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Connecting genetics to childhood trauma in First Episode Psychosis: Mediating pathways and potential epigenetic mechanisms

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Connecting Genetics to Childhood Adversity in First Episode Psychosis:

Mediating pathways and epigenetic mechanisms

by **Luis Alameda**

A thesis submitted for the degree of

Doctor of Philosophy in Psychosis Studies Research

Institute of Psychiatry, Psychology & Neuroscience

King´s College London

2022

Dedicated to Alejandro Fernández Alameda

ACKNOWLEDGEMENTS

I want to express my gratitude to Robin Murray for allowing me to come to the IoPPN to work with his research team. I would like to thank Robin Murray, Chloe Wong and Craig Morgan, my PhD supervisors, for their mentorship and continuous teaching and support during these 4 years and a half of PhD. I thank them for allowing me to have access to the EU-GEI data set that has made this PhD possible. I was not part of the recruitment and data collection of such a unique data set, therefore being able to produce scientific material stemming from it is an extremely generous opportunity and I wanted to express my warmest gratitude for that. In the same line, I also wanted to thank all the collaborators from the EU-GEI project, Work package 2, who have contributed to the preparation and curation of the data set used for Study 5. I also wanted to thank Philippe Conus for granting me access to the TIPP data set, which is part of Study 3.

I would like to thank Victoria Rodriguez, Giulia Trotta and Monica Aas for their help in the various studies that constitute this thesis, for their friendship and support. I want to thank to Marta Di Forti for having been extremely supportive not only as a research collaborator, but also as a clinical colleague, helping me to adapt to the clinical setting in LEO, where I have been working part-time since I started, which in this context has been a great inspiration for the work and questions presented in this thesis. I thank Oliver Howes for allowing me to work in TREAT, also an inspirational clinical setting where some of the points presented in the discussion have come to fruition.

By the time when this thesis was finally printed in August 2023, it had been awarded the 2022 Outstanding King's Prize and the Psychosis studies PhD of the year 2022. This is a recognition far beyond what I expected so I can only thank everybody involved who made it possible in any way.

PREFACE

PERSONAL CONTRIBUTION

I wrote the entirety of this thesis, and the 5 articles are published and have undergone peer review. I circulated each chapter draft to co-authors, and then underwent peer review prior to acceptance for publication.

Chapter 3.3 is a collaboration with the Lausanne University Hospital TIPP group (led by Prof Philippe Conus), who have allowed me to conduct an empirical study based on findings from Chapters 3.1 and 3.2. Chapter 4.2 is based on the data from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study at the Institute of Psychiatry, Psychology and Neuroscience (King's College London). University of Exeter's group led by Prof Jonathan Mill has been responsible for the epigenetic data creation, while the epigenetic data cleaning, processing and quality control procedures of DNA methylation was prepared by Dr Chloe's team at the Social, Genetic & Developmental Psychiatry (Institute of Psychiatry, Psychology and Neuroscience (King's College London). I contributed to the recruitment, assessment and collecting of follow-up data from the baseline EU-GEI study, conducted locally in London as one of the 17 places. However, this data was finally not included in the current PhD. Except for chapters 4.2 and 3.3 which are based on previously collected data set, the rest of the thesis has relied on hypotheses being tested in the available literature through evidence synthesis led by myself.

ORGANISATION OF THE THESIS

This thesis is a "thesis incorporating publications" and is composed by 5 chapters which constituted 5 different studies.

Chapter 3.1 (study 1) is composed of the following journal article which is reproduced in full:

Association Between Specific Childhood Adversities and Symptom Dimensions in People With Psychosis: Systematic Review and Meta-Analysis

Luis Alameda, Angeline Christy, Victoria Rodriguez, Gonzalo Salazar de Pablo, Madeleine Thrush, Yi Shen, Beatriz Alameda, Edoardo Spinazzola, Eduardo Iacoponi, Giulia Trotta, Ewan Carr, Miguel Ruiz Veguilla, Monica Aas, Craig Morgan, and Robin M Murray

Schizophrenia Bulletin doi:10.1093/schbul/sbaa199

Chapter 3.2 (study 2) is composed of the following journal article which is reproduced in full:

A systematic review on mediators between adversity and psychosis: potential targets for treatment

Luis Alameda, Victoria Rodriguez, Ewan Carr, Monica Aas, Giulia Trotta, Paolo Marino, Natasha Vorontsova, Andrés Herane-Vives, Romayne Gadelrab, Edoardo Spinazzola, Marta Di Forti, Craig Morgan and Robin M Murray

Psychological Medicine 1–11. https://doi.org/10.1017/S0033291720002421

Chapter 3.3 (study 3), based on the Tipp data set, is the collaboration with Lausanne University Hospital, is composed of the following journal article which is reproduced in full:

Evidence of mediation of severity of anxiety and depressive symptoms between abuse and positive symptoms of psychosis

Luis Alameda, Philippe Conus, Julie Ramain, Alessandra Solida, Philippe Golay J Psychiatr Res 2021 Nov 22 ;S0022-3956(21)00676 2. Doi:10.1016/j.jpsychires.2021.11.027.

Chapter 4 (study 4) is composed of the following journal article which is reproduced in full:

Can Epigenetics shine a light on the biological pathways underlying major mental disorders?

Luis Alameda, Giulia Trotta, Harriet Quigley, Victoria Rodriguez, Romayne Gadelrab, Daniella Dwir, Emma Dempster, Chloe C. Y. Wong, Marta Di Forti

Psychological Medicine. 2022 Jul;52(9):1645-1665. doi: 10.1017/S0033291721005559.

Chapter 5 (study 5), based on the EUGEI data set, is composed of the following journal article which is reproduced in full:

Exploring the mediation of DNA methylation across the epigenome between childhood adversity and First Episode of Psychosis – findings from the EU-GEI study

Luis Alameda, Zhonghua Liu, Pak C Sham, Monica Aas, Giulia Trotta, Victoria Rodriguez (EUGEI WP2 group), Marta Di Forti, Craig Morgan, Emma Dempster, Eilis Hannon, Joe Burrage, Jonathan; Daniella Dwir, Atheeshaan Arumuham, Jonathan Mill, Professor, Robin M. Murray, Chloe C. Y. Wong.

Molecular Psychiatry. 2023 Apr 17. doi: 10.1038/s41380-023-02044-9.

GENERAL ABSTRACT

Although it is broadly accepted that people exposed to childhood adversity such as abuse and neglect are at a greater risk to develop psychotic disorders, little is known about potential psychopathological mediating mechanisms in this association. Epigenetics, particularly DNA methylation (DNAm), has appeared in the last 15 years as an important factor potentially mediating the gene and environmental interplay in the risk of psychosis and schizophrenia. The fact that DNAm is sensitive to the environment, and that on the other hand, DNAm changes are associated to a broad range of psychiatric conditions based on case-control studies, including psychosis, makes DNAm a potential mediator that can shine a light on the understanding of the biological mechanisms linking childhood adversity and psychosis.

The overall objective of my PhD is to better understand the nature of the association between childhood adversity and the psychopathological profile in first episode of psychosis (FEP), and to investigate possible mediating mechanisms at a psychopathological and at epigenetic (DNAm) level. This will be addressed through the following 5 chapters: one meta-analysis, one systematic review, one narrative review, and 2 experimental studies. One of them is based on a collaboration with Lausanne University Hospital and is based on a sample of 330 people with early psychosis, part of the TIPP (Treatment and Early Intervention in Psychosis) program. The second empirical study, which is related to DNAm data, is based on EU-GEI study (EUropean Network of national schizophrenia networks studying Gene-Environment Interactions); a multisite incidence and case-control study of genetic and environmental determinants involved in the development of psychotic disorders, which sample with epigenetic data used in this study includes 366 cases and 517 controls.

Our results show that: (i) there is a differential association between childhood abuse and neglect in the psychopathological profile of people with psychosis, abuse being specifi-

cally related to positive symptoms of psychosis, while neglect to negative symptoms of psychosis; (ii) various mediators seem to operate in the abuse and positive symptoms or psychosis association, such as dissociation and other PTSD symptoms, negative schemas about the self the world and others, and high levels of depression and anxiety. Our TIPP empirical study shows that the severity of depression and anxiety not only mediates the association between abuse and psychosis onset but also to the severity of symptoms in the long term, therefore being a potential mechanism contributing to treatment resistance psychosis. In terms of epigenetic mechanisms, DNAm changes in genes involved in neuroinflammation, neurodevelopmental processes such as myelinisation, formation of oligodendrocytes and extracellular matrix; or involved in neural signaling, the mitochondrial dysfunction and histaminergic pathways, appear to mediate part of the association between adversity and psychosis. The lack of overlap between mediating genes and pathways according to abuse and neglect is in line with our meta-analysis showing a differential effect of these adversities in the psychopathological dimensions of patients; suggesting a differential biological trajectory between childhood adversity and psychosis depending on the type of adversity.

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LIST OF EMPLOYED ACRONYMS

BDNF	Brain derived neurotrophic factor
CT	Childhood trauma
G&EI	Gene & Environment Interaction/interplay
GWAS	Genome-wide association studies
HPA Axis	Hypothalamus Pituitary Adrenal Axis
PRS	Polygenic Risk Score
SCZ	Psychotic Disorders and Schizophrenia
SNP	Single Nucleotide Polymorphisms
TIPP	Treatment and Early Intervention in Psychosis Program
WHO	World Health Organization
BD	Bipolar Disorder
PD	Psychotic depression
FEP	First episode psychosis
EU-GEI	European network of National Schizophrenia networks Studying gene-
	environment interactions
TRS	Treatment resistant psychosis/Schizophrenia
UTR	Ultra-treatment resistance
ECT	Electroconvulsive therapy

CHAPTER 1
General Introduction

1.1 Summary

1.2 Childhood trauma, definition

Childhood trauma is a construct that can be defined as the subjective experience of an event by a child or adolescent that is emotionally distressful and that can result in lasting mental and physical effects(1). Generally, when we talk about childhood trauma in the context of mental health, we refer to the exposure to experiences that would be associated with a subjective severe negative impact. These include mainly interpersonal types of events such as abuse, neglect, bullying, some forms of separation and other experiences involving hostility, such as parental discord or witnessing violence or serious natural disaster involving threat and death. While some of these negative experiences may have a negative effect on mental health for some people, some individuals may not suffer from such sequalae. Overlapping, with the category of childhood trauma, there are broader concepts such as childhood adversities, or stressful life events. These are experiences that can have a negative and lasting effect on people's mental health, but which would not necessarily be "undoubtedly traumatic" for anyone who experiences them. These can include losing a loved one, relationship breakdowns, witnessing a family member's physical disease, or losing a job, to name a few. That distinction being made, and although these two concepts are sometimes used interchangeably, for the purpose of this thesis I will limit it to the definition of childhood adversity, being the most commonly used concept in the field of psychosis, and I will be referring to experiences of abuse and neglect in their moderate and severe forms.

Sexual abuse refers to sexual molestation and/or rape. Physical abuse generally refers to physical attack or assault, or being repetitively beaten by parents, relatives, or caregivers. Emotional abuse is defined as verbal assaults on a child's sense of worth or well-being or any humiliating or demeaning behaviour directed toward a child by an adult or older person. Physical neglect is defined as the failure of caretakers to provide for a child's basic physical needs, including food, shelter, clothing, safety, and health care. Emotional neglect is defined as the failure of caretakers to meet children's basic emotional and psychological needs, including love, belonging, nurturance, and support. By bullying, we understand being emo-

tionally or physically abused by peers of the same age, and by household discord we understand children experiencing severe arguments and conflict at home by their parents (45).

Exposure to these experiences is common in the general population: a World Health Organization (WHO) survey conducted on 51,945 adults (aged 18 and older) coming from 21 different countries from various socio-economic backgrounds found that physical abuse occurred in 8% of the sample; sexual abuse in 1.6% and neglect was present in 4.4% of the sample, with the prevalence of most of the experiences being relatively similar across socio-economic status. The study also looked at how many participants had been exposed to any form of adversity (here also including other events such as divorce etc) and about 38.8% had faced at least one(2). This study, and others(3), show that childhood adversity is relatively common in the general public worldwide, and thus its impact is not only limited to people with mental health problems, but to society as a whole. Childhood adversity is associated with a broad range of negative behavioural outcomes that are not strictly linked with mental health problems, such as higher rates of delinquency(4), risk taking behaviour(5) or poorer capacity to achieve expected educational outcomes(6). This indirectly impacts on occupational impairment, welfare dependency, and financial instability, contributing to a vast burden for the entire society(5). In terms of social costs, the estimates are difficult to calculate accurately, but studies have suggested an impact of child abuse and neglect on societal costs at USD 103.8 billion per year un USA, 10.7 billion in Australia, or CAD 15.7 billion in Canada(7).

In this work I will be examining childhood adversity in its link with psychosis, in an attempt to explore possible mediating mechanisms. However, it is important to mention that this is just a small part of a much more complex problem. To limit the harmful effects of childhood adversity, interventions and research should not stop at the level of specific disorders but should include a significant change in society, involving a better awareness, global education, preventive measures, and a better legislative system that is adapted and efficient in order, not only to help people exposed to such experiences, but that is able to prevent such events. That said, I will now discuss why childhood adversity is important in people with severe mental health problems, particularly Psychotic Disorders and Schizophrenia (SCZ).

1.3 Psychotic disorders and schizophrenia

SCZ is a mental illness listed among the 10 leading causes of disability worldwide(8). SCZ is characterised by a disintegration of thought, distorted emotional responses and perceptual alteration that alter the behaviour of individuals and their social functioning. SCZ usually begins in late adolescence or young adulthood and symptoms often persist or fluctuate throughout a lifetime. Current treatments help to relieve some positive symptoms such as cardinal hallucinations or delusions, but patients have to cope with many negative symptoms or cognitive impairments for the rest of their lives(9). This chronicity is responsible for an important lifetime prevalence (4 per 1,000 persons)(10) despite a relatively low incidence of the disorder, with a recent study reporting a crude incidence,

21.4 per 100 000 person-years (95% CI, 19.4-23.4 per 100 000 person-years) (11, 12). Moreover, SCZ is associated with substantial morbidity and mortality as well as personal and societal costs(10, 13).

"Psychosis" or "Psychotic disorders" is often referred to a broader category of clinical phenotypes that not only include SCZ, but also less clear clinical entities such as non-specified psychotic disorders, and also the so-called "Affective psychoses (AP)", which include Psychotic Depression (PD) and Bipolar Disorders (BD) with psychotic features. For example, in an Early Intervention Service where including the majority of patients that present a First Episode of Psychosis (FEP) (people that present a full blown psychosis for the first time) in the catchment area of Lausanne, in Switzerland, only around 60% have a diagnosis of Schizophrenia three years after the onset(14). In a multicentric study including 16 European cities called European Network of National Schizophrenia Networks studying Gene Environment Interaction (EU-GEI), only 38% had a diagnosis of Schizophrenia, (15). Data can vary across countries and settings, but it shows that SCZ is just a subgroup of those with psychotic disorders that could be considered to be at the severe end of the spectrum of the psychosis continuum.

There is ongoing debate on whether we should leave behind these diagnostic categories and just focus on psychosis on a continuum scale. On these lines, psychosis is often seen as a dimension, rather than a category, which co-occurs among many others (such as the depressive, manic, anxious, disorganized and those involving the negative symptoms – eg avolition, anhedonia, social withdrawal...). Figure 1 illustrates the idea of the various symptom dimensions of psychosis(16).

Figure 1

The psychopathological dimensions

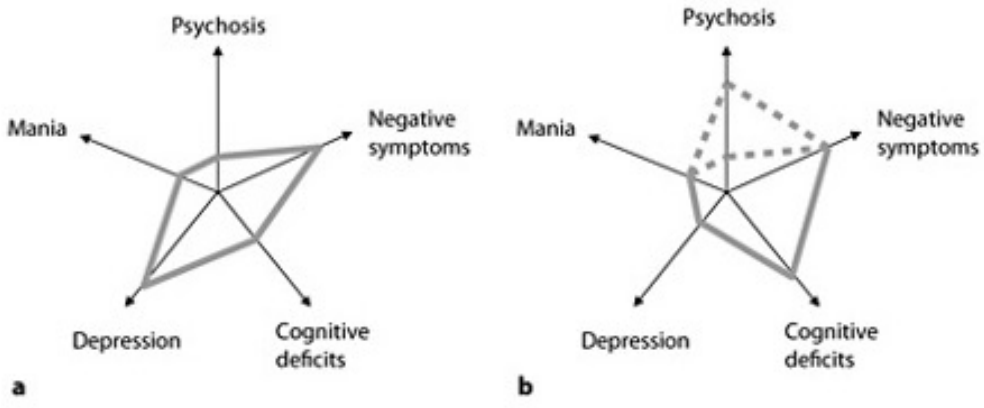


Figure 1 illustrates the main 5 dimensions that can be considered for those with a psychotic disorder (imaged copied from 16, 17). The depressive, mania, cognitive, psychosis (including auditory hallucination and perceptual abnormalities) and the negative which includes items related to diminished expression (blunted affect and alogia), and to apathy (associability, avolition and anhedonia). Other dimensions such as anxiety or disorganized can be considered and multiple configurations exist. This is a simple representation on how in a given patient (A) a predominance and severity of some of the dimensions can be present, as opposed to a given patient B with a different dimensional profile.

Defenders of the use of a dimensional approach argue, among other things, that diagnostic categories are unstable and more stigmatising, and that the use of dimension may be more representative of psychopathological specificities and is better to define targets for treatment(18). Taking a position in this debate is far from being the focus of the current work, but it is worth clarifying that I will focus on Psychotic Disorders, as a broader and more open nosologically entity, rather than on SCZ, the main reason being that the samples used for the studies included in this work have not restricted their population to patients with Schizophrenia alone, but to psychotic disorders as a whole. Moreover, I will conceptually, within the category of Psychotic Disorders, consider the dimensional conceptualisation, thus taking into account the continuous nature of various symptom domains, particularly for Project 1.

1.3.1 The lack of effective treatments for patients with psychotic disorders

A major challenge that psychiatrists face when treating people with psychosis is that, despite a good range of treatment options, some patients remain symptomatic and/or present serious difficulties to function throughout their lives. Treatment resistant schizophrenia (TRS) affects 20-30% of patients with psychiatric disorders; and is associated with increased healthcare burden and costs up to ten-fold higher relative to patients in general(19).

Pharmacological treatments available to date mainly target the dopaminergic circuits, which considerably helps with a reduction of positive symptoms of psychosis (auditory hallucinations, delusions, and also disorganization)(20). Some forms of psychotherapies also help with such symptoms in combination with pharmacology(21), and there is a range of psychosocial interventions that are usually implemented in parallel with such methods, that have shown to help patients to go back to work and improve their social abilities, thus promoting recovery(22). However, a subset of patients remains symptomatic and/or with poor functioning and thus there is an important need to understand the mechanisms operating in these patients. An important conceptualisation in this regard is that of TRS. Definitions vary, but that from the South London and Maudsley NHS TRUST defines it as when a patient continues presenting high severity of symptoms of psychosis after 2 antipsychotics have been trialled, for 2 or 3 weeks at least if it is during the First Episode of Psychosis (FEP), or for 6 weeks for subsequent trials(19). It is then suggested that the psychotic symptoms of those with TRS may involve other biological pathways than the Dopaminergic and the Serotoninergic circuits, which are the ones targeted by all of the antipsychotics currently used. Importantly, there are other patients with Psychotic Disorders that are not TRS and remain symptomatic because they have not adherence to treatment, have ongoing drug use which counters the beneficial effects of antipsychotics (also called "pseudo resistants"(19)), or because they are wrongly diagnosed with SCZ.

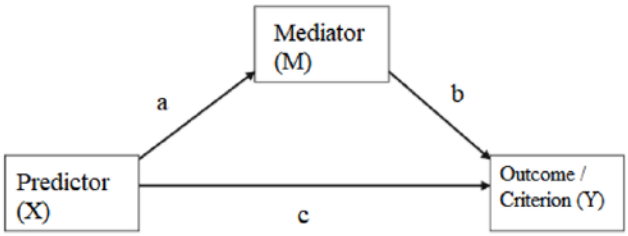
A better understanding of the mechanisms driving to disease, and to TRS, but also to persistence of symptoms in those with Psychotic Disorders as a whole (not only with Schizophrenia) is needed and may help in providing new biological and psychological treatment

targets, and further help this vulnerable population.

1.3.2 How to investigate mechanism of disease? The role of environmental risk factors in the aetiopathogenesis of psychosis

The idea that psychotic disorders are in part caused by exposure to various environmental risk factors (ERF) has received broad empirical support in the last twenty years. These ERF may interplay with genetic vulnerability, including epigenetic changes in the development of disease(23). An enormous effort has been put into detecting which are these ERFs, and to what extent they account for the variance explained for Psychotic Disorders and SCZ(24). This set of epidemiological research studies is extremely important because if we understand the nature (specificity, magnitude, dose-response effect, and temporality) of this association, we can (i) on the one hand address specific preventive strategies that prevent the exposure itself (stopping those vulnerable individuals from facing such risk factors), but also (ii) examine mediating mechanisms. By mediating mechanisms, we understand identifying factors that are operating as mediator between the ERF and the outcome, which in this case is Psychosis, or a specific domain of Psychotic Disorders (for example the hallucinations) (see Figure 2).

Figure 2
The concept of mediation



A mediator variable explains the how or why of an (observed) relationship between an independent variable (eg ERF) and its dependent variable (eg Psychotic Disorder versus controls). In a mediation model, the independent variable cannot influence the dependent variable directly, and instead does so by means of a third variable, a "mediator".

In this line, multiple ERFs are considered to be associated with Psychotic Disorders, including SCZ(24) and non-affective Psychosis (AP: Bipolar Disorder and Psychotic depression(25)). The evidence in this regard can be illustrated in Figure 3. There are a number of well-replicated risk factors for SCZ include older paternal age at birth, obstetric complications, urbanicity, childhood adversity, cannabis use, ethnic minority status, and stressful life events (REF). In addition, there is evidence from systematic reviews and meta-analyses for an increased risk of psychosis after either maternal or childhood infection, as well as following a traumatic brain injury(24, 25). Most of these ERF overlap in those with AP.

Figure 3

Environmental risk factors across the lifespan in affective and non affective psychosis

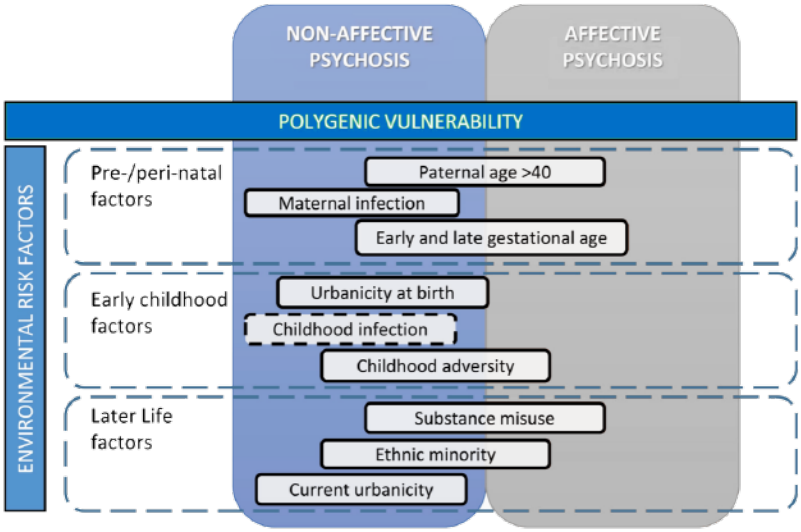


Image copied from (25) showing the different association between environmental risk factors across the Non affective psychosis and affective psychosis across various periods.

Among those ERF that are well replicated and commonly studied is childhood adversity, which will be the focus of this work and offers an important opportunity to investigate the mechanisms of disease and propose potential targets for treatment.

1.4 Links between childhood adversity and psychosis

Psychiatry has long been interested in understanding how exposure to early traumatic life experiences can impact the mental state of patients. Freud already spoke of it with the "traumatic neurosis", interpreting early traumas as the origin of neurotic disorders. Later, he conceptualized (as did subsequent authors such as Benedetti, Bion or Ferenczi) theories in an attempt to explain how trauma can also play a role in psychosis(26).

Thanks to advances over the last decades, these initial hypotheses have been confirmed from a scientific point of view by a significant number of studies, showing that different forms of difficult and stressful experiences taking place during childhood and adolescence are associated with an increased risk of developing a psychotic disorder(27). One of the most widely accepted theories is the so called "Neurodevelopmental model of psychosis", first coined by Prof. Robin Murray during the 80s(28), and which postulates that individuals with a genetic vulnerability, when they are exposed to environmental difficulties early in their development, including social adversity, but also obstetric events or, later on, cannabis use, will present alterations in brain development that will make them prone to presenting, at first prodromal symptoms of psychosis and, later, a full blown psychosis in late adolescent and adulthood (Figure 4). These symptoms may be preceded by some subtle motor and cognitive abnormalities early in childhood, low levels of anxiety and depressive symptoms in teenage years, and subsequently the prodromal that predate the full-blown psychotic episode.

Figure 4

The trajectory to SCZ showing the evolution of symptoms and the main risk factors

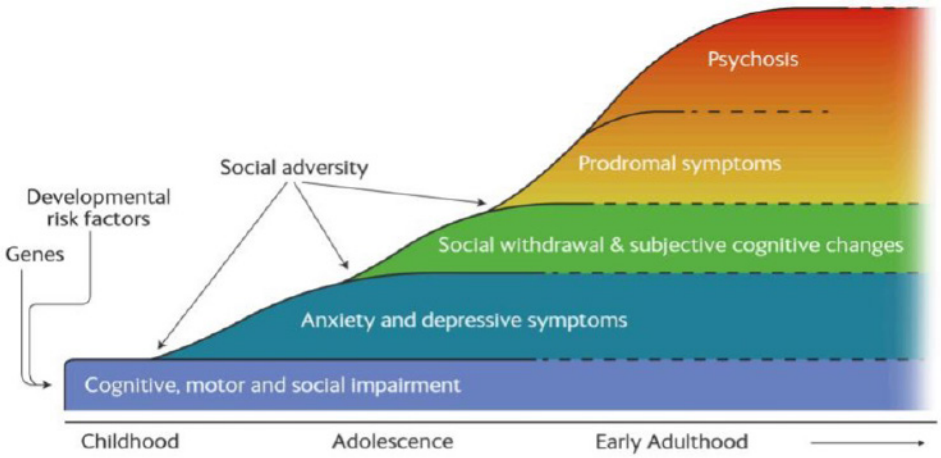


Image copied from (28)

Since 2000, there has been an increasing number of publications supporting the association between early traumatic experiences and psychotic disorders with well replicated evidence. A meta-analysis examining this link in 18 case-control studies, 10 prospective and quasi-prospective studies and 8 population-based cross-sectional studies showed an overall effect of 2.78 (95% CI 5 2.34–3.31). Furthermore, there has been abundant literature showing that childhood trauma is not only associated with greater risk of psychosis but also that, among the patients, those with trauma have poorer recovery rates, poorer functioning(29) and more cognitive deficits(30), more substance use (mainly cannabis(31)), or suicide risk(32). This shows that the impact of childhood adversity does not stop at the level of psychosis onset but is also in many other outcomes that patients suffer from.

In terms of the links between childhood adversity and specific symptom domains, such as the positive and negative dimension of psychosis, as well as the disorganised, the manic and the depressive, research is less abundant. Only one meta-analysis, which search is dated in 2014, has investigated the specific and broad (using a broad measure of adversity, such as being exposed to at least one trauma, or using a composite continuous measure of cumulative exposure to various traumas) association between specific traumas, such as sexual (physical, sexual and emotional) and neglect (physical and emotional), and the positive and negative dimension of psychosis. Authors found that, whilst abuse may affect both dimensions, supporting the presence of general effects, neglect was only associated with the negative symptoms, supporting some evidence of specific effects(33). No meta-analysis has been conducted exploring the depressive, manic and disorganized dimension; thus, it is unclear how childhood adversity affects those domains. This lack of understanding on these links between childhood adversity and symptoms domain is relevant as it can help us to define the profile of patients exposed to specific adversities, thus adapting treatments accordingly, and also could help us to further identify possible mediating mechanisms (biological and psychological). As mentioned before, investigating

mediating pathways between a risk factor and an outcome is not possible if we have not fully understood the nature of the association first. Therefore, there is a need to understand the nature of the association between specific childhood adversities and each of the dimensions in those with psychosis, in order to further move on to the understanding of the potential mechanism. This will be the focus of project 3.1.

1.4.1 Mediating biological and psychological mechanisms linking childhood trauma and psychosis.

Over the course of the last 10 or 15 years, research has moved beyond the understanding of the trauma/adversity-psychosis association, to try to investigate possible mediating mechanism.

From a psychological perspective, research has been conducted examining (i) possible psychopathological mediators such as mood related symptoms(34), dissociation and other PTSD related symptoms(35); and (ii) inspired by the cognitive models of psychosis(36), cognitive processes such as negative schemas about the self, the world and others have been extensively studied(37), as well as other conceptualisation such as attachment theories, developed by Bowlby (38), which also offers a plausible explanation on why a disrupted bond with early parental figures can also affect psychosis (39). This abundant piece of work (details on different theories can be found in project 3.2 and project 3.3) is of great relevance, as psychological processes can be targeted through psychological interventions, thus representing potential useful targets for treatment(40).

In parallel, there have been a great number of publications trying to identify "biomarkers" of disease. A biomarker is a biological parameter that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes or biological responses to a therapeutic intervention(41). Some biomarkers have been studied in relation to childhood adversity in psychosis, mainly correlating the biomarker with levels of adversity in patients with psychosis as compared to controls; or analysing whether the studied biological process is more dysregulated in the patients who have been exposed to childhood adversity, against in those without. This type of research has led to the hypothesis that a set of biological processes may be operating on the adversity-psychosis link. Importantly, this research has the caveat that, despite the vast number of studies exploring pathways as mentioned above, findings studies which formally test mediation (using mediation analyses on such biomarkers on the link between trauma and psychosis or specific symptoms) are less common, and no systematic review or meta-analyses has ever synthesized this type of evidence (see project 1.2 for a systematic review on this area).

A few of the most relevant (some of them interconnected) biological pathways that are hypothesized to link trauma and psychosis are; (i) a sensitisation of the Hypothalamus Pituitary Adrenal Axis (HPA axis), particularly a dysregulation of the glucocorticoid system, which alter the normal development of the hippocampus; (ii) a related small hippocampus volume in those exposed to childhood trauma which has been found in brains of partici-

pants from the general population(42) and in those with psychotic disorders(43), and is a neuroanatomical region that has consistently been found to be smaller in those with psychotic disorders as compared to controls; (iii) a reduction of Brain derived neurotrophic factor (BDNF), which is responsible for neurogenetic processes, has been found to be affected in those with trauma and psychosis(44); (iv) an excess of dopamine in the striatum (mainly associative) as a consequence of stress, as shown in animal models(45), could be also operating between trauma and psychosis, although the evidence of mediation has yet to be proved(46); (v) other pathways such as the role of excessive oxidative stress, led by traumatic experiences and being dysregulated in those with psychotic disorders has also been suggested(47); and (vi) the possible implication of excessive inflammation, given its dual link with social stress(48) and being altered in those with psychosis(49). Evidence on biological pathways and to what extent the role of these biomarkers mediate (and not simply correlated with both trauma and psychosis) is yet to be reviewed systematically and has been the focus of project 3.2 where more details on this area are discussed.

Another emerging potential mechanism that has been suggested to be both related to childhood adversity and psychosis, is epigenetics, particularly DNA methylation (DNAm). This will be discussed in detail in section 1.5 and evidence on the role of this process on the adversity-psychosis association will be discussed in detail in chapter 4.

1.4.2 The Gene & Environment interplay

Another important consideration on the understanding on how childhood adversity may exert its influence on psychosis aetiopathogenesis is by taking into account its relationship with genes. This comes from the observation that, despite the known increased risk of psychosis in those exposed to childhood adversity(27), and the genetic correlation in monozygotic twins, estimated at (41-65%) in SCZ(50), we still do not know why some people with the genetic risk go on to develop psychosis and others do not; and, the other way around, we are not yet able to detect who among those with trauma are going to later develop psychosis.

This "Gene & Environment Interaction/interplay (G&EI)" model postulates that the effect of an individual's genotype depends on environmental exposure and that, conversely, the effect of environmental exposure on disease risk depends on an individual's genotype. This approach differs from the linear gene-phenotype approach by considering disease causation in the synergistic co-participation instead of either genes or environment acting in isolation(23, 51).

Initial studies investigating interactions between exposure to childhood adversity and underlying genetic susceptibility in SCZ focused mainly on candidate genes (exploring specific alleles variants - otherwise called Single Nucleotide Polymorphisms: SNPs), such as AKT1, COMT, BDNF; findings have been inconclusive and difficult to replicate (52-54). It has been suggested that studying single candidate genes may miss important aspects of the etiology of psychoses, as psychotic disorders are polygenic in nature (55, 56), and because

the effect of one single gene is not sufficient to produce the massive and heterogeneous variations normally present in those with SCZ. In this regard, the concept of polygenetic liability, which can be measured with a polygenic risk score (PRS), has emerged and has become a very common tool to investigate the G&EI.

PRSs are calculated by using subsets of Single Nucleotide Polymorphisms (SNPs) from genome-wide association studies (GWAS). PRS are selected according to their p value and weighted by their effect size to calculate a PRS for each individual in an independent validation sample. The PRS can then be tested for its ability to differentiate between cases and controls in the validation dataset (57-59). The PRS explains around 7% of the variation in the liability for SCZ assuming a lifetime risk of 1% (59, 60). The development of PRS techniques has opened a new avenue for studying overall genetic susceptibility. Such a PRS can, in turn, be used to study interaction effects with environmental risk factors.

A recent study of those with a long-standing diagnosis of SCZ provided some evidence of synergistic effects; that is, the combined effect of polygenic risk and childhood trauma was greater than the sum of their individual effects (61). In FEP, one pilot study (N< 200) investigated interaction between childhood trauma and SZ-PRS (62), concluding that higher PRS-SZ and childhood traumas each predicted a case status independent of each other with no strong evidence of interactions. The latest study to date, from our group, on 397 FEP patients and 702 controls from the case-control component of EU-GEI study, suggested possible synergistic effects of genetic liability and childhood trauma experiences in the onset of first-episode psychosis(63). However, larger samples are needed to produce definitive results.

Beyond the interplay between polygenetic liability and childhood adversity exposure, it has been suggested that other biological processes may be also operating in the equation. In this regard the role of epigenetics has emerged as a very important biological process that may be mediating the links between genes and environment on the risk of mental conditions, including psychosis.(64)

1.5 Epigenetics and its role in the gene & environment interplay

In this section, I will describe the main principles of epigenetics. I will then discuss its potential role in the G&EI in mental conditions, suggesting potential venues to be explored in psychotic disorders.

1.5.1 Epigenetics processes

Epigenetics is the reversible regulation of gene expression mediated principally through changes in DNA methylation and chromatin structure, occurring independently of the DNA sequence(65). In other words, by using the Greek meaning of "epic", it can be seen as what is on the top of genes, being able to turn them on or off, independently of the genomic sequence.

The DNA sequence determines the specific mRNA molecules that are made or expressed, but it is the epigenetic regulation of gene expression which determines how much, or when and where, that mRNA is made. The importance that this has for disease is that even genes that do not carry any form of disease-causing mutation or risk variants within them (SNPs), can still be pathogenic if they are expressed at the wrong time, in the wrong amount or the wrong place (65).

A good explanation for the understanding of the complex role of the epigenetic modifications in cell differentiation is the one developed by British biologist Conrad Waddington in 1942, with the idea of Epigenetic landscape(66) (Figure 5).

Figure 5

The epigenetic landscape according to Conrad H. Waddington

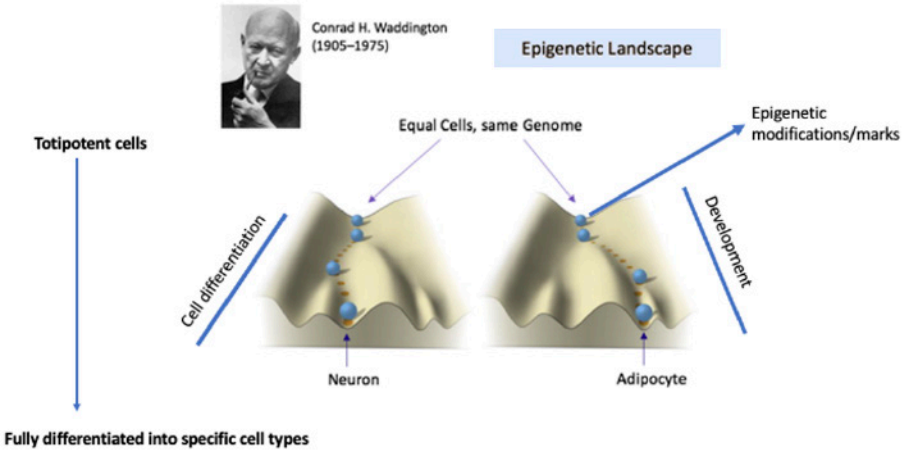


Image adapted from (66). The epigenetic landscape is a concept that was proposed by Conrad Hal Waddington to illustrate the various developmental pathways a cell might take toward differentiation. Waddington envisioned the epigenetic landscape as a series of ridges and valleys a cell can traverse on its way to a final tissue type, coming from a state where they are totipotent to that point where they can fully differentiated.

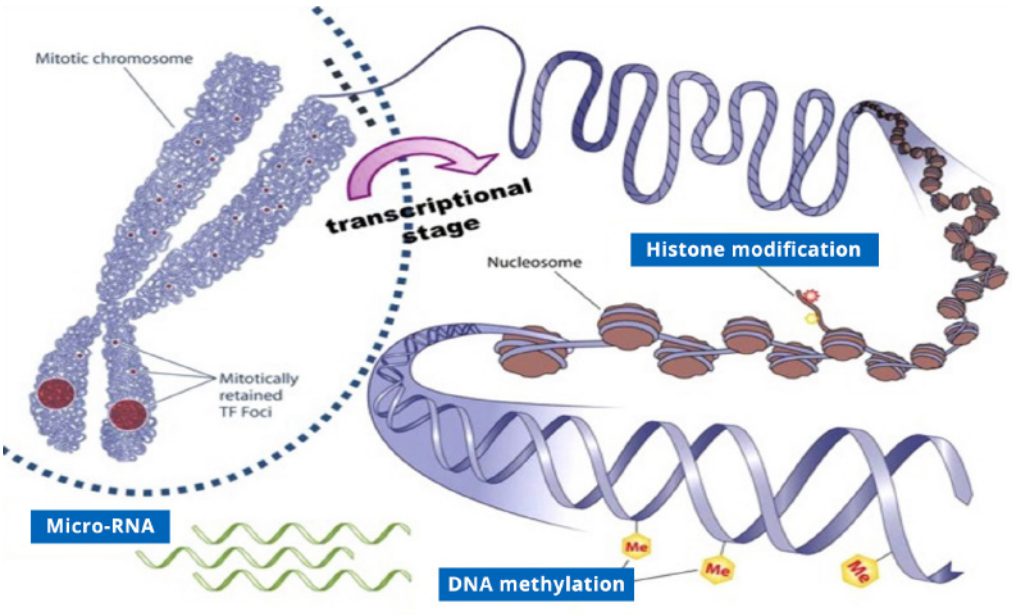
Waddington suggested that, at some point during the development of a cell, there will be key decisional moments (or 'marks", represented by blue spheres along the valleys in the above figure) in the developmental trajectories of cell differentiation. These marks can be seen as "epigenetic marks" that are going to decide when, where, and how much of the DNA is going to be expressed, therefore being determinant in the differentiation into the specific phenotype. This is a normal process that allow us to have multiple different cells in our body, despite having the same genomic sequence.

1.5.2 Epigenetic marks

Epigenetic marks have important consequences on how genes are expressed and how the chromatin is packaged, thus modifying subsequent protein translation within regionally specific parts of the central nervous system(67). The most studied epigenetic marks are DNA methylation (DNAm) and histone tail modifications, but there are also others processes such as the role of micro-RNA and non-coding RNA (Figure 5).

Figure 6

The most important epigenetic marks in mental health disorders



1.5.2.1 DNA-Methylation and hydroxymethylation

DNAm is the covalent addition of a methyl group to the 5th carbon of a Cytosine (C) base, resulting in 5-methylcytosine (5-mC) base. We know that, in mammals, DNAm occurs almost exclusively at Cytosines that are followed by a Guanine (G) base which are bonded by a phosphate forming a CpG dinucleotides. These CpG dinucleotides are often found in the so called "CpG islands", regions often located in promoters of genes where there is normally an accumulation of CG dinucleotides. Methyl groups are added to Cytosine residues

by DNA methyltransferase (DNMT) enzymes, which recognise demethylated CpG strands during cell division and restore fully methylated CpG dinucleotide, which almost always results in silencing of gene expression. A related novel epigenetic mark, hydroxymethylation occurs when a 5mC is oxidized and is converted to 5-hydroxymethylcytosine (5hmC), a process mediated by Ten-eleven translocation (TET) enzymes, and is a process that is considered a key step in the reversibility of the methylation. As it will be presented in Project 2.1, a vast amount of evidence has been collected in humans trying to understand the links between DNAm changes in psychiatric conditions. This process will regulate transcription by blocking the binding of some transcription factors that bind to the DNA and drive gene expression, and also attract proteins onto the structural conformation of the DNA also regulating transcriptional processes.(68)

1.5.2.2 Histone modifications and other epigenetic processes

Another important epigenetic mark is the post-translational modification of histone proteins. These constitute the proteins around which the DNA chromosome is wrapped. Histones are present as an octamer and can be modified through processes such as acetylation, methylation, phosphorylation, ubiquitination, sumoylation, among others(69). These tags tend to occur in the N-terminal tails of different histone types (which are called H1, H3, H2A, H2B...), that protrude from the nucleosome, becoming accessible to other proteins that can be recruited. Depending on which histone they are affecting, these modifications can either silence or promote gene expression, as well as replicate, repair or condensate the chromatin. We know the possible changes mediated by the histones modifications as the "Histone code", and growing evidence supports its role in brain development (70).

The third epigenetic category involves miRNAs, which are single-stranded non-coding RNAs that engage in posttranscriptional repression or mRNA destabilization of many targeted genes(71). Non-coding RNAs are epigenetic modulators that may also be targets of epigenetic modification(72), and they remain under-studied in psychiatric populations, and thus will not be the focus of this work.

1.5.2 DNA methylation in mental disorders.

1.5.2.1 From candidate genes studies to EWAS

Research examining these epigenetic marks (especially DNAm and, to a lesser extent, histone modifications) in psychiatry has evolved across different methodological designs. Initially, studies used a "candidate gene" approach exploring methylation on certain genes of interests based on a priori hypothesis and examining whether DNA-meth changes in different CpG sites within specific genes were related to a particular phenotype. Progressively, research moved to Epigenome Wide Association studies (EWAS), that consist of examining the association of DNAm changes across the entire genome for a particular phenotype, using a hypothesis-free paradigm. While both designs have their advantages and limitations, EWAS might offer a more informative insight on biological pathways(73). This is based on the rationale that chromatin conformation and transcriptional regulation seem

to be more influenced by sets of methylated or unmethylated cytosines across a region, rather than specific CpG sites in isolation. EWAS allow identifying differentially methylated positions (DMP), but also differentially methylated regions (DMRs), which are genomic regions at which multiple adjacent CpG sites show differential DNA methylation patterns(74). EWAS have been performed with increasingly powerful techniques and have moved from pioneer CpG-island microarrays studies that interrogated around 12.000 sites across the DNA(73) to more advanced techniques such as the Illumina's Infinium HumanMethylation450 BeadChip (HM450K), with more than 450,000 methylation sites, or the later Infinium MethylationEPIC BeadChip, that covers more than 850 K CpG methylation sites(75).

1.5.2.2 The links between social stress and DNAm from animal models to humans

There is consistent evidence from animal models to humans showing that the epigenome is sensitive to social stress(76), among other environmental factors such as diet(77), pollution(78) or cannabis use(79), to cite a few of them.

With regards to social or psychological stress, a pioneer study showing its influence on the epigenome is the one by Weaver et al.,(80), who showed that offspring of mothers who showed appropriate maternal care were found to have differences in DNAm (specifically at the level of the glucocorticoid receptor gene), as compared to offspring of mothers providing poor maternal care. These findings were extended during the later years and translated to humans, where also changes in the glucocorticoid receptor gene, and many other genes (see review in chapter 2.1) have been shown to be sensitive to the impact of childhood adversity(81). A vast amount of research has been conducted, exploring different candidate genes studies, where the influence of childhood trauma on CpG sites located in such genes has been investigated (82, 83). Furthermore, emerging research at EWAS level has explored, with a hypothesis free approach, the epigenetic signature of childhood adversity (82, 83) (for an extensive review on this area please refer to project 4.1).

1.5.2.3. The links between DNAm and psychotic disorders

On the other hand, there is a considerable amount of research examining the association between DNAm, in different candidate genes, and EWAS level, in relation to a particular clinical phenotype. This includes major depression(84), eating disorders(85), Post traumatic stress disorder (PTSD)(86) and psychotic disorders including SCZ and bipolar disorders (86). This research has led to a broad number of genes and biological pathways that are associated with such phenotypes. Some of these are pathways related to neurotransmission such as serotonin (87), dopamine or GABA/glutamatergic processes (88); while other pathways involve inflammation (89), oxidative stress (90), synaptic plasticity and neurogenesis (91), or the stress response system (Hypothalamic Pituitary Adrenal Axis – HPA, some of these being pathways that have been suggested as possible mechanisms linking adversity and psychosis as mentioned in 1.4.1. It is important to take into account that some of these processes participate in disease pathogenesis in a parallel manner, such as via the redox

system and through the glutamatergic/GABAergic imbalance (92); or the immune system and the stress response (93), and are often transdiagnostic (thus occurring across various conditions), although it is not very clear which pathways may also be specifically related to some conditions, and connect the risk to disease with childhood adversity. For this reason, in the current work (project 4.1) I will present an extensive review on which of these pathways relate to the main mental conditions, and whether some of these pathways are also associated to childhood adversity, then constituting possible new mediating biological connections between childhood adversity and these conditions, including psychosis.

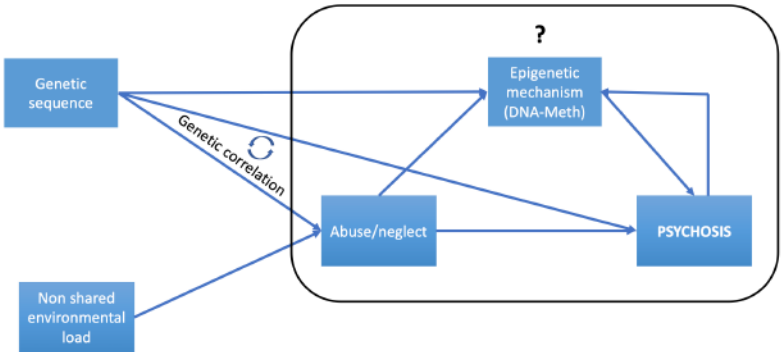
1.5.3 The complex interplay between genes, epigenetics and childhood adversity

As mentioned above, it is widely now accepted that a key biological process on the understanding of gene and environment interaction is epigenetics. Although some studies are trying to investigate to what extent DNAm plays a role in this interplay between genes and social stress(64, 94), this area remains considerably unexplored.

Figure 7 is a schematic summary of this complex interplay, and how it can influence the mediating pathway linking childhood adversity with psychosis, through epigenetic changes (DNAm), which will be the focus of the current work (project 4.2).

Figure 7

Interplay between genes, epigenetic changes (DNAm), childhood adversity (here illustrated as abuse and neglect) and psychosis.



This figure illustrates the complexity of the interplay between genes, epigenetic changes (DNAm), childhood adversity (here illustrated as abuse and neglect) and psychosis.

Although the focus of the current work will be to test whether DNAm mediates the link between childhood adversity and psychosis, other factors such as the influence of the genetic sequence on epigenetic changes needs to be considered, in order to have a broader picture of this topic (this will be discussed in chapter 5). For example, there is evidence that 20 % of the variation in blood DNAm is heritable, and that 50 % of CpG sites present a significant genetic component(95). Second, there is evidence that a great proportion of the environmental exposures are genetically driven (have a genetic component) which means that children are maltreated because they share genetics with their parents that are driving that risk to be exposed to maltreatment. For example, it is estimated that childhood adversity has a twin and family heritability of between 6-62% (95). Furthermore, it is also important to take into consideration that some environmental load can also make people

more prone to being exposed to later childhood traumas (otherwise called environmental confounding); for example, a traumatised mother may, as a consequence of her mental health, neglect or deprive her children(96). Lastly, factors related to psychotic disease itself, including medication(97), can affect DNAm, thus leading to a reverse causation issue if we explore this question with a cross sectional design.

That said, in this work I will try to investigate to what extent DNAm can mediate the childhood adversity association (so only focusing on the square highlighted in Figure 7), and limitations of the current work and future outstanding questions will be reviewed carefully on project 4.1 and 4.2. and in the general discussion (chapter 5).

1.6 Gaps in research on the link between childhood adversity and psychosis

As mentioned above, a better understanding of the nature of the association between childhood adversity and psychosis is needed, exploring not only the influence of a broad measure of trauma, but also specific subtypes of adversities and their link with all the psychotic dimensions. Thus, despite the abundant research on psychological and biological mechanisms between adversity and psychosis, there is no (at the time of the start of the current PhD) systematic review exploring which of these mechanisms are mediating such link. A systematic review on this will allow not only a better understanding of potential biological pathways, but also specific psychological targets for treatment. The systematic review results will allow us to identify specific gaps in the current literature and to address project 3.3, which is an empirical study testing an outstanding hypothesis that the depressive symptoms mediate the link between childhood adversity and positive symptoms of psychosis, not only at onset but also during 3 years of follow-up.

Given the vast amount of research on the links between social stress and DNAm in humans, and the broad evidence linking DNAm changes in multiple biological pathways across all mental disorders, a review on the topic is needed. Results on this project (chalter 4.1), in addition to findings from project 3.1, have allowed us to plan a second empirical study (chapter 4.2): trying to examine whether DNAm changes at EWAS level mediate the CT-Psychosis association in FEP.

1.7 Aims and hypothesis

This section outlines the main aims addressed in this thesis, which consist of a meta-analyses (study 1: chapter 3.1), and a systematic review (study 2: Chapter 3.2), and a related empirical longitudinal study (Study 3: Chapter 3.3) covering some gaps identified in Chapters 3.1 and 3.2. Then Project 2 will include a review on the evidence on epigenetic in mental health (study 4: Chapter 4.1) and another case control empirical study (study 5: chapter 4.2) which will cover gaps identified in Chapters 3.1, 3.2 and 4.1 (studies 1, 2 and 4 respectively).

1.7.1 Objectives

The overall objective of my PhD is to better understand the nature of the association between childhood adversity and the psychopathological profile in FEP, and to investigate possible mediating mechanisms at a psychopathological and at an epigenetic level. This will be addressed through the five Chapters mentioned above, divided into two different projects (1 and 2).

Project 1

1. The aim of Chapter 3.1 is to investigate the nature of the association between specific and broad effects of different experiences of childhood adversity and the main clinical dimension in those with psychotic disorder.
2. The aim of chapter 3.2 will be to systematically review the evidence on psychological and biological mechanisms linking childhood adversity and psychosis across the psychosis spectrum (from low level psychotic symptoms to psychotic disorders).
3. Based on Chapters 3.1, and 3.2, I will test the hypothesis of whether mood related symptoms, as one of the main mediating mechanisms in Chapters 3.2, mediate the links between adversity and psychotic symptoms at onset and during a 3 year follow-up in FEP.

Project 2

1. The aim of Chapter 4.1 is to review the evidence on the role of DNAm in mental health, including psychosis and its link with childhood adversity and other environmental risk factors.
2. The aim of Chapter 4.2 is to test whether epigenetic changes (DNAm) mediate the link between trauma and psychosis, taking into consideration findings in 3.1 and 3.3 on differential roles of abuse and neglect.

1.7.2 Hypotheses

Project 1

Chapter 3.1 (study 1): I hypothesize that neglect and abuse will differently affect the clinical dimensions in psychosis.

Chapter 3.2 (study 2): Mood related symptoms and dissociation mediate the adversity-psychosis association.

Chapter 3.3 (study 3): I hypothesize that the severity of anxiety and depression will mediate the trauma-psychotic symptoms association with those with early psychosis at baseline at follow up, as also shown in general population studies in Chapter 1.2.

Project 2

Chapter 4.1 (study 4): we hypothesise that some biological pathways epigenetically dysregulated will be transdiagnostic while others will be more disorder specific.

Chapter 4.2 (study 5): I hypothesize that (i) DNAm signals in pathways shown in Chapter 2.1 (involving neurogenesis, excitatory inhibitory balance, oxidative stress) will mediate the trauma-psychosis association. I also hypothesize that (ii) a different signature according to abuse and neglect will be present as mediating mechanisms between abuse/neglect and psychosis respectively, in line with the evidence (Chapter 3.1) showing different psychopathological signals related to these two adversities.

CHAPTER 2
Overview of methods

This thesis comprises five studies distributed in two projects: from project 1, the first study (1.1) is a meta-analysis (Chapter 1); the second a systematic review (1.2 Chapter 2) and the third being an empirical study based on the Treatment and Early Intervention in Psychosis Program (TIPP) Lausanne prospective cohort of patients in the Early Phase (EP) of their psychotic illness (1.3: Chapter 3). Project two comprises two studies: one being a literature review on epigenetics (2.1: Chapter 4) and the second another empirical study based on the EU-GEI study (2.2: Chapter 5).

Here I will present an overview with the key elements of the methods of the five studies given that full extensive details are provided in the respective manuscripts and their respective supplementary materials. A careful effort will be made in trying to avoid repetition or redundance in areas that are clearly detailed in the respective Chapters (manuscripts 1-4 are published or accepted for publication whereas manuscript 5 is not submitted yet, but it will be presented in a manuscript format).

2.1 Meta-analysis and the systematic review (chapter 1.1, 1.2 - Studies 1 and 2)

Both works were elaborated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines with the two protocols made available at PROSPERO (registration number: CRD42019129193 in April 2019 and July 2018 CRD42018100846 respectively). The objective of Chapter 1.1 titled *"Association Between Specific Childhood Adversities and Symptom Dimensions in People With Psychosis: Systematic Review and Meta-Analysis"* was to systematically examine quantitatively the association between broadly defined childhood trauma (CT), abuse (sexual/physical/emotional), and neglect (physical/emotional) subtypes, with positive, negative, depressive, manic, and disorganized dimensions in those with psychosis; while that of Chapter 1.2, titled *"A systematic review on mediators between adversity and psychosis: potential targets for treatment"* was to systematically review the evidence on psychological and biological mediators between CT and psychosis across the psychosis spectrum.

For both publications, the main search was conducted in MEDLINE, EMBASE and PsycInfo and Cochrane libraries from 1979 to May 2019 for Chapter 1.1, and to June 2018 for Chapter 1.2 respectively. For project 1.1, we used terms related to psychosis, childhood trauma, and clinical dimensions, while for project 1.2 terms included CT, mediation and psychosis, using the Boolean operator 'AND' for both studies.

For both publications screening and data extraction was conducted in duplicate and checked by a third researcher after a group meeting when inconsistencies were found. Quality assessment was conducted in duplicate through an adapted version of The Newcastle-Ottawa Scale (NOS)(98). For project 1.1 quantitative analyses were calculated using random effects and conducted with Comprehensive Meta-Analysis (CMA)(99); sensitivity analyses and meta-regression exploring various covariates were conducted, in line with Grading of Recommendations, Assessment, Development and Evaluations (GRADE) while for project 1.2, data on the amount of mediation through each psychological and biological pathway was extracted, or calculated when not directly given by authors, providing the percentage of total effect mediated. More details on the methodology of Chapters 1.1 and 1.2 can be found in the respective manuscripts presented below.

2.2. Methods of chapter 1.3 "Evidence of mediation of anxiety and depression between abuse and positive symptoms of psychosis" (chapter 1.3 – Study 3)

2.2.1 Context of the Early Intervention for psychosis

This first of the two empirical studies of this thesis has been developed in collaboration with a team in Lausanne, Switzerland, led by Prof. Philippe Conus, called the Treatment and Early Intervention in Psychosis Program (TIPP). This program was launched in 2004, and is one of the first ones in Europe in providing specialised care for people at the early phase of their psychosis. This Early Intervention (EI) team, and many others(100), have spread around the world, and are now a gold standard treatment for people with a first episode pf psychosis. The main principles that led to the idea came from the observation that a long duration of untreated psychosis (DUP) was associated with poor outcomes(101) and that, if patients are not treated during that "critical window' of vulnerability, there is a greater risk of chronification and poor biological, symptomatic and functional outcomes. Thus, the goal of EI services such as TIPP is to condense the resources during the first few years (3 years of follow up for TIPP) of disease and promoting recovery, independence, equity, and self-sufficiency and of facilitating the uptake of social, educational and employment opportunities. This is done by a multidisciplinary approach which implements a broad range of pharmacological and treatments options, and among its various values is that of placing the young patient at the centre of care and service delivery, at the same time sensitive to age, phase of illness, gender, and cultural background(102).

2.2.2 The TIPP prospective study

Specific details on the recruitment process and the design and instruments used are described in detail in Chapter 1.3. In summary, the entry criteria of the TIPP program are (I) being aged between 18 and 35; (II) residing in the catchment area of about 300,000 inhabitants of Lausanne and surroundings; (III) meeting threshold criteria for psychosis, as defined by the 'Psychosis threshold' subscale of the Comprehensive Assessment of At Risk Mental States scale (CAARMS(103)). Patients are referred to other treatment programs if they have been taking antipsychotic medication for more than a total of 6 months, have psychosis related to intoxication or organic brain disease, or have an intelligence quotient below 70. All patients are treated by a psychiatrist and a case manager, the latter being available for a maximum of two home visits per week. Every TIPP patient goes through a thorough clinical assessment at baseline and evaluations are conducted at regular intervals both by the case manager and a clinical psychologist, charged to evaluate symptoms on the basis of monitoring the patient's evolution.

Childhood adversity exposure is part of a broad range of demographic and clinical questionnaires and scales that are conducted for all the TIPP patients and this is done retrospectively, although the clinical and functional outcomes measurements, which measure the symptoms such as depressive of the positive symptoms of psychosis (e.g. auditory hallucinations and/or delusions) are measured prospectively after 2, 6, 12, 18, 24, and 30 months after onset. This is an unusual prospective design that allows not only examining the influence of some independent variables on the clinical profile at baseline (when patients arrive to the program and usually are acutely unwell), but also at follow-up, allowing investigating into how patients evolve according to a given predictor, and also according to their baseline profile. Another important strength of the TIPP prospective cohort is that the Research and Ethics Committee of the Faculty of Biology and Medicine of Lausanne University granted access for research purposes to all data collected in the frame of the TIPP clinical treatment. Therefore, data stemming from the prospective clinical assessment of all patients treated at TIPP is accessible for research. Furthermore, TIPP program patients are quasi-representative of Lausanne early psychosis population. This is because the mental health system in Lausanne, a very small and well organised city, is centralised around the Lausanne University Hospital, which ensures a set of pathways to care that guarantee that every patient with a FEP is referred to TIPP program. Overall, the prospective design, with multiple time points and lack of selection bias, and the quasi-representative cohort of this naturalistic cohort are important and unique strengths of this setting. Another aspect to consider is that, although most of the TIPP patients are referred in the context of a First Episode of Psychosis, a minority have a longer DUP and had passed a previous untreated episode of psychosis, thus being admitted into the TIPP program for their second psychotic episode. For this reason, I will not refer to TIPP patients as FEP patients, but as early psychosis patients (EPP). More details about the TIPP program can be found here(104).

Details on instruments and statistical methods used are described in detail in Chapter 1.3.

2.3 Methods of chapter 2.1 "Can epigenetics shine a light on the biological pathways underlying major mental disorders?' (Chapter 2.1 – Study 4)

The goal of this narrative review is to review the existing literature on DNAm from human studies of psychiatric diseases to (i) identify epigenetic modifications mapping onto biological pathways either transdiagnostically or specifically related to psychiatric diseases such as Eating Disorders, Post traumatic Stress Disorder, Bipolar and Psychotic Disorder, Depression, Autism and Anxiety Disorder, and (ii) to investigate a convergence between some of these epigenetic modifications and the exposure to known risk factors for psychiatric disorders such as childhood trauma and cannabis use, as well as to other epigenetic confounders in psychiatry research, such as tobacco, medication or alcohol use.

The main two searches have been conducted in MEDLINE, EMBASE and PsycInfo from inception to May 2018, and an alert of the two searches has been created so that the first author (myself) had a regular update of the relevant new papers that were published. Given the complexity of this work, multiple versions and updates of the relevant references have been made at various stages of the PhD (one at the end of 2018, another in June 2019) and the final version was finally submitted in June 2021 with an updated search.

This work provides a narrative summary of the evidence, predominantly on case-control studies, pointing at an association between DNAm changes in the Serotoninergic, Dopaminergic pathways, Excitatory inhibitory balance (including the Glutamatergic and GABAergic dysfunction, Synaptic plasticity and Neurogenesis; the Immune system, Inflammation and Oxidative stress and the major mental conditions (focusing on Eating Disorders: anorexia nervosa and bulimia nervosa, autism spectrum disorder, bipolar disorder and psychotic disorder, depression, PTSD and anxiety disorders). The search involving this section has been conducted using terms such as "DNA methylation", or "Epigenetics" or "Epigenomics" and the respective conditions, as well as terms such as "psychiatry" or "mental health" separated by the Boolean operator "AND". For the second goals, exploring the link between DNAm and ERF (mainly childhood adversity and cannabis use), one additional search has been conducted looking at papers examining the role of cannabis in DNAm, which search included "DNA methylation", or "Epigenetics" or "Epigenomics", and "cannabis", separated by the Boolean operator "AND". For papers including DNAm and childhood adversity in mental health, the first general search has been used, and articles that were relevant for the review have been extracted (full details on methodology can be found in the supplementary material section of the respective chapter).

In terms of the data extraction and inclusion of the papers, given the broad scope of the work and the limited space, we have taken a pragmatic approach where only relevant papers that were judged as high in quality and were informative and representative of the evidence in the respective domain have been selected. For example, if there were ten papers showing links between DNAm variation in the serotoninergic pathway and

depression, only the most relevant and important ones have been cited or discussed. Another consideration is that, in the childhood adversity section, there was a broad set of literature exploring the links between trauma in the general population, without any links to disease(82, 83) so, although these papers are cited and briefly mentioned, data is not extracted in the Table 2, which gathers studies exploring the interplay between childhood adversity, DNAm and clinical features. However, as literature in the domain of cannabis and DNAm in patients is non-existent (against our initial expectation), for that section more emphasis has been put on papers conducted in the general population.

Therefore, although the search has been done in a quasi-systematic way, a more narrative approach has been used to select papers and write the manuscript.

2.4. Overview of the eu-gei study (chapter 2.2 - Study 5)

This fifth study, which corresponds to Chapter 2.2, constitutes the empirical part of the thesis involving data on epigenetics. It is based on the case-control sample from the EU-GEI study (European Network of national schizophrenia networks studying Gene-Environment Interactions). The EU-GEI is a multicentre incidence and case-sibling-control study on genetic and environmental determinants involved in the development and severity of psychotic disorders (http://www.eu-gei.eu/).

2.4.1 Sample

The full EU-GEI sample comprises a total of 2629 participants, including 1130 patients aged 18 to 65 years who presented to the adult psychiatric services in 17 cities across six mostly European countries (five European and Brazil) between May 1, 2010 and April 1, 2015. Cases were selected if they were suffering with their FEP including PD, BD and other psychotic disorders such as SCZ. In addition, 1499 unaffected controls were recruited with a quota sampling approach to represent the local population living in the areas served by the services. The current study is conducted on a subsample from the EU-GEI sample with data on DNAm. This will include 366 FEP and 517 healthy population controls. Further information about methodology of the study is available on the EU-GEI website (www.eu-gei.eu/), previous publications (Gayer-Anderson *et al*., 2020) and will be further described on Chapter 4.

CHAPTER 3

Linking adversity with psychopathology in early psychosis, exploring potential mechanisms and targets for treatment.

3.1 (study 1) this chapter has been reproduced in full from the following paper

Association Between Specific Childhood Adversities and Symptom Dimensions in People With Psychosis: Systematic Review and Meta-Analysis

Luis Alameda, Angeline Christy, Victoria Rodriguez, Gonzalo Salazar de Pablo, Madeleine Thrush, Yi Shen, Beatriz Alameda, Edoardo Spinazzola, Eduardo Iacoponi, Giulia Trotta, Ewan Carr, Miguel Ruiz Veguilla, Monica Aas, Craig Morgan, and Robin M Murray

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Abstract

Despite the accepted link between childhood abuse and positive psychotic symptoms, findings between other adversities, such as neglect, and the remaining dimensions in people with psychosis have been inconsistent, with evidence not yet reviewed quantitatively. The aim of this study was to systematically examine quantitatively the association between broadly defined childhood adversity (CA), abuse (sexual/physical/emotional), and neglect (physical/emotional) subtypes, with positive, negative, depressive, manic, and disorganized dimensions in those with psychosis. A search was conducted across EMBASE, MEDLINE, PsychINFO, and Cochrane Libraries using search terms related to psychosis population, CA, and psychopathological dimensions. After reviewing for relevance, data were extracted, synthesized, and meta-analyzed. Forty-seven papers were identified, including 7379

cases across 40 studies examining positive, 37 negative, 20 depressive, 9 disorganized, and 13 manic dimensions. After adjustment for publication bias, general adversity was positively as- sociated with all dimensions (ranging from r = 0.08 to r = 0.24). Most forms of abuse were associated with de- pressive (ranging from r = 0.16 to r = 0.32), positive (ranging from r = 0.14 to r = 0.16), manic (r = 0.13), and negative dimensions (ranging from r = 0.05 to r = 0.09), while neglect was only associated with negative (r = 0.13) and depressive dimensions (ranging from r = 0.16 to r = 0.20). When heterogeneity was found, it tended to be explained by one specific study. The depressive dimension was influenced by percentage of women (ranging from r = 0.83 to r = 1.36) and poor-quality scores (ranging from r = −0.21 and r = −0.059). Quality was judged as fair overall. Broadly defined adversity and forms of abuse increase transdimensional severity. Being exposed to neglect during childhood seems to be exclusively related to negative and depressive dimensions suggesting specific effects.

Key words: childhood trauma/psychosis/dimensions/ meta-analysis

Introduction

Exposure to adversities, such as abuse and neglect, during childhood and adolescence is associated with psychotic disorders[1] Abundant research has shown that individuals with a psychotic disorder who are exposed to such experiences have a higher severity of hallucinations and delusions [2,3] as well as other clinical outcomes, such as depressive, manic, and disorganized symptoms [4,5] Understanding the nature of the association between such environmental risk factors and each of the psycho- pathological domains is important in subsequently understanding potential causative mediating mechanisms. This may help to detect individuals at risk of poorer psychopathological profile and enable specific interventions to be tailored accordingly [6]

Childhood adversity (CA) is a construct that, in the field of psychosis, usually refers to being exposed to potentially traumatic events, such as abuse (sexual, physical, and emotional), neglect (physical and emotional), bullying or early separation[5] usually before age 16 or 18. It can be measured by using a cumulative score, which adds the number of different exposures, or individually by examining specific adversities in isolation. Evidence suggests that CA, broadly defined by a total cumulative score, may be transsymptomatic and leads to an admixture of constellations of symptom domains rather than in isolation[7,8]. On the other hand, there is evidence on some specific links between adversities and symptoms[2,5,9.] Regarding negative symptoms of psychosis, the evidence is less clear, with multiple inconsistent reports using general measures of CA, [10–12] and some meta-analytic evidence (including 9 studies concerning abuse and 8 with neglect) suggesting a specific link with neglect only[2] .Our understanding of the link between adversity, broadly defined or by specific subtypes, and the remaining fundamental psychopathological domains, such as manic, depressive, and disorganized dimensions, is less clear, with sparser evidence and no consensus so far.

Current literature on the specific effects between CA and individual symptoms is mainly limited to the effects on auditory perceptions or delusional ideas[3,5]. However, studying single symptoms in isolation is far from being representative of real-life clinical settings as symptoms rarely occur in isolation and often co-occur and cluster. Thus, examining the psychopathological dimensions (the positive, negative, disorganized, depressive, and manic/ excited) rather than single symptoms may be more representative to the clinical reality[13,14].

To the best of our knowledge, only one meta-analysis has explored the links between abuse and neglect with the positive and negative dimensions in psychotic populations[2]. This high-quality piece of work found that, whilst abuse may affect instinctively both dimensions, supporting the presence of general effects, neglect was only associated with the negative symptoms, supporting some evidence of specific effects[2]. However, Bailey et al's[2] literature search in this study did not include the term "dimensions," which may have led to missing relevant papers. Second, the authors did not explore depressive, disorganized, and manic/excited symptom dimensions. Third, their search was until December 2014, thus excluding the abundance of re- search that has been conducted since. Lastly, they did not take into account the potential bias led by different instruments used.

Based on these elements, we planned to replicate and update their findings and, extending their work, also cover the disorganized, depressive, and manic/exited dimensions in people with a psychotic disorder and thus provide a more comprehensive synthesis of the different adversities and psychotic dimensions.

Methods

The study protocol was registered on PROSPERO (CRD42019129193) and followed the Preferred Reporting Items for Systematic Reviews and Meta- Analyses[15] guidelines and Moose[16] (see supplementary tables S1 and S2).

Search Strategy and Selection Criteria

The main electronic search was conducted on MEDLINE, EMBASE, and PsycINFO, through Ovid provider, and on Cochrane Libraries, up to May 2019. We searched Medical Subject Headings and keywords related to: (1) psychosis; (2) childhood adversity; and (3) clinical dimensions using the Boolean operator "AND" (full list of search terms provided in the supplementary material— Search Terms). Titles and abstracts, and subsequently selected eligible full texts of articles were screened in- dependently by 2 reviewers (L.A. and M.T.) with 85% agreement. Titles and abstract discrepancies were resolved through discussion at a project group meeting, while full-text discrepancies were screened by a third independent reviewer (M.R.V.). A cross-reference search extracted titles/abstracts from identified reviews, and a full-text check of potentially eligible studies from these reviews was performed by one author (A.C.) and checked in duplicate by another author (L.A.). When data extraction was conducted and new potentially eligible studies were detected from included studies, these were also considered for inclusion.

Inclusion Criteria

Included studies were those that (1) examine the relationship between CA and psychopathological dimensions in individuals with psychosis; (2) were performed in humans; (3) included only psychotic patients with the following diagnoses: SCZ, schizophreniform/brief psychotic episode, bipolar disorder with psychotic features, schizoaffective disorder, major depression with psychotic features, and psychosis not otherwise specified; (4) defined diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R, DSM-IV, and DSM-IV-TR[17]), Research Diagnostic Criteria, or International Classification of Diseases, 9th or 10th Revision (ICD-9 or ICD-10, re- spectively[18]; see supplementary table S3 for full list with respective codes); (5) includes CA occurring before age 18 and involving exposure to CA measured as follows: by a (a) general measure of adversity (GA) broadly de- fined by a composite measure that includes either cumulative scores of different traumas, or use a binary measure that select patients having been exposed to any of the subtypes; (b) SA, (c) physical abuse (PA), (d) emotional abuse (EA), (e) physical neglect (PN), and (f) emotional neglect (EN), (g) bullying, and (h) household discord or equivalent experiences; (6) examine the positive, negative, disorganized, depressive, and manic/excited symptom dimensions[13,14] and are measured using a well-validated instrument (see supplementary table S4 for full list of included instruments); and (7) studies with sufficient information to determine the presence of a statistically positive, negative, or nonsignificant association between any form of CA and each of the dimensions.

Exclusion Criteria

(1) Not being published in the English language; (2) included more than 20% of participants aged 65 years or over in accord with other studies[6,19]; (3) being performed in samples of specific populations, such as pregnant women or samples from forensic settings (to avoid potential confounding by other variables, such as hormonal changes or antisocial traits); (4) being published before 1979 ac- cording to others[1] and because the first known empirical study on CA and psychosis was published around that time[20] and the DSM-III[21] was released in 1980, improving diagnostic consistency.

Quality Assessment and Data Extraction Procedures

Quality assessment was carried out using the Newcastle– Ottawa Scale[22] (NOS) for cohort studies by 2 independent reviewers (Y.S. and A.C.). Details on the instrument items and quality assessment procedures can be found in the supplementary material ("quality assessment procedures").

We extracted all the relevant data of each included study, providing full details on each included paper in supplementary table S5. In order to allow comparisons with the previous meta-analysis in the field[2], we extracted information on correlation coefficients and 95% confidence intervals (CIs), when possible. When associations were provided in other formats (mean differences, standardized β coefficients, or unstandardized regression coefficients), data were transformed using previously pro- posed procedures[23,24]. To combine

Person and Spearman's correlations, Comprehensive Meta-Analysis version v.3 (CMA25) transforms them to Fisher's Z, and then trans- forms those values back to correlations and uses the transformed values for the analyses.

As a predominance of the analyses were conducted using correlations and were not adjusted, unadjusted results were extracted. In order to account for the possible influence of confounders, the following meta-regressions were carried out: (1) age (mean age), (2) sex (percentage of females), (3) quality of the studies included (based on the NOS scores), and (4) variability in instruments used (based on whether they used Positive and Negative Syndrome Scale [PANSS] and Childhood Trauma Questionnaire [CTQ] or not; see details in Data Analysis). The choice of these instruments is because they are the most commonly used in this set of literature, ensuring some methodological homogeneity. When results were given separately between men and women, effects were pooled into one single category. When different time points were reported, we included only measures at baseline to permit comparison between all the studies, but results on prospective analyses were also reported in the detailed tables (supplementary table S5).

Data Analysis

We performed a set of meta-analyses, when data were available, for 6 types of CA in each of the 5 dimensions of interests. The CA categories were (1) GA, (2) SA, (3) PA, (4) EA, (5) PN, (6) EN, (7) bullying, and (8) household discord and, for each of the dimensions, meta-analyses were conducted when a minimum of 3 studies was avail- able. Papers that used a general composite category of abuse or neglect (by aggregating each subtype) could not be included in the quantitative analyses per specific adversities, but results were extracted and presented in supplementary table S5.

The meta-analysis was conducted using CMA.25 Random effects models approach was used since we assume differences in measures, clinical features, and demographics between studies. To assess between-study heterogeneity, we looked at the I2 index and conducted the Q test. Serious heterogeneity was considered when I2 > 50% and Q-test P-value was <.05 according to others[26] .In line with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria, we explored the potential bias related to heterogeneity found in our analyses by exploring the forest plots and researching the presence of potential outliers that could explain the heterogeneity (eg, one individual study going in a different direction to all the others according to others[26]).

To assess publication bias, we looked for asymmetry in the funnel plots and conducted the Egger's test[27] (P <.05 might indicate potential publication bias). Whenever the latter was significant, we employed Duval and Tweedie's trim-and-fill method[28] .This not only assessed the statistical likelihood of publication bias but also provides the adjusted summary effect. When Egger's test was significant, and inspection of the funnel plots suggested potential small effect bias, the trim-and-fill method was carried. Analyses did not "survive" publication bias adjustment if the 95% CI crossed 0 following the trim-and-fill

procedure according to others26 .For those analyses with at least 6 studies per analysis, we conducted meta-regressions by the risk of bias scores, age, and gender and variability in instruments used (whether or not they used the CTQ and PANSS as instruments, which allowed us to estimate potential biases related to studies that used other instruments) and quality assessment scores based on the NOS. To further account for the potential biases due to the heterogeneity of measures measuring CA and symptoms (considering that CTQ and PANSS are the most commonly used), we also conducted sensitivity analyses stratifying analyses based on whether they used CTQ/PANSS or not, considering that other instruments may have led to important heterogeneity. Statistical significance was set at $P < .05$ (2-tailed). Interpretation of correlation coefficients was based on predefined cutoffs as follows: values be- tween 0 and 0.3 indicate a weak positive effect: between 0.3 and 0.7, a moderate positive effect and, above 0.7, a strong positive effect[29].

Results

Database

Overall, 6845 records were identified, 294 full texts were screened and 47 articles were eligible for inclusion (supplementary figure 1). The 47 included articles were published between 1979 and May 2019 (see supplementary table S5).

Study sample sizes ranged from 20 to 1119; the mean age of the entire sample was 30.7 and the proportion of women was 35.31% overall. These studies included both cross-sectional and prospective investigations. However, only 11 studies used the latter, with follow-up periods ranging from 1 week to 5 years; thus, we could not metaanalyze prospective data given the very small number of papers in each subanalysis category. All the studies measured CA retrospectively. Studies were conducted predominantly in Europe (23), Australia (7) the United States, and Canada (8), followed by Turkey (4), Eastern Asia (3), Iran (1), and India (1).

Measures of CA

Details of the instruments used are detailed in supplementary table S5. Overall, GA was the most examined measure among studies, being utilized in 82.9% (n = 39) of the studies included, while 47% (n = 22) examined SA, 38.3% (n = 18) PA, 34% (n = 16) EA, 27.6% (13) PN, and 31.9% (15) EN. The CTQ30 is the most used composite instrument (46.8%; n = 22 studies). GA was measured based on a cumulative measure of different adversities; however, a small proportion used a binary measure based on predefined thresholds (3/18 of those using CTQ). None of the studies examined the association between bullying or household discord and symptom dimensions; so, no meta-analyses could be conducted for those adversities.

Measures Used for the Outcomes (Psychopathological Dimensions)

Details on the instruments used as well as items included in each outcome dimension

are detailed in supplementary table S6. PANSS[31] was the most utilized measure of symptom severity amongst all dimensions. High heterogeneity of measures was found for the depressive domain, which used 10 instruments as compared to 5 for the positive and negative, 2 for the disorganized, and 4 for the manic. Considerable overlap of symptoms assessed was found within the clinical domains across instruments. Details can be found in the supplementary material table S6.

Meta-Analytic Results

Results on the direction and magnitude of the meta- analytic evidence are reported in table 1 and illustrated in figure 1A and 1B. Forest plots of each analysis can be found in supplementary figures 2–27. As a whole, effect sizes found in this review were generally weak for all dimensions (0–0.3) or moderate at best for some of the analyses in the depressive domain (0.3–0.7). GA was positively associated with all dimensions. All abuse categories were positively associated with the depressive and positive dimensions. PA and SA, but not EA, were positively associated with the negative dimension, while only SA was associated with mania. PN and EN were positively associated with the negative and depressive dimensions and not with the others.

Positive Dimension

Forty studies were included concerning this dimension, including 6500 subjects. Data on 2 studies could not be included in analyses because of incompatibility [32,33] (see supplementary table S7). Positive associations, with correlation coefficients between 0.142 and 0.163, indicating weak effect, were found for analyses with general measure of CA (27 studies; r = 0.16, 95% CI = [0.12, 0.20], P < .001), SA (16 studies; r = 0.14, 95% CI = [0.08, 0.19], P < .001), PA (13 studies; r = 0.15, 95% CI = [0.09, 0.21], P < .001), and EA (11 studies; r = 0.16, 95% CI = [0.07, 0.25], P = .001). Smaller correlation coefficients were found for PN and EN at 0.06 and 0.050 respectively, whose CI crossed 0 (the latter corresponds to the coefficient after adjustment for Duval and Tweedie's trim-and-fill method given the presence of substantial publication bias with an Egger test = 0.007).

Negative Dimension

Thirty-seven studies were included concerning this dimension, including 6053 subjects. Data on 4 studies could not be meta-analyzed because of incompatible data format[32,34–36] supplementary table S7. Positive associations with weak effects were found for analyses with GA (25 studies; r = 0.09, 95% CI = [0.05, 0.13], P < .001), SA (16 studies; r = 0.04, 95% CI = [0.00, 0.09], P = .037), and PA (14 studies; r = 0.08, 95%

CI = [0.03, 0.14], P = .002), while no association was found for EA whose CI crossed 0 (12 studies; r = 0.03, 95% CI = [−0.08, 0.15], P = .0568. However, and contrary to the finding concerning positive dimension, positive significant associations with greater (but still weak) effects were found for PN (10 studies; r = 0.13, 95% CI = [0.07, 0.18], P < .001) and EN (11 studies; r = 0.13, 95% CI = [0.08, 0.18], P < .001).

Depressive Dimension

Data on the 20 studies including this dimension could be meta-analyzed, including 3753 subjects. One study could not be included in analyses by subtype because of incomepatible data32 (supplementary table S7). Meta-analyses revealed that all categories were positively associated with the depressive dimensions with weak and moderate effects ranging from 0.16 to 0.32. GA (13 studies; r = 0.24, 95% CI = [0.15, 0.34], P < .001), SA (12 studies; r = 0.21, 95% CI = [0.23, 0.29], P < .001), PA (9 studies; r = 0.16, 95% CI = [0.06, 0.25], P < .001), EA (8 studies; r = 0.31, 95% CI = [0.20, 0.41], P = .001), PN (7 studies; r = 0.16, 95% CI = [0.00, 0.31], P = .047), and EN (7 studies; r = 0.19, 95% CI = [0.06, 0.32], P = .004).

Disorganized Dimension

Data on the 9 studies including this dimension could be meta-analyzed, including 1246 subjects. Disorganized symptoms were associated with GA (7 studies; r = 0.09, 95% CI = [0.03, 0.15], P = .003) and with SA (3 studies; r = 0.10, 95% CI = [−0.04, 0.24], P = .157) with weak effects. No quantitative analyses could be conducted for the remaining subtypes

Manic Dimension

Data on the 13 studies including this dimension could be meta-analyzed, including 2021 subjects. Mania was positively (with weak effect sizes) associated with GA (11 studies; r = 0.08, 95% CI = [0.01, 0.15], P = .020) and with SA (5 studies; r = 0.13, 95% CI = [0.00, 0.24], P = 0.039) but not with the other subtypes.

Table 1

Association between adversities and symptoms dimensions, heterogeneity and publication bias.

	Studies	Sample size	Samples	Correlation coefficient			Heterogeneity		Publication bias			
				Values	95% CI	P	I^2	P	Funnel Plot Asymmetry	Trim & Fill imputed studies	Trim & Fill Adjusted R coeff (95% CI)	Egger P
General Adversity POSITIVE	27	4762	27	0.16	0.12;0.20	0.000	39.14	0.021	No	0	NA	0.726
Sexual abuse POSITIVE	16	2588	16	0.14	0.08;0.19	0.000	41.98	0.035	Possible left	2	0.12 (0.05; 0.18)	0.224
Physical abuse POSITIVE	13	2260	13	0.15	0.09;0.21	0.000	40.54	0.064	Yes left	2	0.13 (0.07; 0.19)	0.21
Emotional abuse POSITIVE	11	1580	11	0.16	0.07;0.25	0.001	69.93	0.000	No	0	NA	0.021
Physical neglect POSITIVE	10	1151	10	0.06	-0.01;0.14	0.124	44.00	0.065	No	0	NA	0.216
Emotional neglect POSITIVE@	12	1663	12	0.10	0.01;0.18	0.021	66.47	0.001	Yes left	3	0.05 (-0.03; 0.13)	0.007
General Adversity NEGATIVE	25	4562	25	0.09	0.05;0.13	0.000	34.32	0.049	No	0	NA	0.460
Sexual abuse NEGATIVE	16	2097	16	0.04	0.00;0.09	0.037	24.96	0.172	No	0	NA	0.111
Physical abuse NEGATIVE	14	2455	14	0.08	0.03;0.14	0.002	43.55	0.041	No	0	NA	0.137
Emotional abuse NEGATIVE	12	1680	12	0.03	-0.08;0.15	0.568	83.91	0.000	No	0	NA	0.744
Physical neglect NEGATIVE	10	1151	10	0.13	0.07;0.18	0.000	0	0.78	Yes left	2	0.11 (0.05; 0.16)	0.545
Emotional neglect NEGATIVE	11	1580	11	0.13	0.08;0.18	0.000	0	0.972	No	0	NA	0.694
General Adversity DEPRESSION	13	2750	13	0.25	0.15; 0.34	0.000	81.62	0.000	Yes left	5	0.12 (0.01; 0.23)	0.150
Sexual abuse DEPRESSION	12	1597	12	0.21	0.13; 0.29	0.000	63.66	0.001	Yes left	2	0.17 (0.07; 0.26)	0.398
Physical abuse DEPRESSION	9	1296	9	0.16	0.06;0.25	0.001	63.35	0.001	No	0	NA	0.050
Emotional abuse DEPRESSION	8	1060	8	0.31	0.20;0.41	0.000	73.33	0.000	Yes left	3	0.23 (0.11; 0.34)	0.316

Physical neglect DEPRESSION	7	832	7	0.16	0.00;0.31	0.047	81.24	0.000	Yes left	2	0.08 (-0.08; 0.23)	0.100
Emotional neglect DEPRESSION	7	832	7	0.19	0.06;0.32	0.004	72.67	0.001	Yes left	3	0.08 (-0.06; 0.22)	0.068
General Adversity MANIA	11	652	11	0.08	0.01-0.15	0.020	44.25	0.056	Possible left	2	0.06 (-0.00; 0.13)	0.217
Sexual abuse MANIA	5	763	5	0.13	0.00; 0.24	0.039	60.60	0.038	Possible left	1	0.11 (-0.00; 0.23)	0.228
Physical abuse MANIA	4	743	4	0.07	-0.05-0.20	0.277	69.10	0.021	Possible left	1	0.03 (-0.08; 0.16)	0.620
Emotional abuse MANIA	3	507	3	0.04	-0.19; 0.27	0.734	85.80	0.001	No	NA	NA	0.296
Physical neglect MANIA	3	507	3	0.05	-0.05; 0.16	0.343	35.60	0.211	No	NA	NA	0.888
Emotional neglect MANIA	3	507	3	-0.00	-0.12;0.11	0.957	43.70	0.169	No	NA	NA	0.007
General Adversity DISORGANIZATION	7	967	7	0.09	0.03;0.15	0.003	0	0.679	No	NA	NA	0.845
Sexual abuse DISORGANIZATION	3	375	3	0.10	-0.04; 0.24	0.157	38.52	0.197	No	NA	NA	0.428

@ for emotional neglect in the positive dimension analysis, substantial publication bias was found (with an Egger test= 0.007) and thus results after adjustment for Duval and Tweedie's trim-and-fill were considered for interpretation and for Figure 1.

Figure 1A

Summary of the meta-analyses conducted by type of adversity in each of the clinical dimensions.

Dimensions	Adversities	No. studies	N	Correlation coefficient [95% C.I.]	P-value
Positive	General adversity	30	5088	0.16 [0.12, 0.20]	<0.001
	Sexual abuse	16	2588	0.14 [0.09, 0.20]	<0.001
	Physical abuse	13	2260	0.15 [0.10, 0.21]	<0.001
	Emotional abuse	11	1580	0.16[i] [0.07, 0.25]	0.001
	Physical neglect	10	1151	0.06 [-0.02, 0.14]	0.124
	Emotional neglect	12	1663	0.05[i] [-0.03, 0.13]	NS*
Negative	General adversity	28	4888	0.10 [0.06, 0.14]	<0.001
	Sexual abuse	16	2097	0.05 [0.00, 0.10]	0.037
	Physical abuse	14	2455	0.09 [0.03, 0.14]	0.002
	Emotional abuse	12	1680	0.04[i] [-0.09, 0.16]	0.568
	Physical neglect	10	1151	0.13 [0.07, 0.19]	<0.001
	Emotional neglect	11	1580	0.13 [0.09, 0.18]	<0.001
Depressive	General adversity	15	3079	0.24[i] [0.16, 0.32]	<0.001
	Sexual abuse	12	1597	0.21[i] [0.13, 0.30]	<0.001
	Physical abuse	9	1296	0.16[i] [0.06, 0.26]	0.001
	Emotional abuse	8	1060	0.32[i] [0.20, 0.42]	<0.001
	Physical neglect	7	832	0.16[i] [0.00, 0.32]	0.047
	Emotional neglect	7	832	0.20[i] [0.07, 0.32]	0.004
Disorg.	General adversity	7	967	0.10 [0.03, 0.16]	0.003
	Sexual abuse	3	375	0.10 [-0.04, 0.24]	0.157
Manic	General adversity	12	1785	0.08 [0.01, 0.14]	0.020
	Sexual abuse	5	763	0.13[i] [0.01, 0.25]	0.039
	Physical abuse	4	743	0.07[i] [-0.06, 0.20]	0.277
	Emotional abuse	3	507	0.04[i] [-0.20, 0.28]	0.734
	Physical neglect	3	507	0.05 [-0.06, 0.17]	0.343
	Emotional neglect	3	507	0.00 [-0.12, 0.12]	0.957

Notes.

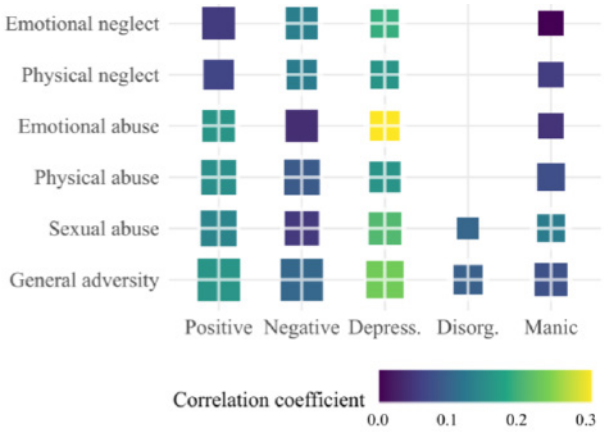
[i] = analyses showed serious heterogeneity, indicated by I^2 > 50% and Q test p-value of < 0.05.

Correlation coefficients and p-values derived from random effect model.

Results adjusted for publication bias by the 'Trim-and-fill' procedure because considerable publication bias was found as reflected by a significant Egger test (p = 0.007).

Figure 1B

Graphic representation summarizing the direction of the evidence, the magnitude and the presence of significant associations among the 26 meta-analyses conducted.



Notes.

Box sizes indicate the sample size of each meta-analysis (from 375 to 5088). The colour of squares represents the size of the correlation coefficient. Statistically significant correlations (p < 0.05) are indicated with a white '+' in the box.

Bias Assessment, Heterogeneity, and Meta-Regressions

The overall quality of included studies was rated as "fair," ranging from 4 to 7 and with a mean of 4.97. The agreed quality grades of each study are presented in supplementary tables S8, and each general score of each study is also reported in supplementary table S5. Following GRADE criteria, we conducted the exploration of forest plots (see supplementary figures 2–27), with all 12 analyses revealing serious heterogeneity, which were: EA (I2 = 69.93; P = .000) and EN (I2 = 66.47; P = .001) in the positive dimension; EA in the negative dimension (I2 = 83.91; P = .000); GA (I2 = 34.32; P = .049), SA (I2 = 63.66; P = .001), PA (I2 = 63.35; P = .001), EA (I2 = 73.33; P = .000), PN (I2 = 81.24; P = .000), and EN (I2 = 72.67; P = .001) in the depressive dimension; SA (I2 = 60.60; P = .038), PA (I2 = 69.10; P = .021), and EA (I2 = 85.80; P = .001) for the manic dimension. Details are provided in the supplementary material. Exploration of the forest plots revealed that the heterogeneity of the majority of analyses could be explained either by one specific study with small effect going in the opposite direction of all the others or because of a combination of studies with small and large effects sizes going in the same direction; thus, this heterogeneity was considered of little importance. However, this was not the case for EN (positive dimension) and EA (negative dimension), where the dispersion was considerable with studies that showed relatively high effect sizes going in the opposite direction. We conducted meta-regressions using as covariates the proportion of women, mean age, use of CTQ vs PANSS, and the NOS scores. Results are presented in supplementary table S9 and detailed narratively in the SM. As a whole, all the analyses between CA with the depressive dimension were influenced by the proportion of women (GA r = 1.02, P = .036; SA r = 1.03, P = .005; PA r = 0.99, P = .019; EA r = 0.83, P = .105; PN r = 1.35, P = .033; EN r = 1.31, P = .003), suggesting that women exposed to trauma tended to show higher severity of depression. Using CTQ and PANSS, as compared to studies that used other instruments did not affect the results. Higher scores on the NOS were negatively associated with depression scores for SA (r = −0.14, P < .001); PA (r = −0.13, P = .004) all the subtypes except for EA, PN (r = −0.21, P = .001), EN (r = −0.19, P < .001), meaning that better quality studies tended to show lower scores in the depres- sive dimension.

Sensitivity Analyses

We conducted sensitivity analyses with at least 8 studies based on whether they used CTQ/PANSS or not, considering that other instruments may have led to important heterogeneity. Given the low number of studies for the manic, disorganized, and depressive dimensions using CTQ and PANSS, we alternatively categorized them ac- cording to whether they used CTQ or not and PANSS or not. None of the analyses revealed a clear difference between studies using this methodology and those that did not. Our results did not change notably when we excluded 6 papers whose composite score of GA also included some experiences that were not in our inclusion criteria[12,37–41]. Results can be seen in supplementary table S10 and the Sensitivity Analyses section in the supplementary material.

Discussion

This is the first meta-analysis examining the association between adversity, as a composite measure and by individual subtypes, and the severity of the main psychopathological dimensions in people with psychotic disorders. Three key findings steam from our results: (1) CA, measured as a composite broad category, as well as with most types of abuse, is associated with a range of psychopathological dimensions with weak effects, thus supporting evidence for general effects on psychosis. (2) Neglect is specifically related to the negative and depressive dimensions but not with the other dimensions, supporting the presence of some specific effects. (3) The depressive dimension seems to be the most affected by all forms of adversities with the greatest correlation coefficients ranging from weak to moderate effects, which highlights the im- portance to address the mood of traumatized individuals with psychosis.

Methodological Considerations

The findings of this review should be interpreted in the context of various methodological considerations. In terms of limitations related to the included studies:

(1) Although a major strength of our work is its large scale, the inclusion of 47 studies and 7379 subjects, enabling us to cover multiple subtypes of adversities across all the study dimensions, the disorganized dimension remained poorly covered: SA was the only subanalysis that we were able to conduct quantitatively; (2) there was a lack of studies examining bullying and household discord, suggesting a new avenue for further work; and (3) only 11 studies overall provided prospective data, hindering the conduction of informative prospective analyses per subtypes of adversities in all the dimensions and, therefore, not allowing comparisons with baseline data.

In terms of limitations of the current work itself: (4) although we tried our best to account for potential heterogeneity resulting from the different instruments used (conducting meta-regression analyses and sensitivity analyses according to studies that used CTQ and PANSS or not) and despite finding no evidence that they may have affected our results, it was impossible to account for all the possible variations across instruments utilized. For example, 6 of the 47 papers[12, 37–39, 42, 43] included in their continuous cumulative scores of GA some other life events that were not among our inclusion criteria. Moreover, although most of the symptom clusters defined by the dimensions overlapped across scales, as shown in supplementary table S3, there was some unavoidable nonoverlap, and this needs to be considered when interpreting our data. (5) Adversities tend to co-occur and are highly correlated[5]; thus, the study of the individual impact of each one separately does not necessarily represent the real-life setting in patients who are exposed to multiple adversities. Thus, when we discuss the presence of specific pathways, the reader needs to consider that such pathways may operate simultaneously in polytraumatized individuals. (6) The effect sizes found in our analyses were generally weak or moderate at best (for the depressive domain). Thus, we need to consider that some of the significant results

found in this review can be highly dependent on sample sizes bias and could be affected by other potential confounding variables that have not been systematically addressed by studies included in this work given a lack of data (such as years of education, duration of untreated psychosis, or the percentage of cannabis smokers).

Evidence for General Effects by CA Broadly Defined and Abuse

CA Broadly Defined (GA): we found evidence for the general effects of overall adversity and all psychopathological dimensions. Our results are not in line with the only previous meta-analysis in the field, which found that a general measure of CA was associated with the positive but not the negative dimension[2]. More precisely, that study found, on negative symptoms, a correlation coefficient of r = 0.04 (P = .095) with negative symptoms, whilst we observe a coefficient of r = 0.09 (P < .001) in our study. This discrepancy could be explained by our larger sample (15 studies and 3712 participants in Bailey et al2 compared to 25 studies and 4562 participants in the current work). In addition to the positive and negative dimensions, we further extended the association to the dis- organized, depressive, and manic domains.

GA was measured mostly by adding different forms of traumas and creating a cumulative continuous score, so our results are capturing the presence of cumulative effects. Thus CA, measured by the cumulation of adversities, is transsymptomatic and leads to a more serious form of psychosis with higher severity of various symptoms that also co-occur[5,7]. There is evidence that some symptoms, particularly low mood, anxiety[6] , or dissociation[44] may be sequentially related to psychosis in traumatized individuals. Thus, it is likely that, in individuals with various forms of abuse and neglect, multiple and dynamic noncompeting mediating mechanisms are operating simultaneously[6], adding complexity when trying to disentangle specific mediating pathways in polytraumatized individuals. On the other hand, this highlights the idea that people with psychosis and multiple traumas are severely impaired in a variety of psychopathological domains, which suggests that we should consider them as a particularly vulnerable population within the psychosis spectrum, requiring special attention in clinical settings.

Abuse: the positive association of abuse categories was consistent for the positive and depressive dimension, weaker for the negative, only tentatively for the manic, and ab- sent for the disorganized. Nonetheless, we found very few studies in the latter 2 dimensions, suggesting that the lack of evidence may be caused by insufficient sample size. In terms of the positive dimension, we replicated findings from Bailey et al,[2] who found an association with SA, being the only subtype examined in their work. We extended their findings by showing that the association found with the positive dimension is also present for emotional and PA as well. This consolidates the evidence that abuse is not only associated with psychosis onset[1] but also with higher severity of the positive dimension in those with the disorder[3,5,45] .In terms of negative symptoms, against a quite widespread belief that the link between CA and negative symptoms is limited to neglect[46] ,and contrary to Bailey et al[2], we found some evidence of a week association between sexual (r = 0.05), physical (r = 0.09)

but not EA and the negative dimension. The weak effects sizes do not allow us to draw conclusions about a possible differential impact between these abuse subtypes on the negative dimension, but, certainly, this needs to be addressed carefully in future research.

Evidence for Specific Effects by Neglect

Neglect subtypes were exclusively related to the negative and depressive dimensions but not with the positive or manic, with not enough studies in the disorganized domain to draw conclusions. This differential impact of neglect on the positive and the negative dimensions replicates what was found by Bailey et al[2] .Research understanding the pathways linking neglect and the negative symptoms is almost nonexistent. To the best of our knowledge, only one study conducted in clinical samples suggests a connecting role of mentalizing abilities and attention deficits[47] .Thus, more research in this area is needed.

The Depressive Dimension is Affected by all Forms of CA

A consistent association between all categories with the depressive symptoms was found, with the stronger effects being present for EA (r = 0.32). This supports the view that the well-known link between trauma with depression[48] also applies when depression is measured as an out- come in those with psychosis. Moreover, it highlights the importance of targeting mood in the treatment of people with psychosis and trauma; not only do those symptoms by themselves strongly impact on functioning and quality of life[49] but also mood appears as a potential mediating mechanism connecting trauma with the positive symptoms as recently suggested[6].

Conclusions

Our meta-analysis suggests that CA measured broadly is associated with greater severity of all main dimensions in psychosis; this is also the case for experiences of abuse, although more studies examining manic and disorganized dimensions are needed. We found evidence for some specific effects, such as the effect of neglect on the de- pressive and negative dimension exclusively, which opens a new avenue for future research investigating possible mediating pathways. Against previous reports[2], we found evidence that sexual and PA, but not EA, are associated with the negative dimension in those with psychosis, which also opens new avenues. The depressive dimension is the most severely affected by all forms of trauma with the strongest effects across all analyses conducted, showing the importance of treating depressive symptoms in traumatized patients with psychosis, given the sup- porting evidence of a partial mediation of mood-related symptoms in the adversity–psychosis association[6]

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References

1. Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient- control, prospective- and cross-sectional cohort studies. Schizophr Bull. 2012;38(4):661–671.

2. Bailey T, Alvarez-Jimenez M, Garcia-Sanchez AM, Hulbert C, Barlow E, Bendall S. Childhood trauma is as- sociated with severity of hallucinations and delusions in psychotic disorders: a systematic review and meta-analysis. Schizophr Bull. 2018;44(5):1111–1122.

3. Bentall RP, de Sousa P, Varese F, et al. From adversity to psychosis: pathways and mechanisms from specific adversi- ties to specific symptoms. Soc Psychiatry Psychiatr Epidemiol. 2014;49(7):1011–1022.

4. Read J, van Os J, Morrison AP, Ross CA. Childhood trauma, psychosis and schizophrenia: a literature review with the- oretical and clinical implications. Acta Psychiatr Scand. 2005;112(5):330–350.

5. Morgan C, Gayer-Anderson C. Childhood adversities and psychosis: evidence, challenges, implications. World Psychiatry. 2016;15(2):93–102.

6. Alameda L, Rodriguez V, Carr E, et al. A systematic review on mediators between adversity and psychosis: potential tar- gets for treatment. Psychol Med. 2020;50(12):1966–1976.

7. van Nierop M, Viechtbauer W, Gunther N, et al; Genetic Risk and OUtcome of Psychosis investigators. Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries.

Psychol Med. 2015;45(6):1277–1288.

8. Bebbington P. Unravelling psychosis: psychosocial epidemi- ology, mechanism, and meaning. Shanghai Arch Psychiatry. 2015;27(2):70–81.

9. Bendall S, Jackson HJ, Hulbert CA. Childhood trauma and psychosis: review of the evidence and directions for psycho- logical interventions. Aust Psychol. 2010;45(4):299–306.

10. Alameda L, Golay P, Baumann PS, Ferrari C, Do KQ, Conus P. Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. J Clin Psychiatry. 2016;77(5):e612–e618.

11. van Dam D, van Nierop M, Viechtbauer W, et al. Childhood abuse and neglect in relation to the presence and persistence of psychotic and depressive symptomatology. Psychol Med. 2015;45(7):1363–1377.

12. Seidenfaden D, Knorr U, Soendergaard MG, et al. The relationship between self-reported childhood adversi- ties, adulthood psychopathology and psychological stress markers in patients with schizophrenia. Compr Psychiatry. 2017;72:48–55.

13. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry. 2016;15(2):118–124.

14. Quattrone D, Di Forti M, Gayer-Anderson C, et al. Transdiagnostic dimensions of psychopathology at first epi- sode psychosis: findings from the multinational EU-GEI study. Psychol Med. 2019;49(8):1378–1391.

15. Moher D, Stewart L, Shekelle P. Implementing PRISMA-P: recommendations for prospective authors. Syst Rev. 2016;5:15.

16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of ob- servational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–2012.

17. American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders. Fourth Edition. Washington, DC: American Psychiatric Association; 1994.

18. World Health Organization The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines Geneva, switzerland: World Health Organization; 1992.

19. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol Med. 2009;39(2):179–195.

20. Friedman S, Harrison G. Sexual histories, attitudes, and behavior of schizophrenic and "normal" women. Arch Sex Behav. 1984;13(6):555–567.

21. Pichot P. [DSM-III: the 3d edition of the diagnostic and statistical manual of mental disorders from the American Psychiatric Association]. Rev Neurol (Paris). 1986;142(5):489–499.

22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–605.

23. Lenhard W, Lenhard A. Calculation of Effect Sizes. Dettelbach, Germany; 2016.

24. Peterson RA, Brown SP. On the use of beta coefficients in meta-analysis. J Appl Psychol. 2005;90(1):175–181.

25. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-Analysis Version 2. Englewood, NJ: Biostat; 2005.

26. Davies C, Segre G, Estradé A, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. Lancet Psychiatry. 2020;7(5):399–410.

27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–634.

28. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta- analysis. Biometrics. 2000;56(2):455–463.

29. Ratner B. The correlation coefficient: Its values range be- tween+ 1/− 1, or do they? J Target Meas Anal Market. 2009;17(2):139–142.

30. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl. 2003;27(2):169–190.

31. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–276.

32. Sayın A, Yüksel N, Konac E, et al. Effects of the adverse life events and Disrupted in Schizophrenia-1 (DISC1) gene polymorphisms on acute symptoms of schizophrenia. DNA Cell Biol. 2013;32(2):73–80.

33. Lysaker PH, Beattie NL, Strasburger AM, Davis LW. Reported history of child sexual abuse in schizo- phrenia: associations with heightened symptom levels and poorer participation over four months in voca- tional rehabilitation. J Nerv Ment Dis. 2005;193(12): 790–795.

34. Ruby E, Rothman K, Corcoran C, Goetz RR, Malaspina D. Influence of early trauma on features of schizophrenia. Early Interv Psychiatry. 2017;11(4):322–333.

35. Sahin S, Yüksel Ç, Güler J, et al. The history of childhood trauma among individuals with ultra high risk for psychosis is as common as among patients with first-episode schizophrenia. Early Interv Psychiatry. 2013;7(4):414–420.

36. Schalinski I, Teicher MH. Type and timing of childhood maltreatment and severity of shutdown dissociation in pa- tients with schizophrenia spectrum disorder. PLoS One. 2015;10(5):e0127151.

37. Kilcommons AM, Morrison AP. Relationships between trauma and psychosis: an exploration of cognitive and dissociative factors. Acta Psychiatr Scand. 2005;112(5): 351–359.

38. Kumari V, Gudjonsson GH, Raghuvanshi S, et al. Reduced thalamic volume in men with antisocial personality disorder or schizophrenia and a history of serious violence and child- hood abuse. Eur Psychiatry. 2013;28(4):225–234.

39. Lindgren M, Mäntylä T, Rikandi E, et al. Childhood adver- sities and clinical symptomatology in first-episode psychosis. Psychiatry Res. 2017;258:374–381.

40. McCabe KL, Maloney EA, Stain HJ, Loughland CM, Carr VJ. Relationship between childhood adversity and clin- ical and cognitive features in schizophrenia. J Psychiatr Res. 2012;46(5):600–607.

41. Stain HJ, Brønnick K, Hegelstad WT, et al. Impact of inter- personal trauma on the social functioning of adults with first- episode psychosis. Schizophr Bull. 2014;40(6):1491–1498.

42. McCabe KL, Maloney EA, Stain HJ, Loughland CM, Carr VJ. Relationship between childhood adversity and clin- ical and cognitive features in schizophrenia. J Psychiatr Res. 2012;46(5):600–607.

43. Stain HJ, Brønnick K, Hegelstad WT, et al. Impact of inter- personal trauma on the social functioning of adults with first- episode psychosis. Schizophr Bull. 2014;40(6):1491–1498.

44. Longden E, Branitsky A, Moskowitz A, Berry K, Bucci S, Varese F. The relationship between dissociation and symptoms of psychosis: a meta-analysis. Schizophr Bull. 2020;46(5):1104–1113.

45. Murray R, Mondelli V, Stilo S, et al. The influence of risk fac- tors on the onset and outcome of psychosis: what we learned from the GAP study. Schizophr Res. 2020;225:63–68.

46. Ross CA, Anderson G, Clark P. Childhood abuse andthe positive symptoms of schizophrenia. Psychiatr Serv. 1994;45(5):489–491.

47. Mansueto G, Schruers K, Cosci F, van Os J; GROUP Investigators. Childhood adversities and psychotic symptoms: the potential mediating or moderating role of neurocognition and social cognition. Schizophr Res. 2019;206:183–193.

48. Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: a meta-analysis of published literature. Childhood trauma and adult depression. Eur Psychiatry. 2015;30(6):665–680.

49. Alameda L, Golay P, Baumann PS, et al. Mild depres- sive symptoms mediate the impact of childhood trauma on long-term functional outcome in early psychosis patients. Schizophr Bull. 2017;43(5):1027–1035.

3.2 (study 2) this chapter has been reproduced in full from the following paper

A systematic review on mediators between adversity and psychosis: potential targets for treatment

Luis Alameda, Victoria Rodriguez, Ewan Carr, Monica Aas, Giulia Trotta, Paolo Marino, Natasha Vorontsova, Andres Herane-Vives, Romayne Gadelrab, Edoardo Spinazzola, Marta Di Forti, Craig Morgan and Robin M Murray

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Key words: Adversity; mechanisms; mediation; psychosis

Abstract

Various psychological and biological pathways have been proposed as mediators between childhood adversity (CA) and psychosis. A systematic review of the evidence in this domain is needed. Our aim is to systematically review the evidence on psychological and biological mediators between CA and psychosis across the psychosis spectrum. This review followed PRISMA guidelines. Articles published between 1979 and July 2019 were identified through a literature search in OVID (PsychINFO, Medline and Embase) and Cochrane Libraries. The evidence by each analysis and each study is presented by group of mediator categories found. The percentage of total effect mediated was calculated. Forty-eight studies were included, 21 in clinical samples and 27 in the general population (GP) with a total of 82 352 subjects from GP and 3189 from clinical studies. The quality of studies was judged as 'fair'. Our results showed (i) solid evidence of mediation between CA and psychosis by negative cognitive schemas about the self, the world and others (NS); by dissociation and other post-traumatic stress disorder symptoms; and through an affective pathway in GP but not in subjects with disorder; (iii) lack of studies exploring biological mediators. We found evidence suggesting that various overlapping and not competing pathways involving post-

traumatic and mood symptoms, as well as negative cognitions contribute partially to the link between CA and psychosis. Experiences of CA, along with relevant mediators should be routinely assessed in patients with psychosis. Evidence testing efficacy of interventions targeting such mediators through cognitive behavioural approaches and/or pharmacological means is needed in future.

Introduction

Evidence has accumulated over the past 15 years showing that exposure to childhood adversity (CA) – in the form of abuse, neglect and bullying – is associated with increased risk of psychosis across the spectrum, from low-level experiences to disorder (Varese et al., 2012b). This has led to substantial research trying to understand possible underlying psychological and bio- logical mechanisms, thus a systematic review in the topic is needed.

In terms of biological mechanisms, evidence covers dysfunction in pathways such as the stress response system (Ruby et al., 2014), dopaminergic neurotransmission (Howes, McCutcheon, Owen, & Murray, 2017), inflammation and redox dysregulation (Steullet et al., 2016), and changes in stress-related brain structures such as the amygdala or the hippo- campus (Van Winkel, Van Nierop, Myin-Germeys, & Van Os, 2013). For example, it has been suggested that excessive exposure to stress might lead to an overactivation of the hypothalamic–pituitary–adrenal axis. This could be toxic for hippocampal functioning (Aas et al, 2014; Teicher, Anderson, & Polcari, 2012), which might in turn contribute to the emergence of psychosis. Furthermore, acute social stress has also been found to increase striatal dopamine release in individuals with a psychotic disorder, and in individuals with CA (Howes et al., 2017). In addition, inflammatory dysfunctions as well as redox dysregulation conditions (Alameda et al., 2018; Steullet et al., 2016) have been found among individuals exposed to CA and among patients with psychosis.

Several psychological models have also been proposed to explain the relationship between CA and psychosis. These models look at the same epiphenomena from different angles and can be complementary, thus they should not be considered necessarily as competing explanations. One theory postulates that CA may lead to psychosis through a pathway of heightened emotional distress, characterised by hypersensitivity to daily-life stressors, leading to anxiety and depression (Bebbington, 2015; Myin-Germeys & van Os, 2007) and it is often called 'affective pathway to psychosis'. Another model proposes that severe forms of CA might lead to cognitive biases, such as negative schema about the self and the world, and others (NS) which, in addition to a heightened tendency to attribute experiences to external causes, might give rise to paranoia, ideas of reference (Garety, Bebbington, Fowler, Freeman, & Kuipers, 2007; Morrison, Frame, & Larkin, 2003). Another putative pathway emphasises the mediating role of post-traumatic stress disorder (PTSD)-related symptoms, such as dissociation and intrusive memories (Hardy, 2017). It is suggested that flash-backs could be interpreted as being externally generated, leading to hallucinatory experiences and hampering reality testing (Allen, Coyne, & Console, 1997; Morrison et al., 2003). Other possible mediators have been proposed such as dysfunctional attachment

(Gumley, Taylor, Schwannauer, & MacBeth, 2014; Read & Gumley, 2010).

Despite the fact that several narrative reviews on the topic exist (Bebbington, 2015; Bentall et al., 2014; Freeman & Garety, 2014; Gibson, Alloy, & Ellman, 2016; Misiak et al., 2017; Morgan & Gayer-Anderson, 2016; Read, Fosse, Moskowitz, & Perry, 2014; Van Winkel et al., 2013), to date only a single systematic review has been conducted (Williams, Bucci, Berry, & Varese, 2018). Williams et al. (2018) examined psychological mediators between CA and psychosis including papers up to September 2017, which consisted of a total of 37 studies. They found evidence for a mediation by cognitive bias, by symptoms of PTSD, and by affective processes. However, this review is limited by the fact that (i) they did not analyse and discuss the evidence of all the mediation pathways tested within each study and limited to the summary of the main conclusions provided by each author; (ii) no information on the percentage of total effect mediated was systematically extracted and summarised; (iii) did not include biological mediators. The present study overcomes these limitations and includes additional papers published up to July 2019, providing an additional period of 22 months of research in the field.

Our aim is to systematically review the evidence on psychological and biological mediators between CA and psychosis across the spectrum from low-level experiences in general populations (GP) to disorder. Based on the concept of psychosis as a continuum (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009), covering all the spectrum may allow a better understanding of the mediational processes operating at different stages. Results will be grouped based on existing proposed theoretical mechanisms and discussed in terms of potential treatment interventions.

Methods

Search strategy

A systematic review of the literature was conducted following Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) (Moher et al., 2009) guidelines and was registered in PROSPERO (Moher, Booth, & Stewart, 2014) in July 2018 (registration number: CRD42018100846). The main search was conducted on MEDLINE, EMBASE and PsycINFO, through Ovid provider, and in Cochrane Libraries in June 2018 and it was updated in July 2019. We searched Medical Subjects Headings (MeSH) and keywords related to: (1) CA, (2) mediation and (3) psychosis, using the Boolean operator 'AND' (full list of search terms as well as details on the screening procedure are provided in online Supplementary Material.

Inclusion and exclusion criteria

Included studies were those that (1) examined psychological or biological mediators of the relationship between CA and (i) psychosis onset (these include case-control studies), (ii) severity of positive symptoms in patients with a psychotic disorder, in subjects at risk for psychosis [as described by the Yung et al. (2005)] or (iii) severity of attenuated psychotic symptoms (these include also studies measuring psychosis proneness and psychotic-like

experiences) in the GP; (2) for clinical studies only (not for GP), psychotic disorder was defined according to Diagnostic and Statistical Manual of Mental Disorders [DSM-III, DSM-III-R, DSM-IV, DSM IV-TR (American Psychiatric Association, 1994)], or International Classification of Diseases, Ninth or Ten Revision (ICD-9, ICD-10) (World Health Organization, 1992); and (3) were performed in humans; (4) included CA occurring before age 18 and involving exposure to sexual, physical and emotional abuse, physical and emotional neglect or bullying (or equivalent experiences); (5) assessed both mediators and outcomes using validated methods and scales; (6) employed a robust method for testing mediation in the analyses and fulfilling the Baron and Kenny criteria (Hayes, 2009); used pathways analyses or structural equation models; (7) had been published as original research.

Exclusion criteria were: (1) including more than 20% of participants aged 65 years or over, in accord with others (Van Os et al., 2009); (2) being performed in homogeneous samples of specific populations (such as pregnant women or samples from forensic settings); (3) including non-psychological mediators (e.g. being exposed to later life hassles or level of education); (4) not being published in the English language.

Quality assessment and data extraction methodology

Quality assessment was carried out using the Newcastle–Ottawa Scale (Stang, 2010) for cohort studies by two independent reviewers (LA and PM). Details on the instrument items and quality assessment procedures can be found in Supplementary Material. The agreed quality grades of each study are presented in Supplementary Table S1a–S1c. To summarise the evidence, we constructed Tables 1–3 and online Supplementary Table S2. We enumerated the number of studies and analyses indicating whether there was evidence for mediation or lack of mediation in clinical samples and in GP studies. These results were extracted from the text or tables of each paper. We included all mediation analyses (i.e. distinct pathways tested) from each paper, meaning the total number of analyses was greater than the number of papers. In Tables 1–3 and online Supplementary Table S2, as well as in the text we provided the 'percentage of analyses showing evidence of mediation', across all categories of mediators (see online Supplementary Material for more details). We also collected information on the percentage of total effect that was mediated, which is equivalent to the amount of mediation in each pathway tested. Figure 1 represents the percentage of the total effect mediated by each analysis for which information was available across the most meaningful categories described in the Results section. The type of adversity and outcome are also shown to have a visual representation of the pathway. As an indicative measure, the median value of all the analyses per category is also highlighted in the figure and presented in the text.

Further details on data extraction procedures can be found in Supplementary Material and in Fig. 1 footnote. In online Supplementary Tables S1a–S1c, we also provide details on the significance of the indirect and direct effects as well as the proportion of total effect mediated in each study.

Table 1

Summary of evidence for mediators between adversity and psychosis in clinical samples (subjects at risk for psychosis and with psychotic disorder) and in general population.

Category (*N* total analyses/studies[a])	Clinical samples Number of analyses (number of studies)			General population Number of analyses (number of studies)			Total
	Evidence of mediation	Null mediation	% analyses supporting mediation	Evidence of mediation	Null mediation	% analyses supporting mediation	% analyses supporting mediation
Dissociation (43/12)	6(4)	20(6)	23%	12(6)	5(1)	70%	42%
Dysfunctional attachment (18/5)	1(1)	3(2)	25%	7(3)	7(2)	50%	44%
Affective pathway (32/15[b,c])	–	3(1)	0%	21(9)	8(5)	72%	66%
Loneliness (7/4)	1(1)	–	100%	4(3)	2(1)	66%	83%
Cognitive biases (53/21[c])	8(6)	13(5)	38%	20(8)	12(7)	62.5%	53%
Others PTSD symptoms (7/4)	5(3)	1(1)	83%	1(1)	–	100%	86%
Others[d] (10/6)	1(1)	1(1)	50%	7(3)	1(1)	87.5%	80%

[a] *We considered one analysis as 'supportive of mediation' when a significant mediation (partial, total or 'suggested') was found, and negative when null mediation was found.*

[b] *Isvoranu et al. was only included in the articles count within but not in the analyses count.*

[c] *Ashford et al. was only included in the articles count but not in the analyses count.*

[d] *Others included anomalous self-experiences; mania; time-perspective capabilities and compulsions as mediators.*

Table 2

Summary of evidence for mediators within the affective pathway category between adversity and psychosis in clinical samples (subjects at risk for psychosis and with psychotic disorder) and in general population.

Category (*N* total analyses/studies[a])	Clinical samples Number of analyses (number of studies)			General population Number of analyses (number of studies)			Total
	Evidence of mediation	Null mediation	% analyses supporting mediation	Evidence of mediation	Null mediation	% analyses supporting mediation	% analyses supporting mediation
Affective pathway (32/15)[b,c]	–	3(1)	0%	21(9)	8(5)	72%	66%
Anxiety (7/4)	–	1(1)	0%	4(2)	2(2)	66%	57%
Depression (9/6)	–	1(1)	0%	4(2)	4(3)	50%	44%
Emotional dysregulation (8/4)	–	1(1)	0%	5(2)	2(2)	71%	62.5%
Stress sensitivity/perception (5/2)	–	–	–	5(3)	–	100%	100%
Composite (2/1)	–	–	–	2(2)	–	100%	100%

[a] *We considered one analysis as 'supportive of mediation' when a significant mediation (partial, total or 'suggested') was found, and negative when null mediation was found.*

[b] *Isvoranu et al. was only included in the articles count within but not in the analyses count.*

[c] *Ashford et al. was only included in the articles count but not in the analyses count.*

Table 3

Summary of evidence for mediators within the cognitive biases category between adversity and psychosis in clinical samples (subjects at risk for psychosis and with psychotic disorder) and in general population.

	Clinical samples Number of analyses (number of studies)			General population Number of analyses (number of studies)			Total
Category (*N* total analyses/studies)	Evidence of mediation	Null mediation	% analyses supporting mediation	Evidence of mediation	Null mediation	% analyses supporting mediation	% analyses supporting mediation
Cognitive biases (53/21)[a]	8(6)	13(5)	38%	20(8)	12(7)	62.5%	53%
Negative schemas (16/7)	5(3)	2(1)	71%	5(4)	4(1)	55.5%	62.5%
ELC (5/3)	-	-	-	4(2)	1(1)	80%	80%

[a] *We considered one analysis as 'supportive of mediation' when a significant mediation (partial, total or 'suggested') was found, and negative when null mediation was found.*

Results

We identified 48 studies that met our inclusion criteria from the 2310 studies found in the initial searches (2018 and 2019 com- bined) (online Supplementary Fig. S1).

Twenty-one studies were conducted in clinical samples [four in First Episode of Psychosis (FEP) or early psychosis patients (Evans, Reid, Preston, Palmier-Claus, & Sellwood, 2015; Morgan et al., 2014; Peach, Alvarez-Jimenez, Cropper, Sun, & Bendall, 2019; Sun et al., 2018), three in Ultra High Risk (UHR) patients (Appiah-Kusi et al., 2017; McDonnell, Stahl, Day, McGuire, & Valmaggia, 2018; Thompson et al., 2016), 14 in non-FEP patients (Cancel et al., 2015; Chatziioannidis et al., 2019; Choi et al., 2015; Hardy et al., 2016; Isvoranu et al., 2017; Perona-Garcelán et al., 2012; Quidé, O'Reilly, Watkeys, Carr, & Green, 2018; Schalinski et al., 2019; Steenkamp, Weijers, Gerrmann, Eurelings-Bontekoe, & Selten, 2019; Styła, Stolarski, & Szymanowska, 2019; Van Dam, Korver-Nieberg, Velthorst, Meijer, & de Haan, 2014; Varese, Barkus, & Bentall, 2012a; Weijers et al., 2018; Wickham & Bentall, 2016) 27 in GP (Ashford, Ashcroft, & Maguire, 2012; Bortolon & Raffard, 2018; Bortolon, Seillé, & Raffard, 2017; Boyda & McFeeters, 2015; Boyda, McFeeters, Dhingra, & Rhoden, 2018; Cole, Newman-Taylor, & Kennedy, 2016; Fisher, Appiah-Kusi, & Grant, 2012, 2013; Gawęda, Göritz, & Moritz, 2019; Gibson, Reeves, Cooper, Olino, & Ellman, 2019; Goodall, Rush, Grünwald, Darling, & Tiliopoulos, 2015; Jaya, Ascone, & Lincoln, 2017; Lincoln, Marin, & Jaya, 2017; Marwaha & Bebbington, 2015; Marwaha, Broome, Bebbington, Kuipers, & Freeman, 2014; McCarthy-Jones, 2018; Mętel et al., 2020; Murphy, Murphy, & Shevlin, 2015; Perona-Garcelán et al., 2014; Pinto-Gouveia, Matos, Castilho, & Xavier, 2014; Rössler, Ajdacic-Gross, Rodgers, Haker, & Müller, 2016; Sheinbaum, Kwapil, & Barrantes-Vidal, 2014; Shevlin, McElroy, & Murphy, 2015; Sitko, Bentall, Shevlin, O'Sullivan, & Sellwood, 2014; van Nierop et al., 2014; Wolke, Lereya, Fisher, Lewis, & Zammit, 2014; Yamasaki et al., 2016)]. Our review included 82 352 subjects from the GP and 3189 subjects from clinical studies. Participant ages ranged from 18.5 to 44.6 years old in clinical samples (30.4 on average)

and between 9.8 and 51.7 in the GP (34.3 on average). In clinical samples, 35% of the participants were women, compared with 37% of the volunteers.

This total number of analyses excludes two studies with an extremely high number of analyses [one used a network-based approach exploring multiple connections between adversity and symptoms (Isvoranu et al., 2017), the other included up to 28 (Ashford et al., 2012)]. These studies would have distorted the numerical summaries and therefore are described narratively but are not considered in the summary tables. Overall, 170 analyses were included in this review (ranging between 1 and 12 analysis per paper). The quality check agreement between the two raters was 81.8%. Overall, the quality was graded as 'fair' (between 4 and 7) for all studies except one, where quality was judged as 'good' (Fisher et al., 2013). Studies of biological mediators tended to be graded with lower scores failing to provide estimates of the only 4/47 studies (Fisher et al., 2013; Lincoln et al., 2017; Thompson et al., 2016; Wolke et al., 2014) used a prospective design. Eight (Ashford et al., 2012; Bortolon et al., 2017; Boyda et al., 2018; Boyda & McFeeters, 2015; Cancel et al., 2015; Isvoranu et al., 2017; Jaya et al., 2017; Marwaha et al., 2014) of the 47 studies reported a mediating effect but failed to provide estimates of the indirect and direct effects and thus were classified as 'suggested mediation', as described above and in online Supplementary. Table 1 summarises the evidence for each analysis by mediator category. Given the high number of analyses and the heterogeneity found for the affective pathway, cognitive schema pathway and dis- sociation, three detailed tables were constructed for these groups (see Tables 2 and 3 and online Supplementary Table S2, respectively) presenting the evidence for each subcategory.

Figure 1 summarises the percentage of total effect mediated for 58 analyses included in 25 papers across the most relevant category of mediators found in our review (only categories being explored in at least three papers are shown in Fig. 1, the percent- age of total effect mediated of the remaining analyses is shown in online Supplementary Tables S1a–S1c). The most relevant categories of mediators found in our review were: dissociation, dysfunctional attachment, affective pathway to psychosis, loneliness, cognitive biases, other PTSD symptoms, other psychological mediators and biological mediators.

Figure 1

Percentage of total effect mediated by each mediator. Presented by adversity types, mediator and outcome.



1. Appiah-Kusi; 2. Bortolon; 3. Chatziioanni; 4. Choi; 5. Cole; 6. Fisher; 7. Gibson; 8. Goodall; 9. Hardy; 10. Lincoln; 11. Marwaha; 12. McCarthy; 13. Mętel; 14. Murphy; 15. Peach; 16. Perona-Garcelan A; 17. Perona-Garcelan B; 18. Schalinski; 19. Sheinbaum; 20. Sitko; 21. Sun; 22. Van Nierop; 23. Varese; 24. Wolke; 25. Yamasaki;

Notes.

Where authors appears more than once, this indicates that multiple analyses were carried out for this same set of predictor, group, and outcome. See tables for details.

We managed to obtain the percentage of total effect mediated for 83.1% of the analyses that found a significant indirect effect (103 out of the 124 positive analyses, 44 of which were already calculated and 59 which were calculated as described in Supplementary Material - Data extraction procedures section). In this table are presented the percentage of the most meaningful categories of mediators found in our results. As presented in the right-hand side of the figure, the type of predictor is detailed by different symbols and the type of outcome is detailed by different colours.

Dissociation

Despite only 42% of analyses showing evidence of mediation, 10/12 studies (Bortolon et al., 2017; Bortolon & Raffard, 2018; Cole et al., 2016; Gibson et al., 2019; Perona-Garcelán et al., 2012, 2014; Schalinski et al., 2019; Sun et al., 2018; Varese et al., 2012a; Yamasaki et al., 2016) were supportive of mediation, against 2/12 that were not (Evans et al., 2015; Thompson et al., 2011). The percentage of total effect mediated was consistently high across analyses within this category, with a median of around 50% of total effect explained (Fig. 1). As illustrated in Fig. 1, most of the studies showing evidence of mediating effects used hallucinations as an outcome and explored trauma as a composite score (Bortolon et al., 2017; Cole et al., 2016; Gibson et al., 2019; Perona-Garcelán et al., 2012, 2014; Varese et al., 2012a; Yamasaki et al., 2016), while only two (Cole et al., 2016; Sun et al., 2018) studies found positive effects with delusions as an outcome . As shown in online Supplementary Table S2, it was not possible to draw conclusions about which dissociative symptoms were more likely to mediate the adversity–psychosis association.

Dysfunctional attachment

Despite overall 44% of analyses showing evidence of mediation, 3/ 5 (Chatziioannidis et al., 2019; Sheinbaum et al., 2014; Sitko et al., 2014) papers showed mixed findings, 1/5 (Van Dam et al., 2014) showed no evidence of mediation and just 1/5 (Goodall et al., 2015) showed consistent evidence of mediation across all its ana- lyses. As seen in Fig. 1, the percentages of total effect mediated showed a small median value of around 12%.

Affective pathway

Only one paper explored this pathway in clinical samples (Thompson et al., 2016) showing no evidence of mediation. The remaining 14 (Ashford et al., 2012; Fisher et al., 2012, 2013; Gibson et al., 2019; Isvoranu et al., 2017; Lincoln et al., 2017; Marwaha et al., 2014; Marwaha & Bebbington, 2015; McCarthy-Jones, 2018; Mętel et al., 2020; Rössler et al., 2016; van Nierop et al., 2014; Wolke et al., 2014; Yamasaki et al., 2016) papers (including 29 analyses) were conducted in GP samples, with 66% of analyses supporting mediation. In total, 12/14 (Ashford et al., 2012; Fisher et al., 2012, 2013; Gibson et al., 2019; Isvoranu et al., 2017; Lincoln et al., 2017; Marwaha et al., 2014; Marwaha & Bebbington, 2015; Mętel et al., 2020; Rössler et al., 2016; van Nierop et al., 2014; Wolke et al., 2014) of the GP studies found evidence of mediation and three of them were prospectively graded high in quality assessment (Fisher et al., 2013; Lincoln et al., 2017; Wolke et al., 2014) (online Supplementary Table S1b).

We divided the affective pathway into these subcategories: anx- iety, depression, affective dysregulation and stress sensitivity (Table 2), results per subcategories showed an overall high pro- portion of analyses supporting mediation (Table 2). As seen in Fig. 1, the median percentages of total effect mediated for anxiety and depression were at around 20% while that of affective dysre- gulation was at around 35%.

Feeling of loneliness

In total, 83% of analyses showed evidence of mediation. Only one study (Steenkamp et al., 2019) was conducted in clinical samples and showed evidence for mediation. In GP, two studies showed evidence of mediation (Boyda & McFeeters, 2015; Jaya et al., 2017) and another showed mixed findings (Shevlin et al., 2015). The low number of analyses did not allow us to draw consistent conclusions in terms of specific pathways between adversity–psychosis (see online Supplementary Tables S1a, S1b for details).

Cognitive biases

In total, 53% of analyses overall showed evidence of mediation in this category. In terms of papers, 17/22 were supportive of mediation (Appiah-Kusi et al., 2017; Ashford et al., 2012; Bortolon et al., 2017; Boyda et al., 2018; Evans et al., 2015; Fisher et al., 2013; Gawęda et al., 2019; Gibson et al., 2019; Hardy et al., 2016; Jaya et al., 2017; McDonnell et al., 2018; Mętel et al., 2020; Murphy et al., 2015; Peach et al., 2019; Pinto-Gouveia et al., 2014; van Nierop et al., 2014; Wickham & Bentall, 2016), 5/20 were not (Fisher et al., 2012; Morgan et al., 2014; Perona-Garcelán et al., 2014; Weijers et al., 2018; Yamasaki et al., 2016). Results were more likely to show evidence of medi- ation when conducted in the GP, compared with clinical samples (62.5% v. 38% of analyses were supportive of mediation, respectively, Table 1).

In order to explore specific domains within the category, we divided this category into: negative schemas about self, others and the world (NS) and external locus of control (ELC) as they were the most represented subdomains. Briefly, the evidence for the former showed that 62.5% of analyses were supportive of mediation with a proportion of total effect mediated of around 47% of median value (Fig. 1). No studies in clinical samples explored the ELC and 2/3 studies in general GP showed evidence of mediation (Fisher et al., 2013; Gibson et al., 2019). Other biases such as maladaptive schemas (Bortolon et al., 2017; Boyda et al., 2018), low self-esteem (Fisher et al., 2013), aberrant salience (Gawęda et al., 2019) were insufficient in numbers of studies to draw conclusions. No specific pathways could be highlighted between some types of adversities and outcomes.

Other PTSD symptoms, time perspective, mania, compulsions and psychological resilience

Other PTSD symptoms not described in the other categories included post-traumatic intrusions, avoidance and numbing, or a general measure of post-traumatic symptoms. Overall, the results suggested evidence of mediation (Choi et al., 2015; Hardy et al., 2016; McCarthy-Jones, 2018; Peach et al., 2019). The percentage of total effect mediated was also high, with a median value just below 50% (see Fig. 1). Other mediators including five studies that did not fit into the aforementioned categories are presented in online Supplementary Table S1a, S1b and include time perspective (Styła et al., 2019), mania (Thompson et al., 2016), compulsions (McCarthy-Jones, 2018), a measure of psychological resilience (Mętel et al., 2020) and self-disturbances (Gawęda et al., 2019). Particularly, strong mediating effects were found through anomalous self-experiences (Gawęda et al., 2019).

Biological mediators

Surprisingly, only two studies examining biological mechanism as potential mediators between CA and psychosis were included (online Supplementary Table S1c). One found no evidence for a mediation of the inferior frontal gyrus activation between CA and positive symptoms (Quidé et al., 2018); another showed that the grey matter density in the dorsolateral prefrontal cortex was mediating the link between emotional neglect and disorganised symptoms in patients (Cancel et al., 2015).

Discussion

From this systematic review of 47 papers, we found evidence of partial mediation between adversity and psychosis through various overlapping and not competing psychological mechanisms. The link between adversity and psychosis was particularly driven by NS, by dissociation and other PTSD symptoms. For GP samples there was good evidence for mediation through an affective pathway (affective dysregulation, anxiety and depression), but there were insufficient studies looking at this in individuals at risk for psychosis and in patients suffering from the disorder to allow conclusions to be drawn about its mediating role in clinical settings. We found no evidence supporting the mediating role of dysfunctional attachment styles in the GP; there were too few studies addressing this mediator in clinical samples to permit conclusions. Other mediators showing interesting findings included loneliness, stress sensitivity, anomalous self-disturbances and ELC, but generalisation of findings is limited due to the low number of studies. Contrary to our expectations, only two papers (Cancel et al., 2015; Quidé et al., 2018) fulfilled our inclusion criteria examining biological mediators. There is evidence that potential biological mediators are associated with adversity and with psychosis, but very few considering mediation effects directly, using psychosis as an outcome in the pathway. So, the speculation on biological mediators is currently mostly conjecture showing an urgent need for more research in this field.

Strengths and limitations

The findings of this review should be interpreted in the context of various strengths and limitations. A major strength is the large scale of this review including 47 studies, 82 352 subjects from the GP and 3189 from clinical studies. This has allowed us to cover multiple mediator groups with a sufficient number of participants and show new pathways that did not appear in William et al., systematic review (Williams et al., 2018), such as the role of loneliness. Second, we have not limited our analysis to the description of the main finding of each study and to report whether the mediation was present or absent, but we have also examined the amount of mediation of each pathway by providing the percentage of total effect mediated (when this was possible). We believe this is an important point given that just limiting to the significance of the p value of the indirect effects is highly dependent on the sample size and thus totally limited. Calculating the proportion of the effect that is mediated provides a more accurate understanding of the mediational processes. Moreover, we believe that our concrete clinical implications (see below) may be useful and could contribute to

a better knowledge of trauma-informed care in services treating individuals with psychosis.

Some limitations must be mentioned. First, only four studies used a prospective design to estimate the indirect effects, while in the remaining studies, it cannot be excluded that the mediator resulted as a consequence of psychosis. Second, CA was measured retrospectively in all studies except two (Fisher et al., 2013; Wolke et al., 2014) which were conducted in GP. In patients, this can constitute a risk of bias given the difficulties of patients to recall their experiences and to disclose these openly in assessment by research assistants. Third, the percentage of total effect could not be obtained nor calculated in 17% of the analyses that were supportive of mediation (authors did not provide details on the indirect, direct and total effects), thus our Fig. 1 is not totally representative of the total number of analyses included in this review. In addition, some mediators (i.e. attachment styles, anxiety and depression) were found to be highly explored in the GP but very little in clinical samples, which is an important limitation of current literature in the field and which limits the extent to which we can extrapolate our conclusions to clinical intervention in clinical settings. Furthermore, papers in this review considered that null mediation occurred when the indirect or mediating effects did not reach a significant p value of <0.05. Considering the p value to test the null hypothesis is limited by the fact that is highly dependent on the sample size. Thus, it is likely that in our review, studies conducted in small samples are underestimating potential mediating effects, and this should be taken into con- sideration when interpreting our conclusions. The age range of studies in the GP was quite wide (9.8–51.7 years), and thus the population included in these studies is quite heterogeneous as different confounding factors may operate at different ages; this should be considered as a limitation when interpreting our results. Furthermore, only three papers took into account different mediating effects based on the timing of adversity (McDonnell et al., 2018; Schalinski et al., 2019; Wolke et al., 2014) which is an important limitation of current research as different mediating mechanisms may operate differently based on the developmental period (McGrath et al., 2017). Lastly, there was a time lag between the systematic literature search, in July 2019, and the submission date in February 2020, which means newer studies were not included in the current work.

Evidence for mediational pathways between childhood adversity and psychosis.

Here we will discuss each pathway separately, but as it will be further developed in the clinical implications (Fig. 2) and the conclusions, we believe that the mediating mechanism between CA and psychosis is complex, possibly involving an interplay between these different complementary, con-competing pathways.

Pathway 1: dissociation and PTSD symptoms

Mediation through this pathway was more common when hallucinations were used as an outcome. These two categories, intimately related, showed the highest percentages of total effect mediated (Fig. 1).

The role of post-traumatic dissociation in psychosis was already the focus of research at

the end of the eighteenth century, when Janet, among others, defined hysterical psychosis as characterised by its dissociative and stress-related nature (Moskowitz, Schäfer, & Dorahy, 2009). Current international classifications do not include dissociation among the diagnostic criteria for any form of psychosis. However, contemporary authors such as Ross (2006) and Moskowitz et al. (2009) suggest the existence of a dissociative type of psychosis that could potentially be responsive to psychotherapy focused on trauma.

Accordingly, our findings showing mediation by PTSD symptoms in clinical samples (Choi et al., 2015; Hardy et al., 2016; Peach et al., 2019) are consistent with reports suggesting that similar mechanisms could be involved in psychotic experiences and symptoms of PTSD. For instance, it has been suggested that some hallucinations represent a dissociated type of post- traumatic intrusion, which may not be recognised as such by people with psychosis (Allen et al., 1997; Moskowitz et al., 2009). Our results therefore support the possibility of applying specific psychological interventions, such as cognitive behavioural therapy (CBT), for patients with psychosis, dissociation and PTSD symptoms and with a history of clear-cut traumatic episode. In this regard, two recent systematic reviews exploring the safety and efficacy of trauma-focused therapies in individuals with comorbid PTSD symptoms and psychosis have shown that trauma-focused CBT is safe (Sin & Spain, 2017), can reduce PTSD symptoms (Swan, Keen, Reynolds, & Onwumere, 2017) and can lead to small improvements in positive symptoms after treatment (Brand, McEnery, Rossell, Bendall, & Thomas, 2018).

Pathway 2: cognitive biases

Cognitive schemas about the self, the world and others were the most consistent mediator between CA and psychosis in both clinical samples and GP. Moreover, this category contributed highly to the total effect between CA and psychosis, with a median percentage mediated of around 46% across all analyses (Fig. 1).

This evidence supports previous cognitive models of the development of positive symptoms (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Morrison et al., 2003) which suggest that exposure to severe trauma might contribute to the development of cognitive bias such as NS. Further exposure to stressors or to subtle perceptual abnormalities that are common in the GP (Van Os et al., 2009), and even more common in genetically predisposed individuals, will lead to anomalous conscious self-experiences which will trigger the search for an explanation. The biased schemas, in combination with anomalous self- experience, disrupt the appraisal process leading to a misinter- pretation of reality, and subsequently delusional ideas (Garety et al., 2001; Howes & Murray, 2014; Morrison et al., 2003). Other factors are important in this process, such as the ELC (Thompson et al., 2011), which has shown evidence for medi- ation, especially in GP (Fisher et al., 2013; Gibson et al., 2019). It would be interesting for future research to explore if other cognitive biases such as jumping to conclusions and meta-cognitive deficits can moderate or mediate the connections between CA and psychosis in combination with NS and ELC.

Pathway 3: affective pathway

We found consistent evidence suggesting that anxiety, depression and affective dysregulation might partially mediate the link between CA and low-level psychotic experiences in the GP. The affective component could be a mediational partner along with other mechanisms such as cognitive bias or PTSD-related symp- toms. For example, Fisher et al. (2013) report on a large prospect- ive study, where 100% of the total effect was mediated only when anxiety and depression were added to the model in combination with cognitive bias and low self-esteem. Unfortunately, our inter- pretation is restricted to GP (and thus to attenuated positive symptoms) due to the lack of studies performed in clinical set- tings. Nevertheless, these results support previous claims that the association between CA and psychosis might be mediated by non-psychotic symptoms [otherwise the so-called 'ancillary symptoms of psychosis' (Bebbington, 2015) such as anxiety and depression and affective dysregulation]. These symptoms might be determinants of paranoid thinking; for example, anxiety might lead to anticipation of threat, and low mood might drive negatively biased interpretations of ongoing experience and impact self-esteem and negative schemas about the self, which in turn are precursors of psychotic symptoms, as illustrated in Fig. 2.

Pathway 4: feeling of loneliness

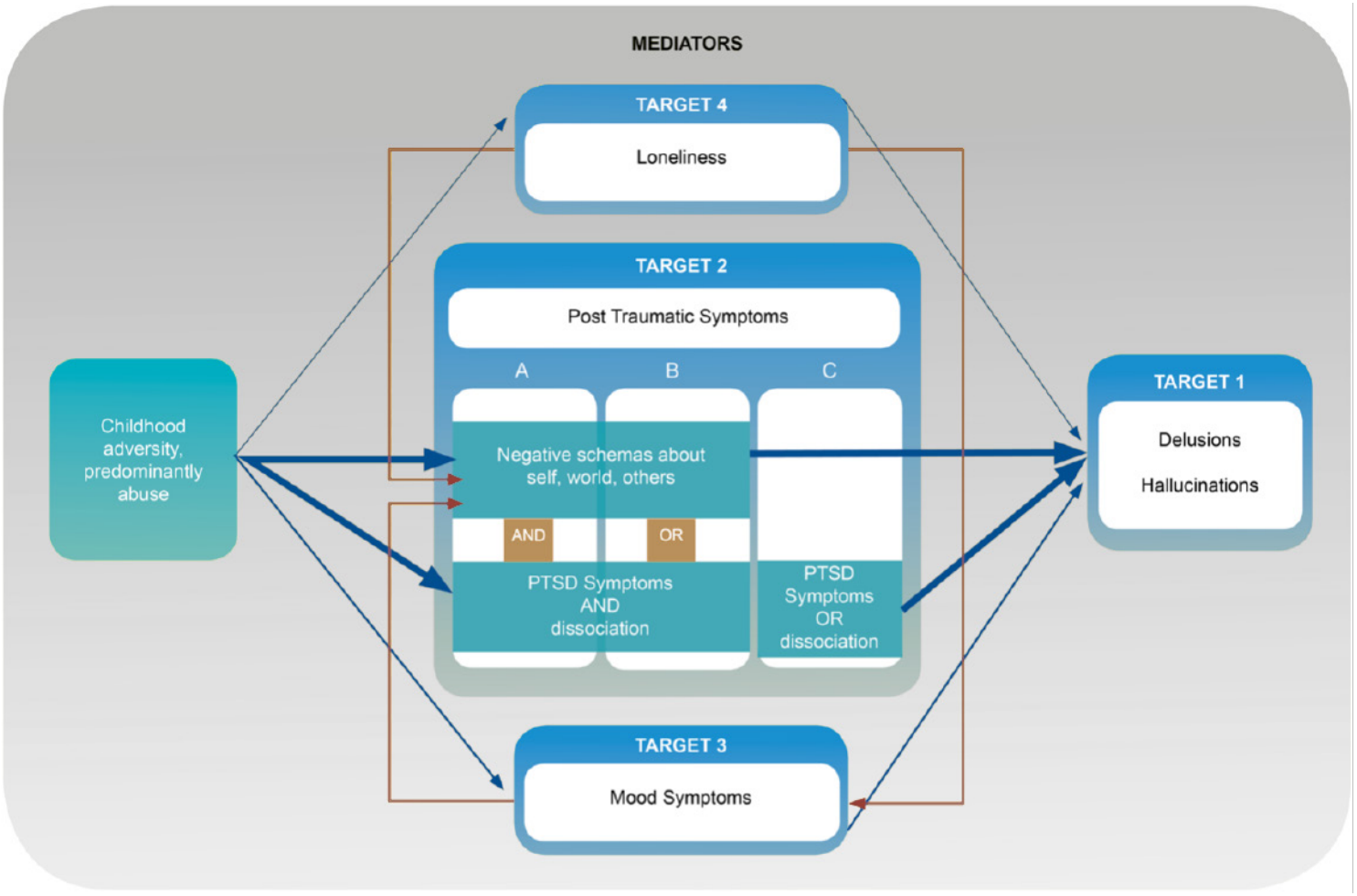
Although only explored in four studies (Boyda & McFeeters, 2015; Jaya et al., 2017; Shevlin et al., 2015; Steenkamp et al., 2019), we found good evidence suggesting that a feeling of lone- liness might mediate the CA–psychosis relationship. We could hypothesise that social withdrawal and loneliness may increase an individual's sensitivity to potential stressors in daily life restrict access to balanced information from the environment, maintaining biased cognitive biases. This could, in turn, predispose an individual to lower mood and anxiety, which would constitute a favourable ground for the emergence of psychotic symptoms. Thus, the feeling of loneliness and isolation must be taken very seriously as it might operate as a potential condition allowing other mediators to operate.

Pathway 5: biological measures

Despite the high emphasis put on the search for biomarkers dur- ing the last 20 years of psychiatric research, we could identify just two eligible papers exploring biological mechanisms using psych- osis as an outcome (Cancel et al., 2015; Quidé et al., 2018). This highlights the limited evidence in this field and the need for future studies testing mediation in longitudinal samples.

Figure 2

Potential targets for treatment based on the evidence of mediational pathways between adversity and psychosis.



This figure displays the potential targets for treatment that could be addressed in individuals with psychosis who have been exposed to adversity. The choice of pathways is based on evidence of mediation found in our review, but the implications remain hypothetical and should be tested empirically with randomized controled trials.
Beyond the traditional treatment of psychotic symptoms ***(Target 1)*** *different clinical presentations with various targets for treatment can occur: related symptoms, including Dissociation. These can be combined in different forms as displayed in* ***Target 2A, 2B*** *and* ***2C****.* ***Target 3*** *represents mood-related symptoms and* ***Target 4*** *represent the presence of feeling of loneliness.*
The treatmente options could be adapted depending on which targets are present or predominant in the clinical picture. For ***Target 2A****: CBT-trauma focused therapy (for PTSD symptoms and NS) + sensory grounding techniques (for dissociation) + SSRI/ antagonists a1 if required (for PTSD symptoms). The implementation of these interventions would be adapted according to the presence/absence of the aforementioned targets (Target 2 B and C). Target 3: CBT techniques such as behavioural activation and graded exposure, relaxation techniques and mindfulness + SSRI if needed for anxiety and depressive symptoms. Target 4: Promoting social inclusion and community membership through therapy/actividy groups and vocational support. Improving existing interpersonal relationships using family therapy approaches. The thickness of the arrows shows the robustness of the evidence according to our results. The square arrows represent a hypothetical connexion not addressed in our review.*

Clinical implications for clinical settings

Our results provide evidence to support some potential treatment implications for traumatised individuals with psychosis, in addition to the treatment of positive symptoms, which often remain high in this vulnerable group (Ajnakina et al., 2016; Alameda et al., 2016). Figure 2 displays a model with the different potential treatment tar- gets derived from the pathways mentioned above. Beyond the trad- itional treatment of psychotic symptoms (Target 1 in Fig. 2), we propose targeting the relevant mediators found in our review, hypothesizing that an improvement in such targets would then have an indirect beneficial effect on positive symptoms.

A common clinical picture corresponds to a situation where a traumatised patient with psychosis suffers from NS and PTSD symptoms, including dissociation. If these are present (Target 2A in Fig. 2), a trauma-focused therapy, such as trauma-focused CBT could be appropriate, integrating treatment of negative schemas and traumatic intrusions, in addition to dissociative symptoms. Briefly, this could include grounding techniques, imaginal exposure, memory updating and cognitive restructuring, along- side more general CBT elements such as the use of behavioural experiments to gather new information about current safety (Hardy, 2017). In some cases, dissociative symptoms may be very disruptive and prevent access to the other targets; in this case, they can be prioritised and targeted using sensory grounding techniques to help the individual reliably regain contact with pre- sent external stimuli (Keen, Hunter, & Peters, 2017; Steel et al., 2017). In addition to psychological interventions, some patients with highly distressing PTSD symptoms might respond to adjunctive pharmacological treatments such as selective serotonin reuptake inhibitors or other antidepressants blocking α1 adrenoceptors commonly used in patients with PTSD (Steckler & Risbrough, 2012). This integrated approach could be adapted depending on which mediators are present or predominant, as described in Fig. 2.

Anxiety and depressive symptoms could be, in isolation or in combination with other mediators (such as cognitive bias and post-traumatic symptoms), another target for treatment (Target 3, Fig. 2) that could indirectly ameliorate positive symptoms as suggested in previous reviews (Bebbington, 2015). The use of anti- depressants and CBT techniques such as behavioural activation and graded exposure (Waller et al., 2013), as well as relaxation techniques and mindfulness, could then be useful, targeting low mood and anxiety, respectively (Waller et al., 2013).

Lastly, it is important to highlight the possible role of loneliness as another mediator that could be targeted for treatment. Promoting social inclusion and community membership through group interventions and vocational support could be beneficial, as well as improving existing interpersonal relationships using family therapy approaches. Also, as previously mentioned, loneliness might co-occur with other mediators.

Our review indicates that routine assessment of trauma history should be necessary in clinical settings treating individuals with psychosis. Furthermore, given the possible impor-

tance of media- tors, it is also important to carry out a careful assessment of the cognitive biases, PTSD, dissociative symptoms, anxiety, mood and feelings of loneliness.

Conclusions

Our review suggests that the association between adversity and psychosis is mediated by various overlapping non-competing mechanisms. Cognitive schemas about the self and the world and post-traumatic symptoms (particularly dissociation) seem to play an important role in the association, while other factors such as mood and feeling of loneliness seem to contribute partially to this link and interact mutually in contributing to the effect. Our findings support the routine assessment of experiences of CA in clinical settings, alongside with all the potential mediators. More evidence testing the efficacy of interventions targeting such media- tors through cognitive behavioural approaches using trauma-focused therapy and/or pharmacological means is needed in future.

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Conflict of interest

None.

References

- Aas, M., Haukvik, U. K., Djurovic, S., Tesli, M., Athanasiu, L., Bjella, T., … Melle, I. (2014). Interplay between childhood trauma and BDNF val66met variants on blood BDNF mRNA levels and on hippocampus subfields volumes in schizophrenia spectrum and bipolar disorders. Journal of Psychiatric Research, 59, 14–21.
- Ajnakina, O., Trotta, A., Oakley-Hannibal, E., Di Forti, M., Stilo, S. A., Kolliakou, A., … Fisher, H. L. (2016). Impact of childhood adversities on specific symptom dimensions in first-episode psychosis. Psychological Medicine, 46, 317–326.

- Alameda, L., Fournier, M., Khadimallah, I., Griffa, A., Cleusix, M., Jenni, R., … Do, K. Q. (2018). Redox dysregulation as a link between childhood trauma and psychopathological and neurocognitive profile in patients with early psychosis. National Academy of Sciences Proceedings of the National Academy of Sciences of the USA, 115, 12495–12500.

- Alameda, L., Golay, P., Baumann, P. S., Ferrari, C., Do, K. Q., & Conus, P. (2016). Age at the time of exposure to trauma modulates the psychopatho- logical profile in patients with early psychosis. The Journal of Clinical Psychiatry, 77, e612–e618.

- Allen, J. G., Coyne, L., & Console, D. A. (1997). Dissociative detachment relates to psychotic symptoms and personality decompensation. Comprehensive Psychiatry, 38, 327–334.

- American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders : DSM-IV (4th ed.). Washington, DC: American Psychiatric Association.

- Appiah-Kusi, E., Fisher, H. L., Petros, N., Wilson, R., Mondelli, V., Garety, P. A., … Bhattacharyya, S. (2017). Do cognitive schema mediate the associ- ation between childhood trauma and being at ultra-high risk for psychosis? Journal of Psychiatric Research, 88, 89–96.

- Ashford, C. D., Ashcroft, K., & Maguire, N. (2012). Emotions, traits and nega- tive beliefs as possible mediators in the relationship between childhood experiences of being bullied and paranoid thinking in a Non-clinical sam- ple. Journal of Experimental Psychopathology, 3, 624–638.

- Bebbington, P. (2015). Unravelling psychosis: Psychosocial epidemiology, mechanism, and meaning. Editorial Department of the Shanghai Archives of Psychiatry Shanghai Archives of Psychiatry, 27, 70–81.

- Bentall, R. P., De Sousa, P., Varese, F., Wickham, S., Sitko, K., Haarmans, M., & Read, J. (2014). From adversity to psychosis: Pathways and mechanisms from specific adversities to specific symptoms. Social Psychiatry and Psychiatric Epidemiology, 49, 1011–1022.

- Bortolon, C., & Raffard, S. (2018). Dissociation mediates the relationship between childhood trauma and experiences of seeing visions in a French sample. Journal of Nervous and Mental Disease, 206, 850–858.

- Bortolon, C., Seillé, J., & Raffard, S. (2017). Exploration of trauma, dissoci- ation, maladaptive schemas and auditory hallucinations in a French sample. Taylor & Francis Cognitive Neuropsychiatry, 22, 468–485.

- Boyda, D., & McFeeters, D. (2015). Childhood maltreatment and social function- ing in adults with sub-clinical psychosis. Psychiatry Research, 226, 376–382. Boyda, D., McFeeters, D., Dhingra, K., & Rhoden, L. (2018). Childhood mal-treatment and psychotic experiences: Exploring the specificity of early mal- adaptive schemas. Journal of Clinical Psychology, 74, 2287–2301.

- Brand, R. M., McEnery, C., Rossell, S., Bendall, S., & Thomas, N. (2018). Do trauma- focussed psychological interventions have an effect on psychotic symptoms? A systematic review and meta-analysis. Schizophrenia Research, 195, 13–22.
- Cancel, A., Comte, M., Truillet, R., Boukezzi, S., Rousseau, P. F., Zendjidjian,
- X. Y., … Fakra, E. (2015). Childhood neglect predicts disorganization in schizophrenia through grey matter decrease in dorsolateral prefrontal cor- tex. Acta Psychiatrica Scandinavica, 132, 244–256.
- Chatziioannidis, S., Andreou, C., Agorastos, A., Kaprinis, S., Malliaris, Y., Garyfallos, G., & Bozikas, V. P. (2019). The role of attachment anxiety in the relationship between childhood trauma and schizophrenia-spectrum psychosis. Psychiatry Research, 276, 223–231.
- Choi, J. Y., Choi, Y. M., Kim, B., Lee, D. W., Gim, M. S., & Park, S. H. (2015). The effects of childhood abuse on self-reported psychotic symptoms in severe mental illness: Mediating effects of posttraumatic stress symptoms. Psychiatry Research, 229, 389–393.
- Cole, C. L., Newman-Taylor, K., & Kennedy, F. (2016). Dissociation mediates the relationship between childhood maltreatment and subclinical psychosis. Journal of Trauma and Dissociation, 17, 577–592.
- Evans, G. J., Reid, G., Preston, P., Palmier-Claus, J., & Sellwood, W. (2015). Trauma and psychosis: The mediating role of self-concept clarity and dis- sociation. Psychiatry Research, 228, 626–632.
- Fisher, H. L., Appiah-Kusi, E., & Grant, C. (2012). Anxiety and negative self- schemas mediate the association between childhood maltreatment and paranoia. Psychiatry Research, 196, 323–324.
- Fisher, H. L., Schreier, A., Zammit, S., Maughan, B., Munafò, M. R., Lewis, G., & Wolke, D. (2013). Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. Schizophrenia Bulletin, 39, 1045–1055.
- Freeman, D., & Garety, P. (2014). Advances in understanding and treating persecutory delusions: A review. Social Psychiatry and Psychiatric Epidemiology, 49, 1179–1189.
- Garety, P. A., Bebbington, P., Fowler, D., Freeman, D., & Kuipers, E. (2007). Implications for neurobiological research of cognitive models of psychosis: A theoretical paper. Psychological Medicine, 37, 1377–1391.
- Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., & Bebbington, P. E. (2001). A cognitive model of the positive symptoms of psychosis. Psychological Medicine, 31, 189–195.
- Gawęda, Ł, Göritz, A. S., & Moritz, S. (2019). Mediating role of aberrant sali- ence and self-disturbances for the relationship between childhood trauma and psychotic-like experiences in the general population. Schizophrenia Research, 206, 149–156.

- Gibson, L. E., Alloy, L. B., & Ellman, L. M. (2016). Trauma and the psychosis spectrum: A review of symptom specificity and explanatory mechanisms. Clinical Psychology Review, 49, 92–105.
- Gibson, L. E., Reeves, L. E., Cooper, S., Olino, T. M., & Ellman, L. M. (2019). Traumatic life event exposure and psychotic-like experiences: A multiple mediation model of cognitive-based mechanisms. Schizophrenia Research, 205, 15–22.
- Goodall, K., Rush, R., Grünwald, L., Darling, S., & Tiliopoulos, N. (2015). Attachment as a partial mediator of the relationship between emotional abuse and schizotypy. Psychiatry Research, 230, 531–536.
- Gumley, A. I., Taylor, H. E. F., Schwannauer, M., & MacBeth, A. (2014). A sys- tematic review of attachment and psychosis: Measurement, construct valid- ity and outcomes. Acta Psychiatrica Scandinavica, 129, 257–274.
- Hardy, A. (2017). Pathways from trauma to psychotic experiences: A theoret- ically informed model of posttraumatic stress in psychosis. Frontiers Research Foundation Frontiers in Psychology, 8, 697.
- Hardy, A., Emsley, R., Freeman, D., Bebbington, P., Garety, P. A., Kuipers, E. E., … Fowler, D. (2016). Psychological mechanisms mediating effects between trauma and psychotic symptoms: The role of affect regulation, intrusive trauma memory, beliefs, and depression. Schizophrenia Bulletin, 42, S34–S43.
- Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. Communication Monographs, 76, 408–420.
- Howes, O. D., McCutcheon, R., Owen, M. J., & Murray, R. M. (2017). The role of genes, stress, and dopamine in the development of schizophrenia. USA Biological Psychiatry, 81, 9–20.
- Howes, O. D., & Murray, R. M. (2014). Schizophrenia: An integrated sociodevelopmental-cognitive model. The Lancet, 383, 1677–1687.
- Isvoranu, A. M., Van Borkulo, C. D., Lou, B. L., Wigman, J. T. W., Vinkers, C. H., Borsboom, D., … Myin-Germeys, I. (2017). A network approach to psychosis: Pathways between childhood trauma and psychotic symptoms. Schizophrenia Bulletin, 43, 187–196.
- Jaya, E. S., Ascone, L., & Lincoln, T. M. (2017). Social adversity and psychosis: The mediating role of cognitive vulnerability. Schizophrenia Bulletin, 43, 557–565.
- Keen, N., Hunter, E. C. M., & Peters, E. (2017). Integrated trauma-focused cognitive-behavioural therapy for post-traumatic stress and psychotic symp- toms: A case-series study using imaginal reprocessing strategies. Frontiers in Psychiatry, 8, 92.
- Lincoln, T. M., Marin, N., & Jaya, E. S. (2017). Childhood trauma and psych- otic experiences in a general population sample: A prospective study on the mediating role of emotion regulation. Masson SAS European Psychiatry, 42, 111–119.

- Marwaha, S., & Bebbington, P. (2015). Mood as a mediator of the link between child sexual abuse and psychosis. Social Psychiatry and Psychiatric Epidemiology, 50, 661–663.
- Marwaha, S., Broome, M. R., Bebbington, P. E., Kuipers, E., & Freeman, D. (2014). Mood instability and psychosis: Analyses of British national survey data. Schizophrenia Bulletin, 40, 269–277.
- McCarthy-Jones, S. (2018). Post-traumatic symptomatology and compulsions as potential mediators of the relation between child sexual abuse and audi- tory verbal hallucinations. Behavioural and Cognitive Psychotherapy, 46, 318–331.
- McDonnell, J., Stahl, D., Day, F., McGuire, P., & Valmaggia, L. R. (2018). Interpersonal sensitivity in those at clinical high risk for psychosis mediates the association between childhood bullying victimisation and paranoid ideation: A virtual reality study. Schizophrenia Research, 192, 89–95.
- McGrath, J. J., Saha, S., Lim, C. C. W., Aguilar-Gaxiola, S., Alonso, J., Andrade, L. H., … Wojtyniak, B. (2017). Trauma and psychotic experiences: Transnational data from the World Mental Health survey. British Journal of Psychiatry, 211, 373–380.
- Mętel, D., Arciszewska, A., Daren, A., Pionke, R., Cechnicki, A., Frydecka, D., & Gawęda, Ł (2020). Mediating role of cognitive biases, resilience and depressive symptoms in the relationship between childhood trauma and psychotic-like experiences in young adults. Early Intervention in Psychiatry, 14, 87–96.
- Misiak, B., Krefft, M., Bielawski, T., Moustafa, A. A., Sąsiadek, M. M., & Frydecka, D. (2017). Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuro- psychological and biological findings. Neuroscience and Biobehavioral Reviews, 75, 393–406.
- Moher, D., Booth, A., & Stewart, L. (2014). How to reduce unnecessary dupli- cation: Use PROSPERO. BJOG: An International Journal of Obstetrics and Gynaecology, 121, 784–786.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. American College of Physicians Annals of Internal Medicine, 151, 264–269.
- Morgan, C., & Gayer-Anderson, C. (2016). Childhood adversities and psych- osis: Evidence, challenges, implications. World Psychiatry, 15, 93–102.
- Morgan, C., Reininghaus, U., Fearon, P., Hutchinson, G., Morgan, K., Dazzan, P., … Craig, T. (2014). Modelling the interplay between childhood and adult adversity in pathways to psychosis: Initial evidence from the AESOP study. Psychological Medicine, 44, 407–419.
- Morrison, A. P., Frame, L., & Larkin, W. (2003). Relationships between trauma and psychosis: A review and integration. British Journal of Clinical Psychology, 42, 331–353.

- Moskowitz, A., Schäfer, I., & Dorahy, M. J. (2009). Psychosis, trauma and dissociation: Emerging perspectives on severe psychopathology. Hoboken, NJ, USA: John Wiley and Sons.

- Murphy, S., Murphy, J., & Shevlin, M. (2015). Negative evaluations of self and others, and peer victimization as mediators of the relationship between childhood adversity and psychotic experiences in adolescence: The moder- ating role of loneliness. British Journal of Clinical Psychology, 54, 326–344. Myin-Germeys, I., & van Os, J. (2007). Stress-reactivity in psychosis: Evidence for an affective pathway to psychosis. Clinical Psychology Review, 27, 409–424.

- Peach, N., Alvarez-Jimenez, M., Cropper, S. J., Sun, P., & Bendall, S. (2019). Testing models of post-traumatic intrusions, trauma-related beliefs, halluci- nations, and delusions in a first episode psychosis sample. British Journal of Clinical Psychology, 58, 154–172.

- Perona-Garcelán, S., Carrascoso- López, F., García-Montes, J. M., Ductor-Recuerda, M. J., López Jiménez, A. M., Vallina-Fernández, O., … Gómez-Gómez, M. T. (2012). Dissociative experiences as mediators between childhood trauma and auditory hallucinations. Journal of Traumatic Stress, 25, 323–329.

- Perona-Garcelán, S., García-Montes, J. M., Rodríguez-Testal, J. F., López-Jiménez, A. M., Ruiz-Veguilla, M., Ductor-Recuerda, M. J., … Pérez-Álvarez, M. (2014). Relationship between childhood trauma, mindfulness, and dissociation in subjects with and without hallucination proneness. Journal of Trauma and Dissociation, 15, 35–51.

- Pinto-Gouveia, J., Matos, M., Castilho, P., & Xavier, A. (2014). Differences between depression and paranoia: The role of emotional memories, shame and subordination. Clinical Psychology and Psychotherapy, 21, 49–61.

- Quidé, Y., O'Reilly, N., Watkeys, O. J., Carr, V. J., & Green, M. J. (2018). Effects of childhood trauma on left inferior frontal gyrus function during response inhibition across psychotic disorders. Psychological Medicine, 48, 1454–1463. Read, J., Fosse, R., Moskowitz, A., & Perry, B. (2014). The traumagenic neurodevelopmental model of psychosis revisited. Neuropsychiatry, 4, 65–79.

- Read, J., & Gumley, A. (2010). Can attachment theory help explain the relationship between childhood adversity and psychosis?. In S. Benamer (Ed.), Telling stories? Attachment-based approaches to the treatment of psychosis (pp. 51–94). Karnac Books. https://psycnet.apa.org/record/2010- 21228-004.

- Ross, C. A. (2006). Dissociation and psychosis: The need for integration of theory and practice. In J. O. Johannessen, B. V. Martindale & J. Cullberg (Ed.), Evolving psychosis (pp. 238–254). Routledge/Taylor & Francis Group. https://psycnet.apa.org/record/2006-05781-014.

- Rössler, W., Ajdacic-Gross, V., Rodgers, S., Haker, H., & Müller, M. (2016). Childhood trauma as a risk factor for the onset of subclinical psychotic experi- ences: Exploring the mediating effect of stress sensitivity in a cross-sectional epidemiological community study. Schizophrenia Research, 172, 46–53.

- Ruby, E., Polito, S., McMahon, K., Gorovitz, M., Corcoran, C., & Malaspina, D. (2014). Pathways associating childhood trauma to the neurobiology of schizophrenia. NIH Public Access Frontiers in Psychological and Behavioral Science, 3, 1–17.
- Schalinski, I., Breinlinger, S., Hirt, V., Teicher, M. H., Odenwald, M., & Rockstroh, B. (2019). Environmental adversities and psychotic symptoms: The impact of timing of trauma, abuse, and neglect. Schizophrenia Research, 205, 4–9.
- Sheinbaum, T., Kwapil, T. R., & Barrantes-Vidal, N. (2014). Fearful attachment mediates the association of childhood trauma with schizotypy and psychotic-like experiences. Psychiatry Research, 220, 691–693.
- Shevlin, M., McElroy, E., & Murphy, J. (2015). Loneliness mediates the rela- tionship between childhood trauma and adult psychopathology: Evidence from the adult psychiatric morbidity survey. Social Psychiatry and Psychiatric Epidemiology, 50, 591–601.
- Sin, J., & Spain, D. (2017). Psychological interventions for trauma in indivi- duals who have psychosis: A systematic review and meta-analysis. Routledge Psychosis, 9, 67–81.
- Sitko, K., Bentall, R. P., Shevlin, M., O'Sullivan, N., & Sellwood, W. (2014). Associations between specific psychotic symptoms and specific childhood adversities are mediated by attachment styles: An analysis of the National Comorbidity Survey. Psychiatry Research, 217, 202–209.
- Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology, 25, 603–605.
- Steckler, T., & Risbrough, V. (2012). Pharmacological treatment of PTSD – established and new approaches. Neuropharmacology, 62, 617–627.
- Steel, C., Hardy, A., Smith, B., Wykes, T., Rose, S., Enright, S., … Mueser, K. T. (2017). Cognitive-behaviour therapy for post-traumatic stress in schizo- phrenia. A randomized controlled trial. Psychological Medicine, 47, 43–51.
- Steenkamp, L., Weijers, J., Gerrmann, J., Eurelings-Bontekoe, E., & Selten, J. P. (2019). The relationship between childhood abuse and severity of psychosis is mediated by loneliness: An experience sampling study. Schizophrenia Research, in press.
- Steullet, P., Cabungcal, J. H., Monin, A., Dwir, D., O'Donnell, P., Cuenod, M., & Do, K. Q. (2016). Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A 'central hub' in schizophrenia pathophysiology? Schizophrenia Research, 176, 41–51.
- Styła, R., Stolarski, M., & Szymanowska, A. (2019). Linking childhood adver- sities with schizophrenia: A mediating role of the balanced time perspective. Schizophrenia Research, 209, 281–283.

- Sun, P., Alvarez-Jimenez, M., Simpson, K., Lawrence, K., Peach, N., & Bendall, S. (2018). Does dissociation mediate the relationship between childhood trauma and hallucinations, delusions in first episode psychosis? Comprehensive Psychiatry, 84, 68–74.

- Swan, S., Keen, N., Reynolds, N., & Onwumere, J. (2017). Psychological inter- ventions for post-traumatic stress symptoms in psychosis: A systematic review of outcomes. Frontiers Research Foundation Frontiers in Psychology, 8, 341.

- Teicher, M. H., Anderson, C. M., & Polcari, A. (2012). Childhood maltreat- ment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. National Academy of Sciences Proceedings of the National Academy of Sciences of the USA, 109, E563– E572.

- Thompson, A., Marwaha, S., Nelson, B., Wood, S. J., McGorry, P. D., Yung, A. R., & Lin, A. (2016). Do affective or dissociative symptoms mediate the association between childhood sexual trauma and transition to psychosis in an ultra-high risk cohort? Psychiatry Research, 236, 182–185.

- Thompson, A., Sullivan, S., Lewis, G., Zammit, S., Heron, J., Horwood, J., … Harrison, G. (2011). Association between locus of control in childhood and psychotic symptoms in early adolescence: Results from a large birth cohort. Cognitive Neuropsychiatry, 16, 385–402.

- Van Dam, D. S., Korver-Nieberg, N., Velthorst, E., Meijer, C. J., & de Haan, L. (2014). Childhood maltreatment, adult attachment and psychotic symptom- atology: A study in patients, siblings and controls. Social Psychiatry and Psychiatric Epidemiology, 49, 1759–1767.

- van Nierop, M., van Os, J., Gunther, N., van Zelst, C., de Graaf, R., ten Have, M., … Van Winkel, R. (2014). Does social defeat mediate the association between childhood trauma and psychosis? Evidence from the NEMESIS-2 Study. Acta Psychiatrica Scandinavica, 129, 467–476.

- Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychological Medicine, 39, 179–195.

- Van Winkel, R., Van Nierop, M., Myin-Germeys, I., & Van Os, J. (2013). Childhood trauma as a cause of psychosis: Linking genes, psychology, and biology. Canadian Psychiatric Association Canadian Journal of Psychiatry, 58, 44–51.

- Varese, F., Barkus, E., & Bentall, R. P. (2012a). Dissociation mediates the relationship between childhood trauma and hallucination-proneness. Psychological Medicine, 42, 1025–1036.

- Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., … Bentall, R. P. (2012b). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. Schizophrenia Bulletin, 38, 661–671.
- Waller, H., Garety, P. A., Jolley, S., Fornells-Ambrojo, M., Kuipers, E., Onwumere, J., … Craig, T. (2013). Low intensity cognitive behavioural ther- apy for psychosis: A pilot study. Journal of Behavior Therapy and Experimental Psychiatry, 44, 98–104.
- Weijers, J., Fonagy, P., Eurelings-Bontekoe, E., Termorshuizen, F., Viechtbauer, W., & Selten, J. P. (2018). Mentalizing impairment as a mediator between reported childhood abuse and outcome in nonaffective psychotic disorder. Psychiatry Research, 259, 463–469.
- Wickham, S., & Bentall, R. (2016). Are specific early-life adversities associated with specific symptoms of psychosis?: A patient study considering just world beliefs as a mediator. Journal of Nervous and Mental Disease, 204, 606–613.
- Williams, J., Bucci, S., Berry, K., & Varese, F. (2018). Psychological mediators of the association between childhood adversities and psychosis: A system- atic review. Clinical Psychology Review, 65, 175–196.
- Wolke, D., Lereya, S. T., Fisher, H. L., Lewis, G., & Zammit, S. (2014). Bullying in elementary school and psychotic experiences at 18 years: A longitudinal, population-based cohort study. Psychological Medicine, 44, 2199–2211.
- World Health Organization (1992). The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization.
- Yamasaki, S., Ando, S., Koike, S., Usami, S., Endo, K., French, P., … Nishida, A. (2016). Dissociation mediates the relationship between peer victimization and hallucinatory experiences among early adolescents. The Authors Schizophrenia Research: Cognition, 4, 18–23.
- Yung, A. R., Yung, A. R., Pan Yuen, H., Mcgorry, P. D., Phillips, L. J., Kelly, D., … Buckby, J. (2005). Mapping the onset of psychosis: The comprehensive assess- ment of at-risk mental states. Journal of Psychiatry, 39, 964–971.

3.3 (study 3) this chapter has been reproduced in full from the following paper

Evidence of Mediation of Anxiety and Depression Between Abuse and Positive symptoms of Psychosis

Running title: depression mediates the abuse-psychosis association.

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Keywords: Early Psychosis; Trauma, mediation, positive symptoms.

Abstract

Background: Considerable evidence on general population suggests that an "Affective pathway to psychosis", involving depression and anxiety dimensions, mediates the abuse-psychosis association. However, this has never been tested in Early Psychosis (EP) patients. We aim at testing whether severity of depressive and anxiety mediates the abuse-positive symptoms dyad in an EP prospective sample.

Methods: 330 EP subjects aged 18–35 were assessed for psychopathology after 2, 6, 12, 18, 24, 30, and 36 months of treatment. Abuse was considered as facing at least one experience of physical, sexual, or emotional abuse before age 16. Positive psychotic symptoms and anxiety were measured with the Positive and Negative Syndrome Scale and depressive symptoms with the Montgomery-Asberg Depression Rating Scale. Mediation analyses were performed to study whether the abuse-positive symptom's link was mediated by depressive, anxiety, and a combination of anxiety/mood symptoms.

Results: Among the 330 EP patient included, 104 (31.5% of the total) were exposed to abuse. Analyses across the 36 months of follow-up showed that depression and anxiety partially mediated 26.7% of the total effect of the abuse-positive symptoms association (indirect effects (IE) = 0.392 and 0.421 respectively), while the combined anxiety/mood model mediated 28.9% (IE = 0.475). Subanalyses at two and 36 months revealed a consistent role of depression, while that of anxiety was only present at baseline.

Conclusion: Our work confirms a mediating role of mood and anxiety in the association between abuse and positive symptoms during the first three years of treatment.

Introduction

Recent meta-analytic evidence suggests that CA, especially abuse, is robustly associated with psychotic disorders(Varese et al., 2012), with delusions and auditory hallucinations(Bai-

ley et al., 2018) and positive psychotic symptoms measured as a dimension(Alameda et al., 2021). Beyond the understanding of the nature of the association between childhood adversity and psychotic disorders, research has evolved trying to understand its mechanisms(Alameda, L. et al., 2020). One of the main hypotheses points out the mediating role of mood-related symptoms such as depressive symptoms, anxiety and emotional dysregulation, otherwise often called "affective pathway to psychosis(Fisher et al., 2013; Isvoranu et al., 2016b; Myin-Germeys and van Os, 2007)". This hypothesis postulates that these symptoms might be determinants for paranoid thinking; for example, anxiety might lead to anticipation of threat, and higher severity of depressive symptoms might drive negatively biased interpretations of ongoing experience and impact self-esteem and negative schemas about the self, which in turn are precursors of psychotic symptoms (Alameda, L. et al., 2020). It has been hypothesized that these mood-related symptoms may not only precede the psychotic onset, but also precipitate relapse(Bebbington, 2015) and negatively affect functioning(Alameda et al., 2017) in those with psychosis and a history of CA. Therefore mood related symptoms should not only be important to consider in terms of psychosis onset but also in the understanding of the persistence of positive symptoms in those with a psychotic disorder, being potentially useful targets for treatment (Alameda, L. et al., 2020). Recent meta-analytic data showed that abuse and neglect are positively associated with higher severity of depressive symptoms in people with psychosis, further strengthening the importance of mood symptoms in those with trauma(Alameda et al., 2021).

Nevertheless, evidence for the possible mediating role of mood-related symptoms between CA and psychosis emerges mainly from general population studies (Alameda, L. et al., 2020). To the best of our knowledge, only two studies in patients with psychosis have addressed this issue. One study(Isvoranu et al., 2016b) found in a sample of individuals with up to 10-year psychosis duration, that anxiety was connecting pathways between abuse and paranoia. Another study on 1,261 patients with similar illness duration found that presence of delusions and hallucinations was contingent on the co-presence of depression, strongly suggesting mediation(van Os et al., 2020). Despite these two high-quality studies, more studies in those with psychosis is needed. Particularly, there are currently no studies addressing this issue with prospective data, which allows the exploration of whether fluctuations in mood/anxiety are actually playing a role in deterioration of positive symptoms, as previously hypothesized based on general population data(Alameda, Luis et al., 2020; Bebbington, 2015). Secondly, no studies in Early Psychosis (EP) patients have been conducted and lastly, although studies mentioned above are indicative of mediation(Isvoranu et al., 2016b; van Os et al., 2020), this has not been formally tested through traditional mediation analyses. This prevents the calculation of the amount of the association that is driven by the mediators (percentage of the total effect mediated), which allows comparisons with previous studies in general population settings(Alameda, L. et al., 2020; Williams et al., 2018).

Given the above, we decided to conduct the current study. We hypothesized that the severity of anxiety and depressive symptoms will mediate the association between abuse and positive symptoms of psychosis, providing support for the presence of a role of mood

related symptoms in the persistence of the positive symptoms of psychosis in a sample of EP. To test this hypothesis, we aimed to explore whether the severity of depressive and anxiety symptoms would mediate the impact of abuse (sexual, physical and emotional) on the positive symptoms of psychosis of EP patients treated in a specialized program, after two and 36 months of treatment.

Methods

Procedure and Subjects

TIPP (Treatment and Early Intervention in Psychosis Program), a specialized early psychosis program, was launched in 2004 at the Department of Psychiatry CHUV, in Lausanne, Switzerland(Baumann et al., 2013). Entry criteria to the program are: (I) age between 18 and 35; (II) residing in the catchment area (Lausanne and surroundings; population about 300 000); (III) meeting threshold criteria for psychosis, as defined by the "Psychosis threshold" subscale of the Comprehensive Assessment of At Risk Mental States (CAARMS(Yung et al., 2005)) Scale. Patients are referred to other treatment programs if they have been taking antipsychotic medication for more than a total of six months, have psychosis related to intoxication or organic brain disease, or have an intelligence quotient below 70. In the TIPP program, each patient is followed up by a psychiatrist and a Case manager. The program offers an integrated biopsychosocial treatment based on psychotherapy, psycho-education, family support, cognitive assessment and remediation (when needed), social support, assistance in finding employment, psychological interventions for cannabis use, and pharmacological treatment. A specially designed questionnaire is completed for all patients enrolled in the program by their Case managers who have up to one hundred instances of contact with patients during the three years of treatment. It assesses demographic characteristics, past medical history, exposure to life events as well as symptoms and functioning. It is completed on the basis of information gathered with patients and their family over the first few weeks of treatment and can be updated during follow-up if new information emerges. Follow-up assessments, exploring various aspects psychopathology are conducted by a research psychologist (for psychopathology) after 2, 6, 12, 18, 24, 30, and 36 months of treatment(Baumann et al., 2013).

This study was approved by the Human Research Ethics Committee of the Canton Vaud (protocol #2020-00272). The data generated by the follow-up of all patients were used in the study if they provided consent. All of them agreed for their clinical data to be used for research. This is a prospective study based on the first 330 patients who had been enrolled in the program for which data on trauma and psychopathology was available and had been in treatment for 36 months.

Assessment of History of Abuse

Clinicians at TIPP are trained to conduct an extensive assessment of patients, including evaluation of exposure to traumatic life events. Case managers meet patients frequently over the treatment period, which provides the framework to establish a trusting relationship, where extensive knowledge of patients' history can be gathered. If patients agree,

information can also be completed with family. Case managers complete a table during the three years of treatment (information regarding trauma exposure is hence gatherer progressively (and not only early in the treatment), and case manages update this information along the treatment phase, in order to include all elements which emerge progressively during the period of care. The data on which this study is based stems from the last version of the table that is produced at the end of the follow-up). Exposure to traumatic life events can be recorded as follows: (1) Type of traumatic life event, rated as present or absent (sexual abuse, physical abuse, emotional and physical neglect, emotional abuse, among others…); (2) time of occurrence in relation to psychosis stage (during the premorbid phase, during the prodrome or after onset of psychosis); (3) age at the time of first exposure to each one of the traumas that occurred; and (4) single or repeated exposure to each one of the traumas that occurred. Considering that the clinicians who assessed exposure to life events did not rate the subjective perception of severity of the different forms of stressful events, patients were considered traumatized if they had been exposed to at least one experience of abuse (physical, sexual, or emotional). The consideration was that such events would undoubtedly be considered as highly traumatizing by anyone and have been shown to be associated with risk for psychosis and functional deficits in psychotic samples(Varese et al., 2012). Sexual abuse refers to sexual molestation and/or rape. Physical abuse refers to physical attack or assault, or being repetitively beaten by parents, relatives, or caregivers. Emotional abuse was defined as verbal assaults on a child's sense of worth or well-being or any humiliating or demeaning behaviour directed toward a child by an adult. Patients were excluded if they were exposed to abuse after age 16 or were in the prodromal phase of the disease when the abuse occurred.

Diagnosis is the result of an expert consensus and is based on the following elements: (1) Diagnosis based on DSM-IV criteria (Association, 1994) reported by a treating psychiatrist in all medical documents and at the end of any hospitalization; (2) longitudinal assessment by psychiatrist, psychologist and clinical case manager over the 3 years of treatment. The consensus diagnosis procedure is realized by a senior psychiatrist and the senior psychologist in charge of scale-based assessment over the treatment period. They both review the entire file once after 18 months and again after 36 months (or at the end of treatment), and conduct a diagnostic process discussing any unclear issue with the clinical case manager. In this study, we considered the diagnostic consensus conducted after 36 months.

Level of Depressive, Anxiety and Positive Symptoms

Level of Depressive, Positive, and Anxiety were evaluated at each measurement occasion (after 2, 6, 12, 18, 24, 30, and 36 months of follow-up) by a psychologist. Depressive symptoms were assessed using the total score of the Montgomery-Asberg Depression Rating Scale (MADRS(Montgomery and Asberg, 1979)). The MADRS is a 10-item scale commonly used to measure the severity of depressive symptoms. The level of positive symptoms was assessed using the total score of the positive component of the Positive and Negative Syndrome Scale (PANSS(Kay et al., 1987)), which contains 7 items each one graded on a 1-7 severity scale. Anxiety was measured by adding the scores (graded 1-7) on the items

of tension (G4) and anxiety (G2), according to others(Emsley et al., 1999). As symptoms of anxiety and depression often co-occur, we also analysed this combined composite cluster previously validated with factor structure analysed with the PANSS(Emsley et al., 2003) including anxiety (G2), tension (G4), depression (G6), guilt feelings (G3), somatic concern (G1).

Statistical analysis

Mediation analysis was performed in order to study whether the relationship between abuse and positive symptoms was mediated by depressive, or anxiety symptoms. For the 2 months, and 36 months measurement occasions, a series of path analysis models were estimated with abuse as the independent variable and MADRS scores or the anxiety cluster score as the mediating variable. Positive PANSS scores were introduced as the dependent variable. Because participants with abuse (n = 104) and without abuse (n = 226) differed ($p<.05$) regarding age, gender, duration of untreated psychosis (DUP- p-value: 0.057), rates of Bullying, of Physical neglect and Emotional neglect (Table 1), we also introduced these variables as independent variables in all mediation models. These mediation models allowed use to determine whether significant indirect effects between abuse and positive symptoms could be observed. Such indirect effect indicates the amount of mediation. Partial mediation is the situation in which the path between trauma and positive symptoms is reduced but still statistically significant when the mediator is introduced. Complete mediation describes the case were the path between abuse and positive symptoms is no longer significant after the introduction of the mediating variable. For each analysis we calculated the percentage of total effect mediated, which provides the amount of the association explained by the mediator.

Since we had multiple measurements across all the three-year follow-up, we also used a two-level random intercept mediation model with measurement occasions nested in individuals. This model has the benefit of incorporating the full three years of data of each patient simultaneously. It translates the agglomerate of every cross-sectional mediation in one single model. This allowed us the estimate the global mediating effect of depression respectively of anxiety on all data available during the three years follow-up. More precisely, we estimated the relationship between the mediator and the dependent variable in the within-subject part (level 1) of the model using all available data from the seven assessments. The intercept was a random effect that varied across individuals and was referred as the PANSS score in the between-subject part (level 2) of the model. Covariates and the mediation of the relationship between trauma and the PANSS score by depression/anxiety were then modeled in the between-subject part of the model. We also estimated mediation models with both anxiety and depression, gathered into one cluster based on Emsley et al.,(Emsley et al., 2003). The path analysis models, and the multi-level mediation models were estimated using the Mplus v8.3 software. We used Bayesian Markov Chain Monte Carlo (MCMC) estimation with the Gibbs sampler methods. Three chains with 50,000 iterations and with different starting values and random seeds were used. Convergence was assessed with the Proportional Scale Reduction (PSR) criteria, and the first half of the chains was discarded as a burn-in phase. All statistical tests were two-tailed and significance was determined at the .05 level.

Results

Patient sample

Analysis was carried out on the data of 330 patients admitted to TIPP between 2004 and 2019 for which data on trauma and psychopathology was available and had been in treatment for 36 months. Baseline demographic and clinical characteristics between the 330 participants and the 106 that we not included can be found in Supplementary Material. 167 subjects were included at time 2, against 124 at time 36, with 49.2% of subjects being non overlapping.

Rates of Trauma, Demographic Characteristics

The diagnostic breakdown, various baseline clinical and demographic characteristics of the sample, as well as differences between abused patients and non-abused patients are described in Table 1. Among the 330 patients, 44 (13% of total) had a history of sexual abuse, 74 (22% of total) of physical abuse, 20 (6.1% of total) of emotional abuse; while bullying was present in 17 (5% of total), physical neglect 9 (3% of total) and physical neglect 39 (12% of total). As compared with non-abused, abused patients were older ($p=0.002$), more likely to be female ($p=0.19$), were more likely to be exposed to bullying ($p=0.002$), physical neglect ($p=0.30$) and emotional neglect (<0.001) and had a longer DUP at a trend level ($p=0.057$), thus mediation models were accounted for these covariates. The most common main diagnosis was Schizophrenia with 190 subjects (57.6% of the sample); a comorbid diagnosis of depression occurred in 41 subjects (12.4% of total), with no differences in diagnosis rates among abused and non-abused participants (Table 1)

Table 1

Demographic and baseline factors related to exposure to sexual, physical and/or emotional abuse (abuse).

	Total N=330	Non-Abuse N = 226	Abuse N = 104	Stat.	P-value
Age in y, M (SD)	24.75 (4.78)	24.19 (4.71)	25.96 (4.73)	t(328) = -3.178	.002
Sex, male, % (N)	65.8 (217)	69.9 (158)	56.7 (59)	$\chi^2(1) = 5.495$	.019
SES, % (N)					
Low	19.4 (64)	18.1 (41)	22.1 (23)	$\chi^2(2) = 3.120$	.210
Intermediate	43.9 (145)	42.0 (95)	48.1 (50)		
High	36.7 (121)	39.8 (90)	29.8 (31)		
GAF Baseline, M (SD)	42.12 (16.93)	42.76 (16.95)	40.70 (16.89)	t(298) = 0.978	.329
Insight at presentation, % (N)					
Absent	28.6 (91)	30.0 (65)	25.7 (26)	$\chi^2(2) = 0.984$	.611
Partial	45.6 (145)	43.8 (95)	49.5 (50)		
Complete	25.8 (82)	26.3 (57)	24.8 (25)		
DUP in weeks, Median (IQR)	12.1 (65.9)	10.4 (64.8)	16.7 (72.1)	U = 10219.5	.057
Exposure to sexual abuse	13.3 (44)	0.0 (0)	42.3 (44)	$\chi^2(1) = 110.325$	<.001
Exposure to physical abuse	22.4 (74)	0.0 (0)	71.2 (74)	$\chi^2(1) = 207.291$	<.001
Exposure to emotional abuse	6.1 (20)	0.0 (0)	19.2 (20)	$\chi^2(1) = 46.266$	<.001
Exposure to Bullying, % (N)	5.2 (17)	2.7 (6)	10.6 (11)	$\chi^2(1) = 9.148$	.002
Exposure to Physical Neglect, % (N)	2.7 (9)	1.3 (3)	5.8 (6)	Fisher Exact Test	.030
Exposure to Emotional Neglect, % (N)	11.8 (39)	7.1 (16)	22.1 (23)	$\chi^2(1) = 15.451$	<.001
Cannabis dependance, % (N)	25.3 (80)	26.0 (56)	23.8 (24)	$\chi^2(1) = 0.190$	.663
Diagnostic, % (N)					
Schizophrenia	57.6 (190)	55.3 (125)	62.5 (65)	Fisher Exact Test	.177
Schizophreniform/BPE.	12.7 (42)	15.5 (35)	6.7 (7)		
Schizoaffective disorder	8.8 (29)	9.3 (21)	7.7 (8)		
Major depression[a]	3.6 (12)	3.5 (8)	3.8 (4)		
Bipolar disorder	7.3 (24)	8.0 (18)	5.8 (6)		
Others	10.0 (33)	8.4 (19)	13.5 (14)		
Co-morbid depression	12.4 (41)	10.6 (24)	16.3 (17)	$\chi^2(1) = 2.147$	.143
MADRS after 2 months	15.16 (9.73)	14.08 (9.09)	17.37 (10.70)	t(157) = -2.013	.045
PANSS Positive after 2 months	13.68 (5.14)	13.19 (5.05)	14.64 (5.22)	t(165) = -1.735	.085
PANSS Negative after 2 months	15.98 (6.19)	15.56 (6.18)	16.80 (6.17)	t(164) = -1.223	.223

Note. IQR: Interquartile range, BPE: Brief psychotic episode. [a] with psychotic features.

Mediating Effects of Depressive Symptoms on the Link Between Abuse and Positive Symptoms of Psychosis During Follow-up

Mediation models (Figure 1 and Table 2) showed that depression fully mediated (direct effects were not significant) the relationship between abuse and positive symptoms at 2 months indirect effect ((IE) = 0.423; 24.4% of total effect) and 36 months (IE = 0.447; 22.2% of total effect). Results of the multilevel mediation model including all measurement occasion over the three years follow-up showed partial mediation (IE= 0.392; 26.7% of total effect). In this model the direct effect was still significant (DE = 1.075).

Mediating Effects of Anxiety Symptoms on the Link Between Abuse and Positive Symptoms of Psychosis During Follow-up

Mediation models (Figure 2 and Table 2) showed that anxiety fully mediated (direct effects were not significant) the relationship between abuse and positive symptoms at 2 months (IE = 0.575; 32.9.4% of total effect), while the mediating effects dropped notable at 36 months, not reaching significance (IE = 0.185; 8.3% of total effect). Results of the multilevel mediation model including all measurement occasion of the three years follow-up showed partial mediation (IE= 0.421; 26.7% of total effect). In this model the direct effect was still significant (DE = 1.075).

Mediating Effects of combined cluster of anxiety/depression on the Link Between abuse and positive symptoms of psychosis During Follow-up

As symptoms of anxiety and mood are often related, we also calculated this combined cluster of depression and anxiety symptoms. Mediation models (Table 2, Figure 3) showed that depression/anxiety cluster fully mediated (direct effects were not significant) the relationship between abuse and positive symptoms at 2 months (IE = 0.546; 29.7% of total effect), while the mediating effects dropped notable at 36 months, not reaching significance (IE = 0.163; 7.7% of total effect). Consistent with previous models, results of the multilevel mediation model including all measurement occasion of the three years follow-up showed partial mediation (IE= 0.475; 29.8% of total effect). In this model the direct effect was still significant (DE = 1.075).

Table 2

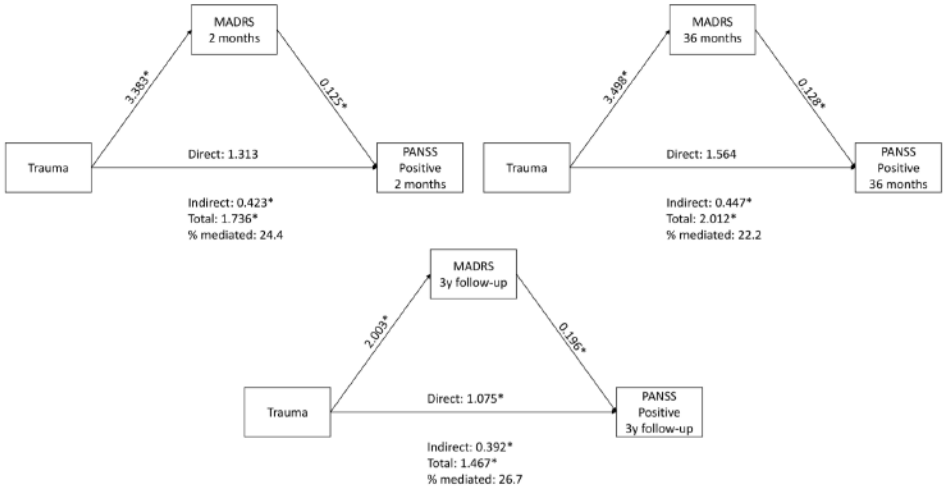
Associations Between Abuse Split Into Total Effects, Direct and Indirect Pathways Via anxiety, Depression and the Combination of both at 2, 36 months follow-up and across the 36 months of treatment at TIPP.

	2 months follow-up				36 months follow-up				Full model across 36 months follow-up			
	Total effect	Direct effect	Indirect effect	% mediated	Total effect	Direct effect	Indirect effect	% mediated	Total effect	Direct effect	Indirect effect	% mediated
Anxiety (PANSS G2 & G4)	1.747*	1.173	0.575*	32.9	2.244*	2.058	0.185	8.3	1.575*	1.155*	0.421*	26.7
Depression (MADRS)	1.736*	1.313	0.423*	24.4	2.012*	1.564	0.447*	22.2	1.467*	1.075*	0.392*	26.7
Anxiety and depression (Emsley cluster)	1.840*	1.294	0.546*	29.7	2.126*	1.963*	0.163	7.7	1.593*	1.118*	0.475*	29.8

Note: adjusted for age, gender, duration of untreated psychosis, bullying, physical neglect and emotional neglect. p<0.05. MADRS: Montgomery-Asberg Depression Rating Scale. PANSS: The Positive and Negative Syndrome Scale. G2: anxiety measure with the PANSS; G4: tension measured with the PANSS.

Figure 1

Associations between abuse split into total effects, direct effects and indirect effects pathways of severity of depressive symptoms after 2, 36 months of follow-up and during the entire 36 months of treatment period.

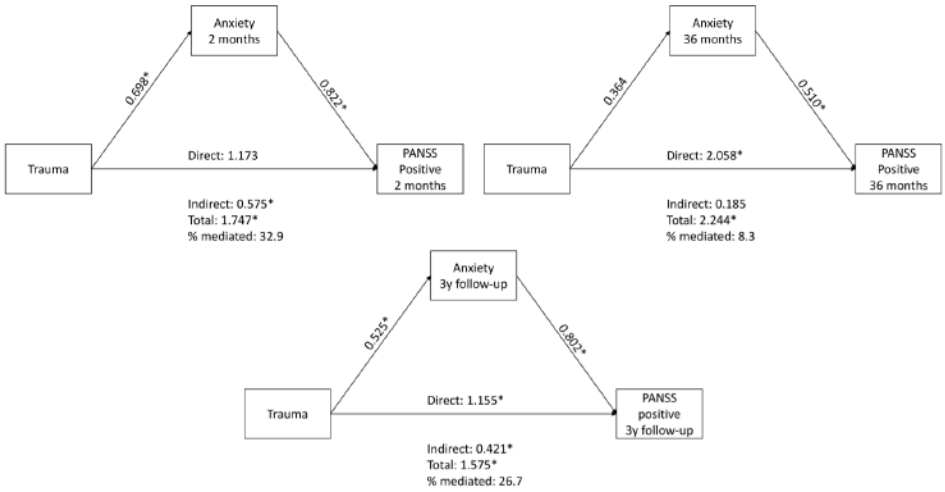


**p<.05*

Control variables (Age, Gender, DUP, Bullying, Physical neglect and Emotional Neglect) are omitted for clarity.

Figure 2

Associations between abuse split into total effects, direct effects and indirect effects pathways of severity of anxiety after 2, 36 months of follow-up and during the entire 36 months of treatment period.



**p<.05*

Control variables (Age, Gender, DUP, Bullying, Physical neglect and Emotional Neglect) are omitted for clarity.

Discusion

This is the first study examining the mediating role of anxiety and depression on the association between abuse and positive symptoms in a sample of Early psychosis patients. Our results show that 27% of the association between abuse and psychotic symptoms is mediated by anxiety and depression during the first three years of treatment. Sub-analyses by specific time points suggest that the role of anxiety may be more pronounced at the beginning of treatment (two month follow-up), while that of depression is present both at the beginning and at the end of the follow-up (36 months follow-up). These results confirm the importance of carefully assessing mood-related symptoms in EP patients exposed to childhood trauma and point out the important role of an affective component in the persistence of positive symptoms of psychosis in those exposed to abuse, which opens possible therapeutic venues.

Evidence of an affective component in the presence and maintenance of positive symptoms

There is evidence that mood and positive symptoms are related and coexist in people with psychosis that have faced experiences of adversity, particularly abuse(Bebbington, 2015). The "affective pathway to psychosis" in those exposed to social adversity stands as one of the most accepted hypotheses on the trauma-psychosis mechanisms(Alameda, L. et al., 2020; Bloomfield et al., 2021; Sideli et al., 2020). To the best of our knowledge only two studies had tested this in a sample of people with psychosis finding evidence suggesting mediation(Isvoranu et al., 2016a; van Os et al., 2020). Our paper confirms such findings in

an EP sample and not only at baseline, but also during the first three years of treatment.

Importantly, mood symptoms do not operate in isolation, and other mediating factors, such as dissociation(Longden et al., 2020), cognitive biased (such as negative schemas about self, the world and others(Gaweda et al., 2018)), as well as loneliness(Steenkamp et al., 2019) are also important mediators of the trauma-psychosis dyad(Alameda, L. et al., 2020). Thus, our findings provide only a fraction of a much more complex picture, where mood symptoms operate simultaneously and in a non-competitive manner, with other processes, as previously suggested (Alameda, L. et al., 2020). For example, loneliness may precede lower mood, which in turn may contribute to cognitive bias, affecting the ability to see others as threatening or to see yourself as potentially vulnerable, which would precipitate paranoia(Howes and Murray, 2014). Moreover, anxiety may predate processes such as dissociation, which according to current evidence is the most powerful mediator between adversity and psychosis(Alameda, L. et al., 2020). Therefore, multiple pathways need to be considered simultaneously which is very difficult to address, and thus our findings need to be seen as just one piece in a more complex picture.

Therapeutic implications

It is now evident that despite of the well-known traditional means to treat positive symptoms of psychosis, those exposed to trauma, particularly abuse, continue to present higher severity of such symptoms, as recently shown in a meta-analysis(L. Alameda, 2021). It has been hypothesized that addressing possible mediators that are operating in the pathogenesis of such symptoms, may offer an additional therapeutic avenue(Alameda, L. et al., 2020; Bebbington, 2015) for those with trauma. Our work supports the idea that mood related symptoms should not only be considered as comorbidity, but actually as part of a causative pathway linking adversity ad psychosis. Addressing anxiety and mood specifically by pharmacological means but also through psychotherapeutic approaches would be beneficial to improve positive symptoms. For example, behavioural activation and graded exposure(Waller et al., 2013), addressing self-esteem, relaxation techniques and meditation(Ernst and D'Mello, 2020) could make part of a trauma-informed approach for EP patients. Despite the well-established knowledge on the role of trauma in psychosis, addressing traumatic experiences in the context of trauma-informed care in early intervention teams is challenging and often debated(Tong et al., 2019). Our results on the mediating role of the affective comorbidity may help build trauma-sensitive approaches for early psychosis. Furthermore, we found that only 12% of the entire sample and 16% of those with trauma (no difference between exposed and non-exposed were found) had a diagnosis of depression, which is a relatively low rate and which could reflect the difficulty to identify formal diagnoses of comorbid depression in those with psychotic disorder. This suggests that clinicians may not only consider the diagnostic threshold to implement interventions for mood and anxiety, but should view that domain as a dimension and carefully assess anxiety and depression at a sub-threshold level. Based on our findings, randomised controlled trials should be conducted in the future, in an attempt to test whether addressing mood related symptoms can improve positive symptoms of psycho-

sis. Finally, our results show that while anxiety appears to be an important mediator early in the follow-up, this is not the case at 36 months (32.9.4% at 2 months, against 8.3% of total effect mediated at 36 months). However, the pervasive mediating effect of depressive symptoms seems more stable (24.4% at 2 months, against 22.2% at 36 months), which suggests that general EP interventions may be more successful for the treatment of anxiety, while that of depression remains an unresolved challenge that requires urgent attention in the future.

Strengths and limitations

The findings of this work should be interpreted in the context of various strengths and limitations. A major strength is the prospective design, that allowed us to examine the possible role of mood and anxiety over a period of three years. Among the 48 articles included in a recent systematic review on the mediating role between adversity and psychosis, only four were conducted with a prospective design(Alameda, L. et al., 2020) which shows the lack of this type of design in current literature. Moreover, this is the first study addressing this issue on an EP sample, and formally testing the mediation through mediation analyses. This provides a quantitative measure of the amount of the association that is explained by the mediating factor. In terms of limitations, among the entire representative sample that took part in TIPP, some patients could not be included because data on trauma or psychopathology was not available. Patients that were included had slightly higher socio-economic level and Insight but did not differ on other important variables like age, gender, baseline GAF, diagnostic or DUP (Supplementary Table 1). Additionally, although the full models covering the entire follow-up period allowed us to include a large sample of 330 EP patients, thus increasing statistical power, the naturalistic nature of the cohort prevented us from including all sample individuals at each time point: 167 subjects were included at time 2, against 124 at time 36, with 49.2% of subjects being non overlapping, thus these variations in each time point could lead to selection bias. Furthermore, exposure to abuse was assessed retrospectively, which may be particularly problematic for patients suffering from psychosis due to recall bias(Howard, 1993). However, exposure to trauma was assessed on the basis of information obtained from patients and their families in the context of a three year therapeutic relationship(Conus et al., 2010), which we believe reduces the risk of recall bias existing in other forms of self-report or cross-sectional research interviews. Furthermore, traumatic experiences tend to co-occur, and for example, the group exposed to abuse had greater rates of exposure to bullying. Although we have adjusted our analyses for various other adversities, we have used a broad binary measure of abuse, thus not accounting for the cumulative effect of various traumas, which is associated with psychosis in a dose response fashion (Morgan and Gayer-Anderson, 2016)

Moreover, we did not have sufficient information to determine whether high severity of symptoms corresponded to non-response to treatment (being a proxy of treatment resistance psychosis). Exploring whether trauma is associated with treatment resistance in psychosis would be of great interest, as it could help to identify additional mechanism involved in the severe forms of psychosis in this group of patients. Hopefully this can be

addressed in the future.

To conclude, our results suggest that a careful assessment of subthreshold anxiety and depressive symptoms is necessary in patients exposed to abuse. EP services should implement specific interventions addressing trauma and its various manifestations, including mood and anxiety which may improve the resolution of psychotic symptoms, if not the global outcome of patients.

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Declaration of interest

None

References

- Alameda, L., Christy, A., Rodriguez, V., Salazar de Pablo, G., Thrush, M., Shen, Y., Alameda, B., Spinazzola, E., Iacoponi, E., Trotta, G., Carr, E., Ruiz Veguilla, M., Aas, M., Morgan, C., Murray, R.M., 2021. Association Between Specific Childhood Adversities and Symptom Dimensions in People With Psychosis: Systematic Review and Meta-Analysis. Schizophr Bull.

- Alameda, L., Golay, P., Baumann, P.S., Progin, P., Mebdouhi, N., Elowe, J., Ferrari, C., Do, K.Q., Conus, P., 2017. Mild Depressive Symptoms Mediate the Impact of Childhood Trauma on Long-Term Functional Outcome in Early Psychosis Patients. Schizophr Bull 43(5), 1027-1035.

- Alameda, L., Rodriguez, V., Carr, E., Aas, M., Trotta, G., Marino, P., Vorontsova, N., Herane-Vives, A., Gadelrab, R., Spinazzola, E., 2020. A systematic review on mediators between adversity and psychosis: potential targets for treatment. Psychological Medicine 50(12), 1966-1976.

- Alameda, L., Rodriguez, V., Carr, E., Aas, M., Trotta, G., Marino, P., Vorontsova, N., Herane-Vives, A., Gadelrab, R., Spinazzola, E., Di Forti, M., Morgan, C., Murray, R.M., 2020. A systematic review on mediators between adversity and psychosis: potential targets for treatment. Psychol Med 50(12), 1966-1976.

- Association, A.A.P., 1994. Diagnostic and statistical manual of mental disorders (DSM-IV). Washington, DC: American Psychiatric Association.
- Bailey, T., Alvarez-Jimenez, M., Garcia-Sanchez, A.M., Hulbert, C., Barlow, E., Bendall, S., 2018. Childhood trauma is associated with severity of hallucinations and delusions in psychotic disorders: a systematic review and meta-analysis. Schizophrenia bulletin 44(5), 1111-1122.
- Baumann, P.S., Crespi, S., Marion-Veyron, R., Solida, A., Thonney, J., Favrod, J., Bonsack, C., Do, K.Q., Conus, P., 2013. Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. Early Interv Psychiatry 7(3), 322-328.
- Bebbington, P., 2015. Unravelling psychosis: psychosocial epidemiology, mechanism, and meaning. Shanghai archives of psychiatry 27(2), 70-81.
- Bloomfield, M.A.P., Chang, T., Woodl, M.J., Lyons, L.M., Cheng, Z., Bauer-Staeb, C., Hobbs, C., Bracke, S., Kennerley, H., Isham, L., Brewin, C., Billings, J., Greene, T., Lewis, G., 2021. Psychological processes mediating the association between developmental trauma and specific psychotic symptoms in adults: a systematic review and meta-analysis. World Psychiatry 20(1), 107-123.
- Conus, P., Cotton, S., Schimmelmann, B.G., McGorry, P.D., Lambert, M., 2010. Pretreatment and outcome correlates of sexual and physical trauma in an epidemiological cohort of first-episode psychosis patients. Schizophr Bull 36(6), 1105-1114.
- Emsley, R., Rabinowitz, J., Torreman, M., 2003. The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. Schizophr Res 61(1), 47-57.
- Emsley, R.A., Oosthuizen, P.P., Joubert, A.F., Roberts, M.C., Stein, D.J., 1999. Depressive and anxiety symptoms in patients with schizophrenia and schizophreniform disorder. J Clin Psychiatry 60(11), 747-751.
- Ernst, A.F., D'Mello, D., 2020. Efficacy of a brief mindfulness intervention upon anxiety in early psychosis patients. Early intervention in psychiatry 14(4), 503-506.
- Fisher, H.L., Schreier, A., Zammit, S., Maughan, B., Munafo, M.R., Lewis, G., Wolke, D., 2013. Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. Schizophr Bull 39(5), 1045-1055.
- Gaweda, L., Metel, D., Arciszewska, A., Daren, A., Nelson, B., Frydecka, D., Cechnicki, A., 2018. Mediating role of resilience and cognitive biases in the relationship between childhood trauma and psychotic-like experiences in the general population. Early Intervention in Psychiatry 12 (Supplement 1), 171.

- Howard, L.M., 1993. Allegations of abuse in psychotic patients. Am J Psychiatry 150(5), 839-840.
- Howes, O.D., Murray, R.M., 2014. Schizophrenia: an integrated sociodevelopmental-cognitive model. Lancet 383(9929), 1677-1687.
- Isvoranu, A.-M., Borsboom, D., van Os, J., Guloksuz, S., 2016a. A network approach to environmental impact in psychotic disorder: brief theoretical framework. Schizophrenia bulletin 42(4), 870-873.
- Isvoranu, A.-M., van Borkulo, C.D., Boyette, L.-L., Wigman, J.T., Vinkers, C.H., Borsboom, D., Investigators, G., 2016b. A network approach to psychosis: pathways between childhood trauma and psychotic symptoms. Schizophrenia bulletin 43(1), 187-196.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin 13(2), 261-276.
- L. Alameda, A.C., V. Rodriguez, G. Salazar de Pablo, M. Thrush, Y. Shen, B. Alameda, E. Spinazzola, E. Iacoponi, G. Trotta, C. Ewan, M.R. Veguilla, M. Aas, C. Morgan, R. M. Murray, 2021. Association between specific childhood adversities and symptom dimensions in people psychosis: systematic review and meta-analysis. Schizophrenia Bulletin (In press).
- Longden, E., Branitsky, A., Moskowitz, A., Berry, K., Bucci, S., Varese, F., 2020. The Relationship Between Dissociation and Symptoms of Psychosis: A Meta-analysis. Schizophr Bull.
- Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br J Psychiatry 134, 382-389.
- Morgan, C., Gayer-Anderson, C., 2016. Childhood adversities and psychosis: evidence, challenges, implications. World Psychiatry 15(2), 93-102.
- Myin-Germeys, I., van Os, J., 2007. Stress-reactivity in psychosis: Evidence for an affective pathway to psychosis.
- Sideli, L., Murray, R.M., Schimmenti, A., Corso, M., La Barbera, D., Trotta, A., Fisher, H.L., 2020. Childhood adversity and psychosis: a systematic review of bio-psycho-social mediators and moderators. Psychol Med 50(11), 1761-1782.
- Steenkamp, L., Weijers, J., Gerrmann, J., Eurelings-Bontekoe, E., Selten, J.-P., 2019. The relationship between childhood abuse and severity of psychosis is mediated by loneliness: An experience sampling study. Schizophrenia Research, No Pagination Specified.
- Tong, J., Simpson, K., Alvarez-Jimenez, M., Bendall, S., 2019. Talking about trauma in therapy: Perspectives from young people with post-traumatic stress symptoms and first episode psychosis. Early intervention in psychiatry 13(5), 1236-1244.

- van Os, J., Pries, L.K., Ten Have, M., de Graaf, R., van Dorsselaer, S., Delespaul, P., Bak, M., Kenis, G., Lin, B.D., Luykx, J.J., Richards, A.L., Akdede, B., Binbay, T., Altınyazar, V., Yalınçetin, B., Gümüş-Akay, G., Cihan, B., Soygür, H., Ulaş, H., Cankurtaran, E., Kaymak, S.U., Mihaljevic, M.M., Petrovic, S.A., Mirjanic, T., Bernardo, M., Mezquida, G., Amoretti, S., Bobes, J., Saiz, P.A., García-Portilla, M.P., Sanjuan, J., Aguilar, E.J., Santos, J.L., Jiménez-López, E., Arrojo, M., Carracedo, A., López, G., González-Peñas, J., Parellada, M., Maric, N.P., Atbaşoğlu, C., Ucok, A., Alptekin, K., Saka, M.C., Arango, C., O'Donovan, M., Rutten, B.P.F., Guloksuz, S., 2020. Evidence, and replication thereof, that molecular-genetic and environmental risks for psychosis impact through an affective pathway. Psychol Med, 1-13.

- Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., Bentall, R.P., 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull 38(4), 661-671.

- Waller, H., Garety, P., Jolley, S., Fornells-Ambrojo, M., Kuipers, E., Onwumere, J., Woodall, A., Emsley, R., Craig, T., 2013. Low intensity cognitive behavioural therapy for psychosis: a pilot study. Journal of behavior therapy and experimental psychiatry 44(1), 98-104.

- Williams, J., Bucci, S., Berry, K., Varese, F., 2018. Psychological mediators of the association between childhood adversities and psychosis: A systematic review. Clinical psychology review 65, 175-196.

- Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. The Australian and New Zealand journal of psychiatry 39(11-12), 964-971.

CHAPTER 4

Childhood adversity and psychosis, potential mediating epigenetic mechanisms

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Can Epigenetics shine a light on the biological pathways underlying major mental disorders?

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Abstract:

A significant proportion of the global burden of disease can be attributed to mental illness. Despite important advances in identifying risk factors for mental health conditions, the biological processing underlying causal pathways to disease onset remain poorly understood. This represents a limitation to implement effective prevention and the development of novel pharmacological treatments. Epigenetic mechanisms have emerged as mediators of environmental and genetic risk factors which might play a role in disease onset, including childhood adversity (CA) and cannabis use (CU). Particularly, human research exploring DNA methylation has provided new and promising insights into the role of biological pathways implicated in the aetio-pathogenesis of psychiatric conditions, including: monoaminergic (Serotonin and Dopamine), GABAergic, glutamatergic, neurogenesis, inflammatory and immune response and oxidative stress. While these epigenetic changes have been often studied as disease-specific, similarly to the investigation of environmental risk factors, they are often transdiagnostic. Therefore, we aim to review the existing literature on DNA methylation from human studies of psychiatric diseases (i) to identify epigenetic modifi-

cations mapping onto biological pathways either transdiagnostically or specifically related to psychiatric diseases such as Eating Disorders, Post traumatic Stress Disorder, Bipolar and Psychotic Disorder, Depression, Autism Spectrum Disorder and Anxiety Disorder, and (ii) to investigate a convergence between some of these epigenetic modifications and the exposure to known risk factors for psychiatric disorders such as CA and CU, as well as to other epigenetic confounders in psychiatry research.

1. Introduction of main epigenetic processes in psychiatry research

Both genetic and environmental factors are implicated in the aetiology of psychiatric disorders, however the key causal mechanisms for guiding effective prevention and treatment remain poorly understood (Jim Van Os, Rutten, & Poulton, 2008). Genetic association studies (Ripke et al., 2014) as well as epidemiological studies addressing the impact of the environment (J. van Os, Kenis, & Rutten, 2010) on disease burden, have not yet explained the non-complete genetic correlation between monozygotic twins in conditions such as schizophrenia (SCZ) (41-65%), Bipolar Disorder (BD) (~60%) (Craddock, O'Donovan, & Owen, 2005) or Major Depression (MDD) (~40%) (Ripke et al., 2013).

In the past decade, growing evidence has shown a link between epigenetic processes, and a range of mental health disorders (Binder, 2017). Epigenetic modifications refer to functional changes in DNA structural packaging or associated proteins without structural alteration of the DNA sequence itself (Jaenisch & Bird, 2003). This biological mechanism has important implications on how genes are expressed and how the chromatin is packaged, thus modifying subsequent protein translation within regionally specific parts of the central nervous system (Binder, 2017). The most studied epigenetic process in humans is DNA methylation (DNAm) (Table 1 for definitions of key terms). Indeed, recent parallel evidence suggests that differential DNAm profiles are associated with exposure to childhood adversity (CA) as well as cannabis use (CU) (Kandaswamy et al., 2020; Markunas et al., 2020; Nöthling, Malan-Müller, Abrahams, Hemmings, & Seedat, 2020). This suggests that epigenetic factors may account for some of the non-explained variance in genetics studies and possibly mediate the interactions between genotype and known environmental risk factors in influencing the onset of complex diseases (Relton & Smith, 2010).

Initially, epigenetic research in psychiatry used a candidate gene approach, and progressively, research moved to Epigenome Wide Association studies (EWAS) (Table 1). While both designs have their advantages and limitations, the breadth of coverage of EWAS offers a more informative insight on biological pathways. This is based on the rational that chromatin conformation and transcriptional regulation are influenced by a set of methylated or unmethylated cytosines across a region, rather than specific CpG sites in isolation (Mill et al., 2008)

Different biological pathways have been implicated in the aetio-pathogenesis across multiple mental disorders. Some of these are pathways related to neurotransmission such as serotonin (Provenzi, Giorda, Beri, & Montirosso, 2016), dopamine or GABA/glutamatergic

processes (McCutcheon, Krystal, & Howes, 2020); while others pathways involve inflammation (Cullen et al., 2019), oxidative stress (Steullet et al., 2016), synaptic plasticity and neurogenesis (Claudino, Gonçalves, Schuch, Martins, & Rocha, 2020), or the stress response system (Hypothalamic Pituitary adrenal Axis – HPA) (Wesarg, Van Den Akker, Oei, Hoeve, & Wiers, 2020). It is important to take into account that some of these processes participate in disease pathogenesis in a parallel manner, such as via the redox system and through the glutamatergic/GABAergic imbalance (Hardingham & Do, 2016); or the immune system and the stress response (Pariante, 2017). Although these processes are often explored within discrete categorical clinical conditions, they often overlap transdiagnostically. For instance, alterations in serotonin pathways are linked to both depression and psychosis phenotypes (Selvaraj, Arnone, Cappai, & Howes, 2014).

In this review, we set to appraise firstly, the evidence of DNAm modifications both from candidate genes and EWAS studies, associated either specifically or transdiagnostically with psychiatric conditions, and secondly, if these DNAm modifications map onto biological pathways. Thirdly, we will explore if the existing findings from studies on DNAm changes associated with CA and CU, two of the environmental exposures most consistently associated with psychiatric disorders (Lindert et al., 2014; Mandelli, Petrelli, & Serretti, 2015; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Lucia Sideli, Quigley, La Cascia, & Murray, 2020; Varese et al., 2012), point at the same biological pathways therefore contributing to the understanding of how these environmental exposures increase transdiagnostic and specific psychiatric liability. Details on methodological considerations can be found in Supplementary Material (SM).

2. Evidence of epigenetic processes in major transdiagnostic pathways

In this section we will review the evidence, predominantly from case-control studies pointing at an association between DNAm changes in the Serotoninergic, Dopaminergic pathways, Excitatory inhibitory balance (including the Glutamatergic and GABAergic dysfunction, Synaptic plasticity and Neurogenesis; the Immune system, Inflammation and Oxidative stress and the major mental conditions (focusing on Eating Disorders (ED): anorexia nervosa (AN) and bulimia nervosa (BN), Autism Spectrum Disorder (ASD), BD and Psychotic Disorder, Depression, Post Traumatic Stress Disorder (PTSD) and Anxiety Disorders). Summary of findings are illustrated in Figure 1; findings on HPA-axis and its association to environmental risk factors are presented in section 3 and Figure 2 and Supplementary Table 1 (SM) summarises the characteristics of the articles mentioned in that section. Table 2 summarised the key elements of studies finding evidence of a link between DNAm on genes involved in each biological pathway across all disorders. Screening

2.1 The serotoninergic pathway

There are preclinical and human studies pointing at an implication of the serotonin (5HT) system dysfunction in a broad range of psychiatric diseases (Kaye, Fudge, & Paulus, 2009). The strongest evidence is at the level of the serotonin transported genes (mainly *SLC6A4*) with candidate genes studies suggesting an increased in methylation in depression (Kang et al., 2013; Philibert et al., 2008; Zhao, Goldberg, Bremner, & Vaccarino, 2013), BD (H Sugawara et al., 2011) and reporting a positive association with symptoms severity (Olsson et al., 2010), comorbid depression in those with panic disorder (Schiele et al., 2019), and improvement from baseline to follow-up (Perez-Cornago, Mansego, Zulet, & Martinez, 2014). It has been suggested that an increased DNAm of *SLC6A4* could repress gene expression, leading to decreased serotonin uptake and lower activity, which ultimately would lead to the manifestation of depressive symptoms (Chen, Meng, Pei, Zheng, & Leng, 2017)

A pattern of hypermethylation has also been found in samples of SCZ (Abdolmaleky et al., 2014). although with mixed evidence(Alelú-Paz et al., 2015). Candidate gene studies in SCZ and BD across various tissues (Abdolmaleky et al., 2011; Carrard, Salzmann, Malafosse, & Karege, 2011; Cheah, Lawford, Young, Morris, & Voisey, 2017) show elevated DNAm of the *5-HTR1A* and *5-HTR2A* genes respectively. Further, EWAS studies have identified differential DNAm in *HTR2A* (Numata, Ye, Herman, & Lipska, 2014), *HTR5A* and *HTR1E* (Nishioka et al., 2013; Pidsley et al., 2014) genes in those with psychosis.

Evidence on ED so far has not found an association with SLC6A4 DNAm and AN (Boehm et al., 2019; Pjetri et al., 2013; Steiger et al., 2019).

In ASD, preliminary evidence indicated higher *HTR2A* promoter DNAm in leukocytes of those carrying the high-risk genotype in the *HTR2A* (Hranilovic, Blazevic, Stefulj, & Zill, 2016).

Another well explored gene of interest in the serotoninergic pathway is *MAO-A* (Shih & Thompson, 1999) which is involved in monoamine degradation and it has established linked with depression (Meyer et al., 2006). While studies in depression have found inconsistent DNAm changes (Domschke et al., 2015; Melas & Forsell, 2015; Melas et al., 2013); in candidate gene studies in anxiety disorders, the evidence points at a pattern of hypomethylation (Ziegler et al., 2016) as shown in acrophobia (Schiele et al., 2018) and obsessive compulsive disorder (OCD) (Domschke et al., 2012). Moreover, increased MAO-A DNAm has been suggested as a potential useful marker of better response to psychotherapy in anxiety disorders (Schiele et al., 2020; Ziegler et al., 2016).

Overall, we find a transdiagnostic link between DNAm changes in genes involved in the serotoninergic pathway, with limited evidence in ED (findings on PTSD discussed in Section 3 and described in Table 2).

2.2 The Dopaminergic pathway

It is widely accepted that dopaminergic dysregulation stands as one of the most supported hypotheses for the pathogenesis of SCZ and psychosis as a whole (Jauhar et al., 2018; McCutcheon et al., 2020). Studies examining DNAm in blood of patients with SCZ as compared with controls have showed both higher and lower DNAm levels in different DA receptor's genes; with decreased DNAm in *DRD3* (Dai et al., 2014) and *DRD4* (Cheng et al., 2014); and in other dopamine receptors (Kordi-Tamandani, Sahranavard, & Torkamanzehi, 2013; Yoshino et al., 2016).

Hypomethylation of the *COMT* membrane-bound isoform, has been identified in samples of people with SCZ across tissues (Abdolmaleky et al., 2006; Nohesara et al., 2011; Nour El Huda et al., 2018; Walton et al., 2014), while the soluble isoform (*S-COMT*) has been reported to be hypermethylated (Melas et al., 2012; Murphy, O'Reilly, & Singh, 2005). EWAS studies comparing SCZ patients with controls have found hypomethylation of *SLC6A3,* a dopamine transporter (Nishioka et al., 2013), *COMTD1* and *FAM63B,* a gene linked to dopaminergic gene expression (Aberg et al., 2014).

In ED, findings of DNAm changes affecting dopaminergic genes *DAT* and *DRD2* are mixed (Frieling et al., 2010; Pjetri et al., 2013). It has been suggested that DNAm variation in the dopamine pathway in ED may related to comorbid Borderline Personality Disorder (Borderline PD) (Groleau et al., 2014) and exposure to CA (section 3 and Supplementary Table 1 (SM)).

None of the EWAS studies conducted in ASD have found evidence supporting an association with DNAm changes involved in the Dopaminergic pathway.

Overall, recent findings support a link between DNAm changes in genes involved in the dopaminergic pathway related to neurodevelopmental disorders such SCZ, with limited evidence suggesting a link with other conditions.

2.3 Glutamatergic/GABAergic pathway and excitatory / Inhibitory balance

Alterations in glutamatergic and GABAergic pathways, which can lead to either excitatory/inhibitory imbalance, have been reported to play a role in the etiopathogenesis of psychotic disorders (McCutcheon et al., 2020) and ASD (Marotta et al., 2020). Furthermore N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDAR) hypofunction as well as a decrease in the parvalbumin-expressing fast spiking interneurons (PVI), both processes being essential for the excitatory/inhibitory balance, have been widely shown to be involved in psychotic disorders (Thuné, Recasens, & Uhlhaas, 2016).

In SCZ and psychosis, there is evidence from candidate genes studies across tissues supporting DNAm differences between cases and controls in genes such as the Parvalbumin (*PVALB*) gene(Fachim, Srisawat, Dalton, & Reynolds, 2018), *GMR2* and *GMR5* of the gluta-

matergic receptors (Kordi-Tamandani, Dahmardeh, & Torkamanzehi, 2013); various CpG sites in the β2 subunit of the GABAa receptor gene (*GABRB2*) (Pun et al., 2011; Zong et al., 2017), and in *GRIN2B*, involved in the function of NMDAR (Fachim et al., 2019). A dysregulation of multiple DNAm positions in the regulatory network of *GAD1*, was identified in patients with SCZ and BD compared to controls (Ruzicka, Subburaju, & Benes, 2015).

In terms of EWAS Mill and colleagues (Mill et al., 2008) performed the first EWAS in post-mortem brains of SCZ and BD subjects compared to controls, and found DNAm changes associated with SCZ and BD at loci involved in glutamatergic (*GRIA 2, GRIND3B*) and GABAergic (*MARLIN-1, KCNJ6, HELT*) neurotransmission, supporting previous candidate genes results. Findings related to *GRIA* family genes have been replicated in latter EWAS studies (Aberg et al., 2012; Numata et al., 2014), and other EWAS studies have confirmed DNAm changes in genes involving GABAergic neurotransmission (*SLC6A12* and *GABBR1*) (E. Hannon et al., 2021).

In ASD, an EWAS study on histone acetylation in participants with the disorder compared to controls found an enrichment of hyperacetylated sites in genes involved in GABA receptor activity (Ramaswami et al., 2020), although this has not been previously found on DNAm (C. Wong et al., 2018).

Lastly, a Depression EWAS (Nagy et al., 2015) of post-mortem brains of suicide victims and controls found 115 differentially methylated regions (DMRs), which included regions related to *GRIK2*.

Overall, there is evidence linking DNAm changes on genes involved in the glutamatergic pathway mainly with psychosis, with some evidence suggesting a link with ASD and MDD.

2.4 Synaptic plasticity and Neurogenesis

Synaptic plasticity anomalies are associated with psychiatric conditions and may account for various symptoms, such as cognitive deficits (Claudino et al., 2020; Di Carlo, Punzi, & Ursini, 2019; Lin & Huang, 2020).

RELN is a well studies gene that has been linked to SCZ (Costa et al., 2002). An aberrant DNAm status in *RELN* has been found in SCZ and BD patient as compared with controls

(Fikri et al., 2017; Tamura, Kunugi, Ohashi, & Hohjoh, 2007). Interestingly, peripheral blood hypomethylation in the *RELN* promoter was associated with poor cognitive functioning (Alfimova, Kondratiev, Golov, & Golimbet, 2018).

In ASD, an EWAS study in post-mortem brain found dysregulation in the pathway of phosphatidylinositol 3-kinase (*PI3K*) activity (C. C. Y. Wong et al., 2019), an enzyme that is involved in cellular growth, proliferation and differentiation, and which has been previously been associated with SCZ (Law et al., 2012)

Brain derived Neurotrophic factor (*BDNF*) is essential for neurogenesis and extensively

studied as a biomarker in psychiatry (Lin & Huang, 2020) There is extensive evidence of difference in DNAm in *BDNF*, as well as EWAS studies showing enrichment for the neurogenesis pathway in SCZ (Di Carlo et al., 2019; Ursini et al., 2016), BD (Dell et al., 2014; Duffy et al., 2019), PTSD(Kim et al., 2017; Uddin et al., 2010), Depression (Hing, Sathyaputri, & Potash, 2018; Kang et al., 2015), Borderline PD (Arranz et al., 2021; Thomas et al., 2018), Anxiety Disorders (D'Addario et al., 2019), ED (Thaler et al., 2014), ASD (Ramaswami et al., 2020) thus making a well replicated epigenetic transdiagnostic finding in psychiatry.

As a whole, transdiagnostic evidence suggest an involvement of DNAm changes in neurogenesis an neural plasticity.

2.5 Immune system and inflammation

Abundant evidence supports the role of neuroinflammation and altered immune processes in the aetiopathogeneses of various mental conditions (Mazza, Lucchi, Rossetti, & Clerici, 2020; Pariante, 2017).

An EWAS by Montano et al. (Montano et al., 2016) found differences in DNAm in genes involved in T-cell development in the blood of SCZ patients (*ZC3H12D*, *TCF3*, and *IKZF4*); other EWAS have also reported an enrichment in the immune system pathway by differently methylated genes (*FR2B, PIK3R3, INPP5D, FCGR2C, IGHA1, FCAR; CD224, LAX1, TXK, PRF1, CD7, MPG*, and *MPOG* (Aberg et al., 2014; Eilis Hannon et al., 2016; J. Liu et al., 2014).

In depression, a discordant monozygotic twin study based on peripheral blood, found 39 DMRs associated to lifetime history of MDD, which were significantly enriched in biological pathways associated to cytokine secretion (Zhu et al., 2019). Another EWAS on post-mortem brain of people with late-MDD (Hüls et al., 2020), found altered DNAm in the YOD1 locus, which is dysregulated in depression (Howren, Lamkin, & Suls, 2009) and its implicated in the regulation of inflammatory processes (Schimmack et al., 2017).

Two EWAS studies in PTSD found differences in DNAm across genes part of biological pathways involved with inflammation and immune response (Kuan et al., 2017; Uddin et al., 2010).

In ASD, various EWAS studies have pointed at dysregulation of pathways related to immune response (Ramaswami et al., 2020; C. C. Y. Wong et al., 2019), and in a genome-wide microRNA (miRNA) expression profiling study (Wu, Parikshak, Belgard, & Geschwind, 2016).

Furthermore, an EWAS study from patients suffering from Panic Disorder found enrichment in genes involved in the regulation of lymphocytes (Shimada-Sugimoto et al., 2017).

We can conclude that there is transdiagnostic, rather than specific, link between DNAm changes in the immune systema and inflammation and neural plasticity, although evidence is more robust in SCZ.

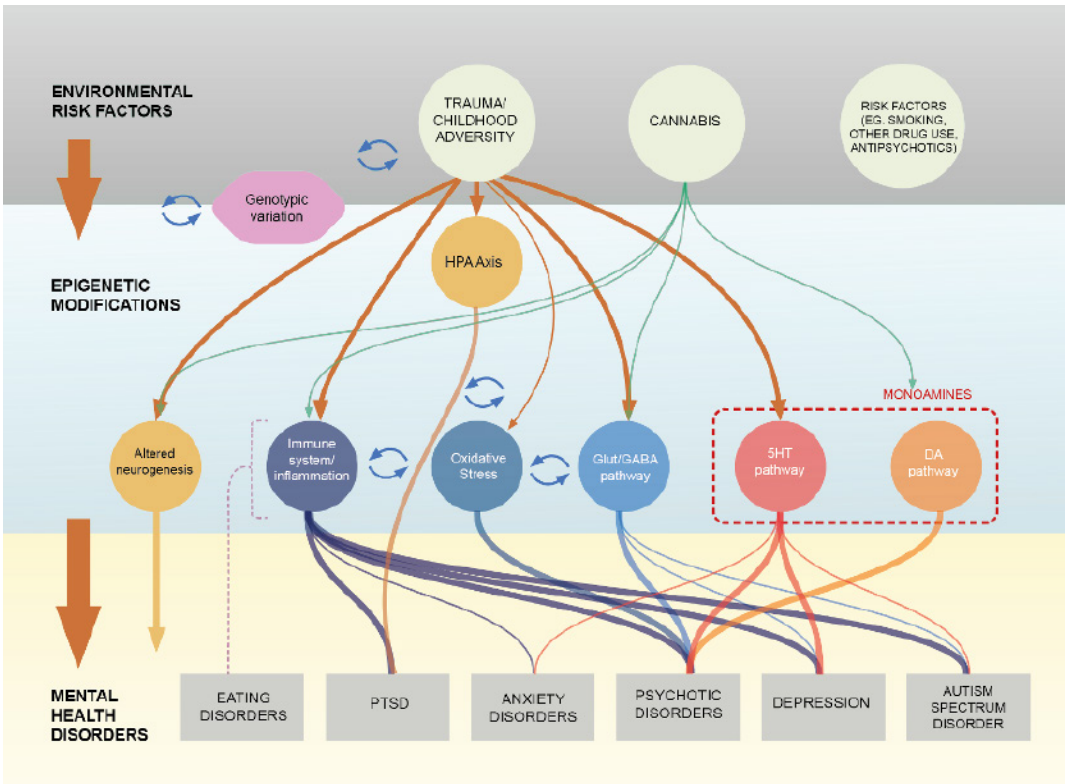
2.6 Oxidative stress

There is converging evidence pointing at a role of redox dysregulation as a possible mechanism involved in the aetiopathogenesis of both ASD (Bjørklund et al., 2020) and psychosis (Perkins, Jeffries, & Do, 2020). Oxidative stress has been shown to play a role in epigenetic modifications, enhancing inflammatory gene transcription (Rahman, Marwick, & Kirkham, 2004). Oxidation of 5mC to the 5-hydroxymethylcytosine (5hmC) is considered a key step in the reversibility of DNA methylation, which can have important therapeutic implications. Moreover, glutathione, the major antioxidant in the brain, is involved in the methionine cycle, and depletion of glutathione can be detrimental for the DNAm process (García-Giménez, Roma-Mateo, Perez-Machado, Peiro-Chova, & Pallardó, 2017).

Although evidence examining this pathway in the context of epigenetics is scarce, some EWAS have shown interesting results: one study examined prospectively the association of EWAS methylation changes with transition to psychosis (Kebir et al., 2017), and found an enrichment of pathways related to oxidative stress regulation in those transitioning. Furthermore, an EWAS study in Borderline PD found differences in methylation in GCT6, which is important in glutathione metabolism (Arranz et al., 2021).

Figure 1

Summary of the evidence on potential pathways linking childhood trauma and cannabis use with psychiatric conditions through DNAm changes



This figure summarises the evidence presented in this review, highlighting the idea that some biological pathways linking environmental risk factors with mental health disorders via epigenetic changed in the form of DNAm are transdiagnostics (e.g immune system/inflammation) while others seem to be more specific (e.g dopaminergic system). 1) The environmental risk factors row and epigenetic modifications row suggest links between childhood adversity (CA), and Cannabis use (CU) and DNAm changes mapping to biological pathways which are also functionally related (Serotoninergic, Dopaminergic pathways, Glutamatergic & GABAergic pathway, Neurogenesis, Immune system & Inflammation and Oxidative stress). 2)The epigenetic modifications row and mental health disorders row illustrate the evidence, from case control studies, of an association between DNAm changes in these pathways and the major mental health conditions (Eating Disorders (anorexia nervosa and bulimia nervosa, Post-traumatic stress disorder, Anxiety Disorders, Psychotic Disorder, Bipolar disorders, Depression and Autism Spectrum Disorders). 3) The arrows connecting the three rows show the potential mediating role of DNAm changes linking CA and CU and risk to develop mental health conditions. The thickness of the lines shows the robustness of the evidence reported in the literature review. The items "genotype: and "other risk factors" are added to highlight the influence of genetic factors and environmental confounders in DNAm studies. The dotted line connecting eating disorders with the pathways indicate that literature was limited and mixed not allowing to draw clear links with the pathways.

Table 1

A glossary of key epigenetic terms and biological function of genes involved in pathways discussed in this review.

Gene	Biological Function
Epigenetic terms	
DNA-methylation	DNA-meth is the covalent addition of a methyl group to the 5th carbon of a Cytosine (C) base, resulting in a 5-methylcytosine (5-mC) base. Epigenetic is the major process by which environment can alter gene expression
Candidate gene approach	Explores methylation on certain genes of interests based on a priory hypothesis. It often examines whether DNAm changes in different CG sites within specific genes are related to a particular phenotype.
Genome-Wide approach	Examines the association of DNAm changes (otherwise called methylome-wide association studies (MWAS)) across the entire genome for a particular phenotype, using a hypothesis free paradigm. EWAS have been performed with increasingly powerful techniques and have moved from pioneer CpG-island microarrays studies that interrogated around 12.000 sites across the DNA (Mill et al., 2008) to more advanced techniques such as Infinium MethylationEPIC BeadChip, that covers more than 850,000 CpG methylation sites (Yong et al., 2016).
Histone acetylation studies	Histone acetylation is a dynamic epigenetic modification that functions in the regulation of DNA-templated reactions, such as transcription. This lysine modification is reversibly controlled by histone (lysine) acetyltransferases and deacetylases.
Methylome-wide association studies (MWAS)	Test a genome-wide set of methylation sites for association with an outcome of interest.

Serotoninergic pathway	
SLC6A4	Regulated serotonergic signalling via transporting 5-HT from synaptic spaces into presynaptic neurons. SLCA2 is involved in the recapture of the Norepinephrine
5-HTR (1A, 2A, 2B 3A, 5A)	These genes encode for the receptors for neurotransmitter serotonin
A (MAOA)	One of two neighbouring gene family members that encode mitochondrial enzymes which catalyze the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin
Dopaminergic pathway	
DRD (2*, 3, 4)	Encode different subtype of the dopamine receptor
COMT*(D1)	Encodes for Catechol-O-methyltransferase enzyme, which catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine important in the degradation of Dopamine (DA)
DAT1*	The dopamine transporter is implicated in a number of dopamine-related disorders, including attention deficit hyperactivity disorder, bipolar disorder, clinical depression, alcoholism, and substance use disorder
FAM63B	Involved in four networks regulated by miRNA, three of which are linked to neuronal differentiation and dopaminergic gene expression
SLC6A3	Provides instructions for making a protein called the dopamine transporter or DAT
Glutamatergic/GABAergic pathway	
GAD1	Encodes one of several forms of glutamic acid decarboxylase, enzyme which is responsible for catalyzing the production of gamma-aminobutyric acid from L-glutamic acid
PVALB	Encodes for Parvalbumin protein, essential for neural synchronisation in some neurons in the CNS
GRIN1 (2,2B 3B, D1)	The protein encoded by this gene is a critical subunit of N-methyl-D-aspartate receptors, members of the glutamate receptor channel superfamily. It plays an important role in the plasticity of synapses
GRIA 2, 3	Encodes for the Glutamate Ionotropic Receptor AMPA Type Subunit 2 and 3 Glutamate receptors, which are the predominant excitatory neurotransmitter receptors in the mammalian brain
MARLIN-1	(synonym of JAKMIPI) code for a protein that may play a role in the microtubule-dependent transport of the GABA-B receptor
KCNJ6	Encodes a member of the G protein-coupled inwardly-rectifying potassium channel family of inward rectifier potassium channels.This type of potassium channel allows a greater flow of potassium into the cell than out of it and thus regulates circuit activities in neural cells. Expressed in GABAergic synapses
HELT	Protein Coding gene involved in DNA-binding transcription factor activity and protein dimerization activity. It is a transcriptional repressor gene which is known to function as a selector gene that determines GABAergic over glutamatergic fate in the mesencephalon
GRIK2	Codes for the Glutamate Ionotropic Receptor Kainate Type Subunit 2. Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain

SLC6A12	Transports betaine and GABA. May have a role in regulation of GABAergic transmission in the brain through the reuptake of GABA into presynaptic terminals, as well as in osmotic regulation.
GABBR1, 2	Encodes a receptor for GABA that functions as a heterodimer with GABA(B) receptor 1 and 2. Defects in this gene may underlie brain disorders such as schizophrenia and epilepsy.
GRIN3B	The protein encoded by this gene is a subunit of an N-methyl-D-aspartate (NMDA) receptor. The encoded protein is found primarily in motor neurons, where it forms a heterotetramer with GRIN1 to create an excitatory glycine receptor. Variations in this gene have been proposed to be linked to schizophrenia
Neurogenesis	
RELN	This gene encodes a large secreted extracellular matrix protein (Reelin) thought to control cell-cell interactions critical for cell positioning and neuronal migration during brain development. expressed in GABAergic interneurons
BDNF	Encodes the brain-derived neurotrophic factor (BDNF), a protein involved in promoting the survival, growth and differentiation of new neurons and synapses
POU5F1, POU6F2. POU3F1	Encodes a transcription factor protein that binds to the octamer motif (5-ATTTGCAT-3) and controls myelination (thought to be involved in embryogenesis and neurogenesis)
NPDC1	Encored for a protein that Suppresses oncogenic transformation in neural and non-neural cells and down-regulates neural cell proliferation. Might be involved in transcriptional regulation
PI3K	Phosphatidylinositol 3-kinases, are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking
CUX1*	Encodes a member of the homeodomain family of DNA binding proteins that regulates gene expression, morphogenesis, and differentiation and it also plays a role in cell cycle progression
CLMN*	Encodes calmin (calponin-like transmembrane domain protein)
SENP7*	Encodes sentrin-specific protease 7
Immune system and inflammation	
ZC3H12D	It is a Protein (Zinc Finger CCCH-Type Containing 12D) Coding gene, which in association with ZC3H12A enhances the degradation of interleukin IL-6 mRNA level in activated macrophages, among other functions
TCF3	This gene encodes a member of the E protein (class I) family of helix-loop-helix transcription factors. E proteins play a critical role in lymphopoiesis, and the encoded protein is required for B and T lymphocyte development, among other functions
IKZF4	Members of the Ikaros family of transcription factors, which includes Eos, are expressed in lymphocytes and are implicated in the control of lymphoid development
YOD1	Protein ubiquitination controls many intracellular processes, including cell cycle progression, transcriptional activation, and signal transduction, involved in IL-1 signalling to NF-κB

IL17RA	Code for Interleukin 17A (IL17A), which is a proinflammatory cytokine secreted by activated T-lymphocytes
TLR1 (3)	Encodes Toll Like Receptor 1, family which plays a fundamental role in pathogen recognition and activation of innate immunity
TNFRSF13C	TNF Receptor Superfamily Member 13C, a membrane protein of the TNF receptor superfamily which recognizes BAFF, an essential factor for B cell maturation and survival
HERC5	This gene is a member of the HERC family of ubiquitin ligases and encodes a protein with a HECT domain and five RCC1 repeats. Pro-inflammatory cytokines upregulate expression of this gene in endothelial cells
FCGR2B	One of the genes thought to influence susceptibility to several autoimmune diseases in humans inhibiting the functions of activating FcyRs, such as phagocytosis and pro-inflammatory cytokine release
PIK3R3	Plays an important role in the regulation of cellular lipid metabolism
INPP5D	Encodes Src homology 2 (SH2) domain containing inositol polyphosphate 5-phosphatase 1 (SHIP1) that functions as negative regulator of cell proliferation and survival
FCGR2C, 2B	Encodes one of three members of a family of low-affinity immunoglobulin gamma Fc receptors found on the surface of many immune response cells and involved in phagocytosis
IGHA1	Encodes a constant (C) segment of Immunoglobulin A heavy chain that plays a critical role in immune function in the mucous membranes
FCAR	Codes for the transmembrane receptor FcαRI, also known as CD89 (Cluster of Differentiation 89), that plays a role in both pro- and anti-inflammatory responses
CD224	This gene is a human gamma-glutamyltransferase catalyzes the transfer of the glutamyl moiety of glutathione to a variety of amino acids and dipeptide acceptors
LAX1	A membrane-associated adaptor protein mainly expressed in B cells, T cells, and other lymphoid-specific cell types
TXK	A member of Tec family nonreceptor tyrosine kinase, is expressed on Th1/Th0 cells, and Txk regulates specifically IFN-gamma gene expression
PRF1	Encodes perforin a pore forming cytolytic protein found in the granules of cytotoxic T lymphocytes (CTLs) and natural killer cells (NK cells)
CD7	Encodes a transmembrane protein which is a member of the immunoglobulin superfamily found on thymocytes and mature T cells that plays an essential role in T-cell interactions and also in T-cell/B-cell interaction during early lymphoid development
MPG	Encodes N-methylpurine DNA glycosylase a specific type of DNA glycosylase involved in the recognition of a variety of base lesions, including alkylated and deaminated purines, and initiating their repair via the base excision repair pathway
MPOG	A member of the XPO subfamily of peroxidase enzyme most abundantly expressed in neutrophil granulocytes
MARC2*	The protein encoded by this gene is an enzyme found in the outer mitochondrial membrane that reduces N-hydroxylated substrates

CEMIP*	Cell migration-inducing and hyaluronal-binding protein, known as KIAA1199, has been shown to bind hyaluronic acid and catalyze its depolymerization its depolymerization independently of CD44 and hyaluronidases
Oxidative stress	
GGT6	Encored for a gamma-glutamyltransferase, that plays a key role in glutathione homoeostasis by providing substrates for its synthesis
GSTM5	(Glutathione S-Transferase Mu 5), important for Glutathione homeosthasis
Hypothalamus pituitary adrenal axis pathway	
NR3C1	Encodes the human glucocorticoid receptor protein, which is the receptor to which cortisol and other glucocorticoids bind
miR124	A microRNA that targets NR3C1
FKBP5 (2, 1B)	Encodes the FK506 binding protein, a member of the immunophilin protein family which may play a role in immunoregulation and basic cellular processes involving protein folding and trafficking
SKA2	Encodes for a component of the spindle and kinetochore-associated protein complex, which is a protein complex involved in regulating chromosomal segregation. SKA2 is important in facilitating GR nuclear transactivation.
Cannabinoid system	
CNR1 and CNR2*	Encodes the cannabinoid receptor gene
Other genes	
DNMTS	This gene encodes an enzyme that transfers methyl groups to cytosine nucleotides of genomic DNA
OXTR	Encodes oxytocin, which is a neuropeptide hormone produced by the hypothalamus and released into systemic circulation by the posterior pituitary
Tobacco signature genes	
AHRR*	The protein encoded by this gene participates in the aryl hydrocarbon receptor (AhR) signaling cascade, which mediates dioxin toxicity, and is involved in regulation of cell growth and differentiation
F2RL3*	Encodes a member of the protease-activated receptor subfamily, part of the G-protein coupled receptor 1 family of proteins. This receptor plays a role in blood coagulation, inflammation and response to pain
GFI1	Encodes a nuclear zinc finger protein that functions as a transcriptional repressor. This protein plays a role in diverse developmental contexts, including haematopoiesis and oncogenesis
MYO1G	Is a plasma membrane-associated class I myosin that is abundant in T and B lymphocytes and mast cells.. This myosin required during immune response for detection of rare antigen-presenting cells by regulating T-cell migration

* genes related to cannabis use

3. The epigenetic signature of childhood adversity and cannabis use

Characteristic of studies described in this section can be found in Supplementary Table 1 (SM), and in Table 2.

3.1 Hypothalamus pituitary adrenal axis pathway

While multiple studies have explored the link between epigenetic modification involved in the HPA-axis, and psychiatric disorders, recent evidence is beginning to indicate that some of these epigenetic modifications might follow exposure to CA. The latter is a robustly replicated risk factors for many psychiatric disorders (Supplementary Table 1 (SM) summarises the main findings on studies examining the link between DNAm and genes involved in the HPA-axis, and key findings are summarised in Figure 2). As a whole, as illustrated in Figure 2, at the level of *NR3C1* there is consistent evidence on a positive correlation between CA and DNAm in Borderline PD and MDD and some clinical outcomes (Farrell et al., 2018; Martin-Blanco et al., 2014; Perroud et al., 2011; Radtke et al., 2015), and a negative correlation with anxiety and PTSD (Labonte, Azoulay, Yerko, Turecki, & Brunet, 2014; Schechter et al., 2015; W. Wang et al., 2017; Yehuda et al., 2015). Lower DNAm in *FKBP5* is associated with CA in psychosis and PTSD (Klengel et al., 2013; Misiak et al., 2020); while in depression, 3 studies found no such link (Bustamante et al., 2018; Farrell et al., 2018; Klinger-König et al., 2019), as opposed to another study (Tozzi et al., 2018). As for NR3C1, findings on *FKBP5* DNAm are different across disorder, suggesting divergent transdiagnostic mechanism involving in HPA related genes (see Figure 2). The *SKA2* interacts with adversity scores in predicting lifetime suicide attempt (Kaminsky et al., 2015), and mediated the association between reduced cortical thickness and PTSD (Sadeh, Spielberg, et al., 2016) and suicide phenotypes (Sadeh, Wolf, et al., 2016).

3.2 Serotoninergic, Dopaminergic and Glutamatergic/ GABAergic pathways

Childhood adversity

With regards to the serotoninergic pathway, while hypomethylation in *SLC6A* is associated with resilience to PTSD (Koenen et al., 2011), hypermethylation of *SLC6A* has been linked to exposure to CA and associated with worst clinical presentation in MDD (Kang et al., 2013). Moreover, hypermethylation in the *5-HT3A-R* gene appeared to mediate the link between exposure to adversity and higher severity of disease parameters in a mixed sample of BD and Borderline PD (Perroud et al., 2016).

Moreover, hypomethylation of *MAOA*, a gene important for degradation of serotonin and DA (Xu, Jiang, Gu, Wang, & Yuan, 2020), appears to partially mediate the known association between CA and depressive symptoms, alongside with other stress related genes such as BDNF and NR3C1 and SLC64 (Peng et al., 2018). Moreover, *MAOA* DNAm was negatively

correlated to life events in a sample of Panic Disorder (Domschke et al., 2012).

In relation to DA, one study in patients with bulimia spectrum disorders found no differences in *DRD2* DNAm when comparing those with exposure and non-exposure to trauma (Groleau et al., 2014).

At the level of the Glutamatergic pathway, one study found that exposure to CA was associated with decreased DNAm in *GAD* in a sample of Panic Disorder (Domschke et al., 2013). Lastly, a candidate gene study (Engdahl, Alavian-Ghavanini, Forsell, Lavebratt, & Rüegg, 2021) and an EWAS (Weder et al., 2014) linked CA to increased methylation levels in *GRIN2B/GRIND1* genes, suggesting evidence that this change may lead to the onset of depressive symptoms.

As a whole, DNAm changes in some of the genes that have been previously linked to major psychiatric conditions (section 2, Table 2), such as *SLC6A, 5HT3A-R, A (MAOA), BDNF, GAD* and the *GRIND* family, (related to the serotoninergic, and glutamatergic pathways respectively) are also associated to CA. This suggest that some of the DNAm changes attributed to these disorders may be partially related to the consequence of CA exposure, as illustrated in Figure 1.

Cannabis use

CU and in particular heavy use (Marconi et al., 2016) has been consistently associated with increased risk for PD, but to a lesser degree for other psychiatric conditions (L. Sideli, Trotta, Spinazzola, La Cascia, & Di Forti, 2020). In recent years, candidate genes studies from peripheral blood have reported changes in DNAm associated with heavy CU in genes involved in dopamine transmission, such as *DRD2* (Gerra et al., 2018), *DAT1* (Grzywacz et al., 2020) and *COMT* (Van der Knaap et al., 2014) and in the *CB1* and *CB2* receptors genes part of the endocannabinoid system (Rotter et al., 2012; Tao et al., 2020). The latter playing an important role in brain development and synaptic transmission.

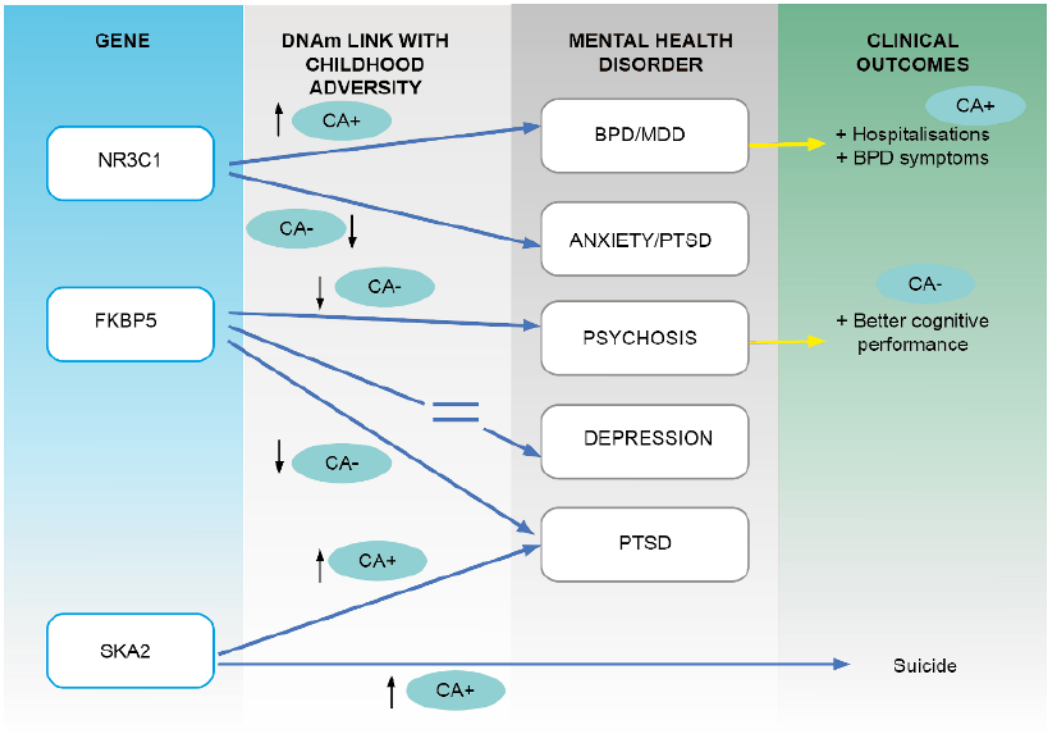
A recent study investigated the effect of heavy CU with and without tobacco on EWAS (Osborne et al., 2020). The analyses in the sample with both cannabis and tobacco use identified differentially methylated sites in 2 genes, *AHRR* and *F2RL*, previously reported to be affected by tobacco exposure. Within the sample of cannabis users without tobacco, while none of the differentially methylated loci reached EWAS significance, an exploratory analysis showed enrichment for genes involved in signaling pathway, including glutamatergic transmission, brain function and mood disorders. Moreover, these exploratory analyses show two differentially methylated sites significantly associated with both only CU and cannabis with tobacco, which are within the *MARC2* gene. The latter previously linked to adverse effects to antipsychotics in schizophrenia (Åberg et al., 2010) and within the *CUX1* gene which is involved in neuronal development (Platzer et al., 2018).

Furthermore, a recent whole blood and cell specific Methylome-wide association studies (MWAS) from a sample of adolescents with CU disorder pointed at many methylation sites

relevant to brain function and to neurodevelopment (Clark et al., 2021). These included CpGs located in the *CLMN* gene and the *SENP7* gene, expressed in the brain and playing a role in brain developmental and synaptic function and organization (Juarez-Vicente, Luna-Pelaez, & Garcia-Dominguez, 2016; Marzinke & Clagett-Dame, 2012). Interestingly, the pathway analyses based on the cell type-specific significant DNAm changes associated with CU implicated pathways such as the Slit-Robo signaling (granulocytes) under the regulatory control of the endocannabinoid system during brain cortical development (Alpár et al., 2014), the *ErbB* signaling pathway (T-cell) and pathways involved in DNA repair (B-cell) (Clark et al., 2021).

Figure 2

Summary of the evidence linking childhood adversity and DNAm chnages on the Hipotalamic Pituitary Adrenal Axis in various conditions as well as with some clinical measures



This Figure illustrates the evidence from candidate gene studies linking childhood adversity (CA) with DNAm in CpG sites located in NR3C1, FKBP5, SKA2 and CA, with various conditions and various clinical outcomes. The gene and DNAm columns, CA+ (with an arrow pointing up) reflects the presence of a positive association between the DNAm in probes located in those genes and CA; CA- (with an arrow pointing down) reflects a negative association. The disorder column shows in which mental health condition that association has been found. Lastly, the clinical outcomes column shows the presence of evidence linking DNAm, with a particular clinical phenotype; CA+ indicated that that the association between DNAm and the clinical outcome was related to CA.

3.3 Inflammation, oxidative stress, synaptic plasticity and neurogenesis

Childhood Adversity

A number of EWAS studies conducted in clinical samples have reported an association between exposure to CA and DNAm changes across genes involved in inflammation. For instance, a study (Prados et al., 2015) found a positive correlation between the *IL17RA* DNAm and CA in a Borderline PD and MDD sample. Other evidence suggests a negative correlation between DNAm in genes enriched for immune pathways (such as *TLR1* and *TLR3*) and CA in PTSD subjects (Uddin et al., 2010); while the *TNFRSF13C* gene was differently methylated between Borderline PD participants with and without CA (Arranz et al., 2021) (See Supplementary Table 1 (SM) – EWAS section).

Candidate genes studies have linked CA with DNAm changes in *BDNF* (Moser et al., 2015, Weder et al., 2014, Thaler et a., 2014), consistently with EWAS data reporting DNAm changes affecting genes involved in neurogenesis (Prados et al., 2015; Uddin et al., 2010). For instance, three EWAS studies in BD (Comes et al., 2019), Borderline PD (Arranz et al., 2021) and MDD (Lutz et al., 2017) have consistently shown changes in DNAm in genes from the *POU* family that are associated with CA (*POU6F2, POU5F1* and *POU3F1* respectively), which are genes involved in myelinisation and neurogenesis (Supplementary Table 1 (SM) - EWAS section).

A recent EWAS study found differences in DNAm of the *GGT6* gene that were associated with exposure to CA in a sample of Borderline PD patients; *GGT6* is key for glutathione homeostasis (Arranz et al., 2021), it is also the main antioxidant and redox regulator that has previously been associated with SCZ aetiopathogenesis (Steullet et al., 2016). Further evidence is summarised in Supplementary Table 2 (SM).

As a whole, candidate gene and EWAS studies suggest a link between CA and genes involved in the inflammatory and neurogenesis pathways, with some preliminary evidence suggesting a link between CA and DNAm and oxidative stress genes (Figure 1).

Cannabis use

The largest to date case-control study to examine the effect of lifetime CU on DNAm reported an epigenome-wide-significantly differentially methylated CpG site within the *CEMIP* gene (Markunas et al., 2020). The *CEMIP* gene, involved in hyaluronic catabolism, which has been shown to have an important role in inflammation, immune processes as well as associated with BD and SCZ previously (Petrey & de la Motte, 2014).

4. Other Environmental exposures that can act as confounders in psychiatric epigenetic

4.1 Tobacco Smoking

A number of publications have identified robust associations between tobacco smoking and DNAm (Elliott et al., 2014; Shenker et al., 2013; Tsaprouni et al., 2014; Zeilinger et al., 2013), with a number of genes (e.g., *AHRR, F2RL3, GFI1* and *MYO1G*) replicated across studies.

The confounding effect of smoking is clearly evidenced in an EWAS study on peripheral blood of SCZ patients (E. Hannon et al., 2016). A similar study examining the impact of CA on the epigenome in a general population found that tobacco consumption was an important confounding when examining the signature of CA (Marzi et al., 2018). Whether some of these epigenetic changes associated with tobacco exposure could also mediate the already reported link between tobacco use and increased risk of psychosis, it is an important question yet to be determined (Gurillo, Jauhar, Murray, & MacCabe, 2015), and tobacco smoking should be accounted for in future epigenetic studies in psychiatry.

4.2 Alcohol use and abuse

There is some initial evidence to suggest that alcohol use is associated with DNAm changes (C. Liu et al., 2016; F. Wang, Xu, Zhao, Gelernter, & Zhang, 2016; Weng, Wu, Lee, Hsu, & Cheng, 2015). Enrichment analyses examined DNAm in alcohol users have revealed enrichment in pathways related to neural degeneration (Weng 2015), and in genes important for neurogenesis (*NPDC1*), inflammation (*HERC5*) and in GABA receptors (a receptor delta and B receptor subunit 1); all of which are pathways previously associated with different mental disorders, as shown in Figure 1. However, studies rarely account for such covariates, which is currently a limitation of current literature.

4.3 Psychiatric medication

The extent of the data reporting the DNAm changes associated with psychiatric medication would require a separate review. Indeed, there is consistent evidence that pharmacological agents can trigger DNAm in similar or opposite directions than those attributed to disease. For example, Lithium, Carbamazepine and Quetiapine, often prescribed for the treatment of BD, are associated with decrease methylation of *SLC6A4* (Asai et al., 2013; Hiroko Sugawara et al., 2015), in contrast with the hypermethylation reported in BD in that gene (Table 2). Similarly, studies who have investigated the effect of antipsychotic medication, have shown, on the one hand, that Haloperidol affects DNAm in leucocytes of SCZ patients (Melas et al., 2012), while on the other hand a recent EWAS study showed that Clozapine exposure leads to DNAm differences in patients with treatment-resistant SCZ (Eilis Hannon et al., 2021) as compared to controls. Thus, it is key to consider the possibility that some of the changes in DNA pathways may be led by agents rather than the disease itself, highlighting the need to account for medication in future studies and to consider epigenetics as a potential mediating mechanism of action of the beneficial effects of medication in the brain.

Table 2

Summary of the direction of the associations between DNAm, mental health disorders and clinical or biological outcomes presented in this review

Gene (hyper ↑ or ↓ hypo DNAm) and citation	Candidate gene or EWAS	Tissue	Condition/sample	Clinical/biological outcome
Serotoninergic pathway				
SLC6A4				
↑Abdolmaleky *et al.*, 2014	Candidate gene	PMB/saliva	SCZ	
Kang *et al.*, 2013	Candidate gene	Blood	Depression	CA → ↑SLC6A4 → clinical severity
Olsson *et al.*, 2010	Candidate gene	Buccal	Depression	↑SLC6A4 → ↑ Depressive symptoms
↑Philibert *et al.*, 2008	Candidate gene	Blood	Depression	↑SLC6A4 → ↑ history MDD
↑Zhao *et al.*, 2013	Candidate gene	Blood	Twin male veterans	↑SLC6A4 → ↑ Depressive symptoms
Perez-Cornago *et al.*, 2014	Candidate gene	Blood	General population	↑SLC6A4 → decrease depressive symptoms from baseline to Follow-up
Boehm *et al.*, 2019	Candidate gene	Blood	Anorexia nervosa	↑SLC6A4 → resting-state functional connectivity→ anorexia symptoms
Koenen *et al.*, 2011	Candidate gene	Blood	PTSD	CA + ↓SLC6A4 → PTSD
Peng *et al.*, 2018	Candidate gene	Blood	General population	CA → ↑SLC6A4 → depressive symptoms
Schiele *et al.*, 2019	Candidate gene	Blood	Panic disorder	↑SLC6A4→ Comorbid depression
5-HTR 1A				
↑Carrard *et al.*, 2011	Candidate gene	Blood	SCZ/BD	
5-HTR 2A				
↑Cheah *et al.*, 2017	Candidate gene	PMB	SCZ	
↑Abdolmaleky *et al.*, 2011	Candidate gene	PMB	SCZ/BD	
↑Hranilovic *et al.*, 2016	Candidate gene	Blood	ASD	
5-HT3A-R				
↑Perroud *et al.*, 2016	Candidate gene	Blood	BD/Borderline PD	CA → ↑*5-HT3A-R* → clinical severity
A MAOA				
↓ Ziegler *et al.*, 2016	Candidate gene	Blood	Panic disorder	↑ → Better response to CBT in agoraphobic symptpms
↓Schiele *et al.*, 2018	Candidate gene	Blood	Agoraphobia	
↓Domschke *et al.*, 2012	Candidate gene	Blood	Panic disorder	CA → ↓*A (MAOA)*
Peng *et al.*, 2018	Candidate gene	Blood	General population	CA → ↓*A (MAOA)* → depressive symptoms
Dopaminergic pathway				
DRD2				
↑Kordi-Tamandani *et al.*, 2013b	Candidate gene	Blood	SCZ	
↓Yoshino *et al.*, 2016	Candidate gene	Blood	SCZ	
↑Frieling *et al.*, 2010	Candidate gene	Blood	Anorexia and Bulimia Nervosa	
DRD3				
↑Dai *et al.*, 2014	Candidate gene	Blood	SCZ	
DRD4				

↑Cheng *et al.*, 2014 ↑Kordi-Tamandani *et al.*, 2013b	Candidate gene Candidate gene	Blood Blood	SCZ SCZ	
DRD5 ↑Kordi-Tamandani *et al.*, 2013b	Candidate gene	Blood	SCZ	
MB-COMT ↓Abdolmaleky *et al.*, 2006 ↓Nohesara *et al.*, 2011 Walton *et al.*, 2014 ↓Nour El Huda *et al.*, 2018	Candidate gene Candidate gene Candidate gene Candidate gene	PMB Saliva Blood Blood	SCZ/BD SCZ/BD SCZ SCZ	↑ *MB-COMT* ->better neural activity in left DLPFC ↑ *MB-COMT*-> ↓excited and depressed symptoms
S-COMT ↑Murphy *et al.*, 2005 ↑Melas *et al.*, 2012	Candidate gene Candidate gene	PMB Blood	SCZ SCZ	
COMTD1 ↓Nishioka *et al.*, 2013	EWAS	Blood	SCZ	
SLC6A3 ↓Nishioka *et al.*, 2013	EWAS	Blood	SCZ	
*DAT1** ↑Frieling *et al.*, 2010	Candidate gene	Blood	Anorexia and Bulimia nervosa	
FAM63B ↓Aberg et al., 2012	EWAS	Blood	SCZ	
Glutamatergic/GABAergic pathway (Excitatory/inhibitory balance)				
PVALB ↑Fachim *et al.*, 2018	Candidate gene	PMB	SCZ	
GMR2, GMR5 ↓Kordi-Tamandani *et al.*, 2013a	Candidate gene	Blood	SCZ	
GRIA 3 ↑Kordi-Tamandani *et al.*, 2013a	Candidate gene	Blood	SCZ	
GRIA 2 ↓Mill *et al.*, 2008 ↓Aberg *et al.*, 2012	EWAS EWAS	PMB Blood	SCZ/BD SCZ	
GRIA 4 ↑Numata *et al.*, 2014	EWAS	PMB	SCZ	
GABBR1 ↑Hannon *et al.*, 2021	EWAS	Blood	Psychosis and SCZ	
GABBR2 ↑Pun *et al.*, 2011 ↑Zong *et al.*, 2017	Candidate gene Candidate gene	Blood Blood	SCZ SCZ	
GRIN 2B ↓Fachim *et al.*, 2019 Engdahl *et al.*, 2021	Candidate gene Candidate gene	Blood Saliva	SCZ General population	CA → ↑*GRIN2B*

GRIND1 Weder *et al.*, 2014	EWAS	Saliva	Trauma/non trauma children	
GAD1 Ruzicka *et al.*, 2015 ↓Domschke *et al.*, 2013	Candidate gene Candidate gene	PMB Blood	SCZ/BD Panic disorder	Life events → ↓GAD1 DNAm
GRIN3B ↓Mill *et al.*, 2008	EWAS	PMB	SCZ/BD	
MARLIN-1 ↑Mill *et al.*, 2008	EWAS	PMB	SCZ/BD	
KCNJ6 ↑Mill *et al.*, 2008	EWAS	PMB	SCZ/BD	
HELT ↑Mill *et al.*, 2008	EWAS	PMB	SCZ/BD	
GRIK2 Nagy *et al.*, 2015	EWAS	PMB	Depression	
SLC6A12 ↑Hannon *et al.*, 2021	EWAS	Blood	Psychosis and SCZ	
Synaptic plasticity and neurogenesis				
RELN Tamura *et al.*, 2007 Alfimova *et al.*, 2018 Fikri *et al.*, 2017	Candidate gene Candidate gene Candidate gene	PMB Blood Blood	SCZ/BD SCZ SCZ	↓DNAm → poor cognition
PI3K Wong *et al.*, 2019	EWAS	PMB	ASD	
BDNF ↑Ursini *et al.*, 2016 ↑Duffy *et al.*, 2019 ↑Dell *et al.*, 2014 ↑Kim *et al.*, 2017 ↑Kang *et al.*, 2015* ↑Peng *et al.*, 2018 ↑Thomas *et al.*, 2018 D'Addario *et al.*, 2019 ↑Thaler *et al.*, 2014 Moser *et al.*, 2015 Weder *et al.*, 2014	Candidate gene Candidate gene Candidate gene Candidate gene Candidate gene Candidate gene Candidate gene Candidate gene Candidate gene EWAS EWAS	Blood Saliva Blood Blood Blood Blood Saliva Blood Blood Saliva Saliva/blood	SCZ BD Unipolar, BD and MDD PTSD Depression Depression Borderline PD OCD Bulimia nervosa PTSD Trauma/non trauma children	↑BDNF->↑depressive symptoms CA -> ↑BDNF→ depressive symptoms CA + Borderline PD →↑BDNF meth CA → ↑BDNF meth / ↑BDNF meth-> maternal anxiety Differently methylated between CA+ and CA-
POU6F2 Comes *et al.*, 2020	EWAS	Blood	BD	↑CA-> ↓POU6F2
POU5F1 Arranz *et al.*, 2021	EWAS	Blood	Borderline PD	↑CA-> ↓POU5F1

POU3F1 Lutz *et al.*, 2017	EWAS	PMB	Depression	↑CA-> ↓POU3F1
*CUX1** Osborne *et al.*, 2020	EWAS	Blood	General population	Differently methylated in CU (exploratory analyses)
CLMN, SENP7** Clark *et al.*, 2021	EWAS	Blood	Adolescents	Differently methylated in CU users
Immune system and inflammation				
ZC3H12D ↓Montano *et al.*, 2016	EWAS	Blood	SCZ	
TCF3 ↑Montano *et al.*, 2016	EWAS	Blood	SCZ	
IKZF4 ↓Montano *et al.*, 2016	EWAS	Blood	SCZ	
YOD1 ↑Hüls *et al.*, 2020	EWAS	PMB	Depression	
IL17RA Prados *et al.*, 2015	EWAS	Blood	Borderline PD/depression	CA → ↑ IL17RA
TLR1 3 Uddin *et al.*, 2010	EWAS	Blood	PTSD	CA → ↓TLR1/3
TNFRSF13C Arranz *et al.*, 2021	EWAS	Blood	Borderline PD	Differently methylated in CA exposed
FCGR2B, PIK3R3, INPP5D, INPP5D, IGHA1, FCAR Aberg *et al.*, 2014	EWAS	Blood	SCZ	
CD224, LAX1, TXK, PRF1, CD7, MPG, MPOG Liu *et al.*, 2014	EWAS	Blood	SCZ	
*MARC2** Osborne *et al.*, 2020	EWAS	Blood	General population	Differently methylated in CU and tobacco users
*CEMIP** Markunas *et al.*, 2020	EWAS	Blood	General population	Differently methylated in CU
Oxidative stress				
↑*GSTM5* Kebir *et al.*, 2017	EWAS	Blood	At risk of psychosis	↑*GSTM5* in converters vs non converters
GGT6 Arranz *et al.*, 2021	EWAS	Blood	Borderline PD	
Hypotalamus pituitary adrenal axis pathway				
NR3C1				

Bustamante *et al.*, 2016	Candidate gene	Blood	Depression	CA → ↓ *NR3C1* DNAm
Farrell *et al.*, 2018	Candidate gene	Blood	Depression	CA → ↑ *NR3C1* DNAm
Martin-Blanco *et al.*, 2014	Candidate gene	Blood	Borderline PD	CA → ↑ *NR3C1* DNAm→ clinical severity
Perroud *et al.*, 2011	Candidate gene	Blood	Borderline PD /MDD	CA→ ↑ *NR3C1* DNAm
Radtke *et al.*, 2015	Candidate gene	Blood	General population	CA + ↑ *NR3C1* DNAm → Borderline PD symptoms
Labonte *et al.*, 2014	Candidate gene	Blood	PTSD	PTSD+ → ↓ *NR3C1* DNAm
Schechter *et al.*, 2015	Candidate gene	Saliva	PTSD	PTSD+ → ↓ *NR3C1* DNAm
Yehuda *et al.*, 2015	Candidate gene	Blood	PTSD	PTSD+ → ↓ *NR3C1* DNAm
↑ Wang *et al.*, 2017	Candidate gene	Blood	GAD	CA → ↓ *NR3C1* DNAm
Peng *et al.*, 2018	Candidate gene	Blood	General population	CA → ↑ *NR3C1*→ depressive symptoms
FKBP5				
Tozzi *et al.*, 2018	Candidate gene	Blood	Depression	CA → ↓ *FKBP5* DNAm
Misiak *et al.*, 2020	Candidate gene	Blood	SCZ	CA → ↓ *FKBP5* DNAm
Klengel *et al.*, 2013	Candidate gene	Blood	PTSD	CA → ↓ *FKBP5* DNAm
SKA2				
Kaminsky *et al.*, 2015	Candidate gene	Blood/saliva	General population	CA ↑ x SKA2↑-> suicide attempt
↑ Sadeh *et al.*, 2016	Candidate gene	Blood	PTSD	CA↑-> SKA2↑-> cortical thickness

*extensive reviews cover the role of BDNF Methylation in depression(Hing *et al.*, 2018), Schizophrenia(Di Carlo *et al.*, 2019), and eating disorders(Thaler and Steiger, 2017), therefore studies mentioned here are just examples of the literature in this particular domain. When various genes are reported in the same pathway and the same study, but no specific information on clinical/biological outcome or specific direction if the association is provided, these genes have been put in the same row (e.g Asberg et al., and Liu et al.,). When an arrow is next to the author's name it reflects the direction of the DNAm of the particular gene in in relation to the condition ↑ : increased ↓: decreased DNAm. When in column 1 there is no arrow is because information could not be obtained or was not clear, and the presence of that gene indicates the association of DNAm in that gene with the respective condition (differently methylated). When a three step sequence separated by an arrow is presented, this refers to mediation analyses (e.g peng et al.,: CA → ↑SLC6A4 → depressive symptoms: DNAm of SLC6A mediates the effect of CA on depressive symptoms. CA: childhood adversity; CU: cannabis use. Definition of each gene is presented in Table 1. DLPFC: Dorsolateral prefrontal cortex. ASD: autism spectrum disorder; SCZ: schizophrenia. PTSD: post-traumatic stress disorder; Borderline PD: Borderline personality disorder; MDD: major depression disorder; BD: bipolar disorder.

5. Summary and outstanding questions

As illustrated in Figure 1, many of the epigenetic dysregulations we report are transdiagnostic, such as those affecting the serotoninergic, inflammatory and neurogenesis pathways, while others such as the Glutamatergic/GABAergic pathway are shared between a couple of disorders (e.g., SCZ and ASD), or disorder specific such as the dopaminergic pathway in PDs. These are pathways that have been classically implicated in the aetiopathogenesis of psychiatric phenotypes; additional emerging pathways such as oxidative stress remain to be further explored.

Moreover, CA, is transdiagnostically associated to psychiatry morbidity, and seems to play a role in the DNAm dysregulation of many of these pathways. Furthermore, the preliminary DNAm changes so far reported associated with CU affect pathways previously link to psychosis, suggesting potential mediating venues to be tested in clinical populations (Figure 1).

In addition, CA is associated with DNAm changes both in the general population (Kandaswamy et al., 2020) as well as in clinical samples with psychiatric diagnosis (Supplementary Table 1 (SM)). This might suggest that the DNAm changes associated to CA exposure predate disease onset and could represent a marker of acquired psychiatric liability. However, evidence formally testing mediating pathways EWAS level between CA and the main clinical conditions is non-existent in humans. Candidate gene studies tend to find inconsistent direction of the association between CA across disorders, or findings are inconsistent within disorders as shown in Figure 2 and Table 2 and Supplementary Table 1 (SM). One explanation could be that there are other causative partners that are being missed in the equation, that may explain such inconsistency, such as the role of genotype, gene expression or a more thorough assessment of specific adversities in the context of protective factors and its link with more carefully selected clinical phenotypes.

The existing findings from epigenetics research need to be appraised in the context of well-known technical limitations epigenetics, such as the blood-brain inconsistencies, tissue-type specificity (Bakulski, Halladay, Hu, Mill, & Fallin, 2016; Nikolova & Hariri, 2015) and the candidate gene versus EWAS issue (see (Palma-Gudiel, Córdova-Palomera, Leza, & Fañanás, 2015). Moreover, evidence suggests that variation in DNAm depends not only on the environment, but also on genetic factors (Bell & Spector, 2012). Although some studies presented in this review have found evidence that some genotypic variation in some risk alleles can influence DNAm (Klengel et al., 2013; Melas et al., 2013; Perroud et al., 2016), EWAS adressing the joint effect of genotype and environment are still in its infancy (Min et al., 2021). Addressing this issue will prove methodologically challenging, but methods quantifying the genetic influences on DNAm, such as the methylation quantitative trait loci (mQTL) should be used in relation to the presence of environmental insults. Moreover, studies included in this work are often small (Supplementary Table 1 (SM)) and thus underpowered, except some exceptions (Eilis Hannon et al., 2021), which presents the

need to create collaborative efforts allowing meta-analysis of comparable epigenetic data. Furthermore, evidence of the environmental exposure impact through epigenetic modification in psychiatric diseases or phenotypes is still limited, with studies focusing mainly on exposure to CA and only preliminary results of the effect of cannabis. Given the replicated but differential impact of multiple environmental risk factors in major psychiatric disorders (Rodriguez et al., 2021), future studies exploring epigenetic variation as mediator between genetic vulnerability and various environmental factors (not only CA) should be addressed, using novel methods specifically developed for mediation using EWAS data (Z. Liu et al., 2021). Another important factor is the phenotypic characterisation for the environmental exposure. For instance, most of the studies in this work have used broad measures of adversity, using a composite cumulative score, rather than differentiating between neglect of abuse. Same can be said for the measures of CU which little reflects the level of exposure none to affect psychiatric liability. Moreover, the outcomes are often considered as SCZ, or MDD or even major psychoses (combining SCZ & BD), which are extremely heterogeneous entities, involving microphenotypes (Maj et al., 2021), and which accordingly may have very different biological underpinnings. Evidence is showing that there are some levels of specificity between adversity subtypes and symptoms domains, for example, abuse is more related to positive symptoms while neglect is not (Alameda et al., 2021) and that CU is associated with paranoia(Freeman et al., 2005). Thus, using a composite measure of CA and broadly defined conditions when trying to understand specific mediating epigenetic pathways may consider such specific links between environment and psychopathology first. Accordingly, this work suggests that some biological pathways are operating transdiagnostically, and therefore a phenotypic characterisation based on clinical dimensions may be more biologically informative than diagnostic categorisations. Furthermore, the timing of environmental exposure should be addressed, given evidence that a disruption in epigenetic programming occurs across different time windows throughout the life span (Massicotte, Whitelaw, & Angers, 2011). In this line, the lack of information on the timing of trauma and of CU initiation could explain some of the inconsistencies mentioned in our review (Figure 2). For example, we reviewed studies showing increased methylation of serotonin transporter in depressed individuals exposed to trauma (usually when adversity occurs before adulthood), which contrasts with the lower methylation in the same gene in PTSD, when exposure tends to be later in life.

6. Conclusions

Future research should include the influence of gender and how it can modulate the links between DNAm and mental disorders, or how it can affect the influence of CA on DNAm. More effort should go towards designing studies that integrate genetic data with the often-neglected effect of environmental exposures (e.g., recreational drugs and psychotropic medication). Specifically, collaborative efforts between geneticists, epigeneticists and epidemiologists will lead to increased understanding of how the DNAm changes mapping to specific pathways, might mediate the biological link between environmental exposures and increased liability to specific or transdiagnostic psychiatric morbidity.

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References

- Abdolmaleky, H. M., Cheng, K.-h., Faraone, S. V., Wilcox, M., Glatt, S. J., Gao, F., . . . Carnevale, J. (2006). Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. Human molecular genetics, 15(21), 3132-3145. Retrieved from

- Abdolmaleky, H. M., Nohesara, S., Ghadirivasfi, M., Lambert, A. W., Ahmadkhaniha, H., Ozturk, S., . . . Thiagalingam, S. (2014). DNA hypermethylation of serotonin transporter gene promoter in drug naive patients with schizophrenia. Schizophrenia Research, 152(2-3), 373-380.

- Abdolmaleky, H. M., Yaqubi, S., Papageorgis, P., Lambert, A. W., Ozturk, S., Sivaraman, V., & Thiagalingam, S. (2011). Epigenetic dysregulation of HTR2A in the brain of patients with schizophrenia and bipolar disorder. Schizophrenia Research, 129(2-3), 183-190.

- Åberg, K., Adkins, D. E., Bukszár, J., Webb, B. T., Caroff, S. N., Miller, D. D., . . . Vladimirov, V. I. (2010). Genomewide association study of movement-related adverse antipsychotic effects. Biological Psychiatry, 67(3), 279-282.

- Aberg, K. A., McClay, J. L., Nerella, S., Clark, S., Kumar, G., Chen, W., . . . Gao, G. (2014). Methylome-wide association study of schizophrenia: identifying blood biomarker signatures of environmental insults. JAMA Psychiatry, 71(3), 255-264.

- Aberg, K. A., McClay, J. L., Nerella, S., Xie, L. Y., Clark, S. L., Hudson, A. D., . . . Hultman, C. M. (2012). MBD-seq as a cost-effective approach for methylome-wide association studies: demonstration in 1500 case–control samples. Epigenomics, 4(6), 605-621.

- Alameda, L., Christy, A., Rodriguez, V., Salazar de Pablo, G., Thrush, M., Shen, Y., . . . Murray, R. M. (2021). Association Between Specific Childhood Adversities and Symptom Dimensions in People With Psychosis: Systematic Review and Meta-Analysis. Schizophrenia Bulletin. doi:10.1093/schbul/sbaa199

- Alelú-Paz, R., González-Corpas, A., Ashour, N., Escanilla, A., Monje, A., Guerrero Marquez, C., . . . Ropero, S. (2015). DNA methylation pattern of gene promoters of major neurotransmitter systems in older patients with schizophrenia with severe and mild cognitive impairment. International journal of geriatric psychiatry, 30(6), 558-565.

- Alfimova, M., Kondratiev, N., Golov, A., & Golimbet, V. (2018). Methylation of the reelin gene promoter in peripheral blood and its relationship with the cognitive function of schizophrenia patients. Molecular Biology, 52(5), 676-685.
- Alpár, A., Tortoriello, G., Calvigioni, D., Niphakis, M. J., Milenkovic, I., Bakker, J., . . . Fuzik, J. (2014). Endocannabinoids modulate cortical development by configuring Slit2/Robo1 signalling. Nature Communications, 5(1), 1-13.
- Arranz, M. J., Gallego-Fabrega, C., Martín-Blanco, A., Soler, J., Elices, M., Dominguez-Clavé, E., . . . Pascual, J. C. (2021). A genome-wide methylation study reveals X chromosome and childhood trauma methylation alterations associated with borderline personality disorder. Translational Psychiatry, 11(1), 5. doi:10.1038/s41398-020-01139-z
- Asai, T., Bundo, M., Sugawara, H., Sunaga, F., Ueda, J., Tanaka, G., . . . Iwamoto, K. (2013). Effect of mood stabilizers on DNA methylation in human neuroblastoma cells. International Journal of Neuropsychopharmacology, 16(10), 2285-2294. Retrieved from
- Bakulski, K. M., Halladay, A., Hu, V. W., Mill, J., & Fallin, M. D. (2016). Epigenetic Research in Neuropsychiatric Disorders: the "Tissue Issue". Current Behavioral Neuroscience Reports, 3(3), 264-274. doi:10.1007/s40473-016-0083-4
- Bell, J. T., & Spector, T. D. (2012). DNA methylation studies using twins: what are they telling us? Genome biology, 13(10), 172.
- Binder, E. B. (2017). Dissecting the molecular mechanisms of gene x environment interactions: implications for diagnosis and treatment of stress-related psychiatric disorders. European Journal Psychotraumatology, 8(sup5), 1412745. doi:10.1080/20008198.2017.1412745
- Bjørklund, G., Meguid, N. A., El-Bana, M. A., Tinkov, A. A., Saad, K., Dadar, M., . . . Kizek, R. (2020). Oxidative stress in autism spectrum disorder. Molecular Neurobiology, 1-19.
- Boehm, I., Walton, E., Alexander, N., Batury, V.-L., Seidel, M., Geisler, D., . . . Ehrlich, S. (2019). Peripheral serotonin transporter DNA methylation is linked to increased salience network connectivity in females with anorexia nervosa. Journal of Psychiatry NeuroScience, 45, 190016.
- Bustamante, A. C., Aiello, A. E., Guffanti, G., Galea, S., Wildman, D. E., & Uddin, M. (2018). FKBP5 DNA methylation does not mediate the association between childhood maltreatment and depression symptom severity in the Detroit Neighborhood Health Study. Journal of Psychiatric Research, 96(Supplement C), 39-48. doi:https://doi.org/10.1016/j.jpsychires.2017.09.016
- Carrard, A., Salzmann, A., Malafosse, A., & Karege, F. (2011). Increased DNA methylation status of the serotonin receptor 5HTR1A gene promoter in schizophrenia and bipolar disorder. Journal of Affective Disorders, 132(3), 450-453.

- Cheah, S.-Y., Lawford, B. R., Young, R. M., Morris, C. P., & Voisey, J. (2017). mRNA expression and DNA methylation analysis of serotonin receptor 2A (HTR2A) in the human schizophrenic brain. Genes, 8(1), 14.
- Chen, D., Meng, L., Pei, F., Zheng, Y., & Leng, J. (2017). A review of DNA methylation in depression. Journal of Clinical Neuroscience, 43, 39-46.
- Cheng, J., Wang, Y., Zhou, K., Wang, L., Li, J., Zhuang, Q., . . . Dai, D. (2014). Male-specific association between dopamine receptor D4 gene methylation and schizophrenia. PLoS One, 9(2).
- Clark, S. L., Chan, R., Zhao, M., Xie, L. Y., Copeland, W. E., Aberg, K. A., & van den Oord, E. J. (2021). Methylomic Investigation of Problematic Adolescent Cannabis Use and Its Negative Mental Health Consequences. Journal of the American Academy of Child & Adolescent Psychiatry.
- Claudino, F. C. D. A., Gonçalves, L., Schuch, F. B., Martins, H. R. S., & Rocha, N. (2020). The effects of individual psychotherapy in BDNF levels of patients with mental disorders: A systematic review. Frontiers in psychiatry, 11, 445.
- Comes, A. L., Andlauer, T. F., Adorjan, K., Budde, M., Gade, K., Degenhardt, F., . . . Kondofersky10, I. (2019). The role of environmental stress and DNA methylation in the longitudinal course of bipolar disorder. Paper presented at the European Neuropsychopharmacology.
- Costa, E., Chen, Y., Davis, J., Dong, E., Noh, J., Tremolizzo, L., . . . Guidotti, A. (2002). REELIN and Schizophrenia. Molecular interventions, 2(1), 47.
- Craddock, N., O'Donovan, M. C., & Owen, M. J. (2005). The genetics of schizophrenia and bipolar disorder: dissecting psychosis. Journal of medical genetics, 42(3), 193-204.
- Cullen, A. E., Holmes, S., Pollak, T. A., Blackman, G., Joyce, D. W., Kempton, M. J., . . . Mondelli, V. (2019). Associations between non-neurological autoimmune disorders and psychosis: a meta-analysis. Biological Psychiatry, 85(1), 35-48.
- D'Addario, C., Bellia, F., Benatti, B., Grancini, B., Vismara, M., Pucci, M., . . . Fenoglio, C. (2019). Exploring the role of BDNF DNA methylation and hydroxymethylation in patients with obsessive compulsive disorder. Journal of Psychiatric Research, 114, 17-23.
- Dai, D., Cheng, J., Zhou, K., Lv, Y., Zhuang, Q., Zheng, R., . . . Duan, S. (2014). Significant association between DRD3 gene body methylation and schizophrenia. Psychiatry research, 220(3), 772-777.
- Dell, B., Palazzo, M. C., Benatti, B., Camuri, G., Galimberti, D., Fenoglio, C., . . . Altamura, A. C. (2014). Epigenetic modulation of BDNF gene: differences in DNA methylation between unipolar and bipolar patients. Journal of Affective Disorders, 166, 330-333.

- Di Carlo, P., Punzi, G., & Ursini, G. (2019). BDNF and Schizophrenia. Psychiatric Genetics, 29(5), 200.
- Domschke, K., Tidow, N., Kuithan, H., Schwarte, K., Klauke, B., Ambrée, O., . . . Kersting, A. (2012). Monoamine oxidase A gene DNA hypomethylation–a risk factor for panic disorder? International Journal of Neuropsychopharmacology, 15(9), 1217-1228.
- Domschke, K., Tidow, N., Schrempf, M., Schwarte, K., Klauke, B., Reif, A., . . . Deckert, J. (2013). Epigenetic signature of panic disorder: a role of glutamate decarboxylase 1 (GAD1) DNA hypomethylation? Progress in Neuro-Psychopharmacology and Biological Psychiatry, 46, 189-196.
- Domschke, K., Tidow, N., Schwarte, K., Ziegler, C., Lesch, K.-P., Deckert, J., . . . Baune, B. T. (2015). Pharmacoepigenetics of depression: no major influence of MAO-A DNA methylation on treatment response. Journal of neural transmission, 122(1), 99-108.
- Duffy, A., Goodday, S. M., Keown-Stoneman, C., Scotti, M., Maitra, M., Nagy, C., . . . Turecki, G. (2019). Epigenetic markers in inflammation-related genes associated with mood disorder: a cross-sectional and longitudinal study in high-risk offspring of bipolar parents. International journal of bipolar disorders, 7(1), 1-8.
- Elliott, H. R., Tillin, T., McArdle, W. L., Ho, K., Duggirala, A., Frayling, T. M., . . . Relton, C. L. (2014). Differences in smoking associated DNA methylation patterns in South Asians and Europeans. Clinical Epigenetics, 6(1), 4. doi:10.1186/1868-7083-6-4
- Engdahl, E., Alavian-Ghavanini, A., Forsell, Y., Lavebratt, C., & Rüegg, J. (2021). Childhood adversity increases methylation in the GRIN2B gene. Journal of Psychiatry Research, 132, 38-43. doi:10.1016/j.jpsychires.2020.09.022
- Fachim, H. A., Loureiro, C. M., Corsi-Zuelli, F., Shuhama, R., Louzada-Junior, P., Menezes, P. R., . . . Reynolds, G. P. (2019). GRIN2B promoter methylation deficits in early-onset schizophrenia and its association with cognitive function. Epigenomics, 11(4), 401-410.
- Fachim, H. A., Srisawat, U., Dalton, C. F., & Reynolds, G. P. (2018). Parvalbumin promoter hypermethylation in postmortem brain in schizophrenia. Epigenomics, 10(5), 519-524.
- Farrell, C., Doolin, K., O'Leary, N., Jairaj, C., Roddy, D., Tozzi, L., . . . Nemoda, Z. (2018). DNA methylation differences at the glucocorticoid receptor gene in depression are related to functional alterations in hypothalamic–pituitary–adrenal axis activity and to early life emotional abuse. Psychiatry research, 265, 341-348.
- Fikri, R. M. N., Norlelawati, A. T., El-Huda, A. R. N., Hanisah, M. N., Kartini, A., Norsidah, K., & Zamzila, A. N. (2017). Reelin (RELN) DNA methylation in the peripheral blood of schizophrenia. Journal of Psychiatric Research, 88, 28-37.

- Freeman, D., Garety, P. A., Bebbington, P. E., Smith, B., Rollinson, R., Fowler, D., . . . Dunn, G. (2005). Psychological investigation of the structure of paranoia in a non-clinical population. The British Journal of Psychiatry, 186(5), 427-435.

- Frieling, H., Romer, K. D., Scholz, S., Mittelbach, F., Wilhelm, J., De Zwaan, M., . . . Bleich, S. (2010). Epigenetic dysregulation of dopaminergic genes in eating disorders. International Journal of Eating Disorders, 43(7), 577-583. doi:10.1002/eat.20745

- García-Giménez, J. L., Roma-Mateo, C., Perez-Machado, G., Peiro-Chova, L., & Pallardó, F. V. (2017). Role of glutathione in the regulation of epigenetic mechanisms in disease. Free Radical Biology and Medicine, 112, 36-48.

- Gerra, M. C., Jayanthi, S., Manfredini, M., Walther, D., Schroeder, J., Phillips, K. A., . . . Donnini, C. (2018). Gene variants and educational attainment in cannabis use: mediating role of DNA methylation. Transl Psychiatry, 8(1), 23. doi:https://dx.doi.org/10.1038/s41398-017-0087-1

- Groleau, P., Joober, R., Israel, M., Zeramdini, N., DeGuzman, R., & Steiger, H. (2014). Methylation of the dopamine D2 receptor (DRD2) gene promoter in women with a bulimia-spectrum disorder: Associations with borderline personality disorder and exposure to childhood abuse. Journal of Psychiatric Research, 48(1), 121-127. doi:https://doi.org/10.1016/j.jpsychires.2013.10.003

- Grzywacz, A., Barczak, W., Chmielowiec, J., Chmielowiec, K., Suchanecka, A., Trybek, G., . . . Rubis, B. (2020). Contribution of dopamine transporter gene methylation status to cannabis dependency. Brain sciences, 10(6), 1-11. doi:http://dx.doi.org/10.3390/brainsci10060400

- Gurillo, P., Jauhar, S., Murray, R. M., & MacCabe, J. H. (2015). Does tobacco use cause psychosis? Systematic review and meta-analysis. The Lancet Psychiatry, 2(8), 718-725.

- Hannon, E., Dempster, E., Viana, J., Burrage, J., Smith, A. R., Macdonald, R., . . . Therman, S. (2016). An integrated genetic-epigenetic analysis of schizophrenia: evidence for co-localization of genetic associations and differential DNA methylation. Genome biology, 17(1), 176.

- Hannon, E., Dempster, E., Viana, J., Burrage, J., Smith, A. R., Macdonald, R., . . . Mill, J. (2016). An integrated genetic-epigenetic analysis of schizophrenia: evidence for co-localization of genetic associations and differential DNA methylation. Genome Biology, 17(1), 176. doi:10.1186/s13059-016-1041-x

- Hannon, E., Dempster, E. L., Mansell, G., Burrage, J., Bass, N., Bohlken, M. M., . . . Di Forti, M. (2021). DNA methylation meta-analysis reveals cellular alterations in psychosis and markers of treatment-resistant schizophrenia. Elife, 10, e58430.

- Hannon, E., Dempster, E. L., Mansell, G., Burrage, J., Bass, N., Bohlken, M. M., . . . Mill,

J. (2021). DNA methylation meta-analysis reveals cellular alterations in psychosis and markers of treatment-resistant schizophrenia. Elife, 10. doi:10.7554/eLife.58430

- Hardingham, G. E., & Do, K. Q. (2016). Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. Nature Reviews Neuroscience, 17(2), 125-134. doi:10.1038/nrn.2015.19

- Hing, B., Sathyaputri, L., & Potash, J. B. (2018). A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 177(2), 143-167.

- Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosomatic Medicine, 71(2), 171-186.

- Hranilovic, D., Blazevic, S., Stefulj, J., & Zill, P. (2016). DNA methylation analysis of HTR2A regulatory region in leukocytes of autistic subjects. Autism Research, 9(2), 204-209.

- Hüls, A., Robins, C., Conneely, K. N., De Jager, P. L., Bennett, D. A., Epstein, M. P., . . . Wingo, A. P. (2020). Association between DNA methylation levels in brain tissue and late-life depression in community-based participants. Translational Psychiatry, 10(1), 262. doi:10.1038/s41398-020-00948-6

- Jaenisch, R., & Bird, A. (2003). Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nature Genetics, 33 Suppl, 245-254. doi:10.1038/ng1089

- Jauhar, S., McCutcheon, R., Borgan, F., Veronese, M., Nour, M., Pepper, F., . . . Howes, O. D. (2018). The relationship between cortical glutamate and striatal dopamine in first-episode psychosis: a cross-sectional multimodal PET and magnetic resonance spectroscopy imaging study. Lancet Psychiatry, 5(10), 816-823. doi:10.1016/s2215-0366(18)30268-2

- Juarez-Vicente, F., Luna-Pelaez, N., & Garcia-Dominguez, M. (2016). The Sumo protease Senp7 is required for proper neuronal differentiation. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1863(7), 1490-1498.

- Kaminsky, Z., Wilcox, H., Eaton, W., Van Eck, K., Kilaru, V., Jovanovic, T., . . . Ressler, K. (2015). Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. Translational psychiatry, 5(8), e627.

- Kandaswamy, R., Hannon, E., Arseneault, L., Mansell, G., Sugden, K., Williams, B., . . . Wong, C. C. Y. (2020). DNA methylation signatures of adolescent victimization: analysis of a longitudinal monozygotic twin sample. Epigenetics, 1-18. doi:10.1080/15592294.2020.1853317

- Kang, H.-J., Kim, J.-M., Bae, K.-Y., Kim, S.-W., Shin, I.-S., Kim, H.-R., . . . Yoon, J.-S. (2015). Longitudinal associations between BDNF promoter methylation and late-life depression. Neurobiology of aging, 36(4), 1764. e1761-1764. e1767.
- Kang, H.-J., Kim, J.-M., Stewart, R., Kim, S.-Y., Bae, K.-Y., Kim, S.-W., . . . Yoon, J.-S. (2013). Association of SLC6A4 methylation with early adversity, characteristics and outcomes in depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 44, 23-28.
- Kaye, W. H., Fudge, J. L., & Paulus, M. (2009). New insights into symptoms and neurocircuit function of anorexia nervosa. Nature Reviews Neuroscience, 10(8), 573-584.
- Kebir, O., Chaumette, B., Rivollier, F., Miozzo, F., Lemieux Perreault, L. P., Barhdadi, A., . . . Krebs, M. O. (2017). Methylomic changes during conversion to psychosis. Molecylar Psychiatry, 22(4), 512-518. doi:10.1038/mp.2016.53
- Kim, T., Kim, S., Chung, H., Choi, J., Kim, S. H., & Kang, J. (2017). Epigenetic alterations of the BDNF gene in combat-related post-traumatic stress disorder. Acta Psychiatrica Scandinavica, 135(2), 170-179.
- Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., & Pariante, C. M. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neuroscience, 16. doi:10.1038/nn.3275
- Klinger-König, J., Hertel, J., Van der Auwera, S., Frenzel, S., Pfeiffer, L., Waldenberger, M., . . . Homuth, G. (2019). Methylation of the FKBP5 gene in association with FKBP5 genotypes, childhood maltreatment and depression. Neuropsychopharmacology, 44(5), 930-938.
- Kordi-Tamandani, D. M., Dahmardeh, N., & Torkamanzehi, A. (2013). Evaluation of hypermethylation and expression pattern of GMR2, GMR5, GMR8, and GRIA3 in patients with schizophrenia. Gene, 515(1), 163-166.
- Kordi-Tamandani, D. M., Sahranavard, R., & Torkamanzehi, A. (2013). Analysis of association between dopamine receptor genes' methylation and their expression profile with the risk of schizophrenia. Psychiatric Genetics, 23(5), 183-187.
- Kuan, P., Waszczuk, M., Kotov, R., Marsit, C., Guffanti, G., Gonzalez, A., . . . Luft, B. (2017). An epigenome-wide DNA methylation study of PTSD and depression in World Trade Center responders. Translational psychiatry, 7(6), e1158-e1158.
- Labonte, B., Azoulay, N., Yerko, V., Turecki, G., & Brunet, A. (2014). Epigenetic modulation of glucocorticoid receptors in posttraumatic stress disorder. Translational psychiatry, 4(3), e368.
- Law, A. J., Wang, Y., Sei, Y., O'Donnell, P., Piantadosi, P., Papaleo, F., . . . Vakkalanka,

R. (2012). Neuregulin 1-ErbB4-PI3K signaling in schizophrenia and phosphoinositide 3-kinase-p110δ inhibition as a potential therapeutic strategy. Proceedings of the national academy of sciences, 109(30), 12165-12170.

- Lin, C.-C., & Huang, T.-L. (2020). Brain-derived neurotrophic factor and mental disorders. biomedical journal.

- Lindert, J., von Ehrenstein, O. S., Grashow, R., Gal, G., Braehler, E., & Weisskopf, M. G. (2014). Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. International Journal of Public Health, 59(2), 359-372. doi:10.1007/s00038-013-0519-5

- Liu, C., Marioni, R., Hedman, Å. K., Pfeiffer, L., Tsai, P., Reynolds, L., . . . Tanaka, T. (2016). A DNA methylation biomarker of alcohol consumption. Molecular psychiatry.

- Liu, J., Chen, J., Ehrlich, S., Walton, E., White, T., Perrone-Bizzozero, N., . . . Calhoun, V. D. (2014). Methylation patterns in whole blood correlate with symptoms in Schizophrenia patients. Schizophrenia bulletin, 40(4), 769-776. doi:http://dx.doi.org/10.1093/schbul/sbt080

- Liu, Z., Shen, J., Barfield, R., Schwartz, J., Baccarelli, A. A., & Lin, X. (2021). Large-Scale Hypothesis Testing for Causal Mediation Effects with Applications in Genome-wide Epigenetic Studies. Journal of the American Statistical Association, 1-15.

- Lutz, P.-E., Tanti, A., Gasecka, A., Barnett-Burns, S., Kim, J. J., Zhou, Y., . . . Almeida, D. (2017). Association of a history of child abuse with impaired myelination in the anterior cingulate cortex: convergent epigenetic, transcriptional, and morphological evidence. American Journal of Psychiatry, appi. ajp. 2017.16111286.

- Maj, M., van Os, J., De Hert, M., Gaebel, W., Galderisi, S., Green, M. F., . . . Malaspina, D. (2021). The clinical characterization of the patient with primary psychosis aimed at personalization of management. World Psychiatry, 20(1), 4-33.

- Mandelli, L., Petrelli, C., & Serretti, A. (2015). The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. European Psychiatry, 30(6), 665-680. doi:10.1016/j.eurpsy.2015.04.007

- Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophrenia bulletin, 42(5), 1262-1269.

- Markunas, C. A., Hancock, D. B., Xu, Z., Quach, B. C., Fang, F., Sandler, D. P., . . . Taylor, J. A. (2020). Epigenome-wide analysis uncovers a blood-based DNA methylation biomarker of lifetime cannabis use. Americal Journal of Medical Genetics B: Neuropsychiatric Genetics. doi:10.1002/ajmg.b.32813

- Marotta, R., Risoleo, M. C., Messina, G., Parisi, L., Carotenuto, M., Vetri, L., & Roccella, M. (2020). The neurochemistry of autism. Brain sciences, 10(3), 163.
- Martin-Blanco, A., Ferrer, M., Soler, J., Salazar, J., Vega, D., & Andion, O. (2014). Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. Journal of Psychiatry Research, 57. doi:10.1016/j.jpsychires.2014.06.011
- Marzi, S. J., Sugden, K., Arseneault, L., Belsky, D. W., Burrage, J., Corcoran, D. L., . . . Caspi, A. (2018). Analysis of DNA Methylation in Young People: Limited Evidence for an Association Between Victimization Stress and Epigenetic Variation in Blood. Americal Journal of Psychiatry, appiajp201717060693. doi:10.1176/appi.ajp.2017.17060693
- Marzinke, M. A., & Clagett-Dame, M. (2012). The all-trans retinoic acid (atRA)-regulated gene Calmin (Clmn) regulates cell cycle exit and neurite outgrowth in murine neuroblastoma (Neuro2a) cells. Experimental cell research, 318(1), 85-93.
- Massicotte, R., Whitelaw, E., & Angers, B. (2011). DNA methylation: a source of random variation in natural populations. Epigenetics, 6(4), 421-427.
- Mazza, M. G., Lucchi, S., Rossetti, A., & Clerici, M. (2020). Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: A meta-analysis and systematic review. The World Journal of Biological Psychiatry, 21(5), 326-338.
- McCutcheon, R. A., Krystal, J. H., & Howes, O. D. (2020). Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World Psychiatry, 19(1), 15-33. doi:10.1002/wps.20693
- Melas, P. A., & Forsell, Y. (2015). Hypomethylation of MAOA s first exon region in depression: a replication study. Psychiatry research, 226(1), 389-391.
- Melas, P. A., Rogdaki, M., Ösby, U., Schalling, M., Lavebratt, C., & Ekström, T. J. (2012). Epigenetic aberrations in leukocytes of patients with schizophrenia: association of global DNA methylation with antipsychotic drug treatment and disease onset. The FASEB Journal, 26(6), 2712-2718.
- Melas, P. A., Wei, Y., Wong, C. C., Sjöholm, L. K., Åberg, E., Mill, J., . . . Lavebratt, C. (2013). Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities. International Journal of Neuropsychopharmacology, 16(7), 1513-1528.
- Meyer, J. H., Ginovart, N., Boovariwala, A., Sagrati, S., Hussey, D., Garcia, A., . . . Houle, S. (2006). Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. Archives of general psychiatry, 63(11), 1209-1216.

- Mill, J., Tang, T., Kaminsky, Z., Khare, T., Yazdanpanah, S., Bouchard, L., . . . Petronis, A. (2008). Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. American Journal of Human Genetics, 82(3), 696-711. doi:10.1016/j.ajhg.2008.01.008

- Min, J. L., Hemani, G., Hannon, E., Dekkers, K. F., Castillo-Fernandez, J., Luijk, R., . . . Suderman, M. (2021). Genomic and phenotypic insights from an atlas of genetic effects on DNA methylation. Nature Genetics, 53(9), 1311-1321.

- Misiak, B., Karpiński, P., Szmida, E., Grążlewski, T., Jabłoński, M., Cyranka, K., . . . Frydecka, D. (2020). Adverse Childhood Experiences and Methylation of the FKBP5 Gene in Patients with Psychotic Disorders. Journal of Clinical Medicine, 9(12). doi:10.3390/jcm9123792

- Montano, C., Taub, M. A., Jaffe, A., Briem, E., Feinberg, J. I., Trygvadottir, R., . . . Feinberg, A. P. (2016). Association of DNA Methylation Differences With Schizophrenia in an Epigenome-Wide Association Study. JAMA Psychiatry, 73(5), 506-514. doi:10.1001/jamapsychiatry.2016.0144

- Murphy, B. C., O'Reilly, R. L., & Singh, S. M. (2005). Site-specific cytosine methylation in S-COMT promoter in 31 brain regions with implications for studies involving schizophrenia. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 133(1), 37-42.

- Nikolova, Y. S., & Hariri, A. R. (2015). Can we observe epigenetic effects on human brain function? Trends in cognitive sciences, 19(7), 366-373.

- Nishioka, M., Bundo, M., Koike, S., Takizawa, R., Kakiuchi, C., Araki, T., . . . Iwamoto, K. (2013). Comprehensive DNA methylation analysis of peripheral blood cells derived from patients with first-episode schizophrenia. Journal of human genetics, 58(2), 91-97.

- Nohesara, S., Ghadirivasfi, M., Mostafavi, S., Eskandari, M.-R., Ahmadkhaniha, H., Thiagalingam, S., & Abdolmaleky, H. M. (2011). DNA hypomethylation of MB-COMT promoter in the DNA derived from saliva in schizophrenia and bipolar disorder. Journal of Psychiatric Research, 45(11), 1432-1438.

- Nöthling, J., Malan-Müller, S., Abrahams, N., Hemmings, S. M. J., & Seedat, S. (2020). Epigenetic alterations associated with childhood trauma and adult mental health outcomes: A systematic review. The World Journal of Biological Psychiatry, 21(7), 493-512.

- Nour El Huda, A. R., Norsidah, K. Z., Nabil Fikri, M. R., Hanisah, M. N., Kartini, A., & Norlelawati, A. (2018). DNA methylation of membrane-bound catechol-O-methyltransferase in Malaysian schizophrenia patients. Psychiatry Clinical Neuroscience. doi:http://dx.doi.org/10.1111/pcn.12622

- Numata, S., Ye, T., Herman, M., & Lipska, B. K. (2014). DNA methylation changes in the postmortem dorsolateral prefrontal cortex of patients with schizophrenia. Frontiers in genetics, 5, 280.

- Olsson, C., Foley, D., Parkinson-Bates, M., Byrnes, G., McKenzie, M., Patton, G., . . . Saffery, R. (2010). Prospects for epigenetic research within cohort studies of psychological disorder: a pilot investigation of a peripheral cell marker of epigenetic risk for depression. Biological Psychology, 83(2), 159-165.

- Osborne, A. J., Pearson, J. F., Noble, A. J., Gemmell, N. J., Horwood, L. J., Boden, J. M., . . . Kennedy, M. A. (2020). Genome-wide DNA methylation analysis of heavy cannabis exposure in a New Zealand longitudinal cohort. Translational psychiatry, 10(1). doi:http://dx.doi.org/10.1038/s41398-020-0800-3

- Palma-Gudiel, H., Córdova-Palomera, A., Leza, J. C., & Fañanás, L. (2015). Glucocorticoid receptor gene (NR3C1) methylation processes as mediators of early adversity in stress-related disorders causality: a critical review. Neuroscience & Biobehavioral Reviews, 55, 520-535.

- Pariante, C. M. (2017). Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. European Neuropsychopharmacology, 27(6), 554-559. doi:10.1016/j.euroneuro.2017.04.001

- Peng, H., Zhu, Y., Strachan, E., Fowler, E., Bacus, T., Roy-Byrne, P., . . . Zhao, J. (2018). Childhood Trauma, DNA Methylation of Stress-related Genes, and Depression: Findings from Two Monozygotic Twin Studies. Psychosomatic Medicine. doi:10.1097/psy.0000000000000604

- Perez-Cornago, A., Mansego, M. L., Zulet, M. A., & Martinez, J. A. (2014). DNA hypermethylation of the serotonin receptor type-2A gene is associated with a worse response to a weight loss intervention in subjects with metabolic syndrome. Nutrients, 6(6), 2387-2403.

- Perkins, D. O., Jeffries, C. D., & Do, K. Q. (2020). Potential Roles of Redox Dysregulation in the Development of Schizophrenia. Biological Psychiatry.

- Perroud, N., Paoloni-Giacobino, A., Prada, P., Olie, E., Salzmann, A., & Nicastro, R. (2011). Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Translational Psychiatry, 1. doi:10.1038/tp.2011.60

- Perroud, N., Zewdie, S., Stenz, L., Adouan, W., Bavamian, S., & Prada, P. (2016). Methylation of serotonin receptor 3a in Adhd, borderline personality, and bipolar disorders: link with severity of the disorders and childhood maltreatment. Depression and anxiety, 33. doi:10.1002/da.22406

- Petrey, A. C., & de la Motte, C. A. (2014). Hyaluronan, a crucial regulator of inflammation. Frontiers in immunology, 5, 101.

- Philibert, R. A., Sandhu, H., Hollenbeck, N., Gunter, T., Adams, W., & Madan, A. (2008). The relationship of 5HTT (SLC6A4) methylation and genotype on mRNA expression and liability to major depression and alcohol dependence in subjects from the Iowa Adoption Studies. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(5), 543-549.

- Pidsley, R., Viana, J., Hannon, E., Spiers, H., Troakes, C., Al-Saraj, S., . . . Bray, N. J. (2014). Methylomic profiling of human brain tissue supports a neurodevelopmental origin for schizophrenia. Genome biology, 15(10), 483.

- Pjetri, E., Dempster, E., Collier, D. A., Treasure, J., Kas, M. J., Mill, J., . . . Schmidt, U. (2013). Quantitative promoter DNA methylation analysis of four candidate genes in anorexia nervosa: a pilot study. Journal of Psychiatry Research, 47(2), 280-282. doi:10.1016/j.jpsychires.2012.10.007

- Platzer, K., Cogné, B., Hague, J., Marcelis, C. L., Mitter, D., Oberndorff, K., . . . van der Smagt, J. J. (2018). Haploinsufficiency of CUX1 Causes Nonsyndromic Global Developmental Delay With Possible Catch-up Development. Annals of neurology, 84(2), 200-207.

- Prados, J., Stenz, L., Courtet, P., Prada, P., Nicastro, R., & Adouan, W. (2015). Borderline personality disorder and childhood maltreatment: a genome-wide methylation analysis. Genes Brain Behaviour, 14. doi:10.1111/gbb.12197

- Provenzi, L., Giorda, R., Beri, S., & Montirosso, R. (2016). SLC6A4 methylation as an epigenetic marker of life adversity exposures in humans: A systematic review of literature. Neuroscience & Biobehavioral Reviews, 71(Supplement C), 7-20. doi:https://doi.org/10.1016/j.neubiorev.2016.08.021

- Pun, F. W., Zhao, C., Lo, W. S., Ng, S. K., Tsang, S. Y., Nimgaonkar, V., . . . Xue, H. (2011). Imprinting in the schizophrenia candidate gene GABRB2 encoding GABA A receptor β 2 subunit. Molecular psychiatry, 16(5), 557-568.

- Radtke, K. M., Schauer, M., Gunter, H. M., Ruf-Leuschner, M., Sill, J., Meyer, A., & Elbert, T. (2015). Epigenetic modifications of the glucocorticoid receptor gene are associated with the vulnerability to psychopathology in childhood maltreatment. Translational Psychiatry, 5, e571.

- Rahman, I., Marwick, J., & Kirkham, P. (2004). Redox modulation of chromatin remodeling: impact on histone acetylation and deacetylation, NF-κB and pro-inflammatory gene expression. Biochemical Pharmacology, 68(6), 1255-1267.

- Ramaswami, G., Won, H., Gandal, M. J., Haney, J., Wang, J. C., Wong, C. C. Y., . . . Geschwind,

D. H. (2020). Integrative genomics identifies a convergent molecular subtype that links epigenomic with transcriptomic differences in autism. Nature Communications, 11(1), 4873. doi:10.1038/s41467-020-18526-1

- Relton, C. L., & Smith, G. D. (2010). Epigenetic epidemiology of common complex disease: prospects for prediction, prevention, and treatment. PLoS medicine, 7(10).

- Ripke, S., Neale, B. M., Corvin, A., Walters, J. T., Farh, K.-H., Holmans, P. A., . . . Huang, H. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature, 511(7510), 421-427.

- Ripke, S., Wray, N. R., Lewis, C. M., Hamilton, S. P., Weissman, M. M., Breen, G., . . . Cichon, S. (2013). A mega-analysis of genome-wide association studies for major depressive disorder. Molecular psychiatry, 18(4), 497.

- Rodriguez, V., Alameda, L., Trotta, G., Spinazzola, E., Marino, P., Matheson, S. L., . . . Vassos, E. (2021). Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies. Schizophrenia Bulletin. doi:10.1093/schbul/sbaa197

- Rotter, A., Bayerlein, K., Hansbauer, M., Weiland, J., Sperling, W., Kornhuber, J., & Biermann, T. (2012). CB1 and CB2 Receptor Expression and Promoter Methylation in Patients with Cannabis Dependence. European Addiction Research, 19(1), 13-20. doi:http://dx.doi.org/10.1159/000338642

- Ruzicka, W. B., Subburaju, S., & Benes, F. M. (2015). Circuit-and diagnosis-specific DNA methylation changes at γ-aminobutyric acid–related genes in postmortem human hippocampus in schizophrenia and bipolar disorder. JAMA Psychiatry, 72(6), 541-551.

- Sadeh, N., Spielberg, J. M., Logue, M. W., Wolf, E. J., Smith, A. K., Lusk, J., . . . McGlinchey, R. E. (2016). SKA2 methylation is associated with decreased prefrontal cortical thickness and greater PTSD severity among trauma-exposed veterans. Molecular psychiatry, 21(3), 357-363.

- Sadeh, N., Wolf, E. J., Logue, M. W., Hayes, J. P., Stone, A., Griffin, L. M., . . . Miller, M. W. (2016). Epigenetic variation at SKA2 predicts suicide phenotypes and internalizing psychopathology. Depression and anxiety, 33(4), 308-315.

- Schechter, D. S., Moser, D. A., Paoloni-Giacobino, A., Stenz, L., Gex-Fabry, M., Aue, T., . . . Manini, A. (2015). Methylation of NR3C1 is related to maternal PTSD, parenting stress and maternal medial prefrontal cortical activity in response to child separation among mothers with histories of violence exposure. Frontiers in psychology, 6.

- Schiele, M. A., Kollert, L., Lesch, K.-P., Arolt, V., Zwanzger, P., Deckert, J., . . . Domschke, K. (2019). Hypermethylation of the serotonin transporter gene promoter in panic disorder–Epigenetic imprint of comorbid depression? European Neuropsychopharma-

cology, 29(10), 1161-1167.

- Schiele, M. A., Thiel, C., Deckert, J., Zaudig, M., Berberich, G., & Domschke, K. (2020). Monoamine Oxidase A Hypomethylation in Obsessive-Compulsive Disorder: Reversibility By Successful Psychotherapy? International Journal of Neuropsychopharmacology, 23(5), 319-323.

- Schiele, M. A., Ziegler, C., Kollert, L., Katzorke, A., Schartner, C., Busch, Y., . . . Deckert, J. (2018). Plasticity of functional MAOA gene methylation in acrophobia. International Journal of Neuropsychopharmacology, 21(9), 822-827.

- Schimmack, G., Schorpp, K., Kutzner, K., Gehring, T., Brenke, J. K., Hadian, K., & Krappmann, D. (2017). YOD1/TRAF6 association balances p62-dependent IL-1 signaling to NF-κB. Elife, 6, e22416.

- Selvaraj, S., Arnone, D., Cappai, A., & Howes, O. (2014). Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. Neuroscience & Biobehavioral Reviews, 45, 233-245.

- Shenker, N. S., Polidoro, S., van Veldhoven, K., Sacerdote, C., Ricceri, F., Birrell, M. A., . . . Flanagan, J. M. (2013). Epigenome-wide association study in the European Prospective Investigation into Cancer and Nutrition (EPIC-Turin) identifies novel genetic loci associated with smoking. Hum Molecular Genetics, 22(5), 843-851. doi:10.1093/hmg/dds488

- Shih, J., & Thompson, R. (1999). Monoamine oxidase in neuropsychiatry and behavior. American Journal of Human Genetics, 65(3), 593.

- Shimada-Sugimoto, M., Otowa, T., Miyagawa, T., Umekage, T., Kawamura, Y., Bundo, M., . . . Kaiya, H. (2017). Epigenome-wide association study of DNA methylation in panic disorder. Clinical epigenetics, 9(1), 1-11.

- Sideli, L., Quigley, H., La Cascia, C., & Murray, R. M. (2020). Cannabis use and the risk for psychosis and affective disorders. Journal of dual diagnosis, 16(1), 22-42.

- Sideli, L., Trotta, G., Spinazzola, E., La Cascia, C., & Di Forti, M. (2020). Adverse effects of heavy cannabis use: even plants can harm the brain. Pain. doi:10.1097/j.pain.0000000000001963

- Steiger, H., Booij, L., Kahan, E., McGregor, K., Thaler, L., Fletcher, E., . . . Szyf, M. (2019). A longitudinal, epigenome-wide study of DNA methylation in anorexia nervosa: results in actively ill, partially weight-restored, long-term remitted and non-eating-disordered women. Journal of Psychiatry & Neuroscience: JPN, 44(3), 205.

- Steullet, P., Cabungcal, J., Monin, A., Dwir, D., O'Donnell, P., Cuenod, M., & Do, K. (2016). Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: a "cen-

tral hub" in schizophrenia pathophysiology? Schizophrenia Research, 176(1), 41-51.

- Sugawara, H., Bundo, M., Asai, T., Sunaga, F., Ueda, J., Ishigooka, J., . . . Iwamoto, K. (2015). Effects of quetiapine on DNA methylation in neuroblastoma cells. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 56, 117-121.

- Sugawara, H., Iwamoto, K., Bundo, M., Ueda, J., Miyauchi, T., Komori, A., . . . Okazaki, Y. (2011). Hypermethylation of serotonin transporter gene in bipolar disorder detected by epigenome analysis of discordant monozygotic twins. Translational psychiatry, 1(7), e24-e24.

- Tamura, Y., Kunugi, H., Ohashi, J., & Hohjoh, H. (2007). Epigenetic aberration of the human REELIN gene in psychiatric disorders. Molecular psychiatry, 12(6), 593-600.

- Tao, R., Li, C., Jaffe, A. E., Shin, J. H., Deep-Soboslay, A., Yamin, R., . . . Kleinman, J. E. (2020). Cannabinoid receptor CNR1 expression and DNA methylation in human prefrontal cortex, hippocampus and caudate in brain development and schizophrenia. Translational psychiatry, 10(1). doi:http://dx.doi.org/10.1038/s41398-020-0832-8

- Thaler, L., Gauvin, L., Joober, R., Groleau, P., Guzman, R., & Ambalavanan, A. (2014). Methylation of BDNF in women with bulimic eating syndromes: associations with childhood abuse and borderline personality disorder. Progress in Neuro-Psychopharmacol Biological Psychiatry, 54. doi:10.1016/j.pnpbp.2014.04.010

- Thomas, M., Knoblich, N., Wallisch, A., Glowacz, K., Becker-Sadzio, J., Gundel, F., . . . Nieratschker, V. (2018). Increased BDNF methylation in saliva, but not blood, of patients with borderline personality disorder. Clinical epigenetics, 10(1), 1-12.

- Thuné, H., Recasens, M., & Uhlhaas, P. J. (2016). The 40-Hz auditory steady-state response in patients with schizophrenia: a meta-analysis. JAMA Psychiatry, 73(11), 1145-1153.

- Tozzi, L., Farrell, C., Booij, L., Doolin, K., Nemoda, Z., Szyf, M., . . . Frodl, T. (2018). Epigenetic Changes of FKBP5 as a Link Connecting Genetic and Environmental Risk Factors with Structural and Functional Brain Changes in Major Depression. Neuropsychopharmacology, 43(5), 1138-1145. doi:10.1038/npp.2017.290

- Tsaprouni, L. G., Yang, T. P., Bell, J., Dick, K. J., Kanoni, S., Nisbet, J., . . . Deloukas, P. (2014). Cigarette smoking reduces DNA methylation levels at multiple genomic loci but the effect is partially reversible upon cessation. Epigenetics, 9(10), 1382-1396. doi:10.4161/15592294.2014.969637

- Uddin, M., Aiello, A. E., Wildman, D. E., Koenen, K. C., Pawelec, G., de Los Santos, R., . . . Galea, S. (2010). Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proceedings of the national academy of sciences, 107(20), 9470-9475.

- Ursini, G., Cavalleri, T., Fazio, L., Angrisano, T., Iacovelli, L., Porcelli, A., . . . Gelao, B. (2016). BDNF rs6265 methylation and genotype interact on risk for schizophrenia. Epigenetics, 11(1), 11-23.
- Van der Knaap, L., Schaefer, J., Franken, I., Verhulst, F., van Oort, F., & Riese, H. (2014). Catechol-O-methyltransferase gene methylation and substance use in adolescents: the TRAILS study. Genes, Brain and Behavior, 13(7), 618-625.
- van Os, J., Kenis, G., & Rutten, B. P. (2010). The environment and schizophrenia. Nature, 468(7321), 203-212. doi:10.1038/nature09563
- Van Os, J., Rutten, B. P., & Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophrenia bulletin, 34(6), 1066-1082.
- Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., . . . Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophrenia Bulletin, 38(4), 661-671. doi:10.1093/schbul/sbs050
- Walton, E., Liu, J., Hass, J., White, T., Scholz, M., Roessner, V., . . . Ehrlich, S. (2014). MB-COMT promoter DNA methylation is associated with working-memory processing in schizophrenia patients and healthy controls. Epigenetics, 9(8), 1101-1107.
- Wang, F., Xu, H., Zhao, H., Gelernter, J., & Zhang, H. (2016). DNA co-methylation modules in postmortem prefrontal cortex tissues of European Australians with alcohol use disorders. Scientifc Reports, 6, 19430. doi:10.1038/srep19430
- Wang, W., Feng, J., Ji, C., Mu, X., Ma, Q., Fan, Y., . . . Zhu, F. (2017). Increased methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of patients with generalized anxiety disorder. Journal of Psychiatric Research, 91(Supplement C), 18-25. doi:https://doi.org/10.1016/j.jpsychires.2017.01.019
- Weder, N., Zhang, H., Jensen, K., Yang, B. Z., Simen, A., Jackowski, A., . . . Perepletchikova, F. (2014). Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. Journal of the American Academy of Child & Adolescent Psychiatry, 53(4), 417-424. e415.
- Weng, J. T., Wu, L. S., Lee, C. S., Hsu, P. W., & Cheng, A. T. (2015). Integrative epigenetic profiling analysis identifies DNA methylation changes associated with chronic alcohol consumption. Computational Biology & Medicine, 64, 299-306. doi:10.1016/j.compbiomed.2014.12.003
- Wesarg, C., Van Den Akker, A. L., Oei, N. Y., Hoeve, M., & Wiers, R. W. (2020). Identifying pathways from early adversity to psychopathology: A review on dysregulated HPA axis functioning and impaired self-regulation in early childhood. European Journal of De-

velopmental Psychology, 17(6), 808-827.

- Wong, C., Smith, R., Hannon, E., Ramaswami, G., Parikshak, N., Assary, E., . . . Sun, W. (2018). Genome-wide DNA methylation profiling identifies convergent molecular signatures associated with idiopathic and syndromic forms of autism in postmortem human brain tissue. bioRxiv, 394387.

- Wong, C. C. Y., Smith, R. G., Hannon, E., Ramaswami, G., Parikshak, N. N., Assary, E., . . . Mill, J. (2019). Genome-wide DNA methylation profiling identifies convergent molecular signatures associated with idiopathic and syndromic autism in post-mortem human brain tissue. Human Molecular Genetics, 28(13), 2201-2211. doi:10.1093/hmg/ddz052

- Wu, Y. E., Parikshak, N. N., Belgard, T. G., & Geschwind, D. H. (2016). Genome-wide, integrative analysis implicates microRNA dysregulation in autism spectrum disorder. Nature neuroscience, 19(11), 1463-1476.

- Xu, Q., Jiang, M., Gu, S., Wang, F., & Yuan, B. (2020). Early Life Stress Induced DNA Methylation of Monoamine Oxidases Leads to Depressive-Like Behavior. Frontiers in Cell and Developmental Biology, 8, 582247. doi:10.3389/fcell.2020.582247

- Yehuda, R., Flory, J. D., Bierer, L. M., Henn-Haase, C., Lehrner, A., Desarnaud, F., . . . Meaney, M. J. (2015). Lower methylation of glucocorticoid receptor gene promoter 1 F in peripheral blood of veterans with posttraumatic stress disorder. Biological Psychiatry, 77(4), 356-364.

- Yoshino, Y., Kawabe, K., Mori, T., Mori, Y., Yamazaki, K., Numata, S., . . . Ohmori, T. (2016). Low methylation rates of dopamine receptor D2 gene promoter sites in Japanese schizophrenia subjects. The World Journal of Biological Psychiatry, 17(6), 449-456.

- Zeilinger, S., Kuhnel, B., Klopp, N., Baurecht, H., Kleinschmidt, A., Gieger, C., . . . Illig, T. (2013). Tobacco smoking leads to extensive genome-wide changes in DNA methylation. PLoS One, 8(5), e63812. doi:10.1371/journal.pone.0063812

- Zhao, J., Goldberg, J., Bremner, J. D., & Vaccarino, V. (2013). Association between promoter methylation of serotonin transporter gene and depressive symptoms: a monozygotic twin study. Psychosomatic Medicine, 75(6).

- Ziegler, C., Richter, J., Mahr, M., Gajewska, A., Schiele, M. A., Gehrmann, A., . . . Helbig-Lang, S. (2016). MAOA gene hypomethylation in panic disorder—reversibility of an epigenetic risk pattern by psychotherapy. Translational psychiatry, 6(4), e773-e773.

- Zong, L., Zhou, L., Hou, Y., Zhang, L., Jiang, W., Zhang, W., . . . Deng, C. (2017). Genetic and epigenetic regulation on the transcription of GABRB2: genotype-dependent hydroxymethylation and methylation alterations in schizophrenia. Journal of Psychiatric Research, 88, 9-17.

4.2 Exploring the mediation of DNA methylation across the epigenome between childhood adversity and First Episode of Psychosis – findings from the EU-GEI study

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Running title
Epigenetic mechanisms between adversity and psychosis

Abstract: 300

Main text: 5513

Abstract

Studies conducted in psychotic disorders have shown that DNA-methylation (DNAm) is sensitive to the impact of Childhood Adversity (CA). However, whether it mediates the association between CA and psychosis is yet to be explored. Epigenome wide association studies (EWAS) using the Illumina Infinium-Methylation EPIC array in peripheral blood tissue from 366 First-episode of psychosis and 517 healthy controls was performed. Adversity scores were created for abuse, neglect and composite adversity with the Childhood Trauma Questionnaire (CTQ). Regressions examining (I) CTQ scores with psychosis; (II) with DNAm EWAS level and (III) between DNAm and caseness, adjusted for a variety of confounders were conducted. Divide-Aggregate Composite-null Test for the composite null-hypothesis of no mediation effect was conducted. Enrichment analyses were conducted with *missMethyl* package and the KEGG database. Our results show that CA was associated with psychosis (Composite: OR = 1.68; p = <0.001; abuse: OR = 2.16; p<0.001; neglect: OR = 2.27; p=<0.001). None of the CpG sites significantly mediated the adversity-psychosis association after Bonferroni correction (p<8.1x10-8). However, 28, 34 and 29 differentially methylated probes associated with 21, 27, 20 genes passed a less stringent discovery threshold (p<5x10-5) for composite, abuse and neglect respectively, with a lack of overlap between abuse and neglect. These included genes previously associated to psychosis in EWAS studies, such as *PANK1, SPEG TBKBP1, TSNARE1* or *H2R*. Downstream gene ontology analyses did not reveal any biological pathways that survived false discovery rate correction. Although at a non-significant level, DNAm changes in genes previously associated with schizophrenia in EWAS studies may mediate the CA-psychosis association. These results and associated involved processes such as mitochondrial or histaminergic disfunction, immunity or neural signalling requires replication in well powered samples. The lack of overlap between mediating genes associated with abuse and neglect suggests differential biological trajectories linking CA subtypes and psychosis.

Introduction

Childhood adversity (CA), in the form of abuse and neglect, is associated with psychotic disorders[1]. Its effect is not limited to psychosis onset but also to a broad range of poor outcomes such as cognitive impairment, social cognitive deficits, and functional outcomes[2,3] as well as poorer prognosis in various clinical dimensions[4]. Several biological processes have been implicated in the CA-psychosis dyad, such as alterations in neurogenesis[5], dopamine dysregulation[6], alterations in the hypothalamic pituitary adrenal axis[7] via its action in the hippocampus, or oxidative stress dysregulation[8]. However, evidence is often limited to correlational analyses between biomarkers involved in such pathways and CA in patients and

controls, or regression analyses examining their association with psychosis as the outcome against healthy controls. Indeed, a recent literature review, examining formal mediation analyses using CA as exposure and psychosis as outcome, revealed very limited evidence at the time of the search in July 2019[9]. This shows that more research formally testing mediational pathways linking CA (in various forms) and psychosis is needed. This research should focus on large curated samples of patients in the early phase of disease in order to better understand this relationship[9].

In recent years, DNA methylation (DNAm), the most commonly studied epigenetic modification, has been proposed as a mechanism by which early adversities influence biological processes through the modulating of gene expression that can later exert negative pleiotropic effects of CA on mental health[10, 11]. A recent review on potential links between CA and DNAm in psychiatric conditions suggests that DNAm may be a potential mediator linking CA and various disorders, including psychosis[12]. Despite this suggestion of a mediating mechanism, a major limitation of available evidence is the lack of formal mediation models testing this hypothesis. Moreover, an epigenome-wide association study (EWAS) examining the influence of CA in people with psychotic disorders has not been conducted.

The traditional regression approach to mediation analysis proposed by Baron and Kenny et al.,1986[13], widely used in the social sciences, calculates mediation effect as the product of the effect of the exposure on the mediator and the effect of the mediator on the outcome. Tests, such as the Sobel test and the joint significant tests, [14] are commonly used methods to detect mediation effects. However, it has been demonstrated that these commonly used tests perform poorly in genome wide analyses[15], for three reasons: (1) the association signals are generally weak and sparse with limited sample sizes; (2) the heavy multiple testing burden that needs to be adjusted for; (3) the composite null nature of the mediation effect testing that has not been taken into account[16]. In this context, the Divide-Aggregate Composite-null has been developed and validated, proving to be a powerful large-scale testing procedure that overcome such limitations and that can be applied efficiently to EWAS data[15, 17].

In the current study, we will address for the first time whether CA, measured as a composite cumulative measure of adversity, is associated with DNAm changes in individuals with a First Episode of Psychosis (FEP) and whether these changes mediate the CA-psychosis association. We will use the DACT method to test for the mediation effects between CA and psychosis at an EWAS scale[17]. Second, given recent evidence of a differential effect of abuse and neglect on various clinical dimensions[4] suggesting a different biological underpinning, similar analyses will be conducted for abuse and neglect separately. This will allow to test whether this differential effect also relates to biological underpinnings in the form of DNAm Supplementary material (SM) (S. Figure 1). Lastly, enrichment analyses will be conducted to explore whether the CA and psychosis-associated differential methylated positions (DMP) cluster onto any relevant biological pathway for psychosis aetiopathogenesis.

Methods

Study design and participants

The sample was drawn from the EU-GEI (European Network of National Schizophrenia Networks Studying Gene–Environment Interactions) multi-centre study[18]. The EU-GEI study is a multicentre incidence and case–sibling–control study of genetic and environmental determinants of psychotic disorders[18]. The current study was based on participants from work the 'Incidence and first-episode'[18] work package of the EU-GEI study. For the analyses presented in this paper, only participants who had complete data on DNAm and CA using the CTQ were included, with no restriction on site or ethnicity. Patients and controls were recruited from 17 different sites. Cases and controls were not related. During the case ascertainment period, participants, aged 18–64 years, were invited to take part in the study if they presented to mental healthcare services with a FEP.

Patients were identified by clinically trained researchers who carried out regular checks across the 17 catchment areas. Exclusion criteria included previous treatment for psychosis, a diagnosis of organic psychosis (ICD-10: F09) or transient psychotic symptoms resulting from acute intoxication (ICD- 10: F1X.5), and language barriers. The diagnosis was confirmed by the Operational Criteria Checklist for Psychotic and Affective Illness within the EU-GEI consortium[19, 20]. As described by Gayer-Anderson et al. 2020[18], research teams were overseen by a psychiatrist with experience in epidemiological research and included trained research nurses and clinical psychologists. Control participants without a lifetime diagnosis of psychotic disorder were recruited from the same population as the cases using guided random and quota sampling strategies. Exclusion criteria for both controls and cases included intelligence quotient <70 and language barriers. Written informed consent was obtained and an institutional review board (IRB) approval was obtained from all centres. Teams received training in epidemiological principles and incidence study design to minimise non-differential ascertainment bias across different local and national health care systems.

Socio-demographic characteristics

Socio-demographic data were collected using the Medical Research Council (MRC) Socio-demographic Schedule modified version[21], and supplemented with additional information from medical records on educational attainment, employment, marital and living status. Ethnicity was self-ascribed using categories employed by the 2001 UK Census (http://www.ons.gov.uk/ons/guide-method/census/census-2001/index.html).

Childhood Trauma Questionnaire (CTQ)

CTQ[22, 23] was used to measure the exposure to past experiences of abuse (sexual, physical, and emotional), neglect (physical and emotional) and to calculate a composite measure of cumulative exposure of the five types of experiences. This self-reported instrument enquires about such types of events occurring prior to the age of 18, with answers rang-

ing from 'never true', through 'rarely true', 'sometimes true', 'often true', to 'very true'. This yields a total score and five sub-scores for physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. The reliability and validity of the CTQ have been demonstrated previously[22]. For this study, data were dichotomised for each childhood adversity domain (0 = 'absent' and 1 = 'present'), based on the moderate to severe cut-off score from the CTQ Manual[23] as follows: ≥13 for emotional abuse; ≥10 for physical abuse; ≥8 for sexual abuse; ≥15 for emotional neglect; and ≥10 for physical neglect. We used a composite category involving the cumulative exposure score to any form of the five adversities (score ranging 0-5), to abuse subtypes (score ranging 0 2; "0" being no abuse, "1" being one abuse and "2" being two or three exposures to different abuse experiences), and to neglect subtypes (score ranging 0-2; "0" being no neglect, "1" being one neglect and "2" being two different neglect exposures). We have used this approach of cumulative score rather than adding the total raw CTQ scores given meta-analytic evidence of a dose-response effect of cumulative trauma in psychosis using similar methods1, also observed in a larger EUGEI sample[24]; and given previous reports examining the same method when exploring the DNAm signature of trauma[12, 25, 26]. Additionally, exploratory analyses have revealed that the effect of CTQ in psychosis (path c) is greater when using the cumulative score based on the predefined severity threshold, rather than the raw original total score SM (*"CTQ operationalisation analyses"*).

Genome-wide DNA methylation analysis

Illumina EPIC chip processing

Genomic DNA was extracted using standard protocols[27, 28]. Whole-blood genomic DNA diluted with water (50 ng/µl) was treated with sodium bisulfite using the EpiTect® Bisulfite Kit from QIAGEN® following the manufacturer's protocol. DNAm was assessed using the Illumina Infinium HumanMethylationEPIC BeadChip kit (Illumina, Inc., San Diego, California) and quantified on an Illumina HiScan System (Illumina, Inc.). The level of methylation is expressed as a 'beta' value (β-value), ranging from 0 (no cytosine methylation) to 1 (complete cytosine methylation). [29]. Data pre-processing and downstream statistical analyses were conducted using R version 3.6.0[30].

Quality control procedures

Quality control of the data in cases and controls was performed by applying the following steps using the watermelon R package[31]: (i) checking the signal intensity and removing probes with a signal below 1500 (N=25); (ii) removing duplicates (N=26); (iii) checking and removing probes when they had less than 80% of conversion with bisulfite (N=5); (iv) gender check by using the clusterGender' function (k-means clustering of principal components highly correlated with gender r > 0.5 to form 2 clusters) and removing those that did not match their reported gender (N=8); (v) sample methylation data was compared to their genotyped data using the 15 SNPs common to both arrays, removing those with a correlation < 0.9 (N=4); (vi) potential confounding effect of batch effects was checked;

(vii) CpG sites with a detection p-value of>0.05 in 1% of the samples identified by the filter function within the watermelon R package[31] were removed (N=1); (viii) bead count per CpG was performed; (ix) testing case control differences in terms of epigenetic age, cell composition, smoking status; comparing the signal between blood and buccal samples. At a later stage, using a previous EPIC quality control pipeline https://github.com/PGC-PTSD-EWAS/EPIC_QC, it was detected that an additional 3330 CpG probes corresponded to probes located in SNPs, and these were removed prior to final analyses. DNAm was explored in 614719 probes at EWAS level after quality control procedures.

From the initial EU-GEI sample that had data on DNAm, 49 participants were excluded because of missing or unreliable data on CTQ, 1 participant because of missing smoking score, and another 1 due to ambiguous information on age. A further 3 cases were excluded because they were taking clozapine which can modulate DNAm in those with schizophrenia (SCZ) [32]. This final data set was comprised of 883 participants (366 FEP cases and 517 controls). All data pre-processing and downstream statistical analyses were performed using R version 3.6.0. QQplots and regional Manhattan plots were generated using the R packages *qqman*[33].

Confounders

Cell-type composition (including monocytes, CD8T, CD4T, natural killers, B cells and granulocytes), was estimated using the Houseman algorithm[34] to adjust for the potential differential cellular heterogeneity. Smoking has been shown to affect the DNAm signature, as described in a recent review[12], therefore smoking was accounted for with a calculated smoking score. This continuous variable consists of a weighted sum of effect sizes of DNAm values on 183 established CpG sites, subtracted from the mean of non-smokers. This score has been shown to be significantly higher in smokers compared to non-smokers and highly correlate with smoking dosage in previous studies[35]. It has been developed in order to capture the real epigenetic impact of smoking; avoiding the common tendency to underreport smoking habits[36, 37] and also allowing to capture passive smoking which is very difficult to assess[38]. To rule out possible confounding effects of medication, a binary category including current use of antipsychotics (yes or no) was included in analyses. Given heterogeneity in populations, 10 principal components (PC) were calculated and included in the models. Other covariates such as batch effects, site (ascertainment area where the study was conducted), gender and age were included in the analyses. Lastly, we conducted a set of preliminary analyses examining whether educational attainment (EA) was a significant confounder that should be included in our models. First, we examined the possible confounding effect of EA on the association between CTQ scores and psychosis status and our results revealed that in our sample the addition of EA to the model (along with age sex, country and CTQ score) did not change the effect of CTQ score on psychosis (CTQ composite coefficient 1.674; p-value 0.000 with EA and 1.680; p-value = 0.000 without EA). Moreover, we conducted a correlation analysis between CTQ composite, and EA and the correlation proved to be non-existent (r= -0.073; p-value= 1.000). Therefore, given these two sets of analyses, we concluded that the possible confounding effect of

EA on CTQ exposure was not major, and we decided not to include it in the final models described below. Details can be found in SM (*"Additional analyses section"*).

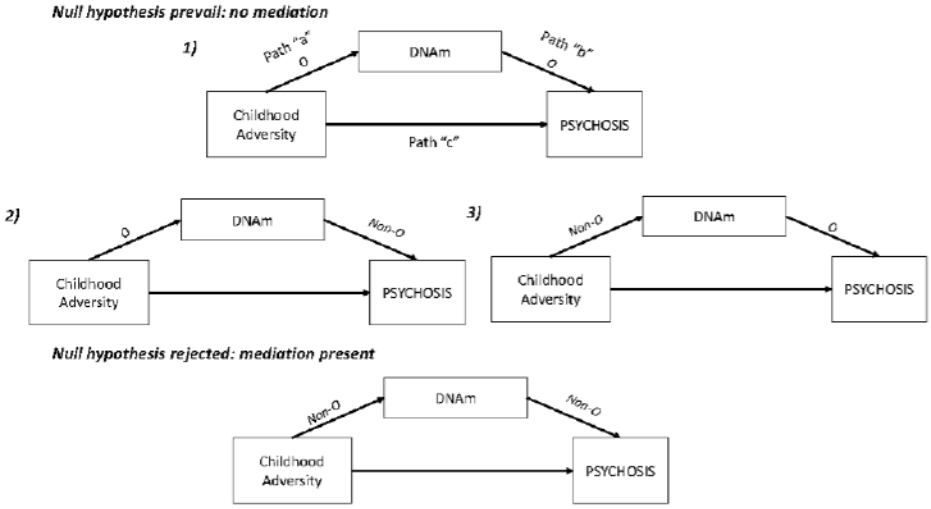
Statistical analyses

To statistically test for mediation, a set of regressions where conducted to examine whether the changes in DNAm EWAS level are at least partially responsible for the effect of CA (cumulative score, abuse, and neglect scores) on psychosis, using data on the 883 participants (cases and controls together): (i) the total effect of CA on psychotic disorder versus controls (path c – Scenario 1 in Figure 1), was calculated using a logistic regression model using the Glm function (glm(case/control~ CTQ +age+sex+country, family = binomial(link = "logit"); (ii) the effect of CA on DNAm level on each of the 614719 EWAS probes (path *a* – Figure 1) was calculated using the linear regression model: lm(DNAm in each probe~CTQ +age+sex+cell types+smoking score+batch+10 PC+ antipsychotics+country); (iii) disease status (case-control) was regressed on DNAm and the confounders with logistic regression (path b) by the model glm(case/control~ (DNAm in each probe)+age+sex+-cell types+smoking score+batch+10 PC+ antipsychotics+country, family = binomial(link = "logit") (codes are available upon request).

Then, to test each DNAm probe for mediation of the CA-psychosis association, the Divide-Aggregate Composite-null Test (DACT) was performed. As illustrated in Figure 1, mediation effect is present if paths *a* and *b* are both non-zero for the same probe. The null hypothesis of no mediation is a composite of 3 scenarios: that either path *a* or path *b* pathways, or both, are absent (Figure 1). DACT uses the EWAS epigenetic data to estimate the frequencies of these three scenarios among the DNAm probes and use this information to create a composite p-value for testing whether paths *a* and *b* are both non-zero for each given probe. This test has been recently validated[16] and shown to be more powerful than more traditional tests such as the Sobel test and the joint significance test or Max P[14]. Details on the development and validation of this method can be found in Liu et al., 2021[16]. Separate mediation analyses were conducted with childhood adversity (composite), abuse and neglect as the outcome variable.

Figure 1

Interpreting the output of mediation analyses



Footnote: Rejection of the hypothesis that DNA methylation level mediates the effect of childhood adversity on psychosis requires both paths "a" and "b" to be non-0. Thus, the null hypothesis is not rejected if path "a" (scenario 2), or path "b" (scenario 3), or both paths (scenario 1), are 0. An estimate of the overall mediation effect is obtained by multiplying the estimates for the effects of paths "a" and "b".

We used Bonferroni corrected p-value significance threshold of p<8.1x10-8 (as calculated by 0.5/614719: total number of probes that passed stringent QC)), and a suggestive nominally-significant P-value threshold of P < 5e-05 based on others studies using EPIC array[39, 40]) was established to identify DMPs mediating CA with psychosis,

Gene ontology pathway analysis

Illumina UCSC gene annotation was used to create a test gene list from the mediating DMPs (P < 5e-05). Gene ontology and pathway analysis were performed, using the *missMethyl* package[41], which takes into account the variable number of EPIC probes associated with each gene. Downstream KEGG pathways analyses were also performed to provide further insights into potential relevant biological processes associated with the significant DMPs (P < 5e-05), according to previous studies[42]. Independent pathways with FDR <0.05 were considered to be significantly associated with CA subtypes, and pathways with p<0.05 were also reported.

Results

Characteristics of the cases and controls of the samples used for the current study are presented in S. Table 1 (SM), and demographic and baseline characteristics comparison between the cases include in this study and the whole EU-GEI sample can be found in SM Table 2. FEP patients taking part in this study tended to be more often of white ethnic

background compared to the others but did not differ in terms of age, gender, adversity scores, diagnosis of non-affective psychosis and years of education. SM S. Figures 2-8 show QQ plots with the Lambda inflation factor of all the EWAS analyses conducted; none of the analyses showed problematic inflation.

Path *a*: the influence of CTQ on DNA methylation in cases and controls

For analyses on the composite measure of adversity, none of the DMP passed EPIC-array Bonferroni threshold significance; however, we identified 35 nominally-significant (P < 5e-5) severe adversity-associated involving 24 genes DMPs (S. Table 3 and SM S. Figure 9). Among these, the top 5 ranking probes were associated with genes including *C1orf168, EVPL, CHRNB4, PLAT, and HLA-J.*

For analyses restricted to abuse subtype, although none of the DMP passed EPIC-array Bonferroni threshold significance, we identified 35 severe adversity-associated DMPs that passed the nominally-significant threshold (P < 5e-5; S. Table 4 and S. Figure 10, SM) spanning across 25 genes, among which the top 5 genes were *EVPL, PTPRS, WAC, NHS, and RFX3.*

For the neglect subtype, we reported one DMP passed EPIC-array Bonferroni threshold significance, called cg11476306 and located on chr 19 and in gene *PIP5K1C*; in addition, we identified 20 nominally-significant psychosis-associated DMPs (P < 5e-5; S. Table 5 and SM Figure 11) spanning across 15 genes. The top 5 genes were *PIP5K1C, APLP1, MEGF11, PDE4D, and CD276.*

Path *b*: examining the influence of DNAm in cases controls status

None of the probes reached Bonferroni significance, however our data revealed 34 nominally-significant severe adversity-associated DMPs (P < 5e-5; S. Table 6 and S. Figure 12) spanning across 21 genes, including *APLN, TFEB, DPYSL3, PRAME,* and *MUC6.*

Path *c*: examining the influence of DNAm in cases controls status

The composite cumulative score of CTQ, as well as abuse and neglect scores were positively associated with psychosis risk (OR = 1.68; p = <0.000) abuse score OR = 2.16; p<0.001; neglect: OR = 2.27; p=<0.001). Results were adjusted by age, sex and country.

The mediating role of DNAm between CA (composite, abuse and neglect) and cases/control status

For analyses with the composite measure of adversity, none of the DMP passed EPIC-array Bonferroni threshold significance, however, we identified 28 nominally-significant severe adversity-associated DMPs (P < 5e-5) for mediation, spanning across 21 genes, whose characteristics can be found in Table 1. Figure 2 is a Manhattan plot displaying the EWAS results:

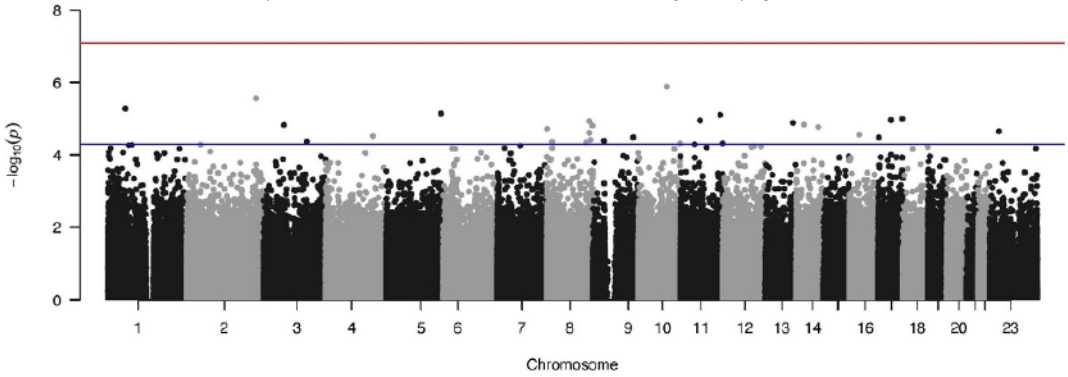
Table 1

Top DMPs (P < 5e-05) associated with composite cumulative measure of adversity using the DACT test

Probe	Genomic location (hg19)	Illumina gene annotation	Relation to UCSC CpG Island	Effect size mediation	p-value mediation
cg19456890	10: 91402272	*PANK1*	N_Shore	0.074	1.30E-06
cg14074251	2: 220299116	*SPEG*	N_Shore	0.075	2.72E-06
cg00812246	1: 55464868	*BSND*	S_Shore	-0.066	5.33E-06
cg12449682	5: 175111543	*HRH2*		-0.059	7.26E-06
cg05220676	11: 125300393	*PKNOX2*		-0.080	7.93E-06
cg21978195	17: 77918905	*TBC1D16*	S_Shore	-0.081	1.01E-05
cg19452633	17: 42164476	*HDAC5*		0.065	1.09E-05
cg11495399	11: 62495898	*HNRNPUL2; TTC9C*	S_Shore	-0.069	1.13E-05
cg02496181	8: 133993505	*TG*	Body	-0.071	1.17E-05
cg26074940	3: 66293457	*SLC25A26*		0.051	1.50E-05
cg04141185	8: 143424755	*TSNARE1*		0.055	1.57E-05
cg05339605	14: 91269861	*TTC7B*		-0.067	1.72E-05
cg14242010	X: 33325900	*DMD*		0.055	2.28E-05
cg14242010	X: 33325900	*DMD*		0.055	2.28E-05
cg27618173	8: 134069863	*SLA*		-0.056	2.49E-05
cg09716762	16: 31383689	*ITGAX*	S_Shore	-0.061	2.77E-05
cg01094918	4: 149862744			-0.052	3.04E-05
cg05438152	9: 127044991	*NEK6*		-0.053	3.34E-05
cg17331920	17: 4081325	*ANKFY1*		-0.048	3.37E-05
cg26654675	8: 137274357			-0.063	3.87E-05
cg00708080	9: 34382709	*C9orf24*	S_Shore	0.055	4.09E-05
cg17219331	3: 139025555			-0.048	4.28E-05
cg06143905	8: 16859872	*FGF20*	S_Shore	0.051	4.35E-05
cg17280975	8: 123875899	*ZHX2*		0.052	4.52E-05
cg05288426	11: 134469461			0.04	4.90E-05

Figure 2

Manhattan plot showing the DNAm mediating DMP between composite cumulative measure of adversity and psychosis.



Footnote: Red line: array-wide multiple testing threshold (p<5.8x10-8); blue line: "discovery" p-value threshold (P < 5e-5).

For analyses limited to abuse, none of the DMP passed EPIC-array Bonferroni threshold significance, nevertheless, we identified 34 nominally-significant severe adversity-associated DMPs for mediation(*P* < 5e-5) spanning across 27 genes (Table 2). Interestingly, six of these 27 genes overlapped with the genes found for composite measure of adversity *(HRH2, HDAC5, HDAC5, NEK6, DMD, BSND,* and L*RRC27)*, S Figure 13 (SM) is a Manhattan plot displaying the EWAS results:

Table 2

Top DMPs (*P* < 5e-05) associated with composite cumulative measure of abuse using the DACT test.

Probe	Genomic location (hg19)	Illumina gene annotation	Relation to UCSC CpG Island	Effect size mediation	p-value mediation
cg08457495	17: 45771936	*TBKBP1*	Island	0.159	5.36E-07
cg22295944	1: 88422041			0.152	1.76E-06
cg21033965	1: 178455800		Island	0.142	4.43E-06
cg01883825	19: 12202105	*ZNF788*	N_Shore	-0.128	4.52E-06
cg19031841	12: 123717296	*C12orf65; MPHOSPH9*	N_Shore	-0.131	4.71E-06
cg12449682	5: 175111543	*HRH2*		-0.111	7.26E-06
cg26654675	8: 137274357			-0.132	7.44E-06
cg26470958	8: 6666420	*XKR5*	S_Shelf	0.125	7.91E-06
cg16495975	16: 8619855	*TMEM114*	Island	0.142	8.12E-06
cg19452633	17: 42164476	*HDAC5*		0.132	1.09E-05
cg03173714	10: 103341227	*POLL*		0.125	1.12E-05
cg05438152	9: 127044991	*NEK6*		-0.108	1.21E-05
cg12028337	13: 107790939			0.127	1.30E-05
cg09832276	14: 63121958			-0.118	1.31E-05
cg25802927	1: 109934098	*SORT1*		0.112	1.35E-05
cg00546808	1: 28560335	*DNAJC8*	S_Shore	-0.129	1.49E-05
cg11346960	11: 5266120	*HBBP1;BGLT3*		-0.126	1.63E-05

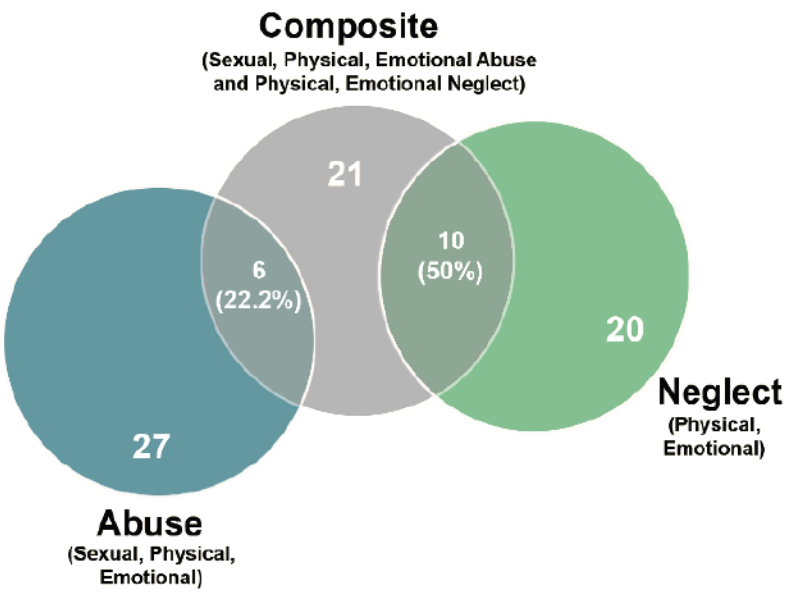
cg01573175	20: 62381851	*ZBTB46*	N_Shore	0.123	1.65E-05
cg24683479	8: 55913574			0.108	1.69E-05
cg14242010	X: 33325900	*DMD*		0.110	1.97E-05
cg13257878	10: 133747771	*PPP2R2D*	N_Shelf	-0.149	2.07E-05
cg00812246	1: 55464868	*BSND*	S_Shore	-0.115	3.37E-05
cg07701041	1: 156768682	*PRCC*		0.120	3.67E-05
cg16609217	8: 56054952	*XKR4*		0.096	3.68E-05
cg02107316	17: 45916907	*SCRN2*	N_Shore	0.100	3.82E-05
cg18202623	4: 126236316	*FAT4*	Island	-0.100	4.21E-05
cg26915952	1: 178456270		Island	0.163	4.22E-05
cg01514465	4: 118004215		N_Shelf	-0.090	4.22E-05
cg26682337	5: 145429192	*SH3RF2*		-0.103	4.31E-05
cg06143905	8: 16859872	*FGF20*	S_Shore	0.090	4.35E-05
cg05302489	6: 31760426	*VARS*	N_Shelf	-0.089	4.52E-05
cg16633756	6: 119766423			-0.120	4.60E-05
cg16012937	3: 35425213	*LOC101928135*		-0.106	4.91E-05
cg10354195	10: 134188789	*LRRC27*		-0.119	4.93E-05

Analyses limited to neglect revealed that none of the DMP passed EPIC-array Bonferroni threshold significance. However, 29 severe adversity-associated DMPs passed the "discovery" P-value of $P < 5e\text{-}5$ for mediation, spanning across 20 genes, that are displayed in S. Table 7 (SM). Of these 20 genes, 10 overlapped with the genes found for composite measure of adversity (*PANK1, SPEG, TBC1D16, ANKFY1, C9orf24, ZHX2, TTC7B, ITGAX, HNRNPUL2,* and *TTC9C*). S Figure 14 (SM) shows a Manhattan plot displaying the EWAS results.

As can be seen in Figure 3, none of the mediating genes involved in the abuse psychosis path overlap with those involved in the neglect psychosis path, while some overlap was present between the composite measure and these two adversity subtypes.

Figure 3

Diagram showing the mediating overlapping genes between composite, abuse and neglect analyses with psychosis.



Footnote: while 6 mediating genes (22.2%) from the composite analyses where common with the abuse analyses, and 10 (50%) were common with the neglect analyses, no overlap was observed between the abuse and neglect analyses.

Gene ontology enrichment analyses

The genes associated with differentially methylated probes that passed the nominally significant threshold (P < 5e-5) (for composite adversity, abuse and neglect) were identified. Exploratory downstream enrichment analyses were performed in those genes using *missMethyl* package with the KEGG data set. The top 10 ranked biological pathways based on DMPs located in the gene body are summarised in the SM (S. Tables 8, 9 and 10 respectively). None of the pathways survived the FDR adjustment.

Lastly, SM S. Figures 15-17 show the top 10 CpG sites for composite, abuse and neglect analyses respectively showing the most significant correlation of DNAm data with smoking score. None of the analyses suggested that the probes were located in SNPs.

Discussion

To our knowledge, this study represents the first analysis that utilised a genome-wide approach to explore whether DNAm mediates the relationship between CA, and for the subtypes abuse and neglect in people with a FEP. We used the DACT approach, specifically developed to address mediation effects in EWAS data[16], that allowed us to interrogate mediating effects of DNAm in 614719 CpG sites across the entire genome.

Although none of the analyses survived to Bonferroni correction, we report nominally significant (P < 5e-5) DMPs, located in multiple genes of interest, mediating the association between composite measure of adversity, abuse, and neglect with psychosis. Some of these

have been previously associated with various phenotypes, including *SCZ*, as shown in Table 3. These included *PANK1, SPEG, TTC7B, ZHX2, HDAC5, NEK6, PKNOX2, TSNARE1; TMEM114, SORT1, PPP2R2D, VARS, NMB* and *LRRC27*. One of the replicated genes, *PANK1*, is the top ranked gene mediating both the composite measure of adversity and neglect with psychosis, which has previously been associated to SCZ in an EWAS study[43]. It codes a protein belonging to the pantothenate kinase family, which is a key regulatory enzyme in the biosynthesis of coenzyme A (CoA) in mammalian cells, important for oxidation of fatty acids, and the oxidation of pyruvate in the citric acid cycle[44]. This enzyme has a crucial role in mitochondrial functioning, which has recently appeared as key biological process involved in psychosis aetiopathogenesis[45]. *SPEG* was the second top ranked gene for both analyses with composite adversity and neglect. Two previous EWAS studies have found that increased methylation at this level was associated with SCZ[32, 43], and another found an association with Alzheimer Disease[46]. This gene encodes a protein with similarity to members of the myosin light chain kinase family, essential for myocyte cytoskeletal development. The top ranked DMP (cg08457495) for analyses of abuse lies within a CpG island at the level of the TSS1500 within the gene *TBKBP1*, which is an important gene regulating immunity. *TBKBP* and its homologue IKKε are serine–threonine kinases that mediate the induction of type I Interferon in antiviral innate immunity[47]; although its molecular role in psychiatric conditions remain unknown, a recent GWAS study in frontotemporal dementia patients found that a genetic variant within that loci was associated with the condition[48]. Abundant evidence supports the role of neuroinflammation and altered immune processes in the aetiopathogeneses of psychosis[49, 50]. Various EWAS studies having found DMPs located in genes involved in the immune system in those with SCZ [51-54], as well as related to CA in different conditions such as borderline personality disorder and post traumatic stress disorder[55-57]. Exploring the specific implications of DNAm changes in *TBK1* in immune processing involved with the disorder is a necessary target for future research.

Table 3

Summary of the evidence on all the genes having survived the nominally significant threshold (P < 5e-5) from the mediating analyses (reported in Tables 1, 2 and S Table 7 (SM)) with other EWAS studies, based on evidence reported in the EWAS Catalog (β http://www.ewascatalog.org/) .

Gene probe	Composite, abuse or neglect (effect size)	Replicating evidence	Condition	Tissue	Probe name; Beta of replication studies
PANK1 (cg19456890)	Composite (0.074) Neglect (0.1349)	Li M. et al.[34]	SCZ	Whole blood	0.00257
SPEG (cg14074251)	Composite (0.075) Neglect (0.120)	Hannon E. et al.[26] Li M. et al.[34] Zhang L. et al.[35]	SCZ SCZ AD	Whole blood Whole blood Prefrontal cortex	0.88 0.0095 0.032
HRH2 (cg12449682)	Composite (-0.059) Abuse (-0.111)	Marioni RE et al.[36]	Cognitive abilities; Phonemic Verbal Fluency	Whole blood	NA
PKNOX2 (cg05220676)	Composite (-0.080)	Li M. et al.[34] Yang BZ et al.[37]	SCZ Child abuse	Whole blood Saliva	cg25136107: NA cg08941173: 0.01 cg27598621: NA
HDAC5 (cg19452633)	Composite (0.065) Abuse (0.132)	Li M. et al. [34]	SCZ	Whole blood	cg23758120: 0.0017
TSNARE1 (cg04141185)	Composite (0.055)	Hannon E. et al.[26] Yang BZ et al.[37]	Psychosis and SCZ Child abuse	Whole blood Saliva	cg06454464: -0.010957 cg19916067: NA
TTC7B (cg05339605)	Composite (-0.067) Neglect (-0.113)	Hannon E. et al.[26] Li M. et al.[34] Zhang L. et al.[35]	Psychosis and SCZ SCZ AD	Whole blood Whole blood Prefrontal cortex	cg06900101: NA cg06900101: -0.01197 cg06937409: 0.035
NEK6 (cg05438152)	Composite (-0.053) Abuse (-0.108)	Li M. et al.[34]	SCZ	Whole blood	cg14196208: 0.0027
ANKFY1 (cg17331920)	Composite (-0.048) Neglect (-0.103)	Zhang L. et al.[35] Dunn EC et al.[38] Rijlaarsdam J et al.[39]	AD Physical or emotional abuse Social communication deficits[39]	Prefrontal cortex Leucocytes Cord blood	cg22090150: 0.042 cg06550546: NA cg21653149: NA
ZHX2 (cg17280975)	Composite (0.052) Neglect (0.1090)	Li M. et al.[34] Marioni RE et al.[36]	SCZ Cognitive abilities; Phonemic Verbal Fluency	Whole blood Whole blood	cg01886570: -0.00798 cg00415665: NA
LRRC27 (cg10354195)	Composite (-0.070) Abuse (-0.119)	Gervin K et al.[40] Roberts S et al.[41]	Paracetamol exposure in children with ADHD versus controls Psychotic experiences [41]	Cord blood Cord blood	cg02952711: NA cg15031103: NA
ZNF788 (cg01883825)	Abuse (-0.128)	Gervin K et al.[40]	Paracetamol exposure in	Cord blood	cg09489445: NA

			children with ADHD versus controls		
TMEM114 (cg16495975)	Abuse (0.142)	Hannon E. et al.[26]	Psychosis and SCZ	Whole blood	cg02003612: 0.65
SORT1 (cg25802927)	Abuse (0.112)	Hannon E. et al.[26]	Psychosis and SCZ	Whole blood	cg09131339: 0.013
DNAJC8 (cg00546808)	Abuse (-0.129)	Yang BZ et al.[37]	Child abuse	Saliva	cg03262242: NA
ZBTB46 (cg01573175)	Abuse (0.123)	Kandaswamy R et al.[30]	Severe adolescent victimization	Buccal	cg02630914: NA
PPP2R2D (cg13257878)	Abuse (-0.149)	Li M. et al.[34]	SCZ	Whole blood	cg20294155: -0.0046
		Yang BZ et al.[37]	Child abuse	Saliva	cg03716738: NA cg24032568: NA
		Gervin K et al.[40]	Paracetamol exposure in children with ADHD versus controls	Cord blood	cg05796331: NA
		van Dongen J. et al[42]	Agressive behaviour	Whole blood	cg12789488: NA
XKR4 (cg16609217)	Abuse (0.096)	Lunnon K et al.[43]	AD	Cross cortex model	cg09075515: NA
FAT4 (cg18202623)	Abuse (0.100)	Yang BZ et al.[37]	Child abuse	Saliva	cg18202623: NA
		Rijlaarsdam J et al.[39]	Social communication deficits	Cord blood	cg04373334: NA
SH3RF2 (cg26682337)	Abuse (-0.103)	Li M. et al.[34]	SCZ	Whole blood	cg11938014: NA
VARS (cg05302489)	Abuse (-0.106)	Li M. et al.[34]	SCZ	Whole blood	cg11620328: -0.03047
		Karlsson Linnér R. et al.[44]	Educational attainment	Whole blood	cg05302489: NA
NMB (cg19517291)	Neglect (-0.111)	Li M. et al.[34]	SCZ	Whole blood	cg26576155: NA
MAP7 (cg16351998)	Neglect (-0.095)	Smith AK et al.[45]	PTSD	Whole blood	cg25289569: -0.071
		Zhang L. et al.[35]	AD	Prefrontal cortex	cg13313598: 0.04 cg00235484: -0.036
		Ju C et al.[46]	Response to antidepressants	Whole blood	cg04453169: NA
TEAD3 (cg04345540)	Neglect (-0.098)	Zhang L. et al.[35]	AD	Prefrontal cortex	cg14909614: 0.02 cg01487910: 0.032
*TBC1D16** (cg21978195)	Composite (-0.081) Neglect (-0.146)	Jeremian R et al.[47]	BD with and without suicidal behavior	White blood cells	Decreased methylation in cases at a five-CpG shore in intron 3 of TBC1D16 (-0.026)
*ZBTB46** (cg01573175)	Abuse (0.123)	Starnawska A et al.[48]	Cognitive functioning	Whole blood	cg05867245 : 0.029

**These two references were not extracted from the EWAS Catalog (β http://www.ewascatalog.org/) but from pub med search.*

Another important gene that appeared among the top ranked DMPs mediating composite adversity and psychosis is *TSNARE1*. As shown in Table 3, it has also been associated to SCZ [32], and with child abuse in EWAS studies[58]. Importantly, a GWAS study involving SCZ patients of Caucasian ancestry identified that two SNPs within *TSNARE1* were associated with SCZ[59], which was later replicated in another whole exome sequency study[60]. A follow-up study in a Chinese population with SCZ confirmed that the minor allele of the SNPs (rs10098073) within *TSNARE1* was associated with a reduced risk of SCZ. Furthermore, gene expression data also points to a dysregulation of *TSNARE1* in SCZ, and another study in pluripotent stem cells showed synergistic effects between *TSNARE1* with other common variants associated to SCZ in altering pre and post synaptic neuronal deficits61. *TSNARE1* plays key roles in docking, priming, and fusion of synaptic vesicles with the presynaptic membrane in neurons, thus synchronizing neurotransmitter release into the synaptic cleft[62], and experimental preclinical studies suggest that it is a negative regulator of endosomal trafficking in cortical neurons[63]. Altogether, strong genetic, epigenetic, gene expression and stem cells in vitro evidence point at a possible involvement of *TSNARE1* in SCZ, with epigenetic evidence suggesting a concurrent involvement of CA in DNAm changes in this gene, which provides a possible pathway in the CA-SCZ association. Other genes involved in the neurodevelopment of the central nervous system that require further exploration are the ITGAX, involved in the modulation of neural differentiation through its action on microglia[64]; *ADGRG1*, involved in myelinisation processes[65, 66] and extracellular matrix[67, 68]; and *MFF*, involved in oligodendrocytes formation[69]. All these processes are important for SCZ aetiopathogenesis[70-72], and therefore are of interest for future research.

None of our gene ontology enrichment analyses passed the FDR threshold, therefore drawing conclusions on the potential biological pathways that stem from our enrichment analyses is not possible. Taking this limitation into consideration, a preliminary exploration of the top 10 biological pathways that survived a more conservative p-value of < 0.05 could still provide some insights, as previously done by others[42, 73]. The top 1 and top 5 pathways for composite measure of adversity and abuse respectively was the histamine-induced gastric acid secretion, led by *HRH2*, (coding for the histamine receptor H2), which was the top 4 gene for composite adversity and abuse. Action on the histaminergic system alongside serotoninergic (5-HT), norepinephrinergic modulation putatively underlies the beneficial effect of atypical antipsychotics in mood and anxiety disorders [74]. The *H2R* is a G-protein coupled receptor located post-synaptically that has high expression in the central nervous system (CNS), as well as the heart and stomach[75, 76]. Within the CNS, *H2R* has a high density of expression in the cortex, basal ganglia, amygdala, and hippocampus[77]. *H2R* is commonly co-expressed with H1R which may account for their similar excitatory function, such as memory consolidation, inflammation, and motor function[78-81]. Clinically, *H2R* antagonists are widely used to inhibit gastric acid secretion[82]. However, following a case report detailing the resolution of acute psychotic symptoms of a patient treated with famotidine, 7 RCTs have explored treatment of SCZ with *H2R* antagonists. These studies have had mixed findings on improvement of positive and negative symptoms. Nevertheless, the impact on cognition was not included in their analyses, which should be consid-

ered for future research given preclinical findings suggesting the role of *H2R* on cognitive processes[83-89]. Genetic variations of *H2R* in SCZ have been studied and subsequently identified *H2R 64949G* allele, the presence of which was 80% more frequent in patients with SCZ compared to controls, while homozygous manifestations of the allele were found to be 180% more frequent in patients[90, 91]. Given the above, future studies examining the implications of *HR2* DNAm on clinical outcomes, and its modulating effect in cognitive processes could be an important target for future research.

In the current study, we conducted analyses separately for the subtypes of abuse and neglect in order to explore whether DNAm changes related to abuse overlapped or differed with those related to neglect. This question stems from recent findings showing a differential impact of both type of adversities on psychopathological outcomes in those with psychosis, with abuse being specifically related to the positive symptoms of psychosis, while neglect appears to be specifically linked to the negative dimension, suggesting different trajectories[4]. Our results, (illustrated in Figure 3) on DNAm show a lack of overlap in the genes that passed the discovery P-value between abuse and neglect, while some overlap was present between the composite measure and these two adversity subtypes: 6/27 DMP associated genes were related to abuse and the composite measure, while this was the case for 10/20 of those from neglect analyses. Although we could not relate the DNAm changes to the psychopathological domains, as described in the limitations, our results suggest different biological signatures of DNAm according to the type of traumatic experience, in the onset of psychotic disorder. Future studies exploring the DNAm relationship between these two adversities with positive and the negative dimensions of psychosis respectively will pose an interesting research area.

This study presents various strengths and limitations. A first relevant strength is the use for the first time in psychiatric populations of the DACT[16] a novel approach specifically designed to explore mediation by DNAm epigenome wide, which takes into account the composite nature of the null hypothesis of no mediation, improving the power of more traditional methods such as the Sobel test and the joint significance test[14]. A second strength is the sample of FEP with a relatively young population of cases (30.5 year old sample mean age), which limits the influence of chronicity of the psychotic disease on epigenetic changes, the impact of age itself[92], as well antipsychotic medication, which is known for being an important modulator of DNAm[93]. Third, we controlled for known important confounders in epigenetic studies including smoking [94], cell type composition in blood[95], PCs as well as antipsychotic medication, thereby, disentangling their confounding effects on DNAm. Fourth, DNAm was quantified using the Illumina EPIC array, which to date is the most robust and highly reliable, currently the best high-throughput platform with content spanning regulatory regions associated with the majority of known annotated genes, allowing us to explore 614719 CpG sites across the entire epigenome. Lastly, we used various forms of adversity measures, not only limiting our analyses to the broader composite measure where the specific biological underpinnings are diluted hampering the study of specific effects.

Nonetheless, the results from our study should be considered with care in light of some limitations. First, we could not map our findings on DNAm related to abuse and neglect with positive and negative dimension of psychosis respectively, as the sample EU-GEI was not assessed with an instrument that could capture symptom severity. This would have been interesting, given previous findings showing a differential effect of those adversities in the respective dimensions[4], as mentioned above. Second, the direction of the mediation is difficult to interpret with the information presented in the study. Whereas a positive mediation could suggest that hypermethylation associated to CA may increase the risk of psychosis, and inversely; previous work shows that such direction (hyper or hypomethylation) is strongly dependent on the genotype, which has not been accounted for in this study. Furthermore, although increased methylation is generally associated to repression of gene expression, this is not always the case[96], and without measures of gene expression, it is not possible to elucidate the impact of DNAm at a molecular level in each specific gene, therefore limiting the understanding of the downstream implication of our results. Therefore, our results remain exploratory and deserve future attention with more specific hypotheses related to specific genes, where the effect of genotype is accounted for, and the functional consequences of DNAm are explored molecularly. Third, despite the current study being the largest to date interrogating the epigenetic signature of DNAm in relation to CA in those with psychosis, it is still underpowered, and a larger sample may be needed in future, to replicate our results and test the same hypotheses in other sources such as saliva or post-mortem brains, given the relatively low blood-brain correlation of DNAm markers[97]. Fourth, different biological processes operate differently across various developmental stages, therefore considering the timing of trauma could give important insights into which processes operate at different ages. Unfortunately, CTQ does not report the age of exposure to CA, which prevents us examining this in the current work. We hope that this will be the object of future attention. Fifth, we have conducted mediation analyses in a cross-sectional study, and although traumatic events were recorded before psychosis onset, we cannot exclude that psychosis itself may lead to changes in the DNAm, and not the other way around as we assume, therefore, posing a reverse causation issue. Therefore, longitudinal studies examining the outcome after the DNAm changes are required. Lastly, we could not account for maternal education which in multiple studies have shown to been used as general cognitive index and has shown to be associated with CA exposure. Although our preliminary analyses revealed that educational attainment (another proxy of cognition) was not related to adversity exposure in our sample, we cannot exclude that other socio-economic variables may have played a confounding role in our results.

In conclusion, the present study was underpowered to identify putative mediation of the impact of CA on psychosis by DNA methylation. Although none of our DMP reached statistical significance based on Bonferroni correction, we reported a number of nominally significant DMPs ($p < 5e\text{-}05$) that are associated with genes that have been previously implicated in the pathogenesis of SCZ in genetic and epigenetic studies, as well as a num-

ber of novel candidate genes. For example, we reported differential DNAm in genes associated in immune and neurodevelopmental process, as well as neural signalling and the mitochondrial dysfunction pathways, which is in line with recent literature in the field suggesting a mediating role of such pathways between CA and psychosis[12]. Although none of our enrichment analyses revealed pathways surviving the FDR correction, the top ranked biological process involved the histaminergic function, which can be an important target for future research, given the direct link with psychopathology and medication therapeutic effects in patients with SCZ. Lastly, low overlap between mediating genes and pathways according to abuse and neglect suggests that biological trajectories between CA and psychosis are distinct depending on the type of adversity.

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Conflicts of interest

M Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of AB-Biotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda. **Dr. Arango. has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Dr Peter B. Jones declare to have consulted for Ricordati and Janssen. Dr Murray has received payments for non-promotional seminars from JANSSEN, SUNOVIAN, LUNDBECK AND OTSUKA.**

Author Contribution Statement

LA conceptualised and designed the study, conducted the statistical analyses and wrote the initial draft; CW and RM conceptualised and designed the study; reviewed the initial draft and supervised the project; LZ created the DACT and conducted statistical analyses and reviewed the initial draft; PCS, MDF contributed to the design and reviewed the initial draft; MA, GT, VR, SAS, RK, CA, MA, MB, JB, LDH, CMD, CGA, LS, PBJ, HEJ, JBK, CLC, AL, ST, PML, PRM, JVO, BPR, JLS, JS, JPS, AS, IT, AT, EV, CM, ED reviewed the first draft and contributed to data collection and EUGEI planning, DD, AA reviewed the first draft, JM, EH, JB, ED reviewed the first draft and contributed to data collection and preparation; DQ data management.

References

1. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull 2012; 38(4): 661-671.

2. Rodriguez V, Aas M, Vorontsova N, Trotta G, Gadelrab R, Rooprai NK et al. Exploring the Interplay Between Adversity, Neurocognition, Social Cognition, and Functional Outcome in People With Psychosis: A Narrative Review. Front Psychiatry 2021; 12: 596949.

3. Christy A, Cavero D, Navajeeva S, Murray-O'Shea R, Rodriguez V, Aas M et al. Association Between Childhood Adversity and Functional Outcomes in People With Psychosis: A Meta-analysis. Schizophr Bull 2022.

4. Alameda L, Christy A, Rodriguez V, Salazar de Pablo G, Thrush M, Shen Y et al. Association Between Specific Childhood Adversities and Symptom Dimensions in People With Psychosis: Systematic Review and Meta-Analysis. Schizophr Bull 2021.

5. Aas M, Haukvik UK, Djurovic S, Tesli M, Athanasiu L, Bjella T et al. Interplay between childhood trauma and BDNF val66met variants on blood BDNF mRNA levels and on hippocampus subfields volumes in schizophrenia spectrum and bipolar disorders. J Psychiatr Res 2014.

6. Howes OD, McCutcheon R, Owen MJ, Murray RM. The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia. Biol Psychiatry 2017; 81(1): 9-20.

7. Ruby E, Polito S, McMahon K, Gorovitz M, Corcoran C, Malaspina D. Pathways Associating Childhood Trauma to the Neurobiology of Schizophrenia. Frontiers in psychological and behavioral science 2014; 3(1): 1-17.

8. Alameda L, Fournier M, Khadimallah I, Griffa A, Cleusix M, Jenni R et al. Redox dysregulation as a link between childhood trauma and psychopathological and neurocognitive profile in patients with early psychosis. Proceedings of the National Academy of

Sciences 2018; 115(49): 12495-12500.

9. Alameda L, Rodriguez V, Carr E, Aas M, Trotta G, Marino P et al. A systematic review on mediators between adversity and psychosis: potential targets for treatment. Psychological Medicine 2020; 50(12): 1966-1976.

10. Binder EB. Dissecting the molecular mechanisms of gene x environment interactions: implications for diagnosis and treatment of stress-related psychiatric disorders. European journal of psychotraumatology 2017; 8(sup5): 1412745.

11. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nature genetics 2003; 33 Suppl: 245-254.

12. Alameda L, Trotta G, Quigley H, Rodriguez V, Gadelrab R, Dwir D et al. Can epigenetics shine a light on the biological pathways underlying major mental disorders? Psychol Med 2022: 1-21.

13. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of personality and social psychology 1986; 51(6): 1173.

14. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. Sociological methodology 1982; 13: 290-312.

15. Barfield R, Shen J, Just AC, Vokonas PS, Schwartz J, Baccarelli AA et al. Testing for the indirect effect under the null for genome-wide mediation analyses. Genetic epidemiology 2017; 41(8): 824-833.

16. Liu Z, Shen J, Barfield R, Schwartz J, Baccarelli AA, Lin X. Large-Scale Hypothesis Testing for Causal Mediation Effects with Applications in Genome-wide Epigenetic Studies. Journal of the American Statistical Association 2021: 1-15.

17. Liu Z, Shen J, Barfield R, Schwartz J, Baccarelli AA, Lin X. Large-scale hypothesis testing for causal mediation effects with applications in genome-wide epigenetic studies. Journal of the American Statistical Association 2022; 117(537): 67-81.

18. Gayer-Anderson C, Jongsma HE, Di Forti M, Quattrone D, Velthorst E, de Haan L et al. The EUropean Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI): Incidence and First-Episode Case-Control Programme. Social Psychiatry & Psychiatric Epidemiology 2020; 55(5): 645-657.

19. Quattrone D, Di Forti M, Gayer-Anderson C, Ferraro L, Jongsma HE, Tripoli G et al. Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study. Psychological medicine 2018: 1-14.

20. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness: development and reliability of the OPCRIT system. Ar-

chives of general psychiatry 1991; 48(8): 764-770.

21. Mallett R, Leff J, Bhugra D, Pang D, Zhao JH. Social environment, ethnicity and schizophrenia. A case-control study. Social psychiatry and psychiatric epidemiology 2002; 37(7): 329-335.

22. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child abuse & neglect 2003; 27(2): 169-190.

23. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. The American journal of psychiatry 1994.

24. Aas M, Alameda L, Di Forti M, Quattrone D, Dazzan P, Trotta A et al. Synergistic effects of childhood adversity and polygenic risk in first-episode psychosis: the EU-GEI study. Psychological Medicine 2021: 1-9.

25. Perroud N, Paoloni-Giacobino A, Prada P, Olie E, Salzmann A, Nicastro R. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Transl Psychiatry 2011; 1.

26. Marzi SJ, Sugden K, Arseneault L, Belsky DW, Burrage J, Corcoran DL et al. Analysis of DNA Methylation in Young People: Limited Evidence for an Association Between Victimization Stress and Epigenetic Variation in Blood. Am J Psychiatry 2018: appiajp201717060693.

27. Bowtell DD. Rapid isolation of eukaryotic DNA. Analytical biochemistry 1987; 162(2): 463-465.

28. Jeanpierre M. A rapid method for the purification of DNA from blood. Nucleic Acids Research 1987; 15(22): 9611.

29. Pidsley R, Viana J, Hannon E, Spiers H, Troakes C, Al-Saraj S et al. Methylomic profiling of human brain tissue supports a neurodevelopmental origin for schizophrenia. Genome biology 2014; 15(10): 483.

30. Bhering LL. Rbio: A tool for biometric and statistical analysis using the R platform. Crop Breeding and Applied Biotechnology 2017; 17: 187-190.

31. Pidsley R, Wong CC, Volta M, Lunnon K, Mill J, Schalkwyk LC. A data-driven approach to preprocessing Illumina 450K methylation array data. BMC genomics 2013; 14(1): 293.

32. Hannon E, Dempster EL, Mansell G, Burrage J, Bass N, Bohlken MM et al. DNA methylation meta-analysis reveals cellular alterations in psychosis and markers of treatment-resistant schizophrenia. eLife 2021; 10: e58430.

33. Turner SD. qqman: an R package for visualizing GWAS results using QQ and manhattan plots. Biorxiv 2014: 005165.

34. Houseman EA, Accomando WP, Koestler DC, Christensen BC, Marsit CJ, Nelson HH et al. DNA methylation arrays as surrogate measures of cell mixture distribution. BMC bioinformatics 2012; 13(1): 1-16.

35. Elliott HR, Tillin T, McArdle WL, Ho K, Duggirala A, Frayling TM et al. Differences in smoking associated DNA methylation patterns in South Asians and Europeans. Clinical epigenetics 2014; 6(1): 1-10.

36. Dietz PM, Homa D, England LJ, Burley K, Tong VT, Dube SR et al. Estimates of nondisclosure of cigarette smoking among pregnant and nonpregnant women of reproductive age in the United States. American journal of epidemiology 2011; 173(3): 355-359.

37. Spencer K, Cowans NJ. Accuracy of self-reported smoking status in first trimester aneuploidy screening. Prenatal Diagnosis 2013; 33(3): 245-250.

38. Elliott HR, Tillin T, McArdle WL, Ho K, Duggirala A, Frayling TM et al. Differences in smoking associated DNA methylation patterns in South Asians and Europeans. Clinical epigenetics 2014; 6(1): 1-10.

39. Kandaswamy R, Hannon E, Arseneault L, Mansell G, Sugden K, Williams B et al. DNA methylation signatures of adolescent victimization: analysis of a longitudinal monozygotic twin sample. Epigenetics 2020: 1-18.

40. Sammallahti S, Cortes Hidalgo AP, Tuominen S, Malmberg A, Mulder RH, Brunst KJ et al. Maternal anxiety during pregnancy and newborn epigenome-wide DNA methylation. Molecular psychiatry 2021; 26(6): 1832-1845.

41. Phipson B, Maksimovic J, Oshlack A. missMethyl: an R package for analyzing data from Illumina's HumanMethylation450 platform. Bioinformatics 2016; 32(2): 286-288.

42. Zou D, Qiu Y, Li R, Meng Y, Wu Y. A Novel Schizophrenia Diagnostic Model Based on Statistically Significant Changes in Gene Methylation in Specific Brain Regions. Biomed Res Int 2020; 2020: 8047146.

43. Li M, Li Y, Qin H, Tubbs JD, Li M, Qiao C et al. Genome-wide DNA methylation analysis of peripheral blood cells derived from patients with first-episode schizophrenia in the Chinese Han population. Molecular psychiatry 2020: 1-11.

44. Daugherty M, Polanuyer B, Farrell M, Scholle M, Lykidis A, de Crécy-Lagard V et al. Complete reconstitution of the human coenzyme A biosynthetic pathway via comparative genomics. Journal of Biological Chemistry 2002; 277(24): 21431-21439.

45. Cuenod M, Steullet P, Cabungcal J-H, Dwir D, Khadimallah I, Klauser P et al. Caught in vicious circles: a perspective on dynamic feed-forward loops driving oxidative stress in

schizophrenia. Molecular psychiatry 2022; 27(4): 1886-1897.

46. Zhang L, Silva TC, Young JI, Gomez L, Schmidt MA, Hamilton-Nelson KL et al. Epigenome-wide meta-analysis of DNA methylation differences in prefrontal cortex implicates the immune processes in Alzheimer's disease. Nature communications 2020; 11(1): 1-13.

47. Zhu L, Li Y, Xie X, Zhou X, Gu M, Jie Z et al. TBKBP1 and TBK1 form a growth factor signalling axis mediating immunosuppression and tumourigenesis. Nature cell biology 2019; 21(12): 1604-1614.

48. Broce I, Karch CM, Wen N, Fan CC, Wang Y, Hong Tan C et al. Immune-related genetic enrichment in frontotemporal dementia: an analysis of genome-wide association studies. PLoS medicine 2018; 15(1): e1002487.

49. Mazza MG, Lucchi S, Rossetti A, Clerici M. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: A meta-analysis and systematic review. The World Journal of Biological Psychiatry 2020; 21(5): 326-338.

50. Birnbaum R, Weinberger DR. A genetics perspective on the role of the (neuro) immune system in schizophrenia. Schizophrenia research 2020; 217: 105-113.

51. Montano C, Taub MA, Jaffe A, Briem E, Feinberg JI, Trygvadottir R et al. Association of DNA Methylation Differences With Schizophrenia in an Epigenome-Wide Association Study. JAMA psychiatry 2016; 73(5): 506-514.

52. Aberg KA, McClay JL, Nerella S, Clark S, Kumar G, Chen W et al. Methylome-wide association study of schizophrenia: identifying blood biomarker signatures of environmental insults. JAMA psychiatry 2014; 71(3): 255-264.

53. Hannon E, Dempster E, Viana J, Burrage J, Smith AR, Macdonald R et al. An integrated genetic-epigenetic analysis of schizophrenia: evidence for co-localization of genetic associations and differential DNA methylation. Genome biology 2016; 17(1): 176.

54. Liu J, Chen J, Ehrlich S, Walton E, White T, Perrone-Bizzozero N et al. Methylation patterns in whole blood correlate with symptoms in Schizophrenia patients. Schizophrenia Bulletin 2014; 40(4): 769-776.

55. Prados J, Stenz L, Courtet P, Prada P, Nicastro R, Adouan W. Borderline personality disorder and childhood maltreatment: a genome-wide methylation analysis. Genes Brain Behav 2015; 14.

56. Uddin M, Aiello AE, Wildman DE, Koenen KC, Pawelec G, de Los Santos R et al. Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proceedings of the National Academy of Sciences 2010; 107(20): 9470-9475.

57. Arranz MJ, Gallego-Fabrega C, Martín-Blanco A, Soler J, Elices M, Dominguez-Clavé E et al. A genome-wide methylation study reveals X chromosome and childhood trauma methylation alterations associated with borderline personality disorder. Transl Psychiatry 2021; 11(1): 5.

58. Yang BZ, Zhang H, Ge W, Weder N, Douglas-Palumberi H, Perepletchikova F et al. Child abuse and epigenetic mechanisms of disease risk. Am J Prev Med 2013; 44(2): 101-107.

59. Sleiman P, Wang D, Glessner J, Hadley D, Gur RE, Cohen N et al. GWAS meta analysis identifies TSNARE1 as a novel Schizophrenia / Bipolar susceptibility locus. Sci Rep 2013; 3: 3075.

60. Li M, Shen L, Chen L, Huai C, Huang H, Wu X et al. Novel genetic susceptibility loci identified by family based whole exome sequencing in Han Chinese schizophrenia patients. Transl Psychiatry 2020; 10(1): 5.

61. Schrode N, Ho SM, Yamamuro K, Dobbyn A, Huckins L, Matos MR et al. Synergistic effects of common schizophrenia risk variants. Nature genetics 2019; 51(10): 1475-1485.

62. Fromer M, Roussos P, Sieberts SK, Johnson JS, Kavanagh DH, Perumal TM et al. Gene expression elucidates functional impact of polygenic risk for schizophrenia. Nat Neurosci 2016; 19(11): 1442-1453.

63. Plooster M, Rossi G, Farrell MS, McAfee JC, Bell JL, Ye M et al. Schizophrenia-Linked Protein tSNARE1 Regulates Endosomal Trafficking in Cortical Neurons. J Neurosci 2021; 41(45): 9466-9481.

64. Lopez-Lengowski K, Kathuria A, Gerlovin K, Karmacharya R. Co-Culturing Microglia and Cortical Neurons Differentiated from Human Induced Pluripotent Stem Cells. J Vis Exp 2021; (175).

65. Ackerman SD, Luo R, Poitelon Y, Mogha A, Harty BL, D'Rozario M et al. GPR56/ADGRG1 regulates development and maintenance of peripheral myelin. J Exp Med 2018; 215(3): 941-961.

66. Chiou B, Gao C, Giera S, Folts CJ, Kishore P, Yu D et al. Cell type-specific evaluation of ADGRG1/GPR56 function in developmental central nervous system myelination. Glia 2021; 69(2): 413-423.

67. Millar MW, Corson N, Xu L. The Adhesion G-Protein-Coupled Receptor, GPR56/ADGRG1, Inhibits Cell-Extracellular Matrix Signaling to Prevent Metastatic Melanoma Growth. Front Oncol 2018; 8: 8.

68. Olaniru OE, Pingitore A, Giera S, Piao X, Castañera González R, Jones PM et al. The adhesion receptor GPR56 is activated by extracellular matrix collagen III to improve β-cell function. Cell Mol Life Sci 2018; 75(21): 4007-4019.

69. Tavares R, Wajnberg G, Scherer NM, Pauletti BA, Cassoli JS, Ferreira CG et al. Unveiling alterative splice diversity from human oligodendrocyte proteome data. J Proteomics 2017; 151: 293-301.

70. Monin A, Baumann P, Griffa A, Xin L, Mekle R, Fournier M et al. Glutathione deficit impairs myelin maturation: relevance for white matter integrity in schizophrenia patients. Molecular psychiatry 2015; 20(7): 827.

71. Cabungcal JH, Steullet P, Morishita H, Kraftsik R, Cuenod M, Hensch TK et al. Perineuronal nets protect fast-spiking interneurons against oxidative stress. Proc Natl Acad Sci U S A 2013; 110(22): 9130-9135.

72. Kolomeets NS, Uranova NA. Reduced number of satellite oligodendrocytes of pyramidal neurons in layer 5 of the prefrontal cortex in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2021.

73. Kebir O, Chaumette B, Rivollier F, Miozzo F, Lemieux Perreault LP, Barhdadi A et al. Methylomic changes during conversion to psychosis. Mol Psychiatry 2017; 22(4): 512-518.

74. Grinchii D, Dremencov E. Mechanism of action of atypical antipsychotic drugs in mood disorders. International Journal of Molecular Sciences 2020; 21(24): 9532.

75. Hu W, Chen Z. The roles of histamine and its receptor ligands in central nervous system disorders: An update. Pharmacology & therapeutics 2017; 175: 116-132.

76. Karlstedt K, Senkas A, Åhman M, Panula P. Regional expression of the histamine H2 receptor in adult and developing rat brain. Neuroscience 2001; 102(1): 201-208.

77. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiological reviews 2008.

78. Dai H, Kaneko K, Kato H, Fujii S, Jing Y, Xu A et al. Selective cognitive dysfunction in mice lacking histamine H1 and H2 receptors. Neuroscience research 2007; 57(2): 306-313

79. Ogawa S, Yanai K, Watanabe T, Wang Z-M, Akaike H, Ito Y et al. Histamine responses of large neostriatal interneurons in histamine H1 and H2 receptor knock-out mice. Brain research bulletin 2009; 78(4-5): 189-194.

80. Iwabuchi K, Kubota Y, Ito C, Watanabe T, Watanabe T, Yanai K. Methamphetamine and brain histamine: A study using histamine-related gene knockout mice. Annals of the New York Academy of Sciences 2004; 1025(1): 129-134.

81. Mobarakeh JI, Takahashi K, Sakurada S, Kuramasu A, Yanai K. Enhanced antinociceptive effects of morphine in histamine H2 receptor gene knockout mice. Neuropharmacology 2006; 51(3): 612-622.

82. Monette J, Mogun H, Bohn RL, Avorn J. Concurrent use of antiulcerative agents. Journal of clinical gastroenterology 1997; 24(4): 207-213.

83. Kaminsky R, Moriarty T, Bodine J, Wolf D, Davidson M. Effect of famotidine on deficit symptoms of schizophrenia. Lancet (London, England) 1990; 335(8701): 1351-1352.

84. Assunção SSM, Ruschel SI, Rosa LdCR, Campos JAO, Alves MJO, Bracco OL et al. Weight gain management in patients with schizophrenia during treatment with olanzapine in association with nizatidine. Brazilian Journal of Psychiatry 2006; 28: 270-276.

85. Farzin D, Hosseini SH, Shafaat A. A randomized double blind clinical trial in famotidine adjuvant therapy in schizophrenia. Iranian Journal of Medical Sciences 2005; 30(2).

86. Meskanen K, Ekelund H, Laitinen J, Neuvonen PJ, Haukka J, Panula P et al. A randomized clinical trial of histamine 2 receptor antagonism in treatment-resistant schizophrenia. Journal of clinical psychopharmacology 2013; 33(4): 472-478.

87. Poyurovsky M, Tal V, Maayan R, Gil-Ad I, Fuchs C, Weizman A. The effect of famotidine addition on olanzapine-induced weight gain in first-episode schizophrenia patients: a double-blind placebo-controlled pilot study. European Neuropsychopharmacology 2004; 14(4): 332-336.

88. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Nizatidine treatment and its relationship with leptin levels in patients with olanzapine-induced weight gain. Human Psychopharmacology: Clinical and Experimental 2003; 18(6): 457-461.

89. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Kilic N. Nizatidine for the treatment of patients with quetiapine-induced weight gain. Human Psychopharmacology: Clinical and Experimental 2004; 19(1): 37-40.

90. Orange P, Heath P, Wright S, Ramchand C, Kolkeiwicz L, Pearson R. Individuals with schizophrenia have an increased incidence of the H2R649G allele for the histamine H2 receptor gene. Molecular psychiatry 1996; 1(6): 466-469.

91. Orange PR, Heath PR, Wright SR, Pearson R. Allelic variations of the human histamine H2 receptor gene. Neuroreport 1996; 7(7): 1293-1296.

92. Unnikrishnan A, Freeman WM, Jackson J, Wren JD, Porter H, Richardson A. The role of DNA methylation in epigenetics of aging. Pharmacology & therapeutics 2019; 195: 172-185.

93. Hannon E, Dempster EL, Mansell G, Burrage J, Bass N, Bohlken MM et al. DNA methylation meta-analysis reveals cellular alterations in psychosis and markers of treatment-resistant schizophrenia. eLife 2021; 10.

94. Elliott HR, Tillin T, McArdle WL, Ho K, Duggirala A, Frayling TM et al. Differences in smoking associated DNA methylation patterns in South Asians and Europeans. Clinical epigenetics 2014; 6(1): 4.

95. Ji H, Ehrlich LI, Seita J, Murakami P, Doi A, Lindau P et al. Comprehensive methylome map of lineage commitment from haematopoietic progenitors. Nature 2010; 467(7313): 338-342.

96. Razin A, Cedar H. DNA methylation and gene expression. Microbiological reviews 1991; 55(3): 451-458.

97. Hannon E, Lunnon K, Schalkwyk L, Mill J. Interindividual methylomic variation across blood, cortex, and cerebellum: implications for epigenetic studies of neurological and neuropsychiatric phenotypes. Epigenetics 2015; 10(11): 1024-1032.

CHAPTER 5
General discussion, limitations and future directions

In this last section, I will first review the lessons taken from the five studies that comprised this thesis, grouped into two main topics: (i) the nature of the association between childhood adversity and psychosis, exploring potential mechanism; (ii) can epigenetics shine some light on the nature of the association between childhood adversity and psychosis? Subsequently, I will summarise the general limitations of the present work and the literature, and make suggestions on how these could be addressed in future research directions in the field of adversity in psychosis.

5.1 Overview of findings and implications

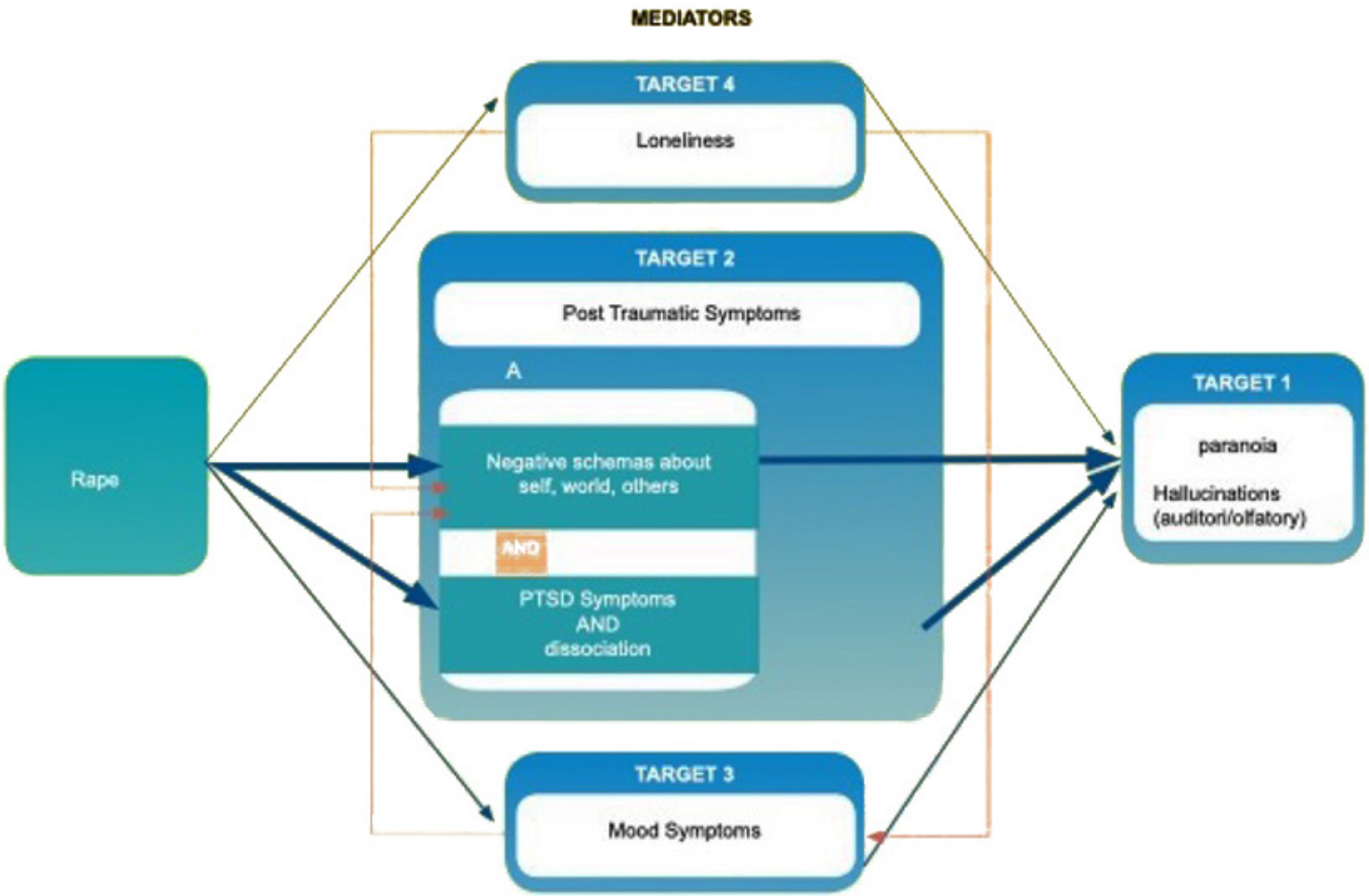
5.1.1 The nature of the association between childhood adversity and psychosis and its potential mechanism, what did we learn?

In Chapters 3.1-3-3 (studies 1-3) we learn that childhood adversity in the form of abuse has different effects than neglect in the clinical domains, abuse affecting the positive symptoms of psychosis and neglect the negative, while any form of adversity leads to a clinical profile characterised by more severe depressive symptoms. The systematic review expanded this finding, showing that severity of depressive symptoms, common in those with adversity and psychosis, can act as a mediator in the association, particularly when we refer to abuse. However, as evidence found in our review was mainly in general population samples, making extrapolation to the clinical situation more questionable, we tested whether this mediation by severity of depressive symptoms was playing a role in the persistence of positive symptoms of psychosis in patients. Based on our Lausanne's TIPP sample collaboration, we could confirm that severity of depressive symptoms, along with severity of anxiety with which it often co-occurs, mediated about 30% of the association between abuse and positive symptoms of psychosis, not only at onset but also up to three years following the onset of psychosis. This shows the importance of assessing the depressive and anxiety domains and considering treatment not only at the level of clinical depression, but also at sub diagnostic/threshold levels as described below.

We also found that other mediating mechanisms, such as dissociation and negative schemas about the self, the world, and others, are important mediating pathways between adversity and psychosis. The evidence of mediation between adversity and psychosis via depressive symptoms, dissociation and negative schemas led to speculating about potential new forms of conceiving the treatment of patients with psychosis and trauma. This model (ch 3.2 – see figure 8 below) points at the idea that clinicians should not only insist on treating the positive symptoms of psychosis, to which actually around 30% of the patients do not respond to regular antipsychotics (those with treatment resistant psychosis Schizophrenia (TRS))[19], but should also take into account a constellation of possible mediating factors in those with adversity, which can be addressed by pharmacological and/or psychotherapeutic means, as shown in the model below.

Figure 8

Potential targets for treatment based on the evidence of mediational pathways between adversity and psychosis.

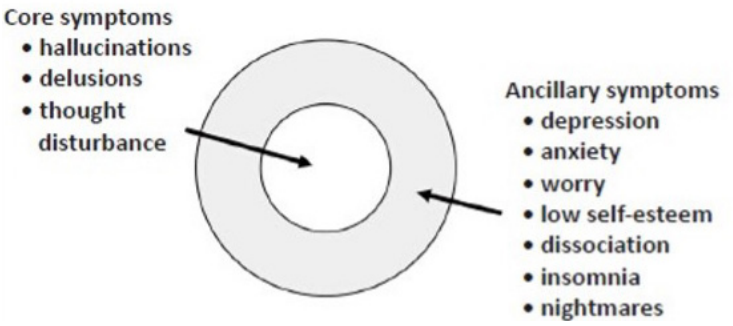


This figure displays the potential targets for treatment that could be addressed in individuals with psychosis who have been exposed to adversity. The choice of the pathways is based on evidence of mediation found in our review, but the implications remain hypothetical and should be tested empirically with randomized controlled trials. Beyond the traditional treatment of psychotic symptoms (Target 1) different clinical presentations with various targets for treatment can occur: Target 2 represent targets from the post traumatic spectrum such as Negative Schemas about the Self, Others and the World (NS) and PTSD related symptoms, including Dissociation. These can be combined in different forms as displayed in Target 2A, 2B and 2C. Target 3 represents mood-related symptoms and Target 4 represents the presence of feeling of loneliness. The treatment options could be adapted depending on which targets are present or predominant in the clinical picture. For Target 2 A: CBT-trauma focused therapy (for PTSD symptoms and NS) + sensory grounding techniques (for dissociation) + SSRI/ antagonists α1 if required (for PTSD symptoms). The implementation of these interventions would be adapted according to the presence/absence of the aforementioned targets (Target 2 B and C). Target 3: CBT techniques such as behavioural activation and graded exposure, relaxation techniques and mindfulness + SSRI if needed for anxiety and depressive symptoms. Target 4: Promoting social inclusion and community membership through therapy/activity groups and vocational support. Improving existing interpersonal relationships using family therapy approaches. The thickness of the arrows shows the robustness of the evidence according to our results. The square arrows represent a hypothetical connection not addressed in our review.

While it is well accepted that patients exposed to abuse have more severe symptoms of psychosis, as shown in our meta-analysis (ch. 3.1 – study 1)(105), this greater severity of symptoms is never conceptualised as treatment resistance psychosis or Schizophrenia (TRS). For some intriguing reason, the research field of trauma in psychosis seems in some ways disconnected from that of TRS. For example, the vast amount of research discussing the important implications and mechanism of those with TRS(19) rarely discuss the pervasive influence of adversity(106-108). On the other hand, literature on adversity and psychosis does not seem to be concerned about its potential role in this complicated group of patients(40, 45). It remains an important and open venue for research to consider this severity of positive symptoms of psychosis as a proxy of treatment resistance. It is more than plausible that some of those with TRS suffer from poorer outcomes, in part, because of the influence of such mediators, which can feed the positive symptoms of psychosis via the aforementioned mediational processes. Although the pervasive role of the so called "ancillary" symptoms of psychosis (symptoms that accompany the primary psychotic symptoms and that are often mood related, such as anxiety, depression, or more directly related to traumatic exposure such as dissociation or traumatic memories) has been already suggested as potential targets for treatment in those with trauma(40), this has not been put in the context of the concept of TRS.

Figure 9

Modelling psychosis symptoms: topographical model of psychosis symptoms



Topographical model of psychosis symptoms as conceptualised by Bebbington et al.,(40).

For example, there is currently no data at all or clinical guide suggesting that in addition to Clozapine, in those with adversity, specific trauma-oriented approaches should be carried on. Although there are a considerable number of options proposed as "augmentation" techniques, such as mood stabilisers such as Lamotrigine(109), addition of other antipsychotics(110, 111) or even Electroconvulsive therapy (ECT)(112), trauma-oriented approaches and targeting the aforementioned mediators are not necessarily considered in the first place. Moreover, trials conducted to test the effects of such augmentation techniques do not stratify patients according to their traumatic exposure. We could speculate that the benefits of such mood stabilisers are to improve the mood of those with trauma

and indirectly induce a positive effect on the targeted positive symptoms of psychosis. In summary, we propose a joint approach addressing the positive symptoms of psychosis, and the related mediators of each individual case in those with trauma and psychosis. We hope to be able to test this empirically in future (see Ch 5.3 - future directions).

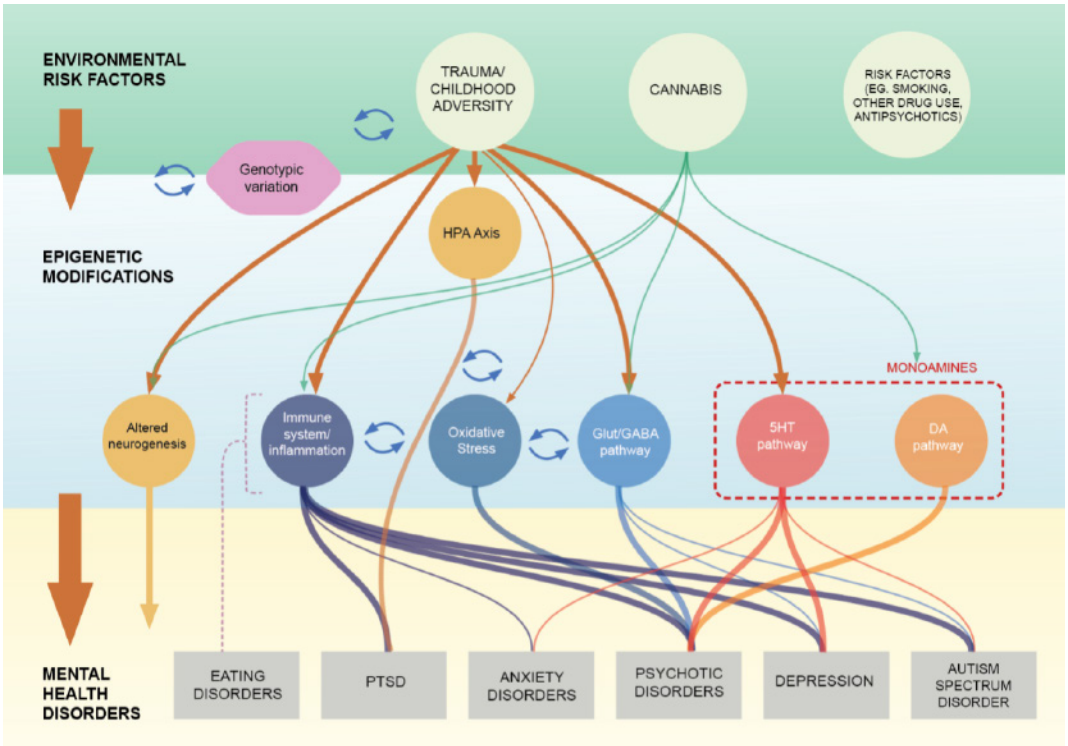
The differential effect between abuse and neglect on the symptoms domains was particularly interesting and suggests that different psychological and biological trajectories may be operating distinctly for each pathway. This motivated us to explore whether distinct biological pathways, affected by DNAm, could be one of the biological processes explaining such differences, as developed in the following section (5.1.2).

5.1.2 What can we learn from findings on DNAm about previous knowledge on the CA psychosis association?

In Chapter 4.1, we reviewed the literature in DNAm mapping into biological pathways that could be mediating the influence of environmental risk factors and the major mental conditions. As shown in Figure 10, we found that many of the epigenetic dysregulations we report are transdiagnostic, such as those affecting the serotoninergic, inflammatory and neurogenesis pathways, while others such as the Glutamatergic/GABAergic pathway are shared between a couple of disorders (e.g., SCZ and autism spectrum disorder), or disorder specific such as the dopaminergic pathway in psychotic disorders.

Figure 10

Summary of the evidence on potential pathways linking childhood trauma and cannabis use with psychiatric conditions through DNAm changes



This figure summarises the evidence presented in this review, highlighlting the idea that some biological pathways linking environmental risk factors with mental health disorders via epigenetic changed in the form of DNAm are transgiagnostics (e.g immune system/inflammation) while others seem to be more specific (e.g dopaminergic system). 1) (green and blue rows) the suggested links between childhood adversity (CA), and Cannabis use (CU) and DNAm changes mapping to biological pathways which are also functionally related (Serotoninergic, Dopaminergic pathways, Glutamatergic & GABAergic pathway, Neurogenesis, Immune system & Inflammation and Oxidative stress). 2) The blue and beige rows illustrate the evidence, from case control studies, of an association between DNAm changes in these pathways and the major mental health conditions (Eating Disorders (anorexia nervosa and bulimia nervosa, Post-traumatic stress disorder, Anxiety Disorders, Psychotic Disorder, Bipolar disorders, Depression and Autism Spectrum Disorders); 3) the potential mediating role of DNAm changes mapping to these between exposure to CA and CU and risk to develop mental health conditions. The thickness of the lines shows the robustness of the evidence reported in the literature review. The items "genotype: and "other risk factors" are added to highlight the influence of genetic factors and environmental confounders in DNAm studies. The dotted line connecting eating disorders with the pathways indicate that literature was limited and mixed not allowing to draw clear links with the pathways.

With regards to psychotic disorders specifically, evidence suggests an association with dopaminergic, serotoninergic, glutamatergic, oxidative stress, the immune system, inflammation as well as neurogenesis. Among these, evidence is indicative of an influence of childhood adversity on neurogenesis, the immune system, oxidative stress, the glutamatergic and serotoninergic system. Therefore, I hypothesize that the pathways that are linked to both adversity and psychosis could represent mediating processes. A limitation of current evidence in this clinical population is that no EWAS study had been conducted in relation to the exposure to childhood adversity. Moreover, although the aforementioned pathways are suggested as possible putative mediators in the context of DNAm, there was a lack of studies formally testing such mediation using DNAm at an EWAS scale. Given the above, I planned the empirical study presented in Chapter 4.2 (study 5), addressing these important questions; also, trying to further understand, whether this psychopathological difference that is related to each specific type of adversity, as shown in Chapter 3.1 (study 1), can relate to differences in the form of DNAm.

Chapter 4.2 (study 5) favours the hypothesis that a differential imprinting of abuse versus neglect on DNAm across the DNA may be mediating the effect in psychosis via distinct biological processes. On the other hand, although no significant DMPs survived the Bonferroni correction, taking into account the less restrictive discovery p-value allowed me to detect multiple genes involved in functions such as myelinisation and neural development, immune and inflammatory pathways, as well as genes involved in the glutamatergic and the dopaminergic function. This replicates and confirms our previous hypothesis presented in the figure 10 (above), stemming from our literature review with a hypothesis free approach, therefore strengthening the validity of those putative mechanisms in the etiopathogenetic of psychosis. Lastly, study 5 also highlights possible new venues that could be the target of future research with potential implications for treatment, such as the role of the histaminergic pathway, led by *HRH* gene, involved in the Histamine 2 R, previous studies in SCZ, as described extensively in Chapter 4.2 (study 5).

5.2 Limitations of present work and of current evidence

Beyond the specific technical limitations that have already been presented in each individual chapter, here I will discuss more broadly the limitations of the current work in a more general context, as well as of the current literature that we have reviewed.

For Chapters 3.1-3.3 (studies 1-3) focusing on the nature of the association between adversity and psychosis and outcome, and the possible mediating mechanisms, a few points need to be considered.

Following the completion of the literature review on mediating mechanism linking adversity and psychosis, we would have liked to be able to test more mediators empirically in clinical samples. For example, the role of dissociation has predominantly, although being explored in general populations samples and when it has been examined in patients, been conducted in fairly small samples (Ch. 3.2). Unfortunately, neither the EU-GEI or the TIPP data sets had information on dissociation allowing us to investigate this further. In the same way, we failed to be able to test the mediating role of the depressive symptoms between CA and psychotic symptoms in the EU-GEI. This was because the EU-GEI measure of psychopathology was done with the OPCRIT instrument, that assesses each psychopathological item in a binary way (absent/present), not on a Likert scale measure of severity. Therefore, although this instrument is excellent to create psychopathological profiles(15), it is less suitable to create a reliable severity score of a particular domain. Furthermore, some important limitations of current literature prevented us from providing a more insightful reflection on the links between adversity and clinical dimensions such as mania or disorganization, also important in those with psychosis. Moreover, despite the now well replicated link between adversity and neglect, with the two meta-analyses in this domain supporting such link (33, 105), mediating pathways of such links remain to be explored in literature and could not be covered in the current work.

In terms of the studies on epigenetics (Chapters 4.1-4.2 – studies 4 and 5), a few limitations and gaps need to be considered. First, given the very large scope of our review on epigenetics in mental health, we were dissuaded from reporting it as a systematic review, and restricted the original search reporting narratively what we believed was relevant for the current state of art in mental health. Although we followed standards protocols (PRISMA, PICO) to run the searches, we used a considerable amount of judgment in the choice of some biological pathways, and conditions to report, in order to limit the word count of the manuscript. For example, word limit constraints forced us to make some choices, and conditions such as Alzheimer or ADHD were left outside the review. Furthermore, we did not report all the pathways that appeared to be implicated in mental conditions. For example, emerging evidence shows that alteration mitochondrial dysfunction could play a role in some mental conditions(113, 114), and some epigenetic data support this(115). However, we decided not to report that pathway and limit to those that are more generally accepted as important players in psychiatry aetiopathogenesis. In addition, although

the influence of childhood adversity was developed extensively, as well as cannabis use, a more superficial overview was considered for other environmental factors such as drugs, alcohol, tobacco and medication, leading to an unavoidable imbalance in the work. The downside of these choices is that the review is not a perfect representative screenshot of the entire epigenetic landscape in mental health, which needs to be considered when interpreting the findings. The positive note is that, contrary to other systematic reviews in the field, in spite of its complexity, it captures a more individual view of the authors, that is sometimes lost with systematic works. That said, it would be interesting to conduct a similar work systematically and check that our findings and conclusions are replicated.

An important limitation of the empirical EU-GEI study on DNAm is the lack of replication sample. The reason we were not able to replicate this study, is because the sample that is available for replication (part of the GAP study(49)), uses a different instrument to assess adversity: the Childhood Experience of Care and Abuse (CECA). This instrument used different cut-off of severity and importantly does not measure neglect, which was a key adversity on the current work, and that in the EU-GEI was only measured with CTQ. Another important obstacle that we found, and which led to another limitation, is that while we could test the differential biological pathways at the level of DNAm, linking abuse with psychosis (as a disorder in the context of the case control status), and neglect with psychosis, we could not test the specific pathways that appeared to exist in our meta-analysis (ch. 3.1) including a link between abuse and positive symptoms of psychosis and neglect-negative symptoms of psychosis. The reason for this, as described above, is that the OPCRIT does not allow one to capture a measure of severity for those domains. More limitations of this chapter can be considered in the next section, as part of future perspectives.

5.3 Future directions in the field

In the current work, I have tried to improve the understanding of the nature of the association between childhood adversity and its forms with psychosis, various of its manifestations, trying to understand possible mediating mechanisms involving epigenetic processes. As mentioned in the introduction, the progress we have made in this field represents just a small fraction of a very much larger puzzle, where various other important factors are relevant for a full understanding of the complex interplay of how childhood adversity leads to psychosis and its clinical complications. I will here overview other important factors in the adversity-psychosis link that need to be considered for future works.

The influence of genes on the environment

Cumulative genetic liability plays a role not only in psychosis but can also lead to a propensity to exposure to experiences such as abuse and neglect(116). This implies that the risk of being exposed to such adversities in people with psychosis is genetically driven for some cases. It is likely that different gene and environment interplays operate within individuals with psychosis with various possible trajectories: some individuals may develop

psychosis following the exposure to non-genetically driven (stochastic effects) environmental insult, which combined with their independent(62), or synergistically(63) genetic predisposition, pushes them towards the threshold of a psychotic episode. Considering here that adversity is the consequence of a family context (which in turn is genetically driven (shared environmental effects)), disentangling the specific contribution of each factor is far more complex. Attempts to better understand this will prove difficult as it will require following up people from early in life and, given than only 2% of the population develop psychosis, a huge number will be required to track the trajectories for an acceptable sample of patients with the condition.

Environmental confounding, correlation and mediation

This complexity is even greater when we bring the notion of environmental confounding. This means that some environmental risk factors may make some individuals prone to exposure to other environmental insults that have therefore an indirect link with the given condition (environmental correlation)(96)(117). In addition, some environmental risk factors may mediate the action of previous insults on the risk of psychosis. For example, we have recently shown in a sample of the EU-GEI project that cannabis use in adolescence partially mediates the association between adversities such as household discord occurring in during childhood and psychosis after age 18 (Trotta et al., 2021 under review). Large prospective samples with careful assessment of various environmental factors at different periods of the development will be needed to better understand this complex interplay and how it can influence epigenetics.

New methods to measure the environmental load have been developed with the so called "exposome" (118), or "environmental risk score"(119); which creates a cumulative environmental metric capturing the totality of the environment involving many exposures over an individual's lifetime(118, 119). Although this approach does not resolve the issue of environmental correlation, it provides an interesting tool to explore gene and environment interactions in a broad way, and it would be interesting to explore it in the context of childhood adversity and epigenetics.

Epigenetic influence by the genotype

In this work I have explored to what extent environmental factors (stochastic or shared) may affect DNAm, and how such changes may mediate its influence on psychosis liability. However, as mentioned in the introduction, DNAm has not only a stochastic or environmental influence, but also a genetic one(95, 120), which is supported by studies of methylation patterns in families(121) and in twins(122).

Methods quantifying the genetic influences on DNAm, such as the methylation quantitative trait loci (mQTL(95)) allow to determine which DNAm traits are genetically driven; research integrating this with childhood adversity EWAS level should be conducted and would be a good addition to the work presented in Chapter 4.2 (study 5).

The timing of adversity

Research in animal models(123) and in patients(124, 125) has shown that the impact of stress in different critical periods of vulnerability can disturb neural and brain regions differently, as well as different biological processes. For example, stress-sensitive structures, such as the hippocampus, prefrontal cortex, or corpus callosum, have been shown to be altered in persons exposed to trauma and displayed various timing patterns of neurodevelopment during the life span(126-128). While the hippocampus volume reductions in adulthood were maximal in women exposed to trauma between 3 and 5 years old, alterations of the corpus callosum were at the maximum when maltreatment occurred at 9 and 10 years of age, and alterations in the prefrontal cortex were maximal when trauma occurred at ages 14–16 years(127). Based on the above, we could hypothesize that the timing of environmental insults levied upon an (at-risk) individual during development may determine which biological pathways may be affected, and this, in combination with specific genetic vulnerability, could differentially affect circuit connectivity associated with positive, negative, manic, depressive(90). Epigenetics in the form of DNAm offers a good opportunity to address this question. In the same way that I explored the differential signature of abuse and neglect, exploring that of experiences occurring at various developmental windows of vulnerability is possible. This could lead to a better understanding of which biological pathways are epigenetically dysregulated as a consequence of childhood adversity, and how this can shine some additional light on the understanding of which biological processes are sensitive to CA at different periods (which would be a good addition to the new insights on the types of adversity addressed in this work).

In summary, more research expanding the findings in this Thesis, by considering the confounding effect of genetic and environmental exposure is needed, as well as examining how environmental insults occurring at various developmental periods can lead to DNAm in psychosis. This work will prove difficult and will require a large, prospective data set with curated evaluation of environmental risk factors at various periods of the lifespan, as well as a close collaboration between geneticist, neuroscientist, and psychiatrist in the planification of future studies.

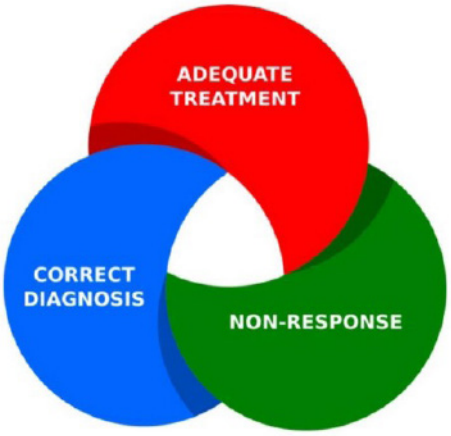
The mysterious role of childhood adversity in treatment resistant psychosis

The concept of TRS consists of the combination of three core components: 1) that correct psychiatric diagnosis has been made; 2) that a patient has received adequate treatment (in psychosis having received at least 2 antipsychotics with inadequate effect); and 3) that the symptoms have not adequately responded despite treatment (Figure 11). Different criteria exist to categorise the third criteria, but widely used is the one by Andreasen et al., (129) which proposed that a patient is not in remission if he or she presents a score of >=3/6 in the relevant items from the positive symptoms of psychosis of the PANSS. Persistence of symptoms despite treatment adequately addressed could be due to primary treatment resistance or, due to other factors, they give the impression of treatment resistance when in fact adequate treatment has not been received (pseudo-resistance). Pseudo resistance may be secondary to an incorrect primary diagnosis, comorbidity or

could be treatment related including, for example, treatment adherence, malabsorption of drug, poor blood brain barrier penetrance of drug, or fast metabolism of drug(19). Moreover, the concept of Ultra Treatment Resistant (UTR) is considered as persistence, in a TRS patient, of either positive, negative, or cognitive symptoms of schizophrenia of at least moderate severity after an adequate trial of Clozapine(130, 131)

Figure 11

Treatment resistance consists of three core components



The three components of treatment resistance as defined by Howes et al.,(19)

In light of this conceptualisation of TRS, our findings on the influence of abuse on severity of positive symptoms of psychosis (Ch 3.1 and Ch 3.3) suggest that CA can add additional levels of comorbid symptoms (depressive, dissociative etc ch. 3.1-3.3) therefore contributing to pseudo-resistance. For example, it could be that a patient with schizophrenia, correctly diagnosed, has also comorbid PTSD, or has low levels of depressive symptoms that are, if we believe our findings on mediation by depressive symptoms (Ch 3.2 and Ch 3.3), contributing to the persistence of positive symptoms, despite adequate treatment. If the influence of childhood adversity is not considered in this equation, the patient could continue receiving treatments for the positive symptoms, such as Clozapine at high doses (with its related complications), and if he continues not to respond, may even be considered as UTR and keep receiving other treatments involving polypharmacy or more invasive interventions such as ECT. Considering the pervasive indirect effect of childhood adversity in the equation, via the possible influence of the mediators, provides an additional therapeutic venue that could be targeted, as already described in Ch 3.2 (and the beginning of the discussion). Testing this hypothesis empirically is paramount and could help better understand not only the solutions for those with childhood adversity and psychosis but also with TRS.

From a pharmacological perspective, some developments in the field of TRS point at immune and inflammatory pathways(132) as potential alternatives to currents agents targeting the classic neurotransmitter systems (dopamine and to a lesser extent serotonin). This is driven by data supporting an immune/inflammatory dysregulation in the pathogenesis of some individuals with SCZ(133, 134). Individuals with childhood adversity have alterations in inflammatory and immune functions(135), and our work on DNAm (ch 4.1 – study 5) supports a possible role of DNAm dysregulation in genes involved in this pathway, as well as in the dopaminergic pathway. Therefore, also at a biological level, our advances in

the understanding of the impact of childhood adversity in psychosis at an epigenetic level can provide new biological targets for research, trying to understand the mechanisms underlying TRS. This potential new line of research will need to consider accounting for confounders such as cell composition and medication, in order to replicate our promising findings on immune and histaminergic pathways. It will be important in future, in turn, that research in the field of childhood adversity and psychosis also pays careful attention to the notion of TRS, for example measuring treatment adherence and providing a careful assessment of the medication prescribed (and taken), in order to know how many of those with high severity of symptoms and childhood adversity are actually TRS, or are patients that are just difficult to treat for other reasons.

Given the above, clinical trials attempting to test the efficacy of drugs targeting the positive symptoms of psychosis will remain limited without an adequate stratification of patients according to the traumatic level of exposure. We propose that childhood adversity, and its related ancillary symptoms (possible mediators(40)), should be systematically measured and taken into consideration when testing biological pathways in the effectiveness of people with psychosis and TRS, and that those with childhood adversity and persistence of symptoms are considered as a possible subgroup of those with TRS.

5.4 Conclusion

The current PhD represents a step forward in the understanding of the specific links between childhood adversity and psychosis. I show that abuse and neglect appear to be related to distinct psychopathological features in patients; I provide DNAm data supporting that different biological underpinning influenced by DNAm, as a consequence of adversity, could play a role in such different trajectories. I presented potential mediators that could be addressed in people with adversity in psychosis, highlighting the importance to address and treat the potential mediating pathways linking such association, such as low levels of depressive symptoms and anxiety. I propose that clinicians should consider all the putative possible mediators linking adversity-psychosis and integrate them in regular assessments and consider them as possible targets for treatment. Moreover, I show the presence of multiple genes that had previously been associated with SCZ in the context of DNAm in EWAS studies, therefore replicating findings and opening new venues for future research; and I confirm the presence of a dysregulation of DNAm in genes involved in the dopaminergic, glutamatergic, histaminergic, immune system and neural development, as possible mediating processes linking childhood adversity and psychosis; this replicates, with an hypothesis free approach, some of the hypotheses made based on our literature review. Lastly, I propose integrating the idea of childhood adversity into the understanding not only of severity of psychopathological outcomes but in the framework of treatment resistant schizophrenia, integrating our approach on assessment and treatment of mediators in this population as an alternative therapeutic tool, which deserves future development and empirical validation for clinical practise. Given the impact of abuse in

the persistence of positive symptoms of psychosis, I hypothesize that some of the DNAm changes associated to such adversity may be explored in the context of TRS.

References:

1. Koenen KC, Roberts AL, Stone DM, Dunn EC. The epidemiology of early childhood trauma. The impact of early life trauma on health and disease: The hidden epidemic. 2010;1.

2. Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. The British Journal of Psychiatry. 2010;197(5):378-85.

3. MacMillan HL, Fleming JE, Trocmé N, Boyle MH, Wong M, Racine YA, et al. Prevalence of child physical and sexual abuse in the community. Results from the Ontario Health Supplement. Jama. 1997;278(2):131-5.

4. Baglivio MT, Wolff KT, Epps N, Nelson R. Predicting adverse childhood experiences: The importance of neighborhood context in youth trauma among delinquent youth. Crime & Delinquency. 2017;63(2):166-88.

5. Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. Lancet. 2009;373(9657):68-81.

6. Romano E, Babchishin L, Marquis R, Fréchette S. Childhood Maltreatment and Educational Outcomes. Trauma Violence Abuse. 2015;16(4):418-37.

7. Habetha S, Bleich S, Weidenhammer J, Fegert JM. A prevalence-based approach to societal costs occurring in consequence of child abuse and neglect. Child Adolesc Psychiatry Ment Health. 2012;6(1):35.

8. Organization WH. The global burden of disease: 2004 update: World Health Organization; 2008.

9. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. New England journal of medicine. 2005;353(12):1209-23.

10. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007;64(10):1123-31.

11. Gayer-Anderson C, Jongsma HE, Di Forti M, Quattrone D, Velthorst E, de Haan L, et al. The EUropean Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI): Incidence and First-Episode Case-Control Programme. Social Psychiatry & Psychiatric Epidemiology. 2020;55(5):645-57.

12. Jongsma HE, Gayer-Anderson C, Lasalvia A, Quattrone D, Mulè A, Szöke A, et al. Treated incidence of psychotic disorders in the multinational EU-GEI study. JAMA psychiatry. 2018;75(1):36-46.

13. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophrenia bulletin. 2004;30(2):279-93.

14. Alameda L, Golay P, Baumann PS, Ferrari C, Do KQ, Conus P. Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. J Clin Psychiatry. 2016;77(5):e612-8.

15. Quattrone D, Di Forti M, Gayer-Anderson C, Ferraro L, Jongsma HE, Tripoli G, et al. Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study. Psychological medicine. 2018:1-14.

16. van Os J, Kapur S. Schizophrenia. Lancet. 2009;374(9690):635-45.

17. Kaiser S, Heekeren K, Simon JJ. The negative symptoms of schizophrenia: category or continuum? Psychopathology. 2011;44(6):345-53.

18. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry. 2016;15(2):118-24.

19. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. Mol Psychiatry. 2021.

20. Mizuno Y, McCutcheon RA, Brugger SP, Howes OD. Heterogeneity and efficacy of antipsychotic treatment for schizophrenia with or without treatment resistance: a meta-analysis. Neuropsychopharmacology. 2020;45(4):622-31.

21. Turner DT, Burger S, Smit F, Valmaggia LR, van der Gaag M. What constitutes sufficient evidence for case formulation–driven CBT for psychosis? Cumulative meta-analysis of the effect on hallucinations and delusions. Schizophrenia bulletin. 2020;46(5):1072-85.

22. Degnan A, Baker S, Edge D, Nottidge W, Noke M, Press C, et al. The nature and efficacy of culturally-adapted psychosocial interventions for schizophrenia: a systematic review and meta-analysis. Psychological Medicine. 2018;48(5):714-27.

23. van Os J, Rutten BP, Myin-Germeys I, Delespaul P, Viechtbauer W, van Zelst C, et al. Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr Bull. 2014;40(4):729-36.

24. Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, et al. What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry. 2018;17(1):49-66.

25. Rodriguez V, Alameda L, Trotta G, Spinazzola E, Marino P, Matheson SL, et al. Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies. Schizophr Bull. 2021.

26. Söderström D. Entre psychose et trauma: perspectives psychanalytiques Médicine & Hygiène. 2009;29(3):145-55.

27. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull. 2012;38(4):661-71.

28. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. Lancet. 2014;383(9929):1677-87.

29. Alameda L, Ferrari C, Baumann PS, Gholam-Rezaee M, Do KQ, Conus P. Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. Psychol Med. 2015;45(13):2727-36.

30. Rodriguez V, Aas M, Vorontsova N, Trotta G, Gadelrab R, Rooprai NK, et al. Exploring the Interplay Between Adversity, Neurocognition, Social Cognition, and Functional Outcome in People With Psychosis: A Narrative Review. Front Psychiatry. 2021;12:596949.

31. Tomassi S, Tosato S, Mondelli V, Faravelli C, Lasalvia A, Fioravanti G, et al. Influence of childhood trauma on diagnosis and substance use in first-episode psychosis. The British Journal of Psychiatry. 2017;211(3):151-6.

32. Conus P, Cotton S, Schimmelmann BG, McGorry PD, Lambert M. Pretreatment and outcome correlates of sexual and physical trauma in an epidemiological cohort of first-episode psychosis patients. Schizophr Bull. 2010;36(6):1105-14.

33. Bailey T, Alvarez-Jimenez M, Garcia-Sanchez AM, Hulbert C, Barlow E, Bendall S. Childhood trauma is associated with severity of hallucinations and delusions in psychotic disorders: a systematic review and meta-analysis. Schizophrenia bulletin. 2018;44(5):1111-22.

34. Isvoranu AM, van Borkulo CD, Boyette LL, Wigman JT, Vinkers CH, Borsboom D, et al. A Network Approach to Psychosis: Pathways Between Childhood Trauma and Psychotic Symptoms. Schizophr Bull. 2017;43(1):187-96.

35. Hardy A. Pathways from trauma to psychotic experiences: a theoretically informed model of posttraumatic stress in psychosis. Frontiers in psychology. 2017;8:697.

36. Morrison AP, Frame L, Larkin W. Relationships between trauma and psychosis: A review and integration. British Journal of Clinical Psychology. 2003;42(4):331-53.

37. Fisher HL, Schreier A, Zammit S, Maughan B, Munafo MR, Lewis G, et al. Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth

cohort. Schizophr Bull. 2013;39(5):1045-55.

38. Bretherton I. The origins of attachment theory: John Bowlby and Mary Ainsworth. Developmental psychology. 1992;28(5):759.

39. Sheinbaum T, Kwapil TR, Barrantes-Vidal N. Fearful attachment mediates the association of childhood trauma with schizotypy and psychotic-like experiences. Psychiatry research. 2014;220(1):691-3.

40. Bebbington P. Unravelling psychosis: psychosocial epidemiology, mechanism, and meaning. Shanghai archives of psychiatry. 2015;27(2):70-81.

41. Venkatasubramanian G, Keshavan MS. Biomarkers in psychiatry-a critique. Annals of neurosciences. 2016;23(1):3.

42. Teicher MH, Anderson CM, Polcari A. Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. Proc Natl Acad Sci U S A. 2012;109.

43. Aas M, Navari S, Gibbs A, Mondelli V, Fisher HL, Morgan C, et al. Is there a link between childhood trauma, cognition, and amygdala and hippocampus volume in first-episode psychosis? Schizophr Res. 2012;137(1-3):73-9.

44. Aas M, Haukvik UK, Djurovic S, Bergmann Ø, Athanasiu L, Tesli MS, et al. BDNF val66met modulates the association between childhood trauma, cognitive and brain abnormalities in psychoses. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2013;46:181-8.

45. Morgan C, Gayer-Anderson C. Childhood adversities and psychosis: evidence, challenges, implications. World Psychiatry. 2016;15(2):93-102.

46. Dahoun T, Nour MM, McCutcheon RA, Adams RA, Bloomfield MA, Howes OD. The relationship between childhood trauma, dopamine release and dexamphetamine-induced positive psychotic symptoms: a [11 C]-(+)-PHNO PET study. Translational psychiatry. 2019;9(1):1-12.

47. Alameda L, Fournier M, Khadimallah I, Griffa A, Cleusix M, Jenni R, et al. Redox dysregulation as a link between childhood trauma and psychopathological and neurocognitive profile in patients with early psychosis. Proceedings of the National Academy of Sciences. 2018;115(49):12495-500.

48. Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, et al. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Archives of pediatrics & adolescent medicine. 2009;163(12):1135-43.

49. Murray R, Mondelli V, Stilo S, Trotta A, Sideli L, Ajnakina O, et al. The influence of risk factors on the onset and outcome of psychosis: What we learned from the GAP study. Schizophrenia Research. 2020.

50. Ripke S, Neale BM, Corvin A, Walters JT, Farh K-H, Holmans PA, et al. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421-7.

51. Van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophrenia bulletin. 2008;34(6):1066-82.

52. Trotta A, Iyegbe C, Yiend J, Dazzan P, David AS, Pariante C, et al. Interaction between childhood adversity and functional polymorphisms in the dopamine pathway on first-episode psychosis. Schizophrenia research. 2019;205:51-7.

53. Modinos G, Iyegbe C, Prata D, Rivera M, Kempton MJ, Valmaggia LR, et al. Molecular genetic gene-environment studies using candidate genes in schizophrenia: a systematic review. Schizophrenia research. 2013;150(2-3):356-65.

54. Aas M, Haukvik UK, Djurovic S, Tesli M, Athanasiu L, Bjella T, et al. Interplay between childhood trauma and BDNF val66met variants on blood BDNF mRNA levels and on hippocampus subfields volumes in schizophrenia spectrum and bipolar disorders. J Psychiatr Res. 2014.

55. Vassos E, Di Forti M, Coleman J, Iyegbe C, Prata D, Euesden J, et al. An Examination of Polygenic Score Risk Prediction in Individuals With First-Episode Psychosis. Biol Psychiatry. 2017;81(6):470-7.

56. Arango C. Candidate gene associations studies in psychiatry: time to move forward. Eur Arch Psychiatry Clin Neurosci. 2017;267(1):1-2.

57. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460(7256):748-52.

58. Dudbridge F. Power and predictive accuracy of polygenic risk scores. PLoS Genet. 2013;9(3):e1003348.

59. Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, et al. Publisher Correction: Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet. 2019;51(7):1193.

60. Schizophrenia Working Group of the Psychiatric Genomics C RS, Neale BM, et al. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421-7.

61. Guloksuz S, Pries LK, Delespaul P, Kenis G, Luykx JJ, Lin BD, et al. Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EU-GEI study. World Psychiatry. 2019;18(2):173-82.

62. Trotta A, Iyegbe C, Di Forti M, Sham PC, Campbell DD, Cherny SS, et al. Interplay between Schizophrenia Polygenic Risk Score and Childhood Adversity in First-Presentation Psychotic Disorder: A Pilot Study. PLoS One. 2016;11(9):e0163319.

63. Aas M, Alameda L, Di Forti M, Quattrone D, Dazzan P, Trotta A, et al. Synergistic effects of childhood adversity and polygenic risk in first-episode psychosis: the EU-GEI study. Psychological Medicine. 2021:1-9.

64. Binder EB. Dissecting the molecular mechanisms of gene x environment interactions: implications for diagnosis and treatment of stress-related psychiatric disorders. European journal of psychotraumatology. 2017;8(sup5):1412745.

65. Henikoff S, Matzke MA. Exploring and explaining epigenetic effects. Trends in genetics: TIG. 1997;13(8):293-5.

66. Baedke J. The epigenetic landscape in the course of time: Conrad Hal Waddington's methodological impact on the life sciences. Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences. 2013;44(4):756-73.

67. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nature genetics. 2003;33 Suppl:245-54.

68. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013;38(1):23-38.

69. Vaquero A, Loyola A, Reinberg D. The constantly changing face of chromatin. Science of aging knowledge environment. 2003;2003(14):4.

70. Campbell RR, Wood MA. How the epigenome integrates information and reshapes the synapse. Nature Reviews Neuroscience. 2019;20(3):133-47.

71. Laurent GS, Wahlestedt C, Kapranov P. The Landscape of long noncoding RNA classification. Trends in genetics. 2015;31(5):239-51.

72. Yao Q, Chen Y, Zhou X. The roles of microRNAs in epigenetic regulation. Current opinion in chemical biology. 2019;51:11-7.

73. Mill J, Tang T, Kaminsky Z, Khare T, Yazdanpanah S, Bouchard L, et al. Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. American journal of human genetics. 2008;82(3):696-711.

74. Rakyan VK, Down TA, Balding DJ, Beck S. Epigenome-wide association studies for common human diseases. Nature reviews Genetics. 2011;12(8):529-41.

75. Yong WS, Hsu FM, Chen PY. Profiling genome-wide DNA methylation. Epigenetics Chromatin. 2016;9:26.

76. Provençal N, Binder EB. The effects of early life stress on the epigenome: from the womb to adulthood and even before. Experimental neurology. 2015;268:10-20.

77. Zhang Y, Kutateladze TG. Diet and the epigenome. Nature communications. 2018;9(1):1-3.

78. Alfano R, Herceg Z, Nawrot TS, Chadeau-Hyam M, Ghantous A, Plusquin M. The impact of air pollution on our epigenome: how far is the evidence?(A systematic review). Current environmental health reports. 2018;5(4):544-78.

79. Markunas CA, Hancock DB, Xu Z, Quach BC, Fang F, Sandler DP, et al. Epigenome-wide analysis uncovers a blood-based DNA methylation biomarker of lifetime cannabis use. Am J Med Genet B Neuropsychiatr Genet. 2020.

80. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nat Neurosci. 2004;7(8):847-54.

81. Perroud N, Paoloni-Giacobino A, Prada P, Olie E, Salzmann A, Nicastro R. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Transl Psychiatry. 2011;1.

82. Kandaswamy R, Hannon E, Arseneault L, Mansell G, Sugden K, Williams B, et al. DNA methylation signatures of adolescent victimization: analysis of a longitudinal monozygotic twin sample. Epigenetics. 2020:1-18.

83. Marzi SJ, Sugden K, Arseneault L, Belsky DW, Burrage J, Corcoran DL, et al. Analysis of DNA Methylation in Young People: Limited Evidence for an Association Between Victimization Stress and Epigenetic Variation in Blood. Am J Psychiatry. 2018:appiajp201717060693.

84. Juruena MF, Gadelrab R, Cleare AJ, Young AH. Epigenetics: A missing link between early life stress and depression. Progress in neuro-psychopharmacology & biological psychiatry. 2020:110231.

85. Hübel C, Marzi SJ, Breen G, Bulik CM. Epigenetics in eating disorders: a systematic review. Mol Psychiatry. 2019;24(6):901-15.

86. Keverne J, Binder EB. A Review of epigenetics in psychiatry: focus on environmental risk factors. Medizinische Genetik. 2020;32(1):57-64.

87. Provenzi L, Giorda R, Beri S, Montirosso R. SLC6A4 methylation as an epigenetic marker of life adversity exposures in humans: A systematic review of literature. Neuroscience & Biobehavioral Reviews. 2016;71(Supplement C):7-20.

88. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World Psychiatry. 2020;19(1):15-33.

89. Cullen AE, Holmes S, Pollak TA, Blackman G, Joyce DW, Kempton MJ, et al. Associations between non-neurological autoimmune disorders and psychosis: a meta-analysis. Biological psychiatry. 2019;85(1):35-48.

90. Steullet P, Cabungcal J, Monin A, Dwir D, O'Donnell P, Cuenod M, et al. Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: a "central hub" in schizophrenia pathophysiology? Schizophrenia research. 2016;176(1):41-51.

91. Claudino FCDA, Gonçalves L, Schuch FB, Martins HRS, Rocha N. The effects of individual psychotherapy in BDNF levels of patients with mental disorders: A systematic review. Frontiers in Psychiatry. 2020;11:445.

92. Hardingham GE, Do KQ. Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. Nat Rev Neurosci. 2016;17(2):125-34.

93. Pariante CM. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2017;27(6):554-9.

94. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci. 2013;16.

95. Gaunt TR, Shihab HA, Hemani G, Min JL, Woodward G, Lyttleton O, et al. Systematic identification of genetic influences on methylation across the human life course. Genome biology. 2016;17(1):61.

96. South SC, Schafer MH, Ferraro KF. Genetic and environmental overlap between childhood maltreatment and adult physical health. Twin research and human genetics. 2015;18(5):533-44.

97. Hannon E, Dempster EL, Mansell G, Burrage J, Bass N, Bohlken MM, et al. DNA methylation meta-analysis reveals cellular alterations in psychosis and markers of treatment-resistant schizophrenia. eLife. 2021;10.

98. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology. 2010;25(9):603-5.

99. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis version 2. Englewood, NJ: Biostat. 2005;104.

100. Power P, McGuire P, Iacoponi E, Garety P, Morris E, Valmaggia L, et al. Lambeth Early Onset (LEO) and outreach & support in south London (OASIS) service. Early Intervention in Psychiatry. 2007;1(1):97-103.

101. Howes OD, Whitehurst T, Shatalina E, Townsend L, Onwordi EC, Mak TLA, et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. World Psychiatry. 2021;20(1):75-95.

102. Bertolote J, McGorry P. Early intervention and recovery for young people with early psychosis: consensus statement. The British Journal of Psychiatry. 2005;187(S48):s116-s9.

103. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. The Australian and New Zealand journal of psychiatry. 2005;39(11-12):964-71.

104. Baumann PS, Crespi S, Marion-Veyron R, Solida A, Thonney J, Favrod J, et al. Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. Early Interv Psychiatry. 2013;7(3):322-8.

105. Alameda L, Christy A, Rodriguez V, Salazar de Pablo G, Thrush M, Shen Y, et al. Association Between Specific Childhood Adversities and Symptom Dimensions in People With Psychosis: Systematic Review and Meta-Analysis. Schizophr Bull. 2021.

106. Hassan AN, De Luca V. The effect of lifetime adversities on resistance to antipsychotic treatment in schizophrenia patients. Schizophr Res. 2015;161(2-3):496-500.

107. Koga A, Bani-Fatemi A, Hettige N, Borlido C, Zai C, Strauss J, et al. GWAS analysis of treatment resistant schizophrenia: interaction effect of childhood trauma. Pharmacogenomics. 2017;18(7):663-71.

108. Rajkumar A, Chitra C, Bhuvaneshwari S, Poonkuzhali B, Kuruvilla A, Jacob K. Clinical predictors of response to clozapine in patients with treatment resistant schizophrenia. Psychopharmacology Bulletin. 2011;44(3):51.

109. Tiihonen J, Wahlbeck K, Kiviniemi V. The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. Schizophrenia research. 2009;109(1-3):10-4.

110. Fleischhacker WW, Heikkinen ME, Olié J-P, Landsberg W, Dewaele P, McQuade RD, et al. Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind,

placebo-controlled trial. The The International Journal of Neuropsychopharmacology. 2010;13(8):1115-25.

111. Barnes TR, Leeson VC, Paton C, Marston L, Davies L, Whittaker W, et al. Amisulpride augmentation in clozapine-unresponsive schizophrenia (AMICUS): a double-blind, placebo-controlled, randomised trial of clinical effectiveness and cost-effectiveness. Health Technology Assessment. 2017;21(49).

112. Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. American Journal of Psychiatry. 2015;172(1):52-8.

113. Callaly E, Walder K, Morris G, Maes M, Debnath M, Berk M. Mitochondrial dysfunction in the pathophysiology of bipolar disorder: effects of pharmacotherapy. Mini reviews in medicinal chemistry. 2015;15(5):355-65.

114. Ni P, Chung S. Mitochondrial dysfunction in schizophrenia. BioEssays : news and reviews in molecular, cellular and developmental biology. 2020;42(6):1900202.

115. Sharma N, Pasala MS, Prakash A. Mitochondrial DNA: Epigenetics and environment. Environmental and molecular mutagenesis. 2019;60(8):668-82.

116. Plomin R. Blueprint: How DNA makes us who we are: Mit Press; 2018.

117. Maynard TM, Sikich L, Lieberman JA, LaMantia A-S. Neural development, cell-cell signaling, and the "two-hit" hypothesis of schizophrenia. Schizophrenia bulletin. 2001;27(3):457-76.

118. Pries L-K, Erzin G, Rutten BP, van Os J, Guloksuz S. Estimating aggregate environmental risk score in psychiatry: the exposome score for schizophrenia. Frontiers in Psychiatry. 2021;12.

119. Vassos E, Sham P, Kempton M, Trotta A, Stilo SA, Gayer-Anderson C, et al. The Maudsley environmental risk score for psychosis. Psychological medicine. 2020;50(13):2213-20.

120. Bell JT, Pai AA, Pickrell JK, Gaffney DJ, Pique-Regi R, Degner JF, et al. DNA methylation patterns associate with genetic and gene expression variation in HapMap cell lines. Genome biology. 2011;12(1):1-13.

121. Bjornsson HT, Sigurdsson MI, Fallin MD, Irizarry RA, Aspelund T, Cui H, et al. Intra-individual change over time in DNA methylation with familial clustering. Jama. 2008;299(24):2877-83.

122. Kaminsky ZA, Tang T, Wang S-C, Ptak C, Oh GH, Wong AH, et al. DNA methylation profiles in monozygotic and dizygotic twins. Nature genetics. 2009;41(2):240-5.

123. Steullet P, Cabungcal JH, Monin A, Dwir D, O'Donnell P, Cuenod M, et al. Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A "central hub" in schizophrenia pathophysiology? Schizophr Res. 2016;176(1):41-51.

124. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. American Journal of Psychiatry. 2013;170(10):1114-33.

125. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. Nature. 2010;468(7321):203-12.

126. Pechtel P, Lyons-Ruth K, Anderson CM, Teicher MH. Sensitive periods of amygdala development: the role of maltreatment in preadolescence. NeuroImage. 2014;97:236-44.

127. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci. 2016;17(10):652-66.

128. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10(6):434-45.

129. Andreasen NC, Carpenter Jr WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. American Journal of Psychiatry. 2005;162(3):441-9.

130. Howes OD, McCutcheon R, Agid O, De Bartolomeis A, Van Beveren NJ, Birnbaum ML, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. American Journal of Psychiatry. 2017;174(3):216-29.

131. Campana M, Falkai P, Siskind D, Hasan A, Wagner E. Characteristics and definitions of ultra-treatment-resistant schizophrenia–A systematic review and meta-analysis. Schizophrenia Research. 2021;228:218-26.

132. Howes OD, McCutcheon R. Inflammation and the neural diathesis-stress hypothesis of schizophrenia: a reconceptualization. Transl Psychiatry. 2017;7(2):e1024.

133. Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, Giordano A, et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. Schizophrenia bulletin. 2015;41(5):1162-70.

134. Fillman S, Weickert T, Lenroot R, Catts S, Bruggemann J, Catts V, et al. Elevated peripheral cytokines characterize a subgroup of people with schizophrenia displaying poor verbal fluency and reduced Broca's area volume. Molecular psychiatry. 2016;21(8):1090-8.

135. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Molecular psychiatry. 2016;21(5):642-9.

APPENDIX

Study 2
Supplementary material

1. **Supplementary methods**
   a. Search Strategy
   b. Data extraction procedures
   c. Quality assessment procedures

2. **Supplementary Tables**
   a. Table S1a. Overview of clinical studies included in this review
   b. Table S1b Overview of General population studies included in this review
   c. Table S1c. Overview of clinical studies examining biological mediators between childhood adversity and psychosis
   d. Table S2. Summary of evidence for mediators within the Dissociation category between adversity and psychosis

3. **Supplementary Figures**
   a. Figure S1. Flow chart

4. **Supplementary references**

1. Supplementary Methods

a. Search Strategy

The present analyses did not consider separation from parents, abandonment and parental loss given the heterogenous definitions used to describe such type of adversities across studies.

Titles and abstracts of articles were screened independently by three reviewers (LA and VR for psychological articles and LA and MA for biological articles, with 95% and 85% agreement; agreement was considered when equal quality assessment scores were). Discrepancies were resolved through discussion at a project group meeting.

Parallelly, a cross-reference search extracting title/abstract from identified reviews plus full-text check of potential additional eligible studies from these reviews was performed by two different authors (PM and GT).

(EMBASE, Psyinfo and MEDLINE through Ovid provider, and Cochrane Libraries through Cochrane website)

Childhood adversity terms

108. sexual abuse.mp.
109. physical abuse.mp.
110. emotional abuse.mp.
114. psychological abuse.mp.
117. maltreat.mp.*
118. bully.mp.*
119. bullied.mp.
123. parental loss.mp.
124. (Separation adj5 parent).mp.
138. childhood trauma.mp.
139. early trauma.mp.
155. Neglect.mp.*
156. (trauma adj5 experienc*).mp.*
160. adversit.mp.*
161. (advers adj5 experienc*).mp.*
233. exp Child Abuse/
234. exp Physical Abuse/
235. exp Sexual Abuse/
236. exp Emotional Abuse/
237. exp Child Neglect/
238. exp Emotional Trauma/
239. exp BULLYING/
240. exp Parental Absence/
241. exp RAPE/

242. exp Domestic Violence/
243. exp Victimization/

Mediation terms

127. mediat.mp.*
130. (psycholog adj3 mechanism*).mp.*
131. (biolog adj3 mechanism*).mp.*
143. path analysis.mp
157. network analysis.mp.
170. structural equation.mp.
171. path analysis.mp
246. exp MEDIATION/
247. exp Structural Equation Modeling/
248. exp Path Analysis/

Psychosis terms

87. psychosis.mp.
88. psychot.mp.*
100. schizophr.mp.*
101. schizotyp.mp.*
102. hallucinat.mp.*
103. parano.mp.*
104. delusion.mp.*
105. persecut.mp.*
167. (disorganiz adj5 symptom*).mp.*
168. (disorganiz adj5 dimension*).mp.*
251. exp PSYCHOSIS/
252. exp SCHIZOPHRENIA/
253. exp CHILDHOOD SCHIZOPHRENIA/
254. exp SCHIZOTYPY/
255. exp HALLUCINATIONS/
256. exp PARANOIA/
257. exp DELUSIONS/
258. exp PERSECUTION/

b. Data extraction procedures

Definition of the different types of mediating effects

Null mediation was considered as the situation in which the indirect or mediating effect is not statistically significant ($p>0.05$). "Partial mediation" is the situation in which the path between adversity and psychosis (also called the direct effect) is reduced but still statistically significant when the mediator is introduced. "Total mediation" describes the case were the path between adversity and psychosis (direct effect) is no longer significant after the introduction of the mediating variable. "Suggested mediation" was considered when

the indirect (or mediating) effect were reported but not the direct effects, not allowing us to determine whether the mediation was total or partial. "Suggested mediation" was also considered in a subset of studies using a regression-based approach, in which an important reduction of the total effect occurred once the mediator was included in the model. Studies including this type of scenario were also considered but where rated and methodologically less robust (section "Assessment of outcome" from the Newcastle Ottawa Scale as described above) than the ones testing mediation with mediation analyses, path analyses, structural equation models (SEM)) and providing the direct and indirect effects. Data extraction was performed in duplicate (50% of papers by LA and GT and 50% by LA and PM).

Estimation of the percentage of total effect mediated

This measure is the proportion of the total effect that is accounted for by the pathway through the mediating variable. Despite reported by authors in most of the papers; when this information was not given, we estimated the percentage by dividing the indirect (or mediating effect) by the total effect (shown in coefficients) and multiplying it by 100 according to previous published studies (Alwin and Hauser, 1975). When results were reported in odd rations, and not in coefficients, these were transformed into log odds before calculating the percentage. Authors were contacted when provided data was not enough to extract as exposed. We managed to obtain this information for 83.1% of the analyses that found a significant indirect effect, details are provided in Figure 2 footnote and the percentage of total effect mediated can also be found in detailed Tables S1a, S1b and S1c.
Estimation of the proportion of analyses showing evidence of mediation
In Tabes 1, 2, 3 and Table S2, as well as in the text we provided the "percentage of analyses showing evidence of mediation", across all categories of mediators. We considered that one analysis showed evidence of mediation when authors reported significant p-values (<0.05) in the indirect (or mediating) effects, or when using a regression-based approach, an important reduction of the total effect occurred once the mediator was included in the model. This allowed us to provide the percentage of analyses supporting mediation per category (as an example: for dissociation in general population there were 17 pathways tested across 6 different studies, 12 of them were supportive of mediation and 5 were not, thus 70% (12/17) of analyses were supportive of mediation through dissociation in the general population).

c. Quality assessment procedures

The quality assessment was carried out using the Newcastle–Ottawa Scale (see Quality Assessment Tool (Stang, 2010)) for cohort studies by two independent reviewers (LA and PM). Those papers over which there was disagreement were discussed at a project group meeting. The Newcastle–Ottawa is a ten-point scale allocating points based on: the selection of cohorts (e.g. representativeness of the sample; 0–4 points), the comparability of cohorts (e.g. whether the study controls for confounding factors; 0–2 points), the identification of the exposure (e.g. objectivity of exposure measurement) and the outcomes of

study participants (e.g. independence of outcome measurement, adequacy of follow-up; 0–3 points). Scores were considered as follows: "poor" quality for 3 or less; "fair" between 4 and 7 and "good" for scores of 8 or above. The agreed quality grades of each study are presented in Table S1 and the specific criteria used for our systematic review are specified in the Newcastle Ottawa Scale displayed below.

Newcastle Ottawa Scale Selection

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

1. **Representativeness of the exposed cohort**
   1) truly representative of the average individuals with psychosis or attenuated psychotic symptoms in the community *
   2) somewhat representative of the average individuals with psychosis or attenuated psychotic symptoms in the community *
   3) selected group of users eg nurses, volunteers
   4) no description of the derivation of the cohort

2. **Selection of the non exposed cohort**
   1) drawn from the same community as the exposed cohort *
   2) drawn from a different source
   3) no description of the derivation of the non-exposed cohort

3. **Ascertainment of exposure**
   1) secure record*
   2) structured interview*
   3) written self-report* (star included here given the common use of self-reports in the field of adversity in psychosis)
   4) no description

4. **Demonstration that outcome of interest was not present at start of study**
   1) yes * (here we considered a start when the mediator was not present at the time of the assessment to traumatic experiences)
   2) no Comparability

5. **Comparability of cohorts on the basis of the design or analysis**
   1) study controls for confounders *
   2) study controls for any additional factor (we considered a start here if studies used a robust method of adjustment for multiple comparison such as bootstrapping)

6. **Outcome**
    1) Assessment of outcome
        a. independent blind assessment *
        b. record linkage *
        c. self-report
        d. no description

7. (in this section we considered none star if studies did not report the indirect and direct effects nor the percentage of total effect mediated. One start if they reported that information partially and two stars if they provided that information fully)

8. Was follow-up long enough for outcomes to occur
    1) yes (if follow-up longer than 6 months) *
    2) no

9. Adequacy of follow up of cohorts
    1) complete follow up - all subjects accounted for *
    2) subjects lost to follow up unlikely to introduce bias - small number lost - > 20 %
    3) follow up rate < 80%) and no description of those lost
    4) no statement

1. Supplementary Tables

Table S1a.

Overview of clinical studies included in this review

Authors Country	Sample Mean Age % female	Design	Measures of childhood adversity	Mediator(s)	Analysis	Boostrap (yes / no) / confounders (yes / no)	Psychosis	Main findings Pathway Total / partial mediation Direct Effect (DE) Indirect effect (IE) % total effect mediated	Quality Score
Appiah-Kusi *et al.* (2017) **UK**	30 UHR; 38 HC 23.9 56.7%	Cross sectional Case control study	EA CTQ	(1) Schematic beliefs (BCSS) 1.a - Negative Self-schemas (NSS)	Regression based approach	Yes Yes (Cannabis use, depression, anxiety)	(1) UHR caseness (2) Paranoia (PSQ)	**EN → BCSS → UHR** Partial mediation (DE = 0.261*; IE = 0.045*) % = 14.7 **EN → BCSS → PSQ** Partial mediation (DE = 1.353*; IE = 0.988*) % = 42.2 Other adversities were not related to outcomes so were not included for mediation analyses	6
Chatziioannidis *et al.* (2019) **Switzerland**	63 SSP; 61 HC 44.4 SSP 30.16% SSP 39.33 HC 29.5% HC	Cross sectional Case control study	Composite CECA.Q	(1) Attachment (ECR-R) 1.a - Avoidance 1.b - Anxiety	Parallel Multiple mediation model	Yes Yes (education)	(A) Caseness (SSP) (MINI)	**CT → 1.b → SSP** Partial mediation (DE = 1.70*; IE = 1.24*) % = 41.9 No significant mediation of attachment avoidance between CT and SSP	6
Choi Ji *et al.* (2015) **Republic of Korea**	126 psychosis 36.1 55.6%	Cross sectional	Composite abuse (CA) Korean CTQ	(1) Posttraumatic stress symptoms (IESR)	SEM	No No	(1) Psychotic symptoms (PS) PSYCH subscale of the PSY-5 factor scale of MMPI-2	**CA → IESR → PS** Partial mediation (DE = 0.30*; IE = 0.171*) % = 36.3	4

Evans *et al.* (2015) **UK**	29 EP; 31 HC 18-38 EP 34.5% EP NA HC 38.7% HC	Cross sectional Case control study	Composite and subscales (SA, PA, EA, PN, EN) CTQ	(1) The Self-Concept Clarity Scale (SCCS) (2) Dissociation (DES-II)	Mediation analysis	Yes No	(1) Caseness (PANSS)	**EN → SCCS → 1** Total mediation (DE = 0.033; IE = 0.157*) % = 82.8 None of the other total effects were significant so no mediation was possible The remaining pathways between EN and caseness through SCCS and DES were not significant	5
Hardy *et al.* (2016) **UK**	228 psychosis 38.2 27.6%	Cross sectional	Childhood sexual abuse (SA), childhood physical abuse (PA) Childhood emotional abuse (EA) THQ	(1) PTSD symptoms (SRS-PTSD) 1.a - Avoidace & Numbing 1.b - Hyperarousal 1.c - Intrusive trauma memory (2) Cognitive bias / schemas (BCSS) 2.a - Negative others beliefs	Mediation analysis	No Yes (age, gender and ethnicity	(A) Positive symptoms A.1 - Auditory hallucinations A.2 - Persecutory hallucinations A.3 - Ideas of reference	**SA → 1.a → A.1** Total mediation (DE = 2.052; IE = 1.475*) % = 48.74 **SA → 1.b → A.1** Total mediation (DE = 2.104; IE = 1.439*) % = 47.5 **EA → 2.a → A.2** Total mediation (DE = 1.889; IE = 1.359*) % = 52.9 Non-significant mediating effects of CSA with A1 through 2.a; CEA with A.3 through 2.a and CSA with A.1 through 1.c	5
Isvoranu *et al.* (2017) **Netherlands**	552 psychosis 30.76 25%	Cross sectional	SA, PA, EA, PN, EN CTQ	(1) 18 items from general psychopathology (PANSS)	Network based analysis	No Yes (all PANSS items)	(1) 6 items from positive dimension (PANSS)	Suggested mediation in pathways: **1) EA → Anxiety → paranoia / suspiciousness** **2) PA → impulse control → grandiosity / excitement / hostility** **3) PN → motor retardation → Negative symptoms** % = N/A	4

McDonnell *et al.* (2018) **UK**	64 UHR 22.5 40.6%	Cross sectional	Bullying severity in childhood / adolescence (BS) RBQ	(1) Interpersonal sensitivity (IS) (IPSM)	Path analysis	Yes No	(1) Paranoid ideation (PI) (SSPS)	**BS (Childhood) → IS → PI** Total mediation (DE = 0.131; IE = 0.129*) % = 49.6 Bullying in adolescence was not significantly associated with paranoid ideation	5
Morgan *et al.* (2014) **UK**	390 FEP; 391 HC 30.5 44.1%	Cross sectional Case control study	Parental separation / death MRC	(1) Self-Esteem (RSES)	Multiple mediation analyses	Yes Yes (age, gender, ethnicity, study centre, parental history of psychosis and IQ)	(1) FEP caseness based on ICD-10	Null mediation	6
Peach *et al.* (2019) **Australia**	66 FEP 20.18 54.5%	Cross sectional	Composite CTQ	(1) Post traumatic intrusions (CAPS) (2) Trauma related beliefs (PTCI)	Simple mediation analyses	Yes No	(A) Hallucinations (PANSS) (B) Delusions (PANSS)	**CT → CAPS → A** Total mediation (DE = 0.01; IE = 0.01*) % = 50 **CT → CAPS → B** Total mediation (DE = 0.01; IE = 0.02*) % = 66.6 **CT → PTCI → A** Total mediation (DE = 0.01; IE = 0.01*) % = 50 **CT → PTCI → B** Total mediation (DE = 0.01; IE = 0.02*) % = 66.6	5

Perona-Garcelán *et al.* (2012) Spain	71 psychosis 39.1 31.5%	Cross sectional	Composite TQ	(1) Dissociation (DES-II) 1.a - Dissociative Amnesia (DAM) 1.b - Absorption and Imaginative Involvement (ABI) 1.c – Depersonalization / Derealization (DP)	Simple and multiple mediation analysis	Yes No	(1) Hallucinations (PANSS) (2) Delusion (PANSS)	**TQ → DES → hallucinations** Total mediation (DE = 0.20; IE = 0.21*) % = 51.2 **TQ → DP → hallucinations** Total mediation (DE = 0.20; IE = 0.19*) % = 46.3 No mediating effects on delusions or mediating effects of ABI, DAM on hallucinations	5
Schalinski *et al.* (2019) Germany	180 psychosis 28.6 31.7%	Cross sectional Case control study	Composite (CT) and specific (abuse, neglect, neglect age 10) MACE	(1) Dissociation (SDS)	Mediation Analysis	Yes Yes (age, gender)	(1) Psychotic symptoms (PANSS)	**CT → SDS → positive symptoms** Total mediation (DE = 0.20; IE = 0.07*) % = 25.9 No mediating effects with specific trauma subscales	6
Steenkamp *et al.* (2019) Netherlands	50 NAP 31.8 42.4%	Cross sectional	Composite abuse (CA) CECA.Q	(1) Loneliness (ESM) (2) Depressive symptoms (ESM) (3) Anxious Symptoms (ESM)	SEM	No No	(A) Positive symptoms (ESM)	**CA → 1 → A** Total mediation (DE = -0.01; IE = 0.08*) % = 11.9 No significant indirect effect of CT on positive symptoms through depressive or anxious feelings	4
Styla *et al.* (2019) Poland	45 SCZ 45 HC 42.4 SCZ 48.9% SCZ 41.78 HC 46.7% HC	Cross sectional Case control study	Composite Childhood adversities (CA) CEQ	(1) Time Perspective (TP) (ZTPI)	Mediation analyses	Yes Yes (education)	Caseness (SCZ) based on ICD-10	**CA → TP → SCZ** Total mediation (DE = 0.352; IE = 0.249*) % = 37	6
Sun *et al.* (2018) Australia	66 FEP 20.18 54.5%	Cross sectional	Composite and Binary CTQ	(1) Dissociation (SCID-D-R)	Simple mediation analyses	Yes No	(1) Positive symptoms (PANSS) 1.a - Hallucinations 1.b - Delusions	**CTQ → SCID-D-R → 1.b** Total mediation (DE = 0.01; IE = 0.02*) % = 66.6 Non-significant mediation of dissociation between Ct and hallucinations	5

Thompson *et al.* (2016) Australia	233 UHR 18.5 at baseline 48.8%	Prospective. Mean of 7.0 years (SD 3.2) follow-up	Sexual trauma (ST) score CTQ	(1) Anxiety (2) Depression (3) Dissociation (4) Mood swings (5) Mania (HAM-A, CAARMS)	Mediation analysis	No No	(1) Transition to psychotic disorder Based on CAARMS BPRS	Null mediation	6
Van Dam *et al.* (2014) USA	131 psychosis 31.2 16%	Cross sectional	Composite CTQ	(1) Attachment (PAM) 1.a - Avoidant 1.b - Anxiety	Regressions analyses following Baron and Kenny criteria	No Yes (age and gender)	(1) Positive symptoms (SAPS)	Null mediation	4
Varese *et al.* (2012) UK	45 psychosis; 20 HC 44.6 46.7%	Cross sectional Case control study	Composite (CATS) and specific (SA, PA, EA, N) CATS	(1) Dissociation (DES)	Mediation analysis	Yes No	(1) Hallucinations (LSHR-R)	**CATS → dissociation → hallucinations** Partial mediation (DE = 0.15*; IE = 0.11*) % = 42.3 **SA → dissociation → hallucinations** Partial mediation (DE = 0.77*; IE = 0.57*) % = 42.8 No mediating effects with specific trauma subscales	5
Weijers *et al.* (2018) Netherlands	87 NAP 31.7 35.6%	Cross sectional	Composite abuse (Abuse) CECA	(1) Mentalising capabilities (MC) (HT)	Mediation analysis	Yes No	(1) Positive PANSS	Null mediating effect with positive symptoms (only with negative partial mediation)	5
Wickham and Bentall (2016) UK	72 psychosis; 72 HC 43.5 36.1%	Cross sectional Case control study	Specific (childhood sexual abuse (SA) ; Childhood emotional neglect (EN) (bullying, PA, EA also initially explored) CTQ and RBC	(1) Perception of injustice (BJW) 1.a - Personal 1.b - General	Mediation analysis	Yes Yes (age, gender, SA, hallucinations and paranoia)	(1) Paranoia (2) Hallucinations (PANSS)	**EN → Personal → Paranoia** Partial mediation (DE = 0.11*; IE = 0.032*) % = N/A No mediating effect of general injustice on paranoia, or personal and general perception of injustice on hallucinations	6

Table S1b.

Overview of General population studies included in this review

Authors Country	Sample Mean Age % female	Design	Measures of childhood adversity	Mediator(s)	Analysis	Boostrap (yes / no) / confounders (yes / no)	Psychosis	Main findings Pathway Total / partial mediation Direct Effect (DE) Indirect effect (IE) % total effect mediated	Quality Score
Ashford *et al.* (2012) **UK**	135 19.8 91.1%	Cross sectional	Bullying subscales: direct physical aggression (DPA); direct verbal aggression (DVA); Indirect aggression (IA) DIAS	(1) Interpersonal sensitivity (IPSM) (2) Anxiety (HADS) (3) Depression (HADS) (4) Negative core beliefs (BCSS) 4.a - Negative self beliefs 4.b - Negative beliefs others	Multiple mediation	Yes Yes (ethnicity, gender and other bullying categories)	(a) Paranoia (ideas of social reference) (GPTS) (b) Paranoia (persecution) (GPTS)	**IA → Depression → a** Suggested mediation (IE = 0.11; DE = N/A % = N/A **IA → Negative self beliefs → a** Suggested mediation (IE = 0.16; DE = N/A) % = N/A **IA → Depression → b** Suggested mediation (IE = 0.10; DE = N/A) % = N/A **IA → Negative self Beliefs → b** Suggested mediation (IE = 0.18; DE = N/A) % = N/A **DVA → Negative beliefs others → a** Suggested mediation (IE = 0.24; DE = N/A) % = N/A **DVA → Negative beliefs others → b** Suggested mediation (IE = 0.11; DE = N/A) % = N/A	5
Bortolon *et al.* (2017) **France**	425 36.23 79.1%	Cross sectional	Specific (PA, EA) CTQ	(1) Maladaptative schemas (MS) (SQ-SF): 1.a - Abandonment (2) Dissociation (DES): 2.a - Defensive dissociation	PLS-SEM	Yes Yes (age, gender, psychopathology)	(1) Auditory hallucination (AH) (LSHS-R)	**PA → 2.a → AH** Suggested mediation (DE = N/A; IE = 0.1081*) % = N/A **EA → 1.a → AH** Suggested mediation (DE = N/A; IE = 0.055*) % = N/A	5

Bortolon and Raffard (2018) France	403 33.24 82.1%	Cross sectional	Composite (CT) CTQ	(1) Defensive dissociation (DES)	SEM	Yes Yes (age, gender, anxiety, depression)	(A) Seeing visions (LSHS) (B) Hearing voices (LSHS)	**CT → 1 → A** Total mediation (DE = 0.008; IE = 0.122*) % = 93.7 **CT → 2 → B** Partial mediation (DE = 0.090*; IE = 0.124*) % = 57.94	6
Boyda and McFeeters (2015) Northern Ireland	7403 46 51.4%	Cross sectional	Specific (SA, EN) Questionnaire	(1) Social functioning 1.a - Loneliness (NA)	Logistic mediation analyses	Yes No	Psychotic-like experiences (PSQ)	**SA → Loneliness → PSQ** Total mediation (DE = 1.38; IE = 0.22*) % = N/A Total mediation **EN → Loneliness → PSQ** Total mediation (DE = 0.94; IE = 0.46*) % = N/A	5
Boyda *et al.* (2018) UK	302 36 69.9%	Cross sectional	Composite, subscales (EA, SA) ACE-IQ	(1) Early Maladaptative Schemas (EMS) (YSQ-SF) 1.a – Defectiveness / Shame 1.b – Dependency / Incompetence 1.c – Enmeshment / Undeveloped self 1.d - Emotional inhibition	Multiple mediation analyses	No Yes (age, gender, urbanicity, ethnicity, socio-economic status, drug use)	(1) Psychotic experiences (PE) (CAPE)	**EA → 1.b → PE** Suggested mediation (DE = N/A; IE = 0.083*) % = N/A **SA → 1.b → PE** Suggested mediation (DE = N/A; IE = 0.073*) % = N/A **EA → 1.c → PE** Suggested mediation (DE = N/A; IE = 0.063*) % = N/A **SA → 1.c → PE** Suggested mediation (DE = NA; IE = 0.043*) % = N/A	5

Cole *et al.* (2016) **UK**	200 19.96 82.5%	Cross sectional	Composite Childhood maltreatment (CM) CATS	(1) Dissociation: 1.a - Dissociative amnesia (DA) (DES-II) 1.b1 - Depersonalization- (CDS) 1.b2 - Depersonalization (DES-II) 1.c - Absorption (Abs) (DES-II)	(A) Simple and (B) multiple mediation analysis	Yes No	(1) Hallucination-proneness (HP) (LSHS-R) (2) Delusional ideation (DI) (PDI)	(A) Simple **CM → Dissociation → HP** Partial mediation (DE = 2.92*; IE = 3.94*) % = 57.4 **CM → Dissociation → DI** Partial mediation (DE = 10.90*; IE = 10.75*) % = 49.6 (B) Multiple **CM → Abs → HP** Total mediation (DE = 1.64; IE = 3.45*) %=50.29 **CM → DA → DI** Partial mediation (DE = 7.45*; IE = -3.68*) % = -16.99 **CM → Abs → DI** Partial mediation (DE = 7.45*; IE = 7.18*) % = 33.1 Remaining items within dissociation were not significant	5
Fisher *et al.* (2012) **UK**	212 27 65.4%	Cross sectional	Specific (EA, PA) CTQ	(1) Depression (BDI) (2)Anxiety (BAI) (3) Negative schematic beliefs (BCSS) 3.a - Negative self-schemas 3.b - Negative others schemas	Mediation analysis	Yes Yes (gender, age, ethnicity, family history)	(1) Paranoia (PSQ)	**EA → Anxiety → Paranoia** Total mediation (DE = 1.16; IE = 1.05*) % = 17.57 No mediation effects of depression, negative self-schemas and other schemas	6
Fisher *et al.* (2013) **UK**	6692 12.9 50.9%	Prospective From childhood (8, 21, 33, 47, 61, 73 months) to mean age of 12.9 yoa	Specific (Harsh parenting (HP), domestic violence (DV) and bullying victimization (BV)) Questionnaire to mothers ; Bullying and Friendship Interview Schedule (BI)	(1) External locus of control (LoC) (12 item version of NSIE) (2) Self Steem (shortened form of Harter`s Self Perception Profile for Children) (3) Affective symptoms (DAWBA and SMFQ) 3.a - Anxiety 3.b - Depression	Multiple mediation analysis	Yes Yes (gender, ethnicity, birth weight, family history of schizophrenia , depression or suicide, child's IQ, and general family adversity)	(1) Psychotic Symptoms (PS)(PLIKSi)	**HP → Anxiety → PS** Total mediation (DE = 1.02; IE = 1.01*) % = 21 **DV → Anxiety → PS** Total mediation (DE = 1.06; IE = 1.00*) % = 8 **BV → Anxiety → PS** Partial mediation (DE = 1.14*; IE = 1.00*) % = 2	8

HP → Depression→ PS
Total mediation (DE = 1.00; IE = 1.03*)
% = 94

DV → Depression → PS
Total mediation (DE = 1.04; IE = 1.01*)
% = 18

BV → Depression → PS

Partial mediation (DE=1.14*; IE = 1.01*)
% = 8

HP → LoC → PS
Total mediation (DE = 1.01; IE = 1.01*)
% = 47

DV → LoC → PS
Total mediation (DE = 1.03; IE = 1.00*)
% = 1

BV → LoC → PS
Partial mediation (DE = 1.13*; IE = 1.02*)
% = 13

HP → Self-steem → PS
Total mediation (DE = 1.00; IE = 1.01*)
% = 97

DV → self-steem → PS
Total mediation (DE = 1.04; IE = 1.00*)
% = 7

BV → Self steem → PS
Partial mediation (DE = 1.13*; IE = 1.01*)
% = 10

HP → all mediators → PS
Total mediation (DE = 0.97; IE = 1.04*)
% = 100

BV → all mediators → PS
Partial mediation (DE = 1.10*; IE = 1.04*)
% = 29

DV → all mediators → PS
Total mediation (DE = 1.03; IE = 1.02*)
% = 42

Gaweda *et al.* (2019) Germany	649 51.1 55.2%	Cross sectional	Composite (CT), Abuse, neglect CTQ	(1) Aberrant salience Inventory (ASI) (2) Anomalous self-experiences (IPASE)	Parallel multiple mediation models	Yes Yes (gender)	Psychotic-like experiences (PLE) (PQ)	**CT → 1 + 2 → PLE** Total mediation (DE = 0.05; IE 1 = 0.076*; IE 2 = 0.1443*) % 1 = 28.1 % 2 = 53.4 **Neglect → 1 + 2 → PLE** Total mediation (DE = 0.01; IE 1 = 0.0451*; IE 2 = 0.1404*) % 1 =26.5 % 2 =82.58 **Abuse → 1 + 2 → PLE** Partial mediation (DE = 0.10*; IE 1 = 0.092*; IE 2 = 0.1188*) % 1 = 29.67 % 2 = 38.32	6
Gibson *et al.* (2019) USA	945 20.13 75.6%	Cross sectional	Composite (CT) CTQ	(1) Perceived Stress (PSS) (2) Dissociation (DES) (3) Cognitive bias 3.1 Negative self-schemas (BCSS) 3.2 Negative others-schemas (BCSS) 3.3 External locus of control (RI-E)	Multiple mediation analyses	Yes Yes (gender, race, age)	(A) Psychotic-Like Experiences (PLE) (PQ)	**Multiple mediation** **CT → 1 → PLE** Total mediation (DE = 0.04; IE = 0.0405*) % = 25.31 **CT → 2 → PLE** Total mediation (DE = 0.04; IE = 0.0549*) % = 34.31 **CT → 3.1 → PLE** Total mediation (DE = 0.04; IE = 0.007*) % = 14.43 **CT → 3.2 → PLE** Total mediation (DE = 0.04; IE = 0.0141*) % = 8.81 **CT → 3.3 → PLE** Total mediation (DE = 0.04; IE = 0.0071*) % = 4.43 Only multiple mediation analyses presented and considered as the total effect of simple analyses are missing	6

Goodall *et al.* (2015) **UK**	283 26.8 72%	Cross sectional	EA analysed in mediation CTQ	(1) Adult Attachment (ECR-R) 1.a - Attachment avoidance (AAv) 1.b - Attachment anxiety (AAn)	Parallel multiple mediation analysis	Yes No	(1) Schizotypy (SPQ-B)	**EA → AAv → Schizotypy** Partial mediation (DE = 0.35*; IE = 0.04*) % = 13 **EA → Aan → Schizotypy** Partial mediation (DE = 0.35*; IE =0.06*) % = 8	5
Jaya *et al.* (2017) **Germany**	2350 32.5 37%	Cross sectional	Composite of Social Adversity (SocA) including bullying and abuse BVQ /NEMESIS	(1) Social rank with the Social Comparison Scale (SCS) (2) Negative schemas Brief Core Schema Scales (BCSS) (3) Loneliness (UCLA)	SEM	Yes No	(1) Positive (PS) and negative symptoms (CAPE) (only positive considered)	**SocA → Loneliness → PS** Suggested mediation (DE = N/A; IE = 0.02*) % = N/A **SocA → BCSS → PS** Suggested mediation (DE = N/A; IE = 0.12*) % = N/A No mediation for SCS on positive symptoms	4
Lincoln *et al.* (2017) **Germany**	562 24.31 49.3%	Prospecti ve (follow up at 4, 8, 12 months)	Composite (CT) NEMESIS	(1) Emotion regulation (ER) (ERSQ)	SEM	Yes No	(1) Subthreshold psychotic experience (CAPE) 1.a - Distress 1.b - Frequency	**CT → ER → Distress** Partial mediation (DE = 0.069*; IE = 0.005*) % = 7.1 No mediating effect for symptom frequency	6
Marwaha *et al.* (2014) **UK**	8580 + 7403 Baseline 2406 FU NA NA	Cross sectional	Sexual abuse (SA) Questionnaire	(1) Mood instability (MI) (BPD section of the SCID-II)	Mediation analysis	No Yes (age, gender, marital status, employment status and ethnicity, PTSD, current affective state and hypomanic symptoms)	(1) Psychotic Phenomena (PSQ) 1.a - Probably psychosis (PP) 1.b - Paranoid ideation (PI) 1.c - Auditory Hallucinations (AH)	**SA → MI → PP** Suggested mediation % = 34.6 **SA → MI → PI** Suggested mediation % = 34.5 **SA → MI → AH** Suggested mediation % = 25.3	4
Marwaha and Bebbingto n (2015) **UK**	5689 N/A N/A	Cross-sectional	Sexual abuse (Non consensual intercourse (NCI), contact abuse (CA)) Questionnaire	(1) Anxiety (CIS-R) (2) Depressive symptoms (CIS-R) (CIS-R) (analyzed together)	Mediation analysis	No Yes (gender, age, ethnicity, education, being brough by both partens until 16)	(1) Psychotic symptoms (PSQ)	**NCI → 1, 2 → PSQ** Partial mediation (DE = 4.08*; IE (together) = 2.41*) % anxiety = 20.4 % depression = 37.4 **CA → 1, 2 → PSQ** Total mediation (DE = 2.14; IE (together) = 1.60*) % anxiety = 24.1 % depression = 37.1 IE shows combined effects of 1, 2 Percentages shows mediators examined separately	5

McCarthy-Jones (2018) Ireland	5788 51.71 55.4%	Cross sectional	Childhood Sexual abuse (CSA) Questionnaire from APMS	(1) Anxiety (CIS-R) (2) Obsessional thought (CIS-R) (3) Compulsions (CIS-R) (4) PTSD (APMS questionnaire) (5) Depression (CIS-R)	Regression-based approach	Yes Yes (age, gender, ethnicity, education, IQ, depression)	Auditory verbal hallucinations (AVH) (PSQ)	**CSA → 3 → AVH** Partial mediation (DE = 5.15*; IE = 1.10*) % = 5.41 **CSA → 4 → AVH** Partial mediation (DE = 5.15*; IE = 1.11*) % = 5.93 Not significamt effect of anxiety, obsessions and depression between CSA and AVH	6
Metel *et al.* (2020) Poland	2684 26.37 62.3%	Cross sectional	Composite TEC CECA-Q	(1) Cognitive biases (DACOBS) (2) Resilience (CD-RISC) (3) Depressive symptoms (CESD-R)	Multiple mediation analysis	Yes No	(1) Psychotic like experiences (PLE) (PQ)	**TEC/CECA-Q → DACOBS → CD-RISC → CESD-R → PLE** Partial mediation (DE = 0.162*; IE = 0.163*) % = 4	4
Murphy *et al.* (2015) UK	785 16.2 56.1%	Cross sectional	Composite ELES	(1) Negative social comparisons (SCS) (2) Trauma-related thoughts and beliefs (PTCI)	Moderated mediation analysis	Yes Yes (recent victimization)	(1) Psychotic experiences (APSS)	**ELES → PTCI → APSS** Partial mediation (non lonely patients) (DE = 0.049*; IE = 0.039*) % = 44.3 **ELES → PTCI → APSS** Total mediation (lonely patients) (DE = 0.032; IE = 0.042*) % = 56.7 No mediation by negative social comparisons either in lonely or non-lonely patients	6
Perona-Garcelán *et al.* (2014) Spain	318 21.41 78.9%	Cross sectional	Composite Trauma Questionnaire (TQ)	(1) Dissociation 1.a - Tellegen Absorption Scale (TAS) 1.b - Depersonalization (CDS) (2) Southampton Mindfulness Questionnaire (SMQ)	Multiple mediation analysis	Yes No	(1) Hallucination proneness (HP) (LSHS-R)	**TQ → Absorption Scale → HP** Total mediation (DE = 0.12; IE = 0.38*) % = 82.6 **TQ → Depersonalisation → HP** Total mediation (DE = 0.12; IE = 0.16*) % = 34.78 (together) No mediation by mindfulness	5

								% depression = 37.1 IE shows combined effects of 1, 2 Percentages shows mediators examined separately	
McCarthy-Jones (2018) Ireland	5788 51.71 55.4%	Cross sectional	Childhood Sexual abuse (CSA) Questionnaire from APMS	(1) Anxiety (CIS-R) (2) Obsessional thought (CIS-R) (3) Compulsions (CIS-R) (4) PTSD (APMS questionnaire) (5) Depression (CIS-R)	Regression-based approach	Yes Yes (age, gender, ethnicity, education, IQ, depression)	Auditory verbal hallucinations (AVH) (PSQ)	**CSA → 3 → AVH** Partial mediation (DE = 5.15*; IE = 1.10*) % = 5.41 **CSA → 4 → AVH** Partial mediation (DE = 5.15*; IE = 1.11*) % = 5.93 Not significamt effect of anxiety, obsessions and depression between CSA and AVH	6
Metel *et al.* (2020) Poland	2684 26.37 62.3%	Cross sectional	Composite TEC CECA-Q	(1) Cognitive biases (DACOBS) (2) Resilience (CD-RISC) (3) Depressive symptoms (CESD-R)	Multiple mediation analysis	Yes No	(1) Psychotic like experiences (PLE) (PQ)	**TEC/CECA-Q → DACOBS → CD-RISC → CESD-R → PLE** Partial mediation (DE = 0.162*; IE = 0.163*) % = 4	4
Murphy *et al.* (2015) UK	785 16.2 56.1%	Cross sectional	Composite ELES	(1) Negative social comparisons (SCS) (2) Trauma-related thoughts and beliefs (PTCI)	Moderated mediation analysis	Yes Yes (recent victimization)	(1) Psychotic experiences (APSS)	**ELES → PTCI → APSS** Partial mediation (non lonely patients) (DE = 0.049*; IE = 0.039*) % = 44.3 **ELES → PTCI → APSS** Total mediation (lonely patients) (DE = 0.032; IE = 0.042*) % = 56.7 No mediation by negative social comparisons either in lonely or non-lonely patients	6

Perona-Garcelán *et al.* (2014) Spain	318 21.41 78.9%	Cross sectional	Composite Trauma Questionnaire (TQ)	(1) Dissociation 1.a - Tellegen Absorption Scale (TAS) 1.b - Depersonalization (CDS) (2) Southampton Mindfulness Questionnaire (SMQ)	Multiple mediation analysis	Yes No	(1) Hallucination proneness (HP) (LSHS-R)	**TQ → Absorption Scale → HP** Total mediation (DE = 0.12; IE = 0.38*) % = 82.6 **TQ → Depersonalisation → HP** Total mediation (DE = 0.12; IE = 0.16*) % = 34.78 (together) No mediation by mindfulness	5
Pinto-Gouveia *et al.* (2014) Portugal	255 36.36 68.2%	Cross sectional	Composite (including threat, submissiveness and feeling unvalued) ELES	(1) External shame (OAS)	Path analysis	Yes Yes (confounders not specified)	(1) Paranoia (GPS)	**ELES → OAS → GPS** Partial mediation (DE = 0.12*; IE = 0.0608*) % = 33.6	6
Rössler *et al.* (2016) Switzerland	820 31.36 55.8%	Cross sectional	Composite (CTQ) and specific (EA, PN, EN) CTQ	(1) Stress sensitivity (SS) (PSS, PANAS-N, SSCS)	Bivariate and mediated multinomial logistic regression path models	Yes Yes (trauma types, education)	(1) Subclinical psychotic experience (SPE) (SIAPA, SPQ-B German version, PARA, and STS and SNS subscales from SCL-90-R)	**CTQ → SS → SPE** Partial mediation (DE = 0.44*; IE = 0.50*) % = 43.05 **EA → SS → SPE** Total mediation (DE = 0.47; IE = 0.578*) % = 46.6 **EN → SS → SPE** Total mediation (DE = -0.31; IE = 0.44*) % = 53.38 **PN → SS → SPE** Total mediation (DE = 0.27; IE = 0.28*) % = 28.71	6

Sheinbaum *et al.* (2014) Spain	546 20.6 82.3%	Cross sectional	Composite factor of physical and emotional trauma (P/E) CTQ	(1) Attachment style (RQ) 1.a - Dismissing 1.b - Preoccupied 1.c - Fearful	Parallel multiple mediation analyses	Yes No	(1) PLEs (CAPE) (2) Paranoid beliefs (SPQ) (3) Schizotypy (WSS)	**P/E → Fearful → Schizotypy** Partial mediation (DE = 0.140*; IE total = 0.028*; IE fearful = 0.010*) % total = 16.6 % fearful = 5.9 **P/E → Fearful → Suspiciousness** Partial mediation (DE = 0.420*; IE total = 0.093*; IE fearful = 0.056*) % total = 18 % fearful = 10.8 **P/E → Fearful → PLE** Partial mediation (DE = 0.822*; IE total = 0.142*; IE fearful = 0.063*) % total = 14.7 % fearful = 6.5 None of the other mediators were significant	5
Shevlin *et al.* (2015) UK	7403 51.12 56.8%	Cross sectional	Specific CSA and/or CPA and CSA + CPA composite scores Questionnaire	(1) Loneliness (SFQ)	Mediation analysis	No Yes (age, gender, education, ethnicity, cannabis use and adult CSA and CPA)	(1) Psychosis diagnosis (SCAN)	**CSA + CPA → Loneliness → Psychosis** Partial mediation (DE = N/A; IE = 0.722*) % = N/A No mediation of the CPA, CSA separately	5
Sitko *et al.* (2014) UK	5877 34.5 50.5%	Cross sectional	History module Specific (Rape, sexual molestatin, PA, Physical assault/attack) UM-CIDI - Life Event	(1) Attachment style (AAQ) 1.a - Secure (reversed) 1.b - Avoidance 1.c - Anxious	Regression based approach	Yes Yes (age and gender)	(1) Lifetime psychotic symptoms (LPS) (Beliefs and Experiences module of the UM-CIDI) 1.A - Paranoia 1.B - Hallucinations	**Neglect → 1.c + 1.b → 1.A** Total mediation (DE = 0.047; IE = N/A) % both = 100 **Rape → 1.c → 1.B** Partial mediation (DE = 0.088*; IE = N/A) % = 3.0	6
Van Nierop *et al.* (2014) Netherland	6646 44 55%	Cross sectional	Composite (CT) NEMESIS-1	(1) Social defeat (SD) (NEMESIS questionnaire) (2) Affective dysregulation (AD) (NEMESIS questionnaire)	Multiple mediation analyses	Yes Yes (CT, age, gender, cannabis use and affective dysregulation)	(1) Psychosis diagnosis (PD) DSM-IV (SCID-I) (2) Extended psychosis phenotype (EPP) (NEMESIS interview)	**CT → AD → EPP** Partial mediation (DE = N/A; IE = 0.04*) % = 49.7 **CT → SD → PD** Partial mediation (DE = N/A; IE = 0.04*) % = 86.6 No significant mediation of SD on the link between CT and EPP and of AD on the link between CT and PD	6

Wolke *et al.* (2014) **UK**	4720 17.1 56.5%	Prospective, assessed for adversity at 8 and 11 yoa, and for symptoms at 12.9 and 18 yoa	Two composite scores peer victimization (PV) (child-reported and mother-reported bullying) BFIS SDQ	(1) Depression symptoms at age 12, 13, 14 yoa (SQFM)	Path analysis	No Yes (gender, any DSM-IV Axis I diagnosis, IQ and internalizing / externalizing behavior)	(1) Psychotic experiences (PE) at age18 yoa (PLIKSi)	**PV → Depression (12.9) → PE (18)** Partial mediation (DE = 0.13*; IE child reported = 0.03*; IE mother reported = 0.02*) % child reported = 18.75 % mother reported = 13.3	7
Yamasaki *et al.* (2016) **Japan**	4277 9.8 46.9%	Cross sectional	Composite score (peer victimization (PV)) OVBQ	(1) Dissociation (CBCL) (2) Depressive symptoms (SMFQ) (3) External locus of control (shortened version of the CNSIE)	SEM	No No	(1) Hallucinations (CBCL)	**PV → Dissociation → CBCL** Total Mediation (DE = 0.02; IE = 0.038* % = 95 No mediation by depression or external locus control	4

Table S1b.

Overview of General population studies included in this review

Authors Country	Sample Mean Age % female	Design	Measures of childhood trauma	Mediator(s)	Analysis	Boostrap (yes / no) / confounders (yes / no)	Psychosis	Main findings Pathway Total / partial mediation Direct Effect (DE) Indirect effect (IE) % total effect mediated	Quality Score
Cancel *et al.* (2015) **France**	21 NAP; 33 HC 32.1 NAP 29% NAP 32.9 HC 33% HC	Cross sectional	Subscales (EN) CTQ	(1) Grey matter volume in DLPFC	Regression based approach and SEM	No Yes (duration of illness and parents' education levels)	(1) Disorganization (SANS)	**EN → DLPFC → Disorganization** Suggested mediation % = NA	4
Quidé *et al.* (2018) **Australia**	112 psychosis; 53 HC 38 psychosis 47% psychosis 38.7 HC 39.6% HC	Cross sectional Case control study	Composite (CTQ) CTQ	(1) Inferior frontal girus (IFG) activation	Mediation analysis	Yes No	(1) Positive symptoms (PANSS)	**CTQ → IFG activation → PANSS positive** Null mediation	4

AAQ: Acceptance and Action Questionnaire; ACE-IQ: Adverse Childhood Experiences International Questionnaire; APMS: Adult Psychiatric Morbidity Survey; APSS: Adolescent Psychotic-like Symptom Screener; BAI: Beck Anxiety Inventory; BCSS: Brief Core Schema Scale; BDI-II: Beck Depression Inventory; BFIS: Bullying and Friendship Interview Schedule; BJW: The General / personal Beliefs in a Just World Scale; BPD: Borderline Personality Disorder; BPRS: Brief Psychiatric Rating Scale; BVQ: Bullying Victimization Questionnaire; CAARMS: Comprehensive Assessment of At Risk Mental States; CAPE: Community Assessment of Psychic Experiences; CAPS: Clinician-Administered PTDS Scale; CATS: the Child Abuse and Trauma Scale; CBCL: Child Behavior Checklist; CDS: Cambridge Depersonalization Scale; CD-RISC: Connor-Davidson Resilience Scale; CECA: Childhood Experiences of Care and Abuse; CECA.Q: Childhood Experiences of Care and Abuse Questionnaire; CESD-R: Center for Epidemiologic Studies-Depression Scale; CHR: Clinical High Risk for psychosis; CIS-R: Clinical Interview Schedule-Revised; CNSIE: Childhood Nowicki–Strickland Internal–External; CTQ: Childhood Trauma Questionnaire; DACOBS: Davos Assessment of Cognitive Biases Scale; DAWBA: Development and Well-Being Assessment; DES-II: Dissociative Experience Scale; DIAS: Modified Direct and Indirect Aggression Scales; DLPFC: Dorsolateral Prefrontal Cortex; EA: Emotional abuse; ECR-R: Experiences in Close Relationships-Revised Questionnaire; ELES: Early Life Experiences Scale; EP: Early Psychosis; ERSQ: Emotion Regulation Skills Questionnaire; ESM: Experience Sampling Method; FEP: First Episode of Psychosis; FKK: German Competence and Control Beliefs Questionnaire; GAF: Global Assessment of Functioning; GPS: General Paranoia Scale; GPTS: Green et al. Paranoid Thought Scales; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; HC: Healthy Control; HT: Hinting Task; ICD-10: International Classification of Diseases, 10th revision; IESR: Impact Event Scale-Revised; IPASE: Inventory of Psychotic-Like Anomalous Self-Experiences; IPSM: Interpersonal sensitivity scale; ISMIS: Internalised Stigma of Mental Illness Scale; IVM: Dutch equivalent of the International Crime Victimization Survey; LSHR-R: Launay-Slade Hallucinations Scale-revised; MACE: Maltreatment and Abuse Chronology of Exposure scale; MADRS: Montgomery Asberg Depression Rating Scale; MCVI: MacArthur Community Violence Instrument; MMPI-2: Minnesota Multiphasic personality Inventory; MRC: MRC Sociodemographic Schedule ; N: Neglect; NAP: non-affective psychosis; NEMESIS: Netherlands Mental Health Survey and Incidence Study; NEO-FFI: assess the Five-factors Model (FFM) personality traits; NSIE: Nowicki–Strickland Internal–External; OAS: Other As Shamer Scale; OVBQ: Olweus Bully/Victims Questionnaire; PACE: Personal Assessment and Crisis Evaluation; PA: Physical abuse; PAM: Psychosis Attachment Scale; PANAS-N: Negative Affect Subscale of the Positive and Negative Affect Scale; PANSS: Positive and Negative Syndrome Scale; PARA: Paranoia Checklist; PDI: Peters et al. Delusion Inventory; PG: prodromal questionnaire; PHQ-9: Japanese version of the Patient Health Questionnaire-9; PLIKSi: Semi-structured Psychosis

Interview; PLS-SEM: Partial least squares – Structural equation models; PQ: Prodromal Questionnaire; PSPS: Personal and Social Performance Scale; PSQ: Psychosis Screening Questionnaire; PSS: Perceived Stress Scale; PTCI: Posttraumatic Cognitions Inventory; PTSD: Post-traumatic stress disorder; QoL: World Health Organization Quality of Life-Bref (WHOQOL-BREF); RBC: ; RBQ: Retrospective Bullying Questionnaire; RSES: Rosenberg Self-Esteem Scale; RQ: Relationship Questionnaire; SA: Sexual abuse ; SAPS: Scales for Assessment of Positive symptoms; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SCID-II: Structured Clinical Interview for DSM-IV Personality Disorders; SCID-D-R: Structured Clinical Interview for DSM-IV Dissociative Disorders; SCL-90-R: Symptom Checklist-90-R; SCS: Social Comparison Scale; SCZ: Schizophrenia; SDQ: Strengths and Difficulties Questionnaire; SDS: Shutdown Dissociation Scale; SEM: Structural Equation Modeling; SFQ: Social Functioning Questionnaire; SFS: Social Functioning Scale; SIAPA: Structured Interview for Assessing Perceptual Anomalies; SNS: Schizophrenia Nuclear Symptom Scale; SOFAS: Social and Occupational Functioning Assessmnet Scale; SPI-A and SPI-CY (for adolescents): Schizophrenia Proneness Instrument; SPQ-B: Schizotypal Personality Questionnaire-Brief; SSP: Schizophrenia-Spectrum Psychosis; SQFM: Short Mood and Feelings Questionnaire; SQ-SF: Young Schema Questionnaire Short Form; SMFQ: Short Mood and Feelings Questionnaire; SRS-PTSD: Self-Rating Scale for Post-traumatic Stress Disorder; SSCS: Screening Scale for Chronic Stress; SSPS: State Social Paranoia Scale; STS: Schizotypal Signs Scale; SVF-KJ: German Stress-Coping-Questionnaires using the version for adults and children / adolescents; TDS : Traumatic Dissociation Scale; TEC: Traumatic Experience Checklist; THQ: Trauma History Questionnaire; TLEC: the life-events checklist; TQ: Trauma Questionnaire; UCLA: ; UHR: Ultra High Risk; UM-CIDI - Life Event: modified version of the Composite International Diagnostic Interview; WSS: Wisconsin Schizotypy Scales; Y-BOCS: Dutch version of the Yale-Brown Obsessive-Compulsive Scale; ZTPI: Zimbardo Time Perspective Inventory.
** p-value ≤ 0.05*
Note= when « Psychosis » is used it means that patients were no FEP.
Note see data extraction procedure for details on definitions of total, partial, null mediation and « suggested mediation ».

d. Table S2

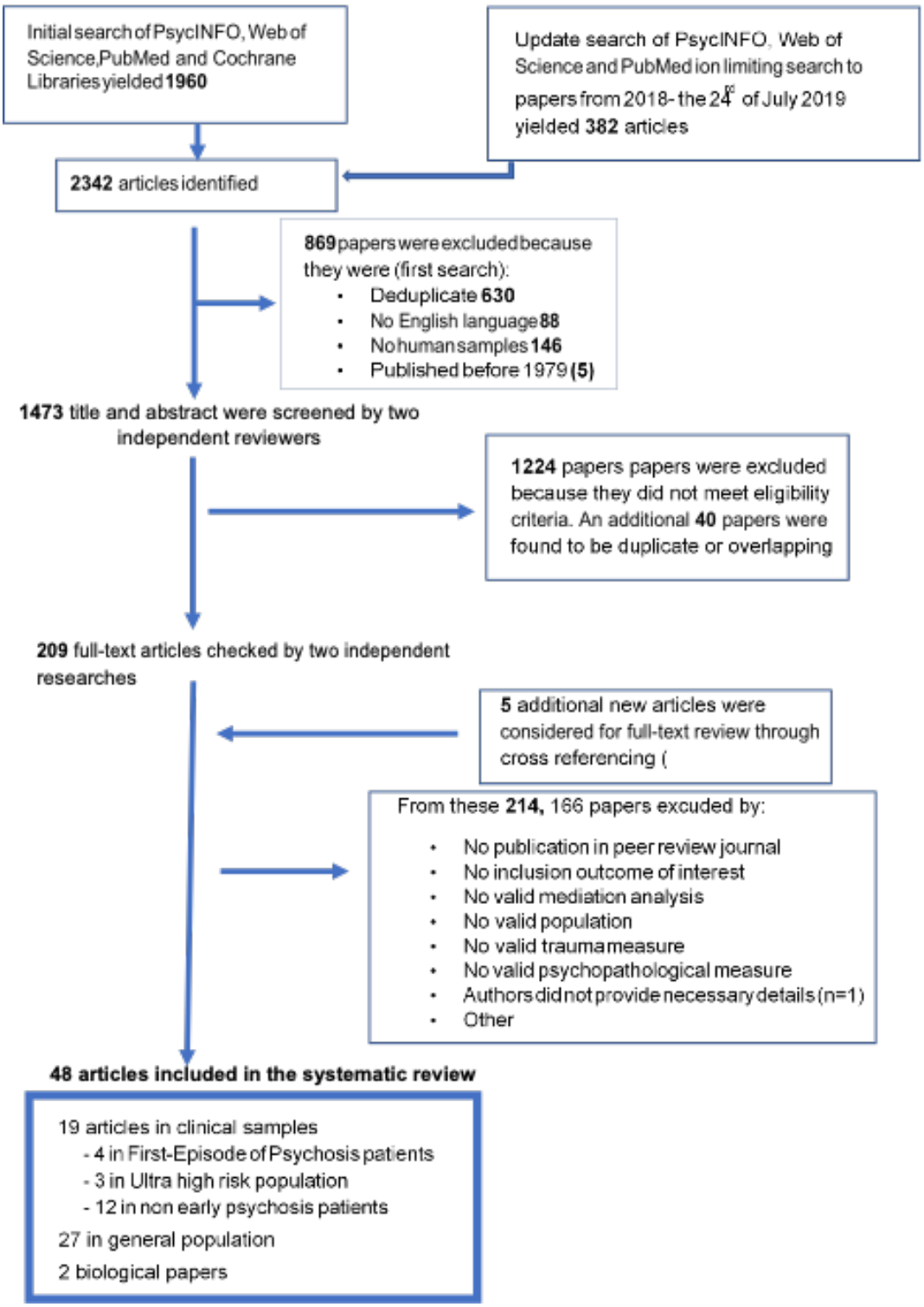
Summary of evidence for mediators within the Dissociation category between adversity and psychosis

	Clinical samples			General population			Total
Category	*Number of analyses. (number of studies)*			*Number of analyses. (number of studies)*			
(N total analyses/studies*)	Evidence of mediation	Null mediation	% analyses supporting mediation	Evidence of mediation	Null mediation	% analyses supporting mediation	% analyse supportin mediation
Dissociation (43/12)	6(4)	20(6)	**23%**	12(6)	5(1)	**70%**	**42%**
Overall measure (24/8)	5(4)	15(5)	**25%**	4(3)	-	**100%**	**37.5%**
Dissociative amnesia (4/2)	-	2(1)	**0%**	1(1)	1(1)	**50%**	**25%**
Defensive dissociation (3/2)	-	-	-	3(2)	-	**100%**	**100%**
Absorption (5/3)	-	2(1)	**0%**	3(2)	-	**100%**	**60%**
Depersonalization (7/3)	1(1)	1(1)	**50%**	1(1)	4(1)	**20%**	**29%**

** We considered that one analysis showed evidence of mediation when authors reported significant p-values (<0.05) in the indirect (or mediating) effects, or when using a regression-based approach, an important reduction of the total effect occurred once the mediator was included in the model. Null mediation was defined as the non significant (p>0.05) indirect or mediating effect or as the lack of reduction of the total effect once the mediator was included in the model when using a regression-based approach.*

2. Supplementary Figures

a. Figure S1. Flow chart



4. Supplementary references

- Alwin DF, Hauser RM (1975) The Decomposition of Effects in Path Analysis. SAGE Publications American Sociological Review 40, 37.
- Appiah-Kusi E, Fisher HL, Petros N, Wilson R, Mondelli V, Garety PA, Mcguire P, Bhattacharyya S (2017) Do cognitive schema mediate the association between childhood trauma and being at ultra-high risk for psychosis? Elsevier Ltd Journal of Psychiatric Research 88, 89–96.
- Ashford CD, Ashcroft K, Maguire N (2012) Emotions, Traits and Negative Beliefs as Possible Mediators in the Relationship between Childhood Experiences of being Bullied and Paranoid Thinking in a Non-Clinical Sample. Journal of Experimental Psychopathology 3, 624–638.
- Bortolon C, Raffard S (2018) Dissociation Mediates the Relationship between Childhood Trauma and Experiences of Seeing Visions in a French Sample. Journal of Nervous and Mental Disease 206, 850–858.
- Bortolon C, Seillé J, Raffard S (2017) Exploration of trauma, dissociation, maladaptive schemas and auditory hallucinations in a French sample. Taylor & Francis Cognitive Neuropsychiatry 22, 468–485.
- Boyda D, McFeeters D (2015) Childhood maltreatment and social functioning in adults with sub-clinical psychosis. Elsevier Psychiatry Research 226, 376–382.
- Boyda D, McFeeters D, Dhingra K, Rhoden L (2018) Childhood maltreatment and psychotic experiences: Exploring the specificity of early maladaptive schemas. Journal of Clinical Psychology 74, 2287–2301.
- Cancel A, Comte M, Truillet R, Boukezzi S, Rousseau PF, Zendjidjian XY, Sage T, Lazergues PE, Guedj E, Khalfa S, Azorin JM, Blin O, Fakra E (2015) Childhood neglect predicts disorganization in schizophrenia through grey matter decrease in dorsolateral prefrontal cortex. Acta Psychiatrica Scandinavica 132, 244–256.
- Chatziioannidis S, Andreou C, Agorastos A, Kaprinis S, Malliaris Y, Garyfallos G, Bozikas VP (2019) The role of attachment anxiety in the relationship between childhood trauma and schizophrenia-spectrum psychosis. Elsevier Ireland Ltd Psychiatry Research 276, 223–231.
- Choi JY, Choi YM, Kim B, Lee DW, Gim MS, Park SH (2015) The effects of childhood abuse on self-reported psychotic symptoms in severe mental illness: Mediating effects of posttraumatic stress symptoms. Elsevier Psychiatry Research 229, 389–393.

- Cole CL, Newman-Taylor K, Kennedy F (2016) Dissociation mediates the relationship between childhood maltreatment and subclinical psychosis. Routledge Journal of Trauma and Dissociation 17, 577–592.
- Evans GJ, Reid G, Preston P, Palmier-Claus J, Sellwood W (2015) Trauma and psychosis: The mediating role of self-concept clarity and dissociation. Elsevier Ireland Ltd Psychiatry Research 228, 626–632.
- Fisher HL, Appiah-Kusi E, Grant C (2012) Anxiety and negative self-schemas mediate the association between childhood maltreatment and paranoia. Elsevier Ltd Psychiatry Research 196, 323–324.
- Fisher HL, Schreier A, Zammit S, Maughan B, Munafò MR, Lewis G, Wolke D (2013) Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. Schizophrenia Bulletin 39, 1045–1055.
- Gawęda Ł, Göritz AS, Moritz S (2019) Mediating role of aberrant salience and self-disturbances for the relationship between childhood trauma and psychotic-like experiences in the general population. Schizophrenia Research 206, 149–156.
- Gibson LE, Reeves LE, Cooper S, Olino TM, Ellman LM (2019) Traumatic life event exposure and psychotic-like experiences: A multiple mediation model of cognitive-based mechanisms. Elsevier B.V. Schizophrenia Research 205, 15–22.
- Goodall K, Rush R, Grünwald L, Darling S, Tiliopoulos N (2015) Attachment as a partial mediator of the relationship between emotional abuse and schizotypy. Elsevier Psychiatry Research 230, 531–536.
- Hardy A, Emsley R, Freeman D, Bebbington P, Garety PA, Kuipers EE, Dunn G, Fowler D (2016) Psychological Mechanisms Mediating Effects between Trauma and Psychotic Symptoms: The Role of Affect Regulation, Intrusive Trauma Memory, Beliefs, and Depression. Schizophrenia Bulletin 42, S34–S43.
- Isvoranu AM, Van Borkulo CD, Boyette L Lou, Wigman JTW, Vinkers CH, Borsboom D, Kahn R, De Haan L, Van Os J, Wiersma D, Bruggeman R, Cahn W, Meijer C, Myin-Germeys I (2017) A network approach to psychosis: Pathways between childhood trauma and psychotic symptoms. Schizophrenia Bulletin 43, 187–196.
- Jaya ES, Ascone L, Lincoln TM (2017) Social adversity and psychosis: The mediating role of cognitive vulnerability. Schizophrenia Bulletin 43, 557–565.
- Lincoln TM, Marin N, Jaya ES (2017) Childhood trauma and psychotic experiences in a general population sample: A prospective study on the mediating role of emotion regulation. Elsevier Masson SAS European Psychiatry 42, 111–119.

- Marwaha S, Bebbington P (2015) Mood as a mediator of the link between child sexual abuse and psychosis. Social Psychiatry and Psychiatric Epidemiology 50, 661–663.
- Marwaha S, Broome MR, Bebbington PE, Kuipers E, Freeman D (2014) Mood instability and psychosis: Analyses of British national survey data. Schizophrenia Bulletin 40, 269–277.
- McCarthy-Jones S (2018) Post-Traumatic Symptomatology and Compulsions as Potential Mediators of the Relation between Child Sexual Abuse and Auditory Verbal Hallucinations. Behavioural and Cognitive Psychotherapy 46, 318–331.
- McDonnell J, Stahl D, Day F, McGuire P, Valmaggia LR (2018) Interpersonal sensitivity in those at clinical high risk for psychosis mediates the association between childhood bullying victimisation and paranoid ideation: A virtual reality study. Elsevier B.V. Schizophrenia Research 192, 89–95.
- Mętel D, Arciszewska A, Daren A, Pionke R, Cechnicki A, Frydecka D, Gawęda Ł (2020) Mediating role of cognitive biases, resilience and depressive symptoms in the relationship between childhood trauma and psychotic-like experiences in young adults. Early Intervention in Psychiatry 14, 87–96.
- Morgan C, Reininghaus U, Fearon P, Hutchinson G, Morgan K, Dazzan P, Boydell J, Kirkbride JB, Doody GA, Jones PB, Murray RM, Craig T (2014) Modelling the interplay between childhood and adult adversity in pathways to psychosis: Initial evidence from the AESOP study. Psychological Medicine 44, 407–419.
- Murphy S, Murphy J, Shevlin M (2015) Negative evaluations of self and others, and peer victimization as mediators of the relationship between childhood adversity and psychotic experiences in adolescence: The moderating role of loneliness. British Journal of Clinical Psychology 54, 326–344.
- Peach N, Alvarez-Jimenez M, Cropper SJ, Sun P, Bendall S (2019) Testing models of post-traumatic intrusions, trauma-related beliefs, hallucinations, and delusions in a first episode psychosis sample. British Journal of Clinical Psychology 58, 154–172.
- Perona-Garcelán S, Carrascoso- López F, García-Montes JM, Ductor-Recuerda MJ, López Jiménez AM, Vallina-Fernández O, Pérez-Álvarez M, Gómez-Gómez MT (2012) Dissociative experiences as mediators between childhood trauma and auditory hallucinations. Journal of Traumatic Stress 25, 323–329.
- Perona-Garcelán S, García-Montes JM, Rodríguez-Testal JF, López-Jiménez AM, Ruiz-Veguilla M, Ductor-Recuerda MJ, Benítez-Hernández M del M, Arias-Velarde MÁ, Gómez-Gómez MT, Pérez-Álvarez M (2014) Relationship Between Childhood Trauma, Mindfulness, and Dissociation in Subjects With and Without Hallucination Proneness. Journal of Trauma and Dissociation 15, 35–51.

- Pinto-Gouveia J, Matos M, Castilho P, Xavier A (2014) Differences between Depression and Paranoia: The Role of Emotional Memories, Shame and Subordination. Clinical Psychology and Psychotherapy 21, 49–61.
- Quidé Y, O'Reilly N, Watkeys OJ, Carr VJ, Green MJ (2018) Effects of childhood trauma on left inferior frontal gyrus function during response inhibition across psychotic disorders. Psychological Medicine 48, 1454–1463.
- Rössler W, Ajdacic-Gross V, Rodgers S, Haker H, Müller M (2016) Childhood trauma as a risk factor for the onset of subclinical psychotic experiences: Exploring the mediating effect of stress sensitivity in a cross-sectional epidemiological community study. Elsevier B.V. Schizophrenia Research 172, 46–53.
- Schalinski I, Breinlinger S, Hirt V, Teicher MH, Odenwald M, Rockstroh B (2019) Environmental adversities and psychotic symptoms: The impact of timing of trauma, abuse, and neglect. Elsevier B.V. Schizophrenia Research 205, 4–9.
- Sheinbaum T, Kwapil TR, Barrantes-Vidal N (2014) Fearful attachment mediates the association of childhood trauma with schizotypy and psychotic-like experiences. Elsevier Psychiatry Research 220, 691–693.
- Shevlin M, McElroy E, Murphy J (2015) Loneliness mediates the relationship between childhood trauma and adult psychopathology: evidence from the adult psychiatric morbidity survey. Social Psychiatry and Psychiatric Epidemiology 50, 591–601.
- Sitko K, Bentall RP, Shevlin M, O'Sullivan N, Sellwood W (2014) Associations between specific psychotic symptoms and specific childhood adversities are mediated by attachment styles: An analysis of the National Comorbidity Survey. Psychiatry Research 217, 202–209.
- Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Springer European Journal of Epidemiology 25, 603–605.
- Steenkamp L, Weijers J, Gerrmann J, Eurelings-Bontekoe E, Selten JP (2019) The relationship between childhood abuse and severity of psychosis is mediated by loneliness: an experience sampling study. Elsevier B.V. Schizophrenia Research.
- Styła R, Stolarski M, Szymanowska A (2019) Linking childhood adversities with schizophrenia: A mediating role of the balanced time perspective. Schizophrenia Research 209, 281–283.
- Sun P, Alvarez-Jimenez M, Simpson K, Lawrence K, Peach N, Bendall S (2018) Does dissociation mediate the relationship between childhood trauma and hallucinations, delusions in first episode psychosis? Elsevier Inc. Comprehensive Psychiatry 84, 68–74.

- Thompson A, Marwaha S, Nelson B, Wood SJ, McGorry PD, Yung AR, Lin A (2016) Do affective or dissociative symptoms mediate the association between childhood sexual trauma and transition to psychosis in an ultra-high risk cohort? Elsevier Psychiatry Research 236, 182–185.

- Van Dam DS, Korver-Nieberg N, Velthorst E, Meijer CJ, de Haan L (2014) Childhood maltreatment, adult attachment and psychotic symptomatology: a study in patients, siblings and controls. Social Psychiatry and Psychiatric Epidemiology 49, 1759–1767.

- Van Nierop M, van Os J, Gunther N, van Zelst C, de Graaf R, ten Have M, van Dorsselaer S, Bak M, Myin-Germeys I, Van Winkel R (2014) Does social defeat mediate the association between childhood trauma and psychosis? Evidence from the NEMESIS-2 Study. Acta Psychiatrica Scandinavica 129, 467–476.

- Varese F, Barkus E, Bentall RP (2012) Dissociation mediates the relationship between childhood trauma and hallucination-proneness. Psychological Medicine 42, 1025–1036.

- Weijers J, Fonagy P, Eurelings-Bontekoe E, Termorshuizen F, Viechtbauer W, Selten JP (2018) Mentalizing impairment as a mediator between reported childhood abuse and outcome in nonaffective psychotic disorder. Elsevier Ireland Ltd Psychiatry Research 259, 463–469.

- Wickham S, Bentall R (2016) Are specific early-life adversities associated with specific symptoms of psychosis?: A patient study considering just world beliefs as a mediator. Journal of Nervous and Mental Disease 204, 606–613.

- Wolke D, Lereya ST, Fisher HL, Lewis G, Zammit S (2014) Bullying in elementary school and psychotic experiences at 18 years: A longitudinal, population-based cohort study. Psychological Medicine 44, 2199–2211.

- Yamasaki S, Ando S, Koike S, Usami S, Endo K, French P, Sasaki T, Furukawa TA, Hasegawa-Hiraiwa M, Kasai K, Nishida A (2016) Dissociation mediates the relationship between peer victimization and hallucinatory experiences among early adolescents. The Authors Schizophrenia Research: Cognition 4, 18–23.

Study 3
Supplementary material

Supplementary Table 1

Demographic and baseline factors related to inclusion in the study.

	Included N=330	Not Included N = 102	Stat.	P-value
Age in y, M (SD)	24.75 (4.78)	23.95 (4.35)	t(430) = -1.498	.135
Sex, male, % (N)	65.8 (217)	69.6 (71)	$\chi^2(1) = 0.520$	.471
SES, % (N)				
Low	19.4 (64)	37.3 (38)	$\chi^2(2) = 14.147$	.001
Intermediate	43.9 (145)	31.4 (32)		
High	36.7 (121)	31.4 (32)		
GAF Baseline, M (SD)	42.12 (16.93)	40.89 (16.52)	t(387) = -0.605	.546
Insight at presentation, % (N)				
Absent	28.6 (91)	37.9 (36)	$\chi^2(2) = 11.648$	.003
Partial	45.6 (145)	52.6 (50)		
Complete	25.8 (82)	9.5 (95)		
DUP in weeks, Median (IQR)	12.1 (65.9)	16.9 (60.7)	U = 15486.500	.223
Cannabis dependance, % (N)	25.3 (80)	25.7 (26)	$\chi^2(1) = 0.007$	.932
Diagnostic, % (N)				
Schizophrenia	57.6 (190)	56.9 (58)	Fisher Exact Test	.595
Schizophreniform/BPE.	12.7 (42)	17.6 (18)		
Schizoaffectif disorder	8.8 (29)	5.9 (6)		
Major depression[a]	3.6 (12)	3.9 (4)		
Biopolar disorder	7.3 (24)	3.9 (4)		
Others	10.0 (33)	11.8 (12)		

Note. IQR: Interquartile range, BPE: Brief psychotic episode.
[a] with psychotic features SES: socio-economic status;
GAF: Global Assessment of Functioning. DUP: Duration of Untreated Psychosis. M: Mean; SD: Standard deviation.

Study 4
Supplementary material

Supplementary Table 1

Studies exploring the interplay between childhood adversity, DNA methylation and clinical features

Author year	Sample size Gender (M/F) Ancestry or population	Design	Measure of adversity	Objective	Tissue	Biological Pathway (gene)	Diagnosis/ psychopathology measure	Analyses/ Confounders	Main Findings
Candidate genes studies									
Hypothalamic Pituitary Adrenal Axis studies									
(Misiak et al., 2020)	85 inpatients with SCZ 56 HC SCZ: 45M/40F HC: 22M/34F Polish sample	Cross-sectional	CECA	(i)Examine *FKBP5* methylation in patients with FEP, acutely relapsed SCZ (SCZ-AR) patients, and HC. (ii) Investigated the association between clinical manifestation, cognitive performance and a history of CA in this group of patients.	Blood (leukocytes)BC + PCR +PYR Pyrosequencing	4 CPGs *FKBP5*	Diagnoses: (OPCRIT) Psychosis: (PANSS) Depression: (MADRS) Mania: (YMRS) Functioning: (GAF) Cognitive performance (RBANS)	Analyses of co-variance Age, sex, body mass index (BMI), cigarette smoking status, cortisol levels and CPZ (chlorpromazine) equivalent	Lower methylation in *FKBP5* CpG4 (and not CpG1, 2 and 3) related to parental antipathy and sexual abuse. (ii) Lower DNAm of FKBP5 associated to better cognitive performance in patients, with an opposite pattern in HC.
(Bustamante et al., 2018)	N= 112 (56 with MDD; 56 without MDD) 50M/62F European American/African American /other	Cross-sectional Case-control (nested)	Adaptation of CTS and the CTQ Composite (CA)	(i) Whether *FKBP5* DNAm mediates CA-Depression	Blood BC + PCR + Pyrosequencing	FKBP5	Depression symptoms severity (PHQ-9)	Mediation (B & K) with regression-based approach Age, sex, race, PBMC count, medication	(i) Null mediation (Path CA-DNAm was not significant)

(Klinger-König et al., 2019)	N=3965 general public 48% Male (2078M/11887F) Caucasian sample	Cross-sectional	CTQ	(I) to test main effects of CA, MDD, and the SNP rs1360780 on DNAm of five CpG sites of intron 7 of the FKBP5 gene, and the mean DNAm of all CpGs (ii) to test the two-way interactions (CA x MDD, CA x SNP, MDD x SNP) and the three-way-interactions (CA x depression x SNP) on FKBP5 DNAm were tested	Blood MALDI-TOF mass spectrometry using EpiTYPER by MassARRAY	Five CpG sites in intron 7 of the FKBP5 gene	Lifetime MDD (M-CIDI) Severity of depressive symptoms (BDI-II) Lifetime MDD: PHQ-9	2- and 3-way interactions effects Smoking, waist circumference, white and red blood cell counts, platelet counts and mean platelet volume, fibrinogen, glycated haemoglobin, cystatin C, triglycerides and time of blood sampling on the methylation levels of the five CpG sites were tested	No main or interaction effects found.
(Tozzi et al., 2017)	Sample 1 31MDD/29HC HC:17F/12M MDD:21F/10M Sample 2 25MDD/21HC HC:13F/8M MDD:15F/10M Irish sample	Cross-sectional	CTQ	(i) whether CA is associated with FKBP5 DNAm in MDD and controls (ii) whether FKBP5 DNAm is associated with structure and function of emotional processing regions.	Blood BC + PCR + Pyrosequencing	CG-6 and CG-7 in the intron 7 region of FKBP5	The Hamilton Depression Scale (HAM-D) 21-item version (Hamilton, 1986), Beck's Depression Inventory (BDI)	General linear model (GLM) Correlations Age, sex, site, and medication	(i) negative correlation CTQ/FKBP5 (ii) lower FKBP5 DNAm associated to reduced grey matter in frontal orbital gyrus bilaterally
(Klengel et al., 2013)	N= 76 Trauma subjects: 30 Non Trauma: 46 22M/8F 36M/10F Predominantly African American	Cross-sectional	CTQ and TEI	*To test whether FKBP5* (genotype) × CA interactions are mediated by epigenetic modifications	Blood BC + PCR + DNAm Validation Using Sequenom's EpiTYPER MassARRAY	FKBP5	Current/lifetime PTSD diagnosis _ symptoms (mPSS and CAPS)	Logistic regression Age and gender, current depressive symptom/CA Bonferroni correction	Demethylation of the FK506 mediate the combined effect of CA and the *FKBP5* risk allele on PTSD

(Bustamante et al., 2016)	N=147 (73 with MDD and 74 without MDD) 56M/91F European American/African American /other	Cross-sectional Case-control (nested)	Adaptation of CTS and the CTQ Composite (CA)	(I) CA & PHQ-9 interaction on NR3C1 (ii) whether NR3C1 differences are associated to gene expression (not detailed)	Blood BC + PCR + Pyrosequencing	NR3C1	Depression symptoms severity (PHQ-9)	Linear regression Age, sex, race, PBMC count, medication	(i)No significant CA & PHQ-9) interactions were observed. Trauma alone was associated with significantly lower NR3C1 GE.
(Farrell et al., 2018)	N=33 MDD/34 Controls 21M/45F	Cross-sectional	CTQ	Associations between CA ad (NR3C1) exon 1F and the FKBP5 gene intron 7	Blood BC + PCR + Pyrosequencing	NR3C1 exon 1F and the FKBP5 gene intron 7	MDD: (M.I.N.I) + scored > 17 on the HAM-D-21	Correlation analyses (no adjustment in CTQ/methylation)	DNAm levels at specific CG sites within the NR3C1 exon 1F were related to childhood emotional abuse severity. (positive association) FKBP5 no association
(Tyrka et al., 2016)	N= HC 340 adults (147 CA+;193 CA-) CA+:59M/88F CA-: 68M/125F 78% white	Cross-sectional Population based	CTQ + interview Composite	(i)impact of psychopathology/CT on NR3C1 1promote region (comparing means between 4 groups)	Blood Leucocytes BC + PCR + Pyrosequencing	NR3C1 1promote region	Anxiety, depressive and substance use disorders SCID	General linear models Age, sex and oral contraceptive use (excluded patients on psychotropic medication)	(i)Number of adversities was negatively associated with NR3C1 methylation in participants with no lifetime disorder but not in those with a lifetime disorder
(Perroud et al., 2011)	N: 230 patients (101 Borderline PD; 114 MDD subjects without PTSD; 15 MDD with comorbid PTSD) Borderline PD: 6M/95F MDD without PTSD: 35M/64F MDD with PTSD: 4M/11F Suisse/French sample (NA race)	Cross-sectional Clinical sample	CTQ composite	(i)Impact of CA on NR3C1 promote region	Blood white cells BC + PCR +Pyrosequencing	exon 1F NR3C+ promoter	Depression and PTSD: French-DIGS Borderline PD: Screening Interview for Axis II Disorders Borderline PD part	Linear regression Gender, primary Axis I diagnosis, alcohol/substance use; PTSD, history of suicide attempt, severity of depression and of Borderline PD and current medication	Childhood sexual abuse, its severity and the number of type of maltreatments positively correlated with NR3C1 methylation In Borderline PD, repetition of abuses and sexual abuse with penetration correlated with a higher methylation percentage
(Wang et al., 2017)	N=149 64 GAD and 85 HC HC: 28/57 GAD: 19/45 HC (Han/other) 82/3 GAD 63/1 Chinese population	Cross-sectional	CTQ	(i) link NR3C1 1F promoter methy-clinical parameters (including CA)	Blood PMBCs BC + PCR	NR3C1 1F promoter	GAD diagnosis DSM-IV axis I + (HAM-A)	Correlation analyses Multiple comparisons None	Overall, NR3C1 1F Meth increased and the mRNA level of GR decreased in the PBMCs in patients with current GAD compared with healthy controls Negative correlation of overall methylation of the NR3C1 1F promoter with its mRNA level in the PBMCs CA tended to induce lower methylation in the NR3C1 1F promoter

(Steiger, Labonté, Groleau, Turecki, & Israel, 2013)	N= 96 64 BN; 32 HC Female sample Canadian sample	Cross-sectional Case control (Nested)	CTI	(i) compare NR3C1 prom meth between BN and HC (ii) in BN impact of CA/suicidality/Borderline PD on NR3c1 prom meth.	Blood Lymphocytes BC + PCR	NR3C1	-EDE for BN, -SCID-I and DIS4 for comorbid DSM-IV axis I diagnosis. CAPTSDI for PTSD SCID-II for comorbid axis II diagnosis axis II diagnosis	ANOVA/ANCOVA Binge frequency, vomit frequency, BMI, medication	(i) more meth in women with BN and or Borderline PD/suicidality vs HC (ii) none effect of CA
(Rachel Yehuda et al., 2015)	N: 122 veterans 61 PTSD 61 Non PTSD (resilients) Male sample 47% Hispanic 26.2% Non-Hispanic white 26.3 Non hispanic back	Case-control (Nested)	ETI	NR3C1-1F promoter meth in PTSD versus Non-PTSD veterans (resilients)	Blood PBMCs BC + PCR	NR3C1-1F promoter	PTSD diagnosis (CAPS)	Bivariate and partial correlations PBMC ratio as covariate	Lower NR3C1-1F promoter methylation in PTSD veterans
(Daniel S Schechter et al., 2015)	N= 45 IPV-PTSD: 28 Controls: 17 Female Swiss sample	Cross-sectional	(BPSAQ) (TLEQ)	Link between CA and NR3C1 1F meth and its inverse correlation with PTSD	Saliva BC + PCR + Pyrosequencing	NR3C1 1F	Current/lifetime PTSD diagnosis symptoms (PCL-S and CAPS)	Correlations Bonferroni corrections	Maternal PTSD severity and parenting stress were negatively correlated with the mean % NR3C1 DNAm, which was associated with mPFC activity in the mother and poorer cooperativeness in the child
(Labonte, Azoulay, Yerko, Turecki, & Brunet, 2014)	N=46 PTSD= 30 Controls (non trauma) =16 PTSD 15M/15F Controls (8M/8F) Canadian sample	Cross-sectional	Index traumatic events	To test whether HPA axis alterations in PTSD are associated with variations in cortisol levels due to changes in NR3C1 expression	Blood Lymphocytes BC + MALDI-TOF mass spectrometry using EpiTYPER by MassARRAY	NR3C1	PTSD: CAPS	Mixed model analysis Correlations Least significant difference post hoc tests Age, sex.	Significant overall and site-specific hypomethylation in NR3C1 promoter (1B and 1C) in the PTSD group compared to controls

(Radtke et al., 2015)	N=46 from general population 28F/18M German sample	Cross-sectional	MACE German version	(i) whether the simultaneous occurrence of ELS and increased NR3C1 DNAm is accompanied by an increased vulnerability to the development of psychopathology.	Blood Lymphocytes GWAS The Human Methylation 450 K array + BC	All probes spanning the NR3C1 gene, which are included on the Human Methylation 450 K array (41 probes)	BSL- 23 HSCL MINI KIDSCREEN-53	Multiple-regression analyses Correlations None	Additive effect of childhood maltreatment and NR3C1 DNAm predicting borderline personality disorder (Borderoline PD)-associated symptoms
(R. Yehuda et al., 2016)	N= 122 combat veterans with similar level of CA (61 PTSD; 61 Non-PTSD)(same amount of adversity) Male sample PTSD Non-PTSD Hispanic 32.8% Non-Hispanic White 37.3% Non-Hispanic Black 26.2%	Cross-sectional	ETI	(i) DNAm NR3C1-1F promoter between PTSD and non-PTSD (ii)Testing whether NR3C1-1F promoter DNAm would be inversely associated with NR3C1-1F expression and PTSD clinical outcomes	Blood BC + Pyrosequencing	NR3C1-1F	PTSD with CAPS)	A multivariate ANOVA Bivariate and partial correlations PBMC ratio	(i) lower NR3C1-1F promoter DNAm in PTSD vs Non-PTSD veterans (ii) NR3C1-1F promoter DNAm correlated PTSD-related symptoms (distress, dissociation, and poorer
(Martin-Blanco et al., 2014)	N = 281 Borderline PD 42/239 Caucasian of European descent	Cross-sectional	CTQ-SF	Association between NR3C1 methylation status, the history of CT, and current clinical severity in subjects with Borderline PD	Blood Leukocytes BC + PCR + Pyrosequencing	NR3C1	Borderline PD (SCID-II, DIB-R)	Linear regression models	NR3C1 methylation in subjects with Borderline PD may be associated not only with CT but also with clinical severity
(Kaminsky et al., 2015)	421 (general population discovery sample) 299F/421M 93.1% African American ancestry	Cross-sectional	CTQ and TEI	(i)methylation SKA2 in relation to CTQ (II)CTQ vs SKA2meth on suicide attempt/PTSD	Blood (replication saliva N=61) Illumina (San Diego, CA, USA) HumanMethylation450 BeadChip PCR + Pyrosequencing	SKA2 methylation	Anxiety symptoms were assessed as a continuous score from the (HAM-A).	Linear regression analysis Age, sex and race	(i)SKA2 methylation interacted with CTQ scores to predict lifetime suicide attempt in saliva and blood (ii)SKA2-meth predicted PTSD caseness when CTQ was considered

(Sadeh, Spielberg, et al., 2016)	200 trauma-exposed veterans 182/18 White non-Hispanic	Cross-sectional	CAPS	Associations between SKA2 methylation, cortical thickness and psychiatric phenotypes linked to suicide	Blood BC + PCR + HumanMethylation450 K microarrays	SKA2	Current depression symptom severity was assessed was assessed via the14-item total depression subscale of the self-report depression anxiety stress scale	Hierarchical linear regression models + Mediation analyses Genotype	PTSD symptom severity was positively correlated with SKA2 DNAm. Mediation analyses showed a significant indirect effect of PTSD on cortical thickness via SKA2 methylation status.
(Sadeh, Wolf, et al., 2016)	466 trauma-exposed veterans and intimate partners 302/164 With non-Hispanic	Cross-sectional	CAPS	Associations between SKA2 DNAm, broad dimensions of psychiatric symptoms, and suicide phenotypes in adults with high levels of trauma exposure	Blood BC + PCR	SKA2	MDD (SCID-I) Internalizing and Externalizing Psychopathology (SCID-IV) Suicide Phenotypes (Major depressive episode module of SCID-I)	Multiple regression analysis Structural equation modelling Hierarchical regression analyses Age, sex, and the first three ancestry principal components	SKA2 methylation may index a general propensity to experience stress-related psychopathology, including internalizing disorders and suicidal thoughts and behaviors.
Studies on the oxytocin pathway									
(Simons, Lei, Beach, Cutrona, & Philibert, 2017)	100 (primary caregivers) Female sample 100% African American ancestry	Longitudinal	Adult adversity (the four-item Unmet Material Needs Scale and the revised version of the community deviance scale developed for the Project on Human Development in Chicago Neighborhoods)	(i) mediation by methylation of OXTR between adversity and negative schemas and depression	Blood BC + Illumina (San Diego, CA) HumanMethylation450 Beadchip	OXTR methylation	Mini-Mood and Anxiety Symptoms Questionnaire	SEM Childhood trauma, age, romantic relationship status, individual differences in cell types, and average level of genome-wide methylation	The effect of adult adversity on distrust and pessimism is largely mediated by methylation of OXTR. The effect of OXTR methylation on depression is fully mediated by its association with distrust and pessimism.

(Smearman et al., 2016)	393 (general population) 70.7% Female 100% African American ancestry	Cross-sectional	CTQ Traumatic Events Inventory	(i) assessing the role of OXTR methylation in the link between abuse and psychopathology	Blood Omni-Quad 1M or the Omni Express BeadChip (Illumina, San Diego, CA)	OXTR methylation	21-item Beck Depression Inventory	Regressions or interactions Age, sex, cellular heterogeneity, and positional effects associate with methylation of one or more OXTR CpG sites	Child abuse associated with higher methylation of two CpG sites yet did not survive correction or serve as a mediator of psychopathology
Studies on the serotoninergic pathway									
(Domschke et al., 2012)	N 65 PD (44F/21M) 65 HC (44F/21M) 100% Caucasian origin	Cross-sectional	Life events (comprehensive scale derived from other life event scales)	(i) investigate DNAm changes associated to PD and its link with life events	Whole blood BC + PCR	MAOA	Diagnosis of PD on the basis of medical records and structured clinical interviews according to the criteria of DSM-IV	Correlations or regressions Gender stratification Bonferroni's correction Age, smoking status and medication	In PD Negative life-events associated to decrease DNAm in MAOA at one CpG site; while positive life events associated with increased MAOA DNAm at another CpG. No such effect was found in controls
(Kang et al., 2013)	N=108 MDD 75% female South Korean population	Prospective (12 weeks)	Questionnaire before age 16 including abuse and another adversities such as financial problems	(i) Link between SLC6A4 DNAm and CA and clinical outcomes At baseline and FU	Blood BC + PCR	SLC6A4	Depression (HAMD), anxiety (HAMA), functioning (SOFAS),	Correlations None	Higher SLC6A4 associated with CA and worst clinical presentation (SOFAS) at baseline only not at FU
(Peng et al., 2018)	119 monozigotic twin pairs 29.5% female USA sample	Cross sectional	ETISR-SF	(i) test mediation between CA and depression via stress related genes	Blood Bisulfite pyrosequencing Or 450K BeadChip.	BDNF, NR3C1, SLC6A4, MAOA, MAOB	Depression (BDI-II)	Mediation analyses via regression models Twin age, family income, cigarette smoking (pack-year), alcohol consumption, physical activity, BMI, and history of PTSD	BDNF and NR3C1 mediated ~20% of the association between CA and depressive symptoms

(Melas et al., 2013)	N: Depression: 82 HC: 92 100% female Swedish population	Cross-sectional Case control (nested)	PART Specific adversities (Familial constraints/problems; Parental death/divorce)	(i) Link between Depression and MAOA methylation (ii) Depression + CA types on NR3C1 1-F region methylation (iii) mediation by MAOA-L between parental death and NR3C1 1-F region methylation	Saliva Leucocytes BC + PCR	MAOA NR3C1 1-F region	Depression (MDI)	Linear regression Age, diagnosis, parental death, financial problems, familial constraints, parental divorce, genotype, smoking	(i)Early parental death associated with increased DNAm at NR3C1; (ii)MAOA-genotypic variations may affect the extent of NR3C1 methylation. (iii)No association between EPD and depression
(Perroud et al., 2016)	N= 349 (Borderline PD: 116; ADHD: 111; BD: 122) Borderline PD: 10M/106F ADHD: 78M/33F BD: 57M/65F European ancestry	Cross-sectional	CTQ	(i)Link between CA/5HT3AR DNAm and severity of the disease (ii)Methylation mediates linkt between CA and psychopathology	Blood BC + PCR	5HT3AR	Borderline PD/ADHD (DIGS); BD (SCID) Clinical index severity (admissions, suicide attempts, comorbid OH use etc..)	(i)Liner regression models (ii)Mediation analysis age, gender, and category of diagnosis (i) Bootstrapping (ii)	CA was associated with clinical severity and this was mediated by meth on two CPGs at 5-HT3A R
(Daniel S. Schechter et al., 2017)	N= 35 IPV-PTSD:18 Non-PTSD mothers (n=17) Female Swiss sample	Cross-sectional	(BPSAQ) (TLEQ)	To explore link between HTR3A DNAm and maternal life stress, IPV and PTSD	Saliva BC + PCR + Pyrosequencing	HTR3A	Current/lifetime PTSD diagnosis symptoms (PCL-S and CAPS)	Correlations and multiple regressions Bonferroni corrections	Methylation status of several CpG sites in the HTR3A gene was associated with maternal IPV and IPV-PTSD severity
(Koenen et al., 2011)	N=100 PTSD: 23 Non PTSD with 1 trauma (resilients): 77 Non PTSD: 32M/45M PTSD: 8M/15F 79% African-American	Nested case-control study	Questionnaire on any traumatic events from a list of 19 (interpersonal and non-interpersonal)	To test whether SLC6A4 genotype and methylation levels were associated with PTSD and modified the effect of the number of traumatic events on risk for PTSD	Blood (PBMC) BC + PCR + Pyrosequencing	SLC6A4	PTSD diagnosis (PTSD checklist, delineated in three different ways)	Main and interaction effects in negative binomal logistic regression age, PBMC count, number of traumatic events,	Neither SLC6A4 genotype nor SLC6A4 meth were associated with PTSD SLC6A4 meth modified the effect of the number of CA on PTSD after controlling for SLC6A4 genotype. Persons with more CA but only at low SLC6A4 meth levels were at increased risk for PTSD.

Studies on Neurogenesis									
(Thaler et al., 2014)	N=66 64 BN; 32 HC Female sample Canadian sample	Cross-sectional	CTI	Link BDNF DNAm- BN; Borderline PD CA	Blood Lymphocytes BC + PCR + MALDI-TOF mass spectrometry using EpiTYPER	BDNF	-EDE for BN, -SCID-I and DIS4 for comorbid DSM-IV axis I diagnosis. CAPTSDI for PTSD SCID-II for comorbid axis II diagnosis	Multilevel modelling (MLM), None	Women with BN showed Increases BNDF DNAm groups composed of individuals with CA or Borderline PD had particularly high levels of DNAm at selected CpG sites
(Moser et al., 2015)	N=46 20 control, 8 subthreshold IPV-PTSD 18 IPV-PTSD+ Female sample Swiss Sample	Cross-sectional	BPSAQ	(i) explore the link between BDNF promoter DNAm and patterns of neural activity that are associated with maternal response to stressful versus non-stressful child stimuli. (ii) test correlations between levels of IPV and BDNF meth	Saliva BC + PCR + Pyrosequencing	BDNF	Lifetime PTSD: CAPS	Correlations Monte Carlo simulation None	(i) Severity of maternal anxiety was significantly correlated with overall DNAm of 4 CpG sites in exon IV of the BDNF promoter region (ii) DNAm of CpG3 was associated with maternal exposure to domestic violence during childhood
Studies on other pathways									
(Domschke et al., 2013)	N=66 Panic disorder 65 HC 67% female German population	Cross sectional twin study	Negative life events (not detailed)	(i) Linkin between DAD1/GAD2 and panic disorder (ii) Linkin between DAD1/GAD2 and CA	Blood BC + PCR	GAD1 GAD2	Panic disorder (SKID-I)	Correlation or regressions Matched sample	(i) Patients with panic disorder had lower average GAD1 (ii) life events was associated with decrease DNAm GAD1.
(Wolf et al., 2017)	N= 339 PTSD Male veterans White non-Hispanic	Prospective 6.5 years after DNA collection and PTSD assessment	TLEQ	(i) link CA/PTSD-accelerated/decelerated epigenetic age (ii) link DNAm age and mortality rates at FU	Blood BC + PCR	Accelerated DNAm age	PTSD diagnosis (CAPS)	(i)Multiple regressions (ii)Cox regression Ancestry (top two PC), sex white blood cell count proportion	(i)No effect. Only Hypeearousal associated with DNAm age (ii)DNAm age associated with 13% greater mortality at FU
(Boks et al., 2015)	N= 96 soldiers 32 low CA 67 high CA Male soldiers Dutch sample	Prospective study (pre-post deployment)	CTQ	(i) Prospectively investigated link DNAm accelerated age and trauma and (ii) PTSD related symptoms at follow-up	Blood BC + PCR Illumina 450K DNA methylation arrays	DNAm accelerated age	PTSD diagnosis (SRIP)	Linear regression analyses Cell composition, alcohol, CA, excluding smokers and medicated subjects	(i) CA significantly accelerated epigenetic ageing (ii) Development of PTSD symptoms was inversely associated with epigenetic ageing

(Sipahi et al., 2014)	N= 60 30 PTSD 30 Non PTSD (resilients) PTSD 7M/23F Resilients 7M/23F 46 (77%)African-American 12(20%) Caucasian 2(1%) Hispanic	Prospective (approx. 1 year pre-post trauma)	Check list of interpersonal and non-interpersonal traumatic experiences	(i) explore pre trauma DNAm differences and whether changes during follow-up predict PTSD	Blood BC + PCR + Pyrosequencing	DNA methyltransferase 1 (DNMT1), DNMT3A, DNMT3B and DNMT3L	PTSD diagnosis was assessed via structured interview administered via telephone according to Breslau et al (1998)	Linear regression models Bonferroni's correction Age, gender and pre-trauma symptom severity	(i) DNMT1 DNAm increased following trauma in PTSD only DNMT3A and DNMT3B DNAm increased following trauma in PTSD/resilients In PTSD only, pre-trauma DNAm was lower at a DNMT3B CpG site lower pre-trauma DNMT3B DNAm at this site was predictive of worsening of PTSS post-trauma
(Kimmel et al., 2016)	N: 51 (66% MDD and 33% bipolar (I, II or NOS)) Female sample John Hopkins cohort: 30% Caucasian/70% African American	Cross-sectional	Sexual abuse (clinical interview)	(i)To investigate if SA is associated with OXTR DNAm; (ii) whether this effect is moderated by PPD status.	Blood BC + PCR + Pyrosequencing	OXTR	MDD: Based on a psychiatric interview according to DSM-IV criteria	Correlation analyses Linear regression Bonferroni correction None	SA status and PPD significantly interacted to modulate OXTR DNAm. Post hoc analysis suggested that SA had independent effects on OXTR-Meth non-PPD women
(Engdahl, Alavian-Ghavanini, Forsell, Lavebratt, & Rüegg, 2021)	N=186 GP 121F/65M Swedish sample	Cross-sectional	General questionnaire	(i) testing whether CA affects *GRIN2B* methylation in humans. (ii) investigate if *GRIN2B* DNAm is associated with MDD	Saliva BC + Pyrosequencing	GRIN2B	(MDI) Sheehan Patient-Related (Panic) Anxiety Scale	Linear regression models Age, sex and CA	CA associated with increased GRIN2B DNAm GRIN2B DNAm not associated with MDD status
(Zou, Huang, Wang, Min, & Zhou, 2020)	113 patients with PD and 130 HC PD 43M/70F HC: 51M/79F Chinese sample	Cross-sectional	CTQ	(i) explore whether inflammatory related genes DNAm may be associated with PD and severity of PD symptoms, (ii) explores the association of DNAm of these genes with CA.	Blood BC + PCR	13 CpG region from the promoter regions of the inflammatory-related genes, *CCL3_, CRP_, CSF2_, CXCL8_, IFNG_1, IFNG_2, IL12B_, IL1A_, IL-4_, IL-6_1, IL-6_2, TNF_1, TNF_2*	Hamilton Anxiety Rating Scale (HAMA) and the Panic Disorder Severity Scale (PDSS) Chinese version.	Correlations False discovery rate multiple comparison correction	(i) IL-4 DNAm higher in PD vs HC (iia)The methylation levels of IL-4 DNAm positively related to the severity of panic and anxiety symptoms. (iib)Hypermethylation of CSF2, CXCL8 and IL-4 associated with higher CA in PD

(Misiak et al., 2015)	N= 96 (48 FES; 48HC) FES: 21/27 HC: 23/25 European (Poland)	Cross-sectional Case-control	(ETISR-SF) Composite FEP+(CA) FEP-(NonCA)	(i) Methylation of LINE-1 and BAGE between FES +, FE- vs HC (ii) signature of CA on LINE and BAGE	Blood/Leucocytes Bisulphite restriction assay (BC + PCR)	Retrotransposon BAGE/LINE	OPCRIT based on DSM-IV and ICD-10	(i) ANOVA (ii) Linear regression Age, gender and BMI, smoking, one-carbon metabolism parameters (Hcy, folate and vitamin B12); medication	(i) FES+ had lower LINE-1 methylation in comparison with FEP – or HC. (ii) EA and total trauma predicted lower LINE-1 methylation in FES patients,

EWAS studies

(Weder et al., 2014)	N= 190 children (94 CA + traumatized and 96 CA -) 79M/111F 17% European American, 38% Hispanic, 30% African American, and 15% biracial	Cross-sectional	KSADS and CTQ and the PVI	To identify novel DNAm markers associated with depression in maltreated children using the Illumina 450K BeadChip.	Saliva Genome-wide Illumina 450K BeadChip array.	Candidate genes were also explored for: LC6A4, BDNF, NR3C1, FKBP5	Depression (MFQ) Other psychiatric diagnoses (KSADS-PL; CBCL; CDC' TRF; PTSD-CL)	(I) LMM EWAS associated to depression Demographic variables age, sex, or race/ethnicity (II) GEE to test the combined effect of CA and each CPG on depression M-values (logit transformation in log2 scale) were used (heteroscedasticity)	-ID3, GRIN1 and (TPPP) meth predicted depression. -Independent effects of Meth and CA on depression (no interaction) -CA_+ vs CA – differed in BDNF, NR3C1, FKBP5
(Prados et al., 2015)	N=189 96 Borderline PD; 93 MDD Borderline PD: 8M/88F MDD: 34M/59F Swiss sample	Cross-sectional	CTQ	Link between CA and EWAS DNAm in Borderline PD/MDD subjects	Blood DNA (whole blood) Genome-wide methylation was assessed using the Illumina 450	Hypothesis free	MDD and Borderline PD diagnosis (SCID-II and DIGS	(1) LSVM model to test link EWAS meth on MDD/Borderline PD (2) generated linear models. To test link between CTQ and EWAS meth LAMBDA of L1-SVM algorithm to test sparseness	CpGs within or near the following genes (*IL17RA, miR124-3, KCNQ2, EFNB1, OCA2, MFAP2, RPH3AL, WDR60, CST9L, EP400, A2ML1, NT5DC2, FAM163A* and *SPSB2*) differently methylated, either in Borderline PD compared with MDD or in relation to CA Pathways: inflammation Neural excitability and development or maintenance of nervous system structure of cell and regulation of cell functions

									molecule transport through cell membranes, calcium-ion-dependent exocytosis in both endocrine and exocrine cells, cycle progression, signal transduction, apoptosis and gene regulation neural plasticity and neurogenesis.
(Mehta et al., 2013)	N:169 HC (CA +): 108 PTSD with SA: 32 PTSD non-SA: 29 HC(CA+): 30M/78F PTSD SA+:5M/27F PTSD Non-SA+:13M/6F NA 93.5% African American	Cross-sectional	CTQ (abuse only) TEI	To interrogate DNAm in individuals with PTSD with or without childhood abuse vs HC with CA+	Blood (whole) Genome wide analyses Human Methylation 450k BeadChip	Hypothesis free	PTSD diagnosis where assessed using with the CAPS and the PSS scales	General linear models Sex, age, ethnicity, substance abuse, and treatment	Gene-expression and DNAm profiles were different in PTSD according to the exposure (or not) to childhood abuse. These gene-expression changes were accompanied and likely mediated by changes in DNA methylation in the same loci to a much larger proportion in the childhood abuse (69%) vs. the non-child abuse-only group (34%)
(Uddin et al., 2010)	N=100 PTSD:23 Non-PTSD:77 (all at least with one PTE) Overall sample: 40M/60F 14% white 79% African American 7% other race	Cross-sectional	Check list of 19 PTE	(i) comparing uniquely methylated and unmethylated genes in PTSD versus non-PTSD and examining those overlapping across the two conditions	Blood Genome wide analysis HM27 DNAm Analysis BeadChip by Illumina (27.000 CpG covering more than 14.000 genes	Hypothesis free	PCL-C	McNemar's $\chi 2$ test. Checked that PTSS and non-PTSD participants did not differ in age, sex, race, or peripheral blood mononuclear cell count	In PTSD participants there was a predominance of uniquely methylated genes involved in Inflammatory response (26 genes), immune response (38 genes) and innate immune response (11 genes) whereas there was a predominance of uniquely methylated genes involved in neurogenetic processes in non-affected PTSD (developmental process (50 genes) and generation of neurons (37 genes)

(Comes et al., 2020)	N=96 BD 50F/46M 100% of caucasians europeans sample	1 year follow-up	(CTS) (non traumatic stress)	(I) Exploring sites in vicinity to candidate genes previously implicated in stress response	Peripheral blood Genome wide/candidate gene EpiTect ® Bisulfite Kit from QIAGEN (850.000 methylation sites)	genes in vicinity to: BDNF, FKBP5, IL6, SLC6A4, and OXTR	Sample of Bipolar disorder parents (no instrument reported)	Linear mixed effects model (LMM) Cell composition, smoking, patients on medication were excluded.	No locus withstood multiple correction testing Limited evidence of association between DNAm and non-traumatic life events Suggestive evidence of association of CTS with *POU6F2* *FER1L6*
(Arranz et al., 2021)	Sample 1 N= 49 Borderline PD CA+/47 Borderline PD CA- and HC=44 Sample 2 N = 293 Borderline PD patients and N = 114 controls 100% female and Caucasian ancestry	Cross-sectional	CTQ	BORDERLINE PD with and without CA EWAS	Peripheral blood genome wide (Illumina Infinium HumanMethylation450 k beadchip)	Hypothesis free	SCID II (DIB-R), McLean Screening Instrument for Borderline Personality Disorder (MSIBorderline PD),	Linear regressions Age, PC, and presence or absence of trauma in the first analysis, and age and PC for the second and third analyses	DNAm differences between Borderline PD+/Borderline PD- and controls In *POU5F1* *GPR55* *GGT6* (REDOX) *TNFRSF13C* (CELL B ACTIV) *FAM113B* DISC2 (NS) DNAm differences between Borderline PD+/Borderline PD- and controls No corrected significant p-value: *NKX2-1* *PXDN* *POU5F1* Enrichment: neurogenesis, regulation of cell differentiation and transport
(Lutz et al., 2017)	N:78 HC:26 MDD CA+:25 MDD CA-:27	Cross-sectional	CECA	(i) DNAm differences between MDD CA+ and HC and links with suicide and depression status	Post-morten brains (Anterior cingulate cortex tissue) Genome Wide Illumina MiSeq (696,000 probes)	Hypothesis free	Diagnoses based on DSM-IV criteria.	Linear regression analyses Age, gender, and RNA integrity number	(i) Top 3 genes different between MDD CA+ and HC are *LINGO3, POU3F1* and *ITGB1* involved in neurogenesis (myelinisation processes and oligodendrocytes formation) depression and suicide did not relate to such DNAm changes

DNA: Deoxyribonucleic acid; DNAm: DNA methylation CA: Childhood Adversity; EA: emotional abuse; SA: sexual abuse; CTS: childhood trauma screener; SCZ: Schizophrenia; FES: First Episode of Psychosis patients; HC: Healthy Controls; CTQ: Childhood Trauma Questionnaire; CTS: Conflict Tactics Scale/screener; MDD: major depressive disorder; BC: Bisulfite conversion; PIV: partner violence inventory; KSADS: Kiddie-Sads Child psychiatry Interview; ID3: DNA-Binding Protein Inhibitor ID–3; GRIN1: Glutamate Receptor, Ionotropic N-methyl-D-aspartate (NMDA) 1; TPP areP: Tubulin Polymerization Promoting Protein; GAD: generalized anxiety disorder; NR3C1: Glucocorticoiddd receptor gene; FKBP5: FK506 binding protein 5; BDNF: Brain Derived Neurotrophic factor; MAOA: Monoamine oxidase A gene; SKA2: Spindle And Kinetochore Associated Complex Subunit 2 gene; SLC6A4: Solute Carrier Family 6 Member 4 (serotonin transporter gene); HTR3A: 5-Hydroxytryptamine Receptor 3A gene; DNMT1: DNA Methyltransferase 1; OXTR: Oxytocin Receptor gene; GRIN2B Glutamate Ionotropic Receptor NMDA Type Subunit 2B; HPA: hypothalamic–pituitary–adrenal axis; CpG: Cytosine, phosphate Guanine (CpG island); SNP: single nucleotide polymorphism; CBCL: the child Behaviour Checklist; SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; PD: Panic Disorder; Borderline PD: Borderline Personality Disorder; PTSD: post-traumatic stress disorder; IPV: Interpersonal violence; ADHD: Attention deficit hyperactivity disorder; DIGS: Diagnostic Interview for Genetic Studies; PART: A Population Based Study of Mental Health in the Stockholm County; EPD: Early parental death; MDI: the Major Depression; Inventory; LES: Life Experiences Survey; PSS: Perceived Stress Scale; HAM-A: Hamilton Anxiety Rating Scale; PMBCs: peripheral blood; DIB-R: Revised Diagnostic Interview for Borderline; EDE: Eating Disorder Examination; CTI: Childhood Trauma Interview; CAPTSDI: Clinician-Administered Post- Traumatic Stress Disorder Scale; PPD: post-partum depression; PVI: Partner Violence Inventory; TLEQ: Traumatic Life-event questionnaire; SRIP: self- report inventory for PTSD; ETI: Early Trauma Inventory; PBMCs: in peripheral blood mononuclear cells; TEI: Trauma Event Inventory; CAPS: clinical administered PTSD Scale; mPSS: Modified PTSD Symptomatic Scale; TLS: Total Life Stress; BPSAQ: Brief Physical and Sexual Abuse Questionnaire; ETISR-SF: Early Trauma Inventory Self Report-Short Form; LINE: Long interspersed nuclear elements; BAGE: B Melanoma Antigen; PCR: Polymerase chain reaction; OPCRIT: Operational Criteria Checklist for Psychotic Illness and Affective Illness; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th edition); ICD-10: International Statistical Classification of Diseases and Related Health Problems; MACE: Maltreatment and Abuse Chronology of Exposure; CECA: Childhood Experience of Care and Abuse Interview; CCL3: C-C Motif Chemokine Ligand 3; CRP: C-Reactive Protein; CSF2: Colony Stimulating Factor 2; CXCL8: C-X-C Motif Chemokine Ligand 8; IFNG: Interferon Gamma; IL: Interleukin; TNF: Tumor necrosis factor; PHQ-9: Patient Health Questionnaire; MINI: Mini International Neuropsychiatric Interview; M-CIDI: Munich-Composite International Diagnostic Interview; BDI-II: Beck-Depression-Inventory-II; HSCL: Hopkins Symptoms Checklist-25; BSL-23: Borderline Symptoms Checklist-23; PANSS: Positive and Negative Syndrome Scale; MADRS: Montgomery–Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale; GAF: Global Assessment of Functioning; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; BMI: Body Mass Index; CPZ: chlorpromazine; TPPP: Tubulin Polymerization Promoting Protein; PTE: Post Traumatic event; PCL-C: PTSD checklist; POU6F2: POU Class 6 Homeobox 2; FER1L6: Fer-1 Like Family Member 6; SCID II: Structured clinical interview for DSM IV axis II personality disorders; NKX2-1: NK2 Homeobox 1; PXDN: Peroxidasin; POU5F1: POU Class 5 Homeobox 1; GPR55: G Protein-Coupled Receptor 55; GGT6: Gamma-Glutamyltransferase 6; KCNQ2: Potassium Voltage-Gated Channel Subfamily Q Member 2; EFNB1: Ephrin-B1 ; OCA2: the P gene; MFAP2: Microfibril Associated Protein 2; RPH3AL: Rabphilin 3A Like Without C2 Domains; WDR60 (dynein 2 intermediate chain 1; CST9L: Cystatin 9 Like; EP400: E1A; Binding Protein P400; A2ML1: Alpha-2-Macroglobulin Like 1; NT5DC2: 5'-Nucleotidase Domain Containing 2; FAM163A: Family With Sequence Similarity 163 Member A; SPSB2: SplA/ Ryanodine Receptor Domain And SOCS Box Containing 2; TNFRSF13C: TNF Receptor Superfamily Member 13C; FAM113B: Family with sequence similarity 113, member B, isoform CRA a; DISC2: a noncoding RNA molecule antisense to DISC1 (disruoted in Schizophrenia); LINGO3: Leucine Rich Repeat And Ig Domain Containing 3; POU3F1: POU Class 3 Homeobox 1; ITGB1: Integrin Subunit Beta 1; LMM: Linear mixed models; GEE: generalized estimating equation; LSVM: linear Support Vector Machine; HM27: Humanmethylation27. HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; SOFAS: Social and Occupational Functioning Assessment Scale; FU: follow-up; SCID: The Structured Clinical Interview for DSM-IV Axis I Disorders.

SUPLEMENTARY METHODS

Search Strategy and Selection Criteria

The main electronic searches were conducted on MEDLINE, EMBASE, and PsycINFO, through Ovid provider, up to May 2019, and were updated in April 2020. Relevant papers that were published after that date were also considered until the date of the submission in June 2021.

For articles included in sections 2 *("Evidence of epigenetic processes in major transdiagnostic pathways")* We searched Medical Subject Headings and keywords related to: (1) Epigenetics (including Epigenetics, EWAS, "epigenomics", CpG island, DNA Methylation); (2) Mental health (covering the different diagnosis and conditions of interest); using the Boolean operator "AND" (full list of search terms provided below).

For papers included in section 3 *("The epigenetic signature of childhood adversity and cannabis use")*, two different searches were conducted:

For the search related to childhood adversity we searched Medical Subject Headings and keywords related to: (1) childhood adversity (including various adversities such as abuse, neglect and other life events etc): (2)

Epigenetics (including Epigenetics, EWAS,"epigenomics", CpG island, DNA Methylation); (3) Mental health (covering the different terms such as mental condition or psychopathy) were combined using the Boolean operator "AND".

For the search related to cannabis use we searched Medical Subject Headings and keywords related to: (1) cannabis use (with term ssuch as Cannabis or "cannabis use") (2)

Epigenetics (including Epigenetics, EWAS,"epigenomics",CpG island, DNA Methylation); (3) Mental health (covering the different terms such as mental condition or psychiatry) were combined using the Boolean operator "AND" (full list of search terms for both searches are provided below).

Titles and abstracts, and subsequently selected eligible full texts of articles were screened independently by one author (LA) and checked by a second author (GT). Titles and abstract discrepancies were resolved through discussion at a project group meeting. A cross-reference search extracted titles/abstracts from identified reviews, and a full-text check of potentially eligible studies from these reviews was conducted by one author (L.A). When data extraction was conducted and new potentially eligible studies were detected from included studies, these were also considered for inclusion. An OVID alert was created for each of the searches so that the main author (L.A) could add new potentially eligible papers until the date of the submission.

Inclusion and exclusion criteria
The inclusion criteria differed depending on the section of the review.

Section 2 "Evidence of epigenetic processes in major transdiagnostic pathways'

In this section we focused on articles that examined an association between epigenetic modifications in the form of DNA Methylation (DNAm), in humans, and one of the conditions of interest (namely Eating disorders (anorexia nervosa and bulimia), Post traumatic stress disorder (PTSD), Anxiety disorders, Psychotic disorders (including Bipolar Disorder), Depression, Autism) or a specific psychopathological measure (for example depressive symptoms in the general population). We restricted our inclusion to publications that were conducted in candidate genes and Epigenome Wide Association Studies (EWAS). The goal was not to provide a systematic summary of all the papers fulfilling these criteria but to select the papers that were the most relevant and representative of each finding: for example, if 5 papers were found for one same gene, the ones judged to be most relevant were selected and reported. After conducting a first screening of the eligible papers, the most common represented biological pathways were delineated, namely the serotoninergic, dopaminergic pathways, dysfunction related to the excitatory and inhibitory balance (including the glutamatergic and GABAergic function), synaptic plasticity and neurogenesis, the immune system and inflammation et oxidative stress. Biological systems that fell outside these ones were finally not considered, given word limit constraints and to limit the scope of the review. For example, there were new potential pathways that are emerging as important for epigenetics in mental health such as mitochondrial dysfunction. However, given that evidence linking a dysfunction in this pathway is involved in major mental conditions, we decided to leave it outside of this work in order to make the review more comprehensive and compact.

Section 3 "The epigenetic signature of childhood adversity and cannabis use"

Section on childhood adversity
We included publications that examined a link between childhood adversity (also including papers looking at more recent life events) and epigenetic changes in samples of patients with the aforementioned mental condition; or that linked childhood adversity with DNAm and any clinical outcome in such samples; as for the previous sections we focused on candidate genes studies and EWAS and restricted to human studies.

Section on cannabis use
We included publications that examined a link between childhood adversity and epigenetic changes in samples of patients with the aforementioned mental condition; or that linked childhood adversity with DNAm and any clinical outcome in such samples. However, and against our initial prediction we found that studies in clinical samples were lacking. Therefore, in this section we decided to also include papers that looked at the association between cannabis use and DNAm (candidate genes and EWAS) in the general population.

Exclusion criteria

We did not focus on studies in animal models, studies that were not published in English, French, Spanish and Italian.

Data extraction methodology

Section 2 "Evidence of epigenetic processes in major transdiagnostic pathways"

For each reported association between DNAm and a clinical outcome or a condition of interest we reported, narratively the text whether there was a dysregulation, a reduced/increased (or hyper/hypo) DNAm, or a enrichment of a specific pathway. We reported, for each study, whether it was a candidate gene study or an EWAS, the tissue used, in which condition and to which pathway of interest that gene belong and the association of DNAm with a particular clinical or biological outcome. This information is also gathered in Table 3 which provide a summary of the above. In some occasions in the text, we refer to table 3 rather than reporting all the details. Table 1 summarised the names and basic function of each gene, allowing the reader to have a summary of the relevant genes mentioned in the review (rather than defining each gene in the text directly).

Section 3 The epigenetic signature of childhood adversity and cannabis use

Section on childhood adversity

In addition to reporting findings narratively as in section 2, Table 2 provides a summary of each of the relevant studies included. The table is separated by a Candidate genes study, and an EWAS section. The candidate genes section is divided into studies examining genes involved in the Hypothalamic Pituitary Adrenal Axis, the oxytocin pathway, the serotoninergic pathway, neurogenesis, and other pathway of interest. The selection of these pathways was made based on the observation that they were the most explored and relevant systems in the context of childhood adversity and DNAm. However, and contrary to section 2, here we also mentioned papers that explored more novel or preliminary pathways (described in the "other pathway of interest" section) The table extracts for each study the name of the author, demographic characteristics such as sample size and gender and clinical population, design, type of instrument used to assess childhood adversity, the goal of the analyses of interest, the DNAm collection methods, the studied gene, how the clinical information was assessed, statistic methods (including covariates included), and the main findings (trying to report when available the direction of the association between childhood adversity and DNAm and with the clinical outcome or condition). Data on section 3 is also gathered in Table 3 similarly than described above.

Section on cannabis use

Data relative to this section was reported narratively, in the same way than for section 2 and 3 but without a detailed table 2. As mentioned above, given the low number of studies in clinical samples, findings related to the general population were considered.

Figures 1 and 2 are illustration on the main findings presented in the review, combining sections 2 and 3 together.

Figure 1 summarises the evidence presented in this review. It illustrates :1) (green and blue rows) the suggested links between childhood adversity (CA), and Cannabis use (CU) and DNAm changes mapping to biological pathways which are also functionally related (Serotoninergic, Dopaminergic pathways, Glutamatergic & GABAergic pathway, Neurogenesis, Immune system & Inflammation and Oxidative stress).

2) The blue and beige rows illustrate the evidence, from case control studies, of an association between DNAm changes in these pathways and the major mental health conditions (Eating Disorders (anorexia nervosa and bulimia nervosa, Post-traumatic stress disorder, Anxiety Disorders, Psychotic Disorder, Bipolar disorders, Depression and Autism); 3) the potential mediating role of the DNAm changes mapping to these between exposure to CA and CU and risk to develop mental health conditions.

The thickness of the lines shows the robustness of the evidence reported in the literature review. The items "genotype: and "other risk factors" are added to highlight the influence of genetic factors and environmental counfounders in DNAm studies

Figure 2 illustrates the evidence from candidate gene studies linking childhood adversity (CA) with DNAm in CpG sites located in the genes NR3C1, FKBP5, SKA2 and CA, with various conditions and various clinical outcomes.

In columns blue and beige, CA+ (with an arrow pointing up) reflects the presence of a positive association between the DNAm in probes located in those genes and CA; CA- (with an arrow pointing down) reflects a negative association. The beige column shows the disorder in which that association has been found. Lastly, the green column shows the presence of evidence linking DNAm, with a particular clinical phenotype; CA+ indicated that that the association between DNAm and the clinical outcome was related to CA.

1. exp epigenetics/ or exp DNA methylation/
2. EWAS.mp.
3. epigenomics.mp.
4. exp CpG island/
5. exp DNA Methylation/ or exp Epigenomics/ or exp CpG Islands/
6. exp EPIGENETICS/
7. DNA methylation.mp.
8. CpG islands.mp.
9. 1 or 4 or 5 or 6
10. 2 or 3 or 7 or 8
11. exp ALCOHOLISM/
12. Alcohol.mp.
13. exp alcohol/ or exp alcoholism/ or exp alcohol abuse/
14. exp ALCOHOLISM/
15. exp Alcohol Abuse/
16. alcohol dependance.mp.
17. exp Alzheimer Disease/
18. 14 or 15
19. exp Alzheimer disease/
20. exp Alzheimer's Disease/
21. 17 or 19 or 20
22. exp psychosis/
23. exp schizophrenia/

24. exp psychosis/
25. exp schizophrenia/
26. 22 or 23
27. 24 or 25
28. exp PSYCHOSIS/
29. exp SCHIZOPHRENIA/
30. psychos*.mp.
31. Schizophren*.mp.
32. 28 or 29
33. exp Bipolar Disorder/
34. exp bipolar disorder/
35. exp Bipolar Disorder/
36. 33 or 34 or 35
37. exp Autism Spectrum Disorder/ or exp Autistic Disorder/
38. exp autism/
39. autistic disorder.mp.
40. autism.mp.
41. exp Autism Spectrum Disorders/
42. 37 or 38 or 41
43. exp DEPRESSION/
44. exp Depressive Disorder/
45. 43 or 44
46. exp depression/
47. exp Major Depression/
48. 45 or 46 or 47
49. depression.mp.
50. exp SMOKING/ or exp TOBACCO SMOKING/
51. exp tobacco/ or exp smoking/ or exp tobacco dependence/
52. exp TOBACCO SMOKING/
53. 50 or 51 or 52
54. smoking tobacco.mp.
55. psychotropic medication.mp.
56. exp antidepressant agent/ or exp psychotropic agent/ or exp neuroleptic agent/ or exp anxiolytic agent/
57. exp Antidepressant Drugs/ or exp Drug Therapy/ or exp Neuroleptic Drugs/
58. exp Antipsychotic Agents/ or exp Psychotropic Drugs/
59. 9 or 10
60. 11 or 13 or 18
61. Alzheimer.mp.
62. bipolar disorder.mp.
63. 12 or 16 or 30 or 31 or 39 or 40 or 49 or 54 or 55 or 61 or 62
64. 26 or 27 or 32
65. 56 or 57 or 58
66. 21 or 36 or 42 or 48 or 53 or 60 or 64 or 65
67. 63 or 66
68. exp psychiatry/
69. exp PSYCHIATRY/
70. psychiatry.mp.
71. exp PSYCHIATRY/
72. 68 or 69 or 70 or 71
73. 59 and 67 and 72

Full searches conducted via OVID provided in sections 3 ("The epigenetic signature of childhood adversity and cannabis use")

For childhood adversity the full search was:

1. Stress, Psychological/
2. Physical Abuse/
3. sex offenses/ or child abuse, sexual/ or rape/
4. emotional abuse.mp.
5. emotional neglect.mp.
6. Physical neglect.mp.
7. Bullying/
8. separation from parents.mp.
9. being taken into care.mp.
10. interpersonal trauma.mp.
11. traumatic exp*.mp.
12. trauma exp*.mp.
13. Early life event*.mp.

14. early life stress.mp.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. stress/ or exp acute stress/ or exp chronic stress/ or exp early life stress/ or exp emotional stress/ or exp interpersonal stress/ or exp life stress/ or exp maternal stress/ or exp mental stress/ or exp parental stress/ or exp school stress/
17. child abuse/ or exp abuse/ or exp domestic violence/ or exp child neglect/ or exp child sexual abuse/
18. exp neglect/ or exp child neglect/
19. exp physical abuse/
20. exp emotional abuse/
21. exp sexual bullying/ or exp bullying/
22. 15 or 16 or 17 or 18 or 19 or 20
23. stress/ or exp chronic stress/ or exp environmental stress/ or exp psychological stress/
24. exp CHILD ABUSE/ or exp EMOTIONAL ABUSE/ or exp PHYSICAL ABUSE/ or exp SEXUAL ABUSE/
25. exp CHILD NEGLECT/
26. exp BULLYING/
27. trauma/ or exp emotional trauma/
28. 22 or 23 or 24 or 25 or 26 or 27
29. exp Epigenomics/
30. EWAS.mp.
31. epigen*.mp.
32. exp CpG Islands/
33. exp Methylation/ or exp DNA Methylation/
34. 29 or 30 or 31 or 32 or 33
35. exp epigenetics/ or exp epigenesis/ or exp DNA methylation/
36. exp CpG island/
37. 34 or 35 or 36
38. exp EPIGENETICS/
39. 37 or 38
40. exp Mental Disorders/
41. Psychiatric vulnerability.mp.
42. mental diseases.mp.
43. 40 or 41 or 42
44. psychopathology/ or adolescent psychopathology/ or child psychopathology/ or psychiatric symptoms/
45. 43 or 44
46. psychopathology.mp. or mental disease/
47. 45 or 46
48. 28 and 39 and 47
49. 29 or 30 or 31 or 32 or 36 or 38
50. exp epigenetics/
51. exp epigenesis/
52. 29 or 30 or 31 or 36 or 50 or 51
53. 40 or 41 or 42
54. 28 and 52 and 53
55. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 21 or 23 or 24 or 25 or 26 or 27
56. Epigenesis, Genetic/
57. 29 or 30 or 31 or 32 or 38 or 56
58. 53 and 55 and 57
59. mental disease/ or exp addiction/ or exp anxiety disorder/ or exp dissociative disorder/ or exp mood disorder/ or exp neurosis/ or exp personality disorder/ or exp psychosis/ or exp psychosomatic disorder/ or exp psychotrauma/
60. exp mental disorders/ or exp anxiety disorders/ or exp dissociative disorders/ or exp mood disorders/ or neurotic disorders/ or exp paraphilic disorders/ or personality disorders/ or exp "schizophrenia spectrum and other psychotic disorders"/ or exp sexual dysfunctions, psychological/ or exp somatoform disorders/ or exp substance-related disorders/ or exp "trauma and stressor related disorders"/

61. mental disorders/ or exp affective disorders/ or exp anxiety disorders/ or exp dissociative disorders/ or exp neurosis/ or exp personality disorders/ or exp psychosis/ or exp schizoaffective disorder/
62. 41 or 59 or 60 or 61
63. 34 and 55 and 62
64. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10 or 11 or 12 or 14 or 17 or 18 or 19 or 20 or 21 or 24 or 25 or 26 or 27
65. 34 and 62 and 64

For cannabis use the full search was:

1. exp epigenetics/
2. exp DNA methylation/
3. exp psychiatry/
4. exp mental health/
5. exp cannabis/
6. exp Epigenomics/
7. exp DNA Methylation/
8. exp Psychiatry/
9. exp Mental Health/
10. exp Cannabis/
11. exp Epigenetics/
12. exp Psychiatry/
13. exp Mental Health/
14. exp Cannabis/
15. epigen*.mp.
16. methylation.mp.
17. "cannabis use".mp.
18. psychiatry.mp.
19. 5 or 10 or 14 or 17
20. 1 or 2 or 6 or 7 or 11 or 15 or 16
21. 3 or 4 or 8 or 9 or 12 or 13 or 18
22. 19 and 20 and 21
23. from 22 keep 1-22
24. 19 and 20

References

- Arranz, M. J., Gallego-Fabrega, C., Martín-Blanco, A., Soler, J., Elices, M., Dominguez-Clavé, E., . . . Pascual, J. C. (2021). A genome-wide methylation study reveals X chromosome and childhood trauma methylation alterations associated with borderline personality disorder. *Translational Psychiatry*, 11(1), 5. doi:10.1038/s41398-020-01139-z

- Boks, M. P., van Mierlo, H. C., Rutten, B. P., Radstake, T. R., De Witte, L., Geuze, E., . . . Broen, J. C. (2015). Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder. *Psychoneuroendocrinology*, 51, 506-512.

- Bustamante, A. C., Aiello, A. E., Galea, S., Ratanatharathorn, A., Noronha, C., Wildman, D. E., & Uddin, M. (2016). Glucocorticoid receptor DNA methylation, childhood maltreatment and major depression. *Journal of Affective Disorders, 206*(Supplement C), 181-188. doi:https://doi.org/10.1016/j.jad.2016.07.038

- Bustamante, A. C., Aiello, A. E., Guffanti, G., Galea, S., Wildman, D. E., & Uddin, M. (2018). FKBP5 DNA methylation does not mediate the association between childhood maltreatment and depression symptom severity in the Detroit Neighborhood Health Study. *Journal of Psychiatric Research, 96*(Supplement C), 39-48. doi:https://doi.

org/10.1016/j.jpsychires.2017.09.016

- Comes, A. L., Czamara, D., Adorjan, K., Anderson-Schmidt, H., Andlauer, T. F. M., Budde, M., . . . Heilbronner, U. (2020). The role of environmental stress and DNA methylation in the longitudinal course of bipolar disorder. *International Journal of Bipolar Disorder, 8*(1), 9. doi:10.1186/s40345-019-0176-6

- Domschke, K., Tidow, N., Kuithan, H., Schwarte, K., Klauke, B., Ambrée, O., . . . Kersting, A. (2012). Monoamine oxidase A gene DNA hypomethylation–a risk factor for panic disorder? *International Journal of Neuropsychopharmacology, 15*(9), 1217-1228.

- Domschke, K., Tidow, N., Schrempf, M., Schwarte, K., Klauke, B., Reif, A., . . . Deckert, J. (2013). Epigenetic signature of panic disorder: a role of glutamate decarboxylase 1 (GAD1) DNA hypomethylation? *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 46,* 189-196.

- Engdahl, E., Alavian-Ghavanini, A., Forsell, Y., Lavebratt, C., & Rüegg, J. (2021). Childhood adversity increases methylation in the GRIN2B gene. *J Psychiatry Research, 132,* 38-43. doi:10.1016/j.jpsychires.2020.09.022

- Farrell, C., Doolin, K., O'Leary, N., Jairaj, C., Roddy, D., Tozzi, L., . . . Nemoda, Z. (2018). DNA methylation differences at the glucocorticoid receptor gene in depression are related to functional alterations in hypothalamic–pituitary–adrenal axis activity and to early life emotional abuse. *Psychiatry research, 265,* 341-348.

- Kaminsky, Z., Wilcox, H., Eaton, W., Van Eck, K., Kilaru, V., Jovanovic, T., . . . Ressler, K. (2015). Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. *Translational psychiatry, 5(*8), e627.

- Kang, H.-J., Kim, J.-M., Stewart, R., Kim, S.-Y., Bae, K.-Y., Kim, S.-W., . . . Yoon, J.-S. (2013). Association of SLC6A4 methylation with early adversity, characteristics and outcomes in depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 44,* 23-28.

- Kimmel, M., Clive, M., Gispen, F., Guintivano, J., Brown, T., Cox, O., . . . Kaminsky, Z. (2016). Oxytocin receptor DNA methylation in postpartum depression. *Psychoneuroendocrinology, 69,* 150-160. doi:10.1016/j.psyneuen.2016.04.008

- Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., & Pariante, C. M. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nature Neuroscience, 16.* doi:10.1038/nn.3275

- Klinger-König, J., Hertel, J., Van der Auwera, S., Frenzel, S., Pfeiffer, L., Waldenberger, M., . . . Homuth, G. (2019). Methylation of the FKBP5 gene in association with FKBP5 genotypes, childhood maltreatment and depression. *Neuropsychopharmacology, 44*(5), 930-938.

- Koenen, K. C., Uddin, M., Chang, S. C., Aiello, A. E., Wildman, D. E., Goldmann, E., & Galea, S. (2011). SLC6A4 methylation modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder. *Depression and anxiety, 28*(8), 639-647.

- Labonte, B., Azoulay, N., Yerko, V., Turecki, G., & Brunet, A. (2014). Epigenetic modulation of glucocorticoid receptors in posttraumatic stress disorder. *Translational psychiatry, 4*(3), e368.

- Lutz, P.-E., Tanti, A., Gasecka, A., Barnett-Burns, S., Kim, J. J., Zhou, Y., . . . Almeida, D. (2017). Association of a history of child abuse with impaired myelination in the anterior cingulate cortex: convergent epigenetic, transcriptional, and morphological evidence. *American Journal of Psychiatry,* appi. ajp. 2017.16111286.

- Martin-Blanco, A., Ferrer, M., Soler, J., Salazar, J., Vega, D., & Andion, O. (2014). Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. *Journal of Psychiatry Research, 57.* doi:10.1016/j.jpsychires.2014.06.011

- Mehta, D., Klengel, T., Conneely, K. N., Smith, A. K., Altmann, A., Pace, T. W., . . . Mercer, K. B. (2013). Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proceedings of the national academy of sciences, 110*(20), 8302-8307.

- Melas, P. A., Wei, Y., Wong, C. C., Sjöholm, L. K., Åberg, E., Mill, J., . . . Lavebratt, C. (2013). Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities. *International Journal of Neuropsychopharmacology, 16*(7), 1513-1528.

- Misiak, B., Karpiński, P., Szmida, E., Grążlewski, T., Jabłoński, M., Cyranka, K., . . . Frydecka, D. (2020). Adverse Childhood Experiences and Methylation of the FKBP5 Gene in Patients with Psychotic Disorders. *Journal of Clinical Medicine, 9*(12). doi:10.3390/jcm9123792

- Misiak, B., Szmida, E., Karpinski, P., Loska, O., Sasiadek, M. M., & Frydecka, D. (2015). Lower LINE-1 methylation in first-episode schizophrenia patients with the history of childhood trauma. *Epigenomics, 7*(8), 1275-1285. doi:10.2217/epi.15.68

- Moser, D. A., Paoloni-Giacobino, A., Stenz, L., Adouan, W., Manini, A., Suardi, F., . . . Rusconi-Serpa, S. (2015). BDNF methylation and maternal brain activity in a violence-related sample. *PLoS One, 10*(12), e0143427.

- Peng, H., Zhu, Y., Strachan, E., Fowler, E., Bacus, T., Roy-Byrne, P., . . . Zhao, J. (2018). Childhood Trauma, DNA Methylation of Stress-related Genes, and Depression: Findings from Two Monozygotic Twin Studies. *Psychosomatic Medicine.* doi:10.1097/psy.0000000000000604

- Perroud, N., Paoloni-Giacobino, A., Prada, P., Olie, E., Salzmann, A., & Nicastro, R. (2011). Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. *Translational Psychiatry, 1.* doi:10.1038/tp.2011.60

- Perroud, N., Zewdie, S., Stenz, L., Adouan, W., Bavamian, S., & Prada, P. (2016). Methylation of serotonin receptor 3a in Adhd, borderline personality, and bipolar disorders: link with severity of the disorders and childhood maltreatment. *Depression and anxiety, 33.* doi:10.1002/da.22406

- Prados, J., Stenz, L., Courtet, P., Prada, P., Nicastro, R., & Adouan, W. (2015). Borderline personality disorder and childhood maltreatment: a genome-wide methylation analysis. *Genes Brain Behavior, 14.* doi:10.1111/gbb.12197

- Radtke, K., Schauer, M., Gunter, H. M., Ruf-Leuschner, M., Sill, J., Meyer, A., & Elbert, T. (2015). Epigenetic modifications of the glucocorticoid receptor gene are associated with the vulnerability to psychopathology in childhood maltreatment. *Translational psychiatry, 5*(5), e571.

- Sadeh, N., Spielberg, J. M., Logue, M. W., Wolf, E. J., Smith, A. K., Lusk, J., . . . McGlinchey, R. E. (2016). SKA2 methylation is associated with decreased prefrontal cortical thickness and greater PTSD severity among trauma-exposed veterans. *Molecular psychiatry, 21*(3), 357-363.

- Sadeh, N., Wolf, E. J., Logue, M. W., Hayes, J. P., Stone, A., Griffin, L. M., . . . Miller, M. W. (2016). Epigenetic variation at SKA2 predicts suicide phenotypes and internalizing psychopathology. *Depression and anxiety, 33*(4), 308-315.

- Schechter, D. S., Moser, D. A., Paoloni-Giacobino, A., Stenz, L., Gex-Fabry, M., Aue, T., . . . Manini, A. (2015). Methylation of NR3C1 is related to maternal PTSD, parenting stress and maternal medial prefrontal cortical activity in response to child separation among mothers with histories of violence exposure. *Frontiers in psychology, 6.*

- Schechter, D. S., Moser, D. A., Pointet, V. C., Aue, T., Stenz, L., Paoloni-Giacobino, A., . . . Dayer, A. G. (2017). The association of serotonin receptor 3A methylation with maternal violence exposure, neural activity, and child aggression. *Behavioural Brain Research, 325*(Part B), 268-277. doi:https://doi.org/10.1016/j.bbr.2016.10.009

- Simons, R. L., Lei, M. K., Beach, S. R. H., Cutrona, C. E., & Philibert, R. A. (2017). Methylation of the oxytocin receptor gene mediates the effect of adversity on negative schemas and depression. *Dev Psychopathol, 29*(3), 725-736. doi:10.1017/s0954579416000420

- Sipahi, L., Wildman, D. E., Aiello, A. E., Koenen, K. C., Galea, S., Abbas, A., & Uddin, M. (2014). Longitudinal epigenetic variation of DNA methyltransferase genes is associated with vulnerability to post-traumatic stress disorder. *Psychological medicine, 44*(15), 3165-3179.

- Smearman, E. L., Almli, L. M., Conneely, K. N., Brody, G. H., Sales, J. M., Bradley, B., . . . Smith, A. K. (2016). Oxytocin receptor genetic and epigenetic variations: association with child abuse and adult psychiatric symptoms. *Child development, 87*(1), 122-134.

- Steiger, H., Labonté, B., Groleau, P., Turecki, G., & Israel, M. (2013). Methylation of the glucocorticoid receptor gene promoter in bulimic women: associations with borderline personality disorder, suicidality, and exposure to childhood abuse. *International Journal of Eating Disorders, 46*(3), 246-255.

- Thaler, L., Gauvin, L., Joober, R., Groleau, P., de Guzman, R., Ambalavanan, A., . . . Steiger, H. (2014). Methylation of BDNF in women with bulimic eating syndromes: Associations with childhood abuse and borderline personality disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 54*(Supplement C), 43-49. doi:https://doi.org/10.1016/j.pnpbp.2014.04.010

- Tozzi, L., Farrell, C., Booij, L., Doolin, K., Nemoda, Z., Szyf, M., . . . Frodl, T. (2017). Epigenetic Changes of FKBP5 as a Link Connecting Genetic and Environmental Risk Factors with Structural and Functional Brain Changes in Major Depression. *Neuropsychopharmacology.* doi:10.1038/npp.2017.290

- Tyrka, A., Parade, S., Welch, E., Ridout, K., Price, L., Marsit, C., . . . Carpenter, L. (2016). Methylation of the leukocyte glucocorticoid receptor gene promoter in adults: associations with early adversity and depressive, anxiety and substance-use disorders. *Translational psychiatry, 6*(7), e848.

- Uddin, M., Aiello, A. E., Wildman, D. E., Koenen, K. C., Pawelec, G., de Los Santos, R., . . . Galea, S. (2010). Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proceedings of the national academy of sciences, 107*(20), 9470-9475.

- Wang, W., Feng, J., Ji, C., Mu, X., Ma, Q., Fan, Y., . . . Zhu, F. (2017). Increased methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of patients with generalized anxiety disorder. *Journal of Psychiatric Research, 91*(Supplement C), 18-25. doi:https://doi.org/10.1016/j.jpsychires.2017.01.019

- Weder, N., Zhang, H., Jensen, K., Yang, B. Z., Simen, A., Jackowski, A., . . . Perepletchikova, F. (2014). Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. *Journal of the American Academy of Child & Adolescent Psychiatry, 53*(4), 417-424. e415.

- Wolf, E. J., Logue, M. W., Stoop, T. B., Schichman, S. A., Stone, A., Sadeh, N., . . . Miller, M. W. (2017). Accelerated DNA Methylation Age: Associations with PTSD and Mortality. *Psychosomatic Medicine.*

- Yehuda, R., Daskalakis, N. P., Bierer, L. M., Bader, H. N., Klengel, T., Holsboer, F., & Binder, E. B. (2016). Holocaust Exposure Induced Intergenerational Effects on FKBP5

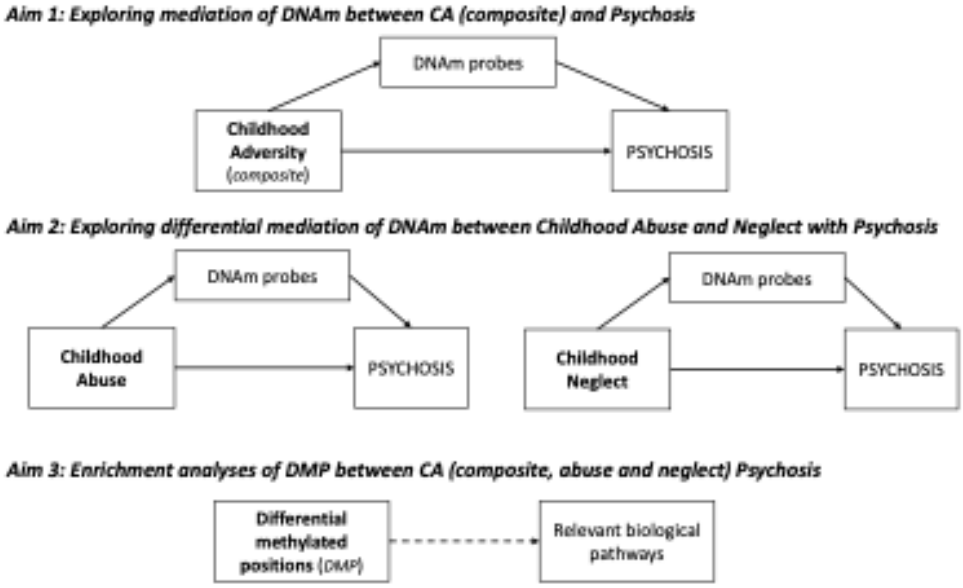
Methylation. *Biol Psychiatry, 80*(5), 372-380. doi:10.1016/j.biopsych.2015.08.005

- Yehuda, R., Flory, J. D., Bierer, L. M., Henn-Haase, C., Lehrner, A., Desarnaud, F., . . . Meaney, M. J. (2015). Lower methylation of glucocorticoid receptor gene promoter 1 F in peripheral blood of veterans with posttraumatic stress disorder. *Biological Psychiatry, 77*(4), 356-364.

- Zou, Z., Huang, Y., Wang, J., Min, W., & Zhou, B. (2020). DNA methylation of IL-4 gene and the association with childhood trauma in panic disorder. *Psychiatry Res, 293,* 113385. doi:10.1016/j.psychres.2020.113385

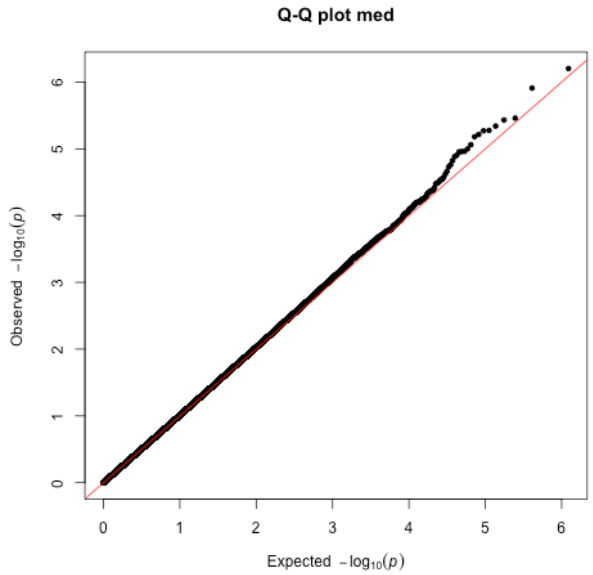
Study 5
Supplementary material

Supplementary Figure 1
Representation of main aims of study



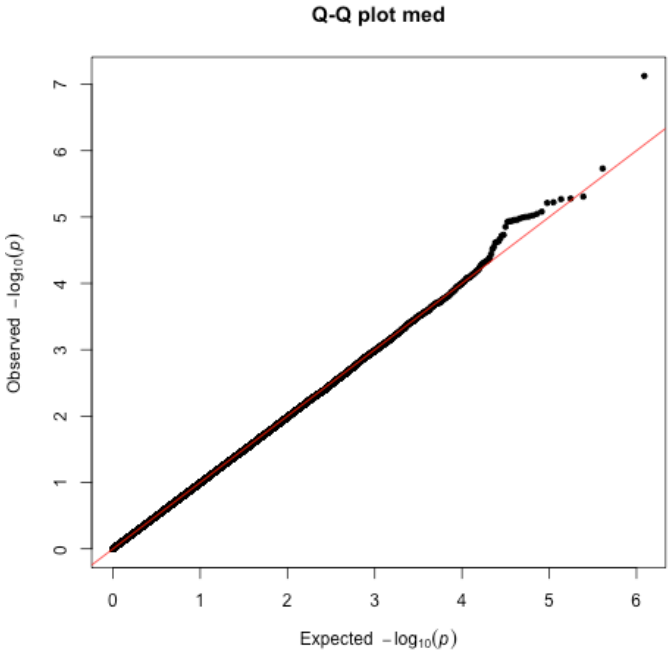
QQ plots

Supplementary Figure 2.
Supplementary Figure 1: Pathway *a*. Composite



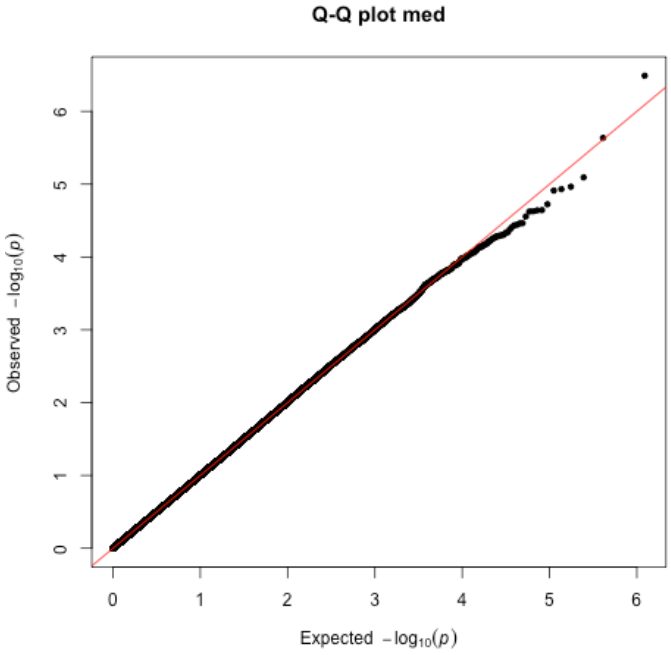
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Supplementary Figure 3: Pathway *b*. Abuse



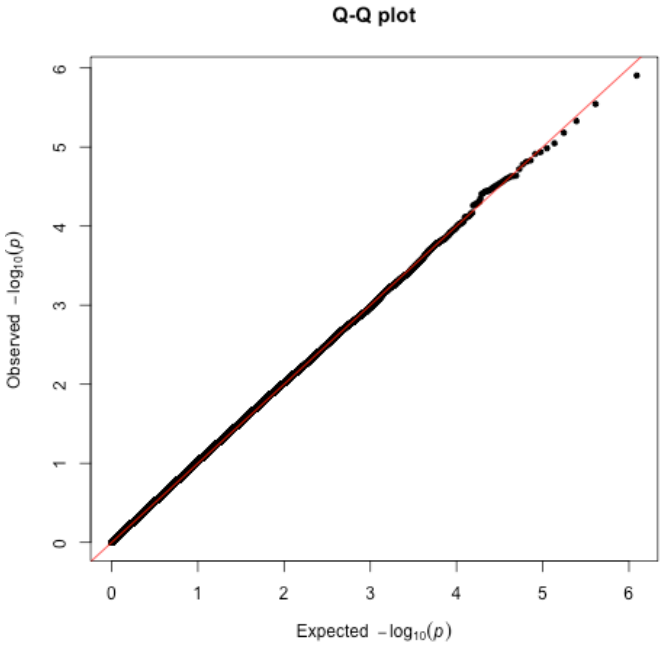
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Supplementary Figure 4: Pathway *a*. Neglect



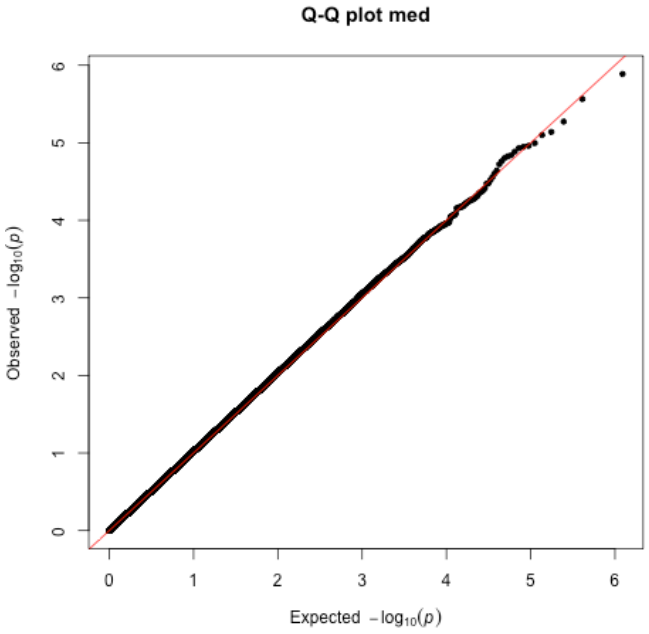
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Supplementary Figure 5: Pathway *b* DNAm-Case control status



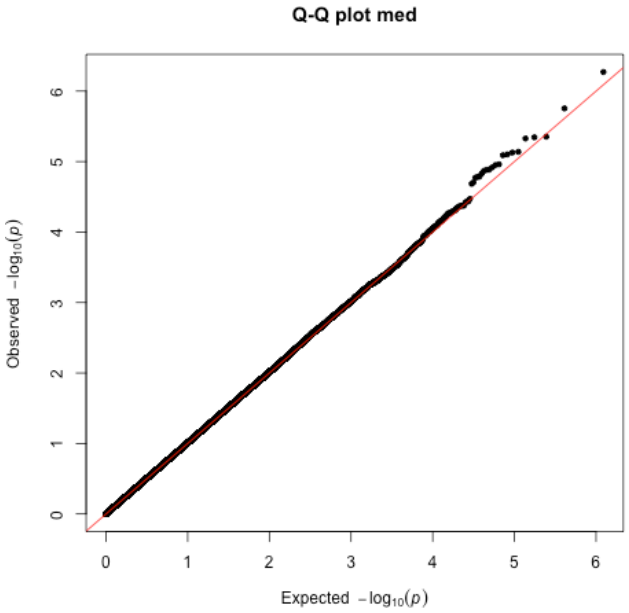
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Supplementary Figure 6: Mediation composite



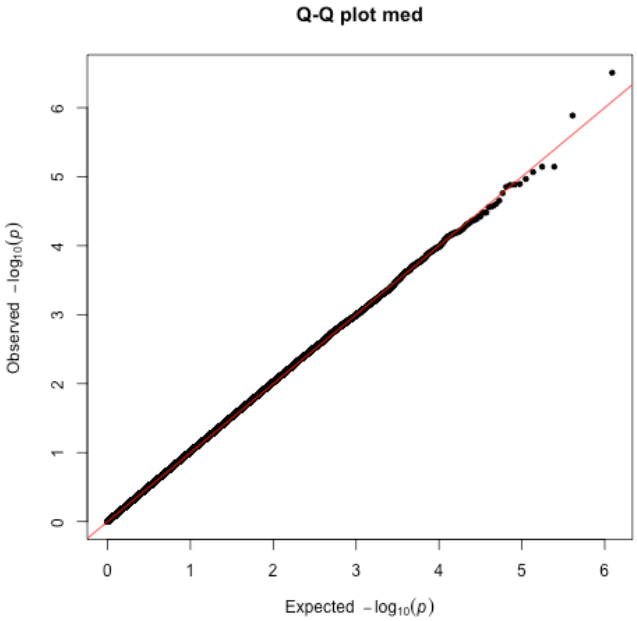
Lambda:1.022617 (SE: 6.505814e-06)

Supplementary Figure 7: Mediation abuse



Lambda: 1.011843 (SE: 5.315356e-06)

Supplementary Figure 8: Mediation neglect



Lambda: 1.015875 SE: 8.53809e-06

Supplementary Table 1

Demographic and clinical characteristics of cases and controls

	Total, *n* = 883	Controls, *n* = 517	Cases, *n* = 366	Controls *vs* Cases	*P* value
Age in years, *M* (*SD*)	35.33 (12.83)	38.75 (13.42)	30.5 (10.15)	t = 9.9195	<0.001
Female, *N* (%)	403 (45.64)	274 (52.10)	129 (35.25)	χ^2 = 27.2200	<0.001
Country, *N* (%)				χ^2 = 7.6440	0.106
France	89 (10.08)	62 (11.99)	27 (7.38)		
Netherlands	232 (26.27)	131 (25.34)	101 (27.60)		
Italy	87 (9.85)	56 (10.83)	31 (8.47)		
Spain	289 (32.73)	159 (30.75)	130 (35.52)		
UK	186 (21.07)	109 (21.08)	77 (21.04)		
Composite trauma score, *M* (*SD*)	0.69 (1.16)	0.45 (0.93)	1.03 (1.35)	t = -7.6100	<0.001
Abuse score, *M* (*SD*)	0.31 (0.61)	0.21 (0.52)	0.45 (0.71)	t = -5.9411	<0.001
Neglect score, *M* (*SD*)	0.35 (0.64)	0.22 (0.52)	0.53 (0.75)	t = -7.1358	<0.001
Affective psychosis, *N* %			87 (23.77)		
Smoking score, *M* (SD)	0.69 (4.65)	-0.25 (4.23)	2.01 (4.91)	t = -7.3360	<0.001
Current cannabis use, *N* (%)	147 (16.65)	67 (12.96)	80 (21.86)	χ^2 = 20.1135	<0.001
Antipsychotic medication, *N* (%)			303 (82.79)		
Batch effects, *M* (SD)	6.25 (3.39)	6.26 (3.44)	6.23 (3.32)	t = 0.1567	0.875

Supplementary Table 2

Demographic and baseline characteristics comparison between cases included in this study and the cases from the general EUGEI WP2 sample that were not included.

	Total, n = 1,134	Epigenetic, n = 366	Other, n = 768	Epigenetic vs Other	P value
Age in years, *M* (*SD*)	31.24 (10.59)	30.5 (10.15)	31.59 (10.79)	*t* = 1.6265	0.052
Female, *N* (%)	434 (38.27)	128 (34.97)	306 (39.84)	χ^2 = 2.4895	0.115
White ethnic backgorund, *N (%)*	714 (63.19)	269 (73.50)	445 (58.25)	χ^2 = 24.7440	<0.001
Years of education, M (SD)	15.32 (14.54)	15.06 (11.27)	15.44 (15.87)	*t* = 0.4141	0.339
Composite trauma score, *M* (*SD*)	42.35 (14.30)	42.06 (14.41)	42.51 (14.25)	*t* = 0.4736	0.317
Abuse score, *M* (*SD*)	22.54 (9.00)	22.26 (8.99)	22.69 (9.02)	*t* = 0.7037	0.240
Neglect score, *M* (*SD*)	19.81 (7.41)	19.79 (7.47)	19.83 (7.38)	*t* = 0.0793	0.468
Non-affective psychosis, *N* (%)	738 (73.73)	237 (74.29)	501 (73.46)	χ^2 = 0.0781	0.780

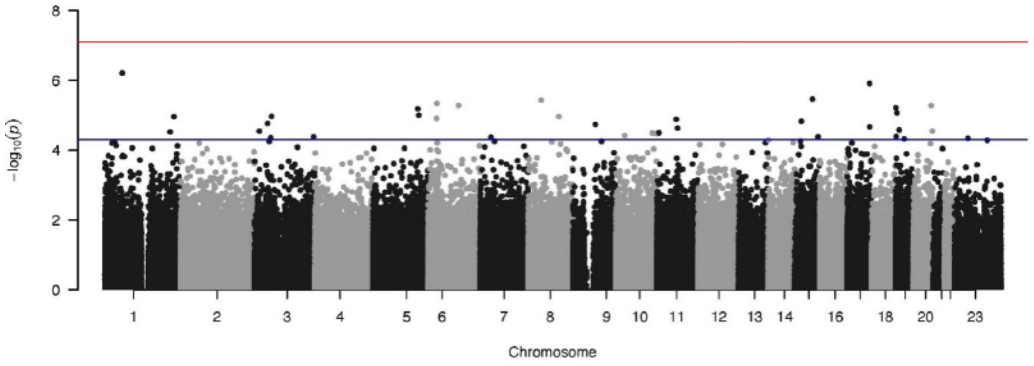
Supplementary Table 3

Top DMPs (*P* < 5e-05) associated between composite cumulative measure of adversity and DNAm (path *a*)

Probe	Genomic location (hg19)	Illumina gene annotation	Relation to UCSC CpG Island	Effect size	p value mediation
cg16347256	1: 57285160	*C1orf168*		-0.008	6.26E-07
cg00691266	17: 74015089	*EVPL*	N_Shelf	-0.005	1.23E-06
cg16404074	15: 78934580	*CHRNB4*	S_Shore	0.005	3.46E-06
cg11530213	8: 42037966	*PLAT*		-0.012	3.70E-06
cg25318809	6: 29974863	*HLA-J; NCRNA00171*	Island	-0.005	4.56E-06
cg03809898	6: 100442553	*MCHR2*	S_Shore	-0.014	5.30E-06
cg01678176	20: 58088902			-0.006	5.35E-06
cg06346838	19: 1466162	*APC2*	Island	0.009	6.09E-06
cg13912639	5: 147603654			-0.010	6.59E-06
cg07676349	19: 5242136	*PTPRS*	N_Shore	-0.005	8.67E-06
cg10269671	5: 150683820	*SLC36A3*		0.0047	1.00E-05
cg04876084	3: 56110939	*ERC2*		-0.006	1.09E-05
cg01457699	8: 100511131	*VPS13B*		0.008	1.10E-05
cg04439128	1: 226497537	*LIN9*	S_Shore	0.004	1.11E-05
cg20691507	6: 28956683		S_Shore	0.004	1.24E-05
cg14319451	11: 63685777	*RCOR2*	Island	0.005	1.31E-05
cg01245433	15: 42440011	*PLA2G4F*		-0.005	1.50E-05
cg01472821	3: 42822769			-0.003	1.73E-05
cg01217481	9: 74570344	*C9orf85*		0.008	1.85E-05
cg20503109	17: 74565795	*ST6GALNAC2*		0.002	2.16E-05
cg14588352	11: 67458806			0.004	2.38E-05
cg17795258	19: 12377690		S_Shore	-0.004	2.66E-05
cg24999924	20: 61428215	*C20orf20*	S_Shore	0.008	2.86E-05
cg24568311	3: 15519117	*COLQ*		0.007	2.87E-05
cg23709475	1: 214320064			-0.007	3.04E-05
cg25869889	11: 6436464	*APBB1*	N_Shelf	-0.004	3.21E-05
cg09924353	10: 120155536			-0.005	3.27E-05
cg08800869	10: 135204621	*PAOX*	S_Shore	-0.007	3.36E-05
cg04170451	10: 28822079	*WAC;WAC-AS1;*	Island	0.003	3.86E-05
cg23740938	19: 2592227	*GNG7*	S_Shelf	-0.006	4.15E-05
cg23314241	15: 97029759			-0.005	4.22E-05
cg27427514	3: 193922037		Island	0.017	4.22E-05
cg06218861	7: 35420759			-0.008	4.35E-05
cg09744376	3: 53080176	*SFMBT1*	Island	0.002	4.47E-05
cg18717600	X: 46404986	*ZNF674;LOC401588*	Island	0.005	4.58E-05
cg08882308	19: 29489929			-0.007	4.77E-05

Supplementary Figure 9

Manhattan plot showing association between composite cumulative measure of adversity and DNAm. *Red line: array-wide multiple testing threshold (p<5.8x10-8); blue line: "discovery" p-value threshold (P < 5e-5).*



Suplementary Table 4

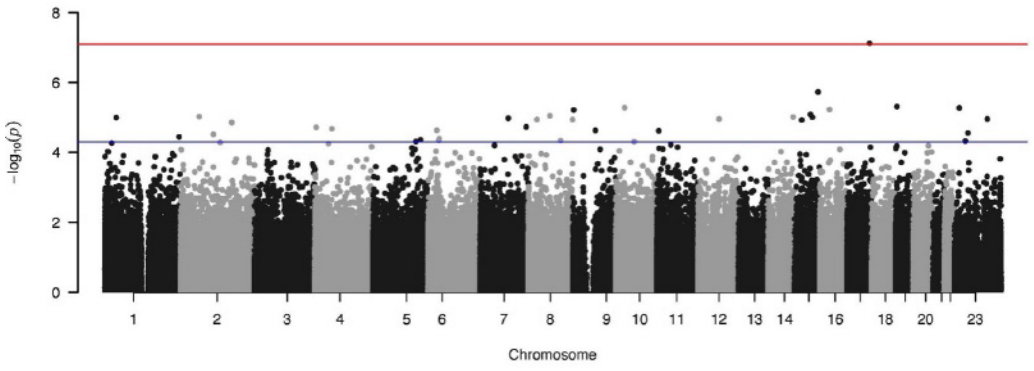
Top DMPs (*P* < 5e-05) associated between abuse and DNAm (path *a*)

Probe	Genomic location (hg19)	Illumina gene annotation	Relation to UCSC CpG Island	Effect size	p value mediation
cg00691266	17:74015089	*EVPL*	N_Shelf	-0.011	7.50E-08
cg23314241	15:97029759			-0.012	1.86E-06
cg07676349	19:5242136	*PTPRS*	N_Shore	-0.011	4.92E-06
cg04170451	10:28822079	*WAC; WAC-AS1*	Island	0.007	5.27E-06
cg16814066	X:17483070	*NHS*		0.013	5.38E-06
cg05227288	16:32489822		Island	-0.012	5.99E-06
cg17787809	9:3300190	*RFX3*		0.014	6.13E-06
cg11504297	15:71902446	*THSD4*		-0.007	8.31E-06
cg20665338	8:71378068			-0.012	8.98E-06
cg20360928	2:61191582	*PUS10*		0.008	9.50E-06
cg17348714	14:102289979	*PPP2R5C*		-0.010	9.81E-06
cg16404074	15:78934580	*CHRNB4*	S_Shore	0.009	9.98E-06
cg21362986	1:38024945	*DNALI1*	S_Shelf	0.008	1.02E-05
cg25496668	7:93144714	*CALCR*		0.0163	1.06E-05
cg12396344	12:69725444			-0.013	1.11E-05
cg12485020	X:110039269	*CHRDL1*	Island	0.011	1.11E-05
cg03719539	8:145560549	*SCRT1*	Island	0.007	1.15E-05
cg16882927	8:28246789		S_Shelf	0.009	1.15E-05
cg26444148	15:43716087	*RNU6-28P; TP53BP1*		0.008	1.18E-05
cg09722259	2:167758744	*XIRP2*		-0.013	1.40E-05
cg01760103	7:151664041	*GALNTL5*		0.009	1.86E-05
cg09299732	4:3807421			-0.008	1.91E-05

cg19420645	4:55983534	*KDR*		-0.017	2.13E-05
cg25318809	6:29974863	*HLA-J; NCRNA00171*	Island	-0.010	2.34E-05
cg01217481	9:74570344	*C9orf85*		0.016	2.37E-05
cg16176398	11:5531941	*UBQLN3*		-0.012	2.43E-05
cg18717600	X:46404986	*ZNF674; LOC401588; ZNF674*	Island	0.009	2.81E-05
cg22120488	2:107199102			0.021	3.06E-05
cg06208834	1:243656201	*SDCCAG8; AKT3*	S_Shelf	-0.006	3.61E-05
cg19115490	6:37483925			-0.004	4.10E-05
cg02520160	5:156589436	*FAM71B*		0.008	4.37E-05
cg09304014	6:35737336		S_Shelf	-0.008	4.57E-05
cg14233855	8:106185570			-0.013	4.62E-05
cg08311767	X:37865052	*SYTL5*		0.019	4.80E-05
cg02999418	5:141041669	*ARAP3*		0.007	4.92E-05
cg01296504	10:60627901			-0.011	4.98E-05

Supplementary Figure 10

Manhattan plot showing association between abuse and DNAm. *Red line: array-wide multiple testing threshold (p<5.8x10-8); blue line: "discovery" p-value threshold (P < 5e-5).*



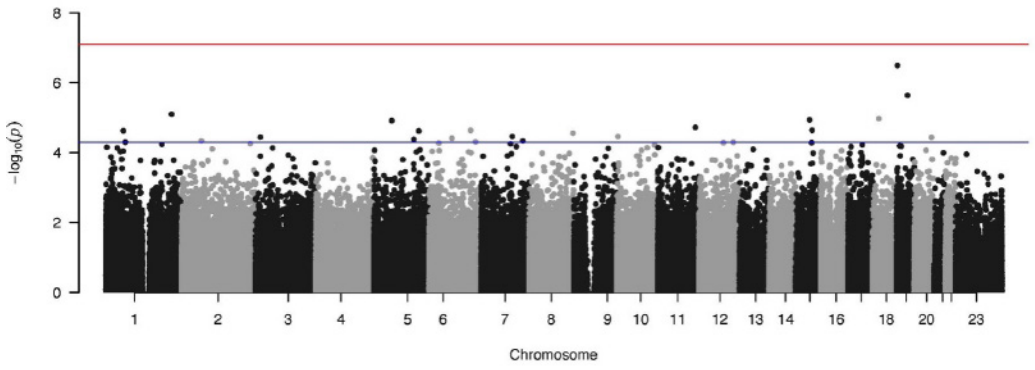
Suplementary Table 5

Top DMPs (*P* < 5e-05) associated between neglect and DNAm (pathway *a*)

Probe	Genomic location (hg19)	Illumina gene annotation	Relation to UCSC CpG Island	Effect size	p value mediation
cg10490670	19:3684882	*PIP5K1C*	N_Shelf	-0.009	3.24E-07
cg07646999	19:36359211	*APLP1*	N_Shore	0.016	2.31E-06
cg18182483	1:215697171			0.012	8.05E-06
cg13682028	18:20424908			0.011	1.08E-05
cg22002893	15:66220351	*MEGF11*		-0.010	1.17E-05
cg12849710	5:58952314	*PDE4D*		-0.008	1.23E-05
cg16981685	11:123305126		S_Shelf	0.011	1.89E-05
cg17805223	15:74002276	*CD276*		0.007	2.27E-05
cg04741336	6:136847372	*MAP7*		-0.012	2.29E-05
cg16347256	1:57285160	*C1orf168*		-0.012	2.35E-05
cg13912639	5:147603654			-0.018	2.38E-05
cg09982504	8:143413495	*TSNARE1*		-0.006	2.78E-05
cg00883590	7:103076127	*SLC26A5*		0.009	3.44E-05
cg03356331	10:3610737	*LOC105376360*		0.012	3.45E-05
cg24568311	3:15519117	*COLQ*		0.013	3.61E-05
cg05995220	20:55964998	*RBM38*	Island	0.006	3.66E-05
cg10699599	6:75855715	*COL12A1*		-0.006	3.87E-05
cg17983064	5:131396357	*IL3*		0.016	4.17E-05
cg01591738	7:137040544			-0.019	4.59E-05
cg14044522	2:64587789			-0.007	4.62E-05
cg21606405	6:152795042	*SYNE1*		-0.013	4.93E-05

Supplementary Figure 11

Manhattan plot showing association between neglect and DNAm. *Red line: array-wide multiple testing threshold (p<5.8x10-8); blue line: "discovery" p-value threshold (P < 5e-5).*



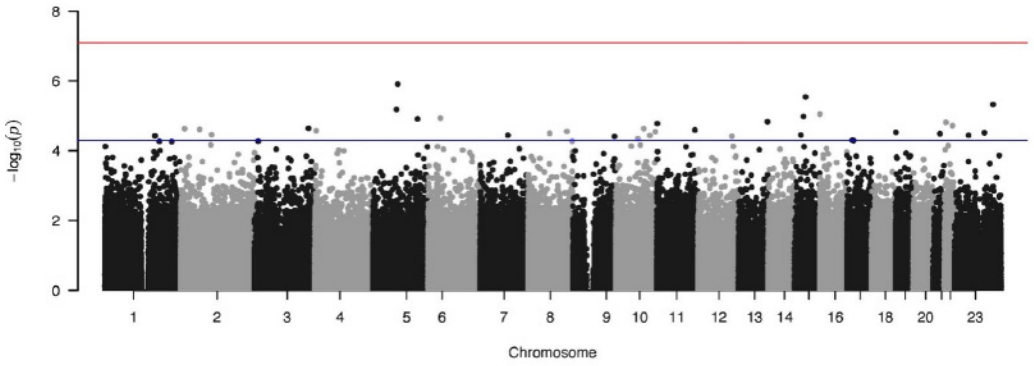
Supplementary Table 6

Top DMPs (*P* < 5e-05) associated between DNAm and psychosis (path *b*)

Probe	Genomic location (hg19)	Illumina gene annotation	Relation to UCSC CpG Island	Effect size	p value mediation
cg00402173	5:81709024			30.177	1.25E-06
cg07650009	15:56112297			22.359	2.86E-06
cg22213006	X:128789768	*APLN*	S_Shore	-21.948	4.70E-06
cg13914094	5:77148665		S_Shore	-28.315	6.60E-06
cg04623458	16:871165		N_Shelf	21.383	8.97E-06
cg06906230	15:48680848			23.900	1.04E-05
cg21233897	6:41657184	*TFEB*		13.462	1.16E-05
cg02595120	5:146832518	*DPYSL3*	N_Shore	33.484	1.22E-05
cg24853340	13:113546294		N_Shelf	18.912	1.48E-05
cg19292908	22:22900159	*PRAME*	N_Shore	-21.314	1.53E-05
cg25358133	11:1020251	*MUC6*	N_Shelf	-26.600	1.66E-05
cg11600511	22:44284127	*PNPLA5*	N_Shelf	26.004	1.90E-05
cg18479241	3:177221418	*LINC00578*		13.523	2.30E-05
cg09509179	10:91598023		S_Shore	18.489	2.34E-05
cg06209574	2:12918241			20.986	2.35E-05
cg12425670	2:62422030	*B3GNT2*	N_Shore	27.258	2.46E-05
cg21299462	11:124953020	*SLC37A2*		-27.773	2.54E-05
cg16243247	4:3803686			-17.506	2.67E-05
cg08507802	8:126912031			-23.867	2.80E-05
cg09276913	10:129807938	*PTPRE*		-25.019	2.87E-05
cg23640575	19:1571440		S_Shelf	-26.133	3.01E-05
cg21776797	X:100662746	*HNRNPH2; GLA; RPL36A-HNRNPH2*	N_Shore	-32.512	3.08E-05
cg03088599	8:70544397	*SULF1*		18.832	3.19E-05
cg09277541	21:34677002			18.533	3.27E-05
cg05560118	2:101850632			14.172	3.43E-05
cg21127508	15:40749867	*BAHD1*		-21.288	3.52E-05
cg07112779	X:48687187	*ERAS*	S_Shore	-18.075	3.60E-05
cg20739360	7:91833683	*KRIT1*		25.418	3.60E-05
cg20329861	10:111716018	*ADD3-AS1*		-19.135	3.65E-05
cg17274057	1:164599431	*PBX1*		26.406	3.75E-05
cg25626273	12:111480104	*CUX2*		26.221	3.86E-05
cg21123355	9:136844644	*VAV2*	Island	8.612	3.93E-05
cg11228898	10:72301873	*PALD1*		-18.821	4.46E-05
cg14808739	17:17741098	*SREBF1*	S_Shore	-30.289	4.95E-05

Supplementary Figure 12

Manhattan plot showing the DNAm associated to psychosis. *Red line: array-wide multiple testing threshold (p<5.8x10-8); blue line: "discovery" p-value threshold (P < 5e-5).*



Supplementary Table 7

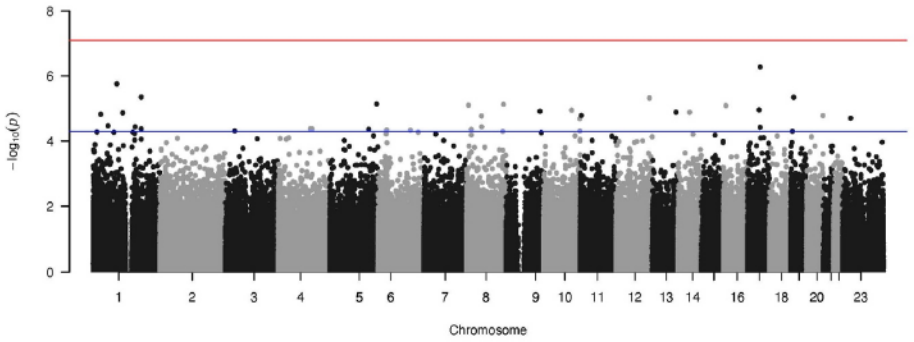
7 Top DMPs (P < 5e-05) associated with composite cumulative measure of neglect using the DACT test.

Probe	Genomic location (hg19)	Illumina gene annotation	Relation to UCSC CpG Island	Effect size med	p value mediation
cg11476306	8: 122273909			-0.142	3.11E-07
cg19456890	10: 91402272	*PANK1*	N_Shore	0.134	1.30E-06
cg14074251	2: 220299116	*SPEG*	N_Shore	0.120	7.17E-06
cg16244155	18: 77905565	*LOC100130522*	Island	0.129	7.17E-06
cg21978195	17: 77918905	*TBC1D16*	S_Shore	-0.146	8.58E-06
cg23315592	16: 57674745	*ADGRG1*		-0.100	1.08E-05
cg17606450	11: 60500636			-0.109	1.28E-05
cg12028337	13: 107790939			0.140	1.30E-05
cg01490742	15: 77223149	*RCN2*	N_Shore	0.096	1.32E-05
cg08324612	8: 1030521			-0.100	1.40E-05
cg01464104	11: 56043040	*OR5T1*		-0.110	1.74E-05
cg19517291	15: 85201039	*NMB*	N_Shore	-0.111	2.22E-05
cg23244948	14: 47096230			0.096	2.48E-05
cg01632958	12: 91619323			-0.077	2.64E-05
cg16351998	6: 136873379	*MAP7*	S_Shore	-0.095	2.72E-05
cg09716762	16: 31383689	*ITGAX*	S_Shore	-0.115	2.77E-05
cg14910138	1: 177178755	*BRINP2*		0.090	3.31E-05
cg04345540	6: 35446409	*TEAD3*		-0.098	3.32E-05
cg17331920	17: 4081325	*ANKFY1*		-0.103	3.37E-05
cg11573143	2: 228192092	*MFF*	S_Shore	-0.095	3.78E-05
cg20350203	20: 47957157			0.094	3.79E-05
cg00708080	9: 34382709	*C9orf24*	S_Shore	0.100	4.09E-05
cg11495399	11: 62495898	*HNRNPUL2;TTC9C*	S_Shore	-0.114	4.19E-05
cg17219331	3: 139025555			-0.092	4.28E-05

cg12641286	8: 141537198		-0.121	4.34E-05
cg17280975	8: 123875899	*ZHX2*	0.1090	4.52E-05
cg05339605	14: 91269861	*TTC7B*	-0.113	4.69E-05
cg10194002	1: 24878007	*LOC100506985*	0.082	4.88E-05
cg05288426	11: 134469461		0.086	4.90E-05

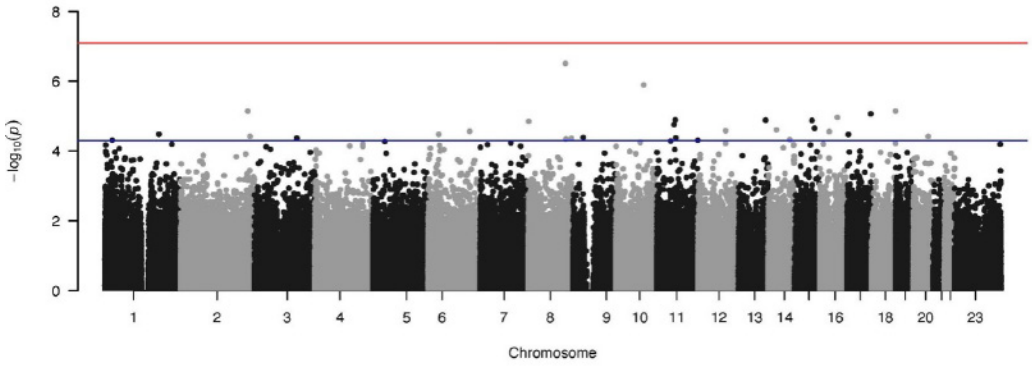
Supplementary Figure 13

Manhattan plot showing the DNAm mediating DMP between cumulative measure of abuse and psychosis. *Red line: array-wide multiple testing threshold (p<5.8x10-8); blue line: "discovery" p-value threshold (P < 5e-5).*



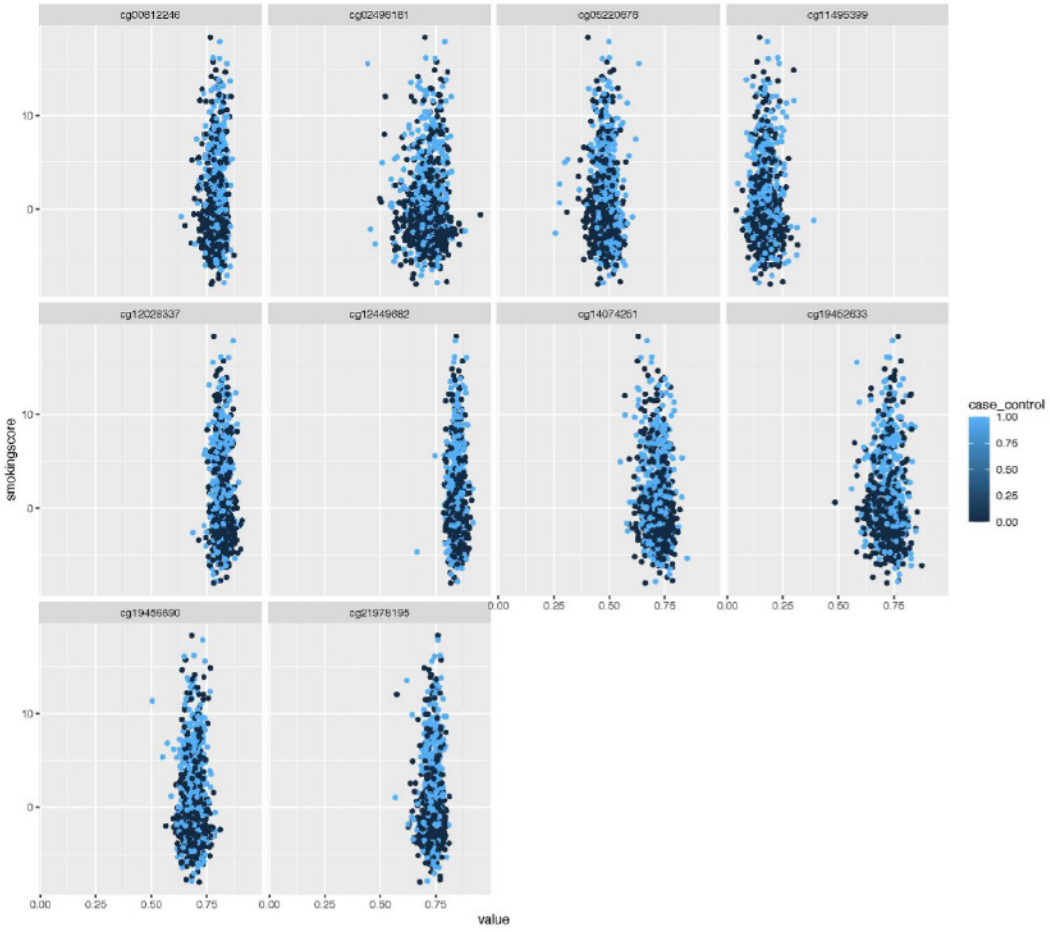
Supplementary Figure 14

Manhattan plot showing the DNAm mediating DMP between cumulative measure of neglect and psychosis. *Red line: array-wide multiple testing threshold (p<5.8x10-8); blue line: "discovery" p-value threshold (P < 5e-5).*



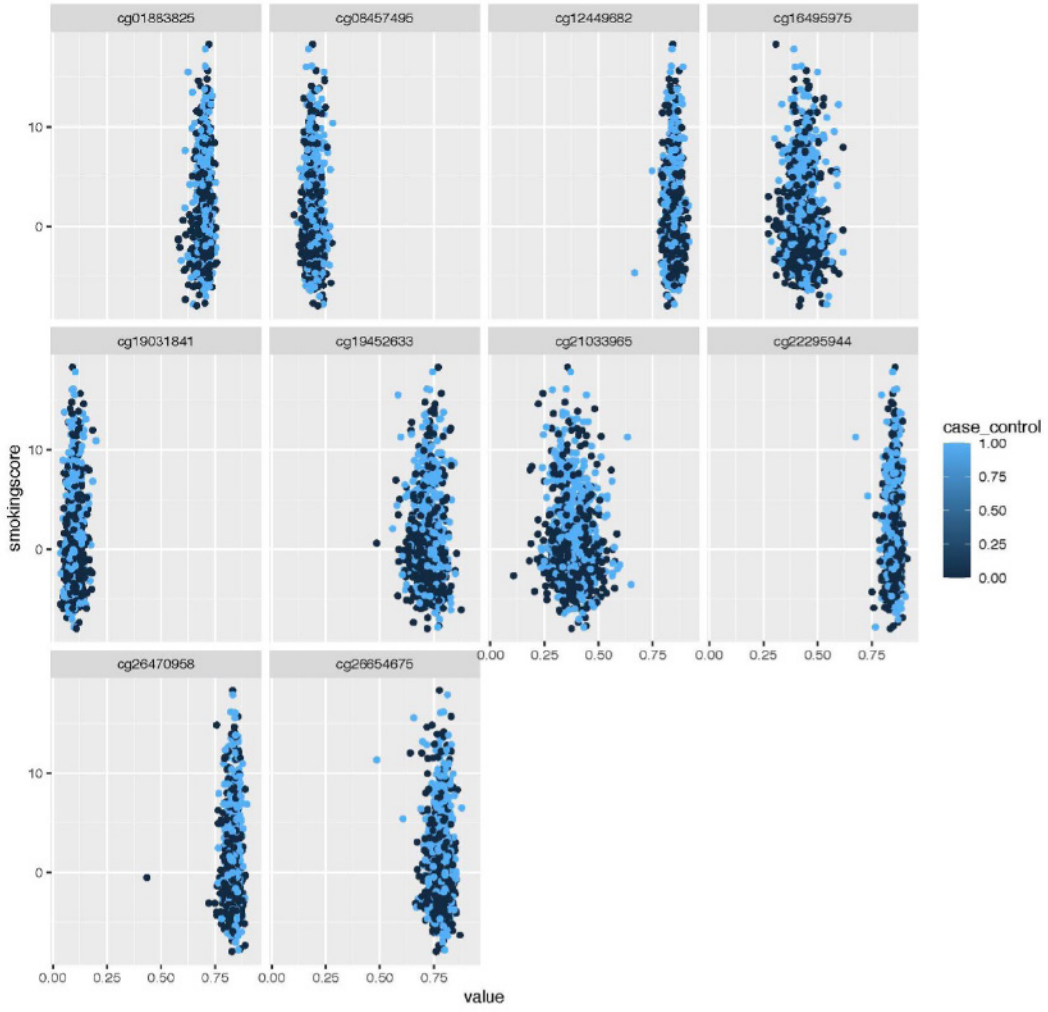
Supplementary Figure 15

The top 10 CpG sites for composite measure of adversity showing the most significant correlation with smoking score. *Each circle represents a subject.*



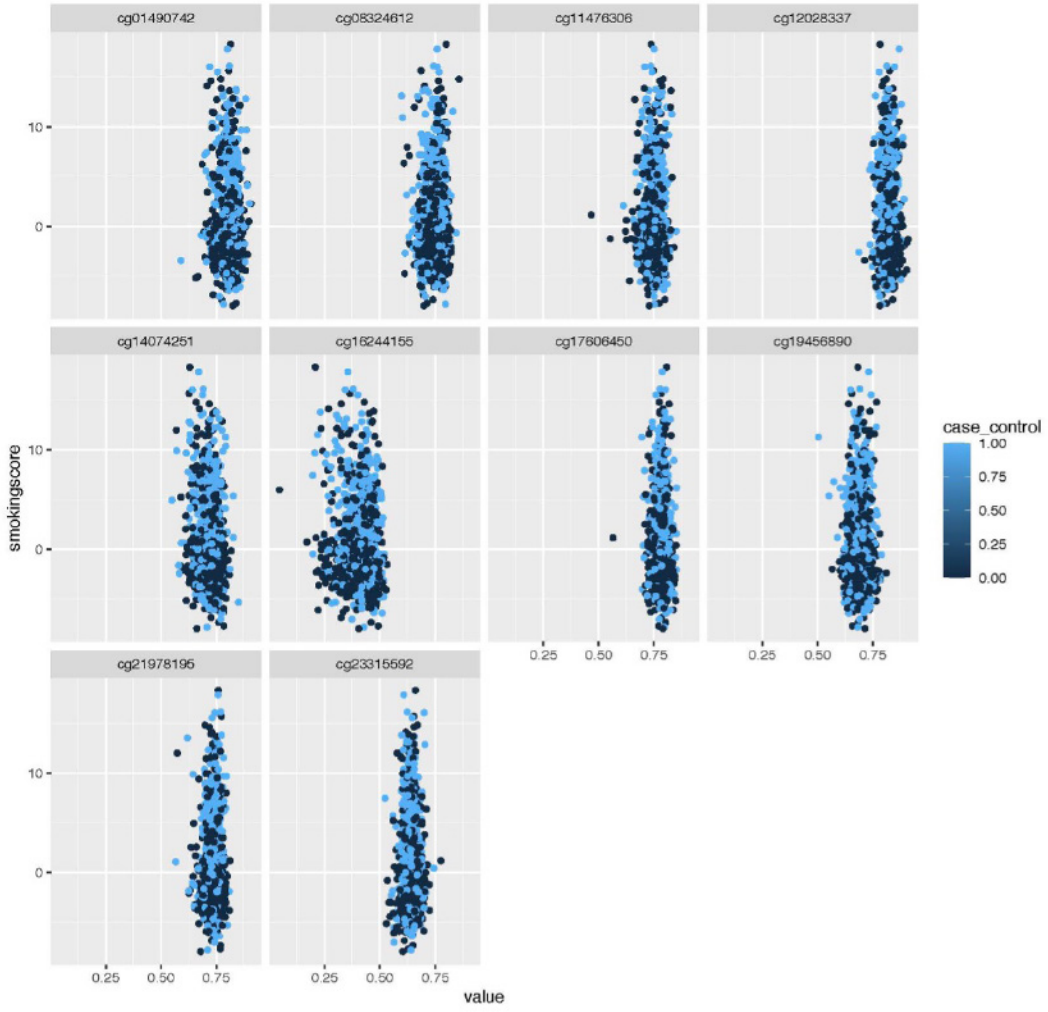
Supplementary Figure 16

The top 10 CpG sites for abuse measure showing the most significant correlation with smoking score. *Each circle represents a sample.*



Supplementary Figure 17

The top 10 CpG sites for neglect measure showing the most significant correlation with smoking score. *Each circle represents a sample.*



Supplementary Table 8

Top 10 biological KEGG pathway analysis of top-ranked differentially methylated positions (DMPs; P-value of P < 5e-5) mediating composite measure of adversity and psychosis.

ID	Ontology	Description	N of DMPs	DE	p-value	FDR	Genes
GO:0001697	BP	histamine-induced gastric acid secretion	1	1	0.002	1	*HRH2*
GO:0015805	BP	S-adenosyl-L-methionine transport	1	1	0.002	1	*SLC25A26*
GO:1901962	BP	S-adenosyl-L-methionine transmembrane transport	1	1	0.002	1	*SLC25A26*
GO:0031641	BP	regulation of myelination	46	2	0.002	1	*ITGAX, TG*
GO:0001698	BP	gastrin-induced gastric acid secretion	2	1	0.002	1	*HRH2*
GO:1905956	BP	positive regulation of endothelial tube morphogenesis	2	1	0.002	1	*ITGAX*
GO:0014809	BP	regulation of skeletal muscle contraction by regulation of release of sequestered calcium ion	4	1	0.005	1	*DMD*
GO:1904340	BP	positive regulation of dopaminergic neuron differentiation	4	1	0.005	1	*FGF20*
GO:0014722	BP	regulation of skeletal muscle contraction by calcium ion signaling	5	1	0.006	1	*DMD*
GO:1905962	BP	glutamatergic neuron differentiation	5	1	0.007	1	*ZHX2*

N, number of genes in the GO or KEGG term; DE, number of genes that are differentially methylated; P.DE, p-value for over-representation of the GO term; FDR, False discovery rate

Supplementary Table 9

Top 10 biological KEGG pathway analysis of top-ranked differentially methylated positions (DMPs; P-value of P < 5e-5) mediating abuse and psychosis.

ID	Ontology	Description	N of DMPs	DE	p-value	FDR	Genes
GO:0001697	BP	histamine-induced gastric acid secretion	1	1	0.002	1	*HRH2*
GO:0015805	BP	S-adenosyl-L-methionine transport	1	1	0.002	1	*SLC25A26*
GO:1901962	BP	S-adenosyl-L-methionine transmembrane transport	1	1	0.002	1	*SLC25A26*
GO:0031641	BP	regulation of myelination	46	2	0.002	1	*ITGAX, TG*
GO:0001698	BP	gastrin-induced gastric acid secretion	2	1	0.002	1	*HRH2*
GO:1905956	BP	positive regulation of endothelial tube morphogenesis	2	1	0.002	1	*ITGAX*
GO:0014809	BP	regulation of skeletal muscle contraction by regulation of release of sequestered calcium ion	4	1	0.005	1	*DMD*
GO:1904340	BP	positive regulation of dopaminergic neuron differentiation	4	1	0.005	1	*FGF20*
GO:0014722	BP	regulation of skeletal muscle contraction by calcium ion signaling	5	1	0.006	1	*DMD*
GO:1905962	BP	glutamatergic neuron differentiation	5	1	0.007	1	*ZHX2*

Supplementary Table 10

Top 10 biological KEGG pathway analysis of top-ranked differentially methylated positions (DMPs - discovery" P-value of P < 5e-5 threshold) mediating neglect and psychosis.

ID	Ontology	Description	N	DE	p-value	FDR	Genes
GO:1900063	BP	regulation of peroxisome organization	3	1	0.001	1	*MFF*
GO:1905956	BP	positive regulation of endothelial tube morphogenesis	2	1	0.002	1	*ITGAX*
GO:0060040	BP	retinal bipolar neuron differentiation	5	1	0.005	1	*ZHX2*
GO:1905962	BP	glutamatergic neuron differentiation	5	1	0.005	1	*ZHX2*
GO:0016559	BP	peroxisome fission	9	1	0.005	1	*MFF*
GO:0043653	BP	mitochondrial fragmentation involved in apoptotic process	9	1	0.006	1	*MFF*
GO:0048284	BP	organelle fusion	138	2	0.006	1	*ANKFY1, MFF*
GO:0021796	BP	cerebral cortex regionalization	7	1	0.007	1	*ADGRG1*
GO:0055059	BP	asymmetric neuroblast division	6	1	0.007	1	*TEAD3*
GO:0015937	BP	coenzyme A biosynthetic process	10	1	0.008	1	*PANK1*

Additional analyses: Possible confounding effect of educational attainment

We examined the possible confounding effect of EA on the association between CTQ scores and psychosis status and our results revealed that in our sample the addition of EA to the model (along with age sex, country and CTQ score) did not change the effect of CTQ score on psychosis as shown below:

Model with EA
. logistic case_control CTQ total, country, age, gender, educational attain.

```
Logistic regression             Number of obs =    705
                                LR chi2(5)    =  154.24
                                Prob > chi2   =  0.0000
Log likelihood = -398.15047     Pseudo R2     =  0.1623

------------------------------------------------------------------------------
  case_control | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
 ctq_composite |   1.674677   .1324753     6.52   0.000     1.434158    1.955534
 country |   .9443545   .0630091    -0.86   0.391     .8285932    1.076289
 age |   .9421039   .0068824    -8.16   0.000     .9287108    .9556901
 gender |   .4604335   .0816155    -4.38   0.000     .3253004    .6517022
Educ attain. |   .9934424   .0100259    -0.65   0.514     .9739851    1.013288
       _cons |   13.84595   5.799058     6.27   0.000     6.092795    31.46509
------------------------------------------------------------------------------
Note: _cons estimates baseline odds.
```

Here is the model without EA as a confounder

. logistic case_control CTQ total, country, age, gender,

```
Logistic regression             Number of obs =    705
                                LR chi2(5)    =  153.80
                                Prob > chi2   =  0.0000
Log likelihood = -398.37235     Pseudo R2     =  0.1618

------------------------------------------------------------------------------
  case_control | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
 ctq_composite |   1.680883   .1324775     6.59   0.000     1.440293    1.961663
 country |   .9484893   .062945    -0.80   0.426     .8328058    1.080242
 age |   .9419723   .0068887    -8.17   0.000     .928567    .9555711
 gender |   .4602207   .0815619    -4.38   0.000     .3251721    .6513569
   _cons |   12.362   4.70644     6.60   0.000     5.861662    26.07095
------------------------------------------------------------------------------
Note: _cons estimates baseline odds.
```

We additionally explored whether the CTQ total score was correlation with EA score and correlation analyse sdi not show association

. pwcorr Educat attain=in_xx CTQ composite

```
             | mrc2_s~x ctq_co~t
-------------+------------------
Educ. attain |   1.0000
  CTQ composite |  -0.0734   1.0000
```

Therefore, given these two sets of analyses, we concluded that the possible confounding effect of EA on CTQ exposure was not major, and we decided not to include it on the analyses.

CTQ operationalisation analyses

In order to explore which CTQ operationalisation strategie was the best predictor of psychosis versus control, we have explored whether path c changes when using the "raw score" rather that our current "cumulative score".

Analyses conducted with the CTQ composite "cumulative score" based on predefined cut-offs are here:

. logistic case_control CTQ raw score, country, age, gender,

```
Logistic regression                     Number of obs     =        705
                                  LR chi2(5)      =     153.80
                                  Prob > chi2     =     0.0000
Log likelihood = -398.37235               Pseudo R2       =     0.1618

------------------------------------------------------------------------------
  case_control | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
 ctq_composite |   1.680883   .1324775     6.59   0.000     1.440293    1.961663
 country |   .9484893   .062945    -0.80   0.426     .8328058    1.080242
 age |   .9419723   .0068887    -8.17   0.000     .928567    .9555711
 gender |   .4602207   .0815619    -4.38   0.000     .3251721    .6513569
   _cons |   12.362   4.70644     6.60   0.000     5.861662    26.07095
------------------------------------------------------------------------------
Note: _cons estimates baseline odds.
```

Here are the results base on the "raw score" score:

. logistic case_control ctq_cumulative country mrc1_socde02 mrc1_socde01

```
Logistic regression                     Number of obs     =        705
                                  LR chi2(4)      =     162.25
                                  Prob > chi2     =     0.0000
Log likelihood = -394.14799               Pseudo R2       =     0.1707

------------------------------------------------------------------------------
case_control | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   ctq_cumulative |   1.053019   .0078509     6.93   0.000     1.037744     1.06852
    country |   .9583718   .0639997    -0.64   0.524      .840797    1.092388
age |   .9414082   .0069709    -8.15   0.000     .9278442    .9551705
gender |   .4651419    .08289    -4.30   0.000     .3280184     .659588
     _cons |   2.451014   1.097218     2.00   0.045     1.019291    5.893775
------------------------------------------------------------------------------
```

Note: _cons estimates baseline odds.

As can be observed in yellow, the signal is much weaker when using the "raw score" (OR=1.68 using the "cumulative score" and 1.053 using the "raw score").

1. Li M, Li Y, Qin H, Tubbs JD, Li M, Qiao C, et al. Genome-wide DNA methylation analysis of peripheral blood cells derived from patients with first-episode schizophrenia in the Chinese Han population. Molecular psychiatry. 2020:1-11.
2. Hannon E, Dempster EL, Mansell G, Burrage J, Bass N, Bohlken MM, et al. DNA methylation meta-analysis reveals cellular alterations in psychosis and markers of treatment-resistant schizophrenia. eLife. 2021;10:e58430.
3. Zhang L, Silva TC, Young JI, Gomez L, Schmidt MA, Hamilton-Nelson KL, et al. Epigenome-wide meta-analysis of DNA methylation differences in prefrontal cortex implicates the immune processes in Alzheimer's disease. Nature communications. 2020;11(1):1-13.
4. Marioni RE, McRae AF, Bressler J, Colicino E, Hannon E, Li S, et al. Meta-analysis of epigenome-wide association studies of cognitive abilities. Molecular psychiatry. 2018;23(11):2133-44.
5. Yang BZ, Zhang H, Ge W, Weder N, Douglas-Palumberi H, Perepletchikova F, et al. Child abuse and epigenetic mechanisms of disease risk. Am J Prev Med. 2013;44(2):101-7.
6. Dunn EC, Soare TW, Zhu Y, Simpkin AJ, Suderman MJ, Klengel T, et al. Sensitive Periods for the Effect of Childhood Adversity on DNA Methylation: Results From a Prospective, Longitudinal Study. Biol Psychiatry. 2019;85(10):838-49.
7. Rijlaarsdam J, Cecil CAM, Relton CL, Barker ED. Epigenetic profiling of social communication trajectories and co-occurring mental health problems: a prospective, methylome-wide association study. Development and psychopathology. 2021:1-10.
8. Gervin K, Nordeng H, Ystrom E, Reichborn-Kjennerud T, Lyle R. Long-term prenatal exposure to paracetamol is associated with DNA methylation differences in children diagnosed with ADHD. Clin Epigenetics. 2017;9:77.
9. Roberts S, Suderman M, Zammit S, Watkins SH, Hannon E, Mill J, et al. Longitudinal investigation of DNA methylation changes preceding adolescent psychotic experiences. Transl Psychiatry. 2019;9(1):69.
10. Kandaswamy R, Hannon E, Arseneault L, Mansell G, Sugden K, Williams B, et al. DNA methylation signatures of adolescent victimization: analysis of a longitudinal monozygotic twin sample. Epigenetics. 2020:1-18.
11. van Dongen J, Hagenbeek FA, Suderman M, Roetman PJ, Sugden K, Chiocchetti AG, et al. DNA methylation signatures of aggression and closely related constructs: A meta-analysis of epigenome-wide studies across the lifespan. Mol Psychiatry. 2021;26(6):2148-62.
12. Lunnon K, Smith R, Hannon E, De Jager PL, Srivastava G, Volta M, et al. Methylomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease. Nat Neurosci. 2014;17(9):1164-70.

13. Karlsson Linnér R, Marioni RE, Rietveld CA, Simpkin AJ, Davies NM, Watanabe K, et al. An epigenome-wide association study meta-analysis of educational attainment. Mol Psychiatry. 2017;22(12):1680-90.
14. Smith AK, Ratanatharathorn A, Maihofer AX, Naviaux RK, Aiello AE, Amstadter AB, et al. Epigenome-wide meta-analysis of PTSD across 10 military and civilian cohorts identifies methylation changes in AHRR. Nat Commun. 2020;11(1):5965.
15. Ju C, Fiori LM, Belzeaux R, Theroux JF, Chen GG, Aouabed Z, et al. Integrated genome-wide methylation and expression analyses reveal functional predictors of response to antidepressants. Transl Psychiatry. 2019;9(1):254.
16. Jeremian R, Chen YA, De Luca V, Vincent JB, Kennedy JL, Zai CC, et al. Investigation of correlations between DNA methylation, suicidal behavior and aging. Bipolar Disord. 2017;19(1):32-40.
17. Starnawska A, Tan Q, McGue M, Mors O, Børglum AD, Christensen K, et al. Epigenome-Wide Association Study of Cognitive Functioning in Middle-Aged Monozygotic Twins. Front Aging Neurosci. 2017;9:413.