal-External scale; OPCRIT: Operational Criteria System; PaDS: Persecution subscale of the Persecution and Deservedness Scale; PAM: Psychosis Attachment Measure; PANAS-N: Positive and Negative Affect Scale; PANSS: Positive and Negative Syndrome Scale; PARA: Paranoia Checklist; PBI: Parental Bonding Instrument; PCL: PTSD Checklist; PCL-S: DSM-III-R Posttraumatic Stress Disorder Checklist Specific; PDEQ: Peritraumatic Dissociative Experiences Questionnaire; PDI: Peters et al. Delusions Inventory; PDI-IV: Personality Disorder Interview-IV; PDS: Posttraumatic Stress Diagnostic Scale; PHQ-D: Patient Health Questionnaire; PIQ: Persecutory Ideation Questionnaire; PQ: Prodromal Questionnaire; PQ-B: Prodromal Questionnaire – Brief version; PSE: Present State Examination; PSQ: Psychosis Screening Questionnaire; PSS: Perceived Stress Scale; PTCI: Posttraumatic Cognitions Inventory; PTS: Paranoid Thought Scales; RDoC: Research Diagnostic Criteria; PVS: Peer Victimization Scale; REF: Referential Thinking Scale; RSES: Rosenberg self-esteem scale; RQ: Relationship Questionnaire; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SAS: Social Anxiety Scale; SCAN: Schedule for Assessment in Neuropsychiatry; SCCS: Self-Concept Clarity Scale; SCS: Social Comparison Scale; SCID-D: Structured Clinical Interview for DSM–IV Dissociative Disorders- Revised; SCID-I: Structured Clinical Interview for the DSM Axis I disorder; SCID-II: Structured Clinical Interview for Axis II disorders; SCL-90-R: Symptom Checklist-90 – Revised; SES: Socialization of Emotion Scale; SIAPA: Structured Interview for Assessing Perceptual Anomalies; SIDP-IV: Structured Interview for DSM-N Personality; SIS-R: Structured Interview for Schizotypy – Revised; SMFQ: Short Moods and Feelings Questionnaire; SMQ: Southampton Mindfulness Questionnaire; SOS: Significant Others Scale; SPQ: Schizotypal Personality Questionnaire; SPQ-B: Schizotypal Personality Questionnaire-Brief; SQ-SF: The Young Schema Questionnaire Short Form; SRS- PTSD: Self- report Scale for Posttraumatic Stress Disorder; SSCS: Screening Scale for Chronic Stress; SSPS: State Social Paranoia Scale; STA: Schizotypal Personality Scale; TAS: Tellegen Absorption Scale; TAS-20: Toronto Alexithymia Scale; TEC: Traumatic Experience Checklist; THQ: Trauma History Questionnaire; TQ: Trauma Questionnaire; UM-CIDI: University of Michigan Composite International Diagnostic Interview; WSS: Wisconsin Schizotypy Scales; YSR: Youth Self-Report.

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