Etiopathogenic differences between affective and non-affective psychosis: filling the gaps

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ETIOPATHOGENIC DIFFERENCES BETWEEN AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS: FILLING THE GAPS

By

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Dedicado a la vaca, el zoquete, al niño y a papi

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Και στον Κωνσταντίνο για το δώρο της αγάπης του.

PREFACE

PERSONAL CONTRIBUTION

Data for this PhD is based on 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). In particular, I contributed in the organisation, recruitment, assessment and collecting of follow-up data conducted locally in London as one of the 17 places. With regards to the general baseline across all the 17 sites of EUGEI study, I cleaned up previously created datasets including diagnosis received in clinical settings, which I used in Study 2, 3 and 4; and variables related to DUP and past and present medication.

I wrote the entirety of this thesis with the following exceptions:

• Chapter 3 (meta-analyses), after I completed the draft, I circulated it to co-authors and then underwent peer review prior to acceptance for publication.
• Chapter 5 (Polygenic Risk Score –PRS- association study), I was in charge of draft the chapter, with the collaboration of co-authors for the subsection of genotyping methods, given that I was provided with this data processed and I did not take part on the process of genotyping and/or quality control. After I completed the draft, I circulated it to co-authors and the work underwent peer review as process of submission for publication (under review).

I developed the intellectual idea and organisation of the design of the Chapter 3 (meta-analyses) and carried out all the analyses with the additional supervision of Dr Sandra Matheson and Prof Kristin Laurens. I was responsible for looking the most appropriate methods to test my hypothesis, and I designed and carried out all of the data analyses presented on Chapters 3, 4, 5 and 6 , under the supervision of Dr Evangelos Vassos and Prof Sir Robin M Murray. For Chapter 4 (incidence study), I received assistance from Dr Hannah Jogsma, Dr Craig Morgan and Dr James Kirkbride. For Chapter 5 and 6 (PRS association analyses and GxE interaction), I utilised the polygenic risk scores calculated by Dr Vassos.

THESIS INCORPORATING PUBLICATION

This thesis is a "thesis incorporating publications". This refers to the fact that two Chapters are composed of published or submitted articles of which I am the first author.

Chapter 3 is composed of the following journal article which is reproduced in full: *Victoria Rodriguez, Luis Alameda, Giulia Trotta, Edoardo Spinazzola, Paolo Marino, Sandra L Matheson, Kristin R Laurens, Robin M Murray, Evangelos Vassos, Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies, Schizophrenia Bulletin, 2021;, sbaa197, https://doi.org/10.1093/schbul/sbaa197*

Chapter 5 is composed of the following journal article which is reproduced in full: *Rodriguez V, Alameda L, Quattrone D, Tripoli G, Gayer-Anderson C, Spinazzola E, Trotta G, Jongsma HE, Stilo S, La Cascia C, Ferraro L, La Barbera D, Lasalvia A, Tosato S, Tarricone I, Bonora E, Jamain, S, Selten JP, Velthorst E, de Haan L, Llorca PM, Arrojo M, Bobes J, Bernardo M, Arango C, Kirkbride J, Jones PB, Rutten BP, Richards A, Sham P, O'Donovan MC, Van Os J, Morgan C, Di Forti M, Murray RM*, Vassos E*. Use of multiple Polygenic Risk Scores for distinguishing Non-affective Psychosis and Affective psychosis categories in a First Episode sample; the EUGEI study* ***, in submission****. [Available as preprint in medRxiv]*

GENERAL ABSTRACT

Background: Classical non-affective psychosis –NAP- and affective psychosis –AP- (in which we would include Bipolar disorder and Psychotic Depression) has constituted the two main pillars of psychosis since Kraepelin established the classical dichotomy back in the 8th century (1910). Due to their similarities in terms of clinical expression, social and individual impact, associated risk factors and high crossed heritability with proven genetic overlap, there has been in the last years a trend to overcome accepted classical diagnostic boundaries and switch towards the concept of psychotic spectrum in line with the notion of unique psychosis. Nonetheless, there are still grounds to believe that a future finer clustering may identify subgroups corresponding to current diagnostic categories. For instance, whereas overall incidence of psychosis is 21-43/100kpy; last meta-analyses pointed NAP to be around 18.7/100kpy, and AP around 4.8/100kpy. Part of the clustering is potentially supported by etiopathogenic factors. Firstly, there is polygenic evidence of differences over the shared liability, which is mostly true when we include major depression with psychotic symptoms. Secondly, despite known shared environmental risk factors (ERF) such as cannabis and childhood trauma, evidence in literature provides much more evidence for the NAP. Notwithstanding, part of these disparities may be caused by the significant gap observed in AP research compared with NAP.

Aims: The focus of this thesis is to explore the overview differences between AP and NAP while contributing to fill part of the gap in relevant areas related to etiopathogenesis. I aim to do this by compiling evidence on relevant environmental risk factor for AP meta-analysing prospective studies; calculating incidence of Bipolar Disorder and Psychotic Depression employing a large first episode psychosis (FEP) multinational sample; studying the genetic architecture of AP throughout the joint use of polygenic scores for major psychiatric disorder across clinical subgroups; and lastly, by studying etiopathogenic pathways differences analysing how polygenic liability and combined ERF exposure interplay in NAP and AP.

Methods: This PhD is mainly based on the EUGEI 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. It comprises a total of 2627 participants, including 1130 patients aged 18 to 64 years diagnosed with NAP, Bipolar Disorder or Psychotic Depression; and 1497 controls in 17 sites across 6 mostly European countries.

Results: Primarily, the performed meta-analysis supports a shared environmental load with NAP, showing significant associations of advanced paternal age (OR 1.17, 95%CI 1.12-1.23), early (OR 1.52, 95%CI 1.07-2.17) and late (OR 1.32, 95%CI 1.05-1.67) gestational age, childhood adversity (OR 1.33, 95%CI 1.18-1.50), substance misuse (OR 2.87, 95%CI 1.37–5.50), and being from an ethnic minority (OR 1.99, 95%CI 1.39-2.84) with onset of AP. Secondly, our results shows previously observed differences on overall incidence between psychotic phenotypes, being around 9.53/100kpy for schizophrenia, compared with around 2.42/100kpy and 2.72/100kpy for Bipolar Disorder and Psychotic Depression respectively, with marked differences across sites which partly account for ethnicity and owner occupancy. When looking at the genetic load employing polygenic risk scores for schizophrenia, bipolar disorder, depression and intelligence, both scores for schizophrenia (OR=0.7, 95 %CI 0.54-0.92) and depression (OR=1.31, 95%CI 1.06-1.61) differentiates AP from NAP; which talks in favour of some clustering over the known genetic overlap. Lastly, although no evidence was found of a synergistic effect of genetic loading on onset of AP, conditional on history of cumulative adverse environmental factors, differential genetic associations based on individual exposure to ERF talks in favour of distinct pathways of disease for AD and NAP. AP seems to be a product of cumulative environmental insults alongside a higher genetic liability for affective disorders; NAP seem to be due to two distinct pathways: PRS-SZ acting additively with ERF, and PRS-BD and PRS-D potentially acting through the affective pathway to psychosis in the light of ERF.

Conclusions and implications: Overall, this thesis provides support for the view that both environment and genetics play their specific role on AP. Despite these factors presenting a noticeable overlap with those factors replicated for NAP, which supports a transdiagnostic effect across psychosis, certain distinctions and differentiations were found for AP. These results require replication, but in combination with future avenues (from biology to sociology), ensure exciting findings in our understanding of the etiopatogenic underpinnings of AP, which will ultimately give us ground to set clearer splits over the lumps.

ORGANISATION OF THE THESIS

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LIST OF EMPLOYED ACRONYMS

AP: Affective Psychosis

BD: Bipolar Disorder

BD-I: Bipolar Disorder type I

BD-II: Bipolar Disorder type II

BD-NOS: Bipolar Disorder type not otherwise specified

BD-P: Bipolar Disorder with psychotic symptoms

CECA.Q: Childhood Experience of Care and Abuse Questionnaire

CEQ: Cannabis Experience Questionnaire

DNA: Deoxyribonucleic acid

DSM: American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders

DUP: Duration of Untreated Psychosis

ERF: environmental risk factor

EUGEI: European network of national schizophrenia networks studying Gene Environment Interaction

FEP: First Episode Psychosis

GA: Gestational Age

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

GWAS: genome-wide association studies

GxE: gene and environment interaction

HR: Hazard Ratio

ICD: World Health Organization's International Statistical Classification of Diseases and Related Health Problems

IQ: Intelligence Quotient

IRR: Incidence Rate Ratio

MDD: Major Depressive Disorder

MDD-P: Major Depression Disorder with psychotic features (*note: used indistinctively from **PD***)

MERS: Maudsley environment risk score for psychosis

MHA: Mental Health Act

MOOSE: Meta-analyses Of Observational Studies in Epidemiology

MRC: Medical Research Council

NAP: Non-affective Psychosis

NHS: National Health Service

NOS: Newcastle-Ottawa Scale

NOS-DUP: Nottingham Onset Schedule – Duration of Untreated Psychosis

OPCRIT: Operational Criteria Checklists

OR: Odds Ratio

PC: Principal Component

PD: Psychotic Depression (*note: used indistinctively from **MDD-P***)

PES: Polyenvironmental Score

PGC: Psychiatric Genomics Consortium

PNOS: Psychosis not otherwise specified

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRS: Polygenic Risk Score

PRS-SZ: Polygenic Risk Score for Schizophrenia

PRS-BD: Polygenic Risk score for Bipolar Disorder

PRS-D: Polygenic Risk Score for broad-defined depression/depressive symptoms

PRS-MDD: Polygenic Risk Score for Major Depressive Disorder

RR: Risk Rate

SAR: Standardised Adjusted Incidence Rates

SCZ: Schizophrenia

SIR: Standardized Incidence Ratio

SNP: Single-nucleotide polymorphism

SLE: Stressful Life Events

SUD: Substance Use Disorder

THC: Tetrahydrocannabinol

95%CI: 95% Confidence Intervals

100kpy: 100.000 person-year

1. GENERAL INTRODUCTION

1.1 SUMMARY

In Chapter 1, I provide an overview of affective psychosis from the origin of the concept to the current definition (Section 1.2); and present an epidemiological overview based on the latter classifications (Section 1.3). I then summarise the upcoming nosological crisis and how one solution is moving to a new conceptualisation of a broad psychosis continuum (Section 1.4). In Section 1.5, I highlight part of the factors that brought the loss of confidence on the Kraepelenian pillars while reviewing the existing literature on the genetic and environmental factors as main etiopathogenic elements in the development of affective psychosis disorders. In Sections 1.6, I show the misbalance on research between affective psychosis and non-affective psychosis. Finally, I outline the key research questions addressed in this thesis.

1.2 ORIGINS OF AFFECTIVE PSYCHOSIS CONSTRUCT TO CURRENT CLASSIFICATIONS

The term "affective disorders" has been traditionally employed in Psychiatry to define the group of disorders that manifest with a primary alteration in mood from which secondary symptoms can then derive. The first record of a mention of the symptoms of mania and depression date to the 460–337 BC when Hippocrates systematically described mania and melancholia (Ackerknecht, 1959) but it was Aretaeus of Cappadocia around the 1st century AD who was the first to explicitly link mania with melancholia (Marneros, 1999). Interestingly, first indices of a psychotic component of melancholia were identified in observations from Galen (129–216 AD), which described that along with depressive symptoms, patients with melancholia showed fixed bizarre ideas with repercussion on their behaviour; and by the previously mentioned Aretaeus of Cappadocia (Telles-Correia and Marques, 2015).

Much later, in 1621, Richard Burton attempted to unify various descriptions of melancholia in his book "The Anatomy of Melancholia"; and he specifically described the presence of ideas of persecution, poisoning and jealousy (Burton, 1883). Also in the 17th century, in the "Sepuchretum", Bonet was known to use the term "*manico-melancolicus"*. In the beginning of 19th century, Pinel (1801) and Esquirol (1838) produced clinical descriptions in which they documented repeated alternations of

mania and melancholia in the same patient (Haustgen and Akiskal, 2006). In this respect, some controversy still arises around whether they adhered to the notion that manic and melancholic episodes were separate syndromes of mental illness. Being that the case, it would be Wilhelm Griesinger, one of the founders of German scientific psychiatry, the one considered as the first describing in 1845 the change from melancholia to mania as inherent condition of a unique disease (Angst and Marneros, 2001). Nonetheless, most historians point at Falret (1854-1864) and Baillarger (1853-1854) as the real originators of bipolar disorder and the first to really capture the notion of the periodic manic-depressive illnesses, under the terms "*circular insanity*" and "*dual-form/double insanity*" respectively (Radden, 2011; Malhi *et al.*, 2018). Of note, Falret is considered the first to observe the heritable nature of this condition and to emphasise that the clinical cyclic course, as opposed to the succession of mania and depression in a single episode (in the case of Baillarger's definition), was the key to diagnosing the illness (Sedler, 1983). They, alongside with the French psychiatrists of that period, attempted to group a wide range of periodic disorder variants consisting of depressive or manic phases, with longer or shorter inter-episode remission, which they named under their own particular denominations (Mayer Gross *et al.*, 1974). Also around that time, in 1895, Séglas developed further the characteristics of melancholic delusion in a way that anticipated accurately the psychotic features specified at DSM-IV (Sèglas, 1895).

No doubt, Falret, Baillarger and the French school were crucial to inspiring Kraepelin's nosology, but the coining of the term "*manic-depressive insanity"* is attributed to Kraepelin, who emphasised the commonalities of these forms and united them under this term (Mayer Gross *et al.*, 1974). From there, the delineation of schizophrenia (*dementia praecox*) and affective psychosis (*manic-depressive insanity*) as two distinct entities is one of Emil Kraepelin's seminal contributions to nosology (Kraepelin and Diefendorf, 1915). When shaping this delineation, illness course was central to Kraepelin's work because he sought to develop diagnoses that would be predictive of future symptoms and functioning (Green *et al.*, 2000); but by doing so, Kraepelin was associating thought and cognitive changes with dementia praecox and affective symptoms with the manic-depression group. This, at the turn of the nineteenth century, will contribute to the progressive abandonment of the idea of melancholia as a disorder causing abnormal beliefs in favour of a disease mostly characterized by affective symptoms, and gradually displaced by the term

depression (Berrios, 1996). Moreover, French alienists such as G. Ballet (1902), J. Tastevin (1911), P.L. Couchoud (1911), A. Devaux and B.J. Logre (1917), and R. Benon (1922) started to distinguish an "intermittent melancholia" (more endogenous and related with Kraepelin's disease) from the "true or simple melancholia" (reactive and less recurrent) (Haustgen and Akiskal, 2006). All this contributions added to the inputs from Angst and Perris (Angst and Perris, 1968), who came with the term "*unipolar*" and are considered as the first in finding genetic evidence for eventually establishing the distinction between bipolar and unipolar forms that we will see later in DSM-III (American Psychiatric Association, 1980). This distinction would consequently place psychotic depression at a different nosographic branch than the rest of psychoses.

Nowadays, affective psychoses, in which we include Bipolar Disorder (BD) and Major Depression Disorder with psychotic features (so called psychotic depression – PD/MDD-D-), fall into different criteria-driven definitions based on current diagnostic classifications. With the first inclusion of mental disorders in the 6th edition of ICD (International Classification of Diseases) in 1948 (ICD-6, 1948) and the 1st edition of DSM (Diagnostic and Statistical Manual of Mental Disorders) by the American Psychiatric Association (APA) in 1952, this diagnosis was still very close to the concept of Kraepelin. For instance, in DSM-I, illusions, delusions and hallucinations were listed as additions to the diagnosis in a time in which psychotic features were conceived as a major component of a wider disease (Mason *et al.*, 2016), but in DSM-II (1968) manic-depression was already listed under "Affective Disorders". It was not until ICD-9 (World Health Organization, 1975) and the DSM-III (American Psychiatric Association, 1980) when there was a formal separation of unipolar and bipolar depression and the term "*manic-depressive illness*" was replaced by BD. In addition, in DSM-III the presence of psychosis was not seen as a core component anymore and it was added with the specifiers of "mood-congruent" or "mood-incongruent" psychotic features (Mason *et al.*, 2016). This change is noted when comparing the Kraepelin's description of mania with mania criteria in DMS-III (**Figure 1.1**). With no major nosographic reorganisations on the DSM-IV or DSM-IV-R (American Psychiatric Association, 1994; Association, 2000), an important distinction from the DSM-5 (American Psychiatric Association:, 2013; Cantor-Graae and Pedersen, 2013) is the split of mood disorders into depressive and bipolar disorder as separate chapters, emphasising their view that these disorders are

distinct. This, on the other hand, has not been the case in the ICD-11 (Organization, 2018), where unipolar and bipolar, despite owning their unique codes, remain under the same super index "Mood disorders".

Figure 1.1 Comparison of Kraepelin's mania description as reported by Dreyfus with DSM-III criteria for mania; source: Kendler, 2020 (Kendler, 2020).

#	Description	Parallel criterion in DSM-III	Summary of DSM criterion
1	Euphoria (quiet cheerfulness up to boundless merriment).	A	… periods with a predominantly elevated, expansive or irritable mood
2	Heightened agitation, which can increase from touchiness to outbreaks of rage with ranting.	A	ditto
3	Distractibility.	B6	Distractibility
4	Pressured hyperactivity (heightened business, talkativeness).	B1	Increase in activity (socially, at work or sexually) or restlessness
		B2	More talkative that is unusual
5	Heightened sense of self (pressure to dominate), recklessness.	B4	Inflated self-esteem (grandiosity which may be delusional)
		B7	Excessive involvement in activities with high potential for painful consequences
6	Lack of inner unity of conceptual processes (losing the thread, mental unrest, flight of ideas).	B3	Flight of ideas or thoughts racing
7	Increased attention and mental activity.	--	
8	Rapid, short-lived change of sad disordered mood to euphoria.	--	
9	Delusional ideas (grandiose delusions, delusional jealousy, etc.)	B4	Inflated self-esteem (grandiosity which may be delusional)

Regarding PD or what had been classically referred as melancholia, although the latter is still employed in clinical settings to refer to certain forms of severe depression generally in the presence of delusions and/or hallucinations (Harrison *et al.*, 2017), it is present in DSM-5 and ICD-11 as "*major depression with melancholic features*" in the former and *"6A80.3. Current depressive episode with melancholia"* in the latter; but anymore for reflecting depression with psychosis that has been instead replaced by the modifier *"with psychotic features/symptoms"*. Nonetheless, the features of melancholia, which are represented in the **Figure 1.2**, are frequently present in PD as well (Peters *et al.*, 2020), and vice versa.

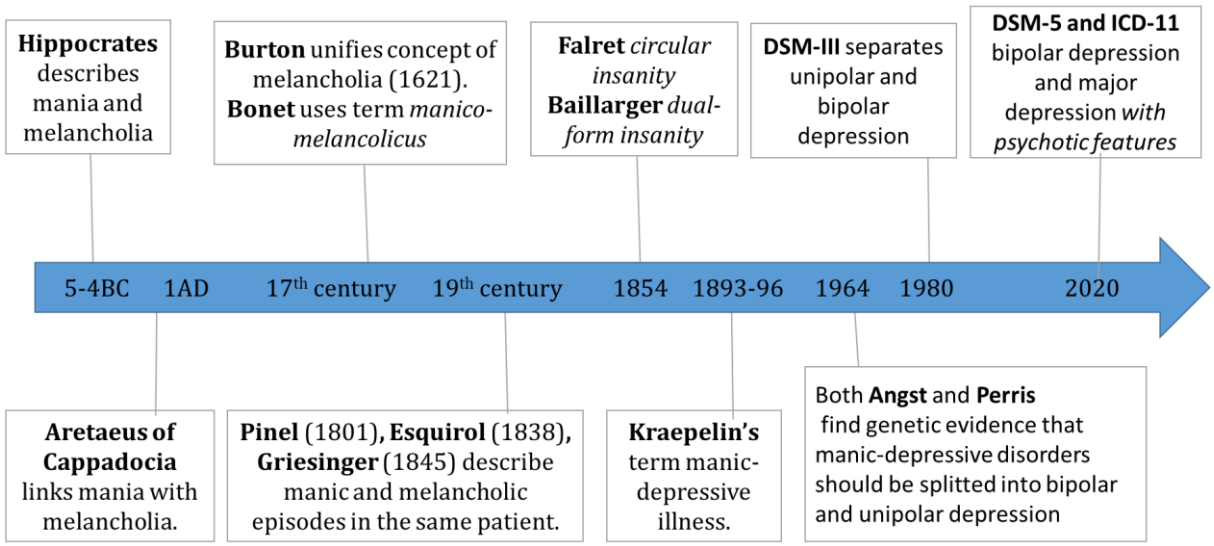
Figure 1.2. Characteristics of melancholic features in current classifications; *adapted from Box 9.2 from "Shorter Oxford Textbook of Psychiatry 7ed (2018)*(Harrison *et al.*, 2017)

Clinical features of depression with 'somatic' or 'melancholic' features

- Loss of interest or pleasure in usual activities
- Lack of emotional reactivity to normally pleasurable surroundings and events
- Early-morning waking (≥2 hours before usual time)
- Depression worse in the morning
- Psychomotor agitation or retardation
- Marked loss of appetite
- Weight loss (5% or more of body weight in last month)
- Distinct quality of depressed mood (DSM-5 only)
- Excessive guilt (DSM-5 only)

At least four of these symptoms are required to make a diagnosis of depression 'with melancholia' (ICD-11) or major depression 'with melancholic features' (DSM-5). DSM-5 also specifically requires either 'loss of interest etc' or 'lack of emotional reactivity etc', to be present.

Figure 1.3. Timeline of Affective psychosis concept



1.3 Epidemiology of Affective Psychosis

In this section, I will present an overview of the epidemiology of Affective Psychosis (AP), covering its impact, incidence and prevalence. Due to the limited availability of studies focusing on Bipolar Disorder with psychotic features (BD-P) and Psychotic Depression (PD) specifically, I will mostly base this summary on Bipolar Disorder in general (BD), providing specific data when available for the psychotic bipolar disorder subgroup. As far as Psychotic Depression is concerned, I will present data for this subgroup only, since reviewing epidemiology of depression in general would be out of the scope of the present work.

1.3.1 Impact and outcome

Affective psychoses are, together with non-affective psychosis (NAP), among the major causes of disability and disease burden worldwide (World Health Organization & World Bank, 2011; Hay *et al.*, 2017), resulting in reduction in quality of life (Michalak *et al.*, 2005; Bonnín *et al.*, 2012; Grunze and Born, 2020) and considerably shorter life expectancy compared with general population (Hayes *et al.*, 2015; Hjorthøj *et al.*, 2017), particularly death by suicide (Tondo, Leonardo *et al.*, 2020).

Despite Bipolar Disorder's outcome is variable, leading to attempts to systematise validated concepts and definitions to describe course and outcomes (Tohen *et al.*, 2009), it is undoubted that Bipolar Disorder has a detrimental impact on functioning (Grande *et al.*, 2016; Sanchez-Moreno *et al.*, 2018), as do affective psychotic disorders in general (Tohen *et al.*, 2000). Moreover, a functional decrement can be observed at onset (Tohen *et al.*, 2003), is believed to remain stable (Martino *et al.*, 2017), but can be also present between episodes due to mainly depressive subthreshold symptoms (Tohen *et al.*, 2006; Bonnín *et al.*, 2012; Murru *et al.*, 2018). Whether or not presence of psychosis in Bipolar Disorder translates into worse functional outcome is still debatable, with studies reporting work and social impairment (van Rossum *et al.*, 2008; Altamura *et al.*, 2019; Shalev *et al.*, 2020) while other studies report no functional impact (Keck *et al.*, 2003; Jiménez-López *et al.*, 2018).

Regarding Psychotic Depression, research is sparser. We know that Major Depression is a the top of the mental disorders causes of disabilities list (Hasin *et al.*, 2018), which is not only due to its high prevalence but because of the marked limitations it causes. Considering that Psychotic Depression implies a worsening in social functioning (Gaudiano *et al.*, 2009; Benard *et al.*, 2020), clinical outcome at different levels (Dold *et al.*, 2019) and suicidality up to two-fold higher (Gournellis, R. *et al.*, 2018), this talks in favour of investing more effort in delineating better knowledge of epidemiological aspects of the illness that may help us in drawing up preventive strategies.

1.3.2 Incidence

Incidence studies aim to investigate new cases in a certain defined population providing crucial information on variations in the development of the disorder of interest, and enabling the identification of risk factors and potential elements of its etiology. Whereas incidence for NAP has attracted much attention, fewer studies have focused on incidence exclusively for bipolar disorder and psychotic depression respectively. In the case of affective psychosis, we can rely on recent meta-analyses on incidence of psychosis reporting secondarily affective psychosis as a whole (Kirkbride *et al.*, 2012; Castillejos *et al.*, 2018), and also bipolar disorder and psychotic depression (Jongsma *et al.*, 2019). Interestingly, Jognsma et al. highlight that any affective psychotic disorder as outcome was clearly understudied, with 32,

20 and 15 citations found for affective psychosis as a whole, bipolar disorder with psychotic features, and psychotic depression respectively, which contrasts with 86 studies on schizophrenia and 59 on overall psychosis (Jongsma *et al.*, 2019).

From the reviewed studies, we can see that NAP is consistently more frequent, with higher incidence rates, of around 18.7-23 per 100000 person-year (100kpy) compared with 4.6-12 per 100kpy for AP, representing less than one third of NAP incidence; and one fourth of the 26.6-31.7 per 100kpy global psychosis rates (Kirkbride *et al.*, 2012; Castillejos *et al.*, 2018; Jongsma *et al.*, 2019). In the two meta-analyses including BD-P and PD they estimated 3.7-6.12 cases per 100kpy for BD-P (Kirkbride *et al.*, 2012; Jongsma *et al.*, 2019), and of 5.3 cases per 100kpy in the only one reporting meta-analysed PD rate (Kirkbride *et al.*, 2012); showing fairly similar incidence rates as the last systematic review specifically on PD epidemiology – from 3.4 to 6.4 per 100kpy- (Jääskeläinen *et al.*, 2018).

Nonetheless, for the cyclic course that characterise AP and not its non-affective counterpart (which we saw that constituted one of the key elements Kraepelin used to establish the dichotomy), some may argue the inherent difficulties in counting first episodes of psychosis (FEP) as bipolar or psychotic depression if we are still lacking knowledge of the course and longitudinal support of these constructs. At this respect, some researchers tried to overcome this flaw by attributing incidence of BD from first episodes of unipolar mania (Kennedy, N. *et al.*, 2005) and can partly explained observed higher rates in studies from case registers than from first contact studies (Jongsma *et al.*, 2019).

Despite the reported global incidence rates, it is important to note that incidence of psychosis varies across regions and across time. Regarding the former, among the risk factors pointed to explain part of these differences in AP rates between regions we find mainly living in urban area (Vassos *et al.*, 2016; Castillejos *et al.*, 2018); and migration – being migrant and especially from black population community in UK at risk- (Kirkbride *et al.*, 2012; Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Szöke, *et al.*, 2018); although this difference is smaller in affective than non-affective psychosis (Jongsma *et al.*, 2019). Regarding the latter, few studies have explored variability of incidence of AP over time, two reporting a decline in rates from 1970 to 1990 and two others suggesting stable incidences between 1955 and 1967

(Soderlund *et al.*, 2015), and 1980 to 2000 (Kirkbride *et al.*, 2009). In line with this, a recent study also supported stability on incidence for BD from 1990 to 2007 (He *et al.*, 2020).

To sum up, AP rates lie around one third of those of NAP, they also tend to be higher in urban areas and areas with higher ethnic minorities; and they tend to remain stable across time.

1.3.3 Prevalence

Prevalence studies quantify the total number of cases in the population and are a key measure to understand the burden of the disorder which can aid to direct health service planning. Bipolar disorder present an estimated lifetime prevalence around 1% calculated in the first meta-analysis (Clemente *et al.*, 2015), which goes in line with the 1% prevalence reported already in the first study based on DSM-III criteria (Bebbington and Ramana, 1995) and in later reviews compiling studies from both European countries (Pini *et al.*, 2005) and US (Kessler *et al.*, 1994; Jonas *et al.*, 2003). Within BD, prevalence of lifetime psychotic symptoms has been estimated in around 58% (Goodwin, Frederick K. and Jamison, 2007) to 65-68% in more recent studies (Keck *et al.*, 2003; Sanchez-Moreno *et al.*, 2018), mostly occurring this in mania. Of note, up to 50% of patients presenting with mania can have co-occurring psychotic symptoms (Azorin *et al.*, 2007).

On the other hand, whereas major depressive disorder (MDD) has a lifetime prevalence between 8% and 12% (Kessler and Bromet, 2013; Fond *et al.*, 2019), the proportion of patients manifesting psychotic symptoms is only around 5% (Gaudiano *et al.*, 2009) to 11% of them (Dold *et al.*, 2019), with similar rates of around 10% Chinese population (Zhou *et al.*, 2020). This leads to a calculated prevalence in general population around 0.35% to 1% as per the only published systematic review on PD (Jääskeläinen *et al.*, 2018). Nonetheless, based on data from an international survey including 47 low and middle-income countries, age- and sex-adjusted prevalences can vary from 0.1% (Sri Lanka, Vietnam) to 9.03% (Brazil) (Koyanagi *et al.*, 2017).

Contrary to what we saw for incidence, a recent review shows evidence of an increase of 49% of cases of BD over time (Ferrari *et al.*, 2016), but this is explained

by the authors as due to the decline on mortality rates and increasing mean population age; and speculated to be also influence by minor changes in diagnostic criteria (He *et al.*, 2020). Reasons of variability in reported prevalences between sites are mainly attributed on differences in diagnostic classifications. On the one hand, due to the inconsistent employ of subcategories of type I and type II for Bipolar Disorder; and on the other hand, due to differences in consideration of lifetime psychotic experiences as enough or not to be granted the transversal diagnosis of PD. Nonetheless, as presented above, it is mainly through the incidence studies where we can extract valuable information about risk factors, which make the incidence study approach more appropriate for the present work as part of the global attempt of exploring etiopathogenic elements in affective psychosis.

1.4 Loss of confidence in classic Psychiatry nosology: Categorical diagnosis vs continuum construct

More than 100 years have passed since Kraepelin established the dichotomy of manic-depressive and dementia praecox as the two fundamental pillars of psychotic illness, which still constitutes the basis of current diagnostic criteria (1909). Interestingly, the 'father of modern psychiatry' himself expressed serious doubts about his taxonomy and was aware of his limitations; but his doubts focused specifically on the unanswered question of whether previously observed melancholia corresponded to transversal observations of his described manic-depressive insanity or if there should be a place for the unipolar construct as a separate entity (Angst and Marneros, 2001). However, recent increasing doubts challenge the question if the two originally proposed categories themselves represent discrete illnesses (Murray *et al.*, 2004; Craddock and Owen, 2007).

1.4.1 Crumble of the two pillars: asserts to a continuum

It is possible to claim that it was already Bleuler (1924) who, besides being the first in using the term "schizophrenia", departed from Kraepelin's view by suggesting that the relationship between AP and what was then *dementia praecox* was more of a continuum rather than a sharp demarcation (Jablensky, 2010). In his view, AP were nonspecific, being the patient's position on the continuum marked by the number of schizophrenic features they presented (Goodwin, Frederick K and Jamison, 2007). As opposed to the most common medical classification model – the

categorical approach or called by others the "*splitters*" view-, accepting the notion of a continuum where no discrete diagnosis entities exist lead us to the dimensional approach. This approach conceptualises the individual patient based on where they fall across a number of different dimensions, being each individual a particular point of intersection of the multiple parameters.

Supporters of the psychosis continuum (also referred as "*lumpers*") base their scepticism on the discrete categories in the accumulated similarities found between schizophrenia (SCZ) and BD, which transcend the known shared clinical expression; such as the observed spectrum on neurocognitive decline (Bora *et al.*, 2010; Lynham *et al.*, 2018); the similar elevation in dopamine synthesis capacity (Jauhar *et al.*, 2017); and the findings of some neuroanatomical correlates (Yu *et al.*, 2010). Another argument relies on the replicable distribution of SCZ and BD at opposing ends of the continuum of severity (Mancuso *et al.*, 2015) translated into the presence of affective or psychotic expressions respectively in alike distribution of severity in general population (Wigman *et al.*, 2014; Shevlin *et al.*, 2017). However, most of the support comes from the replicated observed shared genetic (Bramon and Sham, 2001; Craddock *et al.*, 2006; Cardno and Owen, 2014) and environmental risk factors, that I will further discuss in the next Section.

1.4.2 Categorical approach: contemporary grounds for discrete entities

While more papers add to the pressure in restructuring diagnostic boundaries into a smoother conceptualization of a continuum, we can still find contemporary support of the existence of some disparities at different clinical levels. For instance, some recent papers identified two distinct groups corresponding with the classic division when exploring symptom distribution employing latent class analyses (Derks *et al.*, 2012); or by building machine learning models that predicted individually the belonging to the distinct groups with high rates of success (Jauhar *et al.*, 2018). Regarding cognition, although we mentioned a transdiagnostic spectrum of neurocognitive decline (Bora *et al.*, 2010), how these deficits evolve across life-spam seems to differ, suggesting different underlying etiopathogenic mechanisms (Trotta *et al.*, 2015; Mollon *et al.*, 2020). Moreover, more differences seem to arise when studying social cognition, with no clear differences between BD and control group, both performing better than SCZ group (Lee *et al.*, 2013). Neurodevelopmental trajectories appear to differ as well between SCZ and AP (Jabben *et al.*, 2010),

showing the former earlier social impairment (Payá *et al.*, 2013) that goes in line with a worse social adjustment observed in a group of schizophrenic patients when compared with a group of patients presenting with BD, psychotic on their majority (Pacheco *et al.*, 2010). Also, others exploring subgroups by outcome found support of a main distinction across psychosis groups corresponding with affective and non-affective psychosis (Kotov *et al.*, 2013). To sum up, these studies support the notion of a point of rarity between the two classical pillars.

1.5 ETIOPATHOGENESIS OF AFFECTIVE PSYCHOSIS

In this section, I will review the chronological evidence regarding the genetic component in the development of AP, covering from research supporting a genetic overlap across the psychosis spectrum to other evidence still suggesting the existence of boundaries between diagnostic categories. Then, I will also present the environmental contribution to the etiology; and lastly, I will summarise the way both genetic and environmental elements interact with each other on the development of Affective Psychosis.

1.5.1 Genetics review

1.5.1.1 Heritability of affective psychosis: Family, twin and adoptive studies.

The importance of inherited factors for BD and MDD is widely accepted. This has been supported by classical genetic epidemiological research involving family, twin and adoption studies; which have shown evidence of genetic predisposition to BD (Craddock and Sklar, 2013). In monozygotic twins, the concordance rate for BD is between 40–70% (Craddock and Jones, 1999); and one UK study with sixty-seven twin pairs found a heritability estimated at 85-89% (McGuffin *et al.*, 2003). It is also well-known that depression can run in families. Results from 177 probands from the Maudsley Hospital Twin Register estimated a heritability for MDD between 48-75% (McGuffin *et al.*, 1996). This was partly supported by a review and meta-analysis that estimated a lower heritability of 37% from five twin-studies (Sullivan *et al.*, 2000), which was replicated (38% heritability) in a Swedish twin study with the largest sample to date (Kendler *et al.*, 2006). Interestingly, the heritability rate calculated for PD is very similar, of 39% (Lyons *et al.*, 1998).

Moreover, some classical epidemiological studies suggest that there is a shared genetic liability between mood disorders. On one side, MDD has been thought to be

genetically related with BD (Smoller and Finn, 2003; Goodwin, Frederick K. and Jamison, 2007), and in the other way round, having BD seems to increase risk of recurrent unipolar depression and schizoaffective disorder in relatives (Tsuang and Faraone, 1990). This co-occurrence has also been observed between PD, that was reported to be related with subsequent BD (Østergaard *et al.*, 2013) and more recently with history of manic episode (Benard *et al.*, 2020). Nonetheless, this family co-aggregation between both mood disorders has been questioned by other contemporary family studies (Merikangas *et al.*, 2014; Vandeleur *et al.*, 2014).

What it is better established is the shared genetic load with the non-affective spectrum of psychosis. Replicated evidence (Craddock *et al.*, 2005; Cardno and Owen, 2014) suggests partially common genetic aetiologies between SCZ and BD, with a genetic correlation estimated to 0.60 taken from a large population-based family study from Sweden (Lichtenstein *et al.*, 2009). Another large population-based study from Denmark found that risk of BD was associated with history of SCZ in siblings and parents (Mortensen *et al.*, 2003). Nonetheless, controversial results were found in previous family studies where they failed to find evidence for overlap between BD and SCZ (Kendler *et al.*, 1993; Maier *et al.*, 1993).

1.5.1.2 Advances in genetics. Linkage and association studies

Impressive advances have been made in the field of genetics in medicine in the last decades, leading to a growing contribution to psychiatry as well. The introduction of molecular genetic methods in Psychiatry has indicated that psychiatric illnesses are complex genetic disorders where simple Mendelian single models are rarely applicable; and where part of the overlapping clinical heterogeneity could be explained by shared genetic risk.

Genetic linkage analysis consists of detecting the chromosomal location of disease genes. It is based on the finding that genetic variants that are physically close to each other on a chromosome tend to remain linked during meiosis; are more likely to "co-segregate". This lets us identify genetic regions linked to the disease. A meta-analysis performed by Badner et al on linkage studies identified overlapping associations in genomic regions of 13q and 22q between BD and SCZ (Badner and Gershon, 2002). One year later, Berrettini reported in a narrative review not only these two areas but added other convergent regions in 18p11, 10p14 and 8p22 (Berrettini, 2003).

A different approach is offered by genome-wide association studies, the so-called GWAS. These consist of genotyping samples with a dense array of genetic markers (usually single-nucleotide polymorphism –SNP-). These studies investigate whether one or more of the variants in the SNP nucleotides occurs more frequently than expected in cases than controls. A variant in the SNP rs1006737 in the gene CACNA1C is the most studied genomic alteration associated with BD (Sklar *et al.*, 2008, 2011; Moskvina *et al.*, 2009; Zhang *et al.*, 2013), followed by the association with genes encoding for ANK3 (Ferreira *et al.*, 2008). The "mega-analysis" performed by the Psychiatric Genomics Consortium (PGC) confirmed the association with CACNA1C and added a significant associations with other markers such as in ODZ4 (Sklar *et al.*, 2011; Stahl *et al.*, 2019).

It is worth noting that association studies identified specific shared genes between BD and SCZ in overlapping regions previously identified in linkage studies. In chromosome 13q, SNPs in the G72 gene were associated with SCZ (Chumakov *et al.*, 2002) and BD (Hattori *et al.*, 2003). In the well-known region of 22q11 widely associated to the velocardiofacial syndrome, one promising candidate is catechol-O-methyltransferase (COMT). The latter has been related with cognitive difficulties in SCZ (Egan *et al.*, 2001), SCZ itself (Shifman *et al.*, 2002) and claimed to show evidence of association with BD with its Val/Met polymorphism in an independent meta-analysis (Craddock *et al.*, 2001); however recent GWAS have not confirmed that it has a general role in SCZ or BD.

1.5.1.3 Polygenic risk score; a step forward

We know from GWAS studies that there are hundreds or thousands of common alleles that influence susceptibility to SCZ and BD (Purcell *et al.*, 2009). Despite the growth in sample size due to international collaboration for GWAS studies, evidence shows that there is a significant proportion of phenotypic variation not explained due to lack of power. Nonetheless, it appears that we can gain more explained variance by assembling together small to moderate effect markers into a polygenic risk score (PRS). We can calculate individual PRS in a validation sample based on the cumulative summation of the carried risk SNPs selected in a discovery GWAS according to their p-value, weighted by their effect size (Dudbridge, 2013).

The Psychiatric Genomic Consortium (PGC), the largest consortium in the history of psychiatry, has run GWAS mega-analyses from individual samples for some of the

most common psychiatric disorders. Findings from its last published update shows an estimated liability–based SNP-heritability for BD and MDD of 18.2% (Stahl *et al.*, 2019) and 8.5% (Wray *et al.*, 2018) respectively in case–control samples, whereas the SCZ one remains higher at about 22.2% (Ripke, Neale, Benjamin M, *et al.*, 2014). Noteworthy, a crossed notable genetic correlation was found between SCZ and BD (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.*, 2013; Forstner *et al.*, 2017; Ruderfer *et al.*, 2018; Stahl *et al.*, 2019; Smeland, Shadrin, *et al.*, 2020); but this genetic overlap is not yet that clear with MDD (Sullivan *et al.*, 2017; Wray *et al.*, 2018; Stahl *et al.*, 2019), which only recently has shown polygenic correlation with SCZ and BD (Howard *et al.*, 2019).

Despite the genetic correlation, there is also evidence pointing to genetic differences between BD and SCZ (Ruderfer *et al.*, 2014), with a new GWAS by the PGC recently discovering new specific loci distinguishing between BD and SCZ for the first time (Ruderfer *et al.*, 2018). From the PRS perspective, recent study have arisen employing different PRS from major psychiatric disorders to distinguish specific disorders or subgroups of disorders. For instance, PRS for SCZ (PRS-SZ) was able to discriminate SCZ from all BD subtypes; and within BD subtypes, those with and without psychosis, in particular mood-incongruent psychosis (Allardyce *et al.*, 2017). This stronger association with PRS-SZ was also observed for BD patients with psychotic symptoms in two different studies (Ruderfer *et al.*, 2018; Coombes *et al.*, 2020), with another showing stronger association when psychosis occurred during mania (Markota *et al.*, 2018).

Taken all reviewed evidence together, whereas some may take it as an argument to support the transdiagnostic psychosis continuum view, others can equally see it as an opportunity to identify where the genetic threshold explaining the phenotypes which led to current diagnosis lie. In this respect, a more recent approach is employing combined PRS for different specific phenotypes. By not restricting associations to the scores capturing genetic underpinnings of the disorder itself, its potential utility relies on capturing the clinical heterogeneity by mirroring it with multiple genetic liabilities.

1.5.2 Environmental risk factors

Among the agreed criteria for considering a risk factor as casually associated with a condition, the following needs to be fulfilled: strength of association, biological

gradient (dose-response effect), and temporality (Schulze and McMahon, 2018). Other classically proposed criteria include the consistency of finding across the literature, specificity of association and biological plausibility (Hill, 1965). We can now count on compelling evidence of a wide range of environmental risk factors (ERF) showing association with an increased risk of psychiatric disorders (Bortolato *et al.*, 2017; Köhler *et al.*, 2018; Radua *et al.*, 2018; Stilo and Murray, 2019).
A summary of the main studied modifiable and non-modifiable environmental factors associated with onset of AP are presented below organised based on most frequent time of exposure across lifespan:

- **Prenatal and Perinatal Events:** it is well known that individuals who suffer certain complications during pregnancy and birth carry an increased risk of developing SCZ (Cannon *et al.*, 2002) and psychosis (Davies *et al.*, 2020), but evidence on the effect to develop BD is not that robust yet (Scott *et al.*, 2006). Similarly, the role of perinatal infections for developing BD remain inconclusive (Barichello *et al.*, 2016), with some recent conflicting results around the widely studied association with *Toxoplasma Gondii* (Sutterland *et al.*, 2015; de Barros *et al.*, 2017; Alvarado-Esquivel *et al.*, 2019). Even for psychosis these classically accepted associations with maternal infections, except for HSV-2 and infection NOS, has been recently questioned (Davies *et al.*, 2020). The other replicated early factor for psychosis is advance paternal age; this is believed to increase your odds to experience psychosis if your father was more than 35 years old at the time of your birth (Davies *et al.*, 2020), or predispose you to have later BD-P if it is over 45yo (Lehrer *et al.*, 2016). Nonetheless, this association has been recently questioned for both BD and SCZ, believing previous results were due to spurious association (Weiser *et al.*, 2020).
- **Childhood Events:** history of childhood abuse can be present in up to 50% of patients with BD (Garno *et al.*, 2005) with some subtypes such as sexual abuse increasing the risk to experience hallucinations (Upthegrove *et al.*, 2015). In the last meta-analyses to date based on 19 studies they concluded that patients with BD had 2.6 times more to have experienced a form of adversity during childhood, with emotional abuse presenting the strongest association among subtypes (Palmier-Claus *et al.*, 2016).
- **Later factors:** migration and urbanicity, which were among the factors reported as highly suggestive and suggestive factors respectively in the first umbrella

review for psychosis (Radua *et al.*, 2018), are not as clearly associated with AP. Impact of migration has shown conflicting results in a previous meta-analysis (Swinnen and Selten, 2007), while a large Danish cohort study suggests that it is living abroad the place you were born, rather than being a 2nd generation migrant or ethnic minority, which increases the risk of developing psychotic disorder including BD (Cantor-Graae and Pedersen, 2013). Regarding urbanicity, results points towards a protective factor of rural environment for BD (Kelly *et al.*, 2010). Head injury on the other hand, presents meta-analytic support of its association with later development of both MDD and BD (Perry *et al.*, 2016).

Of note, research specifically addressing associations on previously reported factors for PD is still lacking, with only one study to the best of my knowledge that explored early childhood and adolescent risk factors, and did not find significant associations with either urbanicity, paternal age, perinatal complications, obstetric or embryo indicators of risk or substance use (Nietola *et al.*, 2020).

Overall, it is possible to say that despite some environmental insults, such as early life adversities, seem to be consistent risk factors for AP; accepting definite effects of the wide range of possible ERF requires still ongoing research. Moreover, attending to the previously exposed criteria for causality, there are still major gaps in literature to consider. Part of those limitations comes from the notion that most environmental risk factors studied happen to be non-specific, being associated with a range of mental disorders, which is also true for the subcategories under the term of psychosis. Taking as an example one of the risk factors more consistently studied in the last 50 years, perinatal complications, has been associated in different psychiatric conditions (Buka and Fan, 1999) and within psychotic disorders (Hultman *et al.*, 1999). Also, even ensuring adequate temporality from longitudinal studies, whether environmental insults constitute real causal as opposed to merely provocative or triggering factors is yet to be determined. Thus, studies including genetic component when studying environment exposures can help to produce more consistent and informative grounds for understanding plausible etiopathogenic pathways.

1.5.3 Gene and environment interaction

We talk about Gene x Environment Interactions (GxE) when the effect of genetic or environmental factors is conditional on the other. 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. There is a growing research focusing on the interaction of genetics and environmental factors in AP, with speculation that is particularly salient for MDD, given the higher pleiotropy. In fact, Ripke claims that "MDD can only be understood if genetic and environmental risk factors are modelled simultaneously" (Ripke *et al.*, 2013); and this seems to be also true for BD.

Most GxE studies have employed candidate genes. Starting with a widely studied risk factors for BD, infection during childhood, there is some suggestive data suggesting that exposure to specifically *Toxoplasma Gondii* (and not CMV, HSL-1 or HSV-2) could modulate the influence of a TLR2 polymorphism in increasing BD risk (Oliveira *et al.*, 2016). Nonetheless, most GxE research has focussed on effect of stressful or childhood adverse events during childhood. A recent study showed a moderator effect of the COMT Val158Met polymorphism on the impact of stressful life events (SLE) in those BD patients with more severe depressive episodes (Hosang *et al.*, 2017). One of the most replicated candidate genes for BD, CACNA1C, has recently been claimed to show an interaction effect for risk for developing BD in those who have experienced childhood trauma (Bastos *et al.*, 2020). Specifically related with presence of psychotic features on BD, there are some preliminary findings on the role of a polymorphism of the gene coding for serotonine transporter (5-HTTLPR) increasing the risk either directly and also indirectly through abuse or dependence of cannabis (De Pradier *et al.*, 2010).

As far as MDD is concerned, one of the best-studied GxE interaction is with the serotonin transporter gene (5-HTTLPR) and the presence of stressful life events, but results remain inconclusive, with two meta-analyses presenting contradictory results (Risch *et al.*, 2009; Karg *et al.*, 2011). Moreover, some evidence from a meta-analysis suggests a moderator effect of BDNF variant in those exposed to severe life in favouring the development of MDD (Hosang *et al.*, 2014); but these results are yet to be replicated.

The first study focusing on PRS or genome-wide to test GxE in MDD obtained suggestive results for the interaction with child adversity, by finding an increasing

effects of PRS for MDD (PRS-MDD) in the presence of childhood trauma (Peyrot *et al.*, 2014). Nonetheless, this did not only fail to replicate in a meta-analysis (Peyrot *et al.*, 2017), but even an inverse relationship between childhood trauma and MDD was later observed, where childhood trauma seemed to have greater effect in individuals with lower genetic liability (Mullins *et al.*, 2016). Interestingly, that same study neither found interactions between PRS-MDD and stressful life events, in line with previous studies (Musliner *et al.*, 2015), but opposing to a more recent work showing significant interaction of the PRS-MDD with personal life events (Colodro-Conde *et al.*, 2018). Despite the contradictory results, using PRS is likely to be preferred over candidate gene approach based on the polygenic nature of BD and MDD, although research using polygenic scores is still scarce.

In light of the above, we can say that including ERF along with genetics is crucial in the study of the etiology of AP; where available evidence suggest some susceptibility to environment based on some particular genotypes. Nonetheless, most of the studies are still focusing on candidate genes where replication is still problematic (Musci *et al.*, 2019), but genome-wide approach looks promising in opening new venues to investigating GxE interactions obtaining greater insight into the complex etiology of psychotic mood disorders.

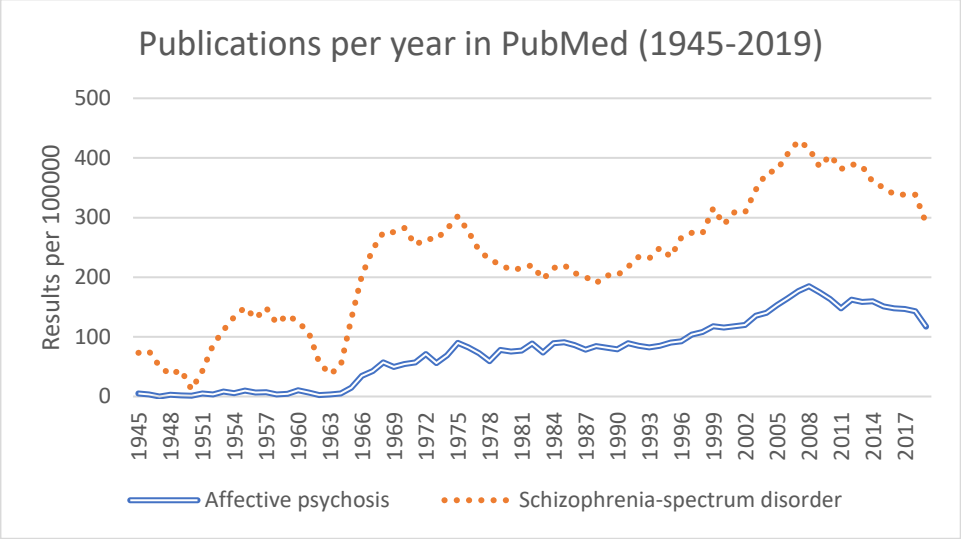
1.6 A GAP IN RESEARCH

Despite the previously discussed tendency to abandon categorical diagnostic groups, with research switching towards the broader term of psychosis as outcome, we should bear in mind that a better understanding of the validity of the classic diagnostic boundaries derive on the availability of quality research for both groups, affective and non-affective psychosis. More precisely, in order to provide the best light to the unanswered subdivision of psychosis, as experts have been pointing for decades, it should be etiological principles rather than symptomatology or course (Murray and Foerster, 1987), the preferred targets in the ongoing quest for finding the point of rarity.

In this respect, one of the potential explanations for the failure to identify boundaries between current diagnostic categories may be the imbalance in the volume of research in favour of non-affective psychosis. As shown in **Figure 1.4**, by checking Pubmed indexed genetic and environmental terms in both subgroups, it is possible to see that schizophrenia and related disorders have attracted much more

attention, with around 17500 papers published from 1945 to the moment of the present writing; compared with less than 5800 articles on affective psychosis (including Bipolar disorder and Psychotic depression), meaning the latter group represent on third of the non-affective psychosis counterpart.

Figure 1.4. Comparison of number of publications per year indexed in Pubmed between 1945 to 2019 of affective psychosis and non-affective psychosis.



Research numbers correspond with those studies focused on epidemiology and atiopathogenic factors of both disorders, and correspond with the following search terms: for Affective Psychosis in blue and continuous line [(Affective psychosis OR manic depressive OR Bipolar Disorder OR Psychotic Depression OR Major Depression with psychosis) AND (aetiology OR incidence OR epidemiology OR genetic OR environment* OR risk factor)]; for Non-affective psychosis in orange and dotted line [(Schizophrenia OR Non-affective psychosis OR Schizoaffective disorder OR Psychosis NOS) AND (aetiology OR incidence OR epidemiology OR genetic* OR environment* OR risk factor)].*

We discussed in Section 1.4 that there is increasing doubt as to whether AP and NAP represent discrete illnesses (Murray *et al.*, 2004; Craddock and Owen, 2010), with more papers adding to the pressure to restructure diagnostic boundaries into the smoother conceptualization of continua. However, we could also take from Section 1.5 that we can still find contemporary support for the existence of distinction based on genetic and environmental factor. This adds to other support at clinical level (Jauhar *et al.*, 2018), that talks in favour of persisting in finding the point of rarity among the known overlap between the two classical pillars. Notwithstanding, a crucial element in the attempt to identify if there is a real basis to justify treating these disorders as independent nosological entities, we must start from overcoming the previously noted academic neglect to other forms of psychosis (Van Os, 2016) that we could see also for epidemiological studies (Jongsma *et al.*, 2019).

1.7 AIMS AND HYPOTHESIS

This Section outlines the main aims addressed in this thesis, which consists of a meta-analyses (Chapter 3), an incidence study (Chapter 4), and two empirical case-control studies (Chapter 5 and 6).

1.7.1 Aims:

- The aim of Chapter 3 is to identify meta-analytic evidence of ERF which have an impact on the development of AP. This meta-analysis includes studies that used a prospective longitudinal design and focused on risk factors previously identified for psychosis.
- The aim of Chapter 4 is to calculate the treated incidence of BD and PD across 17 sites, and how it compared with SCZ and psychosis not otherwise specified (PNOS); exploring sociodemographic contributors to geographic variability.
- The aims of Chapter 5 are first to establish the clinical utility of combining different PRS for distinguishing AP including PD and BD from controls and from NAP patients; and secondly, to delineate the genetic basis underlying AP disorders (BD and PD) from NAP and controls by analysing diagnostic positions across polygenic distributions.
- The aim of Chapter 6 is to examine the effect of GxE interplay on phenotypic differences (AP vs NAP), and to study the cumulative effect of environment exposure through the use of combined polyenvironmental scores. More specifically I studied: first, how different ERF associate in case-control and within clinical group comparisons; second, how the PRSs associations with clinical group differed based on exposure or not of the different ERF; and third, association of PRSs with clinical phenotypes in interaction with a combined polyenvironmental score.

1.7.2 Hypotheses under investigation

- In Chapter 3, I hypothesised to find associations with similar ERF as those previously reported for psychosis, with relative smaller effect sizes of pre-/perinatal and childhood factors, but equal or higher associations with factors that appear later in life, in comparison with NAP, given the more established neurodevelopmental component in the latter.

- In Chapter 4, I expected to observe geographic variation of BD and PD based on previously observed geographic variation of psychosis incidence, showing consistently lower rates than SCZ and PNOS across sites. Based on literature, I do not expect latitude or urban-rural differences to account for this variation, but the variation to be partly explained by ethnicity and sociodemographic variables such as employment and house holding.
- In Chapter 5 in which I explored PRS utility for delineating diagnosis categories the following hypothesis were hold:
    - A) AP patients will have lower PRS-SZ and higher PRS-BD, PRS for depression and intelligence (PRS-D and PRS-IQ) than NAP patients.
    - B) All included PRSs will discriminate AP patients from controls.
    - C) Respective PRSs will distinguish patients with AP from those with NAP by showing opposite direction associations; i.e PRS-BD, PRS-D and PRS-IQ will have positive association with AP, while PRS-SZ will be positively associated with NAP.
    - D) PRS-BD and PRS-D will be differently distributed among patients with diagnosis of BD or PD, with higher PRS-BD and less PRS-D for the former, and the inverse pattern in the latter.
- In Chapter 6, in which I aimed to study impact of ERF in development of AP in conjunction with genetic vulnerability, I held the following hypotheses:

    - A) There will be an association between cannabis, urbanicity, migration, advance parental age, child adversity and stressful life events with the presence of AP when compared with controls.
    - B) I expect to find a dose-response effect based on amount of cumulative exposure of ERF; i.e the higher the number of ERF, the strongest the association.
    - C) PRSs associations will be differently associated in exposed and unexposed for affective and non-affective psychosis.
    - D) Both polyenvironmental and polygenic scores will be associated independently with clinical groups; expecting to find differences in how they interact between those affective and non-affective psychosis.

2. OVERVIEW OF METHODS

This thesis comprises four studies, the first corresponding to a meta-analyses of prospective studies; and the other three being empirical studies all based on the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study.

Here I will present an overview of the methods of the meta-analyses and the three empirical studies, but these will be fully developed in each appropriate chapter.

2.1 SYSTEMATIC REVIEW AND META-ANALYSES (CHAPTER 3)

This work was 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 a protocol made available at PROSPERO on April 2018 (registration number: CRD42018092253). The objective was to study the association between ERF of interest: *pre/perinatal factors* - paternal age at birth, maternal infection, obstetric complications, perinatal stress; *early childhood factors* - urbanicity at birth, childhood infection, childhood adversity; *later life factors* - substance misuse, ethnic minority and migration, urbanicity later in life, stressful life events and traumatic head injury; with AP, BD and PD.

The main search was conducted in MEDLINE, EMBASE and PsycInfo from inception to November 2019, complemented by hand search and cross-referencing of topical reviews. All types of prospective observational studies were included: population, birth cohort studies and high-risk studies. A primary screening looking at the title/abstract, followed by a second screening of full-text of those elected articles were independently performed by different investigators, with any disagreement resolved through consensus.

Two researchers extracted data in duplicate from each paper: first author name, year and country of publication; study design and name of cohort; sample size, range of age (mean/SD) and sex frequencies in comparison groups; diagnosis outcome (BD, PD or AP as a whole) and method through which diagnosis was obtained; ERF of interest; prevalence of risk factor and association measures (preferably unadjusted) with corresponding 95% confidence intervals (95%CI). Missing data was requested from study authors.

Included observational studies were subdue to quality check using The Newcastle-Ottawa Scale (NOS) independently. Outcome-level assessment was assessed using GRADE guidelines. Whenever we had enough data, we carried out random effects meta-analysis to pool quantitative data per each ERF using any AP as outcome. All analyses were done using Stata version 14 (StataCorp, Texas USA). When statistical pooling was not possible, the findings were presented narratively, in tables and figures where appropriate.

2.2 EUGEI STUDY (STUDY 1, 2 AND 3)

These three Studies, which corresponds to Chapter 4, 5 and 6, constitutes the empirical part of the thesis. They are based on the incidence and case-control sample from the EU-GEI study (EUropean Network of national schizophrenia networks studying Gene-Environment Interactions); a multicentre incidence and case-sibling-control study on genetic and environmental determinants involved on the development and severity of psychotic disorders.

2.2.1 Sample

Baseline 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 6 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. Besides, 1499 unaffected controls were recruited with a quota sampling approach to represent the local population living in the areas served by the services. 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. Characteristics of the final case-control sample are summarised on Chapter 5 (**Table 5.1**).

A benefit of the EUGEI sample is that it is more representative of clinical samples as it is based on cases that present to Mental Health services, which also implies including cases with different prognosis. Second, the multicentric design allows gaining external validity by including participants from both North and South Europe and one site in Brazil; and additionally, employing a quota sample approach to select controls captures better the environmental contributors at a population

level. However, the same aspects carry few limitations that should be acknowledge beforehand as well. All FEP sample should take into account the diagnosis instability (Schwartz *et al.*, 2000; Veen *et al.*, 2004), which is further compounded when analysing the genetic underpinnings of current diagnostic categories. This is also given the observed reduced explained variance in incidence samples given the polygenic scores being built on datasets enriched with more chronic participants (Meier *et al.*, 2016). Regarding the multicentric nature of the sample, despite the efforts invested by the EUGEI group in provide with face to face trainings and having shown a high interrater reliability across sites, some methodological biases should be contemplated, including differences in service use (percentage of use and accessibility to private setting; availability of specialised tertiary services), disparities in administrative health/civic information systems or cultural differences; all these potentially having the higher impact on the incidence study (Chapter 4).

2.2.2 Case definition

Case definition included all those identified subjects aged 18 to 64 years who were resident within the study areas (17 sites across 6 countries) and presented to the adult psychiatric services with an untreated FEP (ICD-10 codes F20-F33) not related to organic cause between May 1, 2010 and April 1, 2015 and fulfilling inclusion criteria. Inclusion and exclusion criteria are presented in full in Chapter 4, **Figure 4.1**.

2.2.3 Sociodemographics (Study 1, 2 and 3)

Socio-demographic data were collected using the Medical Research Council (MRC) Socio-demographic Schedule modified version (Mallett et al., 2002), and supplemented by clinical records, with additional information on educational attainment and social functioning measured through 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).

2.2.4 Clinical measures (Study 1, 2 and 3)

I employed two different sources of diagnosis: research-based and a diagnosis provided by a psychiatrist at their first contact with Mental Health services. These

diagnoses were available based on both DSM-IV or ICD-10 criteria. For the three studies, I employed consistently the DSM-IV based diagnosis, only relying on ICD-10 diagnosis for imputing missingness when this was available.

DSM-IV diagnoses were extracted from interviews and mental health records utilizing the Operational Criteria Checklist (OPCRIT) at baseline (McGuffin *et al.*, 1991) and were grouped into: Affective psychosis (Bipolar Disorder, Psychotic Depression and Non-affective psychosis (Schizophrenia and other psychosis).

Additionally, clinical diagnoses received at the moment of first contact by the services were collected as part of the NOS-DUP scale (Nottingham Onset Schedule – Duration of Untreated Psychosis - measurement version) (Singh *et al.*, 2005).

2.2.5 Genotyping and Polygenic risk scores building (Study 2 and 3)

DNA from blood tests or saliva sample was obtained from most participants at baseline (73.6% of cases and 78.5% of controls). EUGEI sample was genotyped centrally at the Cardiff University Institute of Psychological Medicine and Clinical Neurology; with quality control was performed locally. Genotype and Quality control (QC) processes are explained in detail on Chapter 5, Study 2. A Principal Component Analyses with 10 principal components (PC) of the pruned SNPs was run by Dr Vassos. I employed these 10 PC to control for population stratification, and to select a subsample of European ancestry, which constituted the training sample of Study 2 and 3. Details on how this European ancestry was done is provided in detailed in the Supplementary material of Chapter 5 (Appendix 2).

The measure of genetic load is based on PRS, which is an individual quantitative risk factor calculated from the weighted summation of the odds ratios (OR) of carried risk alleles taken from a discovery sample through GWAS. The employed PRSs for SCZ, BD, Depression and IQ, which have been built by Dr Vassos, are based on the last and largest available GWAS. Best SNP p-value thresholds were chosen based on the highest variance explained in distinguishing cases from controls, which was p-value=0.05 for the four scores.

2.2.6 Environmental risk variables (Study 3)

Cannabis use

Lifetime use of cannabis was collected at baseline with the Cannabis Experience Questionnaire (CEQ) modified version (Di Forti *et al.*, 2009). This questionnaire was derived from the CEQ (Barkus et al., 2006), developed to assess psychological experiences associated to cannabis use; and modified to include questions on pattern of cannabis use, type, cost etc. The different variables used from this questionnaire will be discussed in the appropriate sections (Chapter 6).

Urban environment

Using information extracted from the previously mentioned MRC Socio-demographic Schedule modified version (Mallett *et al.*, 2002), I employed a dichotomy variable (rural vs urban environment) based on the absolute population counts of the participants residence at the onset of the illness, as used in previous studies (Krabbendam and van Os, 2005; Peen *et al.*, 2010).

Migration

Place of birth and age of migration information was collected as part of the MRC Socio-demographic Schedule modified version (Mallett *et al.*, 2002). A binary variable was dichotomised indicating if a participant had a migration history or not.

Child adversity

The Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco, 1994) was employed to collect retrospective information on exposure to bullying, house discord, physical abuse, emotional or sexual abuse from any adult before age 17. The different variables used from this questionnaire will be discussed in the appropriate sections (Chapter 6).

Stressful Life Events

A list of 20 potential adverse life events during the 12 month period before onset were recorded at baseline using a modified version of the List of Threatening Experiences (Brugha et al., 1985). The impact on the last week of those recorded events were assessed with a modified version of The Impact of Event Scale reduced to a subset of six items (so called IES-6)(Thoresen *et al.*, 2010).

2.3 STATISTICAL ANALYSES

2.3.1 Study 1. Incidence study

Incidence rates stratified by catchment areas, were calculated for BD and PD, with SCZ and PNOS as comparison; presented as both crude and standardised adjusted by age, sex, and racial/ethnic minority status. Distribution of overall incidence rates across sites by 5-year age-at-onset bands and split by gender for each diagnostic category were also calculated.

In order to explore incidence variance between sites, multilevel random-effects Poisson regression were conducted to analyse the impact of latitude, population density, annual hours of sunshine, percentage of unemployment, owner-occupied housing, and single-person households.

2.3.2 Study 2. Polygenetic association differences in affective and non-affective psychosis

Case-control PRS association with broad clinical groups (AP and NAP) were tested through multinomial logistic regressions including the three disorder PRSs (PRS-SZ, PRS-BD, PRS-D) plus PRS-IQ as independent variable, and 10PCs as covariates for controlling for population stratification. Similarly, I conducted separate multinomial logistic model for case-only analysis, where I measured discrimination ability of PRSs between AP categories (BD and PD) and NAP as reference group.

2.3.3 Study 3. Differences in polygenic and environmental interplay in affective and non-affective psychosis

Firstly, multinomial logistic regression models were used to test associations of different ERF with case-control and within clinical groups comparisons. Secondly, if association between joint polygenetic load (PRSs of SCZ, BD and depression) with case-control or psychotic disorders diagnoses comparisons differ based on environment exposure (urbanicity, migration, parental age, cannabis use and childhood trauma); and thirdly, in order to explore evidence of GxE interaction, models including combined poly-environmental risk scores and their interaction with PRSs were conducted.

3. META-ANALYSIS. ENVIRONMENTAL RISK FACTORS IN BIPOLAR DISORDER AND PSYCHOTIC DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE STUDIES

This chapter has been adapted and reproduced fully from the following paper:

Victoria Rodriguez, Luis Alameda, Giulia Trotta, Edoardo Spinazzola, Paolo Marino, Sandra L Matheson, Kristin R Laurens, Robin M Murray, Evangelos Vassos, Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies, Schizophrenia Bulletin, 2021;, sbaa197, https://doi.org/10.1093/schbul/sbaa197

The Supplementary material will be attached in Appendix 1.1.

3.1 INTRODUCTION

Bipolar Disorder (BD) and unipolar depression with psychotic features (henceforth referred to as Psychotic Depression [PD]), are among the major causes of disability and disease burden worldwide (1). With respective lifetime prevalence of 0.24-1.02% (Perälä *et al.*, 2007; Merikangas *et al.*, 2011; Moreira *et al.*, 2017) and 0.35–1.0% (Perälä *et al.*, 2007; Jääskeläinen *et al.*, 2018), they can result in functional impairment and a reduction in quality of life (Grande *et al.*, 2016). However, no consensus has been reached on the potential risk factors for these frequent yet understudied disorders, which limits our understanding of the underlying mechanism(s) involved in disease aetiopathogenesis.

The neurodevelopmental hypothesis classically associated with Schizophrenia (Murray and Lewis, 1987; Weinberger, 1987), has also been thought by some to be applicable to BD with psychotic features (Arango *et al.*, 2014). Briefly, it postulates that the combination of genetic vulnerability with environmental adverse events during development can lead to the alteration of maturational processes in the brain, resulting in the onset of psychosis in adulthood. Indeed, it is well established that non-affective and affective psychoses share genetic predisposition (Purcell *et al.*, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.*, 2013), with an estimated genetic correlation up to 0.68 between Schizophrenia and BD and of 0.65 between Schizophrenia and Major Depressive Disorder (Smoller *et al.*, 2019). Given this overlap in the genetic underpinnings of these disorders, the differential development of non-affective versus affective psychoses may reflect not only the presence of non-shared genetic vulnerability, but also the operation of distinct environmental risk factors (ERF).

Epidemiological research, focussed predominantly on schizophrenia, has identified well-replicated risk factors for psychosis including older paternal age at birth, obstetric complications, urbanicity, childhood adversity, cannabis use, ethnic minority status, and stressful life events (Vassos *et al.*, 2019). In addition, there is evidence from systematic reviews and meta-analyses for an increased risk of psychosis after either maternal (Khandaker *et al.*, 2013) or childhood infection (Khandaker *et al.*, 2012; Sutterland *et al.*, 2015), as well as following a traumatic brain injury (Molloy *et al.*, 2011). However, the relevance of most of these ERF for affective psychoses is yet to be determined.

Regarding the traditionally used category of affective psychosis, it is a matter of debate whether Bipolar Disorder and Psychotic Depression should be considered as such or if they constitute more discrete disorders(Angst and Gamma, 2008). Nonetheless, despite the term not constituting an official conceptualization in current diagnostic classifications, the term "affective psychosis" is still in current use among clinicians (Jones *et al.*, 2014; Torrent *et al.*, 2018), and we still rely on traditional literature produced utilising former classifications. Therefore, taking these considerations into account, in the current work when we refer to those categories jointly, we will use the term "affective psychosis".

We therefore conducted a systematic review on prospective studies of ERF for affective psychosis, including both BD and PD; and meta-analyses to estimate pooled effect sizes. We included putative risk factors that were previously reported for schizophrenia (Radua *et al.*, 2018; Vassos *et al.*, 2019) as well as affective psychoses (Laurens *et al.*, 2015; Marangoni *et al.*, 2016). This study aims to elucidate why, despite known shared genetic load, some individuals develop non-affective psychosis, bipolar disorder and psychotic depression. Apart from contributing to better insight on the aetiopathogenic mechanisms involved, this could have the potential for guiding preventive strategies in the future.

3.2 METHODS

3.2.1 Search strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) standards were applied (Stroup *et al.*, 2000; Moher *et al.*, 2009) to this systematic review and meta-analysis (PRISMA and MOOSE checklists are provided in *Supplementary Material*, ***eTable3.1*** and ***eTable3.2***), with a protocol registered in PROSPERO in April 2018 (Registration number: CRD42018092253). We conducted a systematic search in MEDLINE (from 1946), PsycINFO (from 1806), and EMBASE (from 1974) through the Ovid platform for articles published from inception to November 2019. We used Boolean combinations of MeSH terms related to Affective psychosis, BD, PD, and the different ERF of interest: paternal age, maternal infection, obstetric complications, urbanicity at birth, childhood infection, childhood adversity, substance misuse, ethnic minority and migration, stressful life events, head injury,

and urbanicity later in life. Details of the full search strategy, definitions and inclusion criteria for each individual ERF can be found in *Supplementary Material*. Further studies were identified through hand searching of the reference lists of all included studies and published reviews of the topic.

3.2.2 Inclusion and exclusion criteria

Studies were included if they satisfied the following criteria: (i) being a prospective study (including population-based, specific cohorts:- birth, high-risk, or nested case-control) examining the association between exposure to ERF and subsequent development of affective psychotic disorders (BD and/or PD); (ii) being written in English; (iii) including diagnoses of BD or PD, including the former "manic-depressive disorder" and "affective psychosis" as described previously, obtained through standardized structured interview, hospital records, or administrative registers; (iv) including a comparison group of controls without a diagnosis of psychosis or mood disorder. Case-control, cross-sectional, or other studies where the exposure was collected retrospectively were excluded as they are prone to recall bias, while prospective design studies, by temporally ordering exposures and outcomes, may also facilitate causal inference (Rothman *et al.*, 2008). We excluded articles measuring the outcome of interest in specific population samples, such as children and adolescents (<18 years old), elderly (>65 years old), forensic individuals, or pregnant women; and those presenting overlapping samples, prioritizing the more recent or with the larger cohort for inclusion.

3.2.3 Screening, data extraction and quality assessment

Primary screening of the title and abstract was performed in duplicate by two investigators (VR, LA) with high levels of agreement (97%). A second screening by four investigators (VR, LA, GT, PM) was then performed in duplicate by critically inspecting the full-text of potentially eligible articles retrieved, with overall similar levels of agreement (82.5%). Any disagreement at either screening stage was resolved through consensus in a group meeting. In parallel, a cross-reference hand search extracted title/abstract from identified reviews, and a full-text check of potential eligible studies from these reviews was performed by two investigators (PM, GT).

The following information from included studies was extracted by VR and checked by ES: name of first author, year and country of publication; study design and name of cohort; diagnosis received and source of diagnosis; ERF of interest and method of assessment; total sample size (in numbers or person-years, when given); counts of specific diagnosis outcomes (any affective psychosis; BD; PD); counts of total exposed, affected among exposed, unexposed, and affected among unexposed. When this information was obtained, effect sizes in form of odds ratio (OR) were calculated (details provided in *Supplementary Material*). Where counts of specific diagnoses or exposed/unexposed numbers were not reported and association measures were given (OR, relative risk –RR-, incidence risk ratio –IRR-, or hazard ratio –HR-), these were extracted together with their 95% confidence intervals (95%CIs). Given the low prevalence of affective psychosis (Perälä *et al.*, 2007), the above effect sizes were used interchangeably (Deeks *et al.*, 2019).

In publications where insufficient data were available, authors were contacted for additional data in order to minimize missing information.

All studies included for meta-analysis underwent a formal quality assessment conducted by two authors (GT, ES) using the Newcastle-Ottawa Scale (Wells *et al.*, 2012), and we assessed overall quality of evidence for each outcome (very low, low, moderate, or high quality) by adapting the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Balshem *et al.*, 2011). More information on quality assessment ranking is provided in *Supplementary Material*.

3.2.4 Statistical analysis

When a minimum of three studies reported on each ERF, we conducted meta-analyses to pool quantitative data. Pooled data was presented as odds ratios (ORs) and 95% CIs to show the association between the different ERF and affective psychosis diagnoses. Information on which effect size was used for each individual study and how effect sizes were pooled is available in *Supplementary Material*. When statistical pooling was not possible, findings were presented narratively. All statistical analyses were performed using Stata version 14 (StataCorp, Texas USA) to calculate random effects mode. Due to the differences in study design, we were expecting high heterogeneity, which was tested in Stata with the I^2 test. We

considered an I^2 value of up to 50% as low, 50-75% as moderate, >75% as high (Higgins and Cochrane Collaboration, 2019).

Analyses were conducted considering individual effects of each ERF with BD, PD or affective psychosis combined. For studies that reported incidences for both BD and PD, individual effect sizes were firstly meta-analysed as fixed-effects and included as affective psychosis in random-effects meta-analyses with results from the other studies.

3.3 RESULTS

3.3.1 Included studies and characteristics of the analysed sample

Figure 3.1 summarizes the flow chart of the study selection. From the 1616 entries identified in initial searches, 59 fulfilled inclusion criteria for the qualitative synthesis and 46 of those were included in the quantitative analysis. Reasons for exclusion of 13 studies from quantitative synthesis were: (i) lack of data to calculate OR when these were not provided, (ii) duplication or overlap of samples; (iii) fewer than three studies to conduct meta-analysis.

Among the 46 longitudinal studies included in meta-analyses: 1) twenty-five were population-based (Marcelis *et al.*, 1998; Eaton *et al.*, 2000; Westman *et al.*, 2006; Fearon, P *et al.*, 2006; Kaymaz *et al.*, 2006; Laursen *et al.*, 2007; Van Laar *et al.*, 2007; Kirkbride *et al.*, 2008; Scott *et al.*, 2010; Mathiasen *et al.*, 2011; Buizer-Voskamp *et al.*, 2011; Manrique-Garcia *et al.*, 2012; Martins *et al.*, 2012; Nosarti *et al.*, 2012; Benros *et al.*, 2013; Kleinhaus *et al.*, 2013; Østergaard *et al.*, 2013; Cantor-Graae and Pedersen, 2013; Abel *et al.*, 2014; McGrath *et al.*, 2014; Paksarian *et al.*, 2015; Feingold *et al.*, 2015; Bergink *et al.*, 2016; Vassos *et al.*, 2016; Mustonen *et al.*, 2018); 2) nine were based on specific cohorts (e.g., birth, high-risk, geographically-defined area) (Brown, A. S. *et al.*, 1995; Brown, Alan S. *et al.*, 1995; Leask *et al.*, 2002; Kelly *et al.*, 2010; Duffy *et al.*, 2012; Lasalvia *et al.*, 2014; Szöke *et al.*, 2014; Freedman *et al.*, 2016; Kirkbride *et al.*, 2017); and, 3) twelve were nested case-control studies drawn from population-cohorts (Hultman *et al.*, 1999; Bain *et al.*, 2000a; Øgendahl *et al.*, 2006; Frans *et al.*, 2008; Xiao *et al.*, 2009; Mortensen *et al.*, 2011; Brown *et al.*, 2013; Parboosing *et al.*, 2013; Chudal, Gissler, *et al.*, 2014; Chudal, Sourander, *et al.*, 2014; Canuti *et al.*, 2015; Freedman *et al.*, 2015). All 46 studies were rated as "good" in the quality assessment; overall quality level of 14 meta-analytic outcomes ranged from

"low" (14%, 2/14), "moderate" (64%, 9/14) to "high" (22%, 3/14) using the GRADE approach (details on ratings are provided in *Supplementary Material*, ***eTable3.3*** and ***eTable3.4***).

Details of studies included are provided in **Table 3.1** and *Supplementary Material* (***eTable3.5***). 71.7% (n=33) examined BD; 13% (n=6) examined PD; and, 30% (n=14) examined affective psychosis as an outcome. With the exception of parental age, light or heavy birth weight, late gestational age (GA) and prenatal stress characterized by no or low heterogeneity, the rest of ERF presented high heterogeneity. **Figure 3.2** (A-C) summarizes the effects of each study, pooled effects of each subcategory, and values of I^2 per ERF.

Fig 3.1. Flow Diagram of database search by November 2019

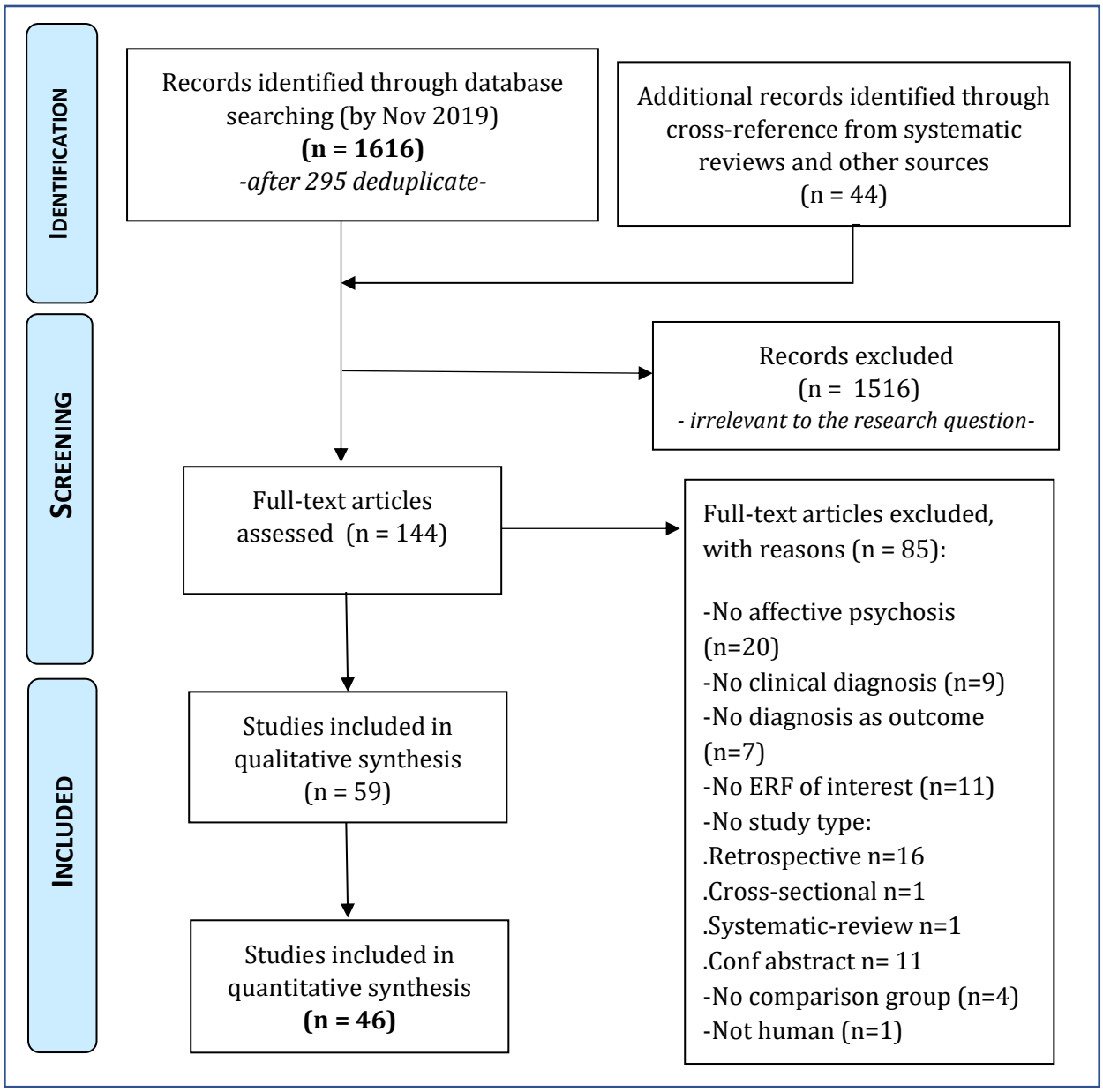


Table 3.1. List of studies per environmental factor included for meta-analyses

Author, Year	Cohort Name, Country	Design, Years of Follow-Up	Risk factor, outcome (measure)	Cases (exposed), Controls/Total population	Significance
PRE-/PERI-NATAL FACTORS					
Paternal age					
Frans, 2008	Sweden	Nested case-control study, 1973-2001	Paternal age >40 yo, BD[a] (ICD-8, ICD-9, ICD-10)	13428 (2067), 67140	Positive
Buizer-Voskamp, 2011	Netherlands	Population-based cohort	Paternal age >40 yo, BD-I, BD-II, BD-NOS[a] (DSM-IV-TR)	1121 (68), 5605	Negative
Brown, 2013	Child Health and Development Study (CHDS), US	Nested case-control study, 1959-1966	Paternal age >45 yo, BD-I, BD-II, BD-NOS, BD with psychosis (DSM-IV)	94 (5), 746	Negative
Østergaard, 2013	Denmark	Population-based cohort, 1955-1990	Paternal age >40 yo, PD (ICD-8, ICD-10)	2183, 2400000	Positive
McGrath, 2014	Denmark	Population-based cohort, 1995-2006	Paternal age, BD[a] (ICD-8, ICD-10)	7309 (557), 2894688	Negative
Chudal, 2014	Finnish Prenatal Study of Bipolar Disorders (FIPS-B), Finland	Population nested case-control study, 1983-1998	Paternal age, BD[a] (ICD-8, ICD-9,ICD-10)	1861 (147), 1009846	Positive
Maternal infection					
Brown, 1995	Netherlands	Birth cohorts, 1957-1958	Influenza, AP[a] (ICD-9)	1220 (236), 980697	Negative
Xiao, 2009	US	Nested case-control study	Toxoplasma Gondii, AP[a] (DSM-IV)	64, 443	Positive
Parboosing, 2013	Child Health and Development Study (CHDS), US	Nested case-control study, 1956-1966	Influenza, BD[a] (DSM-IV-TR)	92 (8), 722	Positive
Canuti, 2015	Collaborative Perinatal Project [CPP] or New England Family Study (NEFS), US	Nested case-control study, 1956-1966	Viral infection, BD with psychosis (DSM-IV)	12 (2), 138	Negative
Freedman, 2016	Child Health and Development Study (CHDS), US	Birth cohort	Toxoplasma Gondii, BD-I, BD-II, BP-NOS, BP with psychosis (DSM-IV-TR)	85 (22), 255	Negative
Obstetric complication					
Hultman, 1999	Sweden	Case-control from population based cohort		198, 990	
			Light weight <2500g, AP[a] (ICD-9)	11, 48	Negative
			Heavy weight >4500g, AP[a] (ICD-9)	4, 27	Negative
			<49cm length, AP[a] (ICD-9)	33, 210	Negative
Bain, 2000	UK	Nested case-control study, 1971-1978	SGA, AP[a] (ICD-9)	301 (17), 602	Negative

Eaton, 2000	Denmark	Birth cohort, 1973-1993	Heavy weight >4000g, manic-depressive illness and other AP[a] (DSM-IIIR)	69 (37), 33389	Negative
Øgendahl, 2006	Denmark	Nested case-control study, 1973-onway		196, 5096	
			Light weight <2500g, BD[a] (ICD-8, ICD-10)	13, 267	Negative
			<49cm length, BD[a] (ICD-8, ICD-10)	14, 447	Negative
Mathiasen, 2011	Denmark	Birth cohort, 1974-1996		1431, 1329776	
			Early GA <37w, BD[a] (ICD-8, ICD-10)	93, 67891	Positive
			Late GA 39-45w, BD[a] (ICD-8, ICD-10)	1218, 1104780	
Nosarti, 2012	Sweden	Population-based cohort, 1973-1985		217, 1301522	
			Early GA <37w, BD[a] (ICD-8, ICD-9, ICD-10)	24, 52989	Positive
			Late GA >42w, BD[a] (ICD-8, ICD-9, ICD-10)	40, 221022	Negative
			SGA, BD[a] (ICD-8, ICD-9, ICD-10)	10, 43334	Negative
			LGA, BD[a] (ICD-8, ICD-9, ICD-10)	5, 29579	Negative
Østergaard, 2013	Denmark	Population-based cohort, 1955-1990		2183, 2400000	
			Light weight <2700g, PD (ICD-8, ICD-10)	n.p.	Negative
			Heavy weight >4000g, PD (ICD-8, ICD-10)	n.p.	Negative
			Early GA <37w, PD (ICD-8, ICD-10)	n.p.	Negative
			SGA (<10th percentile), PD (ICD-8, ICD-10)	n.p.	Negative
Chudal, 2013	Finland	Nested case-control study, 1987-1998		724, 2143	
			Light weight <2500g, BD[a] (ICD-9, ICD-10)	35, 78	Negative
			Heavy weight >4500g, BD[a] (ICD-9, ICD-10)	23, 72	Negative
			Early GA <37w, BD[a] (ICD-9, ICD-10)	82, 207	Negative
			Late GA >42w, BD[a] (ICD-9, ICD-10)	38, 85	Negative
			SGA (<-2 SD), BD[a] (ICD-9, ICD-10)	16, 36	Negative
			LGA (>+2 SD), BD[a] (ICD-9, ICD-10)	20, 74	Negative

Perinatal stress					
Brown, 1995	Netherlands	Birth cohort, 1944-1945	Famine, AP[b] (ICD-9)	945 (122), 146347	Positive
Kleinhaus, 2013	Israel	Population based cohort, 1964-1976	Prenatal stress, BD[a] (ICD-10)	120 (7), 90079	Negative
Abel, 2014	UK	Population based cohort	Maternal breavement, BD with psychosis, PD (ICD-8, ICD-9,ICD-10)	1448 (556), 946994	Negative
Freedman, 2015	Child Health and Development Study (CHDS), US	Nested case-control study	Perinatal oxytocine, BD-I, BD-II, BD-NOS, BD with psychosis (DSM-IV-TR)	93 (8), 738	Positive
EARLY CHILDHOOD FACTORS					
Urbanicity at birth					
Marcelis, 1998	Netherlands	Birth cohort, 1942-1978	Urbanicity at birth, AP[a] (ICD-9)	11270 (9438), 42115py	Positive
Østergaard, 2013	Denmark	Population-based cohort, 1955-1990	Urbanicity at birth, PD (ICD-8, ICD-10)	2183, 29900000py	Partially positive
Abel, 2014	UK	Population-based cohort	Urbanicity at birth, BD with psychosis, PD (ICD-8, ICD-9, ICD-10)	1448 (220), 946994	Positive
Vassos, 2016	Denmark	Population-based cohort, 1955-2006	Urbanicity at birth, BD[a] (ICD-8, ICD-10)	8345, 2894640	Positive
Childhood infection					
Benros, 2013	Denmark	Birth cohort, 1945-1996	Hospitalization for infection, AP[b] (ICD-8, ICD-10)	18717 (29324), 3562260	Positive
Leask, 2002	UK	Birth cohort, 1958	Childhood infection, AP[a] (ICD-8, ICD-10)	45, 17414	Positive
Mortensen, 2011	Denmark	Case-control from population based cohort	Antibodies in serology, BD[a] (ICD-10)	127, 127	Negative
Childhood adversity					
Laursen, 2007	Denmark	Population-based cohort, 1973-onwards	Parental death, BD[a] (ICD-8, ICD-10)	4490 (352), 2100000	Positive
Scott, 2010	New Zealand	Population-based cohort	Other Trauma, BD[a] (DSM-IV)	18, 2144	Positive
Østergaard, 2013	Denmark	Population-based cohort, 1955-1990	Parental death, PD (ICD-8, ICD-10)	2183, 2400000	Partially positive
Abel, 2014	Sweden	Population-based cohort	Parental death, BD with psychotic features and PD (ICD-8, ICD-9, ICD-10)	1448 (556), 946994	Positive
Paksarian, 2015	Denmark	Population-based cohort, 1971-1991	Parental separation, BD[a] (ICD-8, ICD-10)	2726 (1342), 985058	Positive
Bergink, 2016	Denmark	Population-based cohort, 1980-1998		2235, 980554	
			Parental death, BD[a] (ICD-8, ICD-10)	88, 28244	Positive

			Other Trauma, BD[a] (ICD-8, ICD-10)	1068, 350987	Positive
			Parental separation, BD[a] (ICD-8, ICD-10)	173, 29326	Positive
LATER LIFE FACTORS					
Substance misuse					
Feingold, 2015	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Israel	Population-based cohort	Cannabis ever, BD-I, BD-II[a] (DSM-IV-TR)	1029 (625), 28630	Positive
Manrique-Garcia, 2012	Sweden	Population-based cohort	Cannabis ever, AP[a] (ICD-8, ICD-9,ICD-10)	390 (50), 45087	Negative
Van Laar, 2007	Netherlands Mental Health Survey and Incidence Study (NEMESIS), Netherlands	Incidence study	Cannabis ever, BD[a] (DSM-III-R)	4681 (484), 3881	Positive
Mustonen, 2018	NFBC1986, UK	Population-based cohort	Cannabis ever, BD psychotic features, PD[b] (ICD-10)	31 (7), 6534	Positive
Duffy, 2012	Canada	High-risk study	Other SUD, BD-I, BD-II, BD-NOS[a] (DSM-IV)	35 (17), 211	Positive
Martins, 2012	US	Incidence study	Other SUD, BD[a] (DSM-IV)	261, 34653	Positive
Migration and Ethnic minority					
Fearon, 2006	UK	Population-based cohort, 2001	Ethnic minority, Manic psychosis, PD[b] (ICD-10)	92[c], 1600000 py	Positive
Westman, 2006	Sweden	Population-based cohort	Migration (1st generation), AP[a] (ICD-9, ICD-10)	12040 (1837), 4563319	Positive
Kirkbride, 2008	UK	Population-based cohort	Ethnic minority, BD psychotic features,PD (DSM-IV)	122 (72), 828546 py	Positive
Cantor-Graae, 2013	Sweden	Population-based cohort, 1971-2000	Migration (1st and 2nd generation), BD[a] (ICD-8, ICD-10)	2719 (171), 1859419	Positive
Lasalvia, 2014	Italy		Migration (no native), BD with psychotic features, PD (ICD-10)	117, 3077555 py	Positive
Kirkbride, 2017	UK	Naturalistic cohort	Ethnic minority, AP[a] (ICD-10)	84 (30), 2021663 py	Positive
Urbanicity later in life					
Kaymaz, 2006	Netherlands Mental Health Survey and Incidence Study (NEMESIS), Netherlands	Population-based cohort	Later urbanicity, BD[a] (DSM-III-R)	132, 7049	Positive
Kelly, 2010	Ireland	1995-1998	Later urbanicity, AP[a] (DSM-III-R, DSM-IV)	324 (171), 267810	Positive
Lasalvia, 2014	Italy	Multisite naturalistic study	Later urbanicity, BD with psychotic features, PD[b] (ICD-10)	117, 3077555 py	Negative
Skoze, 2014	France	Incidence study	Later urbanicity, BD with psychosis, PD (DSM-IV)	51, 396714	Positive

[a] Not specified distinction between patients with and without psychotic features
[b] Provided specific numbers for bipolar disorder and psychotic depression
[c] Calculated from incidence rates
OR: odds ratio; IRR: incidence rate ratio; BD-I: bipolar disorder type I; BD-II: bipolar disorder type II; BD-NOS: bipolar disorder not otherwise specified; ICD: international classification of diseases; DSM: diagnostic and statistical manual of mental disorders; PD: major depressive disorder with psychotic features; AP: Affective psychosis; GA; gestational age; SGA: small for gestational age; LGA: large for gestational age; SUD: substance use disorder; py: persons year; n.p: not provided

3.3.2 Pre-/Perinatal factors

3.3.2.1 Paternal age

Main analyses were conducted on six studies showing associations between paternal age over 40 (Frans *et al.*, 2008; Buizer-Voskamp *et al.*, 2011; Østergaard *et al.*, 2013; Chudal, Gissler, *et al.*, 2014; McGrath *et al.*, 2014) or 45 years old (Brown, A. S. *et al.*, 1995). They included a total of 25,996 cases (23813 BD, 2183 PD). The combined pooled effect after random-effect analyses showed a significant risk for affective psychoses (OR 1.17, 95%CI 1.12-1.23); with little difference when only BD was considered (OR 1.17, 95%CI 1.11-1.22) (***eFigure 3.1***).

3.3.2.2 Maternal infection

Five studies examining maternal infection were analysed, including a total of 1485 cases (189 BD, 1284 affective psychosis). Two of them measured exposure to influenza (Brown, A. S. *et al.*, 1995; Parboosing *et al.*, 2013), two to Toxoplasma Gondii (Xiao *et al.*, 2009; Freedman *et al.*, 2016), and one to viral infection (Canuti *et al.*, 2015). Results indicated no significant association between maternal infection and later risk of affective psychosis (OR 1.71, 95%CI 0.87-3.36).

3.3.2.3 Obstetric complications

Eight studies were included for quantitative analyses (Hultman *et al.*, 1999; Bain *et al.*, 2000b; Eaton *et al.*, 2000; Øgendahl *et al.*, 2006; Mathiasen *et al.*, 2011; Nosarti *et al.*, 2012; Østergaard *et al.*, 2013; Chudal, Sourander, *et al.*, 2014), grouping a total of 6914 cases (2448 BD, 2183 PD, 2283 affective psychosis). We identified sufficient studies to analyse separately the following obstetric complications: light birth weight (defined as <2500-2700g), heavy birth weight (defined as >4500g), early GA (<37weeks), late GA (>39-42 weeks) and small for GA (as defined in the original papers).

Evidence for associations with affective psychosis was found for both early (OR 1.52, 95%CI 1.07-2.17) and late GA (OR 1.32, 95%CI 1.05-1.67). Interestingly, the only identified study not included in the quantitative analyses due to insufficient data to extract (Done *et al.*, 1991), also found evidence of an association of decreased gestation time with affective disorder (mean difference of 7.3 days, 95%CI 3.1-11.5).

3.3.2.4 Perinatal stress

In the group of perinatal stress, in which we included maternal famine, maternal stress, perinatal oxytocin, and maternal bereavement, we identified four studies (Brown, A. S. *et al.*, 1995; Kleinhaus *et al.*, 2013; Abel *et al.*, 2014; Freedman *et al.*, 2015) involving a total number of 891 cases (213 BD, 678 affective psychosis). Results indicated no significant association between perinatal stress and later risk of affective psychosis (OR 1.18, 95%CI 0.95-1.46).

3.3.3 Early childhood factors

3.3.3.1 Urbanicity at birth

Four studies were meta-analysed (Marcelis *et al.*, 1998; Østergaard *et al.*, 2013; Abel *et al.*, 2014; Vassos *et al.*, 2016), including a total of 15,073 cases (1400 BD, 2183 PD, 11490 affective psychosis). The combined pooled effect showed a non-significant trend (OR 1.12, 95%CI 0.99-1.27). Nonetheless, the one study showing an effect in opposite direction (Østergaard *et al.*, 2013) was the only one exploring PD as an outcome. After removing that study, we observed a significant association (OR 1.22, 95%CI 1.14-1.31) (***eFigure 3.2***); hence, the association of urbanicity at birth with BD is likely.

3.3.3.2 Childhood infection

Three studies (Leask *et al.*, 2002; Mortensen *et al.*, 2011; Benros *et al.*, 2013) were included, aggregating 18,921 cases (127 BD, 18,794 affective psychosis). They measured exposure to a variety of infectious conditions early in life (**Table 3.1**). No significant association was found with affective psychosis (OR 1.10, 95%CI 0.69-1.76).

3.3.3.3 Childhood adversity

Six studies measured the association between a form of childhood adversity and later affective psychosis (Laursen *et al.*, 2007; Scott *et al.*, 2010; Østergaard *et al.*, 2013; Abel *et al.*, 2014; Paksarian *et al.*, 2015; Bergink *et al.*, 2016), with an overall 13100 cases included (9469 BD, 2183 PD, 1448 affective psychosis). As illustrated in Figure 2B, the pooled effect indicated a significant association: (OR 1.33, 95%CI 1.18-1.50). When analysed by diagnosis, we could obtain a pooled effect for BD only, which showed a stronger association (OR 1.46, 95% CI 1.22 - 1.76) (***eFigure 3.3***). The effect for specific subcategories are presented in *Supplementary Material* (***eFigure 3.4***): parental death, parental separation, and other traumas [i.e., being placed into care, parental imprisonment (Bergink *et al.*, 2016), or having a history of child protection services involvement (Scott *et al.*, 2010)].

3.3.4 Later factors

3.3.4.1 Substance misuse

Six studies measuring substance use were meta-analysed (Van Laar *et al.*, 2007; Duffy *et al.*, 2012; Manrique-Garcia *et al.*, 2012; Martins *et al.*, 2012; Feingold *et al.*, 2015; Mustonen *et al.*, 2018), combining 6427 cases (6006 BD, 421 affective psychosis). The overall effect was significant for affective psychosis (OR 2.87, 95%CI 1.63–5.50), which was true also for BD alone (OR 3.07, 95%CI1.84–5.12) (***eFigure 5***). We later subdivided the substance use category into lifetime smoking of cannabis (defined as having used cannabis anytime or ever) and other substance use disorders (SUD), which included non-medical use of opioids (Martins *et al.*, 2012) and undefined substance use disorder (Duffy *et al.*, 2012). Use of cannabis individually was significant (OR 3.03 95%CI1.32-6.96), while there were insufficient studies to estimate the pooled effect for other SUD (***eFigure 3.6***).

3.3.4.2 Ethnic minority and migration

Seven studies examined the association between belonging to an ethnic minority or being a migrant and later affective psychosis, with overall numbers of 15,174 cases (2,719 BD, 12,455 affective psychosis).

We pooled together “belonging to ethnic minority” (Fearon, P *et al.*, 2006; Kirkbride *et al.*, 2008, 2017) or “being migrant” (Westman *et al.*, 2006; Cantor-Graae and

Pedersen, 2013; Lasalvia *et al.*, 2014) (see *Supplementary material* for details on migrant definitions). The pooled effect size was significant (OR 1.99, 95%CI 1.39-2.84), with studies of ethnic minorities showing higher effect (OR=2.84) than studies of migrants (OR=1.46) (***eFigure 3.7***).

3.3.4.3 Urbanicity later in life

Four studies examining living in an urban environment during adulthood were meta-analysed (Kaymaz *et al.*, 2006; Kelly *et al.*, 2010; Lasalvia *et al.*, 2014; Szöke *et al.*, 2014), combining 624 cases (132 BD, 429 affective psychosis). They showed a non-significant pooled effect (OR 1.16, 95%CI 0.64–2.07).

Of note, one study identified in the systematic review (Omer *et al.*, 2016) that measured the impact of rurality rather than urbanicity showed a negative association with affective psychosis (OR 0.96, 95%CI 0.92–1.00), suggesting a protective role of living in non-urban areas.

Two further studies were identified in the search but were not included in quantitative synthesis due to lack of data (see ***eTable3.6***). While Kroon et al.(Kroon *et al.*, 2013) didn't find an association of urbanicity as per density of addresses with BD, results from Sundquist et al.(Sundquist *et al.*, 2004), suggest an association with their "depression" category, in which they included diagnosis of Bipolar Disorder and Manic episode with psychotic features (F30-34) (highest urbanicity quantile HR 1.43, 95%CI1.32-1.55).

3.3.4.4 Stressful Life Events

Only one study, a high-risk cohort of offspring of people with BD, met inclusion criteria (Kemner *et al.*, 2015) for the analysis of the association between stressful life events and later affective psychosis (eTable6). It reported an increase of first mood episodes among those accumulating more stressful life events, without specifying if the episodes were later diagnosed as BD or PD. We conclude there is a lack of prospective studies exploring the effect of stressful life events in affective psychosis.

Figure 3.2. Forest Plots of the associations between environmental risk factors and affective psychosis grouped by A) Pre-/peri-natal factors; B) Early childhood factors; and C) Later Life factors

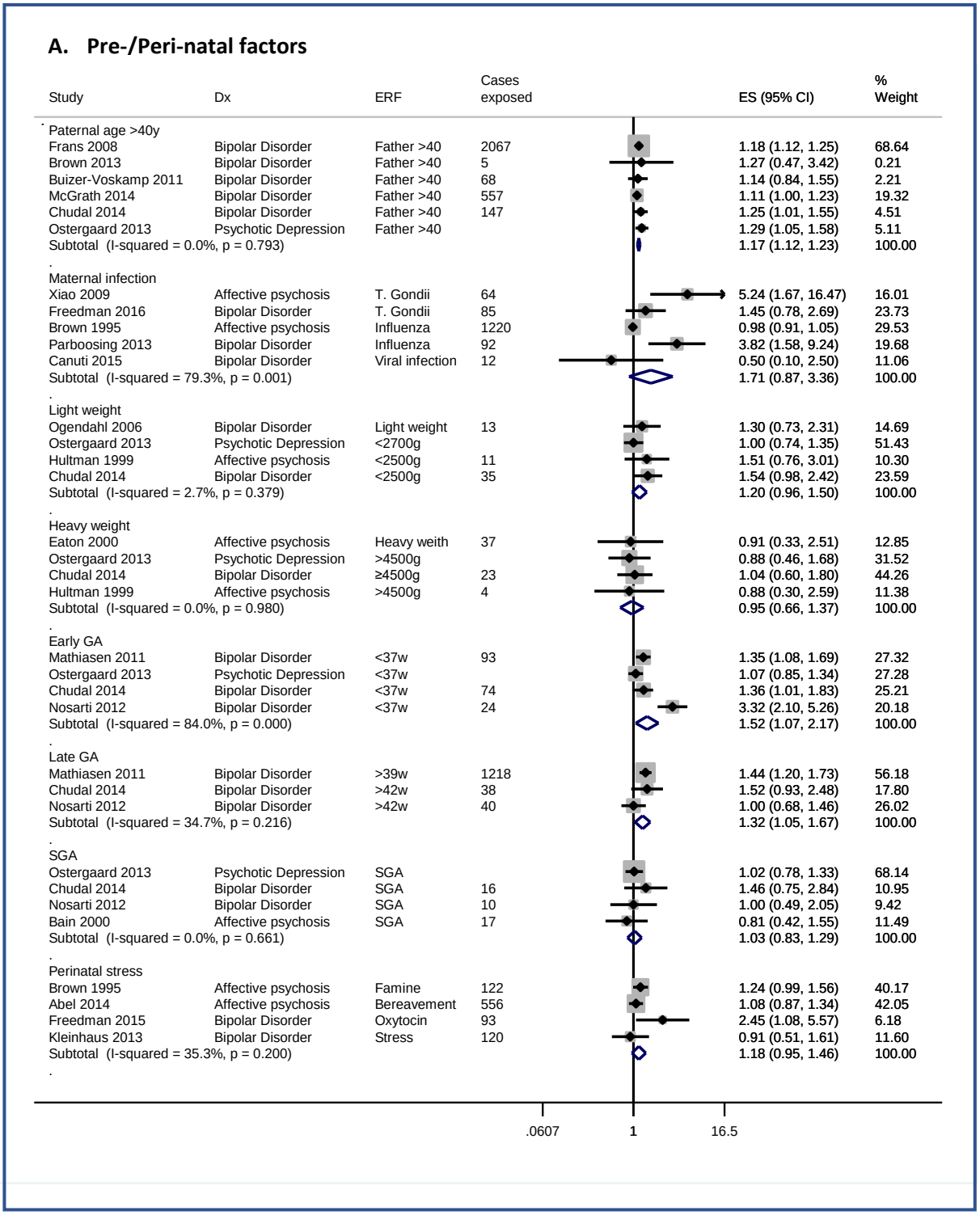
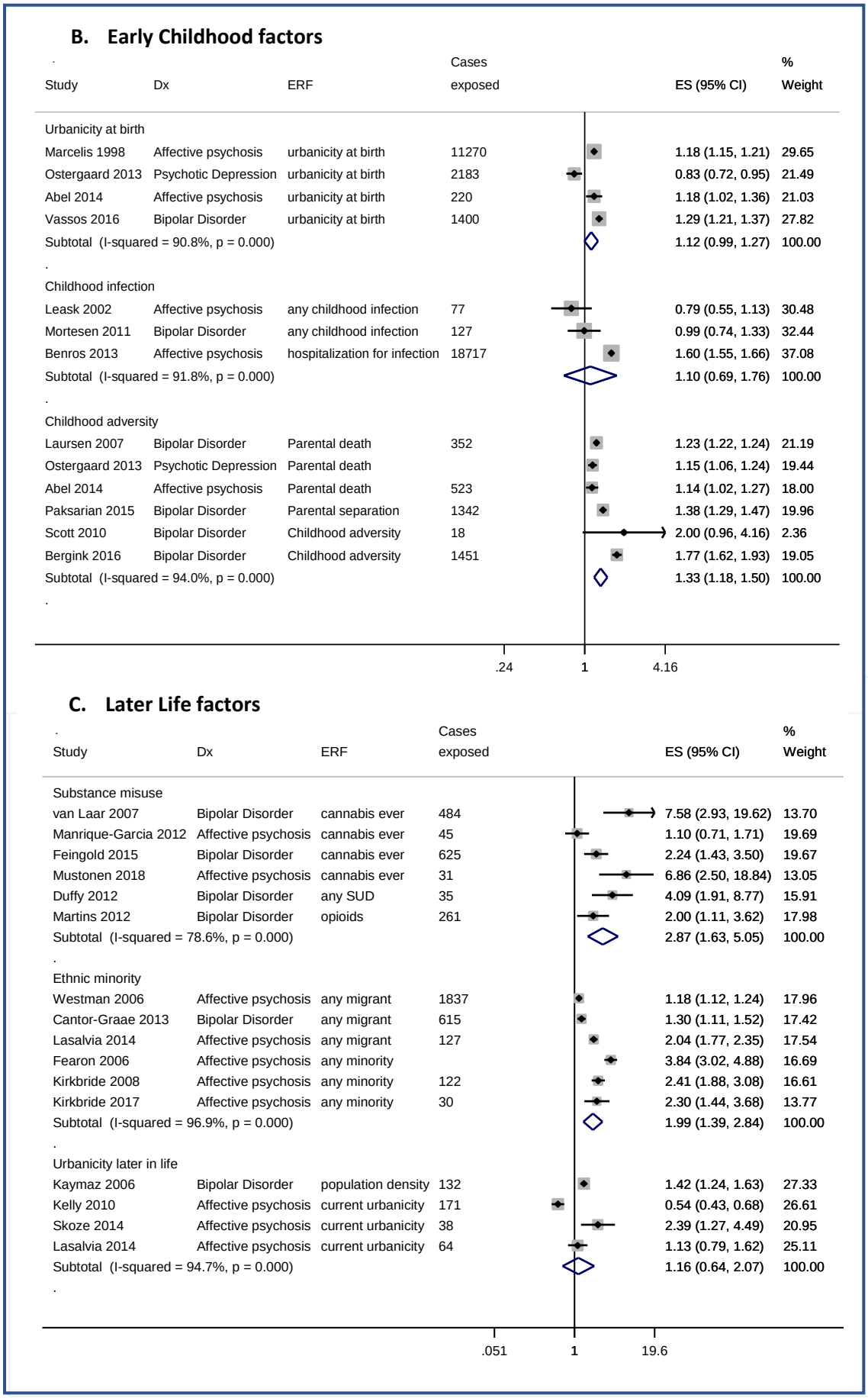


Fig 3.2. *continued*



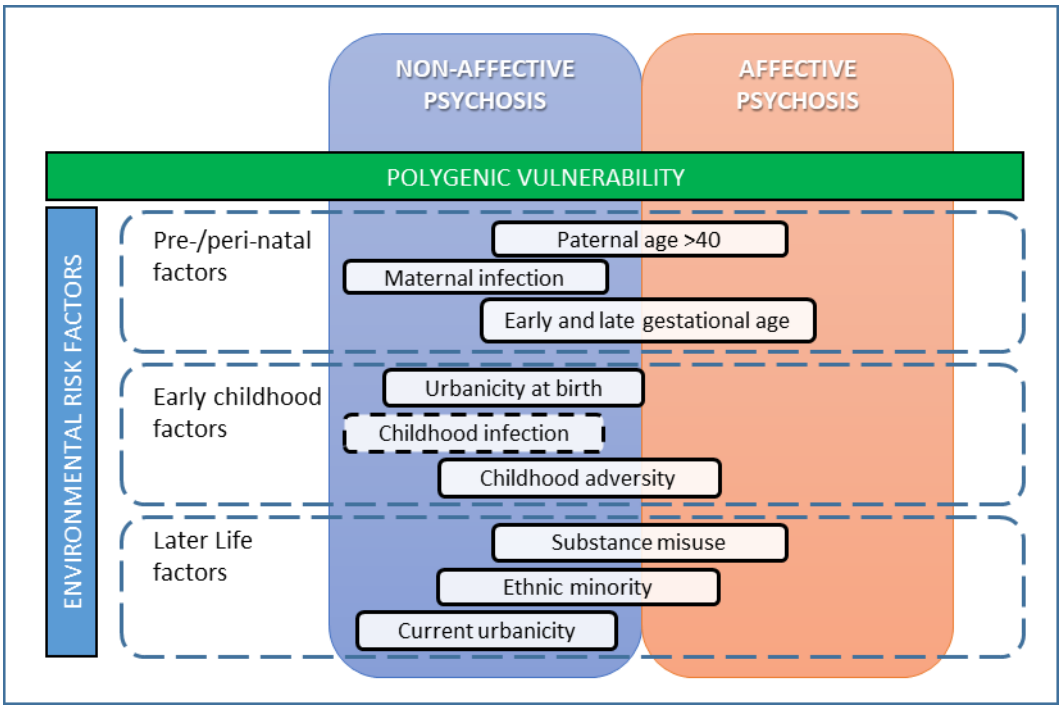
3.3.4.5 Traumatic brain injury

Only two longitudinal cohorts measuring the impact of traumatic head or brain trauma on later development of affective psychosis were identified, thereby precluding meta-analysis of this data. Both studies suggested a positive association with BD. Orlovska et al. (Orlovska *et al.*, 2014) provided a significant IRR of 1.3 (95% 1.10–1.48), and we estimated from raw data an OR of 2.9 (2.53-3.37) for Chang et al. (Chang *et al.*, 2019). Although evidence points to a potentially greater risk of developing affective psychosis after a head trauma or brain injury, the number of studies is scarce.

3.4 DISCUSSION

This comprehensive systematic review examined the association between specific ERF and later development of affective psychosis, including BD and PD. We found evidence supporting an association between affective psychosis and exposure to different insults from early development to adulthood, as is the case for Schizophrenia (Stilo and Murray, 2019). In particular, as illustrated in **Figure 3.3**, our review shows that different risk factors are key/specific in different developmental periods, which goes in line with the neurodevelopmental hypothesis for affective psychosis: from prenatal (paternal age), perinatal (early and late gestational age), early childhood (childhood adversity), and adolescence and adulthood (lifetime cannabis use and ethnic minority status). Our review also shows that there are striking gaps in the evidence: around three quarters of studies focused exclusively on BD, followed by studies examining Affective Psychosis as a composite category, with few studies investigating PD. This precluded us from drawing conclusions in regard to differential impact of any ERF on PD, and we identify only parental age at birth, urbanicity at birth, childhood adversity, and substance use as risk factors for BD.

Figure 3.3. Differential effect of Environmental Risk Factors across the life-span in non-affective (NAP) and affective psychoses (AP).



This graph represents the differential effect for NAP and AP of the different environmental risk factors (ERF) across the life span based on retrieved literature review for NAP and our systematic review and meta-analyses for AP. It spatially represents the strength and level of evidence of association of different ERF with both NAP and AP. We indicate with a dashed line the ERF for which questionable evidence for NAP is available.

3.4.1 Comparison with previous reviews and meta-analyses

Our work supports an association of advanced paternal age at birth and adult affective psychosis. Although the mechanism underlying the association between advance paternal age and psychiatric disorders requires to be clarified (de Kluiver *et al.*, 2017), the fact that this association seems particularly true for BD with psychosis (Lehrer *et al.*, 2016) compared with BD without psychosis raises the question of whether the choice of late fatherhood could be a reflection of common genetic susceptibility with schizophrenia (Gratten *et al.*, 2016). Maternal infection was not found to be a significant risk factor for later development of affective psychosis. Our results contradict the findings of two meta-analyses showing a link between T. Gondii and BD (Sutterland *et al.*, 2015; de Barros *et al.*, 2017) which were not limited to prospective studies. This cautions against accepting this as a definitive risk factor.

Among the obstetric factors analysed, only early or late gestational age increases risk, mainly for BD. Interestingly, one of the identified studies also reported that extreme prematurity (less than 32 weeks' gestation) conferred an even stronger risk of developing BD (Nosarti *et al.*, 2012), suggesting a dose-response association. The only meta-analysis published on obstetric complications and BD (Scott *et al.*, 2006) found no evidence of an association of low birth weight, being small for gestational age or obstetric complications overall with BD, showing only a positive independent association for multiparity. The fact that neither light nor heavy birth weight, nor small for gestational age, proved to increase risk of affective psychosis raises the possibility that the effect of early or late gestational age may be due to some confounder that could induce prematurity or delay of birth, rather than an impact of non-optimal foetal growth or embryo maturity itself.

Neither urbanicity at birth nor later in life increased the odds of developing adult affective psychosis. The only available meta-analyses for current urbanicity (Kelly *et al.*, 2010) showed a protective effect for affective psychosis. Regarding urbanicity at birth, although there is no previous meta-analysis available exploring this association, our results contrast with most of the individual published studies (Marcelis *et al.*, 1998; Abel *et al.*, 2014; Vassos *et al.*, 2016), driven by the findings from one study analysing PD (Østergaard *et al.*, 2013). When repeating analyses only in affective psychosis or BD, the association became significant, suggesting that the association may be specific to BD. The only published meta-analysis of the association between childhood adversity and BD (Palmier-Claus *et al.*, 2016) reports an increase of childhood trauma experiences of 2.63 times among those with BD compared with controls. Nonetheless, among their 19 included studies, only two were prospective, which were included in our results (Laursen *et al.*, 2007; Scott *et al.*, 2010). No evidence was found to support an association of affective psychosis with childhood infection, which remains an understudied field with no previously published systematic reviews or meta-analyses. This may be partly due the scarcity of studies, and the methodological differences characterizing the existing ones.

Regarding later life factors, our results concur with the reported increased odds of 3 in the only previous published meta-analysis (Gibbs *et al.*, 2015) on effect of cannabis in BD, although that study used mania as the outcome rather than coded clinical diagnosis. Finally, our results showed that belonging to an ethnic minority increased the odds of later affective psychosis by around 75%. A previous meta-

analysis (Swinnen and Selten, 2007) of 14 studies explored the effect of migration on mood disorders (including BD), reporting a significant effect of developing any mood disorder among migrants, confirming our results.

Although out of the scope of the present work, it is interesting to note that the evidence of association of environmental risk factors for Major Depressive Disorder and Bipolar Disorder without psychosis is much less conclusive, childhood adversity being the only reported risk factor with convincing (Köhler *et al.*, 2018) and highly convincing evidence(Bortolato *et al.*, 2017) respectively in two recent umbrella reviews of both disorders. Part of the paucity of consistent evidence is due to small number of studies for some environmental factors, where more research is necessary to help us elucidate if there is a differential or shared transdiagnostic environmental influence across the affective disorders spectrum.

Overall, we can conclude that some risk factors seem "universal" for psychosis, showing a strong association with both affective and non-affective psychoses, such as cannabis use (Marconi *et al.*, 2016). Some other factors share the association with an apparent lower effect for affective psychosis. For instance, advanced parental age presents a lower pooled effect size than that reported for schizophrenia(Miller *et al.*, 2011); and while urbanicity at birth is quite consistently reported risk for schizophrenia (Vassos *et al.*, 2012), the evidence to support it as a risk factor for affective psychosis remains weak. Also, in the aforementioned meta-analysis on ethnic minority status (Swinnen and Selten, 2007), association with BD was lower than with schizophrenia. In regard to childhood adversity, we identified a lack of studies for affective psychosis examining the impact of important types of adversity like abuse, neglect, or bullying, which have shown to be relevant for the development of psychosis (Varese *et al.*, 2012). However, both parental separation and parental death increased risk of later developing affective psychosis, suggesting that adversity during childhood is likely to be associated with all types of psychosis. Other factors such as childhood infection remain elusive for both affective psychosis (as evidenced by our work) and for schizophrenia and other non-affective psychoses, as shown by the only available meta-analysis (Khandaker *et al.*, 2012), which concluded that the increase of risk may be restricted to CNS viral infections.

3.4.2 Strengths and limitations

The findings of this review should be interpreted in the context of various strengths and limitations. A major strength includes limiting our inclusion criteria to studies with longitudinal design, which allowed us to establish temporal relationships compared with cross-sectional studies. Nonetheless, it should be noted that we can't totally exclude the possibility that some of the alleged risk factors are a product of prodromal manifestations of the disease, or a response to gene-environment correlation, which constitute a general limitation when exploring environmental exposures. Second, by restricting studies to affective psychosis clinically defined and excluding syndromal manifestations, we may have derived more conservative estimates of risk. Another strength is the scale of this review, examining 11 risk factors, with 59 studies meeting inclusion criteria.

However, limitations of this review include: (i) too few studies of several ERFs were available for meta-analyses, thus limiting our capacity to form firm conclusions regarding those domains; (ii) high levels of heterogeneity were observed for a considerable number of ERFs; (iii) most studies were from high-income countries, limiting the generalizability of the findings; (iv) heterogeneity of outcome definition, including BD, PD and AP prevents us from extrapolating conclusions about individual diagnoses and may have hindered some specific associations; (v) also related with the previous point, another limitation to consider is the changeability of diagnoses, as shown in some studies the existence of shifts in diagnoses with a predominant direction from affective psychosis to NAP of around 14-29% after two years (Schwartz *et al.*, 2000; Veen *et al.*, 2004); (vi) although bipolar patients are considered as having psychosis, most studies didn't specify that the patients presented psychotic symptoms within the manic phases; thus it is plausible that bipolar patients without psychotic features are included, which may have contributed to reduce strength of associations (vii) pooled effect sizes are based on crude effect sizes whenever was possible, which despite constituting usual practice, implies unmeasured confounding may be influencing results; (viii) included studies were limited to English language, which was previously reported to have a small effect on pooled treatment effects from trials (Jüni *et al.*, 2002), and which can limit the external validity of our results to non-English speaking countries; and lastly, (ix) as our search strategy was informed by risk factors associated with non-affective

psychosis (Vassos *et al.*, 2019), it is possible that other risk factors specific to affected psychosis are not fully covered.

3.4.3 Conclusions

Our meta-analysis provides strong support for a role for certain environmental factors, occurring at different periods in the life-span, in increasing the risk of affective psychosis. As per shared genetic loading across schizophrenia and affective psychosis, there may be some overlap in the environmental load between these disorders, suggesting a cross-diagnosis general risk for psychosis. Our systematic review points at important gaps in the literature, as published studies exploring specific factors in this subgroup of patients remain scarce relative to those available for schizophrenia. More longitudinal studies measuring the effect of environmental risk factors on Bipolar Disorder and even more on Psychotic Depression are warranted.

4. STUDY 1. DISPARITIES IN TREATED INCIDENCE IN AFFECTIVE PSYCHOSIS IN THE MULTINATIONAL EUGEI STUDY.

4.1 INTRODUCTION

Affective psychosis (AP), which includes Bipolar Disorder (BD) and Major Depressive Disorder with psychotic features (here MDD-P; also called psychotic depression, PD), is among the major causes of disability and disease burden worldwide (World Health Organization & World Bank, 2011), resulting in a shortening in life expectancy compared with general population (Hayes *et al.*, 2015) of between one to two decades (Nordentoft *et al.*, 2013); and a reduction in quality of life (Michalak *et al.*, 2005; Saarni *et al.*, 2010; Bingham *et al.*, 2019). Two recently published studies based on the Global Burden of Disease Study 2017 claim that incidences of BD and MDD have increased by 47.74% (He *et al.*, 2020) and 49.86% (Liu *et al.*, 2020); with a consequent increase on disability-adjusted life-years (DALYs) of 15.2% and 12.6% respectively from 1990 to 2017 (Kyu *et al.*, 2018). Apart from variation across time, a recent meta-analysis examining the international incidence of psychotic disorders showed a 10-fold variation across affective and non-affective psychosis groups between sites, which was attributed to social, demographic and environmental determinants (Jongsma *et al.*, 2019). These results are in line with previous evidence suggesting that the more frequently studied incidence of Schizophrenia (SCZ) varies as a factor of exposure to urbanicity (Pedersen and Mortensen, 2001) and personal or family history of migration (Cantor-Graae and Selten, 2005). Indeed, there is a wealthy body of literature on how incidence of SCZ and other non-affective psychotic (NAP) disorders is influenced by these and other factors (McGrath *et al.*, 2004a; Fearon, Paul *et al.*, 2006); but less is known about the AP group.

With a global incidence between 7.12/100000 person years (100kpy)(Castillejos *et al.*, 2018) and 12.4/100kpy (Kirkbride *et al.*, 2012), incidence rates of AP represent around one third and one-half of the approximately 23/100kpy of NAP reported in the two recent meta-analyses (Kirkbride *et al.*, 2012; Castillejos *et al.*, 2018). In the one based on studies in England from 1950 to 2009 (Kirkbride *et al.*, 2012), the authors also provide specific rates for BD and MDD-P corresponding to a pooled crude incidence of 3.7/100kpy and 5.3/100kpy respectively, which goes in line with a recent systematic review on MDD-P presenting incident rates varying from 3.0 to 6.4 per 100000 (Jääskeläinen *et al.*, 2018). Of note, other incidence studies focusing on BD both with and without psychotic features, present higher incidence numbers up to 28.4/100kpy (Medici *et al.*, 2015). Interestingly, despite the reported data in

favour of lower incidence rates for AP, two older studies showed either no differences between AP and NAP in a FEP patients (Baldwin *et al.*, 2005); or even higher incidence rates (Crebbin *et al.*, 2008) of MDD-P compared with SCZ, which points out the need to study this further.

One important limitation of studies published so far is that they have been done mainly on North European samples, such as Sweden (Carlborg *et al.*, 2015), Denmark (Cantor-Graae and Pedersen, 2013; Medici *et al.*, 2015), Netherlands (Kroon *et al.*, 2013), UK (Van Os *et al.*, 1996; Kennedy, N. *et al.*, 2005; Crebbin *et al.*, 2008; Kirkbride *et al.*, 2012) and Ireland (Baldwin *et al.*, 2005; Omer *et al.*, 2016), with a lack of incidence studies in areas such as southern Europe. This is of key importance given the recent evidence that different distribution of risk factors plays a major role on the variation of incidence rates of psychosis across countries (Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Cristofalo, *et al.*, 2018). Moreover, in the same way that different environmental risk factors (ERF) seem to affect differently the likelihood to develop AP (BD and MDD-P) (Rodriguez *et al.*, 2021), the different distribution of specific demographic (such as socio-economic status, ethnic minority) and environmental factors (such as latitude or urbanicity), may not only play a role in the incidence variation of psychoses across countries (Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Cristofalo, *et al.*, 2018), but also in differences between diagnostic groups (SCZ, BD, MDD-P, PNOS).

Gaining a better understanding on the factors influencing variation in the incidence of BD and MDD-P is a crucial step towards developing prevention and treatment interventions. Using comparable methods of a previous work on treated incidence of psychosis, my aim is to analyse treated incidence variation of BD and MDD-P, in comparison with SCZ and PNOS; then analyse if the same social and environmental factors account for the hypothesised variance across sites, which subsequently can provide valuable information to unravel the still under-researched etiology of this subgroup of psychosis.

4.2 METHODS

4.2.1 Study design and participants

4.2.1.1 Study design

This study is based on the incidence sample from the *European Network of national schizophrenia networks studying Gene-Environment Interactions* (EUGEI) study; a multisite incidence and case-sibling-control study set out to estimate the incidence of psychosis and to recruit first-episode psychosis (FEP) cases and controls to investigate genetic and environmental determinants of psychotic disorder (Gayer-Anderson *et al.*, 2020).

All subjects between 18-64 years who were referred to mental health services with a suspicion of a first episode of psychosis across the selected catchment areas were screened. The 17 catchment areas belonged to 6 countries: UK (Southeast London, Cambridgeshire), the Netherlands (Amsterdam, Gouda and Voorhout), Italy (Bologna, Veneto, Palermo), France (Paris, Val-de-Marne, Puy-de-Dôme), Spain (Madrid, Barcelona, Valencia, Oviedo, Santiago, Cuenca) and Brazil (Ribeirão Preto); and ranged from rural (Cuenca, 11 people/km^2) to urban (Paris, 33260 people/km^2). Case ascertainment took place predominantly between May 2010, and April 2015, varying from 12 months (London) to 48 months (Val-de-Marne). Written consent was obtained from those participants agreeing to take part on the case-control study, and local research ethics committees in each catchment area approved the extraction of basic demographic and clinical details from patient's records for the remain (Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Cristofalo, *et al.*, 2018).

4.2.1.2 Case identification and diagnosis definition

Inclusion and exclusion criteria are presented in **Figure 4.1**. For all those identified subjects with an untreated FEP (ICD-10 codes F20-F33) fulfilling inclusion criteria, specific diagnoses were obtained with the Operational CRITeria (OPCRIT) system (McGuffin *et al.*, 1991; Williams *et al.*, 1996), which was centrally trained to investigators across sites achieving a high interrater reliability ($\kappa = 0.7$). Assessment with OPCRIT were based, where possible, on a semi structured clinical interview; otherwise on review of case notes and other relevant information.

Figure 4.1 Inclusion and exclusion criteria for cases in EUGEI Study, Work Package 2.

Inclusion criteria	Exclusion criteria
a) Presence of at least one positive psychotic symptom for at least 1 day duration or two negative psychotic symptoms (for at least 6 months duration) within the timeframe of the study b) Aged between 18 and 64 years (inclusive) c) Being resident within the clearly defined catchment area at the time of their first presentation (defined as a minimum of a one night stay at a residential address within the catchment areas)	a) Previous contact with specialist mental health services for psychotic symptoms outside of the study period at each site b) Evidence of psychotic symptoms precipitated by an organic cause (ICD-10: F09) c) Transient psychotic symptoms resulting from acute intoxication (F1X.5) d) Severe learning disabilities, defined by an IQ<50 or diagnosis of intellectual disability (F70–F79) ***and, for the case–control part only:*** e) Insufficient fluency of the primary language at each site to complete assessments.

[As reported by Gayer-Anderson, 2020 (Gayer-Anderson *et al.*, 2020)*]*

OPCRIT can produce specific diagnoses based on ICD-10 and DSM-IV. In order to optimise the higher availability of data I prioritise the use of DSM-IV based labels (with the exception of London that I only had ICD-10 available). Given the acceptable interrater reliability between ICD-10 and DSM-IV criteria, especially for BD (Cheniaux *et al.*, 2009), for those cases with unspecified DSM-IV diagnosis but with ICD-10 available, the latter was imported. Where OPCRIT assessment was not possible, or OPCRIT didn't produce a specific diagnosis for neither DSM-IV nor ICD-10, we relied on the DSM-IV diagnosis made in clinical settings, which was recorded at baseline as part of the modified DUP Version of the Nottingham Onset Schedule (NOS-DUP)(Singh *et al.*, 2005).

I selected only diagnoses falling into the following diagnostic categories: (1) Schizophrenia (ICD-10 code F-20); (2) Bipolar Affective Psychosis (ICD-10 codes F30 and F31); (3) Psychotic Depression (ICD-10 codes F-32); and (4) Other non-organic psychotic syndrome and Unspecified nonorganic psychosis (ICD-10 codes F-28 and F-29), dropping from the analysed sample those labelled as: Schizoaffective disorder (ICD-10 code F-25) or Delusional Disorder (ICD-10 code F-22). Of the 2774 cases of psychotic disorder that were identified in the incidence study (Jongsma,

Gayer-Anderson, Lasalvia, Quattrone, Mulè, Cristofalo, *et al.*, 2018) I managed to collect categorical diagnoses of interest for 2480 of them, mostly from OPCRIT (n= 1993, 80.4%), and completed with diagnosis given on their respective clinical settings from the electronic notes (n= 487, 19.6%). Detailed percentages of diagnosis source by site are provided in **Figure 4.2**, and tree of reconversion of diagnoses is shown in **Figure 4.3.**

Figure 4.2 Percentage of source of diagnosis by site, ascendingly sorted by OPCRIT DSM-IV presence.

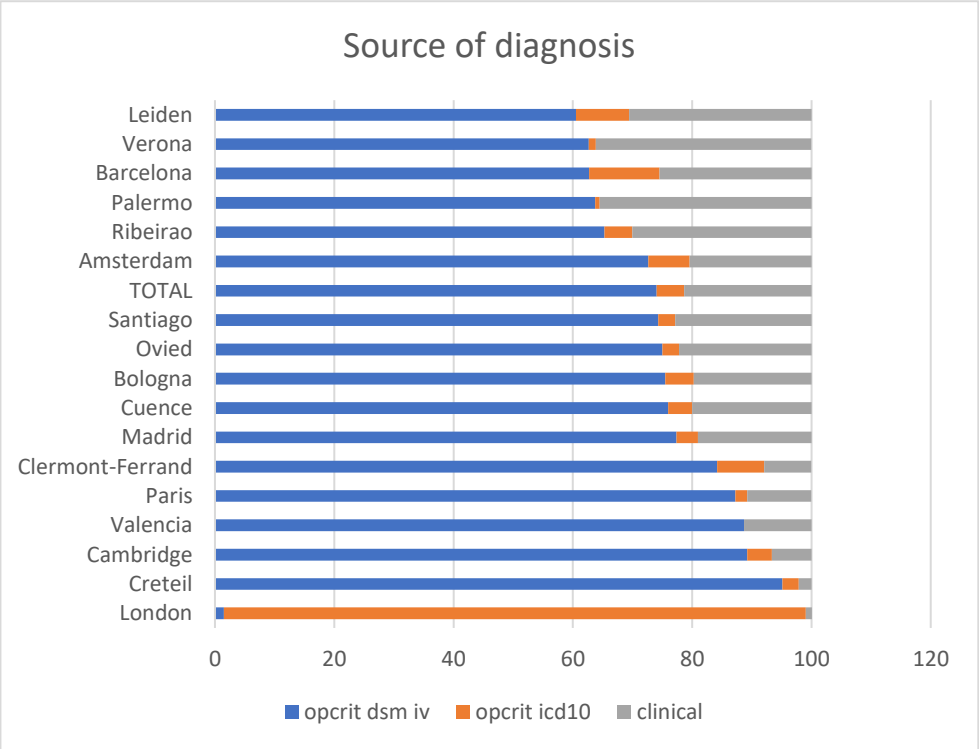
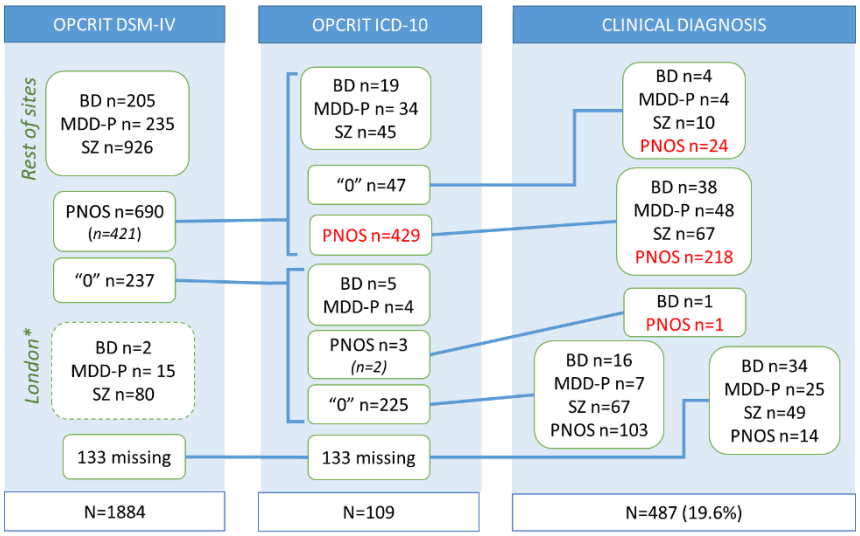


Figure 4.3 Algorithm of diagnosis source and conversion following a hierarchical structure from OPCRIT DSM-IV, ICD-10 and Clinical diagnosis.



**London was primarily based on OPCRIT ICD-10, but was included within the OPCRIT DSM-IV column as a way to show numbers of primary source of diagnosis.*

"0" represents those subjects with no OPCRIT output for the specified criteria

4.2.1.3 Population at risk

The population at risk, for those aged from 18 to 64 years, was calculated based on the most accurate national demographic data available, the national statistics offices for each country (census for England and yearly estimates for the other countries). The population was stratified by age (in 5-year bands from 18 to 64 years), gender and ethnic status (native vs migrant). To estimate person-years at risk, the population was multiplied by case ascertainment duration (in years) in each site.

4.2.2 Measures

4.2.2.1 Individual level data

My primary outcome was research-based diagnosis as exposed in the previous section (Section 4.2.1.2. Case identification and diagnosis definition).

Data on age, gender, ethnicity, and country of birth were collected using the MRC Sociodemographic Questionnaire (Mallet, 1997) and supplemented by clinical records. Ethnicity was defined as a binary variable to distinguish between the ethnic majority population in each catchment area (white for all included sites), and all other ethnic minority groups, with details across sites provided elsewhere (Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Szöke, *et al.*, 2018).

4.2.2.2 Catchment level factors

Latitude was calculated in degrees from the equator and used as both a continuous variable and dichotomised into north and south based on the median. Despite a lacking of a consensus on how to define urbanicity (Dahly and Adair, 2007), most of proposed urbanicity scales includes among other items population density (Cyril *et al.*, 2013). In fact, population density has been previously reported as indicator of urbanicity in SCZ (Vassos *et al.*, 2012). Population density was derived in our sample as number of inhabitants per square kilometre, based on official total population estimates, and used as a continuous variable. An alternative measure of urbanicity was explored by employing definitions provided by the United Nation, Population division (United Nations, Department of Economic and Social Affairs, 2018); which for most of our included countries consider as urban any population over 10000 inhabitants. Since this was fulfilled by all our 17 catchment areas, it did not constitute a valid measure to explore further differences of urbanicity. Hence, only population density was used as a measure for urbanicity.

Three socioeconomic measures reporting unemployment, owner-occupied housing, and single-person households were extracted from the 2011 European Household and Population Census(Eurostat and European Commission, no date) - a census that provides every 10 years comparable data at a provincial level (NUTS-2 [Nomenclature of Territorial Units for Statistics–2] regions). Similar data for Ribeirao Prieto was taken from the 2010 National Census of Brazil (Instituto Brasileiro de Geografia e Estatística, no date).
I further included an environmental measure previously studied as potentially protective factor for psychosis, the amount of sunshine hours (McGrath *et al.*, 2002; Gu *et al.*, 2019). I obtained the annual average of sunshine hours for 14 out of 17 sites from "CurrentResults" website (*Total Annual Sunshine in European Cities - Current Results*, no date). For those 3 sites that we didn't have specific data, I provided the most geographically approximation (i.e a mean of those reported for Katwijk and Utrecht for Gouda; and a mean of hours of sun reported for Albacete and Madrid for Cuenca).

4.2.3 Statistical analyses

I calculated crude incidence rates per 100kpy with their 95% confidence intervals (95%CI) stratified by catchment areas; and overall incidence rates across sites by 5-year age-at-onset bands split by gender for each diagnostic category: Schizophrenia, Bipolar Disorder, Psychotic Depression and Psychosis NOS.

In a second step, I calculated the standardized adjusted incidence rate and ratios as follows. The standardised adjusted incidence rates (SAR) by both age and gender, and by age, gender and minority status were calculated using the number of cases per age, gender, and ethnic minority status band observed in each catchment area from our sample and applied to a standard population as population risk instead. I used the total population of England and Wales (2011 census (Office for National Statistics. Ethnic group by sex by age https://www.nomisweb.co.uk/census/2011/dc2101ew, no date)) as standard population. For obtaining the standardized incidence ratio (SIR), which is the ratio between the observed number of cases and the expected number of cases, we used the total sample of EUGEI stratified by age, gender and ethnic minority status to obtain global incidence rates. I then calculated expected number of cases in each

catchment area applying the calculated overall incidence rates. These were then used as denominator of observed cases to obtain the SIR.

Finally, I used multilevel random-effects Poisson regression to analyse the impact of latitude, population density, and annual hours of sunshine on one hand, and unemployment, owner-occupied housing, and single-person households on other hand in explaining variability of incidence across sites. Rates of unemployment, owner-occupied housing and single-person household were divided by 10 in order to represented associations per 10% increase. Regression analyses were controlled by age, gender, their intercept and minority status.

4.3 RESULTS

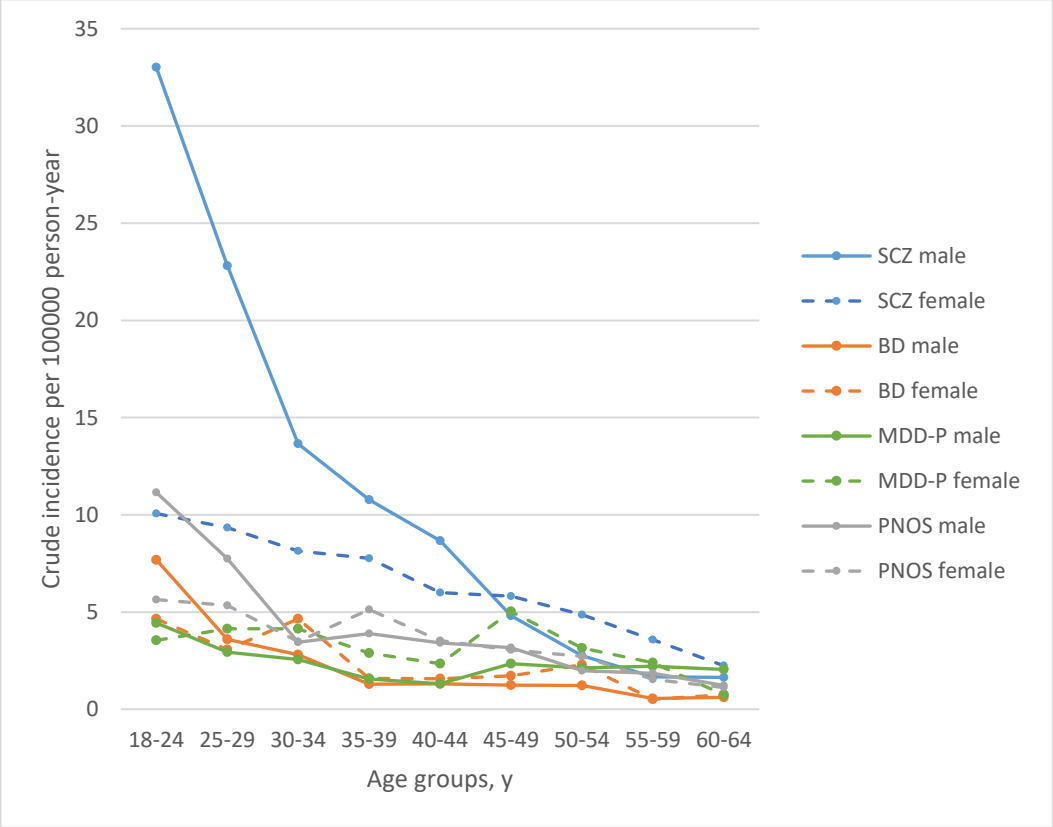
4.3.1 Crude incidence rates

Among the originally reported 2774 people presenting with a FEP disorder (Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Szöke, *et al.*, 2018), I identified 2480 individuals presenting with the diagnosis of interest; 1419 (57.2%) were male, and with a median age at first contact of 30 (interquartile range, 23-41 years). Among the 2480, 1244 (50%) were defined as having a diagnosis of SCZ, 324 (13%) of BD, 372 (15%) of MDD-P and 540 (22%) defined as PNOS, during 12.94 million person-years. These correspond to crude incidences of 9.61 (95% CI, 9.1 – 10.17) per 100kpy for SCZ; 2.51 (95% CI, 2.25 – 2.79) per 100kpy for BD; 2.87 (95% CI, 2.6 – 3.18) per 100kpy for MDD-P; and 4.17 (95% CI, 3.84 – 4.54) per 100kpy for PNOS. Information on overall psychosis incidence can be found in the original EUGEI paper on incidence of psychotic disorders (Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Cristofalo, *et al.*, 2018).

The age pattern of the incidence of SCZ varies between men and women. In both, the crude incidence rate of SCZ peaked between 18-24 years of age –y-, with female presenting around one third of the male's rate (33 per 100kpy; 95%CI 29.5-36.9 for male; and 10.1 per 100kpy; 95%CI 8.2-12.4 for women). From there, males rates decrease rapidly, being lower than female rates from 45-49y until 60-64y; the latter decreased more gradually. Regarding BD, whereas in men the peak also presented between 18-24y (7.7 per 100kpy; 95%CI 6.1-97), for women we can see a bimodal distribution, with one peaks between 18-24y (4.6 per 100kpy; 95%CI 3.4–6.3), and one between 30-34y (4.6 per 100kpy; 95%CI 3.4–6.4). The incidence of MDD-P

showed a small peak in men between the age of 18-24 (4.4 per 100kpy; 95%CI 3.3–6) and a gradual decrease with some fluctuations thereafter; and two peaks in women: a first one between the age of 25 and 34 of around 4.1 per 100kpy; 95% CI 2.9 – 5.9), and a second and higher peak between 45-49 y (5 per 100kpy; 95%CI 3.7–6.9). The crude incidence of PNOS resembled the trend of SCZ. For both men and women there was a peak between 18-24y (of 11.1 per 100kpy; 95%CI 9.2–13.5, and 5.6 per 100kpy; 95%CI 4.3–7.4 respectively), decreasing thereafter more rapidly for men, while women present a plateau until 35-39y. Age patterns by gender for the four conditions are presented in **Figure 4.4**.

Figure 4.4 Patterns of crude incidence rates for schizophrenia, bipolar disorder, psychotic depression and psychosis NOS across 5-year age group by gender.



4.3.2 Variation of incidence of Schizophrenia, Bipolar Disorder, Psychotic Depression, and Psychosis NOS by site and standardised by age, gender and ethnicity

We observed an 8-fold variation in the incidence of SCZ across our catchment areas, from 3.5 per 100kpy (95%CI 2.5 – 5.0) in Barcelona, to 26.8 per 100kpy (95%CI 21.3–33.8) in Paris. Both age-gender standardization and age-gender-ethnic minority status standardization had a negligible effect on this variation.

The incidence of BD across the catchment areas varied from 0.5 cases per 100kpy (95%CI 0.07-3.6) in Cuenca, Spain, to 7.9 per 100kpy (95%CI 5.9 – 10.9) in Creteil, France. After adjusting for age-gender and age-gender-ethnic minority status this variation did not show any remarkable effect. It is possible to observe a similar trend for the incidence of MDD-P across the catchment areas; with no cases reported in Cuenca, Spain, and the highest incidence of 7.2 per 100kpy (95%CI 5.2–10.0) in Creteil, France. Similarly, age-gender and age-gender-ethnic minority adjustment didn't modify main differences in rates across sites.

Lastly, the incidence of PNOS across the catchment areas varied from 0.6 per 100kpy (95%CI 0.4 – 1) in Ribeirao, Brazil, to 23.9 per 100kpy (95%CI 19.7–29.0) in Southeast London, England. Age-gender standardization had a negligible effect on this variation. Additional standardization for racial/ethnic minority status attenuated variance between sites; with the highest standardized incidence rates reducing to 16.1 per 100kpy (95%CI 12.0–20.3) in Southeast London. All crude and standardised incidence rates per site are shown in **Table 4.1** and **Figure 4.5**.

Table 4.1. Crude and adjusted Incidences of Schizophrenia, Bipolar Disorder, Psychotic Depression and Psychosis NOS by site.

SETTING	SCZ	95% CI	BD	95% CI	MDD-P	95% CI	PNOS	95% CI
London								
Crude	19.46	15.7-24.13	0.70	0.23-2.18	3.75	2.3-6.12	**23.92**	**19.7-29.04**
Sex-age adj	18.4	14.3-22.5	0.7	0.23-2.18	3.7	1.8-5.6	**23.4**	**18.7-28.1**
Sex-age-ethn adj	15.8	11.2-20.4	0.5	0.005-1	4.4	1.5-7.4	**16.1**	**12-20.3**
Cambridge								
Crude	8.49	7.16-10.07	2.12	1.51-2.99	3.80	2.94-4.9	1.09	0.68-1.76
Sex-age adj	8.5	7-10	2.12	1.51-2.99	3.7	2.8-4.7	1.1	0.6-1.6
Sex-age-ethn adj	8.5	7.1-10	2.1	1.4-2.8	3.7	2.7-4.6	1	0.5-1.5
Amsterdam								
Crude	20.45	17.18-24.33	4.35	2.98-6.34	2.09	1.22-3.6	17.23	14.25-20.82
Sex-age adj	20.2	16.7-23.7	4.35	2.98-6.34	2	0.9-3.2	17.4	14.1-20.7
Sex-age-ethn adj	15.6	12.3-18.9	4.2	2.6-5.8	1.9	0.7-3.2	13.9	10.7-17.2
Leiden								
Crude	10.56	8.5-13.13	2.61	1.68-4.04	3.26	2.2-4.83	4.04	2.84-5.75
Sex-age adj	11.8	9.2-14.4	2.61	1.68-4.04	3.4	2.1-4.8	4.6	3-6.3
Sex-age-ethn adj	12.2	9.4-15	2.7	1.5-4	3.7	2.1-5.2	5	3.1-6.8

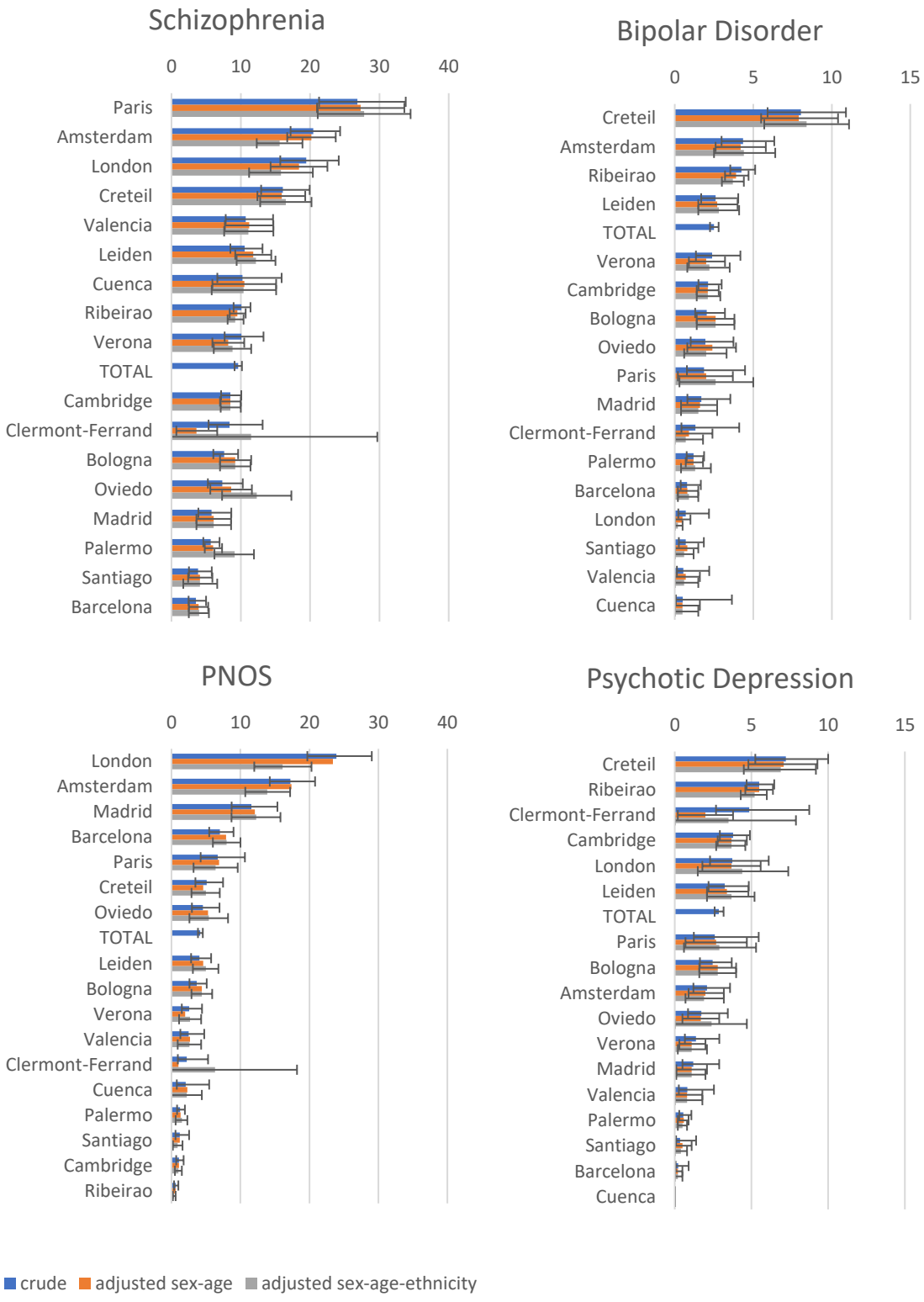
Madrid								
Crude	5.79	3.88-8.63	1.69	0.8-3.54	1.21	0.5-2.9	11.57	8.72-15.36
Sex-age adj	6.1	3.6-8.6	1.69	0.8-3.54	1.1	0.1-2.1	12.1	8.6-15.6
Sex-age-ethn adj	6.1	3.6-8.6	1.6	0.4-2.7	1.1	0.1-2	12.3	8.7-15.8
Barcelona								
Crude	3.51	2.47-4.99	0.79	0.38-1.66	0.23	0.06-0.9	7.01	5.47-9
Sex-age adj	3.9	2.5-5.3	0.79	0.38-1.66	0.2	0-0.5	7.9	5.9-9.9
Sex-age-ethn adj	4	2.5-5.4	0.8	0.2-1.5	0.2	0-0.5	8	6-10
Valencia								
Crude	10.71	7.82-14.66	0.55	0.14-2.2	0.82	0.27-2.55	2.47	1.29-4.75
Sex-age adj	11.2	7.7-14.7	0.55	0.14-2.2	0.8	0-1.8	2.7	0.9-4.5
Sex-age-ethn adj	11.1	7.6-14.7	0.7	0-1.6	0.8	0-1.8	2.6	0.9-4.3
Oviedo								
Crude	7.35	5.25-10.29	1.95	1.01-3.74	1.73	0.86-3.46	4.54	2.96-6.96
Sex-age adj	8.6	5.6-11.6	1.95	1.01-3.74	1.7	0.5-2.9	5.3	3-7.6
Sex-age-ethn adj	12.3	7.3-17.3	2.4	0.8-3.9	2.4	0-4.7	5.4	2.6-8.2
Santiago								
Crude	3.83	2.52-5.81	0.70	0.26-1.85	0.35	0.09-1.39	1.22	0.58-2.55
Sex-age adj	4.1	2.4-5.9	0.7	0.26-1.85	0.5	0-1.1	1.2	0.3-2.1
Sex-age-ethn adj	4.1	1.7-6.6	0.8	0-1.5	0.4	0-0.8	0.9	0.2-1.6
Cuenca								
Crude	10.25	6.61-15.89	0.51	0.07-3.64	0.00	0-0	2.05	0.77-5.46
Sex-age adj	10.5	5.9-15.1	0.51	0.07-3.64	0	0-0	2.3	0-4.5
Sex-age-ethn adj	10.4	5.8-15.1	0.5	0-1.6	0	0-0	2.2	0-4.4
Paris								
Crude	**26.83**	**21.3-33.8**	1.86	0.78-4.48	2.61	1.24-5.47	6.71	4.23-10.65
Sex-age adj	**27.3**	**21-33.6**	1.86	0.78-4.48	2.7	0.7-4.7	6.9	3.7-10.1
Sex-age-ethn adj	**27.8**	**21.1-34.5**	2	0.2-3.7	2.9	0.6-5.3	6.4	3.2-9.6
Creteil								
Crude	16.06	12.93-19.94	**8.03**	**5.91-10.9**	**7.25**	**5.25-10**	5.09	3.47-7.48
Sex-age adj	15.9	12.4-19.3	**8.03**	**5.91-10.9**	**7.1**	**4.8-9.3**	4.6	2.8-6.4
Sex-age-ethn adj	16.5	12.8-20.2	**7.9**	**5.5-10.4**	**6.9**	**4.5-9.2**	5	2.9-7
Clermont-Ferrand								
Crude	8.39	5.35-13.15	1.32	0.43-4.11	4.86	2.69-8.77	2.21	0.92-5.3
Sex-age adj	3.6	0.7-6.6	1.32	0.43-4.11	2	0.2-3.8	1	0-2.4
Sex-age-ethn adj	11.5	0-29.7	0.9	0-2.4	3.5	0-7.9	6.3	0-18.2
Bologna								
Crude	7.62	6.04-9.62	2.04	1.3-3.2	2.47	1.64-3.71	3.65	2.61-5.11
Sex-age adj	9.2	7-11.5	2.04	1.3-3.2	2.8	1.6-4	4.4	2.9-5.9
Sex-age-ethn adj	9.2	7-11.4	2.6	1.4-3.8	2.8	1.6-4	4.4	2.9-5.9

Verona								
Crude	10.09	7.67-13.28	2.37	1.35-4.18	1.38	0.66-2.9	2.57	1.49-4.43
Sex-age adj	8.2	5.9-10.5	2.37	1.35-4.18	1.1	0.3-2	2	0.9-3.1
Sex-age-ethn adj	8.8	6.1-11.5	2	0.9-3.2	1.1	0.2-2.1	2.7	1.1-4.3
Palermo								
Crude	5.64	4.59-6.94	1.19	0.76-1.87	0.56	0.29-1.08	1.25	0.81-1.94
Sex-age adj	6	4.8-7.3	1.19	0.76-1.87	0.6	0.2-0.9	1.3	0.7-1.9
Sex-age-ethn adj	9.1	6.2-11.9	1.2	0.7-1.8	0.5	0.2-0.8	1.5	0.6-2.3
Ribeirao								
Crude	10.11	8.96-11.4	4.26	3.54-5.12	5.51	4.68-6.48	0.61	0.37-0.99
Sex-age adj	9.5	8.4-10.7	4.26	3.54-5.12	5.5	4.6-6.4	0.6	0.3-0.8
Sex-age-ethn adj	9.2	8.1-10.4	3.9	3.2-4.7	5.2	4.3-6	0.4	0.2-0.6
total	**9.62**	**9.1-10.17**	**2.51**	**2.25-2.79**	**2.88**	**2.6-3.18**	**4.18**	**3.84-4.54**

4.3.3 Standardised Incidence Ratios

The standardised incidence ratios (SIR) reflect the perceptual representation of diagnoses between sites. It indicates the over/under-representability of diagnosis in reference with the overall incidences. Regarding SCZ, Paris has more than 2.5 times more incidence than the total incidence across all sites, with the rest of sites presenting representation of SCZ between around 0.5 in Barcelona and 1.7 in Amsterdam. For BD, Cretail shows a clear higher presence of BD diagnosis, with a SIR over three, while appearing underrepresented (up to 0.8) in London, Valencia and Cuenca. For MDD-P, Cretail shows the highest over-representability of more than twice more, followed by Clermont-Ferrand of over two; but with a similar under-representability in Barcelona, Santiago and Palermo. Lastly, I found that in London a diagnosis of PNOS was given more than 3.5 times than the overall incidence rate, followed by Amsterdam and Madrid, which also attributed 3 times more a diagnosis of PNOS.

Figure 4.5. Crude, Age- and Sex-Standardized and Age-, Sex-, and Race/Ethnicity-Standardized Incidence Rates per Catchment Area



PNOS: psychosis not otherwise specified

4.3.4 Variation of incidence across sites

Results confirmed substantial incidence variation between sites for SCZ (incidence rate ratio [IRR] of 0.24; 95%CI 0.11-0.51) and BD (IRR of 0.39; 95%CI 0.16-0.95) after controlling by sex, age, their intercept and ethnic minority, but no significant variation between catchment areas were observed for MDD-P or PNOS. Rates for all four clinical groups were higher in ethnic minority groups (with values between IRR of 1.41; 95%CI 1.11-1.78 for BD and 1.78; 95%CI 1.48-2.15 for PNOS) after multivariable adjustment for age, sex, their interaction, and the other catchment area–level characteristics of interest.

In univariate analyses, results show that greater unemployment rates are associated with lower incidence of BD (IRR for 10% increase 0.36; 95%CI 0.2-0.67) and MDD-P (IRR 0.21; 95%CI 0.11-0.43), While owner occupancy is associated with less incidence of SCZ (IRR for a 10% increase 0.77; 95%CI 0.67-0.89), MDD-P (IRR 0.71; 95%CI 0.54-0.95) and PNOS (IRR 0.65 95%CI 0.5-0.85); living alone presents positive association with higher incidence of SCZ (IRR for a 10% increase 1.43; 95%CI 1.00–2.02) and PNOS (IRR 2.16; 95%CI 0.50–0.85).

In multivariable analyses, as shown in **Table 4.2**, incidence of SCZ decrease with owner occupancy (IRR 0.81; 95%CI 0.71-0.91). Both incidences of BD (IRR 0.4; 95%CI 0.22-0.72) and MDD-P (IRR 0.23; 95%CI 0.12-0.45) are lower in those sites with higher unemployment. Lastly, while PNOS incidence is almost 3 times higher when higher unemployment is present (IRR per 10% increase 2.93; 95%CI 1.35-6.37), it decreases with more owner occupancy (IRR 0.56; 95%CI 0.42-0.73). No other setting-level variables, including single-person household, latitude, hours of sun or population density presented a remarkable influence of incidence rates across catchment areas.

Table 4.2. Univariate and Multivariate intercepts Poisson Regression

UNIVARIATE								
variables	SCZ	95%CI	BD	95%CI	MDD-P	95%CI	PNOS	95%CI
ethnicity	**1.73**	**1.53-1.95**	**1.51**	**1.19-1.92**	**1.58**	**1.27-1.97**	**1.92**	**1.59-2.31**
latitude	1.03	0.99-1.06	1.00	0.96-1.05	1.02	0.96-1.08	1.08	1.02-1.14
Pop density	**1.033**	**1.00-1.07**	0.98	0.94-1.03	0.99	0.94-1.05	1.05	0.99-1.11
unemployment	0.65	0.39-1.07	**0.36**	**0.2-0.67**	**0.21**	**0.11-0.43**	0.99	0.38-2.56
single-person household	**1.43**	**1.00-2.02**	1.2	0.76-2.03	1.55	0.83-2.88	**2.16**	**1.21-3.86**
owner occupancy	**0.77**	**0.67-0.89**	0.84	0.66-1.08	**0.71**	**0.54-0.95**	**0.65**	**0.50-0.85**
sunshine hours	**0.99**	**0.998-0.999**	0.99	0.998-1.00	0.998	0.998-0.999	0.999	0.998-1.00
MULTIVARIATE (adjusted by sex, age, their intercept, ethnicity and those significant factors with lower AIC adding individually to the rest)								
variables	SCZ[a]	95%CI	BD[b]	95%CI	MDD-P[b]	95%CI	PNOS[c]	95%CI
ethnicity	**1.58**	**1.40-1.79**	**1.41**	**1.11-1.78**	**1.54**	**1.24-1.92**	**1.78**	**1.48-2.15**
latitude	0.997	0.97-1.03	0.99	0.96-1.02	0.99	0.96-1.03	1.04	0.98-1.1
Pop density	1.02	0.99-1.04	0.98	0.95-1.02	0.99	0.95-1.03	1.01	0.96-1.05
unemployment	0.97	0.63-1.49	**0.4**	**0.22-0.72**	**0.23**	**0.12-0.45**	**2.93**	**1.35-6.37**
single-person household	1.01	0.67-1.52	0.93	0.62-1.4	0.86	0.56-1.3	1.85	0.93-3.69
owner occupancy	**0.81**	**0.71-0.91**	1.04	0.82-1.3	0.96	0.76-1.21	**0.56**	**0.42-0.73**
sunshine hours	0.99	0.99-1.001	1.00	0.99-1.00	0.99	0.998-1.00	1.00	0.99-1.00

SCZ: schizophrenia; BD: bipolar disorder; MDD-P: MDD with psychotic features; PNOS: psychosis not otherwise specified
a Adjusted for sex, age, their intercept, ethnicity and owner occupancy
b Adjusted for sex, age, their intercept, ethnicity and unemployment
c Adjusted for sex, age, their intercept, ethnicity, unemployment and owner occupancy

4.4 DISCUSSION

4.4.1 Main results and overview of findings

The global annual treated incidences across sixteen European sites and Brazil were of 9.61 per 100kpy for Schizophrenia; 2.51 for Bipolar Disorder; 2.87 for Psychotic Depression; and 4.17 for Psychosis NOS. These incidences were higher in males except for MDD-P, and consistently higher in ethnic minority groups. All four

diagnostic groups presented significant variability across sites, which were partly explained by material deprivation aspects (unemployment, owner occupancy) but also by social fragmentation indicators (single-person household).

4.4.2 Results into context

The calculated global incidence of SCZ of 9.61 is lower than previously reported (McGrath *et al.*, 2004a; Kirkbride *et al.*, 2012; Castillejos *et al.*, 2018). However, variability across sites shows that northern sites such as Paris and London, presenting the highest incidence rates around 20-26/100kpy, are in line with previous meta-analyses (Castillejos *et al.*, 2018); while those sites from Southern Europe countries, the ones are lower, show rates as low as 3.5-3.8 in Barcelona and Santiago. Whereas these numbers go in line with some previously reported incidences in Italy (Tarricone *et al.*, 2012; Lasalvia *et al.*, 2014; Mulè *et al.*, 2017), several incidence studies in other Southern countries such as Spain have been reported as having higher incidence rates of around 12.1 (Pelayo-Terán *et al.*, 2008) and up to 34.7 in Barcelona (Tizón *et al.*, 2007). Due to paucity of published incidence studies on these geographic locations, it is difficult to disentangle if the low rates I found in Spain are partly due to methodological differences.

Similarly, our total calculated incidence for BD and MDD-P are below previous reported incidences (Kirkbride *et al.*, 2012; Castillejos *et al.*, 2018). Again, this seem to be mainly driven by the lower rates reported in Southern Europe, where we can find similar rates for AP on the few published studies in these regions (Tarricone *et al.*, 2012; Lasalvia *et al.*, 2014). Nonetheless, a previous review on prevalence rather than incidence of BD, also showed varied rates across European countries with similar latitude distribution, ranging from 0.1–0.2% for two smaller Spanish studies to 1.8% in the Netherlands (Pini *et al.*, 2005). Overall, our lower reported global incidence may be due to the inclusion of wider range of population as opposed as those restricted to a narrower age range (15-54)(Jablensky *et al.*, 1992; Pelayo-Terán *et al.*, 2008); and can be also explained by the previously observed lower rates in first contact studies than in population registers (Jongsma *et al.*, 2019), that when considering psychosis specifically, are more likely to be affected by indirect factors such as appropriate infrastructure (i.e. availability of early intervention units)(Del-Ben *et al.*, 2019), and other forms of selection bias (expected to be higher in areas around academic centres, it requires that individuals can consent,…).

At individual-level data, incidence rates for SCZ and PNOS were higher in males than women and shows a peak at the earliest age group, which has been consistently reported for non-affective psychosis (Aleman *et al.*, 2003; McGrath *et al.*, 2004b). Moreover, incidence rates appear quite similar between gender for BD, but higher for females in MDD-P. These rates are also in line with literature showing not clear significant gender differences for BD rates (Kennedy, Noel *et al.*, 2005; Kroon *et al.*, 2013), but higher female rates for both MDD-P (Jääskeläinen, Juola, Hirvonen, McGrath, *et al.*, 2013) and overall AP (Castillejos *et al.*, 2018). In terms of age distribution, I observed a bimodal distribution for BD on females with a peak between 18-24 and a later one between 30-34, which has been previously described (Kennedy, N. *et al.*, 2005; Leboyer *et al.*, 2005; Ortiz *et al.*, 2011; Kroon *et al.*, 2013; Manchia *et al.*, 2017); and a late peak of incidence with a much evenly distribution across lifespan for MDD-P, as previously observed (Owoeye *et al.*, 2013). These differences in distribution across the lifespan can reflect differential etiopathogenic pathways with some gender specifity, which can ultimately inform about the etiology of these disorders.

Belonging to an ethnic minority increased the risk of any of the psychotic groups in my sample, with the largest effect for non-affective psychosis (SCZ and PNOS), which goes in line with literature (Kirkbride *et al.*, 2012; Jääskeläinen, Juola, Hirvonen, Mcgrath, *et al.*, 2013; Kroon *et al.*, 2013). This seem to be particularly true for black minority groups (Black African and Black Caribbean) and non-affective psychosis, with most research conducted in Northern Europe (Morgan *et al.*, 2019). Given previous evidence of an underdiagnosis of unipolar depression in African and Afro-caribbean population in UK (Kirov and Murray, 1999), and recent research showing a misdiagnosis of BD in favour of SCZ in African population (Akinhanmi *et al.*, 2018), it may be possible that the observed effect of ethnic minority is underestimated for MDD-P and BD. However, the broad non-white versus native groups presented, prevent us from analysing specific effect of ethnic groups with the different disorders; and in replicating findings of association with Black minorities in Southern Europe sites, which calls for further research to be conducted covering these gaps. Nonetheless, the associations of our broad non-white group with all diagnostic groups talks in favour of common sources of stress on members of ethnic minorities, which can be associated with other important determinants such as

sociocultural adjustment, impact of migration and social context and experiences(Morgan *et al.*, 2019).

At a catchment area level, it is of note that despite the observed disparity between northern and southern sites rates for all diagnostic groups, I did not observe a significant effect of latitude in Poisson regression. This could be explained by concurrent factors differing across these north-south distribution acting as confounders, such as cultural, socio-economic or climate/environmental operators.

A null effect for all psychotic groups was also found for urbanicity measured by population density, except for a trend association with SCZ that disappeared in the adjusted model. This contrast with the consistently reported higher risk of SCZ and other non-affective psychosis in urban environments (Kirkbride *et al.*, 2012; Vassos *et al.*, 2012). Considering that urbanicity has been also defined based on a cut-off threshold on the total population, a potential reason of a lack of association in our results is that even the lowest densely populated (Cuenca, 16p/100km2) fell into the country definition of urban area based on population size (Cuenca, Spain; considered "urban" all municipalities with 10,000 inhabitants or more.) (United Nations, Department of Economic and Social Affairs, 2018). This would imply our observed null effects might be due to either a ceiling effect across our sites or because differences on levels of urbanicity are too narrow to be captured by our analyses. Regarding AP, literature is more ambiguous, as seen in a previous meta-analyses based on studies in England or both groups of affective psychosis (Kirkbride *et al.*, 2012), and as further shown by Kroon 2013, where they failed to find incidence differences in urban and non-urban areas for different BD subtypes (Kroon *et al.*, 2013). Nonetheless, contrary to former studies and my results, a recent study found an association or urbanicity at birth with most of psychiatric disorders – including BD (Vassos *et al.*, 2016). This discrepancy between current or at birth urbanicity calls for further research to identify those factors operating differently for affective and non-affective psychosis behind current or at birth urbanicity.

Differential effects were observed for the explored socioeconomic indicators. When looking at them independently, living alone appeared as a factor associated with higher rates for non-affective psychosis (both SCZ and PNOS), but when including the different factors in the same model, owner-occupancy was the sole factor explaining setting variation, showing a negative association with both disorders,

which could reflect protective effect of a better socioeconomic position or greater social cohesiveness. Regarding AP, unemployment is associated with lower incidence of both BD and MDD-P, which is an unexpected result that would require replication.

4.4.3 Strengths and limitations

The interpretation of results should be made in the context of some strengths and limitations. The present study relies on a large sample size across 17 different settings, with great attention to cohesiveness on methodology through shared training manuals, face-to-face training sessions, regular online meeting and interrater reliability protocols. Being the diagnostic categories the main outcome, I have based most of the diagnoses on a standardised assessment of psychopathology through OPCRIT, which has shown good levels of reliability between different geographical locations (Williams *et al.*, 1996); and which has been previously suggested to improve clinical diagnostic validity (Brittain *et al.*, 2013). Since my main aim was to update literature on BD and MDD-P as traditionally under-studied entities, this is of special relevance as in one study MDD-P was observed to be misdiagnosed in clinical settings for up to 27% of cases (Rothschild *et al.*, 2008). Although we relied on clinical diagnoses in a small percentage of patients, this did not alter our findings.

A number of limitations should be acknowledged. First, this is a first contact incidence study. Given the known issue of those patients that will not attend to services, it should be interpreted as treated incidence rather that general incidence. In line with this, the multicentric nature of the study design might have implied differences in either service use (patients from some sites may rely more on private settings), availability of specialised services (such as early psychosis services), administrative health/civic information systems or cultural differences which may have ultimately influenced ascertainment capacity on one hand and may had an effect on how clinical notes were recorded from where diagnoses were derived on the other hand. Third, targeting FEP means that diagnostic instability in the early course of disorder should be accounted for (Heslin *et al.*, 2016), with shifts in diagnoses occurring predominantly from affective to non-affective psychosis in a frequency of around 14-29% after two years (Schwartz *et al.*, 2000; Veen *et al.*, 2004). Fourth, due to availability of data I needed to add a disparity of the diagnosis

input for one of the sites (London, based on ICD-10 primarily), which may influence slightly the results. Five, I have employed a binary variable to divide native vs ethnic minority group, which based on each countries definition, and translates to "non-white" for most cases. Therefore, our results don't account for observed disparities on different ethnicities (Morgan *et al.*, 2019), and the particular effect of being first or second generation migrant, although recent evidence on the latter failed to support differential effect on psychosis (Selten *et al.*, 2019). Sixth, despite being an international multisite study, 16 out of 17 sites are in Europe, which makes it a homogeneous population and prevent our results to be generalizable to developing countries. For instance, urban living has recently failed to be associated with psychosis risk in developing countries, which suggests that the effects of other factors such as cannabis use, racial discrimination, and socioeconomic disparities may also differ between developing and developed countries (DeVylder *et al.*, 2018). Hence, we cannot make inferences about less urbanized or developing countries. Lastly, despite controlling for some sociodemographic individual and site-level factors, I was not able to account other putative recognised risk factors such as cannabis use, childhood adversity, urban birth or parental mental history, as these normally are not available at denominator level.

4.4.4 Conclusions

In this international multisite study of treated incidence of psychotic disorders I observed significant variability across sites, of around 8-fold for schizophrenia, over 15-fold for Bipolar Disorder, 30-fold for Psychotic depression and 40-fold for psychosis NOS after standardization for age, gender and ethnic minority. Rates of schizophrenia and psychosis NOS are higher in males with a clear peak on younger ages, while Bipolar Disorder and Psychotic Depression are more frequent in women presenting a bimodal peak for the former and more clear later peak on the later. This calls for revising the generalised age-limit inclusion criteria in early psychosis services for women affected from affective psychosis. Despite some material deprivation aspects (unemployment, owner occupancy) accounts for part of the differences across sites, significant variation of incident rates warrants further research to be conducted.

5. STUDY 2. USE OF MULTIPLE POLYGENIC RISK SCORES FOR DISTINGUISHING NON-AFFECTIVE PSYCHOSIS AND AFFECTIVE PSYCHOSIS CATEGORIES IN A FIRST EPISODE SAMPLE; THE EUGEI STUDY.

This chapter has been adapted from the following paper, currently in submission:

Rodriguez V, Alameda L, Quattrone D, Tripoli G, Gayer-Anderson C, Spinazzola E, Trotta G, Jongsma HE, Stilo S, La Cascia C, Ferraro L, La Barbera D, Lasalvia A, Tosato S, Tarricone I, Bonora E, Jamain, S, Selten JP, Velthorst E, de Haan L, Llorca PM, Arrojo M, Bobes J, Bernardo M, Arango C, Kirkbride J, Jones PB, Rutten BP, Richards A, Sham P, O'Donovan MC, Van Os J, Morgan C, Di Forti M, Murray RM, Vassos E*. Use of multiple Polygenic Risk Scores for distinguishing Non-affective psychosis and Affective psychosis categories in a First Episode sample; the EUGEI study,* ***in submission****. [Available as preprint in medRxiv]*

The paper Supplementary material will be attached in Appendix 2.2.

**Please note that in the submission and preprint the term "NAP" (non-affective psychosis) has been substituted by the term "SSD" (schizophrenia spectrum disorder) to represent the same subgroup of disorders.*

5.1 INTRODUCTION

More than 100 years have passed since Kraepelin established the dichotomy of manic-depression and dementia praecox as the two fundamental pillars of psychotic illness, which still constitutes the basis of current diagnostic criteria (Kraepelin, 1899). However, it is a matter of debate whether Schizophrenia (SCZ) and Bipolar Disorder (BD) are discrete illnesses or conditions which are part of an overall conceptual continuum (Murray *et al.*, 2004; Craddock and Owen, 2010; Demjaha *et al.*, 2012). Given the high heritability of these disorders (Smoller *et al.*, 2019), genetic tools can be used to dissect possible biological differences between these diagnostic categories.

Genome Wide Association Studies (GWAS) have shown that, as with other psychiatric conditions, many hundreds or thousands of common alleles influence susceptibility to SCZ and BD (Ripke *et al.*, 2013; Stahl *et al.*, 2019). We can calculate individual polygenic risk scores (PRS) based on the summation of the carried risk of single nucleotide polymorphisms (SNPs) selected in a discovery GWAS according to their *p*-value, weighted by their effect size (Purcell *et al.*, 2009; Dudbridge, 2013). GWAS analyses by the Psychiatric Genomics Consortium (PGC) have estimated liability–based SNP-heritability for SCZ, BD and Major Depressive Disorder (MDD) as about 22.2% (Ripke, Neale, Benjamin M, *et al.*, 2014), 18.2% (Stahl *et al.*, 2019), and 8.5% (Wray *et al.*, 2018) respectively in case–control samples.

In line with previous family and twin studies (Cardno *et al.*, 2002; Craddock and Owen, 2005; Cardno and Owen, 2014), GWAS findings have also supported the notion of genetic overlap among severe mental disorders. A study from the Cross-Disorder Group of PGC (Lee *et al.*, 2019) showed genetic correlation using common SNPs, of around 0.70 between SCZ and BD, 0.34 between SCZ and MDD, and 0.36 between BD and MDD.

On the other hand, some studies provide support for a link between genetic predisposition and current diagnostic categories. A study investigating diagnostic subcategories across the psychosis spectrum employing PRS for SCZ and BD (PRS-SZ and PRS-BD) (Tesli *et al.*, 2014) provided some validation for the existence of subcategories across the SCZ and BD continuum. In line with this, in a more recent study, PRS-SZ discriminated SCZ from BD; and within BD subtypes, between those with and without psychosis (Allardyce *et al.*, 2017). Moreover, Markota et al.

(Markota *et al.*, 2018), found that PRS-SZ seemed to be more closely related with Bipolar Disorder type I (BD-I) with psychotic symptoms during manic phases as compared with BD-I with psychotic symptoms during depressive episodes or presenting without psychosis. Taken together, these findings shed light on the genetic architecture of these severe mental disorders and support the discriminability potential of the polygenic score on diagnostic categories.

Despite this evidence, most studies have only tested the association between PRS-SZ and PRS-BD with their respective diagnostic categories. To the best of our knowledge, only one study has previously examined the relationship between diagnostic categories by employing three polygenic scores, specifically PRS-SZ, PRS-BD and PRS-MDD (Charney *et al.*, 2017), but only examined cases within the BD spectrum. They found a PRS-SZ gradient among affective psychotic categories, with the highest association being schizoaffective followed by BD-I and BD type II (BD-II).

Consistent evidence suggests that cognitive deficits can be considered a core feature for schizophrenia (Green, 2006). It has been long accepted that subjects affected by SCZ perform worse than those with BD on a variety of cognitive domains (Goldberg, 1999; Zanelli *et al.*, 2010), which seems to be validated by a meta-analysis showing that subjects with BD show better cognitive performance than those with SCZ (Krabbendam *et al.*, 2005). Although there remains debate over the extent to which these differences in cognition predate or follow the onset of psychosis (Trotta *et al.*, 2015), it suggests the hypothesis that PRS for measures of cognitive ability including intelligence may be informative for studying genetic differences between these subgroups of patients.

Given the above, the current study aims to explore the potential of joint modelling PRS from three major mental disorders (SCZ, BD, D) and intelligence quotient (IQ) for firstly, analysing the distribution of genetic load of major psychiatric disorders across the diagnostic categories under the psychosis umbrella, thus helping us understand whether current diagnoses represent different genetic subgroups; and secondly, exploring the potential use of PRSs in discriminating affective psychosis (AP) from non-affective psychosis (NAP). We built on a previous study from South London, where it was shown that PRS-SZ differentiated schizophrenia from other psychoses (Vassos *et al.*, 2017). In a time of growing interest in employing PRS as a tool for validating phenotypes or diagnosis, we aim to explore the potential of joint

modelling PRS in discriminating AP from NAP, hypothesizing that PRS can be used to distinguish between diagnostic categories.

5.2 METHODS

5.2.1 Sample

The present study is based on the case-control sample from the EUGEI 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 (Gayer-Anderson *et al.*, 2020).

The baseline sample comprises a total of 2627 participants, including 1130 patients aged 18 to 64 years who were resident within the study areas and presented to the adult psychiatric services between May 1, 2010 and April 1, 2015 in 17 sites across 6 countries: England, the Netherlands, Italy, France, Spain and Brazil. All participants provided informed, written consent. Ethical approval was provided by relevant research ethics committees in each of the study sites. All data was stored anonymously.

Cases were selected if they were experiencing their first episode of psychosis (FEP) including SCZ and related psychosis, BD and Major Depression Disorder with Psychotic features (MDD-P). In addition, 1497 unaffected screened controls with no lifetime psychotic disorder were also recruited in the areas served by the services with a quota sampling approach, a non-probability sampling method in which a specific subgroup is chosen in order to represent the local population. Further information about the methodology of the study is available on the EU-GEI website (www.eu-gei.eu/) and can be found in previous publications (Jongsma, Gayer-Anderson, Lasalvia, Quattrone, Mulè, Szöke, *et al.*, 2018; Quattrone *et al.*, 2018; Di Forti *et al.*, 2019; Gayer-Anderson *et al.*, 2020).

One of the problems when using current PRS is the limited predictive power in multi-ethnic samples as they have derived from mostly European samples (Curtis, 2018). This has been shown in a previous study on FEP patients (Vassos *et al.*, 2017), where PRS_SZ had much lower predictive power in African ancestry population. Given the wide variance across ancestral groups, for the scope of the present study we constrained the sample to those categorised as of European

ancestry based on a Principal Component Analysis (details provided in *Supplementary Material*). Characteristics of the final sample are summarised in **Table 5.1**.

5.2.2 Measures

5.2.2.1 Diagnosis

We used DSM-IV diagnosis (American Psychiatric Association, 1994) from interviews and mental health records utilizing the Operational Criteria Checklist (OPCRIT) at baseline (McGuffin *et al.*, 1991) by centrally trained investigators, whose reliability was assessed throughout the study ($\kappa = 0.7$). These diagnoses were grouped into: non-affective psychosis group (NAP -codes 295.1-295.9 and 297.1-298.9 -) or affective psychosis group (herein called AP -patients diagnosed with codes 296-296.9), which was later stratified into BD (codes 296.0-296.06 and 296.4-296.89) and MDD with psychotic features (MDD-P – codes 296.2-296.36-). For those subjects with missing information for DSM-IV output from OPCRIT, we reconverted ICD-10 diagnosis (n=5) into DSM-IV codes; leaving eventually diagnostic data for 12 cases missing. Those who did not meet criteria from OPCRIT (i.e. undefined diagnosis) were not grouped into either of the groups (n=52) and were excluded from further analyses.

5.2.2.2 Genotyping and Polygenic risk scores building

DNA from blood tests or saliva sample were obtained from the majority of participants at baseline (73.6% of cases and 78.5% of controls), with no sociodemographic differences observed with those without genetic data except for minor age differences (please refer to the *Supplementary material* section1.7). All DNA data collected was genotyped at the Cardiff University Institute of Psychological Medicine and Clinical Neurology, using a custom Illumina HumanCoreExome-24 BeadChip genotyping array covering 570,038 genetic variants; and quality control was performed locally (details provided in *Supplementary material*).

In order to control for population stratification, a Principal Component Analysis generating 10 principal components (PC) was run on pruned variants. After quality control of genetic and clinical data, and selection of individuals of European ancestry

(details provided in *Supplementary material*), the genetic analyses included 573 cases (409 NAP, 74 BD and 90 MDD-P patients) and 1005 controls.

The measure of the aggregate genetic load is based on polygenic risk score, which is an individual quantitative risk factor calculated from the weighted summation of the odds ratios of carried risk alleles taken from a discovery sample. It is represented by the following equation (Evans *et al.*, 2009):

$$PRS = \sum xi * log(ORi)$$

where x is the number of risk alleles of each included variant (i) and OR the respective odds ratio. To build the PRSs, results from the latest available GWAS which did not include the current EUGEI sample, were used as discovery samples. In the case of SCZ and BD, these were derived from the last mega-analyses of the PGC (Ripke, Neale, Benjamin M, *et al.*, 2014; Stahl *et al.*, 2019). Depression PRS was built from a GWAS combining PGC, 23andMe and UK Biobank (Ripke, Neale, Benjamin M, *et al.*, 2014; Howard *et al.*, 2019; Stahl *et al.*, 2019). Finally, we further included the recently developed PRS for IQ (Savage *et al.*, 2018). All PRS were built using PRSice software (Choi and O'Reilly, 2019) , and the selected p-value threshold of 0.05 for SNP inclusion was chosen across the phenotypes on the basis of the published literature explaining the most variance in case-control analysis (Stahl *et al.*, 2019; Savage *et al.*, 2018; Wray *et al.*, 2018; Howard *et al.*, 2019). Each PRS was standardized to a mean of zero and standard deviation of 1 (Lewis and Vassos, 2017).

5.2.3 Statistical analyses

5.2.3.1 Descriptive statistics

Normality of all variables was assessed computing Shapiro-Wilk normality test. The comparisons between cases and controls and between AP and NAP cases were made using chi-square, t-test or Wilcoxon-Mann-Whitney tests when appropriate. Effect sizes were calculated for all the statistical tests using Cohen's d for t-test and Cramer's V (Φc) for chi-square. When Mann-Whitney test was used, effect sizes were calculated from z values.

5.2.3.2 Association analyses

We first analysed PRSs association with broad clinical groups (NAP, AP) compared with controls; and in a second step in a case-only analysis we measured discrimination ability of PRSs between AP categories (BD and MDD-P) and NAP as reference group. For this, we built a series of multinomial or simple logistic regression models in which we included the three disorder PRSs (PRS-SZ, PRS-BD, PRS-D) plus PRS-IQ as independent variables while controlling for population stratification using as confounders the 10 PC and each sample site. Due to the inclusion of the four PRSs in the models, we adjusted the significance level as per Bonferroni's correction (Bland and Altman, 1995), with a new established significance level at $p<0.0125$. Results will be presented in OR, 95% confidence intervals (CI) and p-value. We conducted power calculation analyses utilising the R-package AVENGEME (Dudbridge, 2013), which allows power calculation for PRS analyses. We calculated the required SNP-h^2 or fix covariance in our target sample to obtain 80% of power on each regression model and per each PRS (SZ, BD and D).

5.2.3.3 Fitness of model for NAP and AP discrimination

As a secondary analysis we explored goodness of fit of data of the joint use of PRSs. We built a series of logistic regression models to test discriminability between AP and NAP in which we sequentially added one PRS at a time in order to identify those PRS adding significant value to the discriminability between the clinical groups by comparing models through likelihood ratio test (see *Supplementary material* for more details).

5.3 RESULTS

5.3.1 Socio-demographics

Socio-demographics of the case-control sample are shown in **Table 5.1**, comparing NAP (n=409) and AP (n=164) with controls (n=1005) separately. Compared with controls, patients were younger (mean age of 31.6, SD=10.91 and 32.84, SD=11.56 in NAP and AP respectively; 36.9, SD=13 in controls); and a greater proportion of patients with NAP were men (68% vs 47%). Both NAP and AP were less likely to have received tertiary education and consequently reported fewer total years of education than controls (around over 12.5 years in cases and around 14.7 years for controls). Generally, cases were more likely not to be in a relationship and not to live

independently. More NAP patients were unemployed, but no differences between AP and controls were found.

Table 5.1. Sociodemographic of white subsample (n=1659), case-control comparisons.

DESCRIPTIVE AT BASELINE	Number (%)/ Mean(SD)		Statistics		Number (%)/ Mean(SD)	Statistics	
	Control n= 1005	Non-affective psychosis n= 409	Tests (df)	p value	Affective psychosis n= 164	Tests (df)	p value
Gender			X^2 (1)=50.54	<0.001		X^2(1)=0.67	0.413
Male	474 (47.2)	278 (68)			83 (50.6)		
Female	531 (52.8)	131 (32)			81 (49.4)		
Age (years)	36.9 (13)	31.63 (10.92)	Z=7.21	<0.001	32.84 (11.56)	Z=-3.76	<0.001
EVER USED CANNABIS			X^2 (1)=40.26	<0.001		X^2(1)=15.9	<0.001
No	528 (53)	136 (34.2)			58 (36)		
Yes	469 (47)	262 (65.8)			103 (64)		
EDUCATION LEVEL			X^2 (2)=81.22	<0.001			
No qualification	40 (4)	65 (16.1)			25 (15.3)	X^2 (2)=51.64	<0.001
School education	416 (41.5)	197 (48.6)			87 (53.4)		
Tertiary education	546 (54.5)	143 (35.3)		<0.001	51 (31.3)		<0.001
YEARS IN EDUCATION	14.69 (4.19)	12.94 (4.12)	Z=7.07		12.58 (3.84)	Z=5.92	
SOCIAL FUNCTIONING							
Employment status			X^2 (1)=25.26	<0.001		X^2 (1)=0.48	0.487
Employed	615 (61.6)	141 (45.5)			79 (58.5)		
Unemployed	383 (38.4)	169 (54.5)			56 (41.5)		0.001
Marital status			X^2 (1)=126.23	<0.001		X^2 (1)=11.42	
Steady relationship	626 (62.4)	105 (28.3)			74 (48.1)		
No relationship	378 (37.7)	266 (71.7)			80 (52)		0.001
Living arrangements			X^2 (1)=96.98	<0.001		X^2 (1)=11.85	
Independent living	683 (68.5)	119 (37.5)			73 (53.7)		
No independent living	314 (31.5)	198 (62.5)			63 (46.3)		

SD: standard deviation; df: degrees of freedom

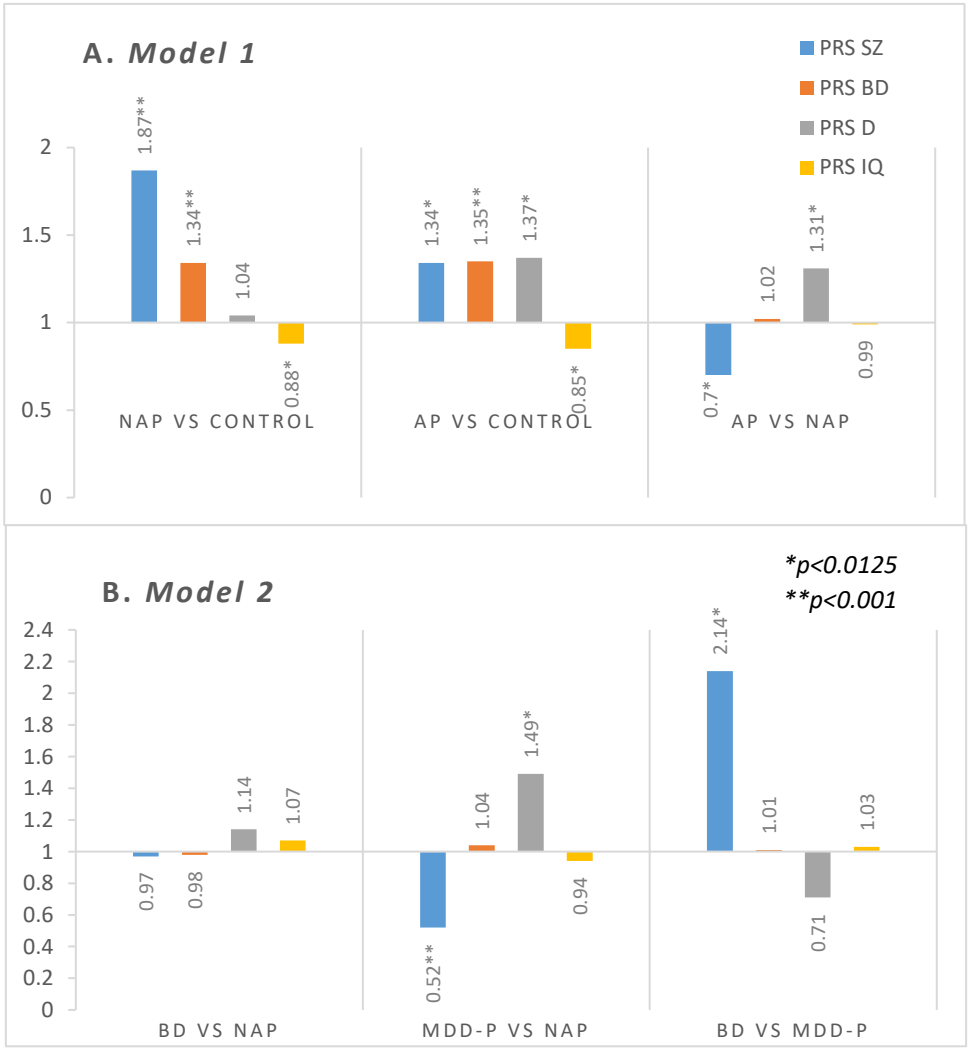
5.3.2 PRS distribution in different clinical subgroups (model 1)

The first multinomial logistic regression model showed that higher scores on both PRS-SZ and PRS-BD were associated with NAP (OR=1.87, 95%CI 1.57-2.2, p<0.001 and OR=1.34, 95%CI 1.15-1.57, p<0.001 respectively), whereas positive associations with AP were found for PRS-BD and PRS-D (OR=1.35, 95%CI 1.09-1.67, p=0.006 and OR=1.37, 95%CI 1.14-1.64, p=0.001 respectively) compared with controls. These effects are shown in **Figure 5.1** with additional details given in *Supplementary Material* (***eTable5.4***).

In the direct comparison between AP and NAP, both PRS-SZ and PRS-D were significantly associated with these diagnoses but in opposite directions. Whereas PRS-D (OR=1.31, 95%CI 1.06-1.61, p=0.011) was associated with increased risk of AP compared with NAP, the opposite was observed for PRS-SZ (OR=0.7, 95%CI 0.54-0.92, p=0.010). Hence, individuals with high PRS-SZ and low PRS-D have more

chances of receiving diagnosis of NAP, while low PRS-SZ and high PRS-D increases the chances of AP (**Figure 5.2**).

Figure 5.1. PRS performance for identifying clinical subgroups and categories based on DSM-IV OPCRIT



*Results of OR from joint model with all PRSs, adjusted by 10PCs and site. SZ: schizophrenia; BD: bipolar disorder; D: depression; IQ: intelligence quotient; NAD: non-affective psychosis; AP: affective psychosis; MDD-P: psychotic depression. *p<0.0125 **p<0.001*

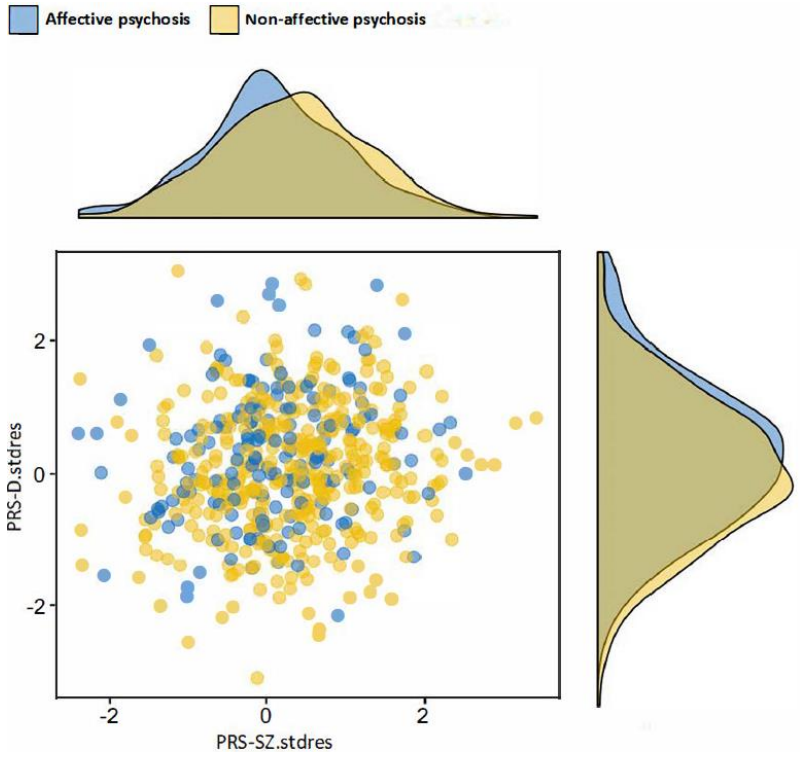
5.3.3 PRS distribution between diagnostic categories within psychosis (model 2)

In model 2 we tested whether PRSs could differentiate individual diagnostic categories included in AP (BD and MDD-P) from the broad group of NAP. As shown in **Figure 5.1 (B)**, no PRS was able to distinguish BD when compared with NAP. Nonetheless, the patterns for NAP and MDD-P diagnoses followed those observed above for NAP and broader AP comparisons. Thus, NAP and MDD-P diagnoses were

differentiated by both PRS-SZ (OR=0.52, 95%CI 0.37-0.74, p=0.011) and PRS-D (OR=1.49, 95%CI 1.14-1.94, p=0.003) in the opposite direction. Further details are given in *Supplementary Material* (***eTable5.5***),

When running simple logistic regression for discriminability between BD and MDD-P, only PRS-SZ could discriminate people diagnosed with BD from those diagnosed with MDD-P (OR=2.14, 95%CI 1.23-3.74, p=0.007) showing a positive association with the former.

Figure 5.2. PRS-SZ and PRS-D distribution in cases with NAP and AP diagnosis



Scatterplot and density distributions of PRS-SZ and PRS-D in AP and NAP. Residuals of polygenic scores converted into z-score after adjustment for principal components and sites. Higher PRS-SZ increases the chances of NAP, while higher PRS-D increases the chances on affective psychosis

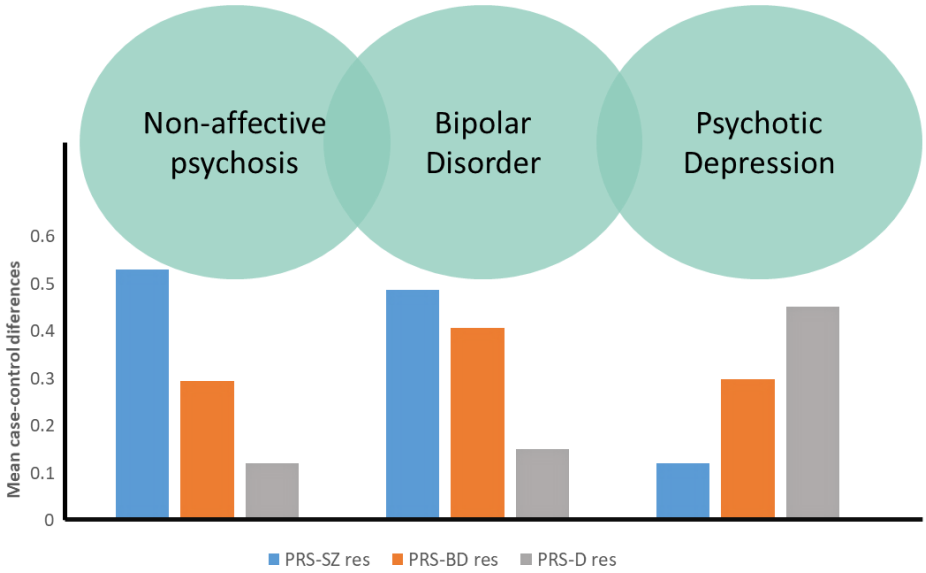
5.3.4 Fitting the model optimising PRS for NAP and AP discrimination

In order to test which combination of PRSs better differentiated NAP and AP as our main outcome, we built a series of regression models sequentially including the four PRSs variables, once at a time. The best fitting data as per likelihood ratio test was by adding PRS-SZ and PRS-D to the model ($\Delta\chi^2(1) = 6.74$, p=0.0094) when compared with a model using only PRS-SZ. No further addition of PRS-BD or PRS-IQ improved the discrimination between clinical categories. Further details are provided in *Supplementary Material* (***eFigure.5.4***)

5.4 DISCUSSION

To the best of our knowledge, this is the largest multisite international case-control study to examine joint polygenic associations with specific diagnostic categories in FEP patients. Our results provide evidence to support an inverse gradient of PRS-SZ and PRS-D across diagnostic categories in the psychosis spectrum, as illustrated in **Figure 5.3**; while they also show a discriminability potential to distinguish NAP from AP, especially from MDD-P. No PRS was able to distinguish BD from SCZ in this sample, while PRS-SZ was the only factor which distinguished BD from MDD-P. Moreover, we found that combining PRS for different disorders improves the prediction model for psychosis-related phenotypes while increasing our understanding of these phenotypes.

Figure 5.3. Visual representation of PRSs distribution across diagnosis categories



Conceptual multidimensional distribution of SNPs for Schizophrenia, Bipolar Disorder and Depression across clinical groups. Based on mean case-control differences, using control as reference of Standardised Residuals of PRS for SZ, BD and D adjusted by 10PC and site.

5.4.1 Interpretation of findings and comparison with other studies

The observed PRS-SZ associations which followed a gradient from Non-affective psychosis to affective diagnosis categories (NAP>BD>MDD-P), are in line with the notion of a psychosis continuum across psychosis diagnostic categories and the observed genetic overlap between disorders (Cardno and Owen, 2014). Other studies have previously shown a similar PRS-SZ gradient (SCZ>BD type I>BD type II) (Allardyce *et al.*, 2017; Charney *et al.*, 2017). However, PRS-SZ could not

differentiate MDD-P from controls in our study. In a recent study, PRS-SZ seems to be specially associated with those presenting psychotic features in the mania phase when compared with the depressive pole (Markota *et al.*, 2018), which could explain our lack of association with MDD-P.

Previous research showed evidence of PRS for MDD discriminate cases with depression from controls (Wray *et al.*, 2018). Moreover, PRS for MDD failed to identify diagnostic subtypes in some case-only comparisons in bipolar disorder (Charney *et al.*, 2017), but seemed to be significantly associated with schizoaffective disorder depressed subtype when compared with schizophrenia cases (Dennison *et al.*, 2020). In our study, PRS-D differentiated MDD-P from both controls and NAP, showing similar effect sizes as PRS-SZ in opposite direction. The discriminability potential of PRS-D in our sample may be due to the increased variance explained when selecting more severe patients with MDD (Verduijn *et al.*, 2017) – only with psychotic features in our case -; the use of more powerful PRS-D built from PGC, UK Biobank and 23andMe data (Howard *et al.*, 2019); or that MDD-P may be phenomenologically different to MDD without psychosis.

In relation to our second aim (ie. whether we could use PRSs in order to distinguish between affective vs schizophrenia spectrum disorder subgroups), both PRS-SZ and PRS-D differentiated global AP from NAP, and the subtype of MDD-P against NAP. Nonetheless, when trying to differentiate the categories of BD and NAP, all PRSs failed to differentiate between them. This may indicate the large genetic correlation between the two disorders, that may only be present to a lesser extent in depressive patients with psychotic features. Indeed, PRS-SZ was also able to distinguish BD from MDD-P, supporting the notion of lower common genetic liability for schizophrenia in those suffering with psychotic depression than in those with bipolar disorder.

These results shed new light on the existence of yet unclear and blurred genetic boundaries between current diagnosis categories. Beyond the evidence of a gradient for risk of psychosis associated with PRS-SZ from NAP to the AP group, we could also observe an inverse gradient in the case of PRS-D. This allows the conceptualization of a model in which the genetic vulnerability of psychotic disorders is distributed across a multidimensional continuum with NAP at one end, BD in the middle and MDD-P at the other extreme (**Figure 5.2**). Among these

groups, only the categories in the extremes were able to be differentiated by current polygenic scores. Further studies with larger samples or when the predictive power by PRSs increase, will allow further discrimination between categories, for example between SCZ and BP or between BP and MDD-P.

We failed to observe differences in PRS-IQ distribution, although it should be noted the effect sizes are almost identical across clinical groups. Among AP, BD has been more widely compared with SCZ as the paradigm disorder within NAP. We know from previous studies that patients with BD tend to present less cognitive impairment than those with SCZ (Murray *et al.*, 2004; Demjaha *et al.*, 2017), but this difference seems to be less clear between individuals with SCZ and BD patients with a history of psychotic symptoms (Hill *et al.*, 2007). Indeed, and in line with this, PRS-IQ showed no statistically significant differences within the case-only comparisons. However, the lack of discriminability potential of PRS-IQ would also be expected under the consideration that some cognitive changes are due to factors associated with the prodromal phase, the onset of the disorder or its treatment, rather than purely being neurodevelopmental, which is yet to be established.

5.4.2 Strengths and limitations

These results should be interpreted in the context of some limitations. First, the number of patients with MDD-P and BD was relatively small which could have led to low power in analyses comparing these groups and possibly contributing to the lack of association between those categories on most PRS variables. Nonetheless, *post-hoc* power calculations of the performed comparisons suggest enough power for PRS-SZ in all comparisons except BD vs MDD-P comparison. Regarding PRS-BD and PRS-D, our study had 80% power to detect an association if the genetic correlation between BD and depression in the respective GWAS and our BD and MDD-P phenotypes were of around 26-48% and 14-24% respectively for the highest and least powered comparisons (more detail information in *Supplementary Material*). With FEP samples there are two main limitation to consider. One relates with the previously noted lower liability explained by PRS in incident samples (Meier *et al.*, 2016), suggesting that part of the captured effect of SNPs corresponds to a more chronic course of illness or to a clearer phenotype, which may have implied type II error in our sample based on first episode of psychosis. The second limitation refers to the changeability of diagnoses and consequently a risk of misclassification in a

proportion of our sample. As shown in some studies, shifts in diagnoses occur with a predominant direction from affective psychosis to NAP in a frequency of around 14-29% after two years (Schwartz *et al.*, 2000; Veen *et al.*, 2004). Furthermore, comparisons between models are limited by the different discriminative power of each PRS (PRS-SZ is currently more powerful than PRS-BD and PRS-D). These models are expected to improve as bigger discovery samples are available for the affective psychotic categories. Finally, all analyses were performed in the people of European ancestry population, which limits the generalisability of the findings in other populations. However, the fact that this is a multicentre well-characterised sample of FEP, allows it to have generalisability within Caucasian European populations.

5.4.3 Conclusions

Overall, this study provides support for the presence of a genetic psychosis continuum (shown by the ability of PRS-SZ to differentiate most case groups from controls following a gradient across categories). Nonetheless, we also observed genetic differences between clinical categories, with schizophrenia spectrum disorders at one end and psychotic depression at the other when looking at genetic loading for SCZ and Depression. This study also shows that combining PRSs for different disorders in a prediction model of psychosis related phenotypes improve our prediction models while contribute to our understanding of these phenotypes. Despite not yet clinically applicable at individual level, this study points towards the potential usefulness as a research tool in specific populations such as high-risk or early psychosis phases, where it may help to suggest different therapeutic approaches (i.e antidepressant versus antipsychotic) or to anticipate prognosis. However, further work is needed to explore if PRS have synergistic effects with environmental exposures before combining all the risk factors into a single prediction model.

6. STUDY 3. POLYGENIC AND POLYENVIRONMENT INTERPLAY ACROSS PSYCHOTIC DIAGNOSIS CATEGORIES; THE EUGEI STUDY.

6.1 INTRODUCTION

Affective psychoses (AP), in which Bipolar Disorder and Psychotic Depression are included, carry a detrimental societal and economical cost (Gaudiano *et al.*, 2009; World Health Organization & World Bank, 2011; Hay *et al.*, 2017), with considerably individual impact on reducing quality of life (Michalak *et al.*, 2005; Saarni *et al.*, 2010) and life expectancy (Hayes *et al.*, 2015), particularly death by suicide (Gournellis, R. *et al.*, 2018; Gournellis, Rossetos *et al.*, 2018; Tondo, Leonardo *et al.*, 2020). However, it remains unclear to date which are the causative factors, and how they interrelate.

On the one hand, the genetic component of bipolar disorder (BD) and major depression disorder (MDD) is well-established (Sullivan *et al.*, 2000; Craddock and Sklar, 2013), with an estimated heritability of 60-80% (Smoller and Finn, 2003) and 37% (Sullivan *et al.*, 2000) respectively, and of around 39% for psychotic depression (Lyons *et al.*, 1998); this heritability being carried by the combined effect of many risk variants (Purcell *et al.*, 2009; Wray *et al.*, 2018). We can group the identified subsets of variants (known as single nucleotide polymorphism –SNPs-) from a discovery GWAS into an individual polygenic risk score (PRS) by summing their weighted effect size (Dudbridge, 2013).

On the other hand, multiple environmental factors play an important role as well. Indeed, in my meta-analysis on environmental risk factors (ERF) for affective psychosis (including psychotic depression and bipolar disorder) I found suggestive evidence of an increased risk for paternal age, early or late gestational age, cannabis use, parental death or separation during childhood and ethnic minority (Rodriguez *et al.*, 2021). Some factors such as impact of ethnic minority or childhood trauma have a transdiagnostic effect; while studies have shown tentative evidence of specificity by other factors such as being migrant, living in urban areas, childhood social withdrawal, and childhood exposure to Toxoplasma gondii (Radua, 2018). Regarding MDD, specific evidence has been found for childhood trauma (Humphreys *et al.*, 2020) and stressful life events (SLEs)(Kendler *et al.*, 1999).

The fact that not all individuals exposed to these environmental insults develop the disorders, and considering the unknown neurobiological mechanism underlying these effects, it is plausible that they act in combination with a previous pre-existing

vulnerability, more so given the known genetic contribution of these disorders. In this respect, studies of gene-environment interactions (GxE) have gained much more attention in the last decade. GxE studies using candidate genes have not been generally replicated, but GxE studies using PRS have started to be published. Initial studies on FEP found no interaction with childhood trauma (Trotta *et al.*, 2016), but a recent multicentric study of chronic schizophrenia spectrum disorders (i.e non-affective psychosis) found evidence of an additive interaction between PRS-SZ and emotional trauma as well as with cannabis use to develop psychosis (Guloksuz *et al.*, 2019). Similarly, an interaction between PRS-SZ and childhood adversity was observed in psychotic symptoms in the general population (Pries, L. K. *et al.*, 2020). Following with childhood trauma but with depression as outcome, an observed interaction between polygenic liability for MDD (Peyrot *et al.*, 2014) among those exposed to childhood adversity was not later replicated (Peyrot *et al.*, 2017). However, recent studies on depression testing the interaction between PRS for MDD with SLE instead, seem to support the diathesis-stress model (Colodro-Conde *et al.*, 2018; Arnau-Soler *et al.*, 2019).

There is evidence that it is not only the type of environmental exposure, but the extent that can have an influence in psychosis, as evidenced within childhood adversity with an increase in risk according to number and severity of exposures (Shevlin *et al.*, 2008; Morgan *et al.*, 2020). Besides, these risk factors often co-occur, e.g. adversities and cannabis use (Conus *et al.*, 2010). Thus, to study them in isolation is not always representative of real-life settings. Several attempts have been made to compile the load of exposure into a quantitative score to capture the differences observed in strength of associations. For instance, Oliver et al (Oliver *et al.*, 2019) suggested a polyrisk score combining different ERFs among others to apply as risk score for transition to psychosis in high risk individuals, but they included both genetic and non-genetic protective factors as well in the model. Another attempt of aggregating environmental exposure comes from Pries et al., by designing the so-called exposome for SCZ (Pries *et al.*, 2019) in which they include exposures of winter birth, hearing impairment, cannabis use and different subtypes of childhood trauma including bullying; but these were captured on binary bases, and missed to include other well-replicated factors such as obstetric complication or urbanicity,. Vassos et al (Vassos *et al.*, 2019) is the most thorough attempt to date in generating a score based exclusively on polyenvironmental exposure by combining

the most robust published evidence of association of six environmental exposures, not limited by specific sample or timing of the illness; which makes it particularly interesting for its use in models exploring interplay with genetics.

Given the above, and the current literature, it is possible to identify five main problems: 1) research is not evenly distributed; with some factors attracting considerably more attention (i.e childhood trauma, with mixed findings and variations depending on the different measures of these); 2) although research on genetics is switching toward the polygenic approach, such research on GxE interaction in psychosis is still scarce; 3) available results are still conflicting and not replicated; 4) the few studies with a polygenic approach are limited to psychosis, SCZ and depression, none has been done yet in AP, neither BD nor psychotic depression; 5) despite the development of the new poly-environmental risk score to capture the broad contributing effect of a broad range of ERFs into a single item, this has not been explored yet in relation to the different PRSs.

Given the aforementioned gaps, the current work aims to: (i) explore environment moderator effect accounting for polygenic vulnerability of the different psychiatric disorders vulnerabilities (SCZ, BD, depression) as previously suggested (Modinos *et al.*, 2013); (ii) attend to the cumulative environmental exposure by combining different factors into a polyenvironmental measure.

6.2 METHODS

6.2.1 Aims and hypotheses

The main aims are to analyse the role of individual and ERFs in the development of AP (major depression with psychotic features and Bipolar disorder with psychotic symptoms) compared with controls and NAP; and to explore if they interact with genetic vulnerability for major psychiatric disorders by using the PRSs for Schizophrenia (PRS-SZ), Bipolar Disorder (PRS-BD) and Depression (PRS-D); based on the following hypotheses:

1) I expect to find a positive association between cannabis, urbanicity, parental age, migration, childhood adversity and SLE with the presence of AP when compared with controls, showing a dose-response effect based on amount of cumulative exposure of ERF.

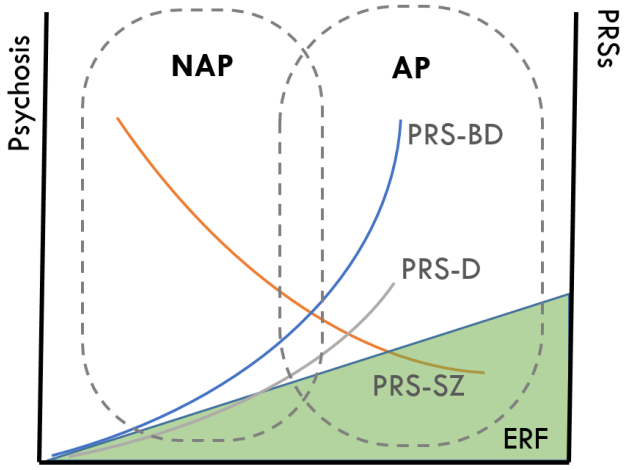
2) I hypothesise that PRSs for SCZ, BD and Depression will be differently associated with AP and NAP based on exposure of each of the aforementioned ERFs, studied independently (for example, whether PRS-SZ is more associated in those non-exposed to cannabis as compared to those exposed). As postulated elsewhere (Kendler and Eaves, 1986), I expect to find higher PRS-SZ in patients with NAP unexposed compared with those exposed (following the additive model and reflecting those whose illness is more genetic/heritable); and stronger associations with "affective" PRSs in those NAP exposed (suggesting a genetic moderation of sensitivity where greater genetic load of BD or depression risk variants would imply higher vulnerability of external factors). In AP, I expect to find a synergistic model following dose-response effect for both affective PRS and environmental exposure, as seen for depression(Colodro-Conde *et al.*, 2018; Arnau-Soler *et al.*, 2019). This hypothesis is illustrated in Figure below (**Figure 6.1**).

3) Lastly, and following same theoretical models (Kendler and Eaves, 1986), I hypothesise that the lower the ERFs exposure, the stronger the effect carried by PRS-SZ for expressing psychosis (additive model with negative interaction); whereas psychosis with high genetic liability for BD and depression will be accompanied by higher environment exposure (genetic moderation of sensitivity with positive interaction). This is illustrated by the **Figure 6.1**.

6.2.2 Sample

A total of 573 cases and 1005 controls with European ancestry were recruited among 17 European and Brazilian sites as part of the EUGEI case-control study. Details on the study design and sample recruitment were provided in previous chapters (Chapter 2, Chapter 4 and Chapter 5). Categorical diagnoses (non-affective psychosis– NAP-, bipolar disorder –BD- and psychotic depression –MDD-P-) were defined based on DSM-IV output from OPCRIT items, as explained in Chapter 3. For the purpose of this Study, I grouped and analysed BD and MDD-P combined into Affective Psychosis (AP) group.

Figure 6.1. Theoretical representation of hypothesis to test on the interplay between environment and genetic load in NAP and AP



NAP: non-affective psychosis; AP: affective psychosis; ERF: environmental risk factors; PRS: polygenic risk score; BD: bipolar disorder; SZ: schizophrenia; D: depression

6.2.3 Variables

6.2.3.1 Polygenic liability

PRS for SCZ, BD and depression (PRS-SZ, PRS-BD and PRS-D) were built on PRSice2 (Choi and O'Reilly, 2019) using data from the largest GWAS available (Ripke, Neale, Benjamin M., *et al.*, 2014; Howard *et al.*, 2019; Stahl *et al.*, 2019), at the p-value threshold that better predicted the respective phenotypes (p-value=0.05), with details provided on Chapter 5. Each PRS was standardized to a mean of zero and standard deviation of 1 (Lewis and Vassos, 2017).

6.2.3.2 Environmental risk factors definition

a. Cannabis use.

Information on cannabis use was collected at baseline with the Cannabis Experience Questionnaire (CEQ) modified version (Di Forti *et al.*, 2009). The CEQ (Barkus et al., 2006) was developed to assess psychological experiences associated to cannabis use. The modified version was expanded including questions on pattern of cannabis use, type, cost etc,

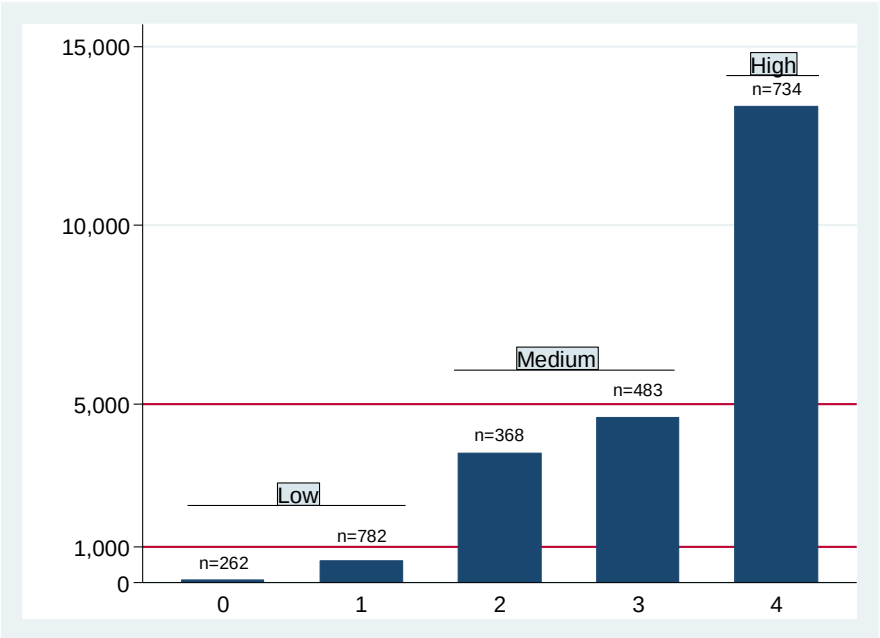
Three measures of cannabis were included to the analyses: (1) lifetime cannabis use, (2) lifetime frequency of use, and (3) cannabis potency. For lifetime cannabis use,

subjects were dichotomised into those who reported lifetime cannabis use and those who never smoked; lifetime frequency represent the maximum frequency of use ever, and was split into: daily, at least weekly, or less than weekly. Lastly, cannabis potency grouped low and high potency based on a cut-off of >10% of tetrahydrocannabinol (THC) labelled as "high", or <10% content of THC labelled as "low" potency.

b. Urban environment

Population density, which has been previously reported as indicator of urbanicity in schizophrenia (Vassos *et al.*, 2012), was derived in our sample as number of inhabitants per square kilometre, based on official total population estimates. I created a categorical variable (low, moderate and high urbanicity) with cut-offs based on five ranked group over population density. As shown in **Figure 6.2**, the cut-offs were stablished at <1000 people/km^2 , 1000-5000 people/km^2 and >5000 people/km^2 . A more general measure was then utilised or the combined models, dichotomising at the 1000 people/km^2 cut-off.

Figure 6.2. Cut-offs of based on population density.



a. Paternal age

It is believed that if the father is more than 35 years old at the time of someone's birth this increases the odds to experience psychosis (Davies *et al.*, 2020); and parental age has been found to predispose also to have later BD with psychotic symptoms if it is over 45yo (Lehrer *et al.*, 2016). In order to capture the effect for both NAP and AP, I dichotomised paternal age with the cut-off at 45yo.

b. Migration

Place of birth and age of migration information was collected as part of the MRC Socio-demographic Schedule modified version (Mallett *et al.*, 2002). I utilised a binary variable indicating whether a participant had a migration history or not, where only first generation migrants were considered.

c. Child adversity

The Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco, 1994) was employed to collect retrospective information on five types of maltreatment before age 17: psychological abuse, physical abuse, sexual abuse, household discord, and bullying.

Psychological abuse comprised humiliation, degradation, extreme rejection, emotional blackmail, terrorizing by a caregiver, or deprivation of basic needs (beyond neglect). Physical abuse was rated for when bodily harm was inflicted by a caregiver resulting in at least bruising. Sexual abuse was defined as any reported unwanted sexual incident. Household discord refers to the amount of fighting between the caregivers and/or with the child. For bullying participants were asked if they had experienced or received from peers any of the following before age 17: mean and hurtful things being said or made fun of; being ignored or excluded or left out of things on purpose; being hit, kicked or shoved, or locked in a room; being told lies or rumours being spread about ones; other hurtful things.

In the CECA.Q each type of adversity is scored based on perpetrator or family arrangement, frequency, severity, overall support, negative support, and official contact. Frequency of abuse was rated on a five-point Likert-scale: (0) never, (1) rarely, once or twice; (2) occasionally, more than two times, but not monthly; (3)

frequently, monthly or more often; and (4) very frequently, weekly or more often. Severity of abuse was rated on a four-point Likert scale: (0) none, (1) some, (2) moderate, and (3) marked, except for household discord, which was scored on a five-point scale that also included (4) violence. For the analyses, each childhood adverse subtype were dichotomised based on severity as follows: "absent" – (0) if none, some or moderate- or "present" - (1) if marked or severe -. In terms of time of first exposure, I didn't categorized in Early or Late, but considered "ever".

After taking into account the different subtypes, I further combined the five traumas into a combined binary variable indicating the presence of any childhood trauma if at least one of the five types ranked as "severe".

d. Stressful Life Events

A list of 20 potential adverse life events during the 12 month period before onset were recorded at baseline using a modified version of the List of Threatening Experiences (Brugha et al., 1985). This modified version covers the past 12 months instead of 6 months, as previously used (Rosmalen *et al.*, 2012); and adds eight stressful experiences to the original 12 items, being the added ones the following: "*birth of a child (you or partner)*", "*any shocking or revealing news about partner or children*", "*serious ongoing problems with partner or children*", "*serious problems at work*", "*serious financial difficulties or debts (you, partner)*", "*serious housing problems, including being homeless*", "*victim of assault (inc. in the home), robbery or burglary*", "*witnessed a serious assault or other traumatic event*". Based on the total count of reported experiences, participants were categorised in "none or less than three events" and "at least three events" in order to capture those with high exposure to threatening life events.

6.2.3.3 Cumulative environment exposures

In order to test the cumulative environmental exposure, I built two different combined measures. I first adapted a score based on the Maudsley environment risk score for psychosis (which I will refer as MERS) (Vassos *et al.*, 2019); and then I built a new polyenvironmental score (PES) by counting the presence of any of the reported ERF, which will be explained below.

a. Maudsley Environmental Risk Score (MERS)

The MERS for psychosis (Vassos et al., 2019) provides a systematic measure of aggregated environmental risk score for psychotic disorders by including six risk factors: ethnic minority status, urbanicity at birth, advanced paternal age, obstetric complications, cannabis use and childhood adversity. I modified this score by not including obstetric complications and by including current urbanicity instead of urbanicity at birth based on availability of data. The MERS attributes certain values per risk factor based on rounded values of log risk ratios extracted from the last available meta-analyses. Definitions of and values attributed per risk factor are shown in **Table 6.2**.

Table 6.2. Definition and values per risk factors to estimate MERS (adapted from Vassos, 2019 (Vassos *et al.*, 2019)**).**

Risk factor	Sub-categories	RR from M-A	Definition in EUGEI sample	MERS
Ethnic minority	Native	1	Native White	−0.5
	Black	4	Black African, Black Caribbean, other Black	5.5
	White	1.8	Migrant white	2
	Other	2	North African, other	2.5
Urbanicity (current)	Low	1.16	<1000 people/km^2	−1.5
	Medium	1.55	1000-5000 people/km2	0
	High	2.07	>5000 people/km^2	1
Paternal age (years)	<40	1	<40	0
	40–50	1.17	40–50	0.5
	>50	1.60	>50	2
Cannabis	No exposure	1	never used	−1
	Little/moderate	1.41	weekly	0
	High exposure	2.77	daily	3
Childhood adversity	No exposure	1	no exposure	−1.5
	Any exposure	2.78	any exposure	2.5

a. Polyenvironmental score (PES)

I built a cumulative polyenvironmental score (PES), reflecting the number of the different risk factor present in each individual, based on the definitions shown in **Table 6.3**. It differs from the MERS mainly in the incorporation of stressful life events in the past 12 months and by counting environmental factors without taking into account their effect sizes. This was used as a continuous variable (with values ranging from 0 to 6).

Table 6.3. Definition of risk factors to estimate PES.

Risk factor	Sub-categories	Definition in our sample	PES
Migration	Native	Native White	0
	Migrant	1st gen migrant	1
Paternal age	Not advanced	<45 yo	0
	Advanced	>45 yo	1
Urbanicity (current)	Rural	<1000 people/km^2	0
	Urban	>1000 people/km2	1
Lifetime cannabis	Never	never used	0
	Ever	At least once	1
Childhood adversity	No exposure	no exposure	0
	Any exposure	any exposure	1
Stressfull Life events	None/low	0-3 SLE	0
	High	>3 SLE	1

6.2.4 Statistical analyses

6.2.4.1 Descriptive and comparison statistics

I first described primary outcomes using frequencies, percentages, mean and standard deviations (SD). Between group comparisons were made with Chi square and Student t. Comparison statistics were done between AP vs controls and between AP vs NAP and will be presented with the main sociodemographics in the **Table 6.4**.

6.2.4.2 Step 1: associations of ERFs with clinical groups

Multinomial univariate logistic regressions were run for each individual ERF to explore their independent association across clinical groups (AP and NAP) when compared with controls, and in combination in a multivariate analyses including the most generic measure per ERF (i.e. dichotomised urbanicity measure; lifetime cannabis use instead of frequency). Additional univariate and multivariate simple logistic regressions were run for AP vs NAP comparisons. All analyses were controlled for age, gender and site.

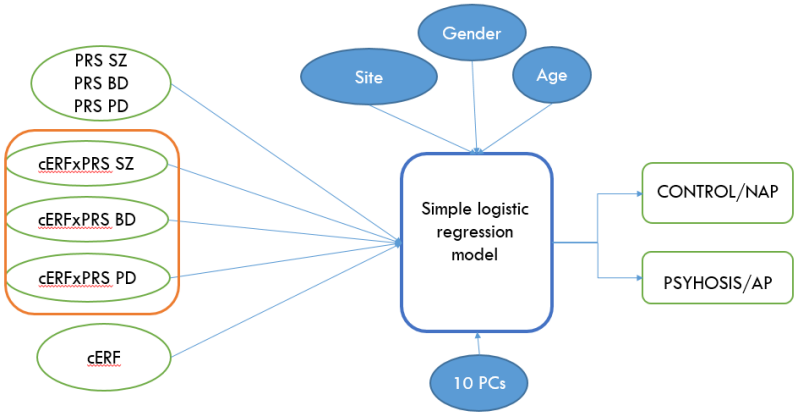
6.2.4.3 Step 2: differences between polygenic prediction in exposed and non-exposed to environmental insults

Multinomial and simple logistic regression models were used to test whether the association of standardised genetic load (PRS-SZ, PRS-BD and PRS-D) with 1) NAP and AP separately vs control and 2) NAP vs AP respectively; differs significantly when stratifying the analyses by exposed or non-exposed subjects based on those ERF that showed significant differences in comparison statistics.

6.2.4.4 Step 3: polygenic and polyenvironment interaction (by multiplicative approach)

Independent logistic models including the aggregated measures of environmental exposure and their interaction terms with each PRSs were run to test a potential polygenic and polyenvironment interaction with AP when compared with controls and for distinguishing NAP and AP. Given the required bigger sample for GxE interaction analyses and in order to optimise our sample size, I also ran another logistic model to test interactions with the whole group of psychosis when compared with controls. Analyses were conducted for each combined poly-environmental risk score separately, and were adjusted by age, gender, 10PCs and site. This is illustrated by **Figure 6.3**.

Figure 6.3. Representation of model exploring multiplicative interaction.



cERF: measure of combined environmental exposure – MERS and PES-; PC: principal component; PRS: polygenic risk score; SZ: schizophrenia; BD: bipolar disorder; D: depression; NAP: non-affective psychosis

6.3 RESULTS

6.3.1 Descriptive and Comparison statistics

The total sample comprised 573 cases (composed by 164 AP and 409 NAP) and 1005 controls. Description of the sociodemographic and distribution of ERFs of AP, NAP and controls is shown in **Table 6.4**.

AP patients of European ancestry were younger than controls (32.84 ±11.56 vs 36.9 ±13.02; p<0.001). Both groups presented similar proportion of females and males, in contrast with a much lower proportion for the NAP (49.39% females for AP vs

32.03% in NAP; $X^2(1)= 15.14$, p<0.001). Those diagnosed with AP had similar years of education as NAP but significantly lower than controls (12.58 ±3.84 in AP vs 14.68 ±4.19 in controls; p<0.001). A higher proportion of AP than controls were single and not living independently, but this was even lower for patients with NAP (46% not living independently and 51.95% single for AP; compared with 62.46% and 71.70% respectively in NAP). Whereas unemployment was similar among AP and controls; this was significantly higher for NAP (41.48% in AP v. 54.52% in NAP, $X^2(1)=6.39$, p=0.011).

Table 6.4. Sociodemographic and ERFs distribution across clinical groups of European ancestry.

	AFFECTIVE PSYCHOSIS	**CONTROL**			**NON-AFFECTIVE PSYCHOSIS**		
	Mean(SD) N(%)	Mean(SD) N(%)	Statistics	P value	Mean(SD) N(%)	Statistics	P value
Age	32.84 (11.56)	36.9 (13.02)	**t 3.76**	**p<0.001**	31.63 (10.92)	t -1.18	p=0.240
Gender			0.67	P=0.413		**15.14**	**p<0.001**
.Male	83 (50.61)	474 (47.16)			**278 (67.97)**		
.Female	81 (49.39)	531 (52.84)			131 (32.03)		
Years of education	12.58 (3.84)	14.68 (4.19)	**t 6**	**p<0.001**	12.94 (4.12)	t 0.936	p=0.35
Living independently (% no)	**63 (46.32)**	314 (31.49)	**11.85**	**p=0.001**	**198 (62.46)**	**10.15**	**p=0.001**
Marital status (% single)	**80 (51.95)**	378 (37.65)	**11.42**	**p=0.001**	**266 (71.70)**	**18.89**	**p<0.001**
Unemployment	56 (41.48)	383 (38.38)	0.48	p=0.487	**169 (54.52)**	**6.39**	**p=0.011**
Lifetime cannabis (% of yes)	**103 (63.98)**	469 (47.04)	**15.9**	**p<0.001**	262 (65.83)	0.174	p=0.677
Lifetime frequency cannabis			**33.71**	**p<0.001**		**9.53**	**p=0.009**
.Weekly	17 (16.83)	68 (14.53)			46 (17.90)		
.Daily	**34 (33.66)**	54 (11.54)			**127 (49.42)**		
Potency of cannabis (% of high)	25 (27.78)	96 (22.43)	1.19	p=0.276	95 (38.31)	3.2	p=0.074
Parental age	31.8 (6.97)	31.62 (6.67)	t -0.31	p=0.621	32.01 (7.34)	0.31	p=0.757
Urbanicity			0.4655	p=0.792		5.3	p=0.071
.Low (<1000/km2)	68 (41.46)	445 (44.28)			129 (31.54)		
.Medium (1000-5000/km2	61 (37.2)	359 (35.72)			185 (45.23)		
.High (>5000/km2)	35 (21.34)	201 (20)			95 (23.23)		
Migration (% of yes)	29 (17.68)	140 (13.93)	1.61	p=0.205	73 (18.43)	0.04	p=0.834
Age migration	15.79 (9.73)	18.49 (12.51)	t 0.98	p=0.332	14.85 (10.68)	t -0.37	p=0.71
Stressful Life events (> 3)	**57 (34.76)**	168 (16.72)	**29.52**	**p<0.001**	92 (22.49)	**9.15**	**p=0.002**
CHILDHOOD TRAUMA (% of yes)							
.Physical abuse	**21 (12.98)**	61 (6.12)	**9.76**	**p=0.002**	59 (15.53)	0.63	p=0.426
.Psychological abuse	**25 (15.43)**	64 (6.42)	**15.97**	**p<0.001**	40 (10.55)	2.55	p=0.11
.Sexual abuse	**9 (5.59)**	27 (2.71)	3.8	p=0.051	16 (4.23)	0.47	p=0.493
.House discord	**69 (42.07)**	277 (28.27)	**12.7**	**p<0.001**	154 (40.53)	0.113	p=0.736
.Bullying	**52 (33.55)**	142 (14.56)	**33.89**	**p<0.001**	114 (30.4)	0.505	p=0.477
TOTAL Childhood trauma	107 (67.72)	413 (42.98)	**33.4**	**p<0.001**	225 (60.65)	2.37	p=0.123

In terms of ERF, a higher percentage of AP had a past of having ever used cannabis than controls (63.98% for AP vs 47.04% in controls; $X^2(1)= 15.9$, p<0.001), but not than those with NAP (65.83%). No differences were observed in terms of potency of cannabis, but AP were more likely to have smoked daily than controls (33.66% for AP vs 11.54% in controls; $X^2(2)= 33.71$, p<0.001), but less than NAP (49.42% for NAP; $X^2(2)= 9.53$, p=0.009). No significant differences between groups were observed for parental age, distribution across urbanicity levels or migration. Higher

proportion of AP (34.76%) were exposed to at least three life adverse events in the past 12 month compared with controls (16.72%; $X^2(1)= 29.52$, p<0.001) and NAP (22.49%; $X^2(1)= 9.15$, p=0.002). Lastly, although non-significant differences were observed between childhood adversity exposure between NAP and AP, the latter were significantly more exposed to any childhood trauma than controls, which was also true if I considered the combined measure of childhood adversity (67.72% of AP v. 42.98% in controls, $X^2(1)=33.4$, p<0.001).

6.3.2 Step 1: ERF association with clinical groups

Associations of independent ERF from univariate analyses with both clinical groups (AP and NAP) when compared with controls; and from multivariate analyses combining all ERF in one model are presented in **Table 6.5**. Additional univariate and multivariate analyses were run for AP vs NAP comparisons (**Table 6.5**).

Univariate regression analyses showed that having ever use cannabis, and more strongly having used daily cannabis, was associated with both AP and NAP, whereas having used cannabis weekly was only associated with NAP. Similarly, being migrant is solely associated with NAP but not AP when compared with controls. Both forms of adversity -current life stressors and childhood adversity- was significantly associated with both clinical groups, being these associations slightly stronger for AP. It is however of note, that despite not significant, the rest of explored ERFs showed OR over 1 in both clinical groups compared with controls, showing some potential effect. In the case-only comparison, daily cannabis appeared significantly associated with NAP (OR 0.50, 95%CI 0.28-0.88), whereas being expose to more than three SLE is associated with AP (1.64, 95%CI 1.06-2.55). Both clinical groups presented a linear association with both cumulative measures when compared with controls; while in the case-only comparison, neither MERS nor PES differed significantly between groups.

In the multivariate analyses, when I included all forms of ERF into one model, I observed that having been exposed to recent SLE and to any form of adversity during childhood are the only remaining significant associated risk factors for AP. Regarding NAP, only any form of childhood trauma remained positively associated. None of the ERF were differentially associated with AP or NAP in the case-only comparison.

Table 6.5. ERFs associations independently and in a combined model with AP and NAP versus controls and case-only comparisons

	AP vs CONTROL			NAP vs CONTROL			AP vs NAP		
	UNIVARIATE								
	OR	p value	95% CI	OR	p value	95% CI	OR	p value	95% CI
urbanicity >1000/km²	6.41	0.076	0.82-49.85	1.1	0.809	0.52-2.30	5.01	0.133	0.61-41.05
Paternal age >45y	1.73	0.144	0.83-3.63	1.63	0.099	0.91-2.89	0.98	0.969	0.43-2.23
cannabis ever	**1.74**	**0.004**	**1.19-2.55**	**1.47**	**0.006**	**1.12-1.94**	1.14	0.586	0.71-1.81
weekly cannabis	1.65	0.124	0.87-3.12	**2.53**	**<0.001**	**1.57-4.09**	0.66	0.245	0.32-1.34
daily cannabis	**3.61**	**<0.001**	**2.07-6.29**	**7.26**	**<0.001**	**4.69-11.24**	**0.50**	**0.017**	**0.28-0.88**
migrant	1.42	0.139	0.89-2.24	**1.64**	**0.005**	**1.17-2.30**	0.87	0.605	0.53-1.46
SLE	**2.47**	**<0.001**	**1.68-3.61**	**1.5**	**0.012**	**1.09-2.04**	**1.64**	**0.027**	**1.06-2.55**
childhood adversity	**2.73**	**<0.001**	**1.87-3.98**	**2.27**	**<0.001**	**1.72-2.97**	1.15	0.524	0.75-1.77
MERS	**1.29**	**<0.001**	**1.20-1.40**	**1.26**	**<0.001**	**1.19-1.34**	1.02	0.633	0.94-1.11
PES	**1.88**	**<0.001**	**1.56-2.27**	**1.52**	**<0.001**	**1.32-1.75**	1.23	0.056	0.99-1.53
	MULTIVARIATE								
	OR	p value	95% CI	OR	p value	95% CI	OR	p value	95% CI
urbanicity >1000/km²	3.59	0.227	0.45-28.59	0.60	0.214	0.27 -1.34	2.92	0.312	0.37 -23.32
Paternal age >45	1.70	0.181	0.78-3.68	1.5	0.203	0.80-2.80	1.02	0.933	0.71-1.46
cannabis ever	1.46	0.074	0.96-2.21	1.23	0.178	0.91-1.66	1.11	0.577	0.77-1.58
migrant	1.40	0.183	0.85-2.32	1.39	0.086	0.95-2.04	1.31	0.120	0.93-1.85
SLE	**2.16**	**<0.001**	1.44-3.26	1.37	0.086	0.95-2.04	1.09	0.600	0.78-1.53
childhood adversity	**2.49**	**<0.001**	1.67-3.71	**2.08**	**<0.001**	1.57-2.77	2.92	0.312	0.37 -23.32

AP: affective psychosis; NAP: non-affective psychosis; SLE: stressful life events

6.3.3 Step 2: differences between polygenic prediction in exposed and non-exposed to environmental insults

Stratified polygenetic associations based on exposure of those identified different ERFs between AP and controls, NAP and controls, and AP and NAP are shown in **Table 6.6**, **Table 6.7** and **Table 6.8** respectively.

6.3.3.1 Affective psychosis vs control

Those that never smoked cannabis but have higher PRS-BD were at higher risk of presenting with AP when compared with controls (OR 1.68, 95%CI 1.04-2.74). Whereas among those who never experienced childhood adversity, I did not find significant associations with any of the three PRSs for developing AP; those who didn't experience at least three SLE in the past year, presented higher risk for AP if they have higher PRS- BD or PRS-SZ (OR 1.51, 95%CI 1.05-2.1 and OR 1.62, 95%CI 1.04-2.51 respectively).

On the other hand, among those that had used cannabis (OR 1.49, 95%CI 1.14-1.95) or that had experienced at least three stressful life events (OR 1.67, 95%CI 1.13-2.46), a higher polygenic score for depression was associated with risk to develop AP. This positive association was only found with higher PRS-BD in those who reported any form of childhood adversity (OR 1.56, 95%CI 1.04-2.33).

Table 6.6. Stratified polygenic associations with AP vs Controls based on exposure to different ERF.

	UNEXPOSED		EXPOSED	
	OR	**95% CI**	**OR**	**95% CI**
Cannabis ever		**N=572**		**N=569**
PRS-SZ	1.5	0.81 – 2.8	1.6	0.96 – 2.61
PRS-BD	**1.68**	1.04 – 2.74	1.31	0.88 – 1.95
PRS-D	1.22	0.88 – 1.69	**1.49**	**1.14 – 1.95**
Stressful life events		**N=941**		**N=223**
PRS-SZ	**1.62**	**1.04 – 2.51**	1.6	0.74 – 3.42
PRS-BD	**1.51**	**1.05 – 2.16**	1.25	0.72 – 2.17
PRS-D	1.25	0.99 – 1.58	**1.67**	**1.13 – 2.46**
Childhood adversity		**N=595**		**N=519**
PRS-SZ	1.77	0.93 – 3.39	1.26	0.77 – 2.04
PRS-BD	1.34	0.80 – 1.25	**1.56**	**1.04 – 2.33**
PRS-D	1.28	0.90 – 1.80	1.29	0.99 – 1.66

6.3.3.2 NAP vs control

Either migrants and natives with higher PRS-SZ or PRS-BD were predisposed to develop NAP; although migrants were more strongly associated with PRS-BD (OR 1.31, 95%CI 1.03-1.66 in natives and OR 2.61, 95%CI 1.41-4.83 in migrants) and were also predisposed to NAP with higher PRS-D (OR 1.57, 95%CI 1.01-2.44). Those that never smoked cannabis but have higher PRS- SZ were at higher risk of presenting NAP when compared with controls (OR 3.4, 95%CI 2.17-5.33); and among those who had smoked cannabis, having both higher PRS-BD (OR 1.51, 95%CI 1.12-2.05) and PRS-SZ also predicted NAP, although the latter with weaker effect than in those unexposed (OR 2.32, 95%CI 1.63-3.33) . Among those NAP who never experienced childhood adversity, I could find significant associations only with PRS-SZ (OR 4, 95%CI 2.55-6.28); while those NAP who experienced childhood trauma had higher PRS- BD or PRS-SZ (OR 1.85, 95%CI 1.27-2.68 and OR 1.61, 95%CI 1.18-2.20 respectively).

Interestingly, associations with those who experienced at least three stressful life events in the past year, were associated differently, with stronger associations with

PRS-SZ among exposed compared with unexposed (OR 3.24, 95%CI 1.61-6.49 and OR 2.62, 95%CI 1.94-3.55 respectively); but showing positive association with PRS-BD only in unexposed (OR 1.41, 95%CI 1.11-1.78).

Table 6.7. Stratified polygenic associations with NAP vs Controls based on exposure to different ERF.

	UNEXPOSED		EXPOSED	
	OR	**95% CI**	**OR**	**95% CI**
Migrant		**N=1181**		**N=212**
PRS-SZ	**2.69**	**2.00 – 3.60**	**2.36**	**1.05 – 5.33**
PRS-BD	**1.31**	**1.03 – 1.66**	**2.61**	**1.41 – 4.83**
PRS-D	1.06	0.91 – 1.24	**1.57**	**1.01 – 2.44**
Cannabis ever		**N=662**		**N=725**
PRS-SZ	**3.4**	**2.17 – 5.33**	**2.32**	**1.63 – 3.33**
PRS-BD	1.36	0.97 – 1.91	**1.51**	**1.12 – 2.05**
PRS-D	1.09	0.87 – 1.37	1.14	0.94 – 1.38
Stressful life events		**N=1148**		**N=257**
PRS-SZ	**2.62**	**1.94 – 3.55**	**3.24**	**1.61 – 6.49**
PRS-BD	**1.41**	**1.11 – 1.78**	1.59	0.98 – 2.60
PRS-D	1.1	0.94 – 1.30	1.36	0.94 – 1.89
Childhood adversity		**N=1148**		**N=637**
PRS-SZ	**4**	**2.55 – 6.28**	**1.85**	**1.27 – 2.68**
PRS-BD	1.35	0.96 – 1.90	**1.61**	**1.18 – 2.20**
PRS-D	1.1	0.87 – 1.39	1.01	0.83 – 1.23

6.3.3.3 Affective psychosis vs NAP

No polygenic associations were found with any of the clinical groups (NAP or AP) among those that did or did not experience at least three SLE. However, while higher PRS- SZ was observed for those NAP having never used cannabis; higher genetic vulnerability for depression was more likely to be present in AP than NAP (OR 1.46, 95%CI 1.09-1.95) among those that reported having ever smoked cannabis..

Table 6.8. Stratified polygenic associations with AP vs NAP based on exposure to different ERF.

	UNEXPOSED		EXPOSED	
	OR	**95% CI**	**OR**	**95% CI**
Cannabis ever		N=185		N=365
PRS-SZ	**0.37**	**0.16 – 0.84**	0.72	0.43 – 1.2
PRS-BD	1.19	0.65 – 2.17	0.90	0.60 – 1.34
PRS-D	1.10	0.77 – 1.58	**1.46**	**1.09 – 1.95**
Stressful life events		N=424		N=145
PRS-SZ	0.62	0.38 – 1.02	0.60	0.26 – 1.39
PRS-BD	1.03	0.69 - 1.53	1.04	0.55 – 1.96
PRS-D	1.22	0.94 – 1.59	1.30	0.88 – 1.93

6.3.4 Step 2: polygenic and polyenvironment interaction (by multiplicative approach)

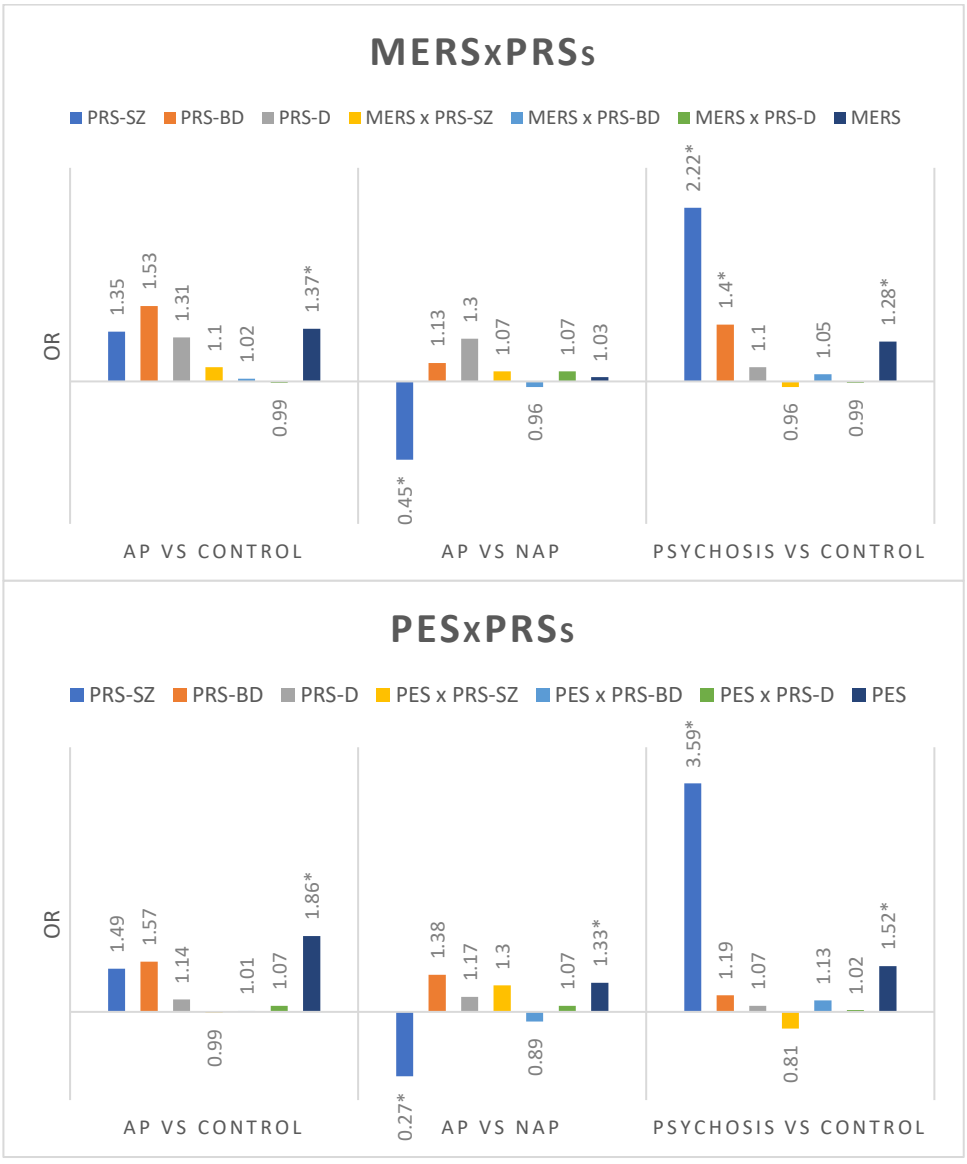
As shown in **Table 6.9**, no evidence of interaction was found between any of the PRS with either MERS or PES in the case-control and case-only comparisons. In the combined model with polygenic and polyenvironment measures, only the polyenvironmental measure remains significantly associated with AP when compared with controls (OR 1.37, 95%CI 1.23-1.52 for MERS and OR 1.86, 95%CI 1.50-2.32 for PES). However, in the Psychosis vs Control comparison, apart from the significant association with both aggregated environmental measures (OR 1.28, 95%CI 1.2-1.36 for MERS and OR 1.52, 95%CI 1.32-1.75 for PES), I also found positive and stronger associations with PRS-SZ (OR 2.22, 95%CI 1.59-3.1 when combined with MERS and OR 3.59, 95%CI 2.07-6.21 when combined with PES) and PRS-BD (OR 1.4, 95%CI 1.08-1.82 only when combined with MERS). It is of note that association with poly-environmental variables were slightly weaker in analyses of psychosis vs control than AP vs control.

Table 6.9. Association of aggregated environmental exposure independently and in interaction with different PRSs (SCZ, BD and MDD) across diagnostic categories, adjusted with 10 PCs and sites

	AP vs CONTROL		**AP vs NAP**		**P vs CONTROL**	
	OR	95% CI	OR	95% CI	OR	95% CI
MERS		N=706		N=360		N=967
PRS SZ	1.35	0.8-1.29	**0.45**	**0.23-0.89**	**2.22**	**1.59-3.1**
PRS BD	1.53	0.98-1.39	1.13	0.68-1.87	**1.4**	**1.08-1.82**
PRS D	1.31	0.97-1.76	1.3	0.94-1.81	1.1	0.92-1.31
MERS x PRS SZ	1.1	0.95-1.28	1.07	0.91-1.26	0.96	0.88-1.06
MERS x PRS BD	1.02	0.91-1.16	0.96	0.85-1.08	1.05	0.98-1.14
MERS x PRS D	0.99	0.91-1.08	1.07	0.97-1.17	0.99	0.96-1.06
MERS	**1.37**	**1.23-1.52**	1.03	0.92-1.15	**1.28**	**1.2-1.36**
PES		N=1073		N=483		N=1410
PRS SZ	1.49	0.61-3.63	**0.27**	**0.08-0.85**	**3.59**	**2.07-6.21**
PRS BD	1.57	0.78-3.14	1.42	0.64-3.15	1.19	0.77-1.82
PRS D	1.14	0.69-1.86	1.17	0.68-2.042	1.07	0.79-1.44
PES x PRS SZ	0.99	0.71-1.39	1.30	0.88-1.93	**0.81**	**0.65-0.99**
PES x PRS BD	1.01	0.78-1.32	0.89	0.68-1.18	1.13	0.95-1.34
PES x PRS D	1.07	0.88-1.29	1.06	0.87-1.29	1.02	0.91-1.15
PES	**1.86**	**1.50-2.32**	**1.33**	**1.04-1.71**	**1.52**	**1.32-1.75**

In the case only comparison (AP vs NAP), the distinction was mainly driven by PRS-SZ, being associated with NAP (OR 0.45, 95%CI 0.23-0.89 when combined with MERS and OR 0.27, 95%CI 0.08-0.85 when combined with PES). Only in the combined model with PES, I also found a positive association with PES, indicating that those with higher environmental exposure were more prone to AP (OR 1.33, 95%CI 1.04-1.71). These results are also presented graphically in **Figure 6.4**.

Figure 6.4. Association of aggregated environmental exposure independently and in interaction with different PRSs (SZ, BD and D) across diagnostic categories



Results of OR from joint model with all PRSs, combined ERF measured (MERS or PES) and their multiplicative intercepts; adjusted by age, gender, 10PCs and site. SZ: schizophrenia; BD: bipolar disorder; D: depression; NAP: non-affective psychosis; AP: affective psychosis; MERS: Maudsley Environmental Risk Score; PES: polyenvironmental score

6.4 DISCUSSION

6.4.1 Main results and overview of findings

This chapter shows exploratory analyses of the effects of combining the genetic vulnerability of three major psychiatric disorders with multiple environmental exposures in the two main clinical groups of Affective Psychosis and Non-affective Psychosis.

Four key findings steam from the results: (i) As expected, having used cannabis, being a migrant and having been exposed to childhood or current SLE were associated with both AP and NAP; and interestingly the associations were stronger in AP; (ii) Genetic vulnerability to AP and NAP changes as a function of specific environmental exposures, suggesting differential pathways to disease; (iii) Genetic liability to AP (BD and depression) predisposes to NAP in the presence of exposure to social environmental insults, which support the hypothesis of an affective pathway to psychosis; (iv) Results don't support the presence of an interaction between polygenic and polyenviroment exposure, but point to the stronger effect of cumulative environmental risk factors for developing AP, and of genetic vulnerability to NAP.

These main findings will now be framed with current literature and discussed in detail.

6.4.2 Individual impact of ERF

My results show that having used cannabis, being a migrant and having been exposed to either childhood or current adversity were more associated with AP and NAP than controls, which has been consistently replicated in psychosis (Stilo and Murray, 2019). Moreover, when combining in the same model, effects of social adversity in the form of recent life events and childhood adversity appeared generally stronger with AP than NAP. Nonetheless, in the case-only comparison, the only significant differences were that daily cannabis appeared associated with NAP, whereas being expose to more than three life events is associated with AP. Of course, cannabis is the most studied risk factor for psychosis (Di Forti *et al.*, 2019) and more specifically schizophrenia (Vaucher *et al.*, 2018); and SLE is among the few ERF with evidence of association with major depression (Kendler *et al.*, 1999) .

The findings of stronger associations with ERFs for AP than NAP in case-control comparisons are in contradiction with the better evidence of environmental associations with NAP than with AP. Given that this is more noted when we put all effects into consideration in a unique model, or by utilising any of the cumulative environmental exposures, it is plausible that AP is more likely to be affected by the conjunction of several ERFs, whereas NAP may be more vulnerable to specific factors when analysed independently (i.e cannabis, ethnic minority, urbanicity), potentially due to an interaction to specific liabilities at certain biological pathways. This requires further research.

6.4.3 Differential genetic association based on environmental exposure; testing the working hypothesis

I started from the working hypothesis that we could conceptualise the affective and non-affective subgroups based on differential associations with genetic and environmental load (illustrated in **Figure 6.1**). I hypothesised that those defined as non-affective psychosis (NAP) non-exposed to certain environmental factors would present higher genetic vulnerability for PRS-SZ; whereas those NAP exposed would present lower vulnerability for SCZ but higher for BD and depression. Additionally, those included in the AP subgroup would present a dose-response effect of the combination of higher polygenic variants for BD and Depression, and higher environmental load.

It is possible to observe than overall, in NAP the effect of PRS-SZ is higher in unexposed and decreases among those exposed to most ERF; alongside a trend for higher effect of affective PRS for those exposed to different ERF, which goes in line with what was hypothesized. This may indicate that individuals can develop NAP by two different pathways: firstly due to a high genetic vulnerability for SCZ; or secondly, despite having not so high genetic vulnerability for SCZ, showing higher sensitivity to the environment (affective pathway to psychosis). On the other hand, also in light with the hypothesis, I observed stronger association of polygenic risk for affective disorders in AP exposed to ERF. Interestingly, we also observe the trend of higher association with PRS-SZ in those AP not exposed to ERF, which may be explained by the observed gradient of genetic liabilities across psychotic disorders, presented in Chapter 5.

6.4.4 Support for an affective pathway to psychosis

When examining the associations of genetic underpinnings in SDD in exposed and non-exposed individuals (**Table 6.7**), I found that the trends of the odds of PRS-D as a whole are greater in those exposed as compared to non-exposed to SLE (OR from 1.1 to 1.36) and to migration (OR from 1.06 to 1.57). Similarly, the odds for PRS-BD are also greater in those exposed to childhood adversity (OR 1.35 to 1.61), SLE (OR 1.41 to 1.59) and in migrants (OR from 1.31 to 2.61). A previous work reported findings in the same direction, showing that childhood adversity, cannabis use, and to a lesser extent urbanicity, displayed departure from additivity risk in those with familial affective liability, in this cases measured by family history for depression (Radhakrishnan *et al.*, 2019). Our findings and those from Radhakrishnan et al., suggest that social adversity may trigger psychosis in those with genetic vulnerability for mood problems and is supported by the hypothesis of an "affective pathway to psychosis". This hypothesis postulates that low mood and anxiety as well as emotional dysregulation may precede the onset of psychosis in those exposed to social adversity (Myin-Germeys and van Os, 2007; Bebbington, 2015). This hypothesis has also been tested in general population studies showing moderate evidence that mood mediates the adversity (specially abuse) and psychosis association, but no studies have included in that equation the influence of PRS (Alameda *et al.*, 2020). Therefore, it would be informative to test whether those that develop psychosis as a consequence of social adversity (especially if mediated by the effects of mood), present higher PRS for BD and/or depression. Additionally, the observed higher genetic liability for mood disorders in both diagnostic groups – NAP and AP- among those exposed to environmental insults talks in favour of future venues exploring polygenic and polyenvironment association in a more continuous fashion or employing a symptom dimensional approach; for instance exploring GxE specificity on affective symptoms or anxiety which would provide support of the affective pathway of disease.

I also found that in those exposed to cannabis, the effect of PRS-BD was also greater than in not exposed (OR from 1.36 to 1.51). One possibility, in relation to the self-medication hypothesis of cannabis, is that individuals at risk for BD and depression may smoke to relieve some pre-existing distressing symptoms such as anxiety and low mood, and then the deleterious effects of THC (Di Forti *et al.*, 2009) put them a greater risk to develop psychosis.

6.4.5 The missing interaction between polygenic and polyenvironment effects

In the combined models including polygenic and polyenvironment exposure, alongside with interaction terms, I observed that when exploring effects for psychosis in general, both genes and environment play a role independently. Nonetheless, when I explored clinical groups, whereas AP appears exclusively associated to combined environmental exposure, genetic liability is the strongest signal for NAP; which is shown in between groups comparison. No evidence of GxE interaction was observed for either AP or psychosis in general, which contrast with previously observed departure from additivity of schizophrenia liability with cannabis and early adversity for NAP (Guloksuz *et al.*, 2019).

The observed sole association of polyenvironmental exposure for AP may be reflecting what was observed in previous works reporting that environmental exposures increase risk of psychotic experiences in affective disorders (Guloksuz *et al.*, 2015). Nonetheless, I would have expected to find also an association with genetic liability of BD and depression both independently and in interaction with environment in AP. It may be possible that the lack of observed interaction is due to lack of power, either for not having enough sample size or due to still limited variance explained by PRS-BD and PRS-D. Nonetheless, the differential association in exposed and unexposed individuals suggests that we could observe these interaction with large samples and as GWAS for BD and depression increase and explain higher variance for AP.

6.4.6 Strengths and limitations

The results presented here should be interpreted in the context of various strengths and limitations. As a major strength, I examined a well-characterised sample of FEP from a multicentric study designed with the purpose of exploring both genetic and environmental aspects of psychosis. Moreover, rather than limiting investigation to one environmental risk factor, my study shows individual but also combined associations of up to six different ERF consistently associated with psychosis. Lastly, it is the first study to date to combine polygenic associations of three major psychiatric disorders with polyenvironmental exposures, which can provide a more realistic picture of how the cumulative exposure can add to the genetic vulnerability.

However, some limitations should be acknowledged: this is a cross-sectional study, which prevent me established causality in relation with environmental exposures; and these were all reported retrospectively at the moment of psychosis onset, that has been reported as conflicting for some factors as childhood adversity (Baldwin *et al.*, 2019). Third, sample size is small for the higher requirements of GxE interaction in case-control studies(Van Os *et al.*, 2008). Fourth, I have based the clinical groups on the dichotomy of affective and non-affective psychosis. This places psychosis not-otherwise specified as non-affective, when it is unsure to claim that the same hypothesis of a more genetic and less environmental weight apply the same way to this groups than to schizophrenia. Fifth, analysing clinical groups based on diagnosis on a FEP sample always requires one to consider the known diagnostic instability (Schwartz *et al.*, 2000; Veen *et al.*, 2004). Last, further limitations pertaining the use of PRSs should be noted. When one employs PRS for SCZ, BD and depression for diagnostic associations, one needs to bear in mind the high heterogeneity of GWAS samples, which includes under the same phenotype samples with very varied psychopathology (Murray and Vassos, 2020). Furthermore, there is some evidence that current GWAS may be enriched of chronic patients, reflected by previously noted lower liability explained by PRS in incident samples (Meier *et al.*, 2016); thus, the effect of identified SNPs potentially capturing a long-lasting course of illness could result in type II error in our analyses given our sample is based on FEP. Additionally, in relation with PRS performance in GxE studies, current SNPs derived from a higher proportion of chronic patients may imply that part of the signals may be also reflecting exposures to environment; while on the other hand GWAS may be inefficient for detecting genes no directly connected to disorder, but whose effects may be conditional on environmental risk, which may hide or soften potential interaction with PRSs (Moffitt *et al.*, 2005).

6.4.7 Conclusions

Genetic and environmental exposures play independent role in increasing risks for psychosis, but these seem to interplay differently in affective and non-affective psychosis. Whereas affective psychosis seem to be a product of cumulative environmental insults alongside a higher genetic liability for affective disorders; non-affective psychosis seem to be due to two distinct pathways, one based on the genetic load for schizophrenia; and other in line with the affective pathway of psychosis, where polygenic risk for affective disorders may carry vulnerability

under certain social adversities. Future research should aim to disentangle the differential biological pathways of how polygenic risk for Bipolar Disorder and Depression, as opposed to schizophrenia, interact with specific environmental exposures in the development of affective or non-affective psychosis.

7. GENERAL DISCUSSION, LIMITATIONS AND FUTURE DIRECTIONS

In this last chapter, I will first review the lessons taken from the four studies that comprised this thesis, grouped into three main topics: environmental perspective, genetic view, and evidence found concerning how they interplay. Secondly, 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. Lastly, I will discuss future directions to develop in the field of etiology in affective psychosis.

7.1 OVERVIEW OF FINDINGS AND IMPLICATIONS

7.1.1 Environmental exposure in Affective Psychosis, what did we learn?

In Chapter 3, I presented a comprehensive review on how different environmental factors for Affective Psychosis (AP) are key in different developmental periods: from prenatal (advanced paternal age), perinatal (early and late gestational age), early childhood (parental death or separation), and adolescence (lifetime cannabis use and ethnic minority status). Most of these factors were later replicated in the empirical study comprising Chapter 6, where these associations were similar but slightly weaker than for non-affective psychosis (NAP). Of note, both the meta-analyses and the empirical study results support some overlap in the environmental load between non-affective and affective psychosis, suggesting a cross-diagnosis general risk for psychosis. However, from the empirical study we can understand that these may operate through distinct pathways in their relationship with genetic vulnerability, as will be discussed later.

From an epidemiological perspective, in Chapter 4 we saw that all four psychotic diagnostic groups (Schizophrenia –SCZ-, Bipolar Disorder –BD-, Psychotic Depression –MDD-P- and Psychosis NOS –PNOS-) presented significant variability in incidence between sites, which was partly explained by material deprivation aspects (unemployment, owner occupancy) but also by social fragmentation indicators (single-person household). Nonetheless, the most notable factor explaining higher incidence in all clinical groups, although more strongly for non-affective psychosis, corresponded to ethnic minority status. Interestingly, results from the meta-analysis also showed that belonging to an ethnic minority increased the odds of later AP by around 75%. The overrepresentation of mental disorder in ethnic minorities has been a subject of extensive debate, with suggested explanations ranging from methodological artefacts to challenging suggestions

regarding the systematic misdiagnosis of psychosis in minority groups (Morgan, 2020). Most recent interest has been placed on the particular social environment around this subgroup of the population, including factors such as background poverty and social disadvantage, high discriminability, or threat and hostility (Morgan, 2020). These, together with the other factors identified in the incidence study (i.e lower owner-occupancy, higher single-household), point to the consideration of a socio-developmental model where more exposure to adverse social factors increases one´s risk to manifest AP as well as other forms of psychosis.

7.1.2 Genetic architecture of Affective Psychosis: nor *lumpers* nor *splitters*: towards an integrated approach.

In Chapter 5 I analysed how polygenic liabilities for SCZ, BD, depression and IQ are associated across psychotic disorder groups; and then I explored the PRS's ability to differentiate between clinical groups with psychosis and how this can inform us about the genetic architecture of AP. I first found evidence suggesting an overlap in gradients of the different disorder liabilities (PRS-SZ, PRS-BD and PRS-D) across the psychosis spectrum. In this, we could place SCZ on one extreme and MDD-P in the other; BD lying in between; mirroring the polygenic distributions of schizophrenia, bipolar disorder and depression (see Fig 5.3). The PRS-SZ association gradient from NAP to AP categories was previously reported and supports the notion of a psychosis continuum across psychotic disorders (Allardyce *et al.*, 2017). Similarly, a gradient of associations of PRS-BD was also seen across BD subtypes (BD type I> BD type II) (Charney *et al.*, 2017), which was later observed in opposite direction for PRS-MDD (BD type II> BD type I)(Stahl *et al.*, 2019), reproducing partly the gradients observed in Study 2. It is of note that these studies, together with a recent systematic review (Almeida *et al.*, 2020) suggest a higher genetic demarcation of BD type I from type II, which is a category still understudied.

Chapter 5 also provides support for the discriminatory potential of PRSs and, more importantly, gives confirmation of a differential genetic architecture across groups. Both PRS-SZ and PRS-D differentiated global AP from NAP, and the subtype of MDD-P against NAP. PRS-SZ was also able to differentiate between BD and MDD-P, being only associated with the former. My results indicate that MDD-P may show more genetic departure from the other two categories (BD and NAP). Given the previously noted demarcation of BD type II, this raises the question of whether we would find

genetic overlap or higher genetic correlation with these two clinical groups, which will require further research.

Additionally, none of the PRSs could differentiate between BD and NAP. Indeed, this marked genetic overlap between NAP and BD goes in line with the replicated familial co-aggregation observed between SCZ and BD from family studies (Van Snellenberg and de Candia, 2009). The lack of distinction between BD and NAP in our results could be also partly explained by the fact that all our BD patients also had psychosis, since recent studies consistently found higher PRS-SZ in those BD expressing psychotic symptoms when compared with BD without psychosis (Allardyce *et al.*, 2017; Stahl *et al.*, 2019; Coombes *et al.*, 2020).

Overall we can state that the schizophrenia, bipolar disorder and depression liabilities are distributed in transdiagnostic gradients across the psychotic disorders spectrum, which goes in line with the *lumpers* view; nonetheless, we can stablish certain points of rarities at the intersections of those and other phenotypes continuums delineating diagnostic categories, which favours the *splitters* perspective. Integrating both splitting and lumping insights may help us define more informative diagnostic boundaries.

7.1.3 PRSxERF interplay; distinct or conjunctive pathways?

Having generated evidence on the independent roles of environmental influence and polygenic liability in the development of AP, in Chapter 6 I explored how genes and environment interplay in AP and how this differs with the non-affective psychosis counterpart.

Firstly, I found evidence that genetic vulnerability to both AP and NAP changes as a function of specific environmental exposures, suggesting differential pathways to illness. More precisely, I observed stronger association of PRS for affective disorders (BD and depression) in those AP exposed to ERF when compared with the non-exposed, suggesting a genetic moderation of sensitivity to environment. Although, to date, we lack studies exclusively looking to polygenic liability to BD; previous evidence was produced of an environmental interaction with polygenic liability for depression and exposure to SLE in line with the diathesis-stress model in mood disorders (Colodro-Conde *et al.*, 2018; Arnau-Soler *et al.*, 2019). In my results I didn't explore interaction with individual factors, but the observed higher polygenic

association specially with PRS-D in those exposed to environmental risk talks in favour of a moderator effect of the genetic liability for affective disorders.

In relation to NAP, results presented in Chapter 6 suggest that genetic liability to affective disorder (BD and depression) also predisposes to the development of NAP in the presence of exposure to social environmental insults, which support the hypothesis of an affective pathway to psychosis. On the contrary, associations with PRS-SZ in those exposed were lower than in those NAP who were not exposed to environmental insults. This, may indicate that polygenic liability to SCZ may work additively but not synergistically with the environmental factors. In fact, despite some recent evidence of significant interaction between PRS-SZ and cannabis and childhood adversity in psychosis (Guloksuz *et al.*, 2019), previous attempts utilizing multiplicative approach failed to find interactions with childhood trauma (Trotta *et al.*, 2016).

Interestingly, incipient research exploring aggregated measures of both genetic risk and environment, suggest that while not so clear for individual environmental factors, the cumulative exposure to adverse environment may increase risk for psychosis in conjunction with polygenic risk for schizophrenia (Pries *et al.*, 2019). However, interaction of aggregated environmental measure with polygenic liability has not been explored to date for AP. In Chapter 6, I explored GxE interactions effects on both AP and the whole group of psychosis employing aggregated measures of genetics (through the use of PRS-SZ, PRS-BD and PRS-D); and of environmental risk (employing both the Maudsley Environmental Risk Score for psychosis –MERS-; and a count score built on six different factors – Polyenvironmental Score, PES-). I couldn't find evidence of interaction between any of the polygenic liabilities and exposome measures, but this may be due to the statistical approach (I tested multiplicative rather additive interaction), or because of a limited statistical power due to sample size. In fact, a fundamental acknowledged classical problem in GxE is that sample sizes required to find GxE effects are several times larger than are needed to detect the main effect of a gene (Smith, 1984). Future studies addressing aggregated GxE measures are required to explore this further in AP.

To sum up, there are some indices suggesting a moderator role of polygenic liability of affective disorders for both NAP and AP groups in conjunction with certain

environmental exposures; while PRS for SCZ may operate through different pathways, acting additively to environmental risk. Moreover, there are good prospects in exploring PRSs of disorder liabilities in conjunction with combined environmental exposures in relation to onset as a way to understand how GxE operate in a more realistic setting; but research on candidate genes focusing on other outcomes such as neuroimaging phenotypes or natural history of disease seem promising as well (Aas *et al.*, 2014; Oliveira *et al.*, 2015; Bootsman, 2016). In accord with this, and given the possible evidence on the candidate genes approach for particular outcomes such as brain abnormalities, a further step may be to replicate and explore new findings of interplay of individual environmental exposures with gene-set or pathway-polygenic risk score that I will discuss on Section 7.3.4.

7.2 LIMITATIONS OF PRESENT WORK AND OF CURRENT EVIDENCE

Specific limitations, based mainly on design, methods and sample, were provided in pertinent chapters. In this section, I will discuss some general limitations I observed in the current literature that may need to be tackled in order to progress in our knowledge of the etiology of AP.

A key point to consider when exploring etiology of a disorder, is how well we can define that disorder. Indeed, a problem encountered by Psychiatry is its imprecise nature starting with the unclear and imprecise operationalised diagnosis. It is easy to understand inherent difficulties to find solid and replicable associations with outcomes that lack enough consistency. In this respect, whether we agree or not with the reported crisis of Psychiatric nosology, it is clear that current diagnosis suffers from some inaccuracies, though these may not be as strong as previously suggested. First, I already exposed in pertinent chapters the problem of diagnosis instability, especially when studying FEP patients (Heslin *et al.*, 2015), which correspond to a longitudinal inaccuracy; but we can also rely on meta-analytic evidence for a certain degree of confidence for the main groups of non-affective and affective psychosis (Fusar-Poli *et al.*, 2016). And second, we should also note cross-sectional inaccuracy from the diagnosis inconsistencies between professionals, with reported lower interrater reliability when based on unstructured interviews (Miller, 2001); and from the heterogeneity of sources (i.e. research vs clinical diagnosis). Although research-based diagnoses show good concordance, they have also been

shown to differ from diagnoses received in clinical settings (Kelly, 2018). Given than we take and accept evidence produced employing both sources, part of the lack of replications and inconsistencies may derive from here.

This is also true when relying on GWAS for specific disorders (i.e schizophrenia) combining heterogeneous datasets where broadly defined first episode patients and chronic schizophrenic patients are treated equally. Although this is explained as due to prioritising the benefits of increasing the sample size in order to capture more genetic signals, slight amends could be implemented. For example, a way to address this heterogeneity would be by providing case definitions of each dataset, and enabling readers to download these data together with the summary statistics; this would allow future studies to build the PRS based on a decided threshold of definition. Additionally, future cohorts aiming to contribute to big genetic consortia should be encouraged to provide both diagnosis –research and clinical- in order to understand the extent of the discrepancies at a higher level.

In similar terms, more emphasis should be placed in incorporating fine-grained phenotypes and well-defined psychopathology when exploring association with etiopathogenic factors. This, affects equally genetics (Cai *et al.*, 2020) or epidemiology, and is mainly referred to the extended problem with heterogeneity in Psychiatry. This could be hiding associations with social, environmental, and biological factors with more homogeneous subgroups, frustrating a better understanding of the disorders (Feczko et al., 2019). The same way I referred above to the importance of precise diagnosis, a finer characterisation of subtypes, such as BD subtypes; or subtypes of MDD -in which we would include MDD-P-, would enable us to acquire a clearer picture of etiopathogenic relationships; this is especially when the big categories overlap, as suggested recently when exploring the genetic underpinning of clinical heterogeneity and comorbidity of BD (Coombes *et al.*, 2020). But still larger samples exploring clinical sub-phenotypes of AP are needed.

Another important limitation is the fact that during decades of research, Psychiatry has been inferring natural course of psychiatric illnesses and building grounds for our taxonomy based on evidence produced on treated populations, leading to a lack of representability of the selected research populations. This, which has been previously pointed out (Waddington, 1997), assumes a selection bias in which those with good prognosis are less likely to either get in contact with, or stay in, mental

health care, making the most of our study samples "enriched" samples for severe cases (Cohen & Cohen, 1984). This being true, the fact that incipient research of psychotic phenomena in non-clinical population confirms a spectrum of severity based on presence on these features in general population (Nuevo, 2012), talks in favour of the same processes underlying the phenomena across the continuum of severity, where we should expect those patients with better prognosis -maybe not yet represented in research-, to lie in between the general population and the treated population but showing similar genetic and environmental etiopathogenic pathways.

Last but not least, a remarkable extended limitation pointed out in Chapter 3 is the observed neglect of AP in current literature, which is more prominent for MDD-P. Indeed, one of the main findings from my systematic review is that there are striking gaps in the evidence: around three quarters of the studies focused exclusively on BD, followed by studies examining AP as a composite category, with very few studies investigating the impact on MDD-P. In line with this, and also needing more research, other neglected phenotypes that would complete the spectrum of psychosis are the previously mentioned BD type II; and the controversial Schizoaffective Disorder (Vollmer-Larsen *et al.*, 2006; Murru *et al.*, 2012).

7.3 FUTURE DIRECTIONS IN THE FIELD

7.3.1 Psychotic Depression: a different entity?

It is important to dedicate a subsection to consider this particular clinical group and reflect on their independence as nosological entity in the light of the evidence from literature and the new information generated in the present thesis.

I said in the introduction that initially the origins of Psychotic Depression were generally aligned with what was initially defined as melancholia, since the first reports identified on it the presence of persecutory ideas and other psychosis. Interestingly, despite being previously treated as equivalent, now it is accepted in current classifications as being at the same level but separate from depression with melancholic features. Indeed, a recent paper shows that the prevalence of psychotic symptoms in both melancholic and non-melancholic severe depressed patients are similar, thus showing that not all the melancholics manifest with psychosis (Tondo,

L. *et al.*, 2020), which also replicated previous findings (Parker *et al.*, 1991; Hadzi-Pavlovic *et al.*, 1995).

Later on, psychotic depression appeared as a severe subtype of unipolar depression or depression in BD in both DSM-IV and ICD-10. Nonetheless, despite psychotic depression seeming to be a more severe form of the disease (Costa *et al.*, 2020), there is evidence talking in favour of further clinical differences over merely intensity of depressive symptoms (Forty *et al.*, 2009; Caldieraro *et al.*, 2013), which suggests that psychotic depression may be in fact a distinct clinical syndrome (Østergaard, Soren Dinesen *et al.*, 2012).

From here, we can summarise that there is support for psychotic depression not being treated as equivalent of melancholic depression and that it is neither just a severe form of depression. Currently included under the modifier of *depression with psychotic features* in both Bipolar Disorders (in DSM 5) and Mood Disorders (in ICD-11) chapters, we saw there are voices in favour to treat it as independent category (Østergaard, Søren Dinesen *et al.*, 2012). Results from Chapter 5 suggest a higher genetic dissimilarity from SCZ than BD, which is equally driven by a negative association with PRS-SZ, and by a strong positive association with PRS-D. Based on this, it should be conceptualised as closer to the affective disorders groups.

Little support of its clinical identity comes from epidemiological research, where efforts should be invested in studying subgroups from the environmental perspective. In Chapter 3, none of the identified studies for AP explored specifically the effect of maternal infection, perinatal stress, childhood infection, substance misuse, ethnic minority, current urbanicity, brain injury or SLE on the risk of developing psychotic depression; and research on other factors was very scarce (Østergaard *et al.*, 2013). Thus, this represents a major gap in the literature.

To sum up, given the studies claiming its separation from other forms of depressions, the incipient genetic evidence separating it from BD, there is some bases to keep digging into the question of establishing psychotic depression as a separate entity. Nonetheless, future studies should aim at two things: to replicate previous findings supporting its condition as separate entity based on clinical measures (Charney and Nelson, 1981; Helms and Smith, 1983; Schatzberg and Rothschild, 1992) with update methods and bigger samples; and second, to replicate genetic differences in samples including BD, severe depression with no psychotic

features, and the BD type II in order to gain also more understanding of where it should lie in the psychosis continuum.

7.3.2 Environmental Risk Factors: where should we head to?

A first thing to address for future research, is the need to develop quality ad-hoc studies for Affective Disorders, including well-characterised subgroups from the whole spectrum covering from the non-psychotic to psychotic. As previously mentioned for improving polygenic prediction, more emphasis should be given to incorporating fine-grained phenotypes and well-defined psychopathology when exploring association with ERFs and the AP group, since we saw in the systematic review that current research is mostly confined to BD and MDD, with few studies focusing on BD subtypes and barely any studies for Psychotic Depression specifically.

A promising trend in research is starting to combine different ERF into single scores in an attempt to capture part of the complexity, and acknowledging the added detrimental effect of the cumulative exposure. In this respect, we previously mentioned the psychosis polyrisk score by Oliver et al. (Oliver *et al.*, 2019); the Maudsley Environmental Score by Vassos et al. (Vassos *et al.*, 2019); and the Exposome Score for Schizophrenia by Pries et al.(Pries *et al.*, 2019). The latter, which includes binary exposures of winter birth, hearing impairment, cannabis use, bullying, and emotional, physical, and sexual abuse along with physical and emotional neglect; has already proven to have some potential in improving risk prediction and stratification in general population (Pries, L.-K. *et al.*, 2020).

Nonetheless, this approach is still in its infancy, and longstanding limitations on environmental research still prevail: the consideration of the timing of exposure (i.e different effect in early childhood or late adolescence(Alameda *et al.*, 2016)); the failure to measure length and intensity of exposures (since some scores are built from binary measures); and the unaccounted hindered interactions within environmental factors, that may be influencing on each other or aggregating in clusters where exposure to one may predispose exposure to others.

Moreover, efforts to date have been confined to psychosis or broad-definition of SCZ, which makes it unclear if the findings are applicable to the AP groups. In fact, between the two tested scores presented in Chapter 6, the sum score based on the

count of environmental factors (PES) performed better than the meta-analytical estimate for psychosis (MERS). Again, another call should be made in encouraging the design of aggregated or combined scores for AP; more so given the preliminary evidence of a higher cumulative effect of ERF on AP than in NAP as presented in Chapter 6. In line with this, meta-analyses exploring specific effects of ERF on AP like the one presented in Chapter 3 could be used to tailor environmental scores for this subgroup.

7.3.3 Future of PRS and translational application in Affective psychosis

Polygenic risk score has claimed clinical utility in three main areas of research: diagnostic (prediction of diagnosis or cross-disorder correlation), prognosis and treatment(Lewis and Vassos, 2020).

In this thesis, I explored its use from the diagnostic perspective, using it to predict the disorders and also testing its use to differentiate between disorders, which is also informative of the genetic architecture of these disorders, as presented in Chapter 5 and previously discussed (Section 7.1.2). Nonetheless, we need to acknowledge limitations for individual-level prediction in Psychiatry until GWAS samples accumulate enough size to empower current PRSs (Schijven *et al.*, 2020). Indeed, it is important to bear in mind that since PRSs are based on actual SNPs effect to explain phenotypic variance that is only partly attributable to genetic factors, PRSs could never thus explain more variance than the SNP-heritability of the target disease. However, its usefulness has already been proven for prediction in other medical conditions, such as breast cancer, cardiovascular disease or improving prediction in Alzheimer (Lewis and Vassos, 2017). This should encourage studies of its utility to psychiatric disorders given their known high heritability; but some adjustments needs to be taken, such as restricting the use to high risk population, reducing heterogeneity of samples or combining with other PRSs or with other type of data.

In line with this, in Chapter 5 I explored how the joint use of different PRSs improved the variance explained in the diagnostic categories, with our results supporting the combined use of PRS for SCZ and depression for diagnostic differentiation of non-affective and affective psychosis. This approach has been limited to date mostly to genetic scores for clinical diagnosis such as MDD or syndromic entities as broad-defined depression. More recently, the approach of

combining PRSs of different phenotypes, has brought valuable information of the potential usefulness on relying on core symptoms as well. For instance, in a recent paper from Coombes et al, alongside a positive association with PRS for SCZ, the strongest variance of BD with psychotic features was explained through a negative associations with PRS for BMI and anhedonia but not MDD (Coombes *et al.*, 2020).

Another point of SCZ and BD commonalities that can be suitable as a polygenic phenotype is the cognitive impairment classically associated with both disorders (Grande, 2016; Owen, 2016). In Chapter 5, PRS-IQ didn't contribute to models for clinical comparisons, with the effect sizes almost identical across clinical groups. The genetic influence of cognition on SCZ has more basis than on BD (Owen and O'Donovan, 2017). Nonetheless, although due to shared genetic liability with SCZ, PRS-BD seem to predict impaired cognition in childhood (Mistry *et al.*, 2019). Additionally, a recent work combining GWAS data from SCZ, BD and general intelligence, showed evidence of genetic overlap of both disorders with intelligence in opposite directions, being 81% of loci shared with SCZ associated with poorer performance and the 75% of BD ones indicating better cognition (Smeland, Bahrami, *et al.*, 2020).This suggests the potential utility of employing combined polygenic scores as a way to capture the clinical heterogeneity mirroring it with multiple genetic liabilities.

An option that can contribute to reducing heterogeneity comes by exploring polygenic associations in higher risk populations or in samples with higher clinical severity. For instance, those with more severe MDD presented higher association with PRS-MDD (Wray *et al.*, 2018); and in the CONVERGE sample on Chinese women, the investigators found an increased genetic signal among those experiencing severe melancholic depression (Cai *et al.*, 2015). Another recent study found evidence for an increased genetic burden for MDD among those patients receiving electroconvulsive therapy (ECT), which can be used as a proxy of severity(Foo *et al.*, 2019). This suggests higher polygenic discriminability on subtypes at the extreme end of clinical severity, and the potential to capture new genetic signals for AP as GWAS are performed on more severe groups. In fact, the Genetics of Electroconvulsive Therapy International Consortium (Gen-ECT-ic) has been recently formed under the Psychiatric Genetic Consortium with the intention to study the genomics of very severe depressive disorders and explore response to a

specific intervention in depression, including depression with psychosis(Baune *et al.*, 2019).

Besides, PRSs can still serve as a useful tool in combination with other sources of data, such as psychiatric signs or symptoms, socio-demographic data, etc. For instance, PRS has been successfully added as part of a battery of factors to compose a polyrisk score for prediction to transition to psychosis on high-risk individuals (Oliver *et al.*, 2019). Moreover, the PRS for SCZ modestly improved individualized psychosis risk prediction when added to a different psychosis risk calculator including cognitive performance and functioning variables (Perkins *et al.*, 2020).

Another future avenue for PRS translational use in AP covers the other two broad uses: prognosis and treatment prediction. In terms of prognosis, a recent study shows that depressive patients with high PRS-BD are more likely to transition to BD, while higher PRS-SZ seems to be more generally associated with progression to either MDD-P or any form of BD (Musliner *et al.*, 2020). The previously mentioned study on BD by Coombs et al., showed that rapid-cycling and suicide were positively related with PRS-MDD but not with PRS-BD for the former, whose variance was also explained by PRS for ADHD and PTSD (Coombes *et al.*, 2020). As a side note on prognosis, PRS has started to be explored in relation with lifespan, so far PRS-SZ and to a lesser extent PRS-BD showing genetic negative association with polygenic proxy of premature mortality (Muntané *et al.*, 2020), providing molecular framework for the accelerated aging hypothesis (Kirkpatrick and Kennedy, 2018).

Regarding treatment, we know that individuals with BD with a low PRS for SCZ (Amare *et al.*, 2018) and for MDD (Amare *et al.*, 2020) respond better to lithium treatment than patients with a high SCZ or MDD PRS; this, has supported the concept of a lithium-responsive biotype. Higher PRS-SZ has also been associated with worse response or less improvement with antipsychotic drug treatment (Zhang *et al.*, 2019), and is suggestive of non-response to treatment in MDD (Fanelli *et al.*, 2020), showing a negative association with response to antidepressant (Pain *et al.*, 2020). Results such as the ones presented in Chapter 5, where PRS-SZ and PRS-D differentiated NAP and AP groups, may contribute in the future in informing treatment decisions in FEP with an affective component. In theory, one could potentially opt to not maintain an antipsychotic if the patient presents in the lower end of PRS-SZ score and high PRS-D score, for instance.

7.3.4 PRS pathway approach, from phenotype to biological pathway

Using PRSs built on phenotypes representing disorders will limit our understanding on the underlying biological mechanism, but some PRS cross-disorder analyses can provide interesting data about biological pathways. Arising from one of the most accepted biological hypothesis of the formation of psychotic phenomena, the dopamine hypothesis of psychosis (Howes *et al.*, 2017), some studies have explored genetic correlation with Parkinson Disease, where dopamine dysfunction is the primary lesion. Upcoming research suggest that common genetic variants might contribute to the mechanisms underlying both SCZ and Parkinson (Smeland, 2020a), despite some with opposite direction effects (Quattrone, 2020); but a genetic correlation has not yet been found between BD and Parkinson (Bandres-Ciga, 2020). Following with neuropsychiatric inputs, a study found evidence for SCZ and BD genetic distinction by showing genetic pleiotropy between SCZ and multiple sclerosis, but not with BD, suggesting that the MHC signals may differentiate SCZ from BD susceptibility (Andreassen, 2015). Thus, digging deeper into biological pathways looks a promising approach in the search for finer genetic clustering.

Another approach is to transition from PRS built on phenotypes to start looking at transcriptome-based polygenic risk score (T-PRS) comprising of gene expression-altering variants or pathway-specific PRS. For instance, a PRS built on GWAS for SCZ including only the variants functionally related with dopamine functioning showed a positive association with impaired working memory in the general population (Wang *et al.*, 2018), which could be tested back to back in NAP and AP in order to explore if the slightly better cognitive performance in AP can be partly explained at this level. Gene-sets comprising serotoninergic, dopaminergic, glutamatergic, and neuroendocrine signalling pathways could be tested across psychotic disorder continuums to add biological specificity to current diagnostic categories.

Besides, using these gene-set PRS may also enable us to disentangle how exposures to certain ERFs impact differently and to gain knowledge on how these operate at different levels: for example, childhood trauma on dopaminergic system and on activation of HPA stress axis; cannabis on dopaminergic and endocannabinoid system; or SLE on HPA stress axis. For instance, in the same way dopaminergic PRS appeared to interact with childhood life events in relation to unemotional traits (Ruisch *et al.*, 2020), it may be interacting with childhood adversity in relation to

some identified cognitive or social cognitive mediators of psychosis outcome, such as functioning (Rodríguez *et al.*, 2021).

Furthermore, ongoing studies go beyond clinical symptoms to define subtypes of disease based on neuroimaging, neurocognitive tests and EEG patterns in relation with genetic markers, with promising value for the nosology of AP (Gordovez and McMahon, 2020). Hence, despite the already gained popularity and widespread use in research, PRS has still exciting avenues to offer.

7.3.5 The missing link between GxE

After discussing the potential advances into both elements of the equation – genes and environment-, another consideration in order to broaden our understanding on this interplay is looking for the missing link by combining the field of Psychiatry and opening up research into these three branches: Sociology, Psychology and Biology.

From the sociological perspective, it would be worth exploring those elements that may be associating with certain environmental factors and could be acting as moderators and confounders in their associations with AP outcome. At this respect, it was already suggested that societal elements such as social discrimination, experienced of racism, higher levels of poverty… may explain parts of the effects of migration or ethnicity in psychosis (Veling and Susser, 2011; Morgan *et al.*, 2019). Similarly, in relation with urbanicity, low social cohesion and crime victimization have proved to increase risk of developing psychotic symptoms (Newbury *et al.*, 2016). These findings, would still need to be replicated in AP, alongside with other elements as social identity, cultural distance or political reality.

Similarly, it is possible to switch the focus into more psychological aspects than can contribute or explain associations with disease in co-occurrence with certain environmental exposures. This would capture educational and parenting elements. For instance, having a parental history of NAP seems associated with lower socio-emotional functioning in offspring independently and in addition to childhood trauma (Matheson *et al.*, 2017). We would also consider here how certain personality traits shape the encounter between vulnerability and the perception and processing of the environment; as well as the key concept of resilience, that has gained more attention also on genetics (Hess *et al.*, 2019). Indeed, resilience is of

paramount importance and its incorporation into models linking genetic vulnerability with sensitivity to environment is warranted.

The third suggested branch to explore within the missing GxE link would be Biology, with promising advances coming from exploring gene-expression levels and epigenetics among others. Regarding the former, gene expression measures in peripheral blood has emerged as a viable candidate for peripheral biomarker in BD (Middleton *et al.*, 2005; Munkholm *et al.*, 2015), with some potential to serve as a differential point between SCZ and BD (Gouvea *et al.*, 2016). Epigenetic modifications refer to non-structural functional changes in DNA or associated proteins that can imply modifying protein translation (Jaenisch and Bird, 2003). With accumulating findings on epigenetic markers in BD (Ludwig and Dwivedi, 2016), and incipient evidence of epigenetic changes with known ERFs, such as exposure to adverse life events (Binder, 2017) or childhood adversity (Tyrka *et al.*, 2016), epigenetics proves to be a promising field linking the complex GxE interactions as well.

Last but not least, another general consideration for future venues investigating GxE relationships would involve switching from the categorical perspective to explore GxE prediction models looking at dimensions of psychopathology. As mentioned in Chapter 6 when discussing around the finding of PRS for BD and depression explaining more variance in those NAP exposed to certain environmental insults, suggesting an affective pathway of disease; exploring specific GxE association for specific symptom dimensions or with general ones (i.e. the p factor) would inform of observed shared and differential pathways of current nosological entities, which eventually would add clarity to both the existing overlap among disorders while potentially also clarify part of the observed heterogeneity within categories.

8. GENERAL CONCLUSION

This thesis aimed to explore different etiological aspects of affective psychosis and its differences with non-affective psychosis, with special emphases on the genetic and environmental pillars of aetiology. It also aimed to contribute to filling the gap in the literature of this neglected category in comparison with its non-affective counterpart. Although waiting to be replicated, preliminary results from an international multisite sample shows incidences of psychotic depression and bipolar disorders of around one third of schizophrenia (2.88 and 2.51per 100kpy respectively), following a bi-modal distribution across ages in female. These incidences, which varies significantly across sites, appeared to be modified mainly in relation to ethnic minority status, which goes in line with a socio-developmental theory of psychosis. Indeed, belonging to an ethnic minority was also identified as a risk factor for affective psychosis with meta-analytic support, alongside other factors occurring across the lifespan: from prenatal (advanced paternal age), perinatal (early and late gestational age), early childhood (parental death or separation), and adolescence/later in life (lifetime cannabis use). It was later sown that some of these environmental factors proved to be individually associated with risk to develop affective psychosis, but also when aggregated into a polyenvironmental score, showing higher effect of environmental insults in affective psychosis than in non-affective psychosis, results that will require replication.

On the other side of the coin, I found support for the presence of a genetic psychosis continuum, shown by a decreasing gradient of PRS-SZ association from the non-affective psychosis group, through bipolar disorder, to a non-association with psychotic depression; and an inverse gradient in the case of PRS-D. This allows the conceptualization of a model in which the genetic vulnerability of psychotic disorders is distributed across a multidimensional continuum with non-affective psychosis at one end, bipolar disorder in the middle and psychotic depression at the other extreme. I also found that polygenic score for schizophrenia and depression can differentiate affective psychosis in general and psychotic depression specifically from the schizophrenia and related disorders, which can have potential usefulness on high-risk or early psychosis phases for treatment planning and prognosis prediction.

Lastly, when exploring how genes and environment interplay, my results suggest that genetic vulnerability for affective and non-affective psychosis can operate differently in its relationship with environment for the different outcomes. This is

shown by the differential effect of polygenic loads for schizophrenia, bipolar disorder and depression with the two clinical groups based on exposure or not to environmental factors. Whereas affective psychosis seems to be a product of cumulative environmental insults alongside a higher genetic liability for affective disorders; non-affective psychosis seem to be due to two distinct pathways. On one hand, there appear to be those NAP patients with higher polygenic score for schizophrenia but less environmental exposure, where GxE appears to act additively, which would correspond to a more heritable or endogenous form of disease. On the other hand, we may find another subgroup of NAP exposed to environmental factors presenting lower polygenic load for schizophrenia but higher polygenic load for affective disorders, that may be inducing sensitivity to those environmental exposures, and would fit with the affective pathway to psychosis. Lastly, no evidence of GxE interaction was observed when I explored polygenic scores with aggregated or cumulative measures of environmental exposure. Future research should aim to disentangle the potential differential biological pathways of how polygenic risk for bipolar disorder and depression, as opposed to schizophrenia, interact with specific environmental exposures in the development of affective or non-affective psychosis.

Overall, this thesis provides support for the view that both environment and genetics play their specific role on affective psychosis. Despite these factors presenting a noticeable overlap with those factors replicated for non-affective psychosis, which supports a transdiagnostic effect across psychosis, certain distinctions and differentiations were found for affective psychosis. These results require replication, and further research needs to be done exploring gene and environment interplay, but some support of differential pathways can be found in this thesis. This, in combination with the upcoming advances from a wide range of new avenues (from biology to sociology), holds out the hope of exciting findings in our understanding of the etiopatogenic underpinnings of affective psychosis, which will ultimately give us ground to set clearer splits over the lumps.

9. REFERENCES

Aas, M, Haukvik, U K, Djurovic, S, Tesli, M, Athanasiu, L, Bjella, T, Hansson, L, Cattaneo, A, Agartz, I, Andreassen, O A and 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*. Elsevier Ltd, **59**, p. 14–21.

Abel, K M, Heuvelman, H P, Jörgensen, L, Magnusson, C, Wicks, S, Susser, E, Hallkvist, J and Dalman, C (2014) Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: Population based cohort study, *BMJ (Online)*, **348**.

Ackerknecht, E H (1959) *A Short History of Psychiatry* . Hafner Publishing Company.

Akinhanmi, M O, Biernacka, J M, Strakowski, S M, McElroy, S L, Balls Berry, J E, Merikangas, K R, Assari, S, McInnis, M G, Schulze, T G, LeBoyer, M, Tamminga, C, Patten, C and Frye, M A (2018) Racial disparities in bipolar disorder treatment and research: a call to action, *Bipolar Disorders*. Blackwell Publishing Inc., p. 506–514.

Alameda, L, Golay, P, Baumann, P S, Ferrari, C, Do, K Q and Conus, P (2016) Age at the Time of Exposure to Trauma Modulates the Psychopathological Profile in Patients With Early Psychosis, *The Journal of Clinical Psychiatry*, **77**, p. e612–e618.

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 and Murray, R M (2020) A systematic review on mediators between adversity and psychosis: Potential targets for treatment, *Psychological Medicine*, **50**, p. 1966–1976.

Aleman, A, Kahn, R S and Selten, J P (2003) Sex differences in the risk of schizophrenia: Evidence from meta-analysis, *Archives of General Psychiatry*. Arch Gen Psychiatry, **60**, p. 565–571.

Allardyce, J, Leonenko, G, Hamshere, M, Pardiñas, A F, Forty, L, Knott, S, Gordon-Smith, K, Porteous, D J, Haywood, C, Di Florio, A, Jones, L, McIntosh, A M, Owen, M J, Holmans, P, Walters, J T R, Craddock, N, Jones, I, O'Donovan, M C and Escott-Price, V (2017) Association Between Schizophrenia-Related Polygenic Liability and the Occurrence and Level of Mood-Incongruent Psychotic Symptoms in Bipolar Disorder, *JAMA Psychiatry*.

Almeida, H S, Mitjans, M, Arias, B, Vieta, E, Ríos, J and Benabarre, A (2020) Genetic differences between bipolar disorder subtypes: A systematic review focused in bipolar disorder type II, *Neuroscience and Biobehavioral Reviews*. Elsevier Ltd, p. 623–630.

Altamura, A C, Buoli, M, Cesana, B M, Fagiolini, A, de Bartolomeis, A, Maina, G, Bellomo, A and Dell'Osso, B (2019) Psychotic versus non-psychotic bipolar disorder: Socio-demographic and clinical profiles in an Italian nationwide study, *Australian and New Zealand Journal of Psychiatry*. SAGE Publications Inc., **53**, p. 772–781.

Alvarado-Esquivel, C, Estrada-Martínez, S and Pérez-Alamos, A R (2019) A Case–Control Seroprevalence Study on the Association Between Toxoplasma gondii Infection and Bipolar Disorder, *Frontiers in Psychiatry*. Frontiers Media S.A., **10**.

Amare, A T, Schubert, K O, Hou, L, Clark, S R, Papiol, S, Heilbronner, U, Degenhardt, F, Tekola-Ayele, F, Hsu, Y H, Shekhtman, T, Adli, M, Akula, N,

Akiyama, K, Ardau, R, Arias, B, Aubry, J M, Backlund, L, Bhattacharjee, A K, Bellivier, F, *et al.* (2018) Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: A genome-wide association study, *JAMA Psychiatry*. American Medical Association, **75**, p. 65–74.

Amare, A T, Schubert, K O, Hou, L, Clark, S R, Papiol, S, Cearns, M, Heilbronner, U, Degenhardt, F, Tekola-Ayele, F, Hsu, Y H, Shekhtman, T, Adli, M, Akula, N, Akiyama, K, Ardau, R, Arias, B, Aubry, J M, Backlund, L, Bhattacharjee, A K, *et al.* (2020) Association of polygenic score for major depression with response to lithium in patients with bipolar disorder, *Molecular Psychiatry*. Springer Nature.

American Psychiatric Association: (2013) *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Washington DC: American Psychiatric Pub.

American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders. 3.* Washington, DC: American Psychiatric Association.

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

Angst, J and Gamma, A (2008) Diagnosis and course of affective psychoses: Was Kraepelin right?, in *European Archives of Psychiatry and Clinical Neuroscience*. Springer, p. 107–110.

Angst, J and Marneros, A (2001) Bipolarity from ancient to modern times: Conception, birth and rebirth, *Journal of Affective Disorders*. Elsevier, p. 3–19.

Angst, J and Perris, C (1968) Zur Nosologie endogener Depressionen - Vergleich der Ergebnisse zweier Untersuchungen, *Archiv für Psychiatrie und Nervenkrankheiten Vereinigt mit Zeitschrift für die Gesamte Neurologie und Psychiatrie*. Springer-Verlag, **210**, p. 373–386.

Arango, C, Fraguas, D, Parellada, M, M, C, R, M, JJ, M and AA, N (2014) Differential Neurodevelopmental Trajectories in Patients With Early-Onset Bipolar and Schizophrenia Disorders, *Schizophrenia Bulletin*. Alcalá de Henares, Alcalá, **40**, p. S138–S146.

Arnau-Soler, A, Adams, M J, Clarke, T K, MacIntyre, D J, Milburn, K, Navrady, L, Hayward, C, McIntosh, A and Thomson, P A (2019) A validation of the diathesis-stress model for depression in Generation Scotland, *Translational Psychiatry*. Nature Publishing Group, **9**.

Association, A P (2000) *DSM-IV-R: Diagnostic and statistical manual of mental disorders. Revised*. Washington, DC: American Psychiatric Association.

Azorin, J M, Akiskal, H, Akiskal, K, Hantouche, E, Châtenet-Duchêne, L, Gury, C and Lancrenon, S (2007) Is psychosis in DSM-IV mania due to severity? The relevance of selected demographic and comorbid social-phobic features, *Acta Psychiatrica Scandinavica*. Acta Psychiatr Scand, **115**, p. 29–34.

Badner, J A and Gershon, E S (2002) Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia, *Molecular Psychiatry*, **7**, p. 405–411.

Bain, M, Juszczak, E, McInneny, K and Kendell, R E (2000a) Obstetric complications and affective psychoses. Two case-control studies based on

structured obstetric records, *British Journal of Psychiatry*, **176**, p. 523–526.

Bain, M, Juszczak, E, McInneny, K and Kendell, R E (2000b) Obstetric complications and affective psychoses, *British Journal of Psychiatry*, **176**, p. 523–526.

Baldwin, J R, Reuben, A, Newbury, J B and Danese, A (2019) Agreement between prospective and retrospective measures of childhood maltreatment: A systematic review and meta-analysis, *JAMA Psychiatry*. American Medical Association, p. 584–593.

Baldwin, P, Browne, D, Scully, P J, Quinn, J F, Morgan, M G, Kinsella, A, Owens, J M, Russell, V, O'Callaghan, E and Waddington, J L (2005) Epidemiology of first-episode psychosis: Illustrating the challenges across diagnostic boundaries through the Cavan-Monaghan study at 8 years, *Schizophrenia Bulletin*, p. 624–638.

Balshem, H, Helfand, M, Schünemann, H J, Oxman, A D, Kunz, R, Brozek, J, Vist, G E, Falck-Ytter, Y, Meerpohl, J, Norris, S and Guyatt, G H (2011) GRADE guidelines: 3. Rating the quality of evidence, *Journal of Clinical Epidemiology*. Elsevier USA, **64**, p. 401–406.

Barichello, T, Badawy, M, Pitcher, M R, Saigal, P, Generoso, J S, Goularte, J A, Simões, L R, Quevedo, J and Carvalho, A F (2016) Exposure to Perinatal Infections and Bipolar Disorder: A Systematic Review., *Current molecular medicine*, **16**, p. 106–18.

Barkus, E J, Stirling, J, Hopkins, R S and Lewis, S (2006) Cannabis-induced psychosis-like experiences are associated with high schizotypy., *Psychopathology*. Karger Publishers, **39**, p. 175–8.

de Barros, J L V M, Barbosa, I G, Salem, H, Rocha, N P, Kummer, A, Okusaga, O O, Soares, J C and Teixeira, A L (2017) Is there any association between Toxoplasma gondii infection and bipolar disorder? A systematic review and meta-analysis., *Journal of affective disorders*, **209**, p. 59–65.

Bastos, C R, Tovo-Rodrigues, L, Ardais, A P, Xavier, J, Salerno, P S V, Camerini, L, Jansen, K, de Mattos Souza, L D, da Silva, R A, Lara, D R and Ghisleni, G (2020) The role of CACNA1C gene and childhood trauma interaction on bipolar disorder, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. Elsevier Inc., **101**.

Baune, B T, Soda, T, Sullivan, P F and Zandi, P (2019) The Genomics of Electroconvulsive Therapy International Consortium (GenECT-ic), *The Lancet Psychiatry*. Elsevier Ltd, p. e23.

Bebbington, P (2015) Unravelling psychosis: psychosocial epidemiology, mechanism, and meaning, *Shanghai Archives of Psychiatry*. Editorial Department of theShanghai Archives of Psychiatry, p. 70–81.

Bebbington, P and Ramana, R (1995) The epidemiology of bipolar affective disorder, *Social Psychiatry and Psychiatric Epidemiology*. Springer-Verlag, p. 279–292.

Benard, V, Pignon, B, Geoffroy, P A, Benradia, I, Roelandt, J L, Rolland, B, Fovet, T, D'Hondt, F, Thomas, P, Vaiva, G and Amad, A (2020) Depression with and without a history of psychotic symptoms in the general population: sociodemographic and clinical characteristics, *Journal of Affective Disorders*. Elsevier B.V., **273**, p. 247–251.

Benros, M E, Waltoft, B L, Nordentoft, M, Ostergaard, S D, Eaton, W W, Krogh, J and Mortensen, P B (2013) Autoimmune diseases and severe infections as risk factors for mood disorders a nationwide study, *JAMA Psychiatry*. American Medical Association, **70**, p. 812–820.

Bergink, V, Larsen, J T, Hillegers, M H J, Dahl, S K, Stevens, H, Mortensen, P B, Petersen, L and Munk-Olsen, T (2016) Childhood adverse life events and parental psychopathology as risk factors for bipolar disorder, *Translational psychiatry*, **6**, p. e929.

Berrettini, W (2003) Evidence for shared susceptibility in bipolar disorder and schizophrenia, *American Journal of Medical Genetics*, **123C**, p. 59–64.

Berrios, G (1996) *The history of mental symptoms: Descriptive psychopathology since the nineteenth century*. Cambridge University Press.

Bifulco, A, Brown, G W and Harris, T O (1994) Childhood Experience of Care and Abuse (CECA): A Retrospective Interview Measure, *Journal of Child Psychology and Psychiatry*. Blackwell Publishing Ltd, **35**, p. 1419–1435.

Binder, E B (2017) Disección de los mecanismos moleculares de las interacciones gen x entorno: Implicaciones para el diagnóstico y tratamiento de trastornos psiquiátricos relacionados con el estrés, *European Journal of Psychotraumatology*. Taylor and Francis Ltd.

Bingham, K S, Whyte, E M, Mulsant, B H, Rothschild, A J, Rudorfer, M V., Marino, P, Banerjee, S, Butters, M A, Alexopoulos, G S, Meyers, B S and Flint, A J (2019) Health-related quality of life in remitted psychotic depression☆, *Journal of Affective Disorders*. Elsevier B.V., **256**, p. 373–379.

Bland, j. M and Altman, D G (1995) Multiple significance tests: The Bonferroni method, *BMJ*. BMJ, **310**, p. 170.

Bonnín, C M, Sánchez-Moreno, J, Martínez-Arán, A, Solé, B, Reinares, M, Rosa, A R, Goikolea, J M, Benabarre, A, Ayuso-Mateos, J L, Ferrer, M, Vieta, E and Torrent, C (2012) Subthreshold symptoms in bipolar disorder: Impact on neurocognition, quality of life and disability, *Journal of Affective Disorders*. Elsevier, **136**, p. 650–659.

Bootsman, F (2016) *Brain structure in bipolar disorder: A longitudinal neuroimaging study in twins*. Utrech University.

Bora, E, Yücel, M and Pantelis, C (2010) Cognitive impairment in schizophrenia and affective psychoses: Implications for dsm-v criteria and beyond, *Schizophrenia Bulletin*. Schizophr Bull, p. 36–42.

Bortolato, B, K?hler, C A, Evangelou, E, Le?n-Caballero, J, Solmi, M, Stubbs, B, Belbasis, L, Pacchiarotti, I, Kessing, L V., Berk, M, Vieta, E and Carvalho, A F (2017) Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses, *Bipolar Disorders*, **19**, p. 84–96.

Bramon, E and Sham, P C (2001) The common genetic liability between schizophrenia and bipolar disorder: a review., *Current psychiatry reports*, **3**, p. 332–7.

Brittain, P J, Stahl, D, Rucker, J, Kawadler, J and Schumann, G (2013) A review of the reliability and validity of OPCRIT in relation to its use for the routine clinical assessment of mental health patients, *International Journal of Methods in Psychiatric Research*. John Wiley & Sons, Ltd, **22**, p. 110–137.

Brown, A, Bao, Y, McKeague, I, Shen, L and Schaefer, C (2013) Parental age and risk of bipolar disorder in offspring, *Psychiatry Research*, **208**, p. 225–231.

Brown, Alan S., Susser, E S, Lin, S P and Gorman, J M (1995) Affective disorders in Holland after prenatal exposure to the 1957 A2 influenza epidemic, *Biological Psychiatry*. Elsevier, **38**, p. 270–273.

Brown, A. S., Susser, E S, Lin, S P, Neugebauer, R and Gorman, J M (1995) Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944-45, *British Journal of Psychiatry*, **166**, p. 601–606.

Brugha, T, Bebbington, P, Tennanp, C and Hurry, L (1985) The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat, *Psychological Medicine*, **15**, p. 189–194.

Buizer-Voskamp, J E, Laan, W, Staal, W G, Hennekam, E A M, Aukes, M F, Termorshuizen, F, Kahn, R S, Boks, M P M and Ophoff, R A (2011) Paternal age and psychiatric disorders: Findings from a Dutch population registry, *Schizophrenia Research*, **129**, p. 128–132.

Buka, S L and Fan, A P (1999) Association of prenatal and perinatal complications with subsequent bipolar disorder and schizophrenia, in *Schizophrenia Research*, p. 113–119.

Burton, R (1883) *The Anatomy of Melancholy*. Philadelphia: E. Claxton & Company.

Cai, N, Bigdeli, T B, Kretzschmar, W, Lei, Y, Liang, J, Song, L, Hu, J, Li, Q, Jin, W, Hu, Z, Wang, G, Wang, L, Qian, P, Liu, Y, Jiang, T, Lu, Y, Zhang, X, Yin, Y, Lie, Y, *et al.* (2015) Sparse whole-genome sequencing identifies two loci for major depressive disorder, *Nature*. Nature Publishing Group, **523**, p. 588–591.

Cai, N, Choi, K W and Fried, E I (2020) Reviewing the genetics of heterogeneity in depression: operationalizations, manifestations and etiologies, *Human molecular genetics*. NLM (Medline), **29**, p. R10–R18.

Caldieraro, M A, Baeza, F L C, Pinheiro, D O, Ribeiro, M R, Parker, G and Fleck, M P (2013) Prevalence of psychotic symptoms in those with melancholic and nonmelancholic depression, *Journal of Nervous and Mental Disease*. J Nerv Ment Dis, **201**, p. 855–859.

Cannon, M, Jones, P B and Murray, R M (2002) Obstetric complications and schizophrenia: Historical and meta-analytic review, *American Journal of Psychiatry*. Am J Psychiatry, p. 1080–1092.

Cantor-Graae, E and Pedersen, C B (2013) Full spectrum of psychiatric disorders related to foreign migration: a Danish population-based cohort study., *JAMA Psychiatry*. American Medical Association, **70**.

Cantor-Graae, E and Selten, J P (2005) Schizophrenia and migration: A meta-analysis and review, *American Journal of Psychiatry*, **162**, p. 12–24.

Canuti, M, Buka, S, Jazaeri Farsani, S M, Oude Munnink, B B, Jebbink, M F, van Beveren, N J M, de Haan, L, Goldstein, J, Seidman, L J, Tsuang, M T, Storosum, J G and van der Hoek, L (2015) Reduced maternal levels of common viruses during pregnancy predict offspring psychosis: Potential role of enhanced maternal immune activity?, *Schizophrenia Research*. Elsevier B.V., **166**, p. 248–254.

Cardno, A G, Rijsdijk, F V., Sham, P C, Murray, R M and McGuffin, P (2002) A Twin Study of Genetic Relationships Between Psychotic Symptoms, *American Journal of Psychiatry*. American Psychiatric Publishing, **159**, p. 539–545.

Cardno, A G and Owen, M J (2014) Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder., *Schizophrenia bulletin*. Oxford University Press, **40**, p. 504–15.

Carlborg, A, Ferntoft, L, Thuresson, M and Bodegard, J (2015) Population study of disease burden, management, and treatment of bipolar disorder in Sweden: A retrospective observational registry study, *Bipolar Disorders*. Blackwell Publishing Inc., **17**, p. 76–85.

Castillejos, M C, Martín-Pérez, C and Moreno-Küstner, B (2018) A systematic review and meta-analysis of the incidence of psychotic disorders: the distribution of rates and the influence of gender, urbanicity, immigration and socio-economic level, *Psychological Medicine*. Cambridge University Press, **48**, p. 2101–2115.

Chang, H K, Hsu, J W, Wu, J C, Huang, K L, Chang, H C, Bai, Y M, Chen, T J and Chen, M H (2019) Risk of attempted suicide among adolescents and young adults with traumatic brain injury: A nationwide longitudinal study, *Journal of Affective Disorders*. Elsevier B.V., **250**, p. 21–25.

Charney, A W, Ruderfer, D M, Stahl, E A, Moran, J L, Chambert, K, Belliveau, R A, Forty, L, Gordon-Smith, K, Di Florio, A, Lee, P H, Bromet, E J, Buckley, P F, Escamilla, M A, Fanous, A H, Fochtmann, L J, Lehrer, D S, Malaspina, D, Marder, S R, Morley, C P, *et al.* (2017) Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder, *Translational Psychiatry*. Nature Publishing Group, **7**.

Charney, D S and Nelson, J C (1981) Delusional and nondelusional unipolar depression: Further evidence for distinct subtypes, *American Journal of Psychiatry*. Am J Psychiatry, **138**, p. 328–333.

Cheniaux, E, Landeira-Fernandez, J and Versiani, M (2009) The diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder and unipolar depression: Interrater reliability and congruence between DSM-IV and ICD-10, *Psychopathology*. Psychopathology, **42**, p. 293–298.

Choi, S W and O'Reilly, P F (2019) PRSice-2: Polygenic Risk Score software for biobank-scale data, *GigaScience*, **8**.

Chudal, R, Gissler, M, Sucksdorff, D, Lehti, V, Suominen, A, Hinkka-Yli-Salomäki, S, Brown, A S and Sourander, A (2014) Parental age and the risk of bipolar disorders, *Bipolar disorders*, **16**, p. 624–632.

Chudal, R, Sourander, A, Polo-Kantola, P P, Hinkka-Yli-Salomäki, S, Lehti, V, Sucksdorff, D, Gissler, M, Brown, A S, Hinkka-Yli-Salom?ki, S, Lehti, V, Sucksdorff, D, Gissler, M and Brown, A S (2014) Perinatal factors and the risk of bipolar disorder in Finland, *Journal of Affective Disorders*, **155**, p. 75–80.

Chumakov, I, Blumenfeld, M, Guerassimenko, O, Cavarec, L, Palicio, M, Abderrahim, H, Bougueleret, L, Barry, C, Tanaka, H, La Rosa, P, Puech, A, Tahri, N, Cohen-Akenine, A, Delabrosse, S, Lissarrague, S, Picard, F-P, Maurice, K, Essioux, L, Millasseau, P, *et al.* (2002) Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia, *Proceedings of the National Academy of Sciences*, **99**, p. 13675–13680.

Clemente, A S, Diniz, B S, Nicolato, R, Kapczinski, F P, Soares, J C, Firmo, J O and Castro-Costa, É (2015) Bipolar disorder prevalence: A systematic review and meta-analysis of the literature, *Revista Brasileira de Psiquiatria*. Associacao Brasileira de Psiquiatria, p. 155–161.

Colodro-Conde, L, Couvy-Duchesne, B, Zhu, G, Coventry, W L, Byrne, E M, Gordon, S, Wright, M J, Montgomery, G W, Madden, P A F, Ripke, S, Eaves, L J, Heath, A C, Wray, N R, Medland, S E and Martin, N G (2018) A direct test of the diathesis–stress model for depression, *Molecular Psychiatry*. Nature Publishing Group, **23**, p. 1590–1596.

Conus, P, Cotton, S, Schimmelmann, B G, McGorry, P D and Lambert, M (2010) Pretreatment and outcome correlates of sexual and physical trauma in an epidemiological cohort of first-episode psychosis patients., *Schizophrenia bulletin*. Oxford University Press, **36**, p. 1105–14.

Coombes, B J, Markota, M, Mann, J J, Colby, C, Stahl, E, Talati, A, Pathak, J, Weissman, M M, McElroy, S L, Frye, M A and Biernacka, J M (2020) Dissecting clinical heterogeneity of bipolar disorder using multiple polygenic risk scores, *Translational Psychiatry*. Springer Nature, **10**.

Costa, F B P da, Trachtenberg, E, Boni, A, Primo de Carvalho Alves, L, Magalhães, P V da S and Rocha, N S (2020) Psychotic depression in hospitalized patients: Longitudinal outcomes of psychotic vs. nonpsychotic depression among inpatients: The role of depressive symptoms on clinical severity, *Journal of Psychiatric Research*. Elsevier Ltd, **129**, p. 73–79.

Craddock, N, Davé, S and Greening, J (2001) Association studies of bipolar disorder., *Bipolar disorders*, **3**, p. 284–98.

Craddock, N and Jones, I (1999) Genetics of bipolar disorder., *Journal of medical genetics*. BMJ Publishing Group, **36**, p. 585–94.

Craddock, N, O'Donovan, M C and Owen, M J (2005) The genetics of schizophrenia and bipolar disorder: dissecting psychosis, *Journal of Medical Genetics*, **42**, p. 193–204.

Craddock, N, O'Donovan, M C and Owen, M J (2006) Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology., *Schizophrenia bulletin*. Oxford University Press, **32**, p. 9–16.

Craddock, N and Owen, M J (2005) The beginning of the end for the Kraepelinian dichotomy, *British Journal of Psychiatry*, **186**, p. 364–366.

Craddock, N and Owen, M J (2007) Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages., *World psychiatry : official journal of the World Psychiatric Association (WPA)*. World Psychiatric Association, **6**, p. 84–91.

Craddock, N and Owen, M J (2010) The Kraepelinian dichotomy - going, going... but still not gone., *The British journal of psychiatry : the journal of mental science*. Royal College of Psychiatrists, **196**, p. 92–5.

Craddock, N and Sklar, P (2013) Genetics of bipolar disorder, *The Lancet*, **381**, p. 1654–1662.

Crebbin, K, Mitford, E, Paxton, R and Turkington, D (2008) First-episode psychosis: An epidemiological survey comparing psychotic depression with schizophrenia, *Journal of Affective Disorders*. J Affect Disord, **105**, p. 117–124.

Cross-Disorder Group of the Psychiatric Genomics Consortium, S H, Lee, S H, Ripke, S, Neale, B M, Faraone, S V, Purcell, S M, Perlis, R H, Mowry, B J, Thapar, A, Goddard, M E, Witte, J S, Absher, D, Agartz, I, Akil, H, Amin, F, Andreassen, O A, Anjorin, A, Anney, R, Anttila, V, *et al.* (2013) Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs., *Nature genetics*, **45**, p. 984–94.

Curtis, D (2018) Polygenic risk score for schizophrenia is more strongly associated with ancestry than with schizophrenia, *Psychiatric Genetics*, **28**, p. 85–89.

Cyril, S, Oldroyd, J C and Renzaho, A (2013) Urbanisation, urbanicity, and health: A systematic review of the reliability and validity of urbanicity scales, *BMC Public Health*. BMC Public Health, **13**.

Dahly, D L and Adair, L S (2007) Quantifying the urban environment: A scale measure of urbanicity outperforms the urban-rural dichotomy, *Social Science and Medicine*. NIH Public Access, **64**, p. 1407–1419.

Davies, C, Segre, G, Estradé, A, Radua, J, De Micheli, A, Provenzani, U, Oliver, D, Salazar de Pablo, G, Ramella-Cravaro, V, Besozzi, M, Dazzan, P, Miele, M, Caputo, G, Spallarossa, C, Crossland, G, Ilyas, A, Spada, G, Politi, P, Murray, R M, *et al.* (2020) Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis, *The Lancet Psychiatry*. Elsevier Ltd, **7**, p. 399–410.

Deeks, J J, Higgins, J P and Altman, D G (2019) Chapter 10: Analysing data and undertaking meta-analyses | Cochrane Training, in *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester (UK): The Cochrane Collaboration and John Wiley & Sons Ltd, p. 241–284.

Del-Ben, C M, Shuhama, R, Loureiro, C M, Ragazzi, T C C, Zanatta, D P, Tenan, S H G, Ferreira Santos, J L, Louzada, P, Dos Santos, A C, Morgan, C and Menezes, P R (2019) Urbanicity and risk of first-episode psychosis: Incidence study in Brazil, *British Journal of Psychiatry*. Cambridge University Press, **215**, p. 726–729.

Demjaha, A, Lappin, J M, Stahl, D, Patel, M X, MacCabe, J H, Howes, O D, Heslin, M, Reininghaus, U A, Donoghue, K, Lomas, B, Charalambides, M, Onyejiaka, A, Fearon, P, Jones, P, Doody, G, Morgan, C, Dazzan, P and Murray, R M (2017) Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors., *Psychological medicine*, **47**, p. 1981–1989.

Demjaha, A, MacCabe, J H and Murray, R M (2012) How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder, *Schizophrenia Bulletin*, **38**, p. 209–214.

Dennison, C, Legge, S, Hubbard, L, Lynham, A, Holmans, P, Cardno, A, Owen, M J, O'Donovan, M and Walters, J (2020) S178. Should Schizoaffective disorder depressed-type be distinct from Schizophrenia? Analyses of genetic liability and lifetime clinical characteristics., *Schizophrenia Bulletin*, **46**, p. S105–S106.

Derks, E M, Allardyce, J, Boks, M P, Vermunt, J K, Hijman, R, Ophoff, R A and GROUP (2012) Kraepelin was right: a latent class analysis of symptom dimensions in patients and controls., *Schizophrenia bulletin*. Oxford University Press, **38**, p. 495–505.

DeVylder, J E, Kelleher, I, Lalane, M, Oh, H, Link, B G and Koyanagi, A (2018) Association of urbanicity with psychosis in low- and middle-income countries, *JAMA Psychiatry*. American Medical Association, **75**, p. 678–686.

Dold, M, Bartova, L, Kautzky, A, Porcelli, S, Montgomery, S, Zohar, J, Mendlewicz, J, Souery, D, Serretti, A and Kasper, S (2019) Psychotic Features in Patients With Major Depressive Disorder, *The Journal of Clinical Psychiatry*. Physicians Postgraduate Press Inc., **80**, p. E1–E7.

Done, D J, Johnstone, E C, Frith, C D, Golding, J, Sepherd, P M and Crow, T . (1991) Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample, *BMJ*, **302**.

Dudbridge, F (2013) Power and Predictive Accuracy of Polygenic Risk Scores, *PLoS Genetics*. Edited by N. R. Wray, **9**, p. e1003348.

Duffy, A, Horrocks, J, Milin, R, Doucette, S, Persson, G and Grof, P (2012) Adolescent substance use disorder during the early stages of bipolar disorder: A prospective high-risk study, *Journal of Affective Disorders*, **142**, p. 57–64.

Duval, S and Tweedie, R (2000) Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis, *Biometrics*. Biometric Society, **56**, p. 455–463.

Eaton, W W, Mortensen, P B and Frydenberg, M (2000) Obstetric factors, urbanization and psychosis, *Schizophrenia Research*, **43**, p. 117–123.

Egan, M F, Goldberg, T E, Kolachana, B S, Callicott, J H, Mazzanti, C M, Straub, R E, Goldman, D and Weinberger, D R (2001) Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia, *Proceedings of the National Academy of Sciences*, **98**, p. 6917–6922.

Eurostat and European Commission (no date) *Population and housing census: census database*.

Evans, D M, Visscher, P M and Wray, N R (2009) Harnessing the information contained within genome-wide association studies to improve individual prediction of complex disease risk, *Human Molecular Genetics*, **18**, p. 3525–3531.

Fanelli, G, Benedetti, F, Kasper, S, Zohar, J, Souery, D, Montgomery, S, Albani, D, Forloni, G, Ferentinos, P, Rujescu, D, Mendlewicz, J, Serretti, A and Fabbri, C (2020) Higher polygenic risk scores for schizophrenia may be suggestive of treatment non-response in major depressive disorder, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. Elsevier Inc.

Fearon, P, Kirkbride, J B, Morgan, C, Dazzan, P, Morgan, K, Lloyd, T, Hutchinson, G, Tarrant, J, Lun Alan Fung, W and Holloway, J (2006) Incidence of

schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study, *Psychological medicine*, **36**, p. 1541–1550.

Fearon, Paul, Kirkbride, J B, Morgan, C, Dazzan, P, Morgan, K, Lloyd, T, Hutchinson, G, Tarrant, J, Lun Alan Fung, W, Holloway, J, Mallett, R, Harrison, G, Leff, J, Jones, P B, Murray, R M, Muga, F, Mietunen, J, Ashby, M, Hayhurst, H, *et al.* (2006) Incidence of schizophrenia and other psychoses in ethnic minority groups: Results from the MRC AESOP Study, *Psychological Medicine*, **36**, p. 1541–1550.

Feingold, D, Weiser, M, Rehm, J and Lev-Ran, S (2015) The association between cannabis use and mood disorders: A longitudinal study, *Journal of Affective Disorders*. Elsevier B.V., **172**, p. 211–218.

Ferrari, A J, Stockings, E, Khoo, J P, Erskine, H E, Degenhardt, L, Vos, T and Whiteford, H A (2016) The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013, *Bipolar Disorders*. Blackwell Publishing Inc., **18**, p. 440–450.

Ferreira, M A R, O'Donovan, M C, Meng, Y A, Jones, I R, Ruderfer, D M, Jones, L, Fan, J, Kirov, G, Perlis, R H, Green, E K, Smoller, J W, Grozeva, D, Stone, J, Nikolov, I, Chambert, K, Hamshere, M L, Nimgaonkar, V L, Moskvina, V, Thase, M E, *et al.* (2008) Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder, *Nature Genetics*, **40**, p. 1056–1058.

Fond, G, Lancon, C, Auquier, P and Boyer, L (2019) Prevalence of major depression in France in the general population and in specific populations from 2000 to 2018: A systematic review of the literature, *Presse Medicale*. Elsevier Masson SAS, **48**, p. 365–375.

Foo, J C, Streit, F, Frank, J, Witt, S H, Treutlein, J, Baune, B T, Moebus, S, Jöckel, K H, Forstner, A J, Nöthen, M M, Rietschel, M, Sartorius, A and Kranaster, L (2019) Evidence for increased genetic risk load for major depression in patients assigned to electroconvulsive therapy, *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*. Blackwell Publishing Inc., **180**, p. 35–45.

Forstner, A J, Hecker, J, Hofmann, A, Maaser, A, Reinbold, C S, Mühleisen, T W, Leber, M, Strohmaier, J, Degenhardt, F, Treutlein, J, Mattheisen, M, Schumacher, J, Streit, F, Meier, S, Herms, S, Hoffmann, P, Lacour, A, Witt, S H, Reif, A, *et al.* (2017) Identification of shared risk loci and pathways for bipolar disorder and schizophrenia, *PLoS ONE*. Public Library of Science, **12**.

Di Forti, M, Morgan, C, Dazzan, P, Pariante, C, Mondelli, V, Marques, T R, Handley, R, Luzi, S, Russo, M, Paparelli, A, Butt, A, Stilo, S A, Wiffen, B, Powell, J and Murray, R M (2009) High-potency cannabis and the risk of psychosis., *The British journal of psychiatry : the journal of mental science*, **195**, p. 488–91.

Di Forti, M, Quattrone, D, Freeman, T P, Tripoli, G, Gayer-Anderson, C, Quigley, H, Rodriguez, V, Jongsma, H E, Ferraro, L, La Cascia, C, La Barbera, D, Tarricone, I, Berardi, D, Szöke, A, Arango, C, Tortelli, A, Velthorst, E, Bernardo, M, Del-Ben, C M, *et al.* (2019) The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study, *The Lancet Psychiatry*. Elsevier Ltd, **6**, p. 427–436.

Forty, L, Jones, L, Jones, I, Cooper, C, Russell, E, Farmer, A, McGuffin, P and

Craddock, N (2009) Is depression severity the sole cause of psychotic symptoms during an episode of unipolar major depression? A study both between and within subjects, *Journal of Affective Disorders*. Elsevier, **114**, p. 103–109.

Frans, E M, Sandin, S, Reichenberg, A, Lichtenstein, P, Långström, N and Hultman, C M (2008) Advancing Paternal Age and Bipolar Disorder, *Archives of General Psychiatry*. American Medical Association, **65**, p. 1034.

Freedman, D, Brown, A S, Shen, L and Schaefer, C A (2015) Perinatal oxytocin increases the risk of offspring bipolar disorder and childhood cognitive impairment, *Journal of Affective Disorders*. Elsevier B.V., **173**, p. 65–72.

Freedman, D, Bao, Y, Shen, L, Schaefer, C A and Brown, A S (2016) Maternal T. gondii, offspring bipolar disorder and neurocognition, *Psychiatry Research*. Elsevier Ireland Ltd, **243**, p. 382–389.

Fusar-Poli, P, Cappucciati, M, Rutigliano, G, Heslin, M, Stahl, D, Brittenden, Z, Caverzasi, E, McGuire, P and Carpenter, W T (2016) Diagnostic Stability of ICD/DSM First Episode Psychosis Diagnoses: Meta-analysis, *Schizophrenia Bulletin*, **42**, p. 1395–1406.

Garno, J L, Goldberg, J F, Ramirez, P M and Ritzler, B A (2005) Impact of childhood abuse on the clinical course of bipolar disorder, *British Journal of Psychiatry*. Br J Psychiatry, **186**, p. 121–125.

Gaudiano, B A, Dalrymple, K L and Zimmerman, M (2009a) Prevalence and clinical characteristics of psychotic versus nonpsychotic major depression in a general psychiatric outpatient clinic, *Depression and Anxiety*. Depress Anxiety, **26**, p. 54–64.

Gayer-Anderson, C, Jongsma, H E, Di Forti, M, Quattrone, D, Velthorst, E, de Haan, L, Selten, J-P, Szöke, A, Llorca, P-M, Tortelli, A, Arango, C, Bobes, J, Bernardo, M, Sanjuán, J, Santos, J L, Arrojo, M, Parellada, M, Tarricone, I, Berardi, D, *et al.* (2020) The EUropean Network of National Schizophrenia Networks Studying Gene–Environment Interactions (EU-GEI): Incidence and First-Episode Case–Control Programme, *Social Psychiatry and Psychiatric Epidemiology*.

Gibbs, M, Winsper, C, Marwaha, S, Gilbert, E, Broome, M and Singh, S P (2015) Cannabis use and mania symptoms: A systematic review and meta-analysis, *Journal of Affective Disorders*, **171**, p. 39–47.

Goldberg, T E (1999) Some fairly obvious distinctions between schizophrenia and bipolar disorder, *Schizophrenia Research*. Elsevier, **39**, p. 127–132.

Goodwin, Frederick K and Jamison, K R (2007) *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. Oxford University Press.

Gordovez, F J A and McMahon, F J (2020) The genetics of bipolar disorder, *Molecular Psychiatry*. Springer Nature, p. 544–559.

Gournellis, Rossetos, Tournikioti, K, Touloumi, G, Thomadakis, C, Michalopoulou, P G, Michopoulos, I, Christodoulou, C, Papadopoulou, A and Douzenis, A (2018) Psychotic (delusional) depression and completed suicide: a systematic review and meta-analysis, *Annals of General Psychiatry*. BioMed Central Ltd., p. 39.

Gournellis, R., Tournikioti, K, Touloumi, G, Thomadakis, C, Michalopoulou, P G,

Christodoulou, C, Papadopoulou, A and Douzenis, A (2018a) Psychotic (delusional) depression and suicidal attempts: a systematic review and meta-analysis, *Acta Psychiatrica Scandinavica*. Blackwell Publishing Ltd, **137**, p. 18–29.

Gouvea, E S, Ota, V K, Noto, C, Santoro, M L, Spindola, L M, Moretti, P N, Carvalho, C M, Xavier, G, Rios, A C, Sato, J R, Hayashi, M A F, Brietzke, E, Gadelha, A, Bressan, R A, Cordeiro, Q and Belangero, S I (2016) Gene expression alterations related to mania and psychosis in peripheral blood of patients with a first episode of psychosis, *Translational Psychiatry*. Nature Publishing Group, **6**, p. e908.

Grande, I, Berk, M, Birmaher, B and Vieta, E (2016) Bipolar disorder, *The Lancet*. Lancet Publishing Group, **387**, p. 1561–1572.

Gratten, J, Wray, N R, Peyrot, W J, McGrath, J J, Visscher, P M and Goddard, M E (2016) Risk of psychiatric illness from advanced paternal age is not predominantly from de novo mutations, *Nature Genetics*. Nature Publishing Group, **48**, p. 718–724.

Green, M F, Kern, R S, Braff, D L and Mintz, J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"?, *Schizophrenia bulletin*. Oxford University Press, **26**, p. 119–36.

Green, M F (2006) Cognitive impairment and functional outcome in schizophrenia and bipolar disorder., *The Journal of clinical psychiatry*, **67 Suppl 9**, p. 3–8; discussion 36-42.

Grunze, H and Born, C (2020) The Impact of Subsyndromal Bipolar Symptoms on Patient's Functionality and Quality of Life, *Frontiers in Psychiatry*. Frontiers Media S.A.

Gu, S, Huang, R, Yang, J, Sun, S, Xu, Y, Zhang, R, Wang, Y, Lu, B, He, T, Wang, A, Bian, G and Wang, Q (2019) Exposure-lag-response association between sunlight and schizophrenia in Ningbo, China, *Environmental Pollution*. Elsevier Ltd, **247**, p. 285–292.

Guloksuz, S, Van Nierop, M, Lieb, R, Van Winkel, R, Wittchen, H U and Van Os, J (2015) Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology, *Psychological Medicine*. Cambridge University Press, **45**, p. 2389–2401.

Guloksuz, S, Pries, L K, Delespaul, P, Kenis, G, Luykx, J J, Lin, B D, 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, *et al.* (2019) Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study, *World Psychiatry*. Blackwell Publishing Ltd, **18**, p. 173–182.

Hadzi-Pavlovic, D, Brodaty, H, Austin, M P, Mitchell, P, Wilhelm, K and Hickie, I (1995) Sub-Typing Depression, II. Clinical Distinction of Psychotic Depression and Non-Psychotic Melancholia, *Psychological Medicine*. Psychol Med, **25**, p. 825–832.

Hair, J, Black, W, Babin, B and Anderson, R (2014) *Multivariate Data Analysis*. 7th Editio.

Harrison, P, Cowen, P, Burns, T and Fazel, M (2017) *Shorter Oxford Textbook of*

Psychiatry. 7th edition. OUP Oxford.

Hasin, D S, Sarvet, A L, Meyers, J L, Saha, T D, Ruan, W J, Stohl, M and Grant, B F (2018) Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States, *JAMA Psychiatry*. American Medical Association, **75**, p. 336–346.

Hattori, E, Liu, C, Badner, J A, Bonner, T I, Christian, S L, Maheshwari, M, Detera-Wadleigh, S D, Gibbs, R A and Gershon, E S (2003) Polymorphisms at the G72/G30 Gene Locus, on 13q33, Are Associated with Bipolar Disorder in Two Independent Pedigree Series*, *The American Journal of Human Genetics*, **72**, p. 1131–1140.

Haustgen, T and Akiskal, H (2006) French antecedents of 'contemporary' concepts in the American Psychiatric Association's classification of bipolar (mood) disorders, *Journal of Affective Disorders*. Elsevier, p. 149–163.

Hay, S I, Abajobir, A A, Abate, K H, Abbafati, C, Abbas, K M, Abd-Allah, F, Abdulle, A M, Abebo, T A, Abera, S F, Aboyans, V, Abu-Raddad, L J, Ackerman, I N, Adedeji, I A, Adetokunboh, O, Afshin, A, Aggarwal, R, Agrawal, S, Agrawal, A, Kiadaliri, A A, *et al.* (2017) Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016, *The Lancet*. Lancet Publishing Group, **390**, p. 1260–1344.

Hayes, J F, Miles, J, Walters, K, King, M and Osborn, D P J (2015) A systematic review and meta-analysis of premature mortality in bipolar affective disorder., *Acta psychiatrica Scandinavica*. Wiley-Blackwell, **131**, p. 417–25.

He, H, Hu, C, Ren, Z, Bai, L, Gao, F and Lyu, J (2020) Trends in the incidence and DALYs of bipolar disorder at global, regional, and national levels: Results from the global burden of Disease Study 2017, *Journal of Psychiatric Research*. Elsevier Ltd, **125**, p. 96–105.

Helms, P M and Smith, R E (1983) Recurrent psychotic depression, *Journal of Affective Disorders*, **5**, p. 51–54.

Heslin, M, Lomas, B, Lappin, J M, Donoghue, K, Reininghaus, U, Onyejiaka, A, Croudace, T, Jones, P B, Murray, R M, Fearon, P, Dazzan, P, Morgan, C and Doody, G A (2015) Diagnostic change 10 years after a first episode of psychosis, *Psychological Medicine*. Cambridge University Press, **45**, p. 2757–2769.

Heslin, M, Lappin, J M, Donoghue, K, Lomas, B, Reininghaus, U, Onyejiaka, A, Croudace, T, Jones, P B, Murray, R M, Fearon, P, Doody, G A, Dazzan, P, Craig, T J and Morgan, C (2016) Ten-year outcomes in first episode psychotic major depression patients compared with schizophrenia and bipolar patients., *Schizophrenia research*. Elsevier, **176**, p. 417–22.

Hess, J L, Tylee, D S, Mattheisen, M, Adolfsson, R, Agartz, I, Agerbo, E, Albus, M, Alexander, M, Amin, F, Andreassen, O A, Arranz, M J, Bacanu, S A, Bakker, S, Band, G, Barroso, I, Begemann, M, Bellenguez, C, Belliveau, R A, Bender, S, *et al.* (2019) A polygenic resilience score moderates the genetic risk for schizophrenia, *Molecular Psychiatry*. Nature Publishing Group, p. 1–16.

Higgins, J P T and Cochrane Collaboration (2019) *Cochrane handbook for systematic reviews of interventions*. 2nd Editio. Edited by J. P. Higgins et al. Chichester

(UK): John Wiley & Sons.

Hill, A B (1965) The Environment and Disease: Association or Causation?, *Journal of the Royal Society of Medicine*. Royal Society of Medicine Press, **58**, p. 295–300.

Hill, S K, Harris, M S H, Herbener, E S, Pavuluri, M and Sweeney, J A (2007) Neurocognitive Allied Phenotypes for Schizophrenia and Bipolar Disorder, *Schizophrenia Bulletin*. Oxford University Press, **34**, p. 743–759.

Hjorthøj, C, Stürup, A E, McGrath, J J and Nordentoft, M (2017) Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis, *The Lancet Psychiatry*. Elsevier Ltd, **4**, p. 295–301.

Hosang, G M, Shiles, C, Tansey, K E, McGuffin, P and Uher, R (2014) Interaction between stress and the BDNFVal66Met polymorphism in depression: a systematic review and meta-analysis, *BMC Medicine*, **12**, p. 7.

Hosang, G M, Fisher, H L, Cohen-Woods, S, McGuffin, P and Farmer, A E (2017) Stressful life events and catechol-O-methyl-transferase (*COMT*) gene in bipolar disorder, *Depression and Anxiety*.

Howard, D M, Adams, M J, Clarke, T K, Hafferty, J D, Gibson, J, Shirali, M, Coleman, J R I, Hagenaars, S P, Ward, J, Wigmore, E M, Alloza, C, Shen, X, Barbu, M C, Xu, E Y, Whalley, H C, Marioni, R E, Porteous, D J, Davies, G, Deary, I J, *et al.* (2019) Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions, *Nature Neuroscience*. Nature Publishing Group, **22**, p. 343–352.

Howes, O D, McCutcheon, R, Owen, M J and Murray, R M (2017) The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia, *Biological Psychiatry*. Elsevier USA, p. 9–20.

Hultman, C M, Sparén, P, Takei, N, Murray, R M, Cnattingius, S and Geddes, J (1999) Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study, *BMJ*, **318**, p. 421–426.

Humphreys, K L, LeMoult, J, Wear, J G, Piersiak, H A, Lee, A and Gotlib, I H (2020) Child maltreatment and depression: A meta-analysis of studies using the Childhood Trauma Questionnaire, *Child Abuse and Neglect*. Elsevier Ltd, **102**.

Instituto Brasileiro de Geografia e Estatística (no date) *2010 Popolation census*.

Jääskeläinen, E, Juola, P, Hirvonen, N, McGrath, J J, Saha, S, Isohanni, M, Veijola, J and Miettunen, J (2013) A systematic review and meta-analysis of recovery in schizophrenia., *Schizophrenia bulletin*, **39**, p. 1296–306.

Jääskeläinen, E, Juola, T, Korpela, H, Lehtiniemi, H, Nietola, M, Korkeila, J and Miettunen, J (2018) Epidemiology of psychotic depression - Systematic review and meta-analysis, *Psychological Medicine*, **48**, p. 905–918.

Jabben, N, Arts, B, Van Os, J and Krabbendam, L (2010) Neurocognitive functioning as intermediary phenotype and predictor of psychosocial functioning across the psychosis continuum: Studies in schizophrenia and bipolar disorder, *Journal of Clinical Psychiatry*. J Clin Psychiatry, **71**, p. 764–774.

Jablensky, A, Sartorius, N, Ernberg, G, Anker, M, Korten, A, Cooper, J E, Day, R and Bertelsen, A (1992) Schizophrenia: manifestations, incidence and course in

different cultures. A World Health Organization ten-country study., *Psychological medicine. Monograph supplement*, **20**, p. 1–97.

Jablensky, A (2010) El concepto diagnóstico de la esquizofrenia: su historia, evolución y perspectivas futuras, *Dialogues in Clinical Neuroscience*. Les Laboratoires Servier, **12**, p. 271–287.

Jaenisch, R and Bird, A (2003) Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals, *Nature Genetics*. Nat Genet, p. 245–254.

Jauhar, S, Nour, M M, Veronese, M, Rogdaki, M, Bonoldi, I, Azis, M, Turkheimer, F, McGuire, P, Young, A H and Howes, O D (2017) A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia, *JAMA Psychiatry*. American Medical Association, **74**, p. 1206–1213.

Jauhar, S, Krishnadas, R, Nour, M M, Cunningham-Owens, D, Johnstone, E C and Lawrie, S M (2018) Is there a symptomatic distinction between the affective psychoses and schizophrenia? A machine learning approach, *Schizophrenia Research*. Elsevier B.V., **202**, p. 241–247.

Jiménez-López, E, Sánchez-Morla, E M, Aparicio, A I, López-Villarreal, A, Martínez-Vizcaíno, V, Rodriguez-Jimenez, R, Vieta, E and Santos, J L (2018) Psychosocial functioning in patients with psychotic and non-psychotic bipolar I disorder. A comparative study with individuals with schizophrenia, *Journal of Affective Disorders*. Elsevier B.V., **229**, p. 177–185.

Jonas, B S, Brody, D, Roper, M and Narrow, W E (2003) Prevalence of mood disorders in a national sample of young American adults, *Social Psychiatry and Psychiatric Epidemiology*. Soc Psychiatry Psychiatr Epidemiol, **38**, p. 618–624.

Jones, I, Chandra, P S, Dazzan, P and Howard, L M (2014) Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period, *The Lancet*. Lancet Publishing Group, p. 1789–1799.

Jongsma, H E, Gayer-Anderson, C, Lasalvia, A, Quattrone, D, Mulè, A, Szöke, A, Selten, J P, Turner, C, Arango, C, Tarricone, I, Berardi, D, Tortelli, A, Llorca, P M, De Haan, L, Bobes, J, Bernardo, M, Sanjuán, J, Santos, J L, Arrojo, M, *et al.* (2018) Treated incidence of psychotic disorders in the multinational EU-GEI study, *JAMA Psychiatry*, **75**, p. 36–46.

Jongsma, H E, Turner, C, Kirkbride, J B and Jones, P B (2019) International incidence of psychotic disorders, 2002–17: a systematic review and meta-analysis, *The Lancet Public Health*. Elsevier Ltd, **4**, p. e229–e244.

Jüni, P, Holenstein, F, Sterne, J, Bartlett, C and Egger, M (2002) Direction and impact of language bias in meta-analyses of controlled trials: Empirical study, *International Journal of Epidemiology*. Oxford University Press, **31**, p. 115–123.

Karg, K, Burmeister, M, Shedden, K and Sen, S (2011) The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-analysis Revisited, *Archives of General Psychiatry*, **68**, p. 444.

Kaymaz, N, Krabbendam, L, Graaf, R, Nolen, W, Have, M and van Os, J (2006) Evidence that the urban environment specifically impacts on the psychotic but not

the affective dimension of bipolar disorder, *Social Psychiatry and Psychiatric Epidemiology*, **41**, p. 679–685.

Keck, P E, McElroy, S L, Havens, J R, Altshuler, L L, Nolen, W A, Frye, M A, Suppes, T, Denicoff, K D, Kupka, R, Leverich, G S, Rush, A J and Post, R M (2003) Psychosis in bipolar disorder: Phenomenology and impact on morbidity and course of illness, *Comprehensive Psychiatry*. W.B. Saunders, **44**, p. 263–269.

Kelly, B D, O'Callaghan, E, Waddington, J L, Feeney, L, Browne, S, Scully, P J, Clarke, M, Quinn, J F, McTigue, O, Morgan, M G, Kinsella, A and Larkin, C (2010) Schizophrenia and the city: A review of literature and prospective study of psychosis and urbanicity in Ireland, *Schizophrenia Research*, **116**, p. 75–89.

Kelly, T (2018) Prospective: Is bipolar disorder being overdiagnosed?, *International Journal of Methods in Psychiatric Research*. John Wiley and Sons Ltd.

Kemner, S M, Mesman, E, Nolen, W A, Eijckemans, M J C and Hillegers, M H J (2015) The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: Results from the Dutch Bipolar Offspring Study, *Psychological Medicine*. Cambridge University Press, **45**, p. 2571–2581.

Kendler, K S, McGuire, M, Gruenberg, A M, O'Hare, A, Spellman, M and Walsh, D (1993) The Roscommon Family Study. IV. Affective illness, anxiety disorders, and alcoholism in relatives., *Archives of general psychiatry*, **50**, p. 952–60.

Kendler, K S, Gatz, M, Gardner, C O and Pedersen, N L (2006) A Swedish National Twin Study of Lifetime Major Depression, *American Journal of Psychiatry*, **163**, p. 109–114.

Kendler, K S (2020) The characteristic signs and symptoms of mania and depression according to Kraepelin circa 1905: A comparison with DSM-III, *Psychological Medicine*. Cambridge University Press.

Kendler, K S and Eaves, L J (1986) Models for the joint effect of genotype and environment on liability to psychiatric illness, *American Journal of Psychiatry*. Am J Psychiatry, **143**, p. 279–289.

Kendler, K S, Karkowski, L M and Prescott, C A (1999) Causal relationship between stressful life events and the onset of major depression, *American Journal of Psychiatry*. American Psychiatric Association, **156**, p. 837–841.

Kennedy, Noel, Boydell, J, Kalidindi, S, Fearon, P, Jones, P B, Van Os, J and Murray, R M (2005) Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England, *American Journal of Psychiatry*, **162**, p. 257–262.

Kennedy, N., Everitt, B, Boydell, J, Van Os, J, Jones, P B and Murray, R M (2005) Incidence and distribution of first-episode mania by age: Results from a 35-year study, *Psychological Medicine*, **35**, p. 855–863.

Kessler, R C, McGonagle, K A, Zhao, S, Nelson, C B, Hughes, M, Eshleman, S, Wittchen, H U and Kendler, K S (1994) Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States: Results from the National Comorbidity Survey, *Archives of General Psychiatry*. Arch Gen Psychiatry, **51**, p. 8–19.

Kessler, R C and Bromet, E J (2013) The epidemiology of depression across

cultures, *Annual Review of Public Health*. NIH Public Access, p. 119–138.

Khandaker, G M, Zimbron, J, Dalman, C, Lewis, G and Jones, P B (2012) Childhood infection and adult schizophrenia: A meta-analysis of population-based studies, *Schizophrenia Research*, **139**, p. 161–168.

Khandaker, G M, Zimbron, J, Lewis, G and Jones, P B (2013) Prenatal maternal infection, neurodevelopment and adult schizophrenia: A systematic review of population-based studies, *Psychological Medicine*, **43**, p. 239–257.

Kirkbride, J B, Barker, D, Cowden, F, Stamps, R, Yang, M, Jones, P B and Coid, J W (2008) Psychoses, ethnicity and socio-economic status, *British Journal of Psychiatry*, **193**, p. 18–24.

Kirkbride, J B, Croudace, T, Brewin, J, Donoghue, K, Mason, P, Glazebrook, C, Medley, I, Harrison, G, Cooper, J E, Doody, G A and Jones, P B (2009) Is the incidence of psychotic disorder in decline? Epidemiological evidence from two decades of research, *International Journal of Epidemiology*. Oxford University Press, **38**, p. 1255–1264.

Kirkbride, J B, Errazuriz, A, Croudace, T J, Morgan, C, Jackson, D, Boydell, J, Murray, R M and Jones, P B (2012) Incidence of schizophrenia and other psychoses in England, 1950-2009: A systematic review and meta-analyses, *PLoS ONE*, **7**.

Kirkbride, J B, Hameed, Y, Ankireddypalli, G, Ioannidis, K, Crane, C M, Nasir, M, Kabacs, N, Metastasio, A, Jenkins, O, Espandian, A, Spyridi, S, Ralevic, D, Siddabattuni, S, Walden, B, Adeoye, A, Perez, J and Jones, P B (2017) The epidemiology of first-episode psychosis in early intervention in psychosis services: Findings from the social epidemiology of psychoses in east Anglia [SEPEA] Study, *American Journal of Psychiatry*. American Psychiatric Association, **174**, p. 143–153.

Kirkpatrick, B and Kennedy, B K (2018) Accelerated aging in schizophrenia and related disorders: Future research, *Schizophrenia Research*. Elsevier B.V., **196**, p. 4–8.

Kirov, G and Murray, R M (1999) Ethnic differences in the presentation of bipolar affective disorder, *European Psychiatry*. Elsevier Masson SAS, **14**, p. 199–204.

Kleinhaus, K, Harlap, S, Perrin, M, Manor, O, Margalit-Calderon, R, Opler, M, Friedlander, Y and Malaspina, D (2013) Prenatal stress and affective disorders in a population birth cohort, *Bipolar Disorders*, **15**, p. 92–99.

de Kluiver, H, Buizer-Voskamp, J E, Dolan, C V. and Boomsma, D I (2017) Paternal age and psychiatric disorders: A review, *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*. Blackwell Publishing Inc., p. 202–213.

Köhler, C A, Evangelou, E, Stubbs, B, Solmi, M, Veronese, N, Belbasis, L, Bortolato, B, Melo, M C A, Coelho, C A, Fernandes, B S, Olfson, M, Ioannidis, J P A and Carvalho, A F (2018) Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies, *Journal of Psychiatric Research*. Elsevier Ltd, p. 189–207.

Kotov, R, Leong, S H, Mojtabai, R, Erlanger, A C E, Fochtmann, L J, Constantino, E, Carlson, G A and Bromet, E J (2013) Boundaries of schizoaffective disorder: Revisiting Kraepelin, *JAMA Psychiatry*. American Medical Association, **70**, p. 1276–1286.

Koyanagi, A, Oh, H, Stubbs, B, Haro, J M and Devylder, J E (2017) Epidemiology of depression with psychotic experiences and its association with chronic physical conditions in 47 low-and middle-income countries, *Psychological Medicine*. Cambridge University Press, **47**, p. 531–542.

Krabbendam, L, Arts, B, van Os, J and Aleman, A (2005) Cognitive functioning in patients with schizophrenia and bipolar disorder: A quantitative review, *Schizophrenia Research*. Elsevier, **80**, p. 137–149.

Krabbendam, L and van Os, J (2005) Schizophrenia and Urbanicity: A Major Environmental Influence--Conditional on Genetic Risk, *Schizophrenia Bulletin*. Oxford University Press, **31**, p. 795–799.

Kraepelin, E (1899) *Psychiatrie: Ein Lehrbuch für Studirende und Aerzte* . Americana. Barth.

Kraepelin, E and Diefendorf, A R (1915) *Clinical psychiatry: a text-book for students and physicians*. New ed., rev. and a…. New York: The Macmillan Company.

Kroon, J S, Wohlfarth, T D, Dieleman, J, Sutterland, A L, Storosum, J G, Denys, D, de Haan, L and Sturkenboom, M C (2013) Incidence rates and risk factors of bipolar disorder in the general population: a population-based cohort study, *Bipolar Disorders*. John Wiley & Sons, Ltd, **15**, p. 306–313.

Kyu, H H, Abate, D, Abate, K H, Abay, S M, Abbafati, C, Abbasi, N, Abbastabar, H, Abd-Allah, F, Abdela, J, Abdelalim, A, Abdollahpour, I, Abdulkader, R S, Abebe, M, Abebe, Z, Abil, O Z, Aboyans, V, Abrham, A R, Abu-Raddad, L J, Abu-Rmeileh, N M E, *et al.* (2018) Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017, *The Lancet*. Lancet Publishing Group, **392**, p. 1859–1922.

Van Laar, M, Van Dorsselaer, S, Monshouwer, K and De Graaf, R (2007) Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population?, *Addiction*, **102**, p. 1251–1260.

Lasalvia, A, Bonetto, C, Tosato, S, Zanatta, G, Cristofalo, D, Salazzari, D, Lazzarotto, L, Bertani, M, Bissoli, S, De Santi, K, Cremonese, C, De Rossi, M, Gardellin, F, Ramon, L, Zucchetto, M, Amaddeo, F, Tansella, M, Ruggeri, M, Brambilla, P, *et al.* (2014) First-contact incidence of psychosis in north-eastern Italy: Influence of age, gender, immigration and socioeconomic deprivation, *British Journal of Psychiatry*. Royal College of Psychiatrists, **205**, p. 127–134.

Laurens, K R, Luo, L, Matheson, S L, Carr, V J, Raudino, A, Harris, F and Green, M J (2015) Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses., *BMC psychiatry*. BioMed Central, **15**, p. 205.

Laursen, T M, Munk-Olsen, T, Nordentoft, M and Mortensen, P B (2007) A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort, *Journal of Clinical Psychiatry*. Physicians Postgraduate Press Inc., **68**, p. 1673–1681.

Leask, S J, Done, D J and Crow, T J (2002) Adult psychosis, common childhood

infections and neurological soft signs in a national birth cohort, *British Journal of Psychiatry*, **181**, p. 387–392.

Leboyer, M, Henry, C, Paillere-Martinot, M L and Bellivier, F (2005) Age at onset in bipolar affective disorders: A review, *Bipolar Disorders*. Blackwell Munksgaard, p. 111–118.

Lee, J, Altshuler, L, Glahn, D C, Miklowitz, D J, Ochsner, K and Green, M F (2013) Social and nonsocial cognition in bipolar disorder and schizophrenia: Relative levels of impairment, *American Journal of Psychiatry*. American Psychiatric Association, **170**, p. 334–341.

Lee, P H, Anttila, V, Won, H, Feng, Y C A, Rosenthal, J, Zhu, Z, Tucker-Drob, E M, Nivard, M G, Grotzinger, A D, Posthuma, D, Wang, M M J, Yu, D, Stahl, E A, Walters, R K, Anney, R J L, Duncan, L E, Ge, T, Adolfsson, R, Banaschewski, T, *et al.* (2019) Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders, *Cell*. Cell Press, **179**, p. 1469-1482.e11.

Lehrer, D S, Pato, M T, Nahhas, R W, Miller, B R, Malaspina, D, Buckley, P F, Sobell, J L, Walsh-Messinger, J, Pato, C N, Abbott, Azevedo, M H, Bromet, E J, Escamilla, M A, Fanous, A H, Fochtmann, L J, Kinkead, B, Knowles, J A, Macciardi, F, Macedo, A, *et al.* (2016) Paternal age effect: Replication in schizophrenia with intriguing dissociation between bipolar with and without psychosis, *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*. Blackwell Publishing Inc., **171**, p. 495–505.

Lewis, C M and Vassos, E (2017) Prospects for using risk scores in polygenic medicine, *Genome Medicine*.

Lewis, C M and Vassos, E (2020) Polygenic risk scores: From research tools to clinical instruments, *Genome Medicine*. BioMed Central Ltd., p. 44.

Lichtenstein, P, Yip, B H, Björk, C, Pawitan, Y, Cannon, T D, Sullivan, P F and Hultman, C M (2009) Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study, *The Lancet*, **373**, p. 234–239.

Liu, Q, He, H, Yang, J, Feng, X, Zhao, F and Lyu, J (2020) Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study, *Journal of Psychiatric Research*. Elsevier Ltd, **126**, p. 134–140.

Ludwig, B and Dwivedi, Y (2016) Dissecting bipolar disorder complexity through epigenomic approach., *Molecular psychiatry*. Nature Publishing Group, **21**, p. 1490–1498.

Lynham, A J, Hubbard, L, Tansey, K E, Hamshere, M L, Legge, S E, Owen, M J, Jones, I R and Walters, J T R (2018) Examining cognition across the bipolar/schizophrenia diagnostic spectrum., *Journal of psychiatry & neuroscience : JPN*. Canadian Medical Association, **43**, p. 170076.

Lyons, M J, Eisen, S A, Goldberg, J, True, W, Lin, N, Meyer, J M, Toomey, R, Faraone, S V, Merla-Ramos, M and Tsuang, M T (1998) A registry-based twin study of depression in men., *Archives of general psychiatry*, **55**, p. 468–72.

Maier, W, Lichtermann, D, Minges, J, Hallmayer, J, Heun, R, Benkert, O and Levinson, D F (1993) Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study., *Archives of general psychiatry*,

50, p. 871–83.

Malhi, G S, Irwin, L, Hamilton, A, Morris, G, Boyce, P, Mulder, R and Porter, R J (2018) Modelling mood disorders: An ACE solution?, *Bipolar Disorders*. Blackwell Publishing Inc., p. 4–16.

Mallet, M R (1997) MRC sociodemographic schedule, *Section of social psychiatry. IoP*.

Mallett, R, Leff, J, Bhugra, D, Pang, D and Zhao, J H (2002) Social environment, ethnicity and schizophrenia, *Social Psychiatry and Psychiatric Epidemiology*, **37**, p. 329–335.

Manchia, M, Maina, G, Carpiniello, B, Pinna, F, Steardo, L, D'Ambrosio, V, Salvi, V, Alda, M, Tortorella, A and Albert, U (2017) Clinical correlates of age at onset distribution in bipolar disorder: a comparison between diagnostic subgroups, *International Journal of Bipolar Disorders*. SpringerOpen, **5**, p. 28.

Mancuso, S G, Morgan, V A, Mitchell, P B, Berk, M, Young, A and Castle, D J (2015) A comparison of schizophrenia, schizoaffective disorder, and bipolar disorder: Results from the Second Australian national psychosis survey, *Journal of Affective Disorders*. Elsevier B.V., **172**, p. 30–37.

Manrique-Garcia, E, Zammit, S, Dalman, C, Hemmingsson, T and Allebeck, P (2012) Cannabis use and depression: a longitudinal study of a national cohort of Swedish conscripts, *BMC Psychiatry*, **12**.

Marangoni, C, Hernandez, M and Faedda, G L (2016) The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies, *Journal of Affective Disorders*, **193**, p. 165–174.

Marcelis, M, Navarro-Mateu, F, Murray, R, Selten, J P and Van Os, J (1998) Urbanization and psychosis: A study of 1942-1978 birth cohorts in The Netherlands, *Psychological Medicine*, **28**, p. 871–879.

Marconi, A, Di Forti, M, Lewis, C M, Murray, R M and Vassos, E (2016) Meta-Analysis of the association between the level of cannabis use and risk of psychosis, *Schizophrenia Bulletin*. Oxford University Press, **42**, p. 1262–1269.

Markota, M, Coombes, B J, Larrabee, B R, McElroy, S L, Bond, D J, Veldic, M, Colby, C L, Chauhan, M, Cuellar-Barboza, A B, Fuentes, M, Kung, S, Prieto, M L, Rummans, T A, Bobo, W V., Frye, M A and Biernacka, J M (2018) Association of schizophrenia polygenic risk score with manic and depressive psychosis in bipolar disorder, *Translational Psychiatry*, **8**, p. 188.

Marneros, A (1999) *Handbuch der unipolaren und bipolaren Erkrankungen.* . Thieme, Stuttgart.

Martino, D J, Igoa, A, Scápola, M, Marengo, E, Samamé, C and Strejilevich, S A (2017) Functional Outcome in the Middle Course of Bipolar Disorder, *The Journal of Nervous and Mental Disease*. Lippincott Williams and Wilkins, **205**, p. 203–206.

Martins, S S, Fenton, M C, Keyes, K M, Blanco, C, Zhu, H and Storr, C L (2012) Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: Longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions, *Psychological Medicine*, **42**, p. 1261–1272.

Mason, B L, Sherwood Brown, E and Croarkin, P E (2016) Historical underpinnings of bipolar disorder diagnostic criteria, *Behavioral Sciences*. MDPI Multidisciplinary Digital Publishing Institute.

Matheson, S L, Kariuki, M, Green, M J, Dean, K, Harris, F, Tzoumakis, S, Tarren-Sweeney, M, Brinkman, S, Chilvers, M, Sprague, T, Carr, V J and Laurens, K R (2017) Effects of maltreatment and parental schizophrenia spectrum disorders on early childhood social-emotional functioning: a population record linkage study, *Epidemiology and Psychiatric Sciences*. Cambridge University Press, **26**, p. 612.

Mathiasen, R, Hansen, B M, Forman, J L, Kessing, L V and Greisen, G (2011) The risk of psychiatric disorders in individuals born prematurely in Denmark from 1974 to 1996, *Acta Paediatrica, International Journal of Paediatrics*, **100**, p. 691–699.

Mayer Gross, W, Slater, E and Roth, M (1974) *Psiquiatria Clinica*. Buenos Aires: Paidós.

McGrath, J, Saha, S, Welham, J, El Saadi, O, MacCauley, C and Chant, D (2004a) A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology, *BMC Medicine*, **2**, p. 1–22.

McGrath, J, Saha, S, Welham, J, El Saadi, O, MacCauley, C and Chant, D (2004b) A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology, *BMC Medicine*. BMC Med.

McGrath, J J, Petersen, L, Agerbo, E, Mors, O, Mortensen, P B and Pedersen, C B (2014) A comprehensive assessment of parental age and psychiatric disorders, *JAMA Psychiatry*. American Medical Association, **71**, p. 301–309.

McGrath, J, Selten, J P and Chant, D (2002) Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration - Data from Australia and the Netherlands, *Schizophrenia Research*. Schizophr Res, **54**, p. 199–212.

McGuffin, P, Farmer, A, Harvey, I, PW, B, CG, H, Feighner JP, Robins E, Guze SB, Woodruffe RA, Winokur G, M R, Spitzer RL, Endicott J, R E, American Psychiatric Association, C on N and S, American Psychiatric Association, C on N and S, Brockington IF, Kendell RE, L J, Stephens JH, Astrup C, Carpenter W, Shaffer JW, G J, RE, K, Gottesman II, S J, Farmer AE, McGuffin P, S E G I, McGuffin P, Festenstein H, Murray RM Farmer AE, Gottesman II, Murray RM, R A, K, S, HC, K, McGuffin P, Sargeant M, Hett G, Tidmarsh S, Whatley S, M R, Endicott J, S R, *et al.* (1991) A Polydiagnostic Application of Operational Criteria in Studies of Psychotic Illness Development and Reliability of the OPCRIT System, *Archives of General Psychiatry*. American Medical Association, **48**.

McGuffin, P, Katz, R, Watkins, S, Rutherford, J, McGuffin P, K R, Tsuang MT, F S, Gershon ES, B W L J F V E M D B, Bertelsen A, H B G M, Slater E, S J, RW, S, S, T, Association, A P, Wender PH, K S R D S F O J L L, Cadoret RJ, O T H E T E, Von Knorring AL, C C B N S S, Andrews G, S G A R H A, Kendler KS, N M K R H A E L, Kendler KS, N M K R H A E L, McGuffin P, K R R J, *et al.* (1996) A Hospital-Based Twin Register of the Heritability of DSM-IV Unipolar Depression, *Archives of General Psychiatry*. American Medical Association, **53**, p. 129.

McGuffin, P, Rijsdijk, F, Andrew, M, Sham, P, Katz, R and Cardno, A (2003) The heritability of bipolar affective disorder and the genetic relationship to unipolar depression., *Archives of general psychiatry*, **60**, p. 497–502.

Medici, C R, Videbech, P, Gustafsson, L N and Munk-Jørgensen, P (2015) Mortality and secular trend in the incidence of bipolar disorder, *Journal of Affective Disorders*. Elsevier, **183**, p. 39–44.

Meier, S M, Agerbo, E, Maier, R, Pedersen, C B, Lang, M, Grove, J, Hollegaard, M V., Demontis, D, Trabjerg, B B, HjorthØj, C, Ripke, S, Degenhardt, F, Nöthen, M M, Rujescu, D, Maier, W, Werge, T, Mors, O, Hougaard, D M, BØrglum, A D, *et al.* (2016) High loading of polygenic risk in cases with chronic schizophrenia, *Molecular Psychiatry*. Nature Publishing Group, **21**, p. 969–974.

Merikangas, K R, Jin, R, He, J-P, Kessler, R C, Lee, S, Sampson, N A, Viana, M C, Andrade, L H, Hu, C, Karam, E G, Ladea, M, Medina-Mora, M E, Ono, Y, Posada-Villa, J, Sagar, R, Wells, J E and Zarkov, Z (2011) Prevalence and Correlates of Bipolar Spectrum Disorder in the World Mental Health Survey Initiative, *Archives of General Psychiatry*, **68**, p. 241.

Merikangas, K R, Cui, L, Heaton, L, Nakamura, E, Roca, C, Ding, J, Qin, H, Guo, W, Yao-Shugart, Y, Zarate, C and Angst, J (2014) Independence of familial transmission of mania and depression: results of the NIMH family study of affective spectrum disorders, *Molecular Psychiatry*. Nature Publishing Group, **19**, p. 214–219.

Michalak, E E, Yatham, L N and Lam, R W (2005a) Quality of life in bipolar disorder: A review of the literature, *Health and Quality of Life Outcomes*. BioMed Central, p. 1–17.

Middleton, F A, Pato, C N, Gentile, K L, McGann, L, Brown, A M, Trauzzi, M, Diab, H, Morley, C P, Medeiros, H, Macedo, A, Azevedo, M H and Pato, M T (2005) Gene expression analysis of peripheral blood leukocytes from discordant sib-pairs with schizophrenia and bipolar disorder reveals points of convergence between genetic and functional genomic approaches, *American Journal of Medical Genetics - Neuropsychiatric Genetics*. Am J Med Genet B Neuropsychiatr Genet, **136 B**, p. 12–25.

Miller, B, Messias, E, Miettunen, J, Alaräisänen, A, Järvelin, M-R, Koponen, H, Räsänen, P, Isohanni, M and Kirkpatrick, B (2011) Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring, *Schizophrenia Bulletin*, **37**, p. 1039–1047.

Miller, P R (2001) Inpatient diagnostic assessments: 2. Interrater reliability and outcomes of structured vs. unstructured interviews, *Psychiatry Research*. Psychiatry Res, **105**, p. 265–271.

Mistry, S, Escott-Price, V, Florio, A D, Smith, D J and Zammit, S (2019) Investigating associations between genetic risk for bipolar disorder and cognitive functioning in childhood, *Journal of Affective Disorders*. Elsevier B.V., **259**, p. 112–120.

Modinos, G, Iyegbe, C, Prata, D, Rivera, M, Kempton, M J, Valmaggia, L R, Sham, P C, van Os, J and McGuire, P (2013) Molecular genetic gene-environment studies using candidate genes in schizophrenia: A systematic review, *Schizophrenia Research*. Schizophr Res, p. 356–365.

Moffitt, T E, Caspi, A and Rutter, M (2005) Strategy for investigating interactions

between measured genes and measured environments, *Archives of General Psychiatry*. American Medical Association, p. 473–481.

Moher, D, Liberati, A, Tetzlaff, J, Altman, D G and PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, *PLoS Medicine*, **6**, p. e1000097.

Mollon, J, Mathias, S R, Knowles, E E M, Rodrigue, A, Koenis, M M G, Pearlson, G D, Reichenberg, A, Barrett, J, Denbow, D, Aberizk, K, Zatony, M, Poldrack, R A, Blangero, J and Glahn, D C (2020) Cognitive impairment from early to middle adulthood in patients with affective and nonaffective psychotic disorders, *Psychological Medicine*. Cambridge University Press, **50**, p. 48–57.

Molloy, C, Conroy, R M, Cotter, D R and Cannon, M (2011) Is Traumatic Brain Injury A Risk Factor for Schizophrenia? A Meta-Analysis of Case-Controlled Population-Based Studies, *Schizophr Bull*, **37**, p. 1104–1110.

Moreira, A L R, Van Meter, A, Genzlinger, J and Youngstrom, E A (2017) Review and meta-analysis of epidemiologic studies of adult bipolar disorder, *Journal of Clinical Psychiatry*. Physicians Postgraduate Press Inc., p. e1259–e1269.

Morgan, C, Gayer-Anderson, C, Beards, S, Hubbard, K, Mondelli, V, Di Forti, M, Murray, R M, Pariante, C, Dazzan, P, Craig, T J, Reininghaus, U and Fisher, H L (2020) Threat, hostility and violence in childhood and later psychotic disorder: Population-based case-control study, *British Journal of Psychiatry*. Cambridge University Press, **217**, p. 575–582.

Morgan, C, Knowles, G and Hutchinson, G (2019) Migration, ethnicity and psychoses: evidence, models and future directions, *World Psychiatry*. Blackwell Publishing Ltd, **18**, p. 247–258.

Mortensen, P B, Pedersen, C B, Melbye, M, Mors, O and Ewald, H (2003) Individual and Familial Risk Factors for Bipolar Affective Disorders in Denmark, *Archives of General Psychiatry*, **60**.

Mortensen, P B, Pedersen, C B, Mcgrath, J J, Hougaard, D M, Nørgaard-Petersen, B, Mors, O, Børglum, A D and Yolken, R H (2011) Neonatal antibodies to infectious agents and risk of bipolar disorder: A population-based case-control study, *Bipolar Disorders*, **13**, p. 624–629.

Moskvina, V, Craddock, N, Holmans, P, Nikolov, I, Pahwa, J S, Green, E, Owen, M J, O'Donovan, M C and O'Donovan, M C (2009) Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk, *Molecular Psychiatry*, **14**, p. 252–260.

Mulè, A, Sideli, L, Capuccio, V, Fearon, P, Ferraro, L, Kirkbride, J B, La Cascia, C, Sartorio, C, Seminerio, F, Tripoli, G, Di Forti, M, La Barbera, D and Murray, R M (2017) Low incidence of psychosis in Italy: confirmation from the first epidemiological study in Sicily, *Social Psychiatry and Psychiatric Epidemiology*, **52**.

Mullins, N, Power, R A, Fisher, H L, Hanscombe, K B, Euesden, J, Iniesta, R, Levinson, D F, Weissman, M M, Potash, J B, Shi, J, Uher, R, Cohen-Woods, S, Rivera, M, Jones, L, Jones, I, Craddock, N, Owen, M J, Korszun, A, Craig, I W, *et al.* (2016) Polygenic interactions with environmental adversity in the aetiology of major depressive disorder., *Psychological medicine*, **46**, p. 759–70.

Munkholm, K, Peijs, L, Vinberg, M and Kessing, L V. (2015) A composite peripheral blood gene expression measure as a potential diagnostic biomarker in bipolar disorder, *Translational Psychiatry*. Nature Publishing Group, **5**, p. e614.

Muntané, G, Farré, X, Bosch, E, Martorell, L, Navarro, A and Vilella, E (2020) The shared genetic architecture of schizophrenia, bipolar disorder and lifespan, *Human Genetics*. Springer.

Murray, R M, Sham, P, Van Os, J, Zanelli, J, Cannon, M, McDonald, C, Os, J Van, Zanelli, J, Cannon, M, McDonald, C, Van Os, J, Zanelli, J, Cannon, M and McDonald, C (2004) A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder, *Schizophrenia Research*. Elsevier, **71**, p. 405–416.

Murray, R M and Foerster, A (1987) Schizophrenia: is the concept disintegrating?, *Journal of psychopharmacology (Oxford, England)*. Sage PublicationsSage CA: Thousand Oaks, CA, **1**, p. 133–9.

Murray, R M and Lewis, S W (1987) Is schizophrenia a neurodevelopmental disorder?, *BMJ*, **295**, p. 681–682.

Murray, R M and Vassos, E (2020) Nature, Nurture, and the Polygenic Risk Score for Schizophrenia, *Schizophrenia Bulletin*. Oxford University Press (OUP), **46**.

Murru, A, Pacchiarotti, I, Nivoli, A M A, Colom, F and Vieta, E (2012) Is Schizoaffective Disorder Still a Neglected Condition in the Scientific Literature?, *Psychotherapy and Psychosomatics*, p. 389–390.

Murru, A, Pacchiarotti, I, Verdolini, N, Reinares, M, Torrent, C, Geoffroy, P A, Bellivier, F, Llorca, P M, Vieta, E and Samalin, L (2018) Modifiable and non-modifiable factors associated with functional impairment during the inter-episodic periods of bipolar disorder, *European Archives of Psychiatry and Clinical Neuroscience*. Dr. Dietrich Steinkopff Verlag GmbH and Co. KG, **268**, p. 749–755.

Musci, R J, Augustinavicius, J L and Volk, H (2019) Gene-Environment Interactions in Psychiatry: Recent Evidence and Clinical Implications, *Current Psychiatry Reports*. Current Medicine Group LLC 1.

Musliner, K L, Seifuddin, F, Judy, J A, Pirooznia, M, Goes, F S and Zandi, P P (2015) Polygenic risk, stressful life events and depressive symptoms in older adults: a polygenic score analysis, *Psychological medicine*. NIH Public Access, **45**.

Musliner, K L, Krebs, M D, Albiñana, C, Vilhjalmsson, B, Agerbo, E, Zandi, P P, Hougaard, D M, Nordentoft, M, Børglum, A D, Werge, T, Mortensen, P B and Østergaard, S D (2020) Polygenic risk and progression to bipolar or psychotic disorders among individuals diagnosed with unipolar depression in early life, *American Journal of Psychiatry*. American Psychiatric Association, **177**, p. 936–943.

Mustonen, A, Niemelä, S, Nordström, T, Murray, G K, Mäki, P, Jääskeläinen, E and Miettunen, J (2018) Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis, *British Journal of Psychiatry*. Royal College of Psychiatrists, **212**, p. 227–233.

Myin-Germeys, I and van Os, J (2007) Stress-reactivity in psychosis: Evidence for an affective pathway to psychosis, *Clinical Psychology Review*. Clin Psychol Rev, **27**, p. 409–424.

Newbury, J, Arseneault, L, Caspi, A, Moffitt, T E, Odgers, C L and Fisher, H L (2016) Why Are Children in Urban Neighborhoods at Increased Risk for Psychotic Symptoms? Findings From a UK Longitudinal Cohort Study, *Schizophrenia Bulletin*. Oxford University Press, **42**, p. 1372–1383.

Nietola, M, Huovinen, H, Heiskala, A, Nordström, T, Miettunen, J, Korkeila, J and Jääskeläinen, E (2020) Early childhood and adolescent risk factors for psychotic depression in a general population birth cohort sample, *Social Psychiatry and Psychiatric Epidemiology*. Springer, **55**, p. 1179–1186.

Nordentoft, M, Wahlbeck, K, Hällgren, J, Westman, J, Ösby, U, Alinaghizadeh, H, Gissler, M and Laursen, T M (2013) Excess Mortality, Causes of Death and Life Expectancy in 270,770 Patients with Recent Onset of Mental Disorders in Denmark, Finland and Sweden, *PLoS ONE*. PLoS One, **8**.

Nosarti, C, Reichenberg, A, Murray, R M, Cnattingius, S, Lambe, M P, Yin, L, MacCabe, J, Rifkin, L and Hultman, C M (2012) Preterm birth and psychiatric disorders in young adult life, *Archives of General Psychiatry*, **69**.

Øgendahl, B K, Agerbo, E, Byrne, M, Licht, R W, Eaton, W W and Mortensen, P B (2006) Indicators of fetal growth and bipolar disorder: A Danish national register-based study, *Psychological Medicine*, **36**, p. 1219–1224.

Oliveira, J, Etain, B, Lajnef, M, Hamdani, N, Bennabi, M, Bengoufa, D, Sundaresh, A, Chaabane, A Ben, Bellivier, F, Henry, C, Kahn, J P, Charron, D, Krishnamoorthy, R, Leboyer, M and Tamouza, R (2015) Combined effect of TLR2 gene polymorphism and early life stress on the age at onset of bipolar disorders, *PLoS ONE*. Public Library of Science, **10**.

Oliveira, J, Kazma, R, Le Floch, E, Bennabi, M, Hamdani, N, Bengoufa, D, Dahoun, M, Manier, C, Bellivier, F, Krishnamoorthy, R, Deleuze, J F, Yolken, R, Leboyer, M and Tamouza, R (2016) Toxoplasma gondii exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene–environment interaction study, *International Journal of Bipolar Disorders*. SpringerOpen, **4**.

Oliver, D, Radua, J, Reichenberg, A, Uher, R and Fusar-Poli, P (2019) Psychosis Polyrisk Score (PPS) for the Detection of Individuals At-Risk and the Prediction of Their Outcomes, *Frontiers in Psychiatry*. Frontiers Media S.A., **10**, p. 174.

Omer, S, Finnegan, M, Pringle, D G, Kinsella, A, Fearon, P, Russell, V, O'Callaghan, E and Waddington, J L (2016) Socioeconomic status at birth and risk for first episode psychosis in rural Ireland: Eliminating the features of urbanicity in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS), *Schizophrenia Research*. Elsevier B.V., **173**, p. 84–89.

Organization, W H (2018) *International classification of diseases for mortality and morbidity statistics (11th Revision)*. Geneva: Author.

Orlovska, S, Pedersen, M S, Benros, M E, Mortensen Dr., P B, Agerbo Dr., E and Nordentoft Dr., M (2014) Head injury as risk factor for psychiatric disorders: A nationwide register-based follow-up study of 113,906 persons with head injury, *American Journal of Psychiatry*. American Psychiatric Association, **171**, p. 463–469.

Ortiz, A, Bradler, K, Slaney, C, Garnham, J, Ruzickova, M, O'Donovan, C, Hajek, T and Alda, M (2011) An admixture analysis of the age at index episodes in bipolar disorder, *Psychiatry Research*. Psychiatry Res, **188**, p. 34–39.

Van Os, J, Takei, N, Castle, D J, Wessely, S, Der, G, MacDonald, A M and Murray, R M (1996) The incidence of mania: Time trends in relation to gender and ethnicity, *Social Psychiatry and Psychiatric Epidemiology*, **31**, p. 129–136.

Van Os, J (2016) 'Schizophrenia' does not exist: Disease classifications should drop this unhelpful description of symptoms, *BMJ (Online)*. BMJ Publishing Group.

Van Os, J, Rutten, B P F and Poulton, R (2008) Gene-environment interactions in schizophrenia: Review of epidemiological findings and future directions, *Schizophrenia Bulletin*. Schizophr Bull, p. 1066–1082.

Østergaard, Søren Dinesen, Rothschild, A J, Uggerby, P, Munk-Jørgensen, P, Bech, P and Mors, O (2012) Considerations on the ICD-11 classification of psychotic depression, *Psychotherapy and Psychosomatics*. Psychother Psychosom, p. 135–144.

Østergaard, Soren Dinesen, Bille, J, Soltoft-Jensen, H, Lauge, N and Bech, P (2012) The validity of the severity-psychosis hypothesis in depression, *Journal of Affective Disorders*. J Affect Disord, **140**, p. 48–56.

Østergaard, S D, Waltoft, B L, Mortensen, P B and Mors, O (2013) Environmental and familial risk factors for psychotic and non-psychotic severe depression, *Journal of Affective Disorders*, **147**, p. 232–240.

Owen, M J and O'Donovan, M C (2017) Schizophrenia and the neurodevelopmental continuum:evidence from genomics, *World Psychiatry*. Blackwell Publishing Ltd, **16**, p. 227–235.

Owoeye, O, Kingston, T, Scully, P J, Baldwin, P, Browne, D, Kinsella, A, Russell, V, O'Callaghan, E and Waddington, J L (2013) Epidemiological and clinical characterization following a first psychotic episode in major depressive disorder: Comparisons with schizophrenia and bipolar i disorder in the cavan-monaghan first episode psychosis study (CAMFEPS), *Schizophrenia Bulletin*. Schizophr Bull, **39**, p. 756–765.

Pacheco, A, Barguil, M, Contreras, J, Montero, P, Dassori, A, Escamilla, M A and Raventós, H (2010) Social and clinical comparison between schizophrenia and bipolar disorder type I with psychosis in Costa Rica, *Social Psychiatry and Psychiatric Epidemiology*. Soc Psychiatry Psychiatr Epidemiol, **45**, p. 675–680.

Pain, O, Hodgson, K, Trubetskoy, V, Ripke, S, Marshe, V S, Adams, M J, Byrne, E M, Campos, A I, Carrillo-Roa, T, Cattaneo, A, Damm Als, T, Souery, D, Dernovsek, M Z, Fabbri, C, Hayward, C, Henigsberg, N, Hauser, J, Kennedy, J L, Lenze, E J, *et al.* (2020) Antidepressant response in major depressive disorder: A genome-wide association study, *medRxiv*. medRxiv, p. 2020.12.11.20245035.

Paksarian, D, Eaton, W W, Mortensen, P B and Pedersen, C B (2015) Childhood Residential Mobility, Schizophrenia, and Bipolar Disorder: A Population-based Study in Denmark, *Schizophrenia Bulletin*. Oxford University Press, **41**, p. 346–354.

Palmier-Claus, J E, Berry, K, Bucci, S, Mansell, W and Varese, F (2016) Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis, *British Journal of Psychiatry*, **209**, p. 454–459.

Parboosing, R, Bao, Y, Shen, L, Schaefer, C A and Brown, A S (2013) Gestational influenza and bipolar disorder in adult offspring, *JAMA Psychiatry*. American Medical

Association, **70**, p. 677–685.

Parker, G, Hadzi-Pavlovic, D, Hickie, I, Boyce, P, Mitchell, P, Wilhelm, K and Brodaty, H (1991) Distinguishing psychotic and non-psychotic melancholia, *Journal of Affective Disorders*. J Affect Disord, **22**, p. 135–148.

Payá, B, Rodríguez-Sánchez, J M, Otero, S, Muñoz, P, Castro-Fornieles, J, Parellada, M, Gonzalez-Pinto, A, Soutullo, C, Baeza, I, Rapado-Castro, M, Sáenz-Herrero, M, Moreno, D and Arango, C (2013) Premorbid impairments in early-onset psychosis: Differences between patients with schizophrenia and bipolar disorder, *Schizophrenia Research*. Elsevier, **146**, p. 103–110.

Pedersen, C B and Mortensen, P B (2001) Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk, *Archives of General Psychiatry*, **58**, p. 1039–1046.

Peen, J, Schoevers, R A, Beekman, A T and Dekker, J (2010) The current status of urban-rural differences in psychiatric disorders, *Acta Psychiatrica Scandinavica*, **121**, p. 84–93.

Pelayo-Terán, J M, Pérez-Iglesias, R, Ramírez-Bonilla, M L, González-Blanch, C, Martínez-García, O, Pardo-García, G, Rodríguez-Sánchez, J M, Roiz-Santiáñez, R, Tordesillas-Gutiérrez, D, Mata, I, Vázquez-Barquero, J L and Crespo-Facorro, B (2008) Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: Insights from the Clinical Programme on Early Phases of Psychosis, *Early Intervention in Psychiatry*. Early Interv Psychiatry, **2**, p. 178–187.

Perälä, J, Suvisaari, J, Saarni, S I, Kuoppasalmi, K, Isometsä, E, Pirkola, S, Partonen, T, Tuulio-Henriksson, A, Hintikka, J, Kieseppä, T, Härkänen, T, Koskinen, S and Lönnqvist, J (2007) Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population, *Archives of General Psychiatry*. American Medical Association, **64**, p. 19.

Perkins, D O, Olde Loohuis, L, Barbee, J, Ford, J, Jeffries, C D, Addington, J, Bearden, C E, Cadenhead, K S, Cannon, T D, Cornblatt, B A, Mathalon, D H, McGlashan, T H, Seidman, L J, Tsuang, M, Walker, E F and Woods, S W (2020) Polygenic Risk Score Contribution to Psychosis Prediction in a Target Population of Persons at Clinical High Risk, *American Journal of Psychiatry*. NLM (Medline), **177**, p. 155–163.

Perry, D C, Sturm, V E, Peterson, M J, Pieper, C F, Bullock, T, Boeve, B F, Miller, B L, Guskiewicz, K M, Berger, M S, Kramer, J H and Welsh-Bohmer, K A (2016) Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis., *Journal of Neurosurgery*, **124**.

Peters, E M, Bowen, R and Balbuena, L (2020) Melancholic depression and response to quetiapine: A pooled analysis of four randomized placebo-controlled trials, *Journal of Affective Disorders*. Elsevier B.V., **276**, p. 696–698.

Peyrot, W J, Milaneschi, Y, Abdellaoui, A, Sullivan, P F, Hottenga, J J, Boomsma, D I and Penninx, B W J H (2014) Effect of polygenic risk scores on depression in childhood trauma, *British Journal of Psychiatry*, **205**, p. 113–119.

Peyrot, W J, Van der Auwera, S, Milaneschi, Y, Dolan, C V., Madden, P A F, Sullivan, P F, Strohmaier, J, Ripke, S, Rietschel, M, Nivard, M G, Mullins, N,

Montgomery, G W, Henders, A K, Heat, A C, Fisher, H L, Dunn, E C, Byrne, E M, Air, T A, Baune, B T, *et al.* (2017) Does Childhood Trauma Moderate Polygenic Risk for Depression? A Meta-analysis of 5765 Subjects From the Psychiatric Genomics Consortium, *Biological Psychiatry*.

Pini, S, De Queiroz, V, Pagnin, D, Pezawas, L, Angst, J, Cassano, G B and Wittchen, H U (2005) Prevalence and burden of bipolar disorders in European countries, *European Neuropsychopharmacology*. Eur Neuropsychopharmacol, **15**, p. 425–434.

De Pradier, M, Gorwood, P, Beaufils, B, Adès, J and Dubertret, C (2010) Influence of the serotonin transporter gene polymorphism, cannabis and childhood sexual abuse on phenotype of bipolar disorder: A preliminary study, *European Psychiatry*. Cambridge University Press, **25**, p. 323–327.

Price, A L, Weale, M E, Patterson, N, Myers, S R, Need, A C, Shianna, K V., Ge, D, Rotter, J I, Torres, E, Taylor, K D D, Goldstein, D B and Reich, D (2008) Long-Range LD Can Confound Genome Scans in Admixed Populations, *American Journal of Human Genetics*. Elsevier, p. 132–135.

Pries, L-K, Erzin, G, van Os, J, ten Have, M, de Graaf, R, van Dorsselaer, S, Bak, M, Rutten, B P F and Guloksuz, S (2020) Predictive Performance of Exposome Score for Schizophrenia in the General Population, *Schizophrenia Bulletin*. Oxford University Press (OUP).

Pries, L K, Lage-Castellanos, A, Delespaul, P, Kenis, G, Luykx, J J, Lin, B D, Richards, A L, Akdede, B, Binbay, T, Altinyazar, V, Yalinçetin, B, Gümüş-Akay, G, Cihan, B, Soygür, H, Ulaş, H, Cankurtaran, E Ş, Kaymak, S U, Mihaljevic, M M, Petrovic, S A, *et al.* (2019) Estimating Exposome Score for Schizophrenia Using Predictive Modeling Approach in Two Independent Samples: The Results from the EUGEI Study, *Schizophrenia Bulletin*. Oxford University Press, **45**, p. 960–965.

Pries, L K, Klingenberg, B, Menne-Lothmann, C, Decoster, J, van Winkel, R, Collip, D, Delespaul, P, De Hert, M, Derom, C, Thiery, E, Jacobs, N, Wichers, M, Cinar, O, Lin, B D, Luykx, J J, Rutten, B P F, van Os, J and Guloksuz, S (2020) Polygenic liability for schizophrenia and childhood adversity influences daily-life emotion dysregulation and psychosis proneness, *Acta Psychiatrica Scandinavica*. Blackwell Publishing Ltd, **141**, p. 465–475.

Purcell, S, Neale, B, Todd-Brown, K, Thomas, L, Ferreira, M A R, Bender, D, Maller, J, Sklar, P, De Bakker, P I W, Daly, M J and Sham, P C (2007) PLINK: A tool set for whole-genome association and population-based linkage analyses, *American Journal of Human Genetics*. Cell Press, **81**, p. 559–575.

Purcell, S M, Wray, N R, Stone, J L, Visscher, P M, O'Donovan, M C, Sullivan, P F, Sklar, P, Purcell (Leader), S M, Stone, J L, Sullivan, P F, Ruderfer, D M, McQuillin, A, Morris, D W, O'Dushlaine, C T, Corvin, A, Holmans, P A, O'Donovan, M C, Sklar, P, Wray, N R, *et al.* (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder, *Nature*, **460**, p. 748–52.

Quattrone, D, Di Forti, M, Gayer-Anderson, C, Ferraro, L, Jongsma, H E, Tripoli, G, La Cascia, C, La Barbera, D, Tarricone, I, Berardi, D, Szöke, A, Arango, C, Lasalvia, A, Tortelli, A, Llorca, P-M, de Haan, L, Velthorst, E, Bobes, J, Bernardo, M, *et al.* (2018) Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study, *Psychological Medicine*.

Cambridge University Press, p. 1–14.

Radden, J (2011) *The Nature of Melancholy: From Aristotle to Kristeva*, *The Nature of Melancholy: From Aristotle to Kristeva*. Oxford University Press.

Radhakrishnan, R, Guloksuz, S, Ten Have, M, De Graaf, R, Van Dorsselaer, S, Gunther, N, Rauschenberg, C, Reininghaus, U, Pries, L K, Bak, M and Van Os, J (2019) Interaction between environmental and familial affective risk impacts psychosis admixture in states of affective dysregulation, *Psychological Medicine*. Cambridge University Press, **49**, p. 1879–1889.

Radua, J, Ramella-Cravaro, V, Ioannidis, J P A, Reichenberg, A, Phiphopthatsanee, N, Amir, T, Yenn Thoo, H, Oliver, D, Davies, C, Morgan, C, McGuire, P, Murray, R M and Fusar-Poli, P (2018) What causes psychosis? An umbrella review of risk and protective factors, *World Psychiatry*. Blackwell Publishing Ltd, p. 49–66.

Ripke, S, Wray, N R, Lewis, C M, Hamilton, S P, Weissman, M M, Breen, G, Byrne, E M, Blackwood, D H R, Boomsma, D I, Cichon, S, Heath, A C, Holsboer, F, Lucae, S, Madden, P A F, Martin, N G, McGuffin, P, Muglia, P, Noethen, M M, Penninx, B P, *et al.* (2013) A mega-analysis of genome-wide association studies for major depressive disorder, *Molecular Psychiatry*, **18**, p. 497–511.

Ripke, S, Neale, Benjamin M, Corvin, A, Walters, J T and Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci, *Nature*, **511**, p. 421–427.

Risch, N, Herrell, R, Lehner, T, Liang, K-Y, Eaves, L, Hoh, J, Griem, A, Kovacs, M, Ott, J and Merikangas, K R (2009) Interaction Between the Serotonin Transporter Gene (5-HTTLPR), Stressful Life Events, and Risk of Depression, *JAMA*, **301**, p. 2462.

Rodriguez, V, Alameda, L, Trotta, G, Spinazzola, E, Marino, P, Matheson, S L, Laurens, K R, Murray, R M and Vassos, E (2021) Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies, *Schizophrenia Bulletin*. Oxford University Press (OUP).

Rodríguez, V, Aas, M, Vorontsova, N, Trotta, G, Gadelrab, R, Rooprai, N K and Alameda, L (2021) Exploring the interplay between adversity, neurocognition, social cognition and functional outcome in people with psychosis: a narrative review, *Frontiers in Psychiatry*. Frontiers, **12**, p. 237.

Rosmalen, J G M, Bos, E H and De Jonge, P (2012) Validation of the long-term difficulties inventory (LDI) and the list of threatening experiences (LTE) as measures of stress in epidemiological population-based cohort studies, *Psychological Medicine*. Psychol Med, **42**, p. 2599–2608.

van Rossum, I, Haro, J M, Tenback, D, Boomsma, M, Goetz, I, Vieta, E and van Os, J (2008) Stability and treatment outcome of distinct classes of mania, *European Psychiatry*. Eur Psychiatry, **23**, p. 360–367.

Rothman, K, Lash, T and Greenland, S (2008) *Modern Epidemiology , 3 rd Edition*. Philadelphia: Lippincott Williams and Wilkins.

Rothschild, A J, Winer, J, Flint, A J, Mulsant, B H, Whyte, E M, Heo, M, Fratoni, S, Gabriele, M, Kasapinovic, S and Meyers, B S (2008) Missed diagnosis of psychotic depression at 4 academic medical centers, *Journal of Clinical Psychiatry*. Physicians

Postgraduate Press Inc., **69**, p. 1293–1296.

Ruderfer, D M, Fanous, A H, Ripke, S, McQuillin, A, Amdur, R L, Gejman, P V., O'Donovan, M C, Andreassen, O A, Djurovic, S, Hultman, C M, Kelsoe, J R, Jamain, S, Landén, M, Leboyer, M, Nimgaonkar, V, Nurnberger, J, Smoller, J W, Craddock, N, Corvin, A, *et al.* (2014) Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia, *Molecular Psychiatry*. Springer Nature, **19**, p. 1017–1024.

Ruderfer, D M, Ripke, S, McQuillin, A, Boocock, J, Stahl, E A, Pavlides, J M W, Mullins, N, Charney, A W, Ori, A P S, Loohuis, L M O, Domenici, E, Di Florio, A, Papiol, S, Kalman, J L, Trubetskoy, V, Adolfsson, R, Agartz, I, Agerbo, E, Akil, H, *et al.* (2018) Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes, *Cell*. Cell Press, **173**, p. 1705-1715.e16.

Ruisch, I H, Dietrich, A, Klein, M, Faraone, S V., Oosterlaan, J, Buitelaar, J K and Hoekstra, P J (2020) Aggression based genome-wide, glutamatergic, dopaminergic and neuroendocrine polygenic risk scores predict callous-unemotional traits, *Neuropsychopharmacology*. Springer Nature, **45**, p. 761–769.

Saarni, S I, Viertiö, S, Perälä, J, Koskinen, S, Lönnqvist, J and Suvisaari, J (2010) Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders, *British Journal of Psychiatry*, **197**, p. 386–394.

Sanchez-Moreno, J, Bonnin, C M, González-Pinto, A, Amann, B L, Solé, B, Balanzá-Martinez, V, Arango, C, Jiménez, E, Tabarés-Seisdedos, R, Garcia-Portilla, M P, Ibáñez, A, Crespo, J M, Ayuso-Mateos, J L, Martinez-Aran, A, Torrent, C, Vieta, E, Alegría, A, Al-Halabi, S, Alonso-Lana, S, *et al.* (2018) Factors associated with poor functional outcome in bipolar disorder: sociodemographic, clinical, and neurocognitive variables, *Acta Psychiatrica Scandinavica*. Blackwell Publishing Ltd, **138**, p. 145–154.

Savage, J E, Jansen, P R, Stringer, S, Watanabe, K, Bryois, J, De Leeuw, C A, Nagel, M, Awasthi, S, Barr, P B, Coleman, J R I, Grasby, K L, Hammerschlag, A R, Kaminski, J A, Karlsson, R, Krapohl, E, Lam, M, Nygaard, M, Reynolds, C A, Trampush, J W, *et al.* (2018) Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence, *Nature Genetics*. Nature Publishing Group, **50**, p. 912–919.

Schatzberg, A F and Rothschild, A J (1992) Psychotic (delusional) major depression: Should it be included as a distinct syndrome in DSM-IV?, *American Journal of Psychiatry*. Am J Psychiatry, p. 733–745.

Schijven, D, Veldink, J H and Luykx, J J (2020) Genetic cross-disorder analysis in psychiatry: From methodology to clinical utility, *British Journal of Psychiatry*. Cambridge University Press, **216**, p. 246–249.

Schulze, T and McMahon, F (2018) *Psychiatric Genetics: A Primer for Clinical and Basic Scientists - Oxford Medicine*. Edited by T. Schulze and F. McMahon. Oxford University Press.

Schwartz, J E, Fennig, S, Tanenberg-Karant, M, Carlson, G, Craig, T, Galambos, N, Lavelle, J and Bromet, E J (2000) Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis, *Archives of General Psychiatry*. American Medical Association, **57**, p. 593–600.

Scott, J, McNeill, Y, Cavanagh, J, Cannon, M and Murray, R (2006) Exposure to obstetric complications and subsequent development of bipolar disorder, *British Journal of Psychiatry*. Cambridge University Press, **189**, p. 3–11.

Scott, K M, Smith, D R and Ellis, P M (2010) Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults, *Archives of General Psychiatry*, **67**, p. 712–719.

Sedler, M J (1983) Falret's discovery: The origin of the concept of bipolar affective illness, *American Journal of Psychiatry*. Am J Psychiatry, **140**, p. 1127–1133.

Sèglas, J (1895) *Leçons cliniques sur les maladies mentales et nerveuses*. Edited by A. et H. (Paris).

Selten, J P, van Os, J and Nolen, W A (2003) First admissions for mood disorders in immigrants to the Netherlands, *Social Psychiatry and Psychiatric Epidemiology*, **38**, p. 547–550.

Selten, J P, Van Der Ven, E and Termorshuizen, F (2019) Migration and psychosis: A meta-analysis of incidence studies, *Psychological Medicine*. Cambridge University Press, **50**, p. 303–313.

Shalev, A, Merranko, J, Gill, M K, Goldstein, T, Liao, F, Goldstein, B I, Hower, H, Ryan, N, Strober, M, Iyengar, S, Keller, M, Yen, S, Weinstock, L M, Axelson, D and Birmaher, B (2020) Longitudinal course and risk factors associated with psychosis in bipolar youths, *Bipolar Disorders*. Blackwell Publishing Inc., **22**, p. 139–154.

Sharmin, S, Kypri, K, Khanam, M, Wadolowski, M, Bruno, R and Mattick, R (2017) Parental Supply of Alcohol in Childhood and Risky Drinking in Adolescence: Systematic Review and Meta-Analysis, *International Journal of Environmental Research and Public Health*. MDPI AG, **14**, p. 287.

Shevlin, M, Houston, J E, Dorahy, M J and Adamson, G (2008) Cumulative traumas and psychosis: An analysis of the national comorbidity survey and the British Psychiatric Morbidity Survey, *Schizophrenia Bulletin*. Oxford University Press, **34**, p. 193–199.

Shevlin, M, McElroy, E, Bentall, R P, Reininghaus, U and Murphy, J (2017) The psychosis continuum: Testing a bifactor model of psychosis in a general population sample, *Schizophrenia Bulletin*. Oxford University Press, **43**, p. 133–141.

Shi, L and Lin, L (2019) The trim-and-fill method for publication bias, *Medicine*, **98**, p. e15987.

Shifman, S, Bronstein, M, Sternfeld, M, Pisanté-Shalom, A, Lev-Lehman, E, Weizman, A, Reznik, I, Spivak, B, Grisaru, N, Karp, L, Schiffer, R, Kotler, M, Strous, R D, Swartz-Vanetik, M, Knobler, H Y, Shinar, E, Beckmann, J S, Yakir, B, Risch, N, *et al.* (2002) A Highly Significant Association between a COMT Haplotype and Schizophrenia, *The American Journal of Human Genetics*, **71**, p. 1296–1302.

Singh, S P, Cooper, J E, Fisher, H L, Tarrant, C J, Lloyd, T, Banjo, J, Corfe, S and Jones, P (2005) Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS), *Schizophrenia Research*, **80**, p. 117–130.

Sklar, P, Smoller, J W, Fan, J, Ferreira, M A R, Perlis, R H, Chambert, K, Nimgaonkar, V L, McQueen, M B, Faraone, S V, Kirby, A, de Bakker, P I W, Ogdie, M N, Thase, M E, Sachs, G S, Todd-Brown, K, Gabriel, S B, Sougnez, C, Gates, C,

Blumenstiel, B, *et al.* (2008) Whole-genome association study of bipolar disorder, *Molecular Psychiatry*, **13**, p. 558–569.

Sklar, P, Ripke, S, Scott, L J, Andreassen, O A, Cichon, S, Craddock, N, Edenberg, H J, Nurnberger, J I, Rietschel, M, Blackwood, D, Corvin, A, Flickinger, M, Guan, W, Mattingsdal, M, McQuillin, A, Kwan, P, Wienker, T F, Daly, M, Dudbridge, F, *et al.* (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4., *Nature genetics*. Inserm, **43**, p. 977–83.

Smeland, O B, Bahrami, S, Frei, O, Shadrin, A, O'Connell, K, Savage, J, Watanabe, K, Krull, F, Bettella, F, Steen, N E, Ueland, T, Posthuma, D, Djurovic, S, Dale, A M and Andreassen, O A (2020) Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence, *Molecular Psychiatry*. Springer Nature, **25**, p. 844–853.

Smeland, O B, Shadrin, A, Bahrami, S, Broce, I, Tesli, M, Frei, O, Wirgenes, K V., O'Connell, K S, Krull, F, Bettella, F, Steen, N E, Sugrue, L, Wang, Y, Svenningsson, P, Sharma, M, Pihlstrøm, L, Toft, M, O'Donovan, M, Djurovic, S, *et al.* (2020) Genome-wide Association Analysis of Parkinson's Disease and Schizophrenia Reveals Shared Genetic Architecture and Identifies Novel Risk Loci, *Biological Psychiatry*. Elsevier USA.

Smoller, J W, Andreassen, O A, Edenberg, H J, Faraone, S V., Glatt, S J and Kendler, K S (2019) Psychiatric genetics and the structure of psychopathology, *Molecular Psychiatry*. Nature Publishing Group, **24**, p. 409–420.

Smoller, J W and Finn, C T (2003) Family, twin, and adoption studies of bipolar disorder, *American Journal of Medical Genetics*, **123C**, p. 48–58.

Soderlund, J, Wicks, S, Jorgensen, L and Dalman, C (2015) Comparing cohort incidence of schizophrenia with that of bipolar disorder and affective psychosis in individuals born in Stockholm County 1955-1967, *Psychological Medicine*. Cambridge University Press, **45**, p. 3433–3439.

Stahl, E A, Breen, G, Forstner, A J, McQuillin, A, Ripke, S, Trubetskoy, V, Mattheisen, M, Wang, Y, Coleman, J R I, Gaspar, H A, de Leeuw, C A, Steinberg, S, Pavlides, J M W, Trzaskowski, M, Byrne, E M, Pers, T H, Holmans, P A, Richards, A L, Abbott, L, *et al.* (2019) Genome-wide association study identifies 30 loci associated with bipolar disorder, *Nature Genetics*. Nature Publishing Group, **51**, p. 793–803.

Stilo, S A and Murray, R M (2019) Non-Genetic Factors in Schizophrenia, *Current Psychiatry Reports*. Current Medicine Group LLC 1.

Stroup, D F, Berlin, J A, Morton, S C, Olkin, I, Williamson, G D, Rennie, D, Moher, D, Becker, B J, Sipe, T A and Thacker, S B (2000) Meta-analysis of observational studies in epidemiology: A proposal for reporting, *Journal of the American Medical Association*. American Medical Association, **283**, p. 2008–2012.

Sullivan, P F, Agrawal, A, Bulik, C, Andreassen, O A, Borglum, A, Breen, G, Cichon, S, Edenberg, H, Faraone, S V, Gelernter, J, Mathews, C A, Nievergelt, C M, Smoller, J, O'Donovan, M and Consortium, P G (2017) Psychiatric Genomics: An Update and an Agenda, *bioRxiv*. Cold Spring Harbor Laboratory, p. 115600.

Sullivan, P F, Neale, M C and Kendler, K S (2000) Genetic Epidemiology of Major

Depression: Review and Meta-Analysis, *American Journal of Psychiatry*, **157**, p. 1552–1562.

Sundquist, K, Frank, G and Sundquist, J (2004) Urbanisation and incidence of psychosis and depression: Follow-up study of 4.4 million women and men in Sweden, *British Journal of Psychiatry*, **184**, p. 293–298.

Sutterland, A L, Fond, G, Kuin, A, Koeter, M W J, Lutter, R, van Gool, T, Yolken, R, Szoke, A, Leboyer, M and de Haan, L (2015) Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: Systematic review and meta-analysis, *Acta Psychiatrica Scandinavica*. Blackwell Publishing Ltd, **132**, p. 161–179.

Swinnen, S G H A and Selten, J P (2007) Mood disorders and migration: Meta-analysis, *British Journal of Psychiatry*, p. 6–10.

Szöke, A, Charpeaud, T, Galliot, A M, Vilain, J, Richard, J R, Leboyer, M, Llorca, P M and Schürhoff, F (2014) Rural-urban variation in incidence of psychosis in France: A prospective epidemiologic study in two contrasted catchment areas, *BMC Psychiatry*. BioMed Central Ltd., **14**.

Tarricone, I, Mimmi, S, Paparelli, A, Rossi, E, Mori, E, Panigada, S, Carchia, G, Bandieri, V, Michetti, R, Minenna, G, Boydell, J, Morgan, C and Berardi, D (2012) First-episode psychosis at the West Bologna Community Mental Health Centre: Results of an 8-year prospective study, *Psychological Medicine*. Psychol Med, p. 2255–2264.

Telles-Correia, D and Marques, J G (2015) Melancholia before the twentieth century: Fear and sorrow or partial insanity?, *Frontiers in Psychology*. Frontiers Research Foundation.

Tesli, M, Espeseth, T, Bettella, F, Mattingsdal, M, Aas, M, Melle, I, Djurovic, S and Andreassen, O A (2014) Polygenic risk score and the psychosis continuum model, *Acta Psychiatrica Scandinavica*, **130**, p. 311–317.

Thoresen, S, Tambs, K, Hussain, A, Heir, T, Johansen, V A and Bisson, J I (2010) Brief measure of posttraumatic stress reactions: Impact of Event Scale-6, *Social Psychiatry and Psychiatric Epidemiology*, **45**, p. 405–412.

Tizón, J L, Ferrando, J, Parés, A, Artigué, J, Parra, B and Pérez, C (2007) Trastornos esquizofrénicos en la atención primaria a la salud mental, *Atencion Primaria*. Ediciones Doyma, S.L., **39**, p. 119–124.

Tohen, M, Hennen, J, Zarate, C M, Baldessarini, R J, Strakowski, S M, Stoll, A L, Faedda, G L, Suppes, T, Gebre-Medhin, P and Cohen, B M (2000) Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features, *American Journal of Psychiatry*. Am J Psychiatry, **157**, p. 220–228.

Tohen, M, Zarate, C A, Hennen, J, Khalsa, H M K, Strakowski, S M, Gebre-Medhin, P, Salvatore, P and Baldessarini, R J (2003) The McLean-Harvard first-episode mania study: Prediction of recovery and first recurrence, *American Journal of Psychiatry*, **160**, p. 2099–2107.

Tohen, M, Bowden, C L, Calabrese, J R, Lin, D, Forrester, T D, Sachs, G S, Koukopoulos, A, Yatham, L and Grunze, H (2006) Influence of sub-syndromal

symptoms after remission from manic or mixed episodes, *British Journal of Psychiatry*. Cambridge University Press, **189**, p. 515–519.

Tohen, M, Frank, E, Bowden, C L, Colom, F, Ghaemi, S N, Yatham, L N, Malhi, G S, Calabrese, J R, Nolen, W A, Vieta, E, Kapczinski, F, Goodwin, G M, Suppes, T, Sachs, G S, Chengappa, K N R, Grunze, H, Mitchell, P B, Kanba, S and Berk, M (2009) The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders, *Bipolar Disorders*. Bipolar Disord, p. 453–473.

Tondo, L., Vázquez, G H and Baldessarini, R J (2020) Melancholic versus Nonmelancholic Major Depression Compared, *Journal of Affective Disorders*. Elsevier B.V., **266**, p. 760–765.

Tondo, Leonardo, Vázquez, G H and Baldessarini, R J (2020) Prevention of Suicidal Behavior in Bipolar Disorder, *Bipolar Disorders*. John Wiley & Sons, Ltd, p. bdi.13017.

Torrent, C, Reinares, M, Martinez-Arán, A, Cabrera, B, Amoretti, S, Corripio, I, Contreras, F, Sarró, S, González-Pinto, A, Lobo, A, Cuesta, M J, Sánchez-Torres, A, Bergé, D, Castro-Fornieles, J, Moreno, C, Bernardo, M and Vieta, E (2018) Affective versus first-episode non-affective first-episode psychoses: A longitudinal study, *Journal of Affective Disorders*. Elsevier B.V., **238**, p. 297–304.

Total Annual Sunshine in European Cities - Current Results (no date).

Trotta, A, Iyegbe, C, Di Forti, M, Sham, P C, Campbell, D D, Cherny, S S, Mondelli, V, Aitchison, K J, Murray, R R M, Vassos, E, Fisher, H H L, Schäfer, I, Fisher, H H L, Varese, F, Smeets, F, Drukker, M, Lieverse, R, Lataster, T, Viechtbauer, W, *et al.* (2016) Interplay between Schizophrenia Polygenic Risk Score and Childhood Adversity in First-Presentation Psychotic Disorder: A Pilot Study, *PloS one*. Edited by C. Walss-Bass. Public Library of Science, **11**, p. e0163319.

Trotta, A, Murray, R M and Maccabe, J H (2015) Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-Analysis, *Psychological Medicine*. Cambridge University Press, **45**, p. 381–394.

Tsuang, M T and Faraone, S V. (1990) *The genetics of mood disorders*. Johns Hopkins University Press.

Tyrka, A R, Ridout, K K and Parade, S H (2016) Childhood adversity and epigenetic regulation of glucocorticoid signaling genes: Associations in children and adults, in *Development and Psychopathology*. Cambridge University Press, p. 1319–1331.

United Nations, Department of Economic and Social Affairs, P D (2018) *World Urbanization Prospects: The 2018 Revision, Online Edition*.

Upthegrove, R, Chard, C, Jones, L, Gordon-Smith, K, Forty, L, Jones, I and Craddock, N (2015) Adverse childhood events and psychosis in bipolar affective disorder, *British Journal of Psychiatry*. Royal College of Psychiatrists, **206**, p. 191–197.

Vandeleur, C L, Merikangas, K R, Strippoli, M-P F, Castelao, E and Preisig, M (2014) Specificity of psychosis, mania and major depression in a contemporary

family study, *Molecular Psychiatry*. Nature Publishing Group, **19**, p. 209–213.

Varese, F, Smeets, F, Drukker, M, Lieverse, R, Lataster, T, Viechtbauer, W, Read, J, van Os, J and 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**, p. 661–671.

Vassos, E, Pedersen, C B, Murray, R M, Collier, D A and Lewis, C M (2012) Meta-analysis of the association of urbanicity with schizophrenia, *Schizophrenia Bulletin*, **38**, p. 1118–1123.

Vassos, E, Agerbo, E, Mors, O and Bøcker Pedersen, C (2016) Urban-rural differences in incidence rates of psychiatric disorders in Denmark, *British Journal of Psychiatry*. Royal College of Psychiatrists, **208**, p. 435–440.

Vassos, E, Di Forti, M, Coleman, J, Iyegbe, C, Prata, D, Euesden, J, O'Reilly, P, Curtis, C, Kolliakou, A, Patel, H, Newhouse, S, Traylor, M, Ajnakina, O, Mondelli, V, Marques, T R, Gardner-Sood, P, Aitchison, K J, Powell, J, Atakan, Z, *et al.* (2017) An Examination of Polygenic Score Risk Prediction in Individuals With First-Episode Psychosis, *Biological Psychiatry*. Elsevier, **81**, p. 470–477.

Vassos, E, Sham, P, Kempton, M, Trotta, A, Stilo, S A, Gayer-Anderson, C, Di Forti, M, Lewis, C M, Murray, R M and Morgan, C (2019a) The Maudsley environmental risk score for psychosis., *Psychological medicine*. Cambridge University Press, p. 1–8.

Vaucher, J, Keating, B J, Lasserre, A M, Gan, W, Lyall, D M, Ward, J, Smith, D J, Pell, J P, Sattar, N, Paré, G and Holmes, M V. (2018) Cannabis use and risk of schizophrenia: A Mendelian randomization study, *Molecular Psychiatry*. Nature Publishing Group, **23**, p. 1287–1292.

Veen, N D, Selten, J P, Schols, D, Laan, W, Hoek, H W, Van Der Tweel, I and Kahn, R S (2004) Diagnostic stability in a Dutch psychosis incidence cohort, *British Journal of Psychiatry*. Br J Psychiatry, **185**, p. 460–464.

Veling, W and Susser, E (2011) Migration and psychotic disorders, *Expert Review of Neurotherapeutics*, **11**, p. 65–76.

Verduijn, J, Milaneschi, Y, Peyrot, W J, Hottenga, J J, Abdellaoui, A, de Geus, E J C, Smit, J H, Breen, G, Lewis, C M, Boomsma, D I, Beekman, A T F and Penninx, B W J H (2017) Using Clinical Characteristics to Identify Which Patients With Major Depressive Disorder Have a Higher Genetic Load for Three Psychiatric Disorders, *Biological Psychiatry*, **81**, p. 316–324.

Vollmer-Larsen, A, Jacobsen, T B, Hemmingsen, R and Parnas, J (2006) Schizoaffective disorder - the reliability of its clinical diagnostic use, *Acta Psychiatrica Scandinavica*, **113**, p. 402–407.

Wang, C, Liu, B, Zhang, X, Cui, Y, Yu, C and Jiang, T (2018) Multilocus genetic profile in dopaminergic pathway modulates the striatum and working memory, *Scientific Reports*. Nature Publishing Group, **8**, p. 5372.

Weinberger, D R (1987) Implications of Normal Brain Development for the Pathogenesis of Schizophrenia, *Archives of General Psychiatry*, **44**, p. 660.

Weiser, M, Fenchel, D, Frenkel, O, Fruchter, E, Burshtein, S, Yehuda, A Ben, Yoffe, R, Bergman-Levi, T, Reichenberg, A, Davidson, M and Sandin, S (2020)

Understanding the association between advanced paternal age and schizophrenia and bipolar disorder, *Psychological Medicine*. Cambridge University Press, **50**, p. 431–437.

Wells, G, Shea, B, O'Connell, D, Peterson, J, Welch, V, Losos, M and Tugwell, P (2012) *The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses*.

Westman, J, Johansson, L M and Sundquist, K (2006) Country of birth and hospital admission rates for mental disorders: a cohort study of 4.5 million men and women in Sweden, *European Psychiatry*, **21**, p. 307–314.

Wigman, J T W, Van Os, J, Abidi, L, Huibers, M J H, Roelofs, J, Arntz, A, Kelleher, I and Peeters, F P M L (2014) Subclinical psychotic experiences and bipolar spectrum features in depression: Association with outcome of psychotherapy, *Psychological Medicine*. Psychol Med, **44**, p. 325–336.

Williams, J, Farmer, A E, Ackenheil, M, Kaufmann, C A and McGuffin, P (1996a) A multicentre inter-rater reliability study using the OPCRIT computerized diagnostic system, *Psychological Medicine*, **26**, p. 775–783.

World Health Organization (1975) *The ICD-9 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: Author.

World Health Organization & World Bank (2011) *WHO | World report on disability*. World Health Organization.

Wray, N R, Ripke, S, Mattheisen, M, Trzaskowski, M, Byrne, E M, Abdellaoui, A, Adams, M J, Agerbo, E, Air, T M, Andlauer, T M F, Bacanu, S A, Bækvad-Hansen, M, Beekman, A F T, Bigdeli, T B, Binder, E B, Blackwood, D R H, Bryois, J, Buttenschøn, H N, Bybjerg-Grauholm, J, *et al.* (2018) Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression, *Nature Genetics*. Nature Publishing Group, **50**, p. 668–681.

Xiao, J, Buka, S L, Cannon, T D, Suzuki, Y, Viscidi, R P, Torrey, E F and Yolken, R H (2009) Serological pattern consistent with infection with type I Toxoplasma gondii in mothers and risk of psychosis among adult offspring, *Microbes and Infection*, **11**, p. 1011–1018.

Yu, K, Cheung, C, Leung, M, Li, Q, Chua, S and McAlonan, G (2010) Are bipolar disorder and schizophrenia neuroanatomically distinct? An anatomical likelihood meta-analysis, *Frontiers in Human Neuroscience*. Frontiers Media S. A., **4**, p. 189.

Zanelli, J, Reichenberg, A, Morgan, K, Fearon, P, Kravariti, E, Dazzan, P, Morgan, C, Zanelli, C, Demjaha, A, Jones, P B, Doody, G A, Kapur, S and Murray, R M (2010) Specific and Generalized Neuropsychological Deficits: A Comparison of Patients With Various First-Episode Psychosis Presentations, *American Journal of Psychiatry*, **167**, p. 78–85.

Zhang, J P, Robinson, D, Yu, J, Gallego, J, Fleischhacker, W W, Kahn, R S, Crespo-Facorro, B, Vazquez-Bourgon, J, Kane, J M, Malhotra, A K and Lencz, T (2019) Schizophrenia polygenic risk score as a predictor of antipsychotic efficacy in first-episode psychosis, *American Journal of Psychiatry*. American Psychiatric Association, **176**, p. 21–28.

Zhang, X, Zhang, C, Wu, Z, Wang, Z, Peng, D, Chen, J, Hong, W, Yuan, C, Li, Z, Yu, S

and Fang, Y (2013) Association of genetic variation in CACNA1C with bipolar disorder in Han Chinese, *Journal of Affective Disorders*. J Affect Disord, **150**, p. 261–265.

Zheng, W, Zhang, Q E, Cai, D Bin, Ng, C H, Ungvari, G S, Ning, Y P and Xiang, Y T (2018) Neurocognitive dysfunction in subjects at clinical high risk for psychosis: A meta-analysis, *Journal of Psychiatric Research*. Elsevier Ltd, **103**, p. 38–45.

Zhou, Y, Li, Z, Wang, Y, Huang, H, Chen, W, Dong, L, Wu, J, Chen, J, Miao, Y, Qi, L, Zhang, S, Lang, X and Zhang, X (2020) Prevalence and clinical correlates of psychotic depression in first-episode and drug-naïve outpatients with major depressive disorder in a Chinese Han population, *Journal of Affective Disorders*. Elsevier B.V., **263**, p. 500–506.

10. APPENDICES

10.1 APPENDIX 1 – SUPPLEMENTARY MATERIAL OF META-ANALYSIS

ONLINE SUPPLEMENTARY MATERIAL

Environmental Risk Factors In Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies

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eAppendix 1. Ovid search strategy

Database: Embase <1974 to 2019 Week 43>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 29, 2019>, PsycINFO <1806 to October Week 3 2019>
Search Strategy:
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1 exp Affective Disorders, Psychotic/ or exp Bipolar Disorder/ (132713)
2 1 use ppez (40967)
3 exp affective psychosis/ or manic depressive psychosis/ or exp bipolar disorder/ or exp bipolar II disorder/ or exp bipolar I disorder/ or bipolar mania/ or exp depressive psychosis/ or exp melancholia/ (359002)
4 3 use oemez (73797)
5 exp Affective Psychosis/ or Bipolar Disorder/ or exp Mania/ (142580)
6 5 use psyh (29981)
7 (affective psychosis or bipolar disorder or manic-depressive or manic depress* or Psychotic Depression or (Depression adj2 psycho*) or (MDD adj2 psychosis) or melancholic depression).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh] (192598)
8 7 use ppez,oemez,psyh (192598)
9 or/2,4,6,8 (202827)
10 exp Pregnancy Complications/ or exp Obstetric Labor Complications/ or exp Pregnancy Complications, Infectious/ or exp Central Nervous System Infections/ or exp Child Abuse/ or exp Child Abuse, Sexual/ or exp "Emigration and Immigration"/ or exp Minority Groups/ or exp Urbanization/ or exp Urban Population/ or exp Brain Injuries/ or exp Brain Damage, Chronic/ or exp Life Change Events/ or exp Cannabis/ or Cocaine/ or Amphetamines/ or Lysergic Acid Diethylamide/ (1773449)
11 10 use ppez (822706)
12 exp parental age/ or exp pregnancy complication/ or exp labor complication/ or exp central nervous system infection/ or exp child abuse/ or exp migration/ or exp immigration/ or exp urban rural difference/ or exp urban population/ or exp brain injury/ or exp brain damage/ or exp "cannabis use"/ or exp cocaine/ or exp amphetamine abuse/ or exp lysergide/ (1766679)
13 12 use oemez (826554)
14 exp Obstetrical Complications/ or exp Child Abuse/ or exp Immigration/ or exp Minority Groups/ or exp URBAN ENVIRONMENTS/ or exp Brain Damage/ or exp Traumatic Brain Injury/ or exp CANNABIS/ or exp COCAINE/ or exp AMPHETAMINE/ or exp Lysergic Acid Diethylamide/ (532661)
15 14 use psyh (157691)
16 (environmental risk or parental age or obstetric factor or pregnancy factor or pregnancy complication or obstetric complications or perinatal infection or child* adversity or child* trauma or child* abuse or neglect or incest or child* victimization or child* CNS viral infections or migration or ethnic minority or urban* or brain injury or brain damage or stressful life events or cannabis or cocaine or amphetamine or lysergic acid).mp. (2026470)
17 16 use ppez,oemez,psyh (2026470)
18 or/11,13,15,17 (3094861)
19 exp Longitudinal Studies/ or exp Prospective Studies/ or exp Cohort Studies/ or follow-up studies/ (3860772)
20 19 use ppez (1916621)
21 exp longitudinal study/ or exp prospective study/ or exp cohort analysis/ or exp high risk population/ (3144137)
22 21 use oemez (1189233)
23 exp LONGITUDINAL STUDIES/ or exp Prospective Studies/ (1321122)
24 23 use psyh (16291)
25 (longitudinal study or prospective study or birth cohort or population cohort or high-risk).mp. (1849957)
26 25 use ppez,oemez,psyh (1849957)
27 or/20,22,24,26 (3941618)
28 9 and 18 (14055)
29 9 and 27 (19200)
30 9 and 18 and 27 (2080)
31 limit 30 to english language (2021)
32 remove duplicates from 31 (1620)

eAppendix 2. Methods

2.1 Definition of outcome

- Bipolar disorder

Most of the studies didn't specified subtype of Bipolar disorder (BD) included. Only 6 studies out of 33 provided specific definitions, which included Bipolar disorder type I and type II in all of them(Buizer-Voskamp *et al.*, 2011; Duffy *et al.*, 2012; Brown *et al.*, 2013; Feingold *et al.*, 2015; Freedman *et al.*, 2015, 2016); with 3 also including BD-NOS(Buizer-Voskamp *et al.*, 2011; Duffy *et al.*, 2012; Brown *et al.*, 2013). Ten out of the 33 studies examining BD specified the presence of psychotic symptoms(Fearon, P *et al.*, 2006; Kirkbride *et al.*, 2008; Brown *et al.*, 2013; Abel *et al.*, 2014; Lasalvia *et al.*, 2014; Szöke *et al.*, 2014; Canuti *et al.*, 2015; Freedman *et al.*, 2015, 2016; Mustonen *et al.*, 2018), but only Freedman et al. provided separately BD with and without psychotic features(Freedman *et al.*, 2016).

- Psychotic Depression

Only one study included Psychotic Depression as the main outcome (Ostergaard, 2013). Psychotic depression patients were also included in 5 studies as part of Affective psychosis category, all of them defines as MDD with psychotic features based on ICD (see eTable1).

- Affective psychosis

Fourteen studies used the classification of Affective psychosis, nine(Brown, A. S. *et al.*, 1995; Marcelis *et al.*, 1998; Hultman *et al.*, 1999; Bain *et al.*, 2000b; Leask *et al.*, 2002; Westman *et al.*, 2006; Manrique-Garcia *et al.*, 2012; Abel *et al.*, 2014; Kirkbride *et al.*, 2017) based on ICD and five(Eaton *et al.*, 2000; Kirkbride *et al.*, 2008; Xiao *et al.*, 2009; Kelly *et al.*, 2010; Szöke *et al.*, 2014) based on DSM but didn't provided specific definition of subcategories included (see eTable1).

2.1 Definition of environmental risk factors

- Paternal age

Paternal age was defined by most studies as having a father aged over 40 years at the time of their child's birth, either directly provided (Frans *et al.*, 2008; Buizer-Voskamp *et al.*, 2011) or calculated from raw data (Chudal, Gissler, *et al.*, 2014; McGrath *et al.*, 2014). Only Brown et al. (Brown *et al.*, 2013) differed, providing effect size for paternal age over 45 years old.

- Maternal infection

Both studies of exposure to Toxoplasma Gondii (Xiao *et al.*, 2009; Freedman *et al.*, 2016) explored the risk of exposure by detecting T. Gondii in sera during pregnancy. For Influenza, Parboosing et al. (Parboosing *et al.*, 2013) recorded mothers directly affected by Influenza virus infection during pregnancy, whereas Brown et al. (Brown, A. S. *et al.*, 1995) studied the cohort exposed during pregnancy to the 1957 type A2 Influenza epidemic, without specific measures in the mother. Canuti et al (Canuti *et al.*, 2015) explored serological presence of a battery of virus in pregnant mothers.

- Obstetric complications

Light weight was precisely defined by some studies as a weight of <2500 grams at birth (Hultman *et al.*, 1999; Chudal, Sourander, *et al.*, 2014) or <2700 grams (Østergaard *et al.*, 2013), while others specified "light weight" without providing cut-off values (Eaton *et al.*, 2000; Øgendahl *et al.*, 2006). Heavy weight represented weight >4500 grams for three of the studies (Hultman *et al.*, 1999; Østergaard *et al.*, 2013; Chudal, Sourander, *et al.*, 2014). Early gestational age differed between being born before the 37th (Chudal, Sourander, *et al.*, 2014) or the 36th week (Hultman *et al.*, 1999; Nosarti *et al.*, 2012; Østergaard *et al.*, 2013); and late gestational age from being born after the 39th week (Mathiasen *et al.*, 2011) or the 42nd week (Nosarti *et al.*, 2012; Chudal, Sourander, *et al.*, 2014). None of the studies provided detailed calculations on how small or large for gestational age was defined,but these were based on records from hospital registries.

- Perinatal stress

Four studies were included in the perinatal stress factors in order to pooled other categories that may have impacted through inducing stress in the mother during pregnancy. Brown et al.(Brown, Alan S. *et al.*, 1995) recorded those mothers exposed to famine during wither 1st, 2nd or 3rd trimester. As we wanted to capture the stress induced by the sociodemographic context, we pooled three values and used as famine during pregnancy. Abel et al.(Abel *et al.*, 2014) measured the impact of bereavement during pregnancy. Freedman et al.(Freedman *et al.*, 2015) measured the use of perinatal oxytocin. Lastly, Kleinhaus et al.(Kleinhaus *et al.*, 2013) explored a general measure of prenatal stress effect in general for increasing odds of BD on offspring.

- Urbanicity

Vassos and Ostergaard et al., provided effect sizes for the effect of living in a capital city compared with rural areas (Østergaard *et al.*, 2013; Vassos *et al.*, 2016). Similarly, Marcelis (Marcelis *et al.*, 1998) provided the

effect size of living in the densest urban area based on population size compared with the lowest; while Abel et al. (Abel *et al.*, 2014) presented only the effect size without providing clear definition of urban birth. For urbanicity later in life, Kaymaz (Kaymaz *et al.*, 2006) provide a linear OR based on population density; Lasalvia (Lasalvia *et al.*, 2014) compare areas defined as "high" vs "low/medium" density; both Szoke (Szöke *et al.*, 2014) and Kelly (Kelly *et al.*, 2010) compared urban areas vs three and two different rural areas based on town size or density respectively.

- Childhood infection

Whereas two of the studies explored association with serological evidence of a broad range of infectious agents (Leask *et al.*, 2002; Mortensen *et al.*, 2011), Benros et al. (Benros *et al.*, 2013) considered exposure as a history of hospitalization due to an infection.

- Childhood adversity

We considered parental death for either the mother, father, or both mother and father; and we did not distinguish natural or unnatural death. When detailed split information was provided by cause of death or by parent affected (Østergaard *et al.*, 2013; Bergink *et al.*, 2016), the effect sizes were combined. Moreover, some studies provided different associations regarding the moment of death (Laursen *et al.*, 2007; Abel *et al.*, 2014). Here, we combined them into a unique effect size representing a general exposure of parental loss. We defined as parental separation the reported "placement out of care home" and "parental imprisonment" in the case of Bergink et al. (Bergink *et al.*, 2016); and pooled maternal and paternal separation for Paksarian et al. (Paksarian *et al.*, 2015). As "other trauma", we included the reported "family disruption" in Bergink et al (Bergink *et al.*, 2016), and having a positive history of previous contact with a child protection agency in the study of Scott et al. (Scott *et al.*, 2010).

- Substance misuse

Most of the analysed studies provided the exposure of having ever used cannabis (Van Laar *et al.*, 2007; Manrique-Garcia *et al.*, 2012; Feingold *et al.*, 2015; Mustonen *et al.*, 2018). The only two included in the quantitative analyses that differed were Duffy et al. (Duffy *et al.*, 2012), which studied the association of a previous substance use disorder; and Martins et al. (Martins *et al.*, 2012), which analysed the impact of misuse of opioids.

- Ethnic minority and migration

Being a migrant was defined by studies as: being an immigrant from Surinam, from the Netherlands Antilles, Turkey and Morocco, compared to natives from the Netherlands (Selten *et al.*, 2003); being a first generation migrant (Westman *et al.*, 2006); or extending the definition to include second generation migrants and having any history of living abroad in natives (Cantor-Graae and Pedersen, 2013; Lasalvia *et al.*, 2014). All three studies assessing ethnic minority (Fearon, P *et al.*, 2006; Kirkbride *et al.*, 2008, 2017) were done in UK, and considered ethnic minority as any ethnicity other than white British.

2.3 Data extraction

When extracting data in the presence of more than one measure of adversity, we used the most global assessment available. Where counts of specific diagnoses or exposed/unexposed numbers were not reported and association measures were given, these were extracted as follows: Incidence Rate Ratios (IRRs), Odds Ratios (ORs), Relative Risk (RRs) or Hazard Ratio (HRs) together with their 95% confidence intervals (CIs). Some papers presented the results of both unadjusted analyses and those adjusting for different covariates. To increase comparability among studies, whenever possible, we included the unadjusted results in the main analyses.

In those papers presenting only adjusted results, where multiple levels of adjustment were provided, we extracted the data from analyses using the smallest number of demographic and/or clinical covariates.

Where some information was unavailable, we calculated aggregated effect sizes for each type of adversity by meta-analysing as fixed-effects the individual effect sizes provided (e.g., paternal age groups of 40-45, 46-50, 51-55, and >56 years were aggregated into >40 years), which were then added to the main analysis.

2.4 Quality assessment

2.4.1 Study level (Newcastle-Ottawa Scale)

The Newcastle-Ottawa Scale (NOS) uses three domains to evaluate prospective studies: 1) selection of exposed and non-exposed participants (four items: representativeness of the exposed cohort, selection of the non-exposed participants, ascertainment of the exposure, and demonstration that the outcome of interest was absent at the beginning of the study); 2) comparability (one item: comparability of cohorts on the basis of the design of the analysis; if it was appropriately adjusted for potential confounding factors); and 3) outcome ascertainment (three items: adequacy of outcome, length of follow-up, and adequacy of follow-up). A study

can be awarded a maximum of 1 point for each assessed domain, with the exception of comparability, which can receive a maximum of two points, yielding a maximum score of 9 (highest quality). A study was defined as "good" quality if it received 3 or 4 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A "fair" quality score required 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes. A study was rated as "poor" if it received 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in outcomes (Sharmin *et al.*, 2017). In case of disagreement between rates, a consensus was reached through discussion.

All 46 studies included in the meta-analyses underwent quality assessment using the NOS, with 100% of the studies receiving ratings of "good" quality. The agreed quality rating of each study are presented in **eTable3**.

2.4.2 Outcome level (GRADE)

We based the outcome-level quality assessment on criteria adapted from GRADE (Grading of Recommendations, Assessment, Development and Evaluations). GRADE methods involves an initial assignment of "low" ranking to observational studies, which can be downgraded based on risk of bias, indirectness of evidence, imprecision or publication bias; or upgraded if some elements are present (large effect, dose-response relationship, etc.). In our case, we started from maximum level of ranking (high), but applied the upgrade/downgrade criteria proposed by GRADE, as employed on previous studies(Zheng *et al.*, 2018).

The detailed ranking of the fourteen meta-analysed outcomes are presented in **eTable4**.

2.5 Calculation of Odds Ratios

The odds ratio (OR) was calculated as:

$$OR = \frac{a/b}{c/d} = \frac{a \times d}{b \times c}$$

where a = cases in exposed group, b = controls in exposed group, c = cases in unexposed group and d = controls in unexposed group; with the standard error of the log odds ratio being:

$$\mathrm{SE}\{\ln(OR)\} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

and the 95% confidence interval:

$$95\%\ \mathrm{CI} = \exp\left(\ \ln(OR) - 1.96 \times \mathrm{SE}\{\ln(OR)\}\ \right) \quad \text{to} \quad \exp\left(\ \ln(OR) + 1.96 \times \mathrm{SE}\{\ln(OR)\}\ \right)$$

2.6 Detailed statistical analysis

Planned analyses as per PROTOCOL

We planned to conduct our analyses in two steps: firstly, we aimed to consider individual effects of each ERF within risk groups (e.g., early gestational age, late gestational age, small for gestational age, etc. within obstetric complications) on affective psychosis in general regardless of specific diagnosis (i.e., combining BPD or PD).

Secondly, in order to examine the differential impact of the ERF on BPD and in PD, where sufficient data was available, we planned separate subgroup analysis according to the two diagnostic categories. These estimates were to be adjusted for gender, age, and ethnicity, when available. Sensitivity analyses were to be conducted to test the robustness of the results according to: differences in study quality, method of assessments, effects of 'influencers' or outliers, and the use of adjusted ORs.

Publication bias
As specified in the protocol, visual inspection of funnel plot (asymmetry) and Egger's linear regression test were to be used to assess publication bias for environmental risk factors for which there were a a minimum of 10 studies identified (Higgins and Cochrane Collaboration, 2019). For this specific test, a p-value of less than 0.1 indicates significant asymmetry and therefore publication bias.

Where Egger's linear regression test revealed a potential publication bias, we planned to use Duval and Tweedie's trim and fill method to test the data (Duval and Tweedie, 2000; Shi and Lin, 2019). We planned also to use the so-called leave-one-out function for doing sensitivity analysis, where number of retrieved studies were sufficient. This method consists of the removal of one study at a time from the dataset to run the meta-analysis without it. This analysis tests if the effect size of the meta-analysis is driven by one study.

Since for none of the evaluated ERF the required minimum of 10 studies was achieved, analyses of publication bias were not performed.

eTable1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist

Section/topic	#	Checklist item	Page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7 & Suppl
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 & Suppl

Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias (e.g. publication bias, selective reporting within studies)	7 & Suppl
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Suppl
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8,9, Fig1 & Suppl
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1 & Suppl
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot..	eTable4, Fig2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12, Fi2, Suppl
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	N/A, Suppl
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-16, 18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support; role of funders for the systematic review.	18

eTable2. MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist

Criteria		Reported (Yes/No)	Reported on Page No
Reporting of background			
√	Problem definition	Yes	4-5
√	Hypothesis statement	Yes	4
√	Description of study outcomes	Yes	5
√	Type of exposure or intervention used	Yes	5-6
√	Type of study designs used	Yes	6
√	Study population	Yes	6
Reporting of search strategy			
√	Qualifications of searchers (eg, librarians and investigators)	Yes	6
√	Search strategy, including time period included in the synthesis and keywords	Yes	5,6 and Suppl
√	Effort to include all available studies, including contact with authors	Yes	7
√	Databases and registries searched	Yes	5
√	Search software used, name and version, including special features used (eg, explosion)	Yes	5 and Suppl
√	Use of hand searching (eg, reference lists of obtained articles)	Yes	6
√	List of citations located and those excluded, including justification	Yes	8 and Fig1
√	Method for addressing articles published in languages other than English	No	N/A
√	Method of handling abstracts and unpublished studies	No	N/A
√	Description of any contact with authors	Yes	7
Reporting of methods			
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	7
√	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	7 and Suppl
√	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	6-7

√	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	No	N/A
Criteria		**Reported (Yes/No)**	**Reported on Page No**
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	7 and Supple
√	Assessment of heterogeneity	Yes	8
√	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	7-8 and Suppl
√	Provision of appropriate tables and graphics	Yes	8-9 and Suppl
Reporting of results			
√	Table giving descriptive information for each study included	Yes	9
√	Results of sensitivity testing (eg, subgroup analysis)	Yes	9-12
√	Indication of statistical uncertainty of findings	Yes	17
Reporting of discussion			
√	Quantitative assessment of bias (eg, publication bias)	Yes	Suppl
√	Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	16-17
√	Assessment of quality of included studies	Yes	8-9 and Suppl
Reporting of conclusions should include			
√	Consideration of alternative explanations for observed results	Yes	14-16
√	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	13-14, 16
√	Guidelines for future research	Yes	18
√	Disclosure of funding source	Yes	18

eTable3. Quality assessment ratings as per Newcastle-Ottawa Scale

Author, Year	Selection	Comparability	Outcome	Total score	Qualitative score
Nosarti, 2012	****	**	***	9/9	Good
Paksarian, 2015	****	**	***	9/9	Good
Manrique-Garcia, 2012	***	**	***	8/9	Good
Kaymaz, 2006	****	**	***	9/9	Good
Ostergaard, 2013	****	**	***	9/9	Good
Buizer-Voskamp, 2011	****	**	***	9/9	Good
Scott, 2010	***	**	***	8/9	Good
Mustonen, 2018	***	**	***	8/9	Good
Benros ME, 2013	****	**	***	9/9	Good
Canton-Graee, 2013	****	**	***	9/9	Good
Vassos, 2016	****	**	***	9/9	Good
Westman, 2006	****	**	***	9/9	Good
Abel KM, 2014	****	**	***	9/9	Good
Hultman, 1999	****	**	**	8/9	Good
Mortensen, 2011	****	**	***	9/9	Good
Canuti, 2015	****	*	***	8/9	Good
Brown, 2013	***	**	***	8/9	Good
Bain M, 2000	****	*	**	7/9	Good
Chudal, 2013	****	**	***	9/9	Good
Freedman, 2015	****	**	***	9/9	Good
Parboosing, 2013	****	**	***	9/9	Good
Ogendahl, 2006	****	**	***	9/9	Good
Frans, 2008	****	**	***	9/9	Good
Xiao, 2009	****	*	***	8/9	Good
Feingold, 2015	****	**	***	9/9	Good
Kirkbride, 2008	****	**	***	9/9	Good
van Laar, 2007	****	**	***	9/9	Good
Kirkbride, 2017	****	**	***	9/9	Good
Martins, 2012	****	**	**	8/9	Good
Fearon, 2006	****	**	***	9/9	Good
Duffy, 2012	****	**	***	9/9	Good
Brown, 1995	****	**	***	9/9	Good
Marcelis, 1998	****	*	***	8/9	Good
Mathiasen, 2011	****	**	***	9/9	Good
Leask, 2002	****	**	***	9/9	Good
Freedman, 2016	****	**	***	9/9	Good
Eaton, 2000	****	**	***	9/9	Good
McGrath, 2014	****	**	***	9/9	Good
Chudal, 2014	****	**	***	9/9	Good
Lasalvia, 2014	****	**	***	9/9	Good
Kelly, 2010	****	**	***	9/9	Good
Szoke, 2014	****	**	***	9/9	Good
Kleinhaus, 2013	****	**	***	9/9	Good
Bergink V, 2016	****	**	***	9/9	Good
Laursen, 2007	****	**	***	9/9	Good
Brown , 1995	****	**	***	9/9	Good

eTable4. GRADE evidence quality assessment of meta-analysed outcomes

Meta-analytic outcomes	Studies (N)	Risk of bias[a]	Inconsistency[b]	Indirectness	Imprecision[c]	Publication bias[d]	Large effect	Overall quality of evidence[f]
Paternal age>40y	6 (2844*)	No	No	No	No	N/A	No	+/+/+/+/; High
Maternal Infection	5 (1473)	No	High	No	No	N/A	No	+/+/+/−/; Moderate
Light weight	4 (59*)	No	Low	No	High	N/A	No	+/+/+/−/; Moderate
Heavy weight	4 (64*)	No	No	No	High	N/A	No	+/+/+/−/; Moderate
Early GA	4 (191*)	No	High	No	No	N/A	No	+/+/+/−/; Moderate
Late GA	3 (1296)	No	Low	No	No	N/A	No	+/+/+/−/; Moderate
SGA	4 (43*)	No	No	No	High	N/A	No	+/+/+/−/; Moderate
Perinatal stress	4 (891)	No	Low	No	No	N/A	No	+/+/+/+/; High
Urbanicity at birth	4 (15073)	No	High	No	No	N/A	No	+/+/+/−/; Moderate
Childhood Infection	3 (18921)	No	High[a]	No	High	N/A	No	+/+/−/−/; Low
Childhood adversity	6 (3686*)	No	High	No	No	N/A	No	+/+/+/−/; Moderate
Substance misuse	6 (1481)	No	High	No	No	N/A	Large	+/+/+/+/; High
Ethnic minority	6 (2731*)	No	High	No	No	N/A	No	+/+/+/−/; Moderate
Urbanicity later in life	4 (405)	No	High	No	High	N/A	No	+/+/−/−/; Low

*Underestimated; one of the studies didn't provide specific numbers of cases and were not included in total counts.

[a] Risk of bias based on quality rating from Newcastle-Ottawa Scale; all rated as "good"

[b] Inconsistency based on I^2 value, considering "Low" up to 50%, 50-75% as"Moderate", >75% as "High"

[c] "High" if wide 95% CI which includes appreciable protective or harmful effect (an OR under 0.75 or over 1.25); and if very few events

[d] Publication bias was not assessed for any of the meta-analytic outcomes for not reaching the minimum of 10 studies

[e] "Large" effect are considered if OR>2

[f] GRADE Working Group grades of evidence: High quality = we are very confident that the effect in the study reflects the actual effect. Moderate quality = we are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different. Low quality = the true effect may differ significantly from the estimate. Very low quality = the true effect is likely to be substantially different from the estimated effect

eTable5. Detailed list of studies included in the examination of each environmental risk factor, with employed effect size for meta-analyses

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome (measure)	Cases (exposed), Controls/ Total population	Reported effect size	Summary of results
PRE-/PERI-NATAL FACTORS						
Paternal age						
Frans, 2008	Sweden	Nested case-control study, 1973-2001	Paternal age >40 yo, BD[a] (ICD-8, ICD-9, ICD-10)	13428 (2067), 67140	OR, calculated	Evidence of an association; highest risk observed for offspring of fathers over 55 years, and remained after controlling for maternal age.
Buizer-Voskamp, 2011	Netherlands	Population-based cohort	Paternal age >40 yo, BD-I, BD-II and BD-NOS[a] (DSM-IV-TR)	1121 (68), 5605	aOR, given	No association.
Brown, 2013	CHDS, US	Nested case-control study, 1959-1966	Paternal age >45 yo, BD-I, BD-II, BD-NOS and BD with psychosis (DSM-IV)	94 (5), 746	aOR, given	For every 10-year increment in paternal age, there was no significant association with BD when adjusting for maternal age.
Ostergaard, 2013	Denmark	Population-based cohort, 1955-1990	Paternal age >40 yo, PD (ICD-8, ICD-10)	2183, 2400000	IRR, given	Paternal age >35 years increased risk for Psychotic Depression.
McGrath, 2014	Denmark	Population-based cohort, 1995-2006	Paternal age, BD[a] (ICD-8, ICD-10)	7309 (557), 2894688	Pooled OR, given	No association.
Chudal, 2014	FIPS-B, Finland	Population nested case-control study, 1983-1998	Paternal age, BD[a] (ICD-8, ICD-9, ICD-10)	1861 (147), 1009846	OR, calculated	U-shaped association of unadjusted OR for BD was seen for different paternal age groups, with the odds increasing at both ends of the age spectrum.
Maternal infection						
Brown, 1995	Netherlands	Birth cohorts, 1957-1958	Influenza, AP[a] (ICD-9)	1220 (236), 980697	OR, calculated	No association.
Xiao, 2009	US	Nested case-control study	Toxoplasma Gondii, AP[a] (DSM-IV)	64, 443	OR, calculated	Maternal serologic Toxoplasma related to 5-fold increased risk of BD with psychotic features.
Parboosing, 2013	CHDS, US	Nested case-control study, 1956-1966	Influenza, BD[a] (DSM-IV-TR)	92 (8), 722	OR, given	Nearly 4-fold increase of risk for BD after exposure to maternal influenza at any time during pregnancy (unadjusted).

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome	Cases (exposed), Controls/ Total population	Reported effect size	Summary of results
Canuti, 2015	CPP or NEFS, US	Nested case-control study, 1956-1966	Viral infection, BD with psychotic features (DSM-IV)	12 (2), 138	OR, calculated	Enhanced immune activity against viral infections in maternal blood might increase odds of psychosis in offspring.
Freedman, 2016	CHDS, US	Birth cohort	T. Gondii, BD-I, BD-II, BP-NOS and with psychosis (DSM-IV-TR)	85 (22), 255	OR, calculated	No association. Maternal T. gondii may be specific to SCZ among psychotic disorders.
Obstetric complication						
Hultman, 1999	Sweden	Case-control from population based cohort		198, 990		
			Light weight, AP[a] (ICD-9)	11, 48	OR, calculated	No association.
			Heavy weight, AP[a] (ICD-9)	4, 27	OR, calculated	No association.
			<49cm length, AP[a] (ICD-9)	33, 210	OR, calculated	No association.
Bain, 2000	UK	Nested case-control study, 1971-1978	SGA, AP[a] (ICD-9)	301 (17), 602	Pooled OR	It is unlikely that the incidence of SGA is raised in people with AP of early onset.
Eaton, 2000	Denmark	Birth cohort, 1973-1993	Heavy weight, manic-depressive illness and other AP[a] (DSM-III-R)	69 (37), 33389	aOR, given	No association.
Ogendahl, 2006	Denmark	Nested case-control study, 1973-onway		196, 5096		
			Light weight, BD[a] (ICD-8, ICD-10)	13, 267	OR, given	Birthweight <2500g could not be identified as a risk factor.
			<49cm length, BD[a] (ICD-8, ICD-10)	14, 447	OR, given	Length in cm <49 could not be identified as risk factor.
Mathiasen, 2011	Denmark	Birth cohort, 1974-1996		1431, 1329776		
			Early GA, BD[a] (ICD-8, ICD-10)	93, 67891	IRR, given	BD rate in preterm group was significantly higher.
			Late GA, BD[a] (ICD-8, ICD-10)	1218, 1104780	OR, calculated	

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome	Cases (exposed), Controls/ Total population	Reported effect size	Summary of results
Nosarti, 2012	Sweden	Population-based cohort, 1973-1985		217, 1301522		
			Early GA, BD[a] (ICD-8, ICD-9, ICD-10)	24, 52989	Pooled OR, given	If born at 32-36 weeks, 2 times odds to have BD; if less than 32 weeks, more than 7 odds.
			Late GA, BD[a] (ICD-8, ICD-9, ICD-10)	40, 221022	aHR, given	No association.
			SGA, BD[a] (ICD-8, ICD-9,ICD-10)	10, 43334	HR, given	No association.
			LGA, BD[a] (ICD-8, ICD-9,ICD-10)	5, 29579	HR, given	No association.
Ostergaard, 2013	Denmark	Population-based cohort, 1955-1990		2183, 2400000		
			Light weight, PD (ICD-8, ICD-10)	n.p.	IRR, given	No association. This risk appeared to be confined to children with birth weight below 2700 g.
			Heavy weight, PD (ICD-8, ICD-10)	n.p.	IRR, given	No association.
			Early GA, PD (ICD-8, ICD-10)	n.p.	IRR, given	No association.
			SGA, PD (ICD-8, ICD-10)	n.p.	IRR, given	No association.
Chudal, 2013	Finland	Nested case-control study, 1987-1998		724, 2143		
			Light weight, BD[a] (ICD-9, ICD-10)	35, 78	Pooled OR, given	No association.
			Heavy weight, BD[a] (ICD-9, ICD-10)	23, 72	OR, given	No association.
			Early GA, BD[a] (ICD-9, ICD-10)	82, 207	Pooled OR, given	No association.
			Late GA, BD[a] (ICD-9, ICD-10)	38, 85	OR, given	No association.
			SGA, BD[a] (ICD-9, ICD-10)	16, 36	OR, given	No association.
			LGA, BD[a] (ICD-9, ICD-10)	20, 74	OR, given	No association.
Prenatal stress						
Brown, 1995	Netherlands	Birth cohort, 1944-1945	Famine, AP[b] (ICD-9)	945 (122), 146347	RR, given	Risk of AP among exposed to famine during the 2nd trimester was significantly increased.

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome	Cases (exposed), Controls/ Total population	Reported effect size	Summary of results
Kleinhaus, 2013	Israel	Population based cohort, 1964-1976	Prenatal stress, BD[a] (ICD-10)	120 (7), 90079	OR, calculated	No association.
Abel, 2014	UK	Population based cohort	Maternal breavement, BD with psychotic features and PD (ICD-8, ICD-9, ICD-10)	1448 (556), 946994	OR, given	Maternal bereavement stress preconception or during the prenatal period was not associated with a significant excess of psychosis in offspring.
Freedman, 2015	CHDS, US	Nested case-control study	Perinatal oxytocine, BD-I, BD-II, BP-NOS and BP with psychotic features (DSM-IV-TR)	93 (8), 738	HR, given	Perinatal oxytocin was associated with a 2.4 times increased odds of later BD.
EARLY CHILDHOOD FACTORS						
Urbanicity at birth						
Marcelis, 1998	Netherlands	Birth cohort, 1942-1978	Urbanicity at birth, AP[a] (ICD-9)	11270 (9438), 42115 py	IRR, given	Urban birth was linearly associated with later AP.
Ostergaard, 2013	Denmark	Population-based cohort, 1955-1990	Urbanicity at birth, PD (ICD-8 and ICD-10)	2183, 29900000 py	IRR, given	Provincial towns had the highest risk of severe depression compared to be born in more urban or more rural areas.
Abel, 2014	UK	Population-based cohort	Urbanicity at birth, BD with psychosis and PD (ICD-8, ICD-9 and ICD-10)	1448 (220), 946994	OR, calculated	Urban birth was associated with AP.
Vassos, 2016	Denmark	Population-based cohort, 1955-2006	Urbanicity at birth, BD[a] (ICD-8 and ICD-10)	8345, 2894640	aOR, given	Birth in an urban environment was associated with BD.
Childhood infection						
Benros, 2013	Denmark	Birth cohort, 1945-1996	Childhood infection, AP[b] (ICD-8, ICD-10)	18717 (29324), 3562260	IRR, given	Previous hospitalization for infection didn't increased odds of AP.
Leask, 2002	UK	Birth cohort, 1958	Childhood infection, AP[a] (ICD-8 and ICD-10)	45, 17414	Pooled OR, given	Infection determined by medical examination at school and from family interview. Significant risk for adult AP after exposure to meningitis and tuberculosis

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome	Cases (exposed), Controls/ Total population	Reported effect size	Summary of results
Mortensen, 2011	Denmark	Case-control from population based cohort	Childhood infection, BD[a] (ICD-10)	127, 127	Pooled OR, calculated	This analysis does not support maternal infection with HSV-1, HSV-2, CMV, or Toxoplasma gondii as risk factors for BD.
Childhood adversity						
Laursen, 2007	Denmark	Population-based cohort, 1973-onwards	Parental death, BD[a] (ICD-8 and ICD-10)	4490 (352), 2100000	Pooled OR, given	Loss of a parent (especially by suicide) was a risk factor for BD.
Scott, 2010	New Zealand	Population-based cohort	Other Trauma, BD[a] (DSM-IV)	18, 2144	OR, given	Significant association between prospectively ascertained child maltreatment and BD.
Ostergaard, 2013	Denmark	Population-based cohort, 1955-1990	Parental death, PD (ICD-8 and ICD-10)	2183, 2400000	Pooled OR, given	Effect of parental loss was more pronounced for the unnatural death of a mother.
Abel, 2014	Sweden	Population-based cohort	Parental death, BD with psychotic features and PD (ICD-8, ICD-9 and ICD-10)	1448 (556), 946994	Pooled OR, given	Postnatal bereavement stress in mothers increased risk of psychosis in offspring, specially high for AP after suicide in nuclear family, not explained by family psychiatric history.
Paksarian, 2015	Denmark	Population-based cohort, 1971-1991	Parental separation, BD[a] (ICD-8 and ICD-10)	2726 (1342), 985058	Pooled OR, given	Parental separation during childhood is a risk factor for BD.
Bergink, 2016	Denmark	Population-based cohort, 1980-1998		2235, 980554		
			Parental death, BD[a] (ICD-8 and ICD-10)	88, 28244	Pooled OR, given	Parental death was more commonly observed among patients with BD.
			Other Trauma, BD[a] (ICD-8 and ICD-10)	1068, 350987	aHR, given	
			Parental separation, BD[a] (ICD-8 and ICD-10)	173, 29326	Pooled OR, given	

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome	Cases (exposed), Controls/ Total population	Reported effect size	Summary of results
LATER LIFE FACTORS						
Substance misuse						
Feingold, 2015	NESARC, Israel	Population-based cohort	Cannabis ever, BD-I and BD-II[a] (DSM-IV-TR)	1029 (625), 28630	OR, given	Crude associations were found between cannabis use and consequent mania.
Manrique-Garcia, 2012	Sweden	Population-based cohort	Cannabis ever, AP[a] (ICD-8, ICD-9 and ICD-10)	390 (50), 45087	HR, given	No association.
Van Laar, 2007	NEMESIS, Netherlands	Incidence study	Cannabis ever, BD[a] (DSM-III-R)	4681 (484), 3881	Pooled OR, given	No association.
Mustonen, 2018	NFBC1986, UK	Population-based cohort	Cannabis ever, BD psychotic features and PD[b] (ICD-10)	31 (7), 6534	Pooled OR	Higher risk of AP in individuals who had tried cannabis.
Duffy, 2012	Canada	High-risk study	Other SUD, BD-I, BD-II and BD-NOS[a] (DSM-IV)	35 (17), 211	OR, calculated	SUD is a common comorbidity during the early course of BD, even before the first episode.
Martins, 2012	US	Incidence study	Other SUD, BD[a] (DSM-IV)	261, 34653	aOR, given	Lifetime nonmedical prescription opioid use was associated with the incidence of BD.
Migration and Ethnic minority						
Fearon, 2006	UK	Population-based cohort, 2001	Ethnic minority, Manic psychosis and PD[b] (ICD-10)	92[c], 1600000 py	IRR, given	Ethnic minority groups at increased risk for psychotic illness; especially African-Caribbean and Black African groups for risk for mania.
Westman, 2006	Sweden	Population-based cohort	Migration, AP[a] (ICD-9 ,ICD-10)	12040 (1837), 4563319	OR, calculated	Several groups of immigrants, had higher risks of hospital admission for AP compared to Swedish-born reference group.
Kirkbride, 2008	UK	Population-based cohort	Ethnic minority, BD with psychosis and PD (DSM-IV)	122 (72), 828546 py	IRR, given	Mixed White and Black Caribbean and other White had elevated rates of affective psychoses.
Cantor-Graae, 2013	Sweden	Population-based cohort, 1971-2000	Migration, BD[a] (ICD-8 and ICD-10)	2719 (171), 1859419	IRR, given	Native Danes with a history of foreign residence had significantly increased IRRs for BD.

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome	Cases (exposed), Controls/ Total population	Reported effect size	Summary of results
Lasalvia, 2014	Italy		Migration, BD with psychotic features and PD (ICD-10)	117, 3077555 py	aIRR, given	Immigrants had markedly higher incidence rates compared with the Italian host population for affective psychoses.
Kirkbride, 2017	UK	Naturalistic cohort	Ethnic minority, AP[a] (ICD-10)	84 (30), 2021663 py	IRR, given	Rates of AP increased for ethnic minority groups.
Urbanicity later in life						
Kaymaz, 2006	NEMESIS, Netherlands	Population-based cohort	Current urbanicity, BD[a] (DSM-III-R)	132, 7049	OR, calculated	The rate of BD was progressively higher in more urbanised areas.
Kelly, 2010	Ireland	1995-1998	Current urbanicity, AP[a] (DSM-III-R and DSM-IV)	324 (171), n.p.	aIRR, given	Incidence of AP was lower in urban compared to rural areas.
Lasalvia, 2014	Italy	Multisite naturalistic study	Current urbanicity, BD with psychotic features and PD[b] (ICD-10)	117, 3077555 py	IRR, given	Urbanicity was not found to be related to AP.
Skoze, 2014	France	Incidence study	Current urbanicity, BD with psychotic features and PD (DSM-IV)	51, 396714	OR, calculated	In the rural centre, greater levels of urbanicity were associated with an increase in the incidence of AP

[a] Not specified distinction between patients with and without psychotic features

[b] Provided specific numbers for bipolar disorder and psychotic depression

[c] Calculated from incidence rates

CHDS: Child Health and Development Study; FIPS-B: Finnish Prenatal Study of Bipolar Disorders; CPP: Collaborative Perinatal Project; NEFS: New England Family Study; NESARC: National Epidemiologic Survey on Alcohol and Related Conditions; NEMESIS: Netherlands Mental Health Survey and Incidence Study; BD-I: bipolar disorder type I; BD-II: bipolar disorder type II; BD-NOS: bipolar disorder not otherwise specified; ICD: international classification of diseases; DSM: diagnostic and statistical manual of mental disorders; PD: major depressive disorder with psychotic features; AP: affective psychosis; GA; gestational age; SGA: small for gestational age; LGA: large for gestational age; SUD: substance use disorder; py: person year; OR: odds ratio; aOR: adjusted odds ratio; IRR: incidence rate ratio; aIRR: adjusted incidence rate ratio; RR: relative risk; HR: hazard ratio; aHR: adjusted hazard ratio; n.p.: not provided

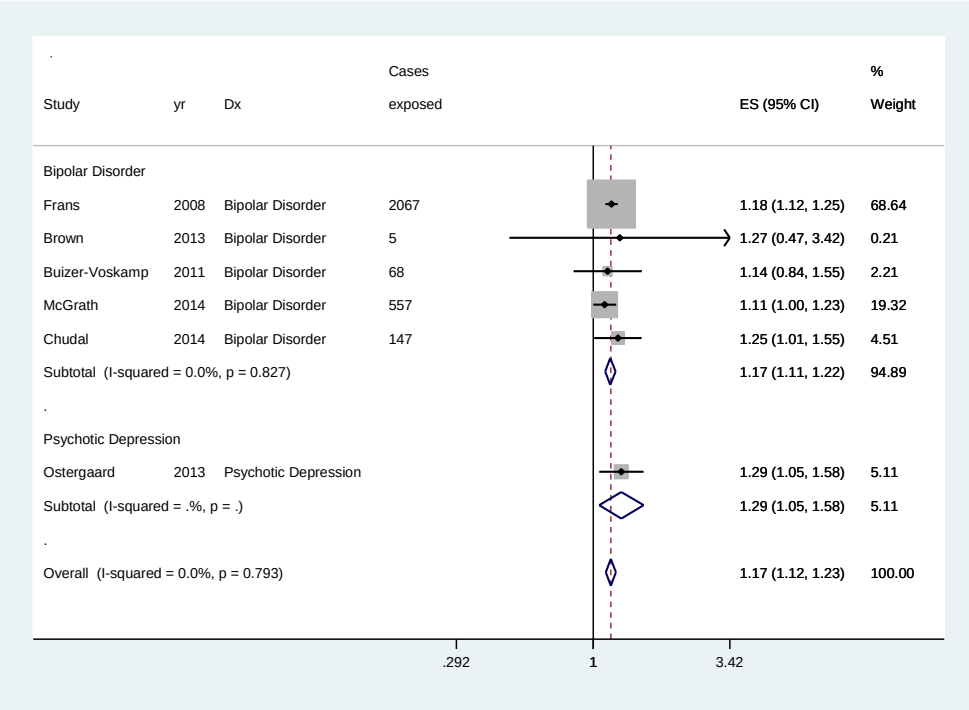
eTable6. Detailed list of identified studies not included in meta-analyses, with reason for exclusion.

Author, Year	Cohort Name, and/or Country	Design, Years of Follow-Up	Risk factor (definition), outcome	Cases (exposed), Controls/Total population	Reason to exclude
Done, 1991	British perinatal mortality survey, UK	Population-based cohort, 1974-86	Obstetric complications, BD	44, 20	Lack of data
Brown, 2000	Dutch Hunger Winter 1944-45, Netherlands	Birth cohorts, 1970 to 1977 and 1992 to 1996	Gestational famine, BD	182 (84), 146347	Overlap with Brown 1995, with smaller sample
Mortensen, 2003	Denmark	Population-based cohort, 1970 to 1998	Parental loss, urbanicity at birth, BD	2299, 2100000	overlap Laursen 2007 and Vassos 2016
Sundquist, 2004	Sweeden	Population-based cohort, 1997 to 1999	Urbanicity and migration, AP	n.p., 4437491	lack of data
Pedersen, 2006	Denmark	Population-based cohort, 1971 to 2001	Urbanicity at birth, BD	2232 (436), 2035101	overlap with Vassos 2016
Menezes, 2010	Sweden	Population-based cohort, 1974 to 2002	Paternal age, BD	493 (35), 711989	overlap with Frans 2008, with smaller sample
Kroon, 2013	Netherlands	Population-based cohort, 1996 to 2007	Urbanicity, BD	649 (n.p.), 408028	Lack of data
Orlovska, 2014	Denmark	Population-based cohort, 1987 to 2010	Traumatic Head Injury, BP	1859 (191), 16269924py	Lack of studies to meta-analyse
Canetta, 2014	CHDS, US	Nested case-control, 1993 to 2009	Maternal infection, BD	85, 170	Overlap with Parboosing 2013, with smaller sample
D'Onofrio, 2014	Sweeden	Population-based cohort, 1973 to 2001	Paternal age, BD	6819 (n.p.), 2615081	overlap Frans 2008, with smaller sample
Kemner, 2015	Dutch Bipolar Offspring Study, Netherlands	High risk cohort, 1997 to 2009	Stressful Life Events, BD	16 (n.p.), 140	Lack of studies to meta-analyse
Omer, 2016	CAMFEPS, Ireland	Nested case-control, 1971 to 2002	Urbanicity, AP	86, 328	Disparity of ERF (rurality instead of urbanicity)
Chang, 2019	TBI cohort, Netherlands	Longitudinal cohort, 1998 to 2008	Traumatic Brain Injury, BD	776 (326), 157995	Lack of studies to meta-analyse

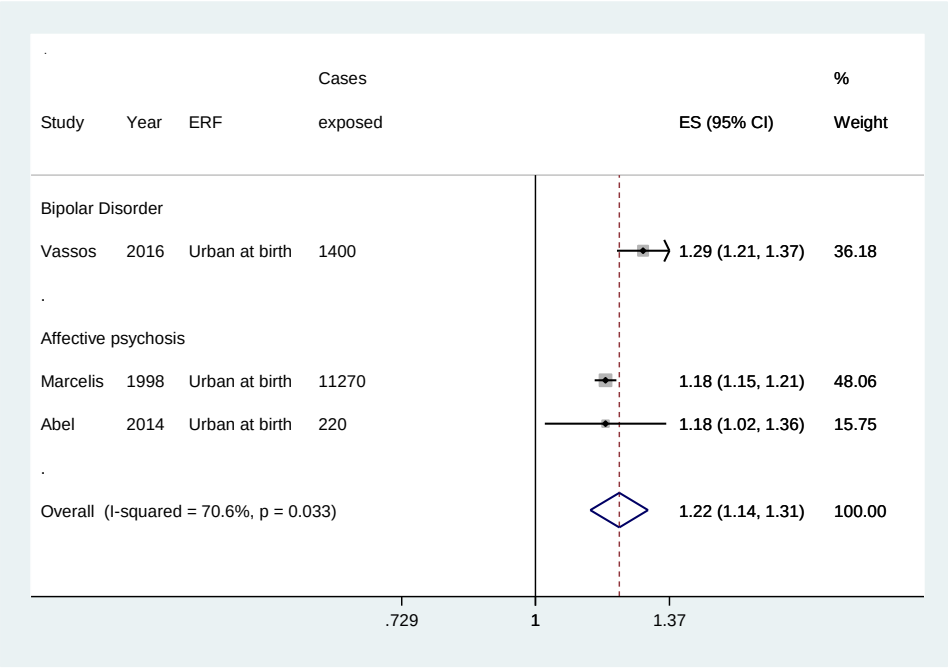
BD: bipolar disorder; AP: affective psychosis; CHDS: Child Health and Development Study; py: person year; ERF: environmental risk factor; CAMFEPS: Cavan-Monaghan First Episode Psychosis Study; TBI: Traumatic Brain Injuy; n.p.: not provided

eFigures. Supplementary Forest Plots

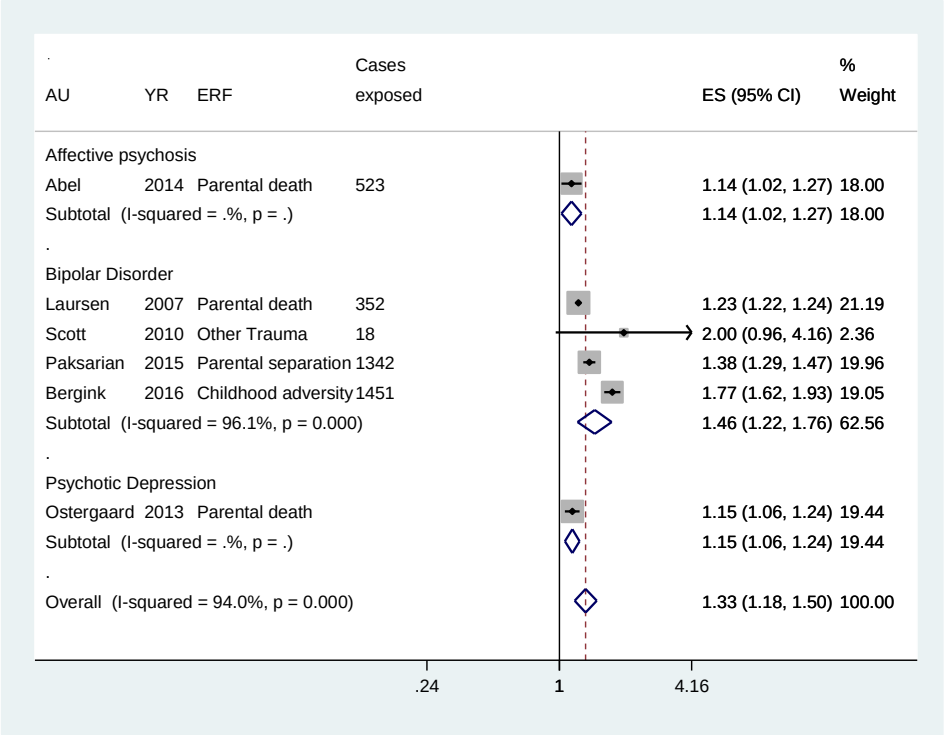
eFigure 1. Paternal age by diagnostic group



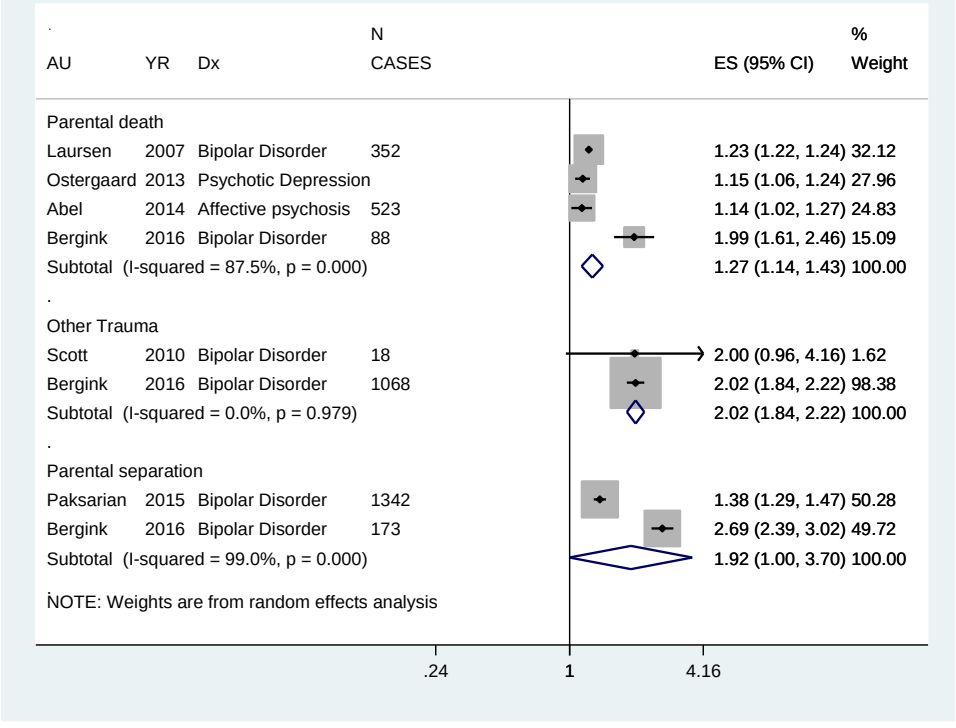
eFigure 2. Urbanicity at birth restricted to affective psychosis and Bipolar Disorder



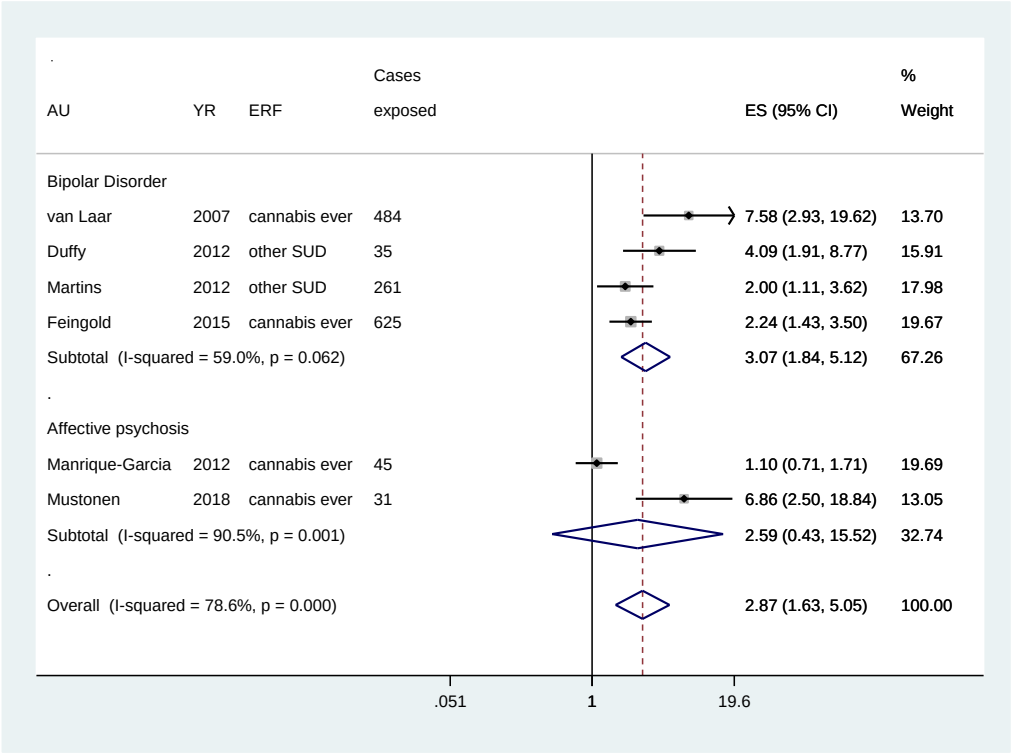
eFigure 3. Childhood adversity by diagnostic group



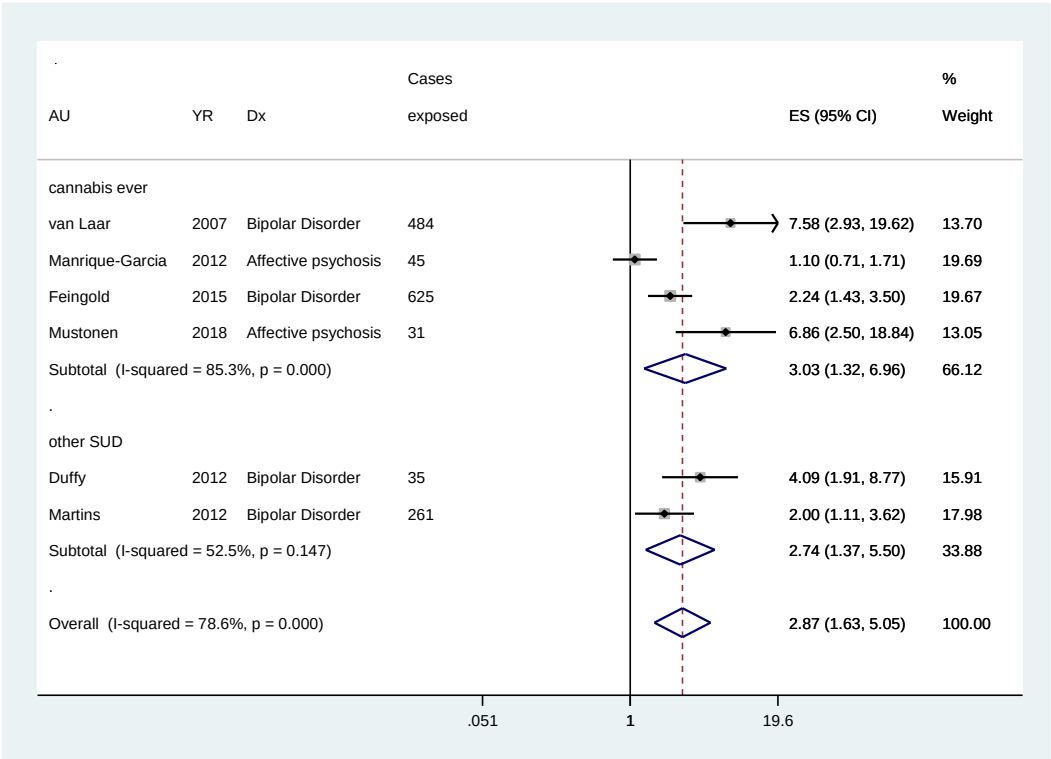
eFigure 4. Childhood adversity by subtype



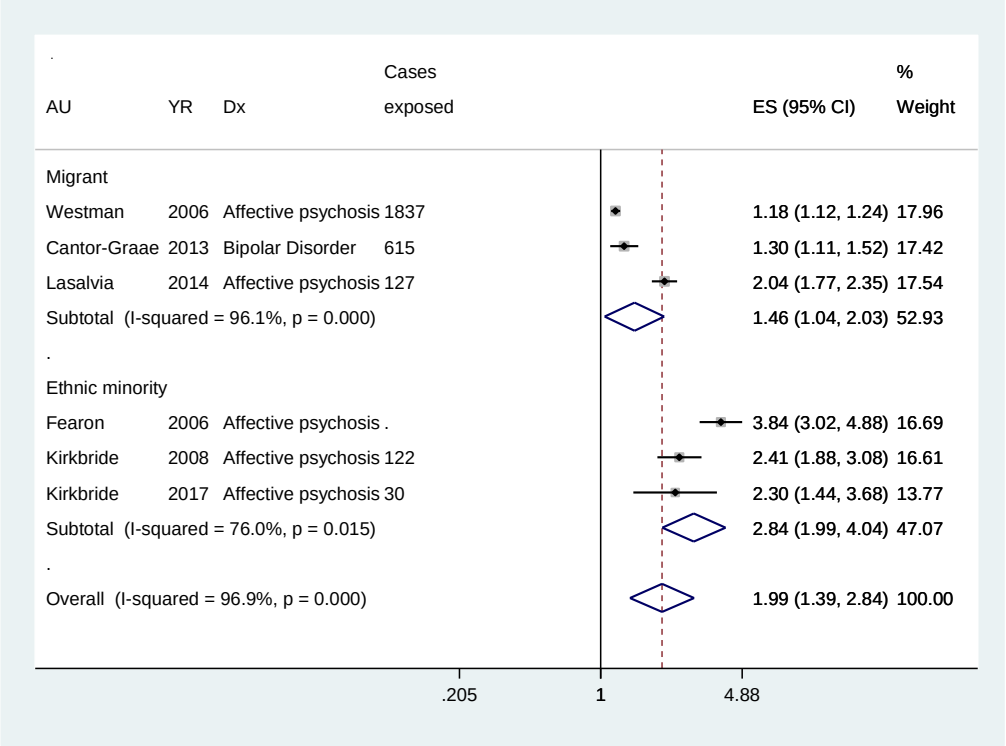
eFigure 5. Substance misuse by diagnosis



eFigure 6. Substance misuse by subtype



eFigure 7. Ethnic minority and migration by subtype



eReferences

Abel, K M, Heuvelman, H P, Jörgensen, L, Magnusson, C, Wicks, S, Susser, E, Hallkvist, J and Dalman, C (2014) Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: Population based cohort study, *BMJ (Online)*, **348**.

Bain, M, Juszczak, E, McInneny, K and Kendell, R E (2000) Obstetric complications and affective psychoses, *British Journal of Psychiatry*, **176**, p. 523–526.

Benros, M E, Waltoft, B L, Nordentoft, M, Ostergaard, S D, Eaton, W W, Krogh, J and Mortensen, P B (2013) Autoimmune diseases and severe infections as risk factors for mood disorders a nationwide study, *JAMA Psychiatry*. American Medical Association, **70**, p. 812–820.

Bergink, V, Larsen, J T, Hillegers, M H J, Dahl, S K, Stevens, H, Mortensen, P B, Petersen, L and Munk-Olsen, T (2016) Childhood adverse life events and parental psychopathology as risk factors for bipolar disorder, *Translational psychiatry*, **6**, p. e929.

Brown, A, Bao, Y, McKeague, I, Shen, L and Schaefer, C (2013) Parental age and risk of bipolar disorder in offspring, *Psychiatry Research*, **208**, p. 225–231.

Brown, Alan S., Susser, E S, Lin, S P and Gorman, J M (1995) Affective disorders in Holland after prenatal exposure to the 1957 A2 influenza epidemic, *Biological Psychiatry*. Elsevier, **38**, p. 270–273.

Brown, A. S., Susser, E S, Lin, S P, Neugebauer, R and Gorman, J M (1995) Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944-45, *British Journal of Psychiatry*, **166**, p. 601–606.

Buizer-Voskamp, J E, Laan, W, Staal, W G, Hennekam, E A M, Aukes, M F, Termorshuizen, F, Kahn, R S, Boks, M P M and Ophoff, R A (2011) Paternal age and psychiatric disorders: Findings from a Dutch population registry, *Schizophrenia Research*, **129**, p. 128–132.

Cantor-Graae, E and Pedersen, C B (2013) Full spectrum of psychiatric disorders related to foreign migration: a Danish population-based cohort study., *JAMA Psychiatry*. American Medical Association, **70**.

Canuti, M, Buka, S, Jazaeri Farsani, S M, Oude Munnink, B B, Jebbink, M F, van Beveren, N J M, de Haan, L, Goldstein, J, Seidman, L J, Tsuang, M T, Storosum, J G and van der Hoek, L (2015) Reduced maternal levels of common viruses during pregnancy predict offspring psychosis: Potential role of enhanced maternal immune activity?, *Schizophrenia Research*. Elsevier B.V., **166**, p. 248–254.

Chudal, R, Gissler, M, Sucksdorff, D, Lehti, V, Suominen, A, Hinkka-Yli-Salomäki, S, Brown, A S and Sourander, A (2014) Parental age and the risk of bipolar disorders, *Bipolar disorders*, **16**, p. 624–632.

Chudal, R, Sourander, A, Polo-Kantola, P P, Hinkka-Yli-Salomäki, S, Lehti, V, Sucksdorff, D, Gissler, M, Brown, A S, Hinkka-Yli-Salom?ki, S, Lehti, V, Sucksdorff, D, Gissler, M and Brown, A S (2014) Perinatal factors and the risk of bipolar disorder in Finland, *Journal of Affective Disorders*, **155**, p. 75–80.

Duffy, A, Horrocks, J, Milin, R, Doucette, S, Persson, G and Grof, P (2012) Adolescent substance use disorder during the early stages of bipolar disorder: A prospective high-risk study, *Journal of Affective Disorders*, **142**, p. 57–64.

Duval, S and Tweedie, R (2000) Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis, *Biometrics*. Biometric Society, **56**, p. 455–463.

Eaton, W W, Mortensen, P B and Frydenberg, M (2000) Obstetric factors, urbanization and psychosis, *Schizophrenia Research*, **43**, p. 117–123.

Fearon, P, Kirkbride, J B, Morgan, C, Dazzan, P, Morgan, K, Lloyd, T, Hutchinson, G, Tarrant, J, Lun Alan Fung, W and Holloway, J (2006) Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study, *Psychological medicine*, **36**, p. 1541–1550.

Feingold, D, Weiser, M, Rehm, J and Lev-Ran, S (2015) The association between cannabis use and mood disorders: A longitudinal study, *Journal of Affective Disorders*. Elsevier B.V., **172**, p. 211–218.

Frans, E M, Sandin, S, Reichenberg, A, Lichtenstein, P, Långström, N and Hultman, C M (2008) Advancing Paternal Age and Bipolar Disorder, *Archives of General Psychiatry*. American Medical Association, **65**, p. 1034.

Freedman, D, Brown, A S, Shen, L and Schaefer, C A (2015) Perinatal oxytocin increases the risk of offspring bipolar disorder and childhood cognitive impairment, *Journal of Affective Disorders*. Elsevier B.V., **173**, p. 65–72.

Freedman, D, Bao, Y, Shen, L, Schaefer, C A and Brown, A S (2016) Maternal T. gondii, offspring bipolar disorder and neurocognition, *Psychiatry Research*. Elsevier Ireland Ltd, **243**, p. 382–389.

Higgins, J P T and Cochrane Collaboration (2019) *Cochrane handbook for systematic reviews of interventions*. 2nd Editio. Edited by J. P. Higgins et al. Chichester (UK): John Wiley & Sons.

Hultman, C M, Sparén, P, Takei, N, Murray, R M, Cnattingius, S and Geddes, J (1999) Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study, *BMJ*, **318**, p. 421–426.

Kaymaz, N, Krabbendam, L, Graaf, R, Nolen, W, Have, M and van Os, J (2006) Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder, *Social Psychiatry and Psychiatric Epidemiology*, **41**, p. 679–685.

Kelly, B D, O'Callaghan, E, Waddington, J L, Feeney, L, Browne, S, Scully, P J, Clarke, M, Quinn, J F, McTigue, O, Morgan, M G, Kinsella, A and Larkin, C (2010) Schizophrenia and the city: A review of literature and prospective study of psychosis and urbanicity in Ireland, *Schizophrenia Research*, **116**, p. 75–89.

Kirkbride, J B, Barker, D, Cowden, F, Stamps, R, Yang, M, Jones, P B and Coid, J W (2008) Psychoses, ethnicity and socio-economic status, *British Journal of Psychiatry*, **193**, p. 18–24.

Kirkbride, J B, Hameed, Y, Ankireddypalli, G, Ioannidis, K, Crane, C M, Nasir, M, Kabacs, N, Metastasio, A, Jenkins, O, Espandian, A, Spyridi, S, Ralevic, D, Siddabattuni, S, Walden, B, Adeoye, A, Perez, J and Jones, P B (2017) The epidemiology of first-episode psychosis in early intervention in psychosis services: Findings from the social epidemiology of psychoses in east Anglia [SEPEA] Study, *American Journal of Psychiatry*. American Psychiatric Association, **174**, p. 143–153.

Kleinhaus, K, Harlap, S, Perrin, M, Manor, O, Margalit-Calderon, R, Opler, M, Friedlander, Y and Malaspina, D (2013) Prenatal stress and affective disorders in a population birth cohort, *Bipolar Disorders*, **15**, p. 92–99.

Van Laar, M, Van Dorsselaer, S, Monshouwer, K and De Graaf, R (2007) Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population?, *Addiction*, **102**, p. 1251–1260.

Lasalvia, A, Bonetto, C, Tosato, S, Zanatta, G, Cristofalo, D, Salazzari, D, Lazzarotto, L, Bertani, M, Bissoli, S, De Santi, K, Cremonese, C, De Rossi, M, Gardellin, F, Ramon, L, Zucchetto, M, Amaddeo, F, Tansella, M, Ruggeri, M, Brambilla, P, *et al.* (2014) First-contact incidence of psychosis in north-eastern Italy: Influence of age, gender, immigration and socioeconomic deprivation, *British Journal of Psychiatry*. Royal College of Psychiatrists, **205**, p. 127–134.

Laursen, T M, Munk-Olsen, T, Nordentoft, M and Mortensen, P B (2007) A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort, *Journal of Clinical Psychiatry*. Physicians Postgraduate Press Inc., **68**, p. 1673–1681.

Leask, S J, Done, D J and Crow, T J (2002) Adult psychosis, common childhood infections and neurological soft signs in a national birth cohort, *British Journal of Psychiatry*, **181**, p. 387–392.

Manrique-Garcia, E, Zammit, S, Dalman, C, Hemmingsson, T and Allebeck, P (2012) Cannabis use and depression: a longitudinal study of a national cohort of Swedish conscripts, *BMC Psychiatry*, **12**.

Marcelis, M, Navarro-Mateu, F, Murray, R, Selten, J P and Van Os, J (1998) Urbanization and psychosis: A study of 1942-1978 birth cohorts in The Netherlands, *Psychological Medicine*, **28**, p. 871–879.

Martins, S S, Fenton, M C, Keyes, K M, Blanco, C, Zhu, H and Storr, C L (2012) Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: Longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions, *Psychological Medicine*, **42**, p. 1261–1272.

Mathiasen, R, Hansen, B M, Forman, J L, Kessing, L V and Greisen, G (2011) The risk of psychiatric disorders in individuals born prematurely in Denmark from 1974 to 1996, *Acta Paediatrica, International Journal of Paediatrics*, **100**, p. 691–699.

McGrath, J J, Petersen, L, Agerbo, E, Mors, O, Mortensen, P B and Pedersen, C B (2014) A comprehensive assessment of parental age and psychiatric disorders, *JAMA Psychiatry*. American Medical Association, **71**, p. 301–309.

Mortensen, P B, Pedersen, C B, Mcgrath, J J, Hougaard, D M, Nørgaard-Petersen, B, Mors, O, Børglum, A D and Yolken, R H (2011) Neonatal antibodies to infectious agents and risk of bipolar disorder: A population-based

case-control study, *Bipolar Disorders*, **13**, p. 624–629.

Mustonen, A, Niemelä, S, Nordström, T, Murray, G K, Mäki, P, Jääskeläinen, E and Miettunen, J (2018) Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis, *British Journal of Psychiatry*. Royal College of Psychiatrists, **212**, p. 227–233.

Nosarti, C, Reichenberg, A, Murray, R M, Cnattingius, S, Lambe, M P, Yin, L, MacCabe, J, Rifkin, L and Hultman, C M (2012) Preterm birth and psychiatric disorders in young adult life, *Archives of General Psychiatry*, **69**.

Øgendahl, B K, Agerbo, E, Byrne, M, Licht, R W, Eaton, W W and Mortensen, P B (2006) Indicators of fetal growth and bipolar disorder: A Danish national register-based study, *Psychological Medicine*, **36**, p. 1219–1224.

Østergaard, S D, Waltoft, B L, Mortensen, P B and Mors, O (2013) Environmental and familial risk factors for psychotic and non-psychotic severe depression, *Journal of Affective Disorders*, **147**, p. 232–240.

Paksarian, D, Eaton, W W, Mortensen, P B and Pedersen, C B (2015) Childhood Residential Mobility, Schizophrenia, and Bipolar Disorder: A Population-based Study in Denmark, *Schizophrenia Bulletin*. Oxford University Press, **41**, p. 346–354.

Parboosing, R, Bao, Y, Shen, L, Schaefer, C A and Brown, A S (2013) Gestational influenza and bipolar disorder in adult offspring, *JAMA Psychiatry*. American Medical Association, **70**, p. 677–685.

Scott, K M, Smith, D R and Ellis, P M (2010) Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults, *Archives of General Psychiatry*, **67**, p. 712–719.

Selten, J P, van Os, J and Nolen, W A (2003) First admissions for mood disorders in immigrants to the Netherlands, *Social Psychiatry and Psychiatric Epidemiology*, **38**, p. 547–550.

Sharmin, S, Kypri, K, Khanam, M, Wadolowski, M, Bruno, R and Mattick, R (2017) Parental Supply of Alcohol in Childhood and Risky Drinking in Adolescence: Systematic Review and Meta-Analysis, *International Journal of Environmental Research and Public Health*. MDPI AG, **14**, p. 287.

Shi, L and Lin, L (2019) The trim-and-fill method for publication bias, *Medicine*, **98**, p. e15987.

Szöke, A, Charpeaud, T, Galliot, A M, Vilain, J, Richard, J R, Leboyer, M, Llorca, P M and Schürhoff, F (2014) Rural-urban variation in incidence of psychosis in France: A prospective epidemiologic study in two contrasted catchment areas, *BMC Psychiatry*. BioMed Central Ltd., **14**.

Vassos, E, Agerbo, E, Mors, O and Bøcker Pedersen, C (2016) Urban-rural differences in incidence rates of psychiatric disorders in Denmark, *British Journal of Psychiatry*. Royal College of Psychiatrists, **208**, p. 435–440.

Westman, J, Johansson, L M and Sundquist, K (2006) Country of birth and hospital admission rates for mental disorders: a cohort study of 4.5 million men and women in Sweden, *European Psychiatry*, **21**, p. 307–314.

Xiao, J, Buka, S L, Cannon, T D, Suzuki, Y, Viscidi, R P, Torrey, E F and Yolken, R H (2009) Serological pattern consistent with infection with type I Toxoplasma gondii in mothers and risk of psychosis among adult offspring, *Microbes and Infection*, **11**, p. 1011–1018.

Zheng, W, Zhang, Q E, Cai, D Bin, Ng, C H, Ungvari, G S, Ning, Y P and Xiang, Y T (2018) Neurocognitive dysfunction in subjects at clinical high risk for psychosis: A meta-analysis, *Journal of Psychiatric Research*. Elsevier Ltd, **103**, p. 38–45.

10.2 APPENDIX 2 – SUPPLEMENTARY MATERIAL OF STUDY 2

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work

SUPPLEMENTARY

1. eAppendix 1. Methods

1.1 Sociodemographics characteristics

Socio-demographic data was collected using the Medical Research Council (MRC) Socio-demographic Schedule modified version(Mallett *et al.*, 2002) and supplemented by clinical records. For educational level, we stratified the sample into three categories: No qualification, school education (GCSE, 'O' levels and 'A' levels equivalent) and tertiary education (vocational, college, university or professional qualification). We dichotomized employment (employed vs. unemployed), marital status (married/in a stable relationship vs. no relationship) and living arrangement (independent living vs. no independent living).

1.2 Genotyping and PRS building

DNA from blood tests or saliva sample was obtained from most participants at baseline (73.6% of cases and 78.5% of controls). EUGEI sample was genotyped at Cardiff University Institute of Psychological Medicine and Clinical Neurology, using custom Illumina HumanCoreExome-24 BeadChip genotyping arrays containing probes for 570038 genetic variants (Illumina, San Diego, CA). Genotype data were called using the GenomeStudio package and transferred into PLINK format for further analysis.

Quality control was conducted in PLINK v1.07(Purcell *et al.*, 2007) or with custom Perl scripts. Variants with call rate < 98% and with Hardy-Weinberg Equilibrium p-value < 1e-6 were excluded from the dataset. After QC, 559505 variants remained. Samples with call rate < 98% were excluded from the dataset. A linkage disequilibrium pruned set of variants was calculated using the --indep-pairwise command in PLINK (maximum r2=0.25, window size=500 SNPs, window step size = 50 SNPs) and used for further analyses. Homozygosity F values were calculated using the --het command in PLINK, and outlier samples (F < -0.11 or F > 0.15) excluded. The genotypic sex of samples was calculated from X chromosome data using the --check-sex command in PLINK, and samples with different genotypic sex to their database sex excluded.

Identity-by-descent (IBD) values were calculated for the sample in PLINK. Samples with 2 or more database siblings in the database that were not supported by the genotypic data, or with 1 or more siblings among the genotyped samples according to the database but no identified genotypic siblings (defined as PI-HAT > 0.35 and < 0.65) were excluded. After visually observing clustering of errors by genotyping chip, we decided to further exclude chips with a high proportion of errors. All samples on chips with 5 or more sample exclusions due to heterozygosity or call rate (out of 12 possible samples) were excluded. All samples on chips with 4 or more sample exclusions due to sex or relative checks were also excluded, unless their identity was corroborated by concordance between database and genotype relatedness data with a sample on another chip

For constructing PRSs, clumping was performed in imputed best-guess genotypes for each dataset using PLINK (maximum r2=0.1, window size=500kb, minimum MAF=5%), and variants within regions of long-range LD around the genome (including the MHC) excluded(Price *et al.*, 2008). PRS were then constructed from best-guess genotypes using PLINK at 10 different p-value thresholds (PT=1, 0.5, 0.2, 0.1, 0.05, 0.01, $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$, $5x10^{-8}$). We used PT=0.05 for our primary analysis, as this explained the most variation in the phenotype of schizophrenia(Ripke, Neale, Benjamin M, *et al.*, 2014), bipolar disorder(Stahl *et al.*, 2019), depression(Howard *et al.*, 2019) and IQ(Savage *et al.*, 2018).

1.3 PCA analyses and definition of European ancestry based on PC

Principal components were calculated in PLINK using LD pruned variants across the whole sample. We ranked the sample in centiles based on PC1, and calculated proportion of self-reported European ethnicity in a dichotomy fashion (yes/no) on each centile. We established the cut-off point in the stacked PC1 when three groups in a row reported less than 0.5 of whiteness. We repeated the process for PC2 and used the two cut-off point as threshold in which those who fell within them were considered as European.

1.4 Diagnostic subcategories

Further DSM-IV OPCRIT diagnosis(American Psychiatric Association, 1994) were grouped as follows: Schizophrenia (DSM-IV code 295.2-295.9), Schizoaffective Disorder (DSM-IV code 295.7), other psychosis (including delusional -295.1- and psychosis NOS -298.9 -), Bipolar disorder (DSM-IV codes 296-296.06 and 296.4-296.9) and psychotic depression (codes 296.2-296.36) in order to make comparisons between them and with controls.

1.5 Justification of regression model and detailed regression analysis

We built our models on multinomial logistic regression as it is used when the dependent variable is multicategorical (or *multinomial*), when there are more than two categories and these can't be ordered in a meaninful way. This regression model assumes that: 1) each independent variable has a specific value for each observation; 2) the independent variable can't predict perfectly the dependent variable in any case; 3) collinearity is relatively low. For using multinomial logistic regression there is no need for the independent variables to be statistically different, and after checking for multicollinearity within our independent variables using Stata command *estat vif* , overall VIF was 2.56, which falls below suggested tolerance threshold stablish on 10.0 (Hair *et al.*, 2014).

Firstly, a multinomial logistic regression model was built to compare the association of NAP and AP with controls; followed by a simple logistic regression model comparing the association between NAP and AP groups. In our second multinomial logistic model, we tested how PRSs performed in differenciating BD and PD from NAP as reference group. Additionally and only included in supplementary material we built an additional model to analyse how PRSs distribute across all psychotic diagnostic categories. We included a multicategorial variable as dependent variable using control as reference group and the four PRSs as independent variable. The diagnostic categories included in this multicategorical variable were: schizophrenia (SCZ), schizoaffective disorder (SAD), other psychosis (OP), Bipolar disorder (BD) and Psychotic depression (PD). Lastly, an individual multiple logistic regression model was performed to compare PRSs associations between BD and PD.

The effect size output provided by multinomial logistic regression is Relative Risk Ratio - RRR -, which should be interpreted as the Odds Ratio between each category and always the stablished reference category. For our model 1, control is the reference category, while in model 2 we stablished as reference group the NAP.

1.6 Power calculation of main analyses

We conducted power calculation analyses utilising the R-package AVENGEME(Dudbridge, 2013), which allows power calculation for PRS analyses. We calculated the required SNP-h^2 or fix covariance in our target sample to obtain 80% of power on each regression model and per each PRS (SZ, BD and D). Whenever the estimated covariance is too low, reflecting a SNP-h^2 in the target sample lower than the SNP-h^2 of the training sample, it can be considered plausible, and therefore accepted the 80% power. In our case, calculated SNP-h^2 were only lower for PRS-SZ. Regarding PRS-BD and PRS-D, our study had 80% power to detect an association if the genetic correlation between BD and depression in the respective GWAS and our BD and MDD-P phenotypes were of around 26-48% and 14-24% respectively for the highest and least powered comparisons. A limitation is that this procedure only allows calculating power on associations with phenotypes tested on training samples, which prevent to calculate power of those associations between PRSs with other phenotypes (i.e associations with PRS IQ, or power of PRS BD in the "NAP vs control" association).

AVENGEME calculations assumed the following values:

	PRS SZ	PRS BD	PRS D
Number of SNP after QC on target sample	559505	559505	559505
Training sample size	150064	51710	807553
p-value threshold in training samples	0.1	0.1	0.1
Fix variance value (SNP-h)	**0.21** (Ripke, 2014)	**0.17-0.23 (0.20)**(Stahl *et al.*, 2019)	**0.089** (Howard *et al.*, 2019)
Fix null prop to value	0.95	0.95	0.95
Training trait prevalence	0.01	0.015	0.15
Training sampling factor	0.246488	0.39358	0.305073
Target trait prevalence	0.01	0.015	0.15

Estimated covariance and SNP-h^2 values for 80% of power of the different comparison for the appropriate PRSs are provided on the table below.

Info in target sample	Sample size	Sampling factor	Estimated covariance	Estimated SNP-h^2	Power
NAP vs CONTROL .PRS SZ	1414	0.2893	0.12	**0.069**	84%
AP vs CONTROL .PRS BD .PRS D	1169	0.1403 0.1403	**0.26** **0.14**	**0.338** **0.22**	78.9% 83.6%
AP vs NAP .PRS SZ .PRS BD .PRS D	573	0.7138 0.2862 0.2862	0.18 0.29 0.15	**0.154** **0.42** **0.25**	80.9% 80% 81%
BD vs CONTROL .PRS BD	1078	0.068	0.37	**0.685**	79.3%
MDD-P vs CONTROL .PRS D	1096	0.083	0.18	**0.36**	81.6%
BD vs MDD-P .PRS BD .PRS D	164	0.4451 0.5549	**0.48** **0.24**	**2.589** **0.65**	79.8% 78.7%

1.7 Representability of included sample

No differences in gender, educational level and diagnosis but only small differences on age were found between included subjects with genotype data and those without DNA information available; suggesting a good representability of the whole sample.

1.8.1 eTable 1. Comparison of sociodemographic of included and excluded samples based on genetic availability

DESCRIPTIVE AT BASELINE	Number (%)/Mean(SD)		Statistics	
	Subjects with DNA n= 2026	Subjects without PRS n= 605	Tests (df)	p value
Gender			X2(1)=0.172	0.679
Male	1079 (53.3)	328 (54.2)		
Female	947 (46.7)	277 (45.8)		
Age (years), mean (SD)	34.3 (12.3)	33 (12.3)	U=-2.7	0.009
EDUCATION LEVEL			X2(2)=4.39	0.111
No qualification	199 (9.9)	57 (9.6)		
School education	888 (44.1)	290 (48.9)		
Tertiary education	925 (46)	246 (41.5)		
YEARS IN EDUCATION	14.29 (6.5)	15.52 (12.3)	U=0.216	0.829
OPCRIT DSM IV DIAGNOSIS			X2(2)=0.42	0.811
Non-affective psychosis	542 (73.1)	197 (74.3)		
Affective psychosis				
Bipolar disorder	95 (12.8)	35 (13.2)		
Psychotic depression	104 (14.1)	33 (12.5)		

SD: standard deviation; df: degrees of freedom

2. eAppendix 2. Results

2.1 Sociodemographics comparison with effect sizes

2.1.1 eTable 2. Case-control comparison of sociodemographic in white subsample (n=1659)

DESCRIPTIVE AT BASELINE	Number (%)/Mean(SD)		Statistics		
	Cases n= 654	Control n= 1005	Tests (df)	Effect sizes	p value
Gender			X2(1)=39.91	V=.15 (.11-.20)	<0.001
Male	412 (63)	474 (47.2)			
Female	242 (37)	531 (52.8)			
Age (years), mean (SD)	31.8 (10.95)	36.9 (13)	U=7.66	r= 0.19	<0.001
EVER USED CANNABIS			X2(1)=48.46	V=0.17 (0.13-0.22)	<0.001
No	224 (35.3)	528 (53)			
Yes	410 (64.7)	469 (47)			
EDUCATION LEVEL			X2(2)=102.87	V=0.25 (0.20-0.3)	<0.001
No qualification	100 (15.4)	40 (4)			
School education	327 (50.5)	416 (41.5)			
Tertiary education	221 (34.1)	546 (54.5)			
YEARS IN EDUCATION	12.87 (4.08)	14.69 (4.19)	U=8.26	r=0.20	<0.001
SOCIAL FUNCTIONING					
Employment status			X2(1)=17.7	V=0.11 (0.06-0.16)	<0.001
Employed	256 (50.3)	615 (61.6)			
Unemployed	253 (49.7)	383 (38.4)			
Marital status			X2(1)=125.2	V=0.28 (0.23-0.33)	<0.001
Steady relationship	201 (33.5)	626 (62.4)			
No relationship	399 (66.5)	378 (37.7)			
Living arrangements			X2(1)=95.96	V=0.25 (0.2-0.3)	<0.001
Independent living	220 (42.5)	683 (68.5)			
No independent living	298 (57.5)	314 (31.5)			
OPCRIT DSM IV DIAGNOSIS					
Non-affective psychosis	409 (71.4)	-			
Affective psychosis	164 (28.4)	-			
Bipolar disorder	73 (12.7)	-			
Psychotic depression	91 (15.8)	-			

SD: standard deviation; df: degrees of freedom

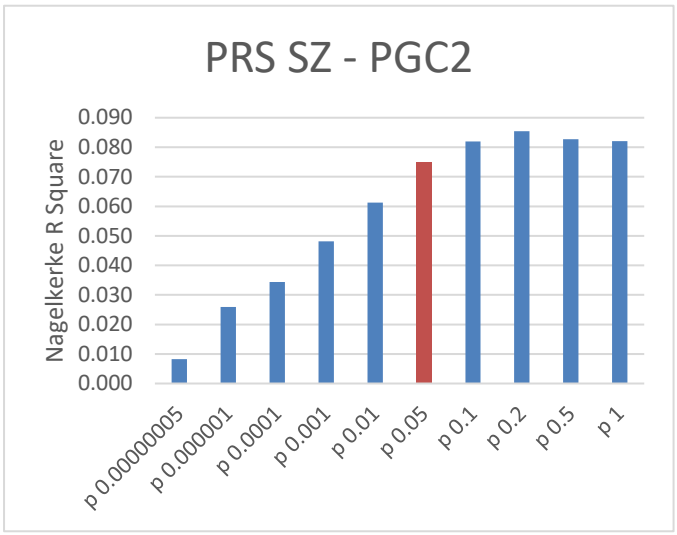
2.1.2 eTable 3. Affective vs Non-affective psychosis sociodemographic comparison in white subsample (n=573)

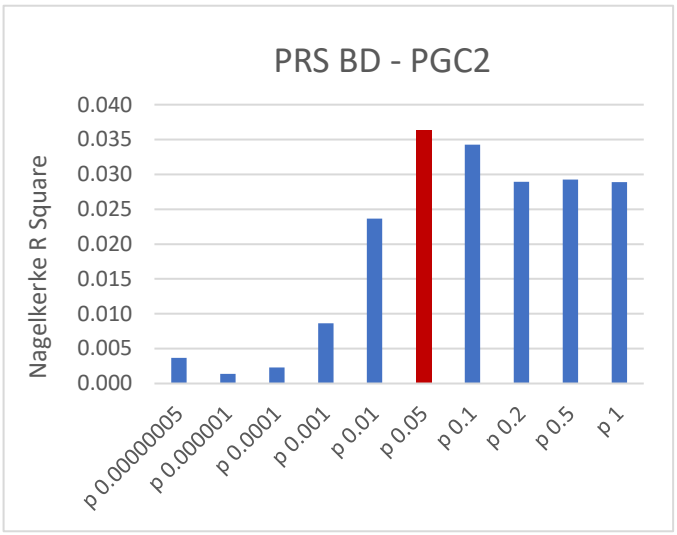
DESCRIPTIVE AT BASELINE	Number (%)/Mean(SD)		Statistics		
	Affective psychosis n= 164	Non-affective psychosis n= 409	Tests (df)	Effect sizes	p value
Gender			X2(1)=15.14	V=0.16 (0.09-0.25)	<0.001
Male	83 (50.6)	278 (68)			
Female	81 (49.4)	131 (32)			
Age (years), mean (SD)	32.84 (11.56)	31.63 (10.92)	z=-1.013	r= -0.042	0.240
EVER USED CANNABIS			X2(1)=0.17	V=0.018 (0.04-0.1)	0.677
No	58 (36)	136 (34.2)			
Yes	103 (64)	262 (65.8)			
EDUCATION LEVEL					
No qualification	25 (15.3)	65 (16.1)	X2(2)=1.107	V=0.04 (0.06-1.13)	0.575
School education	87 (53.4)	197 (48.6)			
Tertiary education	51 (31.3)	143 (35.3)			
YEARS IN EDUCATION	12.58 (3.84)	12.94 (4.12)	Z=0.55	r: 0.023	0.581
SOCIAL FUNCTIONING					
Employment status			X2(1)=6.39	V=0.12 (0.05-0.22)	0.011
Employed	79 (58.5)	141 (45.5)			
Unemployed	56 (41.5)	169 (54.5)			
Marital status			X2(1)=18.89	V=0.19 (0.12-0.28)	<0.001
Steady relationship	74 (48.1)	105 (28.3)			
No relationship	80 (52)	266 (71.7)			
Living arrangements			X2(1)=10.15	V=0.15 (0.08-0.25)	0.001
Independent living	73 (53.7)	119 (37.5)			
No independent living	63 (46.3)	198 (62.5)			

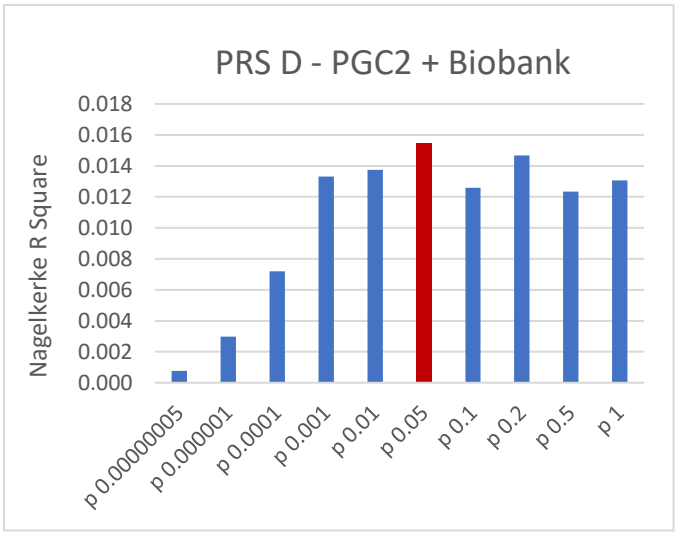
SD: standard deviation; df: degrees of freedom

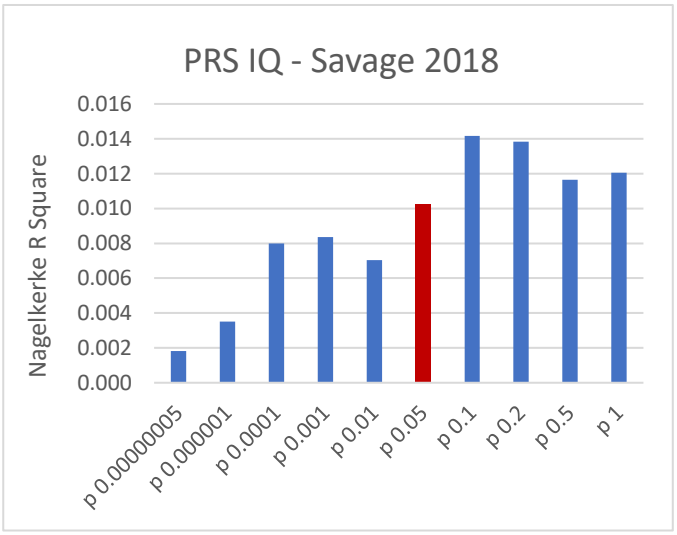
2.2 Case-control variance explained of employed PRSs (eFigure1)

2.2.1 eFigure1. Variance expressed by Nagelkerke R Square of PRS SZ, BD, D and IQ at 10 different p-values thresholds on case-control (all psychosis vs control) associations adjusted by 10PCs



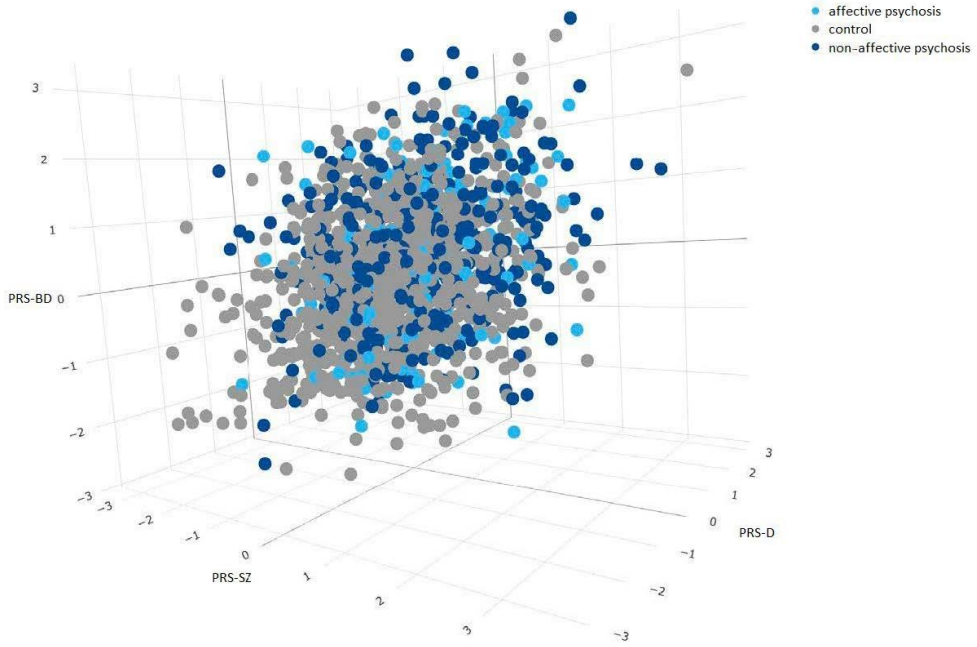






2.3 Visual representation of data

2.3.1 eFigure2. Three-dimensional scatterplot of the PRS distribution in the three groups of affective, non-affective psychosis (NAP) and controls



Three-dimensional scatterplot of the PRS distribution in the three groups of affective (AP), non-affective psychosis (NAP) and controls. The three axes correspond to each PRS (z-score after adjustment for PCs and site) and the dots are coloured by group. We observed a large overlap of PRS between the three groups of affective, non-affective psychosis and controls.

2.4. Detailed results of association of different associations on Model 1 and Model 2.

2.4.1 eTable 4. Model 1: Association of different PRSs (SZ, BD, D and IQ) with multicategorical DSMIV OPCRIT clinical groups adjusted with 10 PCs in white population (total n=1576)

Model 1a	**PseudoR**	**Prob > chi2**		
N=1578	0.1089	<0.001		
	OR	**p value**	**95% CI**	
NAP vs CONTROL				
PRS SZ	**1.87**	**<0.001**	1.57	2.2
PRS BD	**1.34**	**<0.001**	1.15	1.57
PRS D	1.04	0.566	0.91	1.19
PRS IQ	**0.88**	**0.056**	0.77	1.00
AP vs CONTROL				
PRS SZ	**1.34**	**0.014**	1.06	1.68
PRS BD	**1.35**	**0.006**	1.09	1.67
PRS D	**1.37**	**0.001**	1.14	1.64
PRS IQ	0.85	0.074	0.71	1.02
Model 1b	**PseudoR**	**Prob > chi2**		
N=573	0.0858	0.0013		
AP vs NAP				
PRS SZ	**0.7**	**0.010**	0.54	0.92
PRS BD	1.02	0.857	0.81	1.3
PRS D	**1.31**	**0.011**	1.06	1.61
PRS IQ	0.99	0.979	0.81	1.23

NAP: non-affective psychosis; AP: affective psychosis, SZ: schizophrenia; BD: bipolar disorder; D: depression; IQ: intelligence quotient

2.4.2 eTable 5. Model 2: Association of different PRSs (SZ, BD, D and IQ) with multicategorical DSMIV OPCRIT variable adjusted with 10 PCs in white population (non-affective psychosis as reference)

Model 2a	**PseudoR**	**Prob > chi2**		
N=573	0.1106	0.0008		
	OR	**p value**	**95% CI**	
BD vs NAP				
PRS SZ	0.97	0.865	0.68	1.39
PRS BD	.98	0.893	0.71	1.35
PRS D	1.14	0.364	0.86	1.41
PRS IQ	1.07	0.315	0.81	1.41
MDD-P vs NAP				
PRS SZ	**0.52**	**<0.001**	0.37	0.74
PRS BD	1.04	0.814	0.77	1.4
PRS D	**1.49**	**0.003**	1.14	1.94
PRS IQ	0.94	0.655	0.72	1.23
Model 2b	**PseudoR**	**Prob > chi2**		
N=164	0.20	0.0347		
BD vs MDD-P				
PRS SZ	**2.14**	**0.007**	1.23	3.74
PRS BD	1.01	0.959	0.64	1.61
PRS D	0.71	0.092	0.48	1.06
PRS IQ	1.03	0.878	0.71	1.49

NAP: non-affective psychosis; AP: affective psychosis, SZ: schizophrenia; BD: bipolar disorder; D: depression; IQ: intelligence quotient

2.5 PRS performance for identifying all psychotic diagnostic categories based on OPCRIT using control as reference (eTable 6 and eFigure3).

We further wanted to study the association of the three four PRS among individual diagnostic categories from the whole psychosis spectrum. Among three PRSs, PRS-SZ presented significant association with most of the diagnostic groups showing the following gradient: SAD (OR=2.38, 95% 1.36 – 4.17, p=0.002) >SCZ (OR=2.02, 95% 1.66 – 2.46, p<0.001) >BD (OR=1.76, 95% 1.26 – 2.46, p<0.001) >other psychosis (OR=1.47, 95% 1.1 – 1.98, p=0.009), but not being significantly associated with PD.

Moreover, PRS-BD was significantly associated primarily with other psychosis (OR=1.55, 95% 1.18 – 2.03, p=0.001) and interestingly, PRS-BD showed also a trend of association with MDD-P versus control (OR=1.32 95% CI 1.01 - 1.73, p=0.049).

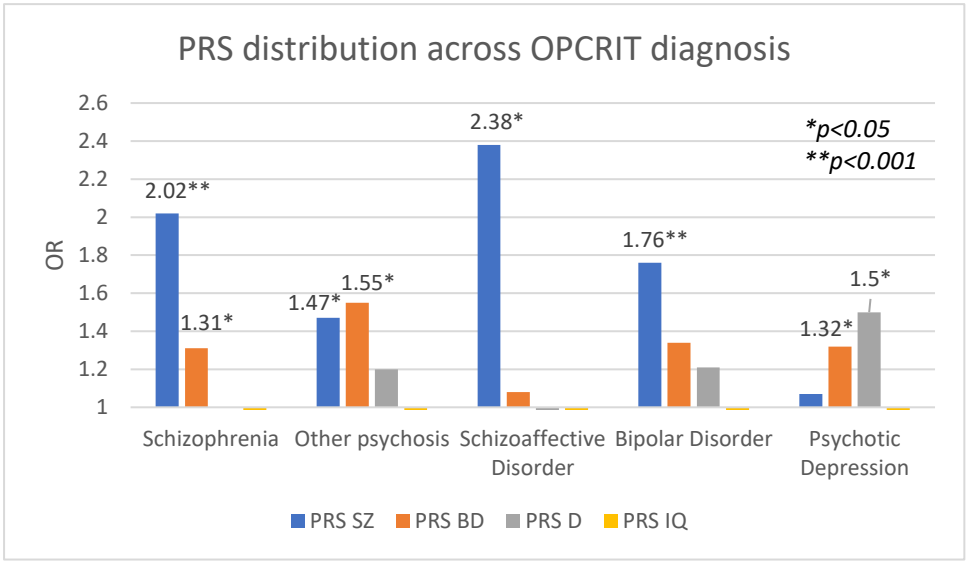
PRS-D was only significantly associated with MDD-P versus control (OR=1.5, 95% 1.19 – 1.9, p=0.001), and we could not find significant association for PRS-IQ with any group category.).

***eTable 6**. Association of PRSs (for SZ, BD, D and IQ) between OPCRIT diagnostic categories (SCZ, OP, SAD, BD and MDD-P) and control as reference adjusted by 10 PCs in white population.*

Model 1	**PseudoR**	**Prob > chi2**		
	0.1192	<0.001		
	OR	**p value**	**95% CI**	
SCHIZOPHRENIA				
PRS SZ	**2.02**	**<0.001**	1.66	2.46
PRS BD	**1.31**	**0.003**	1.09	1.56
PRS D	1.00	0.962	0.86	1.17
PRS IQ	0.90	0.165	0.77	1.05
OTHER PSYCHOSIS				
PRS SZ	**1.47**	**0.009**	1.10	1.98
PRS BD	**1.55**	**0.001**	1.18	2.03
PRS D	1.20	0.114	0.96	1.52
PRS IQ	0.87	0.241	0.69	1.10
SCHIZOAFFECTIVE DISORDER				
PRS SZ	**2.38**	**0.002**	1.36	4.17
PRS BD	1.08	0.770	0.64	1.83
PRS D	0.85	0.448	0.56	1.29
PRS IQ	0.71	0.130	0.46	1.10
BIPOLAR DISORDER				
PRS SZ	**1.76**	**<0.001**	1.26	2.46
PRS BD	1.34	0.057	0.99	1.82
PRS D	1.21	0.150	0.93	1.58
PRS IQ	0.91	0.510	0.70	1.19
PSYCHOTIC DEPRESSION				
PRS SZ	1.07	0.651	0.80	1.44
PRS BD	**1.32**	**0.049**	1.00	1.73
PRS D	**1.50**	**0.001**	1.19	1.90
PRS IQ	0.80	0.063	0.64	1.01

SZ: schizophrenia; BD: bipolar disorder; D: depression; IQ: intelligence quotient
SZ (n=487); Other psychosis (n=205); Schizoaffective disorder (n=47); BD (n=130), MDD-P (n=137)

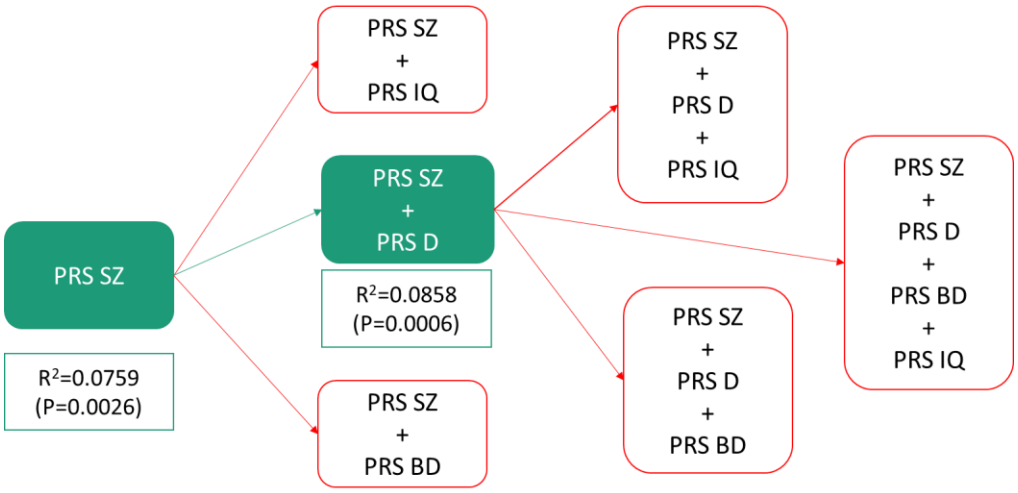
***eFigure 3.** PRS performance across all psychotic spectrum DSM4 OPCRIT categories.*



SZ: schizophrenia; BD: bipolar disorder; D: depression; IQ: intelligence quotient

2.6 *Goodness of fit of data of join model combining three major psychiatric disorder polygenic scores (SZ, BD, D) and polygenic score for intelligence for NAP and AP comparison.*

eFigure4.



Green lines represent improvement of model. Red lines represent non-significant likelihood-ratio tests. SZ: schizophrenia; BD: bipolar disorder; D: depression; IQ: intelligence quotient

Goodness of fit of data was explored through likelihood ratio test while sequentially adding the four PRSs to the models in order to identify those PRS adding value to the discriminability between clinical groups (NAP and AP). The best fitness of data by per likelihood ratio test was by adding PRS-SZ and PRS-D to the model ($\Delta\chi^2(1) = 6.74$, $p = 0.0094$).

eAppendix 3. References

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

Dudbridge, F (2013) Power and Predictive Accuracy of Polygenic Risk Scores, *PLoS Genetics*. Edited by N. R. Wray, **9**, p. e1003348.

Hair, J, Black, W, Babin, B and Anderson, R (2014) *Multivariate Data Analysis*. 7th Editio.

Howard, D M, Adams, M J, Clarke, T K, Hafferty, J D, Gibson, J, Shirali, M, Coleman, J R I, Hagenaars, S P, Ward, J, Wigmore, E M, Alloza, C, Shen, X, Barbu, M C, Xu, E Y, Whalley, H C, Marioni, R E, Porteous, D J, Davies, G, Deary, I J, *et al.* (2019) Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions, *Nature Neuroscience*. Nature Publishing Group, **22**, p. 343–352.

Mallett, R, Leff, J, Bhugra, D, Pang, D and Zhao, J H (2002) Social environment, ethnicity and schizophrenia, *Social Psychiatry and Psychiatric Epidemiology*, **37**, p. 329–335.

Price, A L, Weale, M E, Patterson, N, Myers, S R, Need, A C, Shianna, K V., Ge, D, Rotter, J I, Torres, E, Taylor, K D D, Goldstein, D B and Reich, D (2008) Long-Range LD Can Confound Genome Scans in Admixed Populations, *American Journal of Human Genetics*. Elsevier, p. 132–135.

Purcell, S, Neale, B, Todd-Brown, K, Thomas, L, Ferreira, M A R, Bender, D, Maller, J, Sklar, P, De Bakker, P I W, Daly, M J and Sham, P C (2007) PLINK: A tool set for whole-genome association and population-based linkage analyses, *American Journal of Human Genetics*. Cell Press, **81**, p. 559–575.

Ripke, S, Neale, Benjamin M, Corvin, A, Walters, J T and Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci, *Nature*, **511**, p. 421–427.

Ripke, S, Neale, Benjamin M., Corvin, A, Walters, J T R, Farh, K H, Holmans, P A, Lee, P, Bulik-Sullivan, B, Collier, D A, Huang, H, Pers, T H, Agartz, I, Agerbo, E, Albus, M, Alexander, M, Amin, F, Bacanu, S A, Begemann, M, Belliveau, R A, *et al.* (2014) Biological insights from 108 schizophrenia-associated genetic loci, *Nature*, **511**, p. 421–427.

Savage, J E, Jansen, P R, Stringer, S, Watanabe, K, Bryois, J, De Leeuw, C A, Nagel, M, Awasthi, S, Barr, P B, Coleman, J R I, Grasby, K L, Hammerschlag, A R, Kaminski, J A, Karlsson, R, Krapohl, E, Lam, M, Nygaard, M, Reynolds, C A, Trampush, J W, *et al.* (2018) Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence, *Nature Genetics*. Nature Publishing Group, **50**, p. 912–919.

Stahl, E A, Breen, G, Forstner, A J, McQuillin, A, Ripke, S, Trubetskoy, V, Mattheisen, M, Wang, Y, Coleman, J R I, Gaspar, H A, de Leeuw, C A, Steinberg, S, Pavlides, J M W, Trzaskowski, M, Byrne, E M, Pers, T H, Holmans, P A, Richards, A L, Abbott, L, *et al.* (2019) Genome-wide association study identifies 30 loci associated with bipolar disorder, *Nature Genetics*. Nature Publishing Group, **51**, p. 793–803.