Exploring psychotic experiences in the context of multidimensional psychopathology

Exploring Psychotic Experiences in the Context of Multidimensional Psychopathology:

A Longitudinal Community-based Approach

Umut Kırlı

DESIGN | EREN TAYMAZ • İstanbul

EXPLORING PSYCHOTIC EXPERIENCES IN THE CONTEXT OF MULTIDIMENSIONAL PSYCHOPATHOLOGY:

A Longitudinal Community-based Approach

DISSERTATION

to obtain the degree of Doctor at the Maastricht University,
on the authority of the Rector Magnificus,
Prof.dr. Rianne M. Letschert
in accordance with the decision of the Board of Deans,
to be defended in public
on Wednesday November 18th 2020, at 10.00 hours

by
Umut Kırlı
Born in 29th September 1986, Manisa, Turkey

Supervisor:
Prof J. van Os

Co-supervisors:
Dr M. Drukker
Dr T. Binbay (Dokuz Eylul University, Turkey)

Assessment Committee:
Prof Dr Ph.A.E.G. Delespaul (chair)
Dr S. Gülöksuz
Prof Dr B.P.F. Rutten
Prof Dr A. Üçok (Istanbul University, Turkey)
Prof Dr R. van Winkel (KU Leuven, Belgium)

The research presented in this thesis was conducted at the School of Medicine, Department of Psychiatry, Ege University, Izmir, Turkey in conjunction with the Department of Psychiatry and Psychology at Maastricht University, South Limburg Mental Health Research and Teaching Network, School for Mental Health and Neuroscience, Maastricht, the Netherlands. This thesis is part of a TürkSch Project and has been supported by the Scientific and Technological Research Council of Turkey (programme 1001) with the grants 107S053 and 112S476.

To the best days we have not experienced yet…

Paranymphs
Mesut Işık
Duygu Keskin Gökçelli

Don't worry… It is common to ascribe madness to the souls that are not understood
Peyami Safa

Suspicion causes fatigue .
Sophocles

Oh my loneliness, my plural songs
The more we live without lies, the better it is…
Can Yücel

Another thing is that i want
Does not look like a tree or a cloud
A journey like falling down a tree
Longer than the life itself
And another life, to the greenness of the grass you are into…
Can Yücel

TABLE OF CONTENTS

CHAPTER 1

Introduction

The Relativity of Psychosis

> *"The whole development of the theory turns on the question of whether there are physically preferred states in Nature. Also, concepts and distinctions are only admissible to the extent that observable facts can be assigned to them without ambiguity. This postulate, pertaining to epistemology, proves to be of fundamental importance"* (Einstein 1967).

These fundamental ideas on '*the Theory of Relativity*' were expressed by Albert Einstein in a lecture delivered in acknowledgement of the Nobel Prize in 1923 (Einstein 1967), three decades before the release of the first edition of the Diagnostic and Statistical Manual of Mental disorders (DSM) (American Psychiatric Association 1952). Looking into this ground-breaking theory from the perspective of psychosis expression in the community, may provide some productive insights, as formulated below.

The theory is deceptively simple: An object's velocity, or its momentum, or how it experiences time can only be measured relative to something else. For example, there is no object with absolute 'zero' velocity in the universe (A mountain, which seems to be immobile according to an earthbound observer, in fact has a velocity of 1300 km/h relative to the axis of the Earth). In other words, there is no 'absolute' frame of reference. In medicine, anything that phenotypically is a spectrum is commonly categorized for practical purposes (e.g. lower bound for hypertension is 120/80 mm Hg arterial blood pressure). This is accomplished by defining '*preferred states*', namely thresholds, based on regularly reviewed scientific evidence. Following this type of reasoning, a question arises: To what degree is psychosis expression in the community best – in terms of clinical practice, public health and research – described as a binary phenomenon or as a spectrum, such as arterial blood pressure? (van Os and Kapur 2009)

Focusing on definitions of psychosis nomenclature in the glossary of technical terms in DSM-5 (American Psychiatric Association 2013)

gives some guidance. Here, the term **delusion** is defined as a: "*false* and *fixed belief* that is not amenable to change in light of conflicting evidence". An **overvalued idea** is again a "*false belief* but not held '*as firmly as*' is the case with the *delusions*". Finally, the term **attenuated delusion** (A1 criterion for attenuated psychosis syndrome-APS in DSM-5) is defined as "a *delusion* that does not have *'the fixed nature'* that is necessary for the diagnosis of a psychotic disorder" (American Psychiatric Association 2013). Therefore, by definition, the distinction between these thought content symptoms relies on the *amount* of '*fixation*' on the belief, which is a *quantitative* rather than a *qualitative* difference**.** A similar type of graded spectrum reasoning may be found in the definition of (attenuated) disorganized speech in DSM-5 (American Psychiatric Association 2013)**.**

Two points in the definition of the term **hallucination** similarly require attention:

i) "A hallucinating person '*may or may not have insight'* into the non-veridical nature of the hallucination. One hallucinating person *may recognize* the false sensory experience, whereas another may be convinced that the experience is grounded in reality" (American Psychiatric Association 2013). However, the distinction of the severe form of the attenuated hallucination (A2 criterion of APS in DSM 5) with threshold hallucination is defined as: "These perceptual abnormalities may disrupt behaviour, but *scepticism about their reality can still be induced*" (American Psychiatric Association 2013). It is not easy to make a precise distinction between these two terms as both include the state of partly preserved reality testing and insight in the false sensory experience, indicating a partly intertwined state.

ii) "*Transient* hallucinatory experiences *may occur without a mental disorder*"(American Psychiatric Association 2013).

These statements, clearly, subscribe to the view that psychotic phenomena may form a **spectrum which includes both illness and normality states** in terms of **intensity, persistence and re-**

ality testing. For the last decades, epidemiological research has provided robust evidence for this proposition: Psychosis expression in the community is not an all-or-none phenomenon. Rather, there are psychotic experiences (PEs) which are of subthreshold severity and impact but also share demographic, environmental, familial and psychopathological features with the psychotic syndromes (Linscott and van Os 2013). Thus, the ***extended psychosis phenotype*** can be defined as the range from subthreshold PEs in non-clinical populations gradually blending into clinical-threshold psychotic disorders (PDs) such as severe and recurrent schizophrenia (Kaymaz and van Os 2010).

Although weak expressions of negative and disorganization symptoms are prevalent in the community (Dominguez *et al.* 2010a;Walss-Bass *et al.* 2015), the term **PEs** mostly refer to **subthreshold positive psychotic symptoms** in the literature (van Os and Reininghaus 2016). In order to be consistent, the term PEs will be used in this meaning throughout this thesis. When **subthreshold negative and disorganized expressions** are indicated, these terms (negative/disorganised) will be used as such.

Current classification systems define an **operational threshold of '*frank*' psychosis** in the context of a psychotic syndrome. The threshold is mainly based on persistence of distress or clear-cut impairment in social, occupational, or other important areas of functioning, along with impact on reality testing and insight (American Psychiatric Association 2013). For example, in DSM-5 , the distinction between the diagnoses '*substance intoxication or withdrawal, with perceptual disturbances*' and '*substance-induced psychotic disorder*' was defined in terms of being *sufficiently severe to warrant clinical attention* and the level of *reality testing* (American Psychiatric Association 2013). This threshold inevitably includes some grey areas (McGorry and van Os 2013), inducing a dilemma of reliability and validity as shown below in *figure 1* (van Os *et al.* 2000a;Linscott *et al.* 2010). Along with other reasons detailed below, this dilemma demonstrates the

need for the conceptualization of psychosis along a spectrum including normality states (Guloksuz and van Os 2017).

Figure 1: Reliability-Validity Dilemma in Level of Psychosis Expression and the Need for a Psychosis Spectrum

If we limited the 'iceberg' to only the image clearly visible above the water, we would ignore the part inside the water which yields much better consistency of the observation. In the area of psychosis, the results of a cross-national study including 256.445 subjects provided data that are consistent with that proposition. Individuals reporting a lifetime diagnosis of schizophrenia (1.04%) are indeed a very small part of the individuals with a psychosis endorsement (12.52%) (Nuevo *et al.* 2012).

Distribution of Psychosis Spectrum in Psychiatric Nosology

Epidemiological studies have consistently shown that subthreshold psychosis is more common in those who are helpseeking and distressed -so called clinical populations- than in the non-helpseeking general populations. PEs in clinical populations, mostly diagnosed with a non-psychotic disorder (i.e. depression/anxiety/substance-use disorders), have similar risk factors but poorer outcomes than PEs in general non-helpseeking populations (Varghese *et al.* 2009;van Nierop *et al.* 2011;Saha *et al.* 2012;van Os and Linscott 2012;Wigman *et al.* 2012;DeVylder *et al.* 2014;Stochl *et al.* 2014;Johns *et al.* 2018;Scott *et al.* 2018).

Studies, sampling helpseeking and distressed individuals in clinical settings, have also evaluated psychosis expression below the operational threshold of '*frank*' psychosis within high-risk categories, i.e. categories considered to predict a high risk of conversion to clinical psychotic disorder (McGorry and van Os 2013) (i.e. At Risk Mental States- ARMS,

Ultra-High Risk-UHR, Clinical High Risk-CHR, DSM-5 Attenuated Psychosis Syndrome-APS) (Klosterkötter *et al.* 1996;Miller *et al.* 2003;Schultze-Lutter *et al.* 2008;Yung and Nelson 2011;American Psychiatric Association 2013;Schultze-Lutter *et al.* 2017). These clinical high risk categories phenotypically have substantial similarities and overlap with general population samples of helpseeking and distressed subjects with PEs as the majority of individuals meeting high-risk criteria have a diagnosis of a non-psychotic disorder (depression/anxiety/substance use disorders) (Ruhrmann *et al.* 2010;Simon and Umbricht 2010;van Os and Linscott 2012;American Psychiatric Association 2013;Addington *et al.* 2014;Fusar-Poli *et al.* 2014;Falkenberg *et al.* 2015;Lin *et al.* 2015;Lo Cascio *et al.* 2016;Woodberry *et al.* 2016;Schultze-Lutter *et al.* 2017;van Os and Guloksuz 2017). When the high-risk criteria, developed in clinical samples seeking help at psychiatric services, are assessed in non-helpseeking general population samples, attenuated positive symptoms meeting the threshold of high-risk criteria only apply to a fraction of PEs (about 10-20%). Furthermore, risk factors associated with high risk categories were similar to those of the PEs in non-clinical populations (Zammit *et al.* 2013;Schultze-Lutter *et al.* 2017). Finally, attenuated positive symptoms within high risk categories in helpseeking clinical samples have poorer prognosis than PEs in non-clinical populations (van Os and Linscott 2012;Fusar-Poli *et al.* 2013;Linscott and van Os 2013;Fusar-Poli *et al.* 2014;Lin *et al.* 2015;van Os and Guloksuz 2017;Polari *et al.* 2018;Radua *et al.* 2018;Oliver *et al.* 2019). Taken together, these results point out to two propositions: i. *High-risk categories in helpseeking non-psychotic clinical samples* may be considered as a subsample of *subthreshold psychosis in non-helpseeking general population samples*. ii. *Subthreshold psychosis in non-helpseeking general populations* and *in clinical populations* may be related to each other in the sense of being at different positions of a spectrum of severity (van Os and Linscott 2012;van Os and Guloksuz 2017).

There is substantial evidence demonstrating shared associations between *subthreshold psychosis in general populations* and *threshold psychotic disorders* (van Os *et al.* 2008;van Os and Linscott 2012;Linscott and van Os 2013). Similarly, shared associations between *subthreshold psychosis in non-psychotic clinical populations* and *threshold psychotic disorders* has caught attention (van Os and Reininghaus 2016;Fusar-Poli *et al.* 2017;Schultze-Lutter *et al.* 2017;Radua *et al.* 2018;Oliver *et al.* 2019). Furthermore, individuals with subthreshold psychosis (in clinical non-psychotic and to a lesser extent in non-clinical general population samples) have much more risk for later psychotic disorders in comparison with those who do not, indicating a temporal continuity (van Os and Linscott 2012;Linscott and van Os 2013;McGorry *et al.* 2018).

Threshold psychotic disorders are currently classified across a myriad of categories, embracing a polythetic approach. Some of these disorders, in which the psychotic symptoms are considered to be the core factor, are classified in schizophrenia spectrum and other psychotic disorders in DSM-5: Schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance/medication/another medical condition induced psychotic disorder (American Psychiatric Association 2013). Additionally, inclusion of a schizo-obsessive disorder category is being discussed (Scotti-Muzzi and Saide 2016). However, there are other disorders with threshold psychotic symptoms (i.e. psychotic features) which are classified elsewhere: Depression/bipolar disorders with psychotic features, obsessive compulsive and related disorders with absent insight/delusional beliefs, major neurocognitive disorders with behavioural disturbances (Guloksuz et al. 2015;van Os 2016;Guloksuz and van Os 2017). Furthermore, behavioural disturbances in the context of psychotic features is common in neurodevelopmental disorders (Cochran et al. 2013;Kokurcan and Atbasoglu 2015) (figure 2).

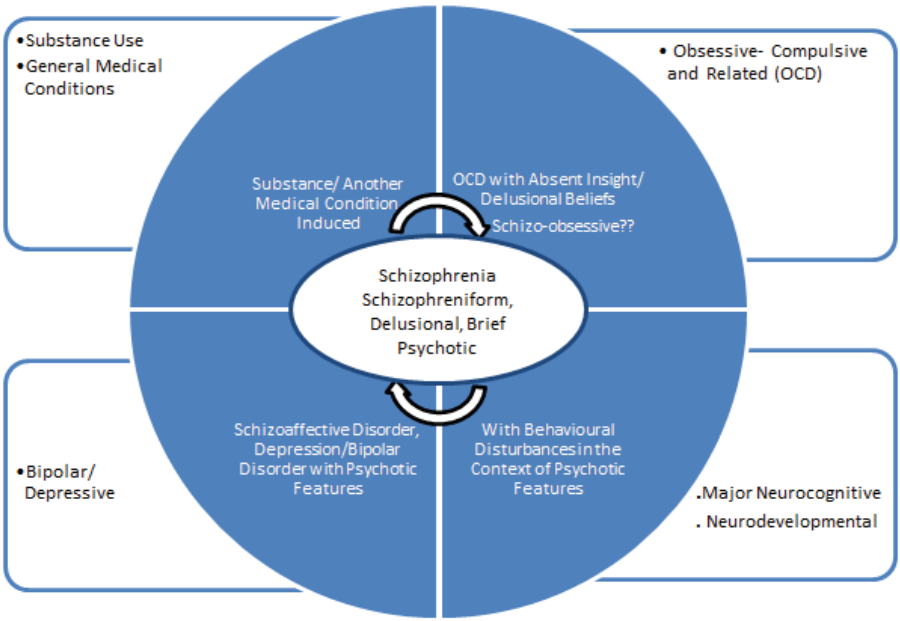


Figure 2: Current Categories of Threshold Psychosis

The primary objective of the abovementioned classification is to generate categories which are both as exhaustive as possible, and mutually exclusive (Reininghaus *et al.* 2012). However, from the perspective of the postulate mentioned in the starting point of the thesis, "*concepts and distinctions are only admissible to the extent that observable facts can be assigned to them without ambiguity*" (Einstein 1967), a question arises: Can we assign (at least most of the) observable facts to the current categories?

Recent large genome-wide genotype data has shown a remarkable amount of shared genetic risk loci among different diagnostic categories (i.e. schizophrenia, bipolar disorder and major depressive disorder) (Lee *et al.* 2013;Brainstorm *et al.* 2018;Cross-Disorder Group of the Psychiatric Genomics Consortium 2019). Furthermore, the polygenic risk for schizophrenia has been associated with the dimensional domains of psychosis across diagnostic categories (van Os *et al.* 2017). These results are consistent with the evidence from previous twin (Kendler *et*

al. 2003) and family history studies (Dean *et al.* 2010;Mortensen *et al.* 2010;DeVylder and Lukens 2013;Chou *et al.* 2017). In addition to shared genetic liability, there are a remarkable number of shared factors between different diagnostic categories with threshold psychosis: phenomenology (van Os *et al.* 2000a;Tamminga *et al.* 2013), cognition (Bora *et al.* 2009;van Os and Linscott 2012;Hill *et al.* 2013;Menkes *et al.* 2019), neuroimaging findings (Ivleva *et al.* 2013;Goodkind *et al.* 2015;Jauhar *et al.* 2017) as well as environmental exposures (Radhakrishnan *et al.* 2014a;Guloksuz *et al.* 2015;Isvoranu *et al.* 2016;Misiak *et al.* 2017;Pries *et al.* 2018).

About half of first episode psychosis (FEP) patients are classified in *schizophrenia spectrum and other psychotic disorders*, and the remaining in *disorders with 'psychotic features'* specifiers (Henry *et al.* 2007;McGorry *et al.* 2018;Quattrone *et al.* 2019). The diagnoses are subject to considerable change over time (Pope *et al.* 2013;Fusar-Poli *et al.* 2016;Guloksuz and van Os 2017). Differential diagnoses between distinct disorders with threshold psychosis are based on: i. the duration, number, relative proportion and chronological association of symptom domains in the combination ii. being attributable to the physiological effects of a substance/medication use/general medical condition (van Os and Kapur 2009;American Psychiatric Association 2013). These diagnoses are both strongly correlated with each other and diagnosable concurrently, causing high rates of comorbidity (van Os *et al.* 2019). Relatedly, there is a lack of zones of relative rarity between these diagnoses (Andrews *et al.* 2009;Carpenter *et al.* 2009;Reininghaus *et al.* 2012). Furthermore, the medications that patients with different diagnoses respond to are similar (e.g. patients suffering from an affective disorder with an admixture of psychosis respond to second-generation antipsychotics, conversely, patients suffering from schizophrenia with an admixture of affective symptoms respond to lithium) (Guloksuz and van Os 2017). Finally, individuals within the same category have a high variability of prognosis (van Os *et al.* 1997;Allardyce and van Os

2010;Zipursky *et al.* 2013;Castagnini and Fusar-Poli 2017;Guloksuz and van Os 2017).

In summary, the evidence for true diagnostic value of the distinction between these diagnoses is questionable, as evidenced by low diagnostic likelihood ratios as regards risk factors, symptoms, treatment and outcome (van Os *et al.* 2000b;Kelleher and Cannon 2014;van Os and Reininghaus 2016). Indeed, the distinction may obscure natural overlap throughout the psychosis spectrum (Crow 1990;van Os *et al.* 2000a;Moller 2003). Therefore, a research approach based on distinct categories of psychosis may cause a loss of power and precision (Kraemer 2007;Kelleher *et al.* 2018a;Isvoranu *et al.* 2019a). Furthermore**,** the approach to generate distinct categories of psychosis may be giving an implicit suggestion as these disorders are binary conditions which are possessed by a group of 'rare and unfortunate' individuals rather than being some end of a spectrum and thus, in part, fuelling stigmatization and internalized negative expectations (Zipursky *et al.* 2013;Lasalvia *et al.* 2015;Guloksuz and van Os 2017;Guloksuz and van Os 2018). Taken together with the evidence on subthreshold phenotypes, psychosis expression in psychiatric nosology may be considered along a spectrum of intensity and severity as follows (Guloksuz and van Os 2017):

i) *Subthreshold* psychosis in *non-clinical* populations

ii) *Subthreshold* psychosis in *clinical* populations (in the context of *non-psychotic disorders,* e.g. depression/anxiety/substance-use disorders, including high risk groups)

iii) *Threshold* psychosis outside *schizophrenia spectrum disorders* (in disorders with 'psychotic features' specifiers)

iv) *Schizophrenia spectrum disorders*

From this point of view, the hypothetic distribution of psychosis spectrum in psychiatric nosology is summarised in figure 3.

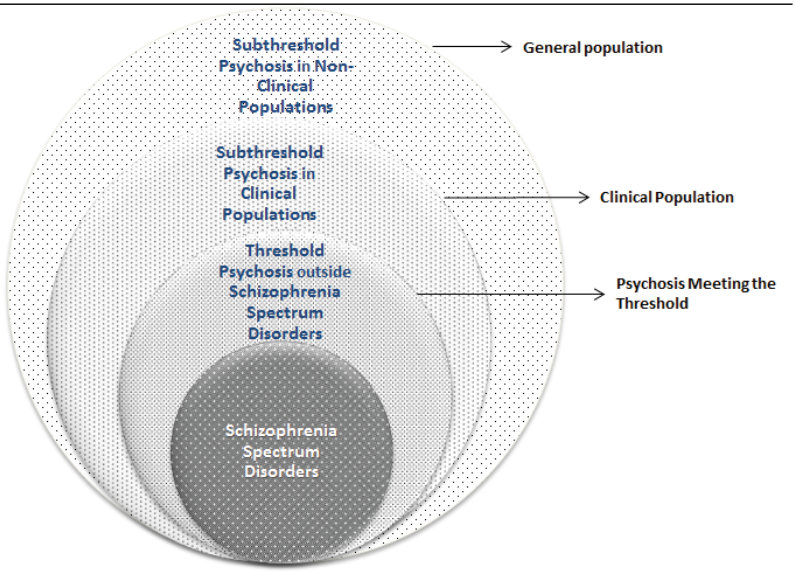


Figure 3: Distribution of Psychosis Spectrum in Psychiatric Nosology

**Intensity of dots represents the intensity of psychosis*

Subthreshold Psychosis in Clinical Populations (including High Risk Groups): DSM-5 Attenuated Psychosis Syndrome-APS; At Risk Mental States- ARMS/ Ultra-High Risk-UHR/ Clinical High Risk-CHR, Common Non-Psychotic Disorders (Depression/Anxiety/Substance use etc.) with Subthreshold PEs

Threshold Psychosis outside Schizophrenia Spectrum Disorders (in Disorders with 'Psychotic Features' Specifiers): Bipolar and Related Disorders with Psychotic Features, Depressive Disorders with Psychotic Features, Major Neurocognitive/ Neurodevelopmental Disorders with Behavioural Disturbances in the Context of Psychotic Features, Obsessive-Compulsive and Related Disorders with Absent Insight/Delusional Beliefs" etc.

Schizophrenia Spectrum Disorders: Disorders included in this category in current classification systems

Transdiagnostic Psychosis Phenotype in Relation to Psychosis Spectrum

Psychosis expression in the community, from lower to higher levels of intensity and severity (figure 3), is typically expressed as a mixture of signs and symptoms within multiple domains (van Os 2013). For instance, in *general non-clinical populations*, there is a well-established link between PEs and motivational alterations, subclinical affective dysregulation and anxiety states (van Os *et al.* 1999;Verdoux *et al.* 1999;Hanssen *et al.*

2003;Stefanis *et al.* 2004;van Rossum *et al.* 2009;van Os and Linscott 2012). Furthermore, subthreshold negative and disorganisation experiences commonly co-occur with PEs in these samples (van Os *et al.* 2000b;Krabbendam *et al.* 2004;Dominguez *et al.* 2010a;Walss-Bass *et al.* 2015;van Os and Reininghaus 2016). A similar pattern is observed at the level of *subthreshold* psychosis in *clinical* populations (including high risk for psychosis groups) (Fusar-Poli *et al.* 2014;van Os *et al.* 2017). PEs are 2-3 fold more common in individuals with non-psychotic mental disorders (i.e. affective/anxiety disorders), and the occurrence of PEs in these disorders is associated with the general severity of psychopathology, rather than the type of the disorder (Varghese *et al.* 2009;van Nierop *et al.* 2011;Saha *et al.* 2012;van Os and Linscott 2012;Wigman *et al.* 2012;DeVylder *et al.* 2014;Stochl *et al.* 2014;Johns *et al.* 2018;Scott *et al.* 2018). Negative symptoms are also common in these samples (i.e. high risk samples), with a similar prevalence as threshold psychotic disorders (Sauvé *et al.* 2019). Finally, such co-occurrence of symptoms within multiple domains is also observed among individuals with threshold psychosis, as well as their relatives (Tsuang 1979;Buckley *et al.* 2008;McMillan *et al.* 2009;Dean *et al.* 2010;Mortensen *et al.* 2010;DeVylder and Lukens 2013). In summary, psychosis expression in the community throughout different levels of severity and intensity co-occurs and overlaps with symptoms from multiple dimensions, as well as with disorder states from different diagnostic spectra, suggesting a *transdiagnostic psychosis phenotype* in addition to the *extended psychosis phenotype* (van Os and Reininghaus 2016).

Growing research has suggested that *the extended and transdiagnostic psychosis phenotype in the community* may be complemented by specific *non-affective (positive, negative and disorganisation) and affective dimensions,* which, when used in combination, could help for a more accurate conceptualisation (Reininghaus *et al.* 2012;Shevlin *et al.* 2017;Reininghaus *et al.* 2018;Quattrone *et al.* 2019).

Hypothetical Network Model of Psychosis Dimensions across the Spectrum

Emerging evidence has questioned the traditional framework that investigates 'direct' associations between risk factors and specific disorders (Isvoranu *et al.* 2019b). First, as described in detail above, risk factors do not seem to be specific to particular diagnostic categories, but rather appear to be shared across different categories (van Os and Reininghaus 2016;McGorry *et al.* 2018). Conversely, specific symptom domains within a single disorder may be associated with different risk factors (Dominguez *et al.* 2010b;Varese *et al.* 2012;Fried *et al.* 2013), which (at least to a degree) may explain various clinical presentations and prognostic states of a unique disorder (Gong *et al.* 2014;Isvoranu *et al.* 2016;Isvoranu *et al.* 2017). In addition, both environmental (Carpenter *et al.* 2009;Heinz *et al.* 2013;Gevonden *et al.* 2014;Radhakrishnan *et al.* 2014b;van Nierop *et al.* 2014;Misiak *et al.* 2017) and genetic risk (Carpenter *et al.* 2009;van Os *et al.* 2017;Isvoranu *et al.* 2019a) may influence multiple domains (Guloksuz *et al.* 2018a;Guloksuz *et al.* 2018b;Cross-Disorder Group of the Psychiatric Genomics Consortium 2019).

Recent research has demonstrated different pathways of risk exposure and emergence of psychosis: Exposure to risk may be expressed as an increasing severity and persistence of common subtle alterations in daily life, causing symptoms, and, subsequently, impairment (Cougnard *et al.* 2007;Linscott and van Os 2013;McGorry and van Os 2013). In addition, risk factors may impact on the connectivity between different domains of psychosis (Guloksuz *et al.* 2015;Smeets *et al.* 2015;Guloksuz *et al.* 2016;Isvoranu *et al.* 2016). Connectivity between subthreshold non-affective and affective domains seems to be associated with greater cross-sectional severity of psychopathology, as well as poorer long term outcomes (Kaymaz *et al.* 2007;Perlis *et al.* 2010;Rössler *et al.* 2011;Kaymaz *et al.* 2012;Wigman *et al.* 2012;American Psychiatric Association 2013;Kelleher *et al.* 2018b). As discussed in detail above, *PEs and affective/anxiety* states may

bidirectionally indicate severity of the index psychopathology (van Rossum *et al.* 2009;Varghese *et al.* 2009;Dominguez *et al.* 2010a;van Nierop *et al.* 2011;Saha *et al.* 2012;van Os and Linscott 2012;Wigman *et al.* 2012;DeVylder *et al.* 2014;Stochl *et al.* 2014;McGrath *et al.* 2016;Johns *et al.* 2018;Scott *et al.* 2018). Furthermore, co-occurrence of the negative and disorganized experiences with PEs has been associated with an increased risk of psychotic impairment over time (Dominguez *et al.* 2010a;Werbeloff 2012;van Os and Reininghaus 2016;Pries *et al.* 2018).

A recent novel theoretical framework is also suggestive of some direct interactive effects between symptoms (Borsboom and Cramer 2013;Isvoranu *et al.* 2016;Epskamp 2017;Fried and Cramer 2017). In other words, some domains of psychopathology may be causal agents for others. For example, stress may lead to poor sleep which may lead to fatigue, and fatigue may lead to low concentration (Schmittmann *et al.* 2013;Fried *et al.* 2015). Another example may be the triggering of social withdrawal by paranoid ideation over time, and vice-versa. These causal associations may lead to feedback loops between domains, and may collectively constitute disorder states (Isvoranu *et al.* 2019b). Taken together, emergence of psychotic impairment cannot be explained by simple linear models, instead complemented by the complex interplay between symptoms and genetic and environmental exposures (Pries *et al.* 2018) (Figure 4).

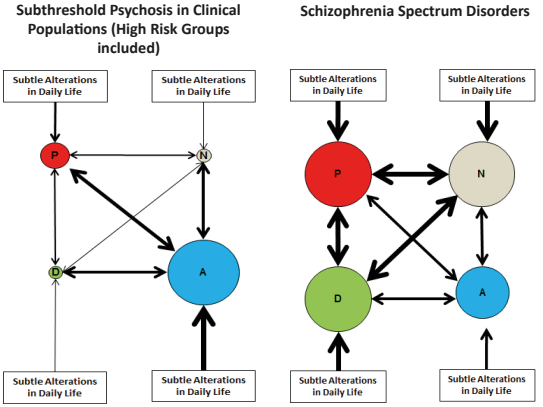


Figure 4: Hypothetic Network Model of Dimensions along the Psychosis Spectrum in Psychiatric Nosology
**P: Positive, N: Negative, D: Disorganization, A: Affective, Thickness of the arrows represents the degree of influence of one on the other*
Through gene by environment interactions (GxE), subtle and non-clinical alterations in daily life may become persistent and clinically relevant, forming symptoms. On the other hand, GxE may play a role in increasing the connectivity between symptoms. Symptoms both within a single dimension (delusions and hallucinations) and across different dimensions (delusions and social withdrawal) reciprocally impact on each other, collectively giving rise to functional impairment states.
Clinical relevance appears to be a consequence of the severity of the impact on each domain (either in terms of impact by risk factors or impact through symptom by symptom interactions). However, the complex interplay between symptoms and GxE are dynamic in nature, explaining the change of the clinical presentation as well as the categorical diagnoses over time (Quattrone *et al.* 2019).

Aims

The *extended and transdiagnostic psychosis phenotype* represents an excellent framework from which to study the psychosis expression in the context of multidimensional psychopathology. In this thesis, psychosis was assessed along a spectrum of severity including both clinical and non-clinical individuals, based on a six-year follow-up of a representative general population-based sample. Predominantly longitudinal etiological and phenomenological associations along the whole phenotypic spectrum as well as with other dimensions of psychopathology were under investigation.

Chapter 2 describes the outlines, framework and methodology of the cohort project in detail. The *Izmir Mental Health Cohort for Gene-Environment Interaction in Psychosis (TürkSch)* is a prospective, longitudinal study consisting of several data collection stages. The design of the study provided unique opportunities to meet the challenges of evaluating the different dimensions of, and the multifactorial (genetic and non-genetic) risk for psychosis. Owing to the large, representative general population-based sample and diagnostic interviews conducted by a psychiatrist in the field, the psychosis phenotype from subthreshold-non clinical expressions to threshold psychotic disorders could be covered. Furthermore, the risk factors in the wider social environment such as neighbourhood-level risk factors could be taken into account besides factors at individual and family level. Blood sampling in the field also enabled to evaluate targeted gene-environment interactions in the psychosis spectrum covering the subthreshold phenotypes.

In this chapter, besides the detailed design of the project, analyses of factors associated with non-response and refusal at follow-up, which are of importance in planning future general population-based cohort studies, were presented. Finally, dynamic transitions in the psychosis spectrum over the six-year period were presented.

In **Chapter 3**, the natural overlap as well as the reciprocal associations over time between the extended psychosis phenotype and affective states was investigated. For this aim, the extended psychosis phenotype was stratified by severity, using both self-report information and diagnostic interviews, including *threshold psychotic disorders, clinical-subthreshold psychosis* and *subclinical-subthreshold psychosis*. Longitudinal bidirectional associations between the extended psychosis phenotype and the affective states were assessed. Furthermore, plausible additive interactions as well as synchronous and cross-lagged correlations over time were evaluated. Finally, shared and unshared etiological associations were explored.

In **chapter 4,** the longitudinal outcomes of PEs in the context of psychopathology pertaining to any diagnostic spectrum were investigated. To this end, the six-year structured clinical interview for DSM (SCID) results of a sub-group of the cohort (individuals with baseline clinical-subthreshold psychosis) were given in detail. Furthermore, the role of co-occurrence of symptoms within a single domain (delusions and hallucinations) and within different domains (positive and affective) as well as socio-demographic and familial risk on the outcome (presence of any disorder, psychotic or non-psychotic disorder) were evaluated, adjusting for other familial and common environmental exposures.

In chapter 5, a genetic locus with multiple variants (BDNF), hypothesized a priori to have relevance in this context, was analysed in relation to the dimensional and transdiagnostically expressed psychosis phenotype. Analyses were based on the positive dimension (along a spectrum of severity including subthreshold as well as threshold levels), cutting across boundaries of the diagnostic categories of the current classification systems (expressed both in non-psychotic and psychotic disorders over time, detailed in chapter 4). The phenotype was epidemiological, longitudinally assessed through a nested case-control sample within the cohort, and the associations were adjusted for socio-demographics and common environmental exposures.

Similar to various genetic and environmental risk factors, BDNF has been pleiotropically associated with various disorders cutting across diagnostic categories (mood, anxiety, schizophrenia spectrum disorders etc.). On the other hand, findings on the associations with single syndromal states (e.g. schizophrenia) are inconsistent, which suggests a need to explore the impact on dimensional liabilities (including subthreshold phenotypes) rather than syndromal states which consist of merely threshold symptoms from multiple dimensions, occasioning much heterogeneity from sample to sample. Therefore, the aim of the chapter, in regard to this thesis, is to contribute to the increasing need for a novel dynamic and dimensional perspective on risk assessment in the psychosis area (van Os and Reininghaus 2016;McGorry *et al.* 2018).

References

- Addington J, Case N, Saleem MM, Auther AM, Cornblatt BA , Cadenhead KS (2014). Substance use in clinical high risk for psychosis: a review of the literature. *Early Interv Psychiatry* 8, 104-112.
- Allardyce J , van Os J (2010). The Natural History of the Course and Outcome of Schizophrenia. 51-65.
- American Psychiatric Association (1952). *Diagnostic and statistical manual of mental disorders*. American Psychiatric Association Mental Hospital Service: Washington, DC.
- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, - 5th edition: DSM-5*. American Psychiatric Association: Washington, DC.
- Andrews G, Goldberg DP, Krueger RF*, et al.* (2009). Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? *Psychological medicine* 39, 1993-2000.
- Bora E, Yucel M , Pantelis C (2009). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *The British journal of psychiatry : the journal of mental science* 195, 475-482.
- Borsboom D , Cramer AOJ (2013). Network Analysis: An Integrative Approach to the Structure of Psychopathology. *Annual Review of Clinical Psychology* 9, 91-121.
- Brainstorm C, Anttila V, Bulik-Sullivan B*, et al.* (2018). Analysis of shared heritability in common disorders of the brain. *Science* 360.
- Buckley PF, Miller BJ, Lehrer DS , Castle DJ (2008). Psychiatric Comorbidities and Schizophrenia. *Schizophrenia Bulletin* 35, 383-402.
- Carpenter WT, Bustillo JR, Thaker GK, van Os J, Krueger RF , Green MJ (2009). The psychoses:

cluster 3 of the proposed meta-structure for DSM-V and ICD-11. *Psychological medicine* 39, 2025-2042.

- Castagnini AC , Fusar-Poli P (2017). Diagnostic validity of ICD-10 acute and transient psychotic disorders and DSM-5 brief psychotic disorder. *European psychiatry : the journal of the Association of European Psychiatrists* 45, 104-113.

- Chou IJ, Kuo CF, Huang YS*, et al.* (2017). Familial Aggregation and Heritability of Schizophrenia and Co-aggregation of Psychiatric Illnesses in Affected Families. *Schizophrenia Bulletin* 43, 1070-1078.

- Cochran DM, Dvir Y , Frazier JA (2013). "Autism-plus" Spectrum Disorders. *Child and Adolescent Psychiatric Clinics of North America* 22, 609-627.

- Cougnard A, Marcelis M, Myin-Germeys I*, et al.* (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness–persistence model. *Psychological Medicine* 37, 513.

- Cross-Disorder Group of the Psychiatric Genomics Consortium (2019). Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* 179, 1469-1482 e1411.

- Crow TJ (1990). Nature of the genetic contribution to psychotic illness - a continuum viewpoint. *Acta psychiatrica Scandinavica* 81, 401-408.

- Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E , Pedersen CB (2010). Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Archives of general psychiatry* 67, 822-829.

- DeVylder JE, Burnette D , Yang LH (2014). Co-occurrence of psychotic experiences and common mental health conditions across four racially and ethnically diverse population samples. *Psychological Medicine* 44, 3503-3513.

- DeVylder JE , Lukens EP (2013). Family history of schizophrenia as a risk factor for axis I psychiatric conditions. *Journal of psychiatric research* 47, 181-187.

- Dominguez M-d-G, Saka MC, Lieb R, Wittchen H-U , van Os J (2010a). Early Expression of Negative/Disorganized Symptoms Predicting Psychotic Experiences and Subsequent Clinical Psychosis: A 10-Year Study. *American Journal of Psychiatry* 167, 1075-1082.

- Dominguez MD, Saka MC, Lieb R, Wittchen HU , van Os J (2010b). Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: a 10-year study. *American Journal of Psychiatry* 167, 1075-1082.

- Einstein A (1967). "Fundamental Ideas and Problems of the Theory of Relativity," delivered 11 July 1923 to the Nordic Assembly of Naturalists at Gothenburg in acknowledgement of the Nobel Prize. In *Nobel Lectures: 1901–1921*, pp. 482-490. Elsevier: New York.

- Epskamp S (2017). Network psychometrics., p. 300. University of Amsterdam: Amsterdam.

- Falkenberg I, Valmaggia L, Byrnes M, *et al.* (2015). Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? *Psychiatry research* 228, 808-815.

- Fried EI, Bockting C, Arjadi R, *et al.* (2015). From loss to loneliness: The relationship between bereavement and depressive symptoms. *Journal of abnormal psychology* 124, 256-265.

- Fried EI , Cramer AOJ (2017). Moving Forward: Challenges and Directions for Psychopathological Network Theory and Methodology. *Perspectives on Psychological Science* 12, 999-1020.

- Fried EI, Nesse RM, Zivin K, Guille C , Sen S (2013). Depression is more than the sum score of its parts:

individual DSM symptoms have different risk factors. *Psychological medicine* 44, 2067-2076.

- Fusar-Poli P, Borgwardt S, Bechdolf A, *et al.* (2013). The Psychosis High-Risk State. *JAMA psychiatry* 70, 107.

- Fusar-Poli P, Cappucciati M, Rutigliano G, *et al.* (2016). Diagnostic Stability of ICD/DSM First Episode Psychosis Diagnoses: Meta-analysis. *Schizophrenia Bulletin* 42, 1395-1406.

- Fusar-Poli P, Nelson B, Valmaggia L, Yung AR , McGuire PK (2014). Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophr Bull* 40, 120-131.

- Fusar-Poli P, Tantardini M, De Simone S, *et al.* (2017). Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry* 40, 65-75.

- Gevonden MJ, Myin-Germeys I, van den Brink W, van Os J, Selten JP , Booij J (2014). Psychotic reactions to daily life stress and dopamine function in people with severe hearing impairment. *Psychological Medicine* 45, 1665-1674.

- Gong Q, Fried EI , Nesse RM (2014). The Impact of Individual Depressive Symptoms on Impairment of Psychosocial Functioning. *PloS one* 9, e90311.

- Goodkind M, Eickhoff SB, Oathes DJ, *et al.* (2015). Identification of a common neurobiological substrate for mental illness. *JAMA psychiatry* 72, 305-315.

- Guloksuz S, Rutten BPF, Pries LK, *et al.* (2018a). The Complexities of Evaluating the Exposome in Psychiatry: A Data-Driven Illustration of Challenges and Some Propositions for Amendments. *Schizophrenia Bulletin* 44, 1175-1179.

- Guloksuz S, van Nierop M, Bak M, *et al.* (2016). Exposure to environmental factors increases connectivity

between symptom domains in the psychopathology network. *BMC psychiatry* 16.

- Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen HU , 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* 45, 2389-2401.

- Guloksuz S , van Os J (2017). The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological medicine* 48, 229-244.

- Guloksuz S , van Os J (2018). Renaming schizophrenia: 5 × 5. *Epidemiology and Psychiatric Sciences* 28, 254-257.

- Guloksuz S, van Os J , Rutten BPF (2018b). The Exposome Paradigm and the Complexities of Environmental Research in Psychiatry. *JAMA Psychiatry* 75, 985-986.

- Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H , van Os J (2003). How psychotic are individuals with non-psychotic disorders? *Social Psychiatry and Psychiatric Epidemiology* 38, 149-154.

- Heinz A, Deserno L , Reininghaus U (2013). Urbanicity, social adversity and psychosis. *World Psychiatry* 12, 187-197.

- Henry LP, Harris MG, Amminger GP*, et al.* (2007). Early Psychosis Prevention and Intervention Centre long-term follow-up study of first-episode psychosis: methodology and baseline characteristics. *Early Intervention in Psychiatry* 1, 49-60.

- Hill SK, Reilly JL, Keefe RS*, et al.* (2013). Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *The American journal of psychiatry* 170, 1275-1284.

- Isvoranu A-M, Borsboom D, van Os J , Guloksuz S (2016). A Network Approach to Environmental Impact in Psychotic Disorder: Brief

Theoretical Framework. *Schizophrenia Bulletin* 42, 870-873.

- Isvoranu A-M, Guloksuz S, Epskamp S, van Os J , Borsboom D (2019a). Toward incorporating genetic risk scores into symptom networks of psychosis. *Psychological medicine*, 1-8.

- Isvoranu A-M, van Borkulo CD, Boyette L-L, Wigman JTW, Vinkers CH , Borsboom D (2017). A Network Approach to Psychosis: Pathways Between Childhood Trauma and Psychotic Symptoms. *Schizophrenia Bulletin* 43, 187-196.

- Isvoranu AM, Boyette LL, Guloksuz S , Borsboom D (2019b). Symptom network models of psychosis. In *Psychotic Disorders: Comprehensive Conceptualization and Treatments* (ed. J. van Os, U. Reininghaus, E. I. Ivleva and C. A. Tamminga). Oxford University Press: Oxford.

- Ivleva EI, Bidesi AS, Keshavan MS, *et al.* (2013). Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *The American journal of psychiatry* 170, 1285-1296.

- Jauhar S, Nour MM, Veronese M, *et al.* (2017). A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia. *JAMA psychiatry* 74, 1206-1213.

- Johns LC, Cannon M, Singleton N, *et al.* (2018). Prevalence and correlates of self-reported psychotic symptoms in the British population. *British Journal of Psychiatry* 185, 298-305.

- Kaymaz N, Drukker M, Lieb R, *et al.* (2012). Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychological Medicine* 42, 2239-2253.

- Kaymaz N , van Os J (2010). Extended psychosis phenotype--yes: single continuum--unlikely. *Psychological medicine* 40, 1963-1966.
- Kaymaz N, van Os J, de Graaf R, ten Have M, Nolen W , Krabbendam L (2007). The impact of subclinical psychosis on the transition from subclinicial mania to bipolar disorder. *Journal of affective disorders* 98, 55-64.
- Kelleher I , Cannon M (2014). Whither the psychosis-neurosis borderline. *Schizophrenia Bulletin* 40, 266-268.
- Kelleher I, Jenner JA , Cannon M (2018a). Psychotic symptoms in the general population – an evolutionary perspective. *British Journal of Psychiatry* 197, 167-169.
- Kelleher I, Keeley H, Corcoran P*, et al.* (2018b). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *British Journal of Psychiatry* 201, 26-32.
- Kendler KS, Prescott CA, Myers J , Neale MC (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of general psychiatry* 60, 929-937.
- Klosterkötter J, Ebel H, Schultze-Lutter F , Steinmeyer EM (1996). Diagnostic validity of basic symptoms. *European Archives of Psychiatry and Clinical Neuroscience* 246, 147-154.
- Kokurcan A , Atbasoglu EC (2015). [Differential Diagnosis of Schizophrenia: Psychotic Symptoms in Neurodevelopmental Disorders and Psychotic Disorders due to other Medical Conditions]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 26, 279-290.
- Krabbendam L, Myin-Germeys I, De Graaf R*, et al.* (2004). Dimensions of depression, mania and psychosis in the general

population. *Psychological Medicine* 34, 1177-1186.

- Kraemer HC (2007). DSM categories and dimensions in clinical and research contexts. *International Journal of Methods in Psychiatric Research* 16, S8-S15.

- Lasalvia A, Penta E, Sartorius N , Henderson S (2015). Should the label "schizophrenia" be abandoned? *Schizophrenia Research* 162, 276-284.

- Lee SH, Ripke S, Neale BM, *et al.* (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature genetics* 45, 984-994.

- Lin A, Wood SJ, Nelson B, Beavan A, McGorry P , Yung AR (2015). Outcomes of Nontransitioned Cases in a Sample at Ultra-High Risk for Psychosis. *American Journal of Psychiatry* 172, 249-258.

- Linscott RJ, Allardyce J , van Os J (2010). Seeking Verisimilitude in a Class: A Systematic Review of Evidence That the Criterial Clinical Symptoms of Schizophrenia Are Taxonic. *Schizophrenia Bulletin* 36, 811-829.

- Linscott RJ , van Os J (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine* 43, 1133-1149.

- Lo Cascio N, Saba R, Hauser M, *et al.* (2016). Attenuated psychotic and basic symptom characteristics in adolescents with ultra-high risk criteria for psychosis, other non-psychotic psychiatric disorders and early-onset psychosis. *European Child & Adolescent Psychiatry* 25, 1091-1102.

- McGorry P , van Os J (2013). Redeeming diagnosis in psychiatry: timing versus specificity. *Lancet* 381, 343-345.

- McGorry PD, Hartmann JA, Spooner R , Nelson B (2018). Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry* 17, 133-142.

- McGrath JJ, Saha S, Al-Hamzawi A, *et al.* (2016). The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *American Journal of Psychiatry* 173, 997-1006.

- McMillan KA, Enns MW, Cox BJ , Sareen J (2009). Comorbidity of Axis I and II Mental Disorders with Schizophrenia and Psychotic Disorders: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *The Canadian Journal of Psychiatry* 54, 477-486.

- Menkes MW, Armstrong K, Blackford JU, Heckers S , Woodward ND (2019). Neuropsychological functioning in early and chronic stages of schizophrenia and psychotic bipolar disorder. *Schizophrenia Research* 206, 413-419.

- Miller TJ, McGlashan TH, Rosen JL, *et al.* (2003). Prodromal Assessment With the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms: Predictive Validity, Interrater Reliability, and Training to Reliability. *Schizophrenia Bulletin* 29, 703-715.

- Misiak B, Krefft M, Bielawski T, Moustafa AA, Sasiadek MM , Frydecka D (2017). Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neuroscience and biobehavioral reviews* 75, 393-406.

- Moller HJ (2003). Bipolar disorder and schizophrenia: distinct illnesses or a continuum? *The Journal of clinical psychiatry* 64 Suppl 6, 23-27; discussion 28.

- Mortensen PB, Pedersen MG , Pedersen CB (2010). Psychiatric family history and schizophrenia risk in Denmark: which mental

disorders are relevant? *Psychological medicine* 40, 201-210.

- Nuevo R, Chatterji S, Verdes E, Naidoo N, Arango C , Ayuso-Mateos JL (2012). The continuum of psychotic symptoms in the general population: a cross-national study. *Schizophrenia bulletin* 38, 475-485.

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

- Perlis RH, Uher R, Ostacher M*, et al.* (2010). Association Between Bipolar Spectrum Features and Treatment Outcomes in Outpatients With Major Depressive Disorder. *Archives of general psychiatry* 68, 351.

- Polari A, Lavoie S, Yuen HP*, et al.* (2018). Clinical trajectories in the ultra-high risk for psychosis population. *Schizophrenia Research*.

- Pope MA, Joober R , Malla AK (2013). Diagnostic stability of first-episode psychotic disorders and persistence of comorbid psychiatric disorders over 1 year. *Canadian journal of psychiatry. Revue canadienne de psychiatrie* 58, 588-594.

- Pries L-K, Guloksuz S, ten Have M*, et al.* (2018). Evidence That Environmental and Familial Risks for Psychosis Additively Impact a Multidimensional Subthreshold Psychosis Syndrome. *Schizophrenia bulletin* 44, 710-719.

- Quattrone D, Di Forti M, Gayer-Anderson C*, et al.* (2019). Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study. *Psychological medicine* 49, 1378-1391.

- Radhakrishnan R, Wilkinson ST , D'Souza DC (2014a). Gone to Pot - A Review of the Association between Cannabis and Psychosis. *Frontiers in psychiatry* 5, 54.

- Radhakrishnan R, Wilkinson ST , Dâ€™Souza DC

(2014b). Gone to Pot â€“ A Review of the Association between Cannabis and Psychosis. *Frontiers in psychiatry* 5.

- Radua J, Ramella-Cravaro V, Ioannidis JPA*, et al.* (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry* 17, 49-66.

- Reininghaus U, Böhnke JR, Hosang G*, et al.* (2018). Evaluation of the validity and utility of a transdiagnostic psychosis dimension encompassing schizophrenia and bipolar disorder. *British Journal of Psychiatry* 209, 107-113.

- Reininghaus U, Priebe S , Bentall RP (2012). Testing the Psychopathology of Psychosis: Evidence for a General Psychosis Dimension. *Schizophrenia Bulletin* 39, 884-895.

- Rössler W, Hengartner MP, Ajdacic-Gross V, Haker H, Gamma A , Angst J (2011). Sub-clinical psychosis symptoms in young adults are risk factors for subsequent common mental disorders. *Schizophrenia research* 131, 18-23.

- Ruhrmann S, Schultze-Lutter F, Salokangas RKR*, et al.* (2010). Prediction of Psychosis in Adolescents and Young Adults at High Risk. *Archives of general psychiatry* 67, 241.

- Saha S, Scott J, Varghese D , McGrath J (2012). Anxiety and depressive disorders are associated with delusional-like experiences: a replication study based on a National Survey of Mental Health and Wellbeing. *BMJ open* 2.

- Sauvé G, Brodeur MB, Shah JL , Lepage M (2019). The Prevalence of Negative Symptoms Across the Stages of the Psychosis Continuum. *Harvard Review of Psychiatry* 27, 15-32.

- Schmittmann VD, Cramer AOJ, Waldorp LJ, Epskamp S, Kievit RA , Borsboom D (2013). Deconstructing the construct: A network perspective on psychological phenomena. *New Ideas in Psychology* 31, 43-53.

- Schultze-Lutter F, Michel C, Ruhrmann S , Schimmelmann BG (2017). Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychological medicine* 48, 1167-1178.

- Schultze-Lutter F, Ruhrmann S, Berning J, Maier W , Klosterkotter J (2008). Basic Symptoms and Ultra-high Risk Criteria: Symptom Development in the Initial Prodromal State. *Schizophrenia Bulletin* 36, 182-191.

- Scott J, Chant D, Andrews G, Martin G , McGrath J (2018). Association between trauma exposure and delusional experiences in a large community-based sample. *British Journal of Psychiatry* 190, 339-343.

- Scotti-Muzzi E , Saide OL (2016). Schizo-obsessive spectrum disorders: an update. *CNS Spectrums* 22, 258-272.

- Shevlin M, McElroy E, Bentall RP, Reininghaus U , Murphy J (2017). The Psychosis Continuum: Testing a Bifactor Model of Psychosis in a General Population Sample. *Schizophrenia Bulletin* 43, 133-141.

- Simon AE , Umbricht D (2010). High remission rates from an initial ultra-high risk state for psychosis. *Schizophrenia Research* 116, 168-172.

- Smeets F, Lataster T, Viechtbauer W , Delespaul P (2015). Evidence That Environmental and Genetic Risks for Psychotic Disorder May Operate by Impacting on Connections Between Core Symptoms of Perceptual Alteration and Delusional Ideation. *Schizophrenia bulletin* 41, 687-697.

- Stefanis NC, Delespaul P, Smyrnis N*, et al.* (2004). Is the excess risk of psychosis-like experiences in urban areas attributable to altered cognitive development? *Social Psychiatry and Psychiatric Epidemiology* 39, 364-368.

- Stochl J, Khandaker GM, Lewis G*, et al.* (2014).

Mood, anxiety and psychotic phenomena measure a common psychopathological factor. *Psychological medicine* 45, 1483-1493.

- Tamminga CA, Ivleva EI, Keshavan MS*, et al.* (2013). Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *The American journal of psychiatry* 170, 1263-1274.

- Tsuang MT (1979). Long-term Outcome of Major Psychoses. *Archives of general psychiatry* 36, 1302.

- van Nierop M, van Os J, Gunther N*, et al.* (2011). Phenotypically Continuous With Clinical Psychosis, Discontinuous in Need for Care: Evidence for an Extended Psychosis Phenotype. *Schizophrenia bulletin* 38, 231-238.

- van Nierop M, Viechtbauer W, Gunther N*, et al.* (2014). Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries. *Psychological Medicine* 45, 1277-1288.

- van Os J (2013). The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. *The American journal of psychiatry* 170, 695-698.

- van Os J (2016). "Schizophrenia" does not exist. *BMJ* 352, i375.

- van Os J, Gilvarry C, Bale R*, et al.* (2000a). Diagnostic value of the DSM and ICD categories of psychosis: an evidence-based approach. UK700 Group. *Social psychiatry and psychiatric epidemiology* 35, 305-311.

- van Os J , Guloksuz S (2017). A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry* 16, 200-206.

- van Os J, Guloksuz S, Vijn TW, Hafkenscheid A , Delespaul P (2019). The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: time for change? *World psychi-*

atry : official journal of the World Psychiatric Association 18, 88-96.

- van Os J, Hanssen M, Bijl RV , Ravelli A (2000b). Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophrenia Research* 45, 11-20.

- van Os J , Kapur S (2009). Schizophrenia. *The Lancet* 374, 635-645.

- van Os J , Linscott RJ (2012). Introduction: The Extended Psychosis Phenotype--Relationship With Schizophrenia and With Ultrahigh Risk Status for Psychosis. *Schizophrenia bulletin* 38, 227-230.

- van Os J, Linscott RJ, Myin-Germeys I, Delespaul P , Krabbendam L (2008). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological Medicine* 39, 179-195.

- van Os J , Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World psychiatry : official journal of the World Psychiatric Association* 15, 118-124.

- van Os J, van der Steen Y, Islam MA, Guloksuz S, Rutten BP , Simons CJ (2017). Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. *Psychological medicine* 47, 2421-2437.

- van Os J, Verdoux H, Maurice-Tison S, *et al.* (1999). Self-reported psychosis-like symptoms and the continuum of psychosis. *Social Psychiatry and Psychiatric Epidemiology* 34, 459-463.

- van Os J, Wright P , Murray RM (1997). Follow-up studies of schizophrenia I: Natural history and non-psychopathological predictors of outcome. *European Psychiatry* 12, 327s-341s.

- van Rossum I, Dominguez MdG, Lieb R, Wittchen HU , van Os J (2009). Affective Dysregulation and Real-

ity Distortion: A 10-Year Prospective Study of Their Association and Clinical Relevance. *Schizophrenia Bulletin* 37, 561-571.

- Varese F, Smeets F, Drukker M*, et al.* (2012). Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies. *Schizophrenia bulletin* 38, 661-671.

- Varghese D, Scott J, Welham J*, et al.* (2009). Psychotic-Like Experiences in Major Depression and Anxiety Disorders: A Population-Based Survey in Young Adults. *Schizophrenia Bulletin* 37, 389-393.

- Verdoux H, Van Os J, Maurice-Tison S, Gay B, Salamon R , Bourgeois ML (1999). Increased occurrence of depression in psychosis-prone subjects: A follow-up study in primary care settings. *Comprehensive Psychiatry* 40, 462-468.

- Walss-Bass C, Werbeloff N, Dohrenwend BP*, et al.* (2015). The Association between Negative Symptoms, Psychotic Experiences and Later Schizophrenia: A Population-Based Longitudinal Study. *PloS one* 10, e0119852.

- Werbeloff N (2012). Self-reported Attenuated Psychotic Symptoms as Forerunners of Severe Mental Disorders Later in Life. *Archives of general psychiatry* 69, 467.

- Wigman JTW, van Nierop M, Vollebergh WAM*, et al.* (2012). Evidence That Psychotic Symptoms Are Prevalent in Disorders of Anxiety and Depression, Impacting on Illness Onset, Risk, and Severity--Implications for Diagnosis and Ultra-High Risk Research. *Schizophrenia bulletin* 38, 247-257.

- Woodberry KA, Seidman LJ, Bryant C*, et al.* (2016). Treatment Precedes Positive Symptoms in North American Adolescent and Young Adult Clinical High Risk Cohort. *Journal of Clinical Child & Adolescent Psychology* 47, 69-78.

- Yung AR , Nelson B (2011). Young people at ultra high risk for psychosis: a re-

search update. *Early Intervention in Psychiatry* 5, 52-57.

- Zammit S, Kounali D, Cannon M, *et al.* (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *The American journal of psychiatry* 170, 742-750.

- Zipursky RB, Reilly TJ , Murray RM (2013). The myth of schizophrenia as a progressive brain disease. *Schizophrenia Bulletin* 39, 1363-1372.

CHAPTER 2

Izmir mental health cohort for gene-environment interaction in psychosis (Türksch): Assessment of the extended and transdiagnostic psychosis phenotype and analysis of attrition in a six years follow-up of a community-based sample

Umut Kırlı [1, 2]

Tolga Binbay [3]

Hayriye Elbi [4]

Marjan Drukker [2]

Bülent Kayahan [4]

Ferda Özkınay [5]

Hüseyin Onay [5]

Köksal Alptekin [3]

Jim van Os[2, 6, 7]

Frontiers in Psychiatry 2019; 10, 554 DOI: 10.3389/fpsyt.2019.00554

[1] Yuzuncu Yil University, Faculty of Medicine, Department of Psychiatry, 65040, Van, Turkey

[2] Maastricht University Medical Centre, School of Mental Health and Neuroscience, Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, PO Box 616, Vijverdal, 6200 MD, Maastricht, The Netherlands

[3] Dokuz Eylul University, Faculty of Medicine, Department of Psychiatry, 35340, Izmir, Turkey

[4] Ege University, Faculty of Medicine, Department of Psychiatry, 35140, Izmir, Turkey

[5] Ege University, Faculty of Medicine, Department of Medical Genetics, 35140, Izmir, Turkey

[6] King's College, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, UK

[7] Dept. Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre, PO BOX 85500, 3508 GA Utrecht, The Netherlands.

Abstract

Objective: TürkSch is a prospective, longitudinal study in a representative community sample (İzmir, Turkey), consisting of several data collection stages, in order to screen and follow-up mental health outcomes with a special focus on the extended and transdiagnostic psychosis phenotype. The aim of the present paper is to describe the research methodology, data collection results and associations with non-contact and refusal in the longitudinal arm.

Methods: Households were contacted in a multistage clustered probability sampling frame covering 11 districts and 302 neighborhoods at baseline (n=4011) and at 6-year follow-up (n=2185). Both at baseline and at follow-up, participants were interviewed with the Composite International Diagnostic Interview. Participants with probable psychotic disorder were re-interviewed with the SCID-I either at the hospital or the participant's residence. Relevant neighborhood-level measures were assessed in a separate sample (n=5124) in addition to individual-level measures. Candidate gene-by-environment interactions were investigated using two nested case-control studies.

Results: Individuals with a mental health problem had lower refusal rates. Older and lower educated individuals had a lower probability of non-contact.

Discussion: The TürkSch study has an advanced design, in order to meet the challenges of evaluating the multidimensional etiological and phenomenological nature of the extended and transdiagnostic psychosis phenotype.

Introduction

After nearly two decades of epidemiological studies, there is evidence suggesting that psychosis is distributed as a spectrum (Linscott and van Os 2013). The spectrum of psychosis extends from the clinical psychotic syndrome to non-psychotic diagnoses with a degree of psychosis admixture and, finally, to non-clinical populations with subthreshold psychotic experiences (Kaymaz and van Os 2010;van Nierop *et al.* 2011;van Os and Linscott 2012). Thus, the *extended psychosis phenotype* is the range from psychotic experiences (PEs) gradually blending into psychotic disorders (PDs) (Kaymaz and van Os 2010).

The majority of individuals with PEs have a diagnosis of non-psychotic disorder. Conversely, high prevalence of PEs has been demonstrated in individuals with non-psychotic disorders where they can be considered as a marker of clinical severity (Guloksuz *et al.* 2015). Furthermore, PEs and non-psychotic disorders have been shown to predict subsequent occurrence of each other, bidirectionally (McGrath *et al.* 2016). It has been suggested that these findings point to *a transdiagnostic psychosis phenotype* in the general population (van Os and Reininghaus 2016).

To date, the definition of PEs and the type of screening instrument used have varied across studies (Kelleher *et al.* 2011), contributing to heterogeneity of results in this area. In the majority of studies, definitions of PEs were based on attenuated forms of delusional thinking and hallucinatory perceptions (van Os *et al.* 2009;Linscott and van Os 2013;Fonseca Pedrero and Debbane 2017). However, negative, disorganization and affective dimensions of psychosis have been identified in addition to the positive dimension. These dimensions should also be taken into account (van Os and Reininghaus 2016).

Longitudinal studies have demonstrated that PEs are mostly transitory. Persistent PEs have been associated with greater risk of need for care (Dominguez *et al.* 2009) and prolonged exposure

to environmental risks (childhood adversity, minority position, discrimination, urban upbringing and residency, stress in the wider social environment, substance misuse etc.), possibly interacting with genetic liability (Collip *et al.* 2007). Hence, a growing number of studies have tried to disentangle the components of interactions between genes and environment underlying the *extended and trans-diagnostic psychosis phenotype* (Dominguez *et al.* 2009;Wigman *et al.* 2012;Kelleher *et al.* 2013;Zammit *et al.* 2013). Although these studies provided new insights, most were not designed to specifically study the psychosis spectrum phenotype. Thus, risk factors included were not selected for their association with psychosis. In addition, factors in the wider social environment such as neighborhood-level risk factors were not included, and studies were not genetically sensitive, with a few notable exceptions (Linney *et al.* 2003;Hanssen *et al.* 2005;Polanczyk *et al.* 2010). Furthermore, diagnoses were mostly based on lay-interviewer assessments and re-interviews were mostly not performed by clinicians.

The Izmir Mental Health Survey for Gene-Environment Interaction in Psychosis (TürkSch) was therefore conducted to provide new insights into and knowledge of *the extended and trans-diagnostic psychosis phenotype,* and to identify effects of social-environmental risks in interaction with genetic background (Binbay *et al.* 2011;Binbay *et al.* 2012a;Binbay *et al.* 2012b).

The present paper describes the methods of the TürkSch follow-up. Furthermore, dynamic transitions over time in the extended psychosis phenotype are presented. Finally, the associations between various variables and non-contact/ refusal in the longitudinal arm are analyzed.

Methods

Overview of the Design of the TürkSch Cohort

TürkSch is a prospective, longitudinal study to screen and follow-up mental health outcomes in a representative general population sample of Izmir, Turkey. The TürkSch consists of two separate assessments (T_1 and T_2), and several stages of data

collection. The study assessed the prevalence of the extended psychosis phenotype. In addition, associations between various individual-level variables and the extended psychosis phenotype were investigated (*stage 1, T_1*). Associations between neighborhood-level variables (e.g. socioeconomic deprivation and social capital of neighborhoods) and the extended psychosis phenotype were assessed by a separate data collection independent from the main data collection (*stage 2, T_1, n=5124*). Furthermore, a nested case-control study recruited individuals with PEs and PDs as well as individuals with no psychotic symptoms from stage 1, and included blood sampling for analysis of gene-environment interactions (*stage 3, T_1*).

Six years after baseline, mental health and environmental exposure were assessed (*stage 4, T_2*). Finally, a longitudinal nested case-control study recruited individuals using the results of *stage 1 and 4*, and blood samples were collected for further genetic analysis (*stage 5, T_2*). The TürkSch study was approved by the Institutional Ethics Review Board of Ege University, Turkey, and is compliant with the precepts of the Declaration of Helsinki. Each participant provided written informed consent for examination and procedures.

Sample

At baseline, The Turkish Institute of Statistics (TurkStat) randomly selected 6000 households representative of the Izmir metropolitan area, using a multistage sampling procedure stratified by urbanicity in four categories, and covering 11 districts and 302 neighborhoods. Addresses were contacted in person. One household member aged between 15 and 64 years and available to complete the interview was randomly selected using the Kish within-household sampling method (Kish 1949). Out of 6000 addresses, 5242 households were eligible for interview. A total of 4011 individuals were successfully interviewed, yielding a response rate of 76.5% in *stage 1*. Response was higher in older age groups and in females. Full details on the Izmir metropoli-

tan area, sampling, representativeness, instruments, procedures of T_1 and the map of neighborhoods included can be found in a previous article (Binbay *et al.* 2011). Participants and addresses of T_1 formed the targeted population for T_2.

Fieldwork

Follow-up assessments (T_2) were performed approximately six years after the baseline assessments (T_1). To optimize response, T_2 fieldwork was spread over a relatively long period (2 years) so that there was sufficient time to re-contact potential respondents. At T_2, addresses of T_1 participants were visited in person by trained lay-interviewers with a brochure reminding the study, providing results from baseline, seeking participation for a new interview, and explaining the study goals in detail. The brochure also referred to a website, full names of the study team, and a phone number of the research office. If the participant could not be reached at the address, the study team telephoned the participants using numbers from T_1. In these calls, the team ascertained whether the participant was reachable, and if this was the case, appointments were made for face to face interviews. Any contact information of the participants who could not be reached was collected by asking neighbors in the area or the neighborhood authorities. If additional information was obtained, the person was contacted at the new contact address. Any T_1 participant was defined as 'unreachable' at T_2 after at least three consecutive visits to the address.

Interviewers, interviewer training and quality control

At T_1, lay interviewers had at least high school education, a health-related profession, and/or were experienced in doing field surveys. At T_2, lay interviewers were psychology graduates. At T_2, both the lay interviewers and the psychiatrist who conducted the clinical re-interviews (UK) had not participated at T_1, and thus were blind to baseline results. At both assessments, lay interview-

ers had a two-week formal training which included basic information on common mental disorders, symptom dimensions of psychosis, and ethical aspects of the project, as well as practical training. The field work was closely monitored by the study team (UK, TB, HE, BK, KA). Each interview at T_1 and T_2 was conducted according to a standard procedure, with recording and quality coding. If any of the three following problems were determined: i) the quality of the interview was considered low ii) any missing value was present iii) there was a doubt on whether the endorsed symptom was a 'true' symptom, as described below, a phone call or a second visit (T_1 n= 392; T_2 n= 560) was planned by the study team. The missing values still present after the second visit were assessed by the psychiatrist following the clinical re-interview.

Screening Instrument

In order to assess mental health outcomes, screening was based on the relevant sections of the Composite International Diagnostic Interview (CIDI) 2.1 (Andrews and Peters 1998). The CIDI is a fully structured interview developed by the World Health Organization (WHO) (Robins 1988) and has been used in various surveys around the world, including ones in Turkey (Cilli and Kaya 2003;Deveci *et al.* 2007;Alptekin *et al.* 2009). Primarily designed for use in epidemiological studies of mental disorders, the CIDI can be used by both clinicians and trained interviewers. CIDI-based screening of symptoms provides diagnoses in accordance with the definitions and criteria of the International Classification of Diseases, Tenth Revision (ICD-10), and the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV), along with information about frequency, duration, help-seeking, severity of symptoms, and psychosocial impairment. CIDI 2.1 has organic exclusion rules, which are used to construct final diagnoses, for each endorsed symptom, in order to ascertain that symptoms were not exclusively due to a somatic cause, an injury, or use of drugs, alcohol or medication. Previous research reported acceptable-to-good concordance between the CIDI 2.1 diagnoses and blind clinical diagnoses

(Andrade *et al.* 2003;Kessler *et al.* 2004;Kessler *et al.* 2010). The CIDI was found to have excellent inter-rater reliability in almost all sections with kappa values ranging from 0.67 to 0.97 (Wittchen *et al.* 1991). In particular, kappa for agreement between clinicians for delusions and hallucinations was found to be 0.85 and 0.87, respectively. Furthermore, the sensitivity of the CIDI was found to be higher than its specificity for both delusions (0.93 vs. 0.55) and hallucinations (0.86 vs. 0.50) (Cooper *et al.* 1998). The reliability and validity functions of the Turkish version of the CIDI were studied as part of an international study (Rezaki *et al.* 1995).

Mental health screening at both T_1 and T_2 included CIDI screening sections on alcohol and substance-related disorders, depressive and dysthymic disorders, manic and bipolar affective disorders, schizophrenia and other PDs, posttraumatic stress disorder, and 2 final sections containing concluding questions, interviewer observations, and interviewer ratings (Binbay *et al.* 2011). The time frame of the T_2 CIDI interview was the last six years

Assessment of the Dimensions of Psychosis

Assessment of the positive dimension was based on 14 CIDI delusions items (G1, G2, G3, G4, G5, G7, G8, G9, G10, G11, G12, G13, G13b and G14) and 5 CIDI hallucinations items (G17, G18, G20, G20C, and G21). All items were rated dichotomously indicating presence or absence. Rating of the PEs can be difficult because sometimes individuals can be describing a plausible event or a religious or superstitious belief that in the CIDI may be rated as a PE. Therefore, the following procedure was followed. First, during the interview, each time a participant endorsed a CIDI PE, the participant was asked to give an example, which was written down verbatim by the interviewer for later review with the mental health clinician on the team. All CIDI interviews were reviewed by the study team. When it was not clear whether or not the participant had truly endorsed a positive PE, the participant was re-contacted by a clinician over the telephone to

confirm the PE. Thus, delusional and hallucinatory experiences were coded positive if the team clinician confirmed the PE at review. Our results showed that the inter-rater reliability of the CIDI psychosis section had a kappa value of 0.45 at T_1 (Binbay *et al.* 2011) and 0.67 at T_2.

Assessment of the negative and disorganization dimensions were based CIDI P section which is on interviewer observations. The negative dimension was based on 4 symptom items (flat affect, slow speech, poverty of speech, and impaired ability to initiate activity) and the disorganization dimension was based on 3 symptom items (neologism, thought disorder, and hallucinatory behavior).

Assessment of the affective dimension was based on CIDI section E (depressive and dysthymic disorders) and section F (manic and bipolar affective disorders). For depression, participants were asked if they had experienced an episode lasting at least two weeks during which they felt depressed, or had a lack of interest. If endorsed, participants were asked if, during this period, they had experienced lack of energy, appetite change, sleep problems, being slow or restless, feelings of worthlessness or guilt, decreased self-esteem, trouble thinking or indecisiveness, and thoughts of death. For manic and hypomanic episodes, participants were asked whether they had experienced elevated mood or irritability for a period of at least four consecutive days either noticed by others or causing problems. If this was the case, participants were asked if, during this period, they had experienced excessive goal-directed activity, psychomotor agitation, spending sprees, sexual indiscretions, increased talkativeness, flight of ideas, loss of normal social inhibitions, increased self-esteem or grandiosity, decreased need for sleep, and distractibility. For both depressive and manic episodes, the final assessment included questions on probable association of symptoms with substance use or physical illness, help-seeking due to symptoms, the route of help-seeking, clinician diagnosis, and treatment history. All responses were re-evaluated by a team of clinicians.

Depressive episode and hypomanic/manic episode were coded positive in accordance with the definitions and criteria of DSM-IV.

Diagnostic Interviews and Construction of the Extended Psychosis Phenotype

At both T_1 and T_2, sections were devoted to define patterns of help-seeking for mental health problems. Questions included any self-report mental problem, help-seeking for a mental problem, the route of help-seeking, the probable outcome of the help-seeking (diagnosis), as well as prescribed medicines and any hospitalization over the time frame (lifetime and last 12 months at T_1 and last six years at T_2). If this was the case, the person was asked for permission to contact the clinician involved in the diagnosis or the treatment of the participant in order to verify the diagnosis and review case material.

A measure of impairment associated with PEs was defined using CIDI items G25 (duration of the PE: between 1 day and 6 months or more), G26, G28, G29 and G29A (level of dysfunction), G16 and G23 (told doctor about psychotic beliefs) (Binbay *et al.* 2012a;Binbay *et al.* 2012b). Furthermore, *a probable PD case* was defined if any of the following screening findings were endorsed:

1) Any self-reported diagnosis of psychotic or bipolar disorder

2) Any self-reported hospitalization due to a mental health problem

3) Any self-reported medication of any antipsychotic (typical or atypical) and/or lithium or mood-stabilizing anticonvulsant drugs

4) In the CIDI section F for bipolar disorder: a lifetime manic episode

5) In the CIDI section G for positive dimension: any clinically relevant positive PE (led to dysfunction or help-seeking), or at least 3 symptoms regardless of clinical relevance. If the participant had a clinically relevant positive PE at T_1, he/she was directly defined as a *probable case* regardless of the CIDI endorsement at T_2.

6) In the CIDI section P for negative and disorganization dimensions: a rating of positive formal thought disorder, negative symptoms, behavior that suggests the person is having hallucinations, or catatonic symptoms; or the interviewer comments were indicative of a PD.

If a participant was deemed to have a diagnosis of *probable PD* according to the algorithm mentioned above, the participant was re-contacted by the team psychiatrist and invited to the hospital for a clinical evaluation with the Structured Clinical Interview for DSM-IV (SCID) (Spitzer 1992). When the participant did not attend the hospital, clinical interviews were conducted at the participant's residence by the psychiatrist. Thus, 225 participants at T_1 and 263 participants at T_2 were clinically re-interviewed in order to identify participants with PD.

An *extended psychosis phenotype* variable was constructed including 4 categories using the SCID results and *the measure of impairment associated with PEs. The psychotic disorder group* included all individuals diagnosed with any DSM-IV disorder with psychotic features. *The clinical PE group* included individuals who had a CIDI PE leading to any of the 7 CIDI impairment items but who did not have a diagnosis of a PD. *The subclinical PE group* included individuals with a CIDI PE not leading to any distress, impairment or help-seeking. All other individuals were included in the *'no psychosis'* category. The flowchart of the assessment of the extended psychosis phenotype and the numbers of individuals in each group are presented in Figure 1

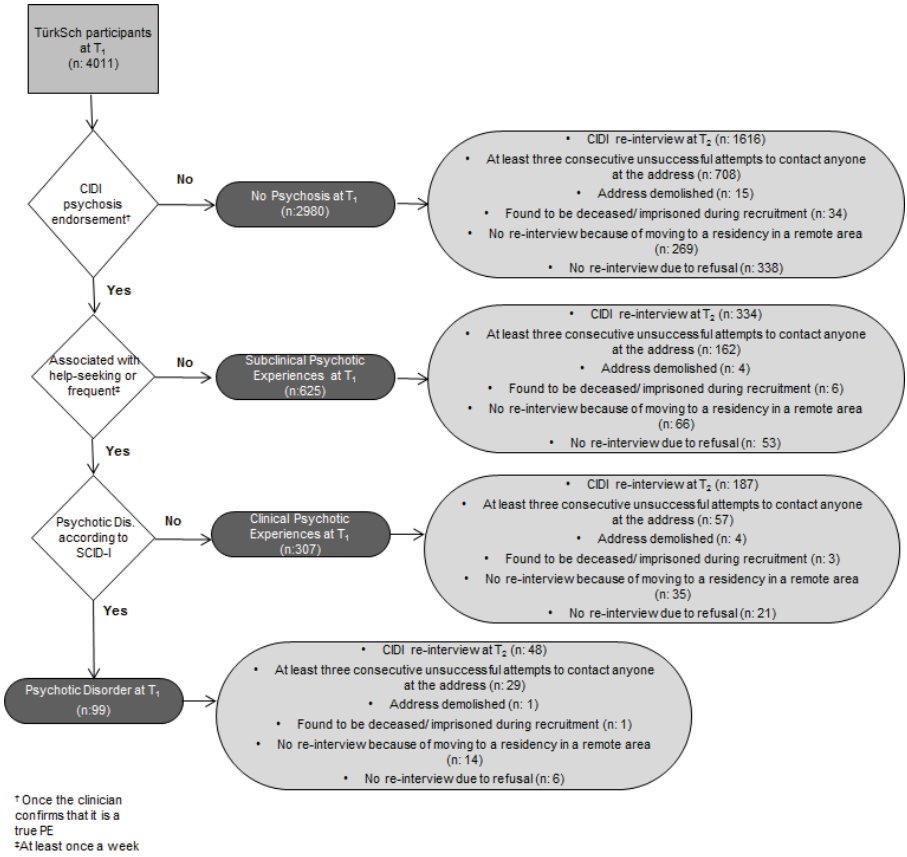


Figure 1: Assessment of the extended psychosis phenotype and data collection results at follow-up

Assessment of Environmental Exposures at the Individual Level

A sociodemographic questionnaire was included at T_2 in order to determine temporal changes in background characteristics (*age, educational status, marital status, employment, socioeconomic status, health insurance, housing, and monthly household income*). The T_1 interview also included *educational and occupational status of parents, birth year of parents, migration pattern and probable reasons for migration, ethnic group, and any history of early childhood adversity (parental loss, divorce, separation). Socioeconomic status* was estimated using profession and recoded into 4 ordinal categories (1: I and II professional

and IIIA non-manual high employees, 2: IIIB non-manual low employee and V and VI skilled workers and technicians, 3: IVA, IVB, and IVC owners of small businesses, and 4: VIIA and B manual workers (Binbay *et al.* 2012b;Goldthorpe 2016).

The variable *'traumatic events'* was obtained using the post-traumatic stress disorder section of the CIDI. The events were war experience, life-threatening accident, fire, flood or other natural disaster, witnessing someone being badly injured or killed, rape, sexual molestation, being physically attacked or assaulted. Furthermore, the interview included the *List of Threatening Life Events* (Brugha and Cragg 1990) so as to cover most of the stressful life events experienced by individuals. *Threatening life events* were a serious illness, injury or an assault (suffering or happening to a close relative); death of a relative or a close friend, divorce, separation, serious problems with a relative/ neighbor/ close friend, being dismissed from the job, unemployment, major financial problems, police/ court appearance. Time frame was the last six years.

Alcohol, cannabis and other substance use were assessed using screening questions on CIDI alcohol and substance-related disorders section (Ulaş *et al.* 2017). Using information from both T_1 and T_2, the continuum of alcohol, cannabis and other substance use during the follow-up period was defined.

Assessment of Neighborhood-Level Measures

At T_1, urbanicity (birth place, places of residence at age 0-15 years, and current place of residence) were assessed. In a separate sample, socioeconomic deprivation and the social capital of the resided neighborhoods were assessed (Binbay *et al.* 2011). T_2 assessment included questions on changes in place of residence. Furthermore, *the description of the visited neighborhood and building* was coded by the interviewer in five categories (village/ slum /semi-urban/ urban/ luxury area). *Urbanicity*

of the place of residence was defined using the classification of the Turkish Institute of Statistics (TurkStat). The classification depended on the level of organized features of streets and buildings (regularity of sidewalks, status of road, completeness of drainage system, and quality of outer paintings of buildings, etc.) (Binbay *et al.* 2012a). *Social capital of the neighborhood* was assessed using two assessments: *informal social control and social disorganization*. Questions on *informal social control* were derived from the Sampson collective efficacy scale (Sampson 1997), adapted for use in the Turkish population (Binbay *et al.* 2012a). The informal social control scale measures the willingness to intervene in hypothetical neighborhood threatening situations, for example, in the case of children misbehaving. The items were assessed using a five-point Likert scale ranging from ' strongly agree ' to 'strongly disagree'. Eight items assessing the *social disorganization* were derived from the McCulloch instrument (Buckner 1988;McCulloch 2003). Respondents rated the frequency of certain scenarios occurring in their neighborhood (presence of graffiti, teenagers on street, vandalism, attacks due to race or skin color, other attacks, burglary and the theft of, or from, vehicles). Each item was assessed using a four-point Likert scale ranging from 'very common' to 'not at all common' (Binbay *et al.* 2012a).

Assessment of Familial Measures

Using questions derived from the Family Interview for Genetic Studies (NIMH 1992), history of mental disorders in the father, mother, siblings, and offspring was assessed. Thus, *a family history of mental disorders variable* was defined and coded guided by previous literature (Mortensen *et al.* 2010): 0=No or undefined family history of mental disorders; 1=Common mental disorder (depression/anxiety disorders) in at least one family member but no severe mental illness; 2=Severe mental illness (bipolar disorder/ psychotic disorder/ hospitalization/ completed suicide) in at least one family member (Binbay *et al.* 2012b).

Blood Sampling and Assessment of Candidate Gene-Environment Interactions

At $T_{1,}$ a nested case-control study (*stage 3*, n=366) recruited individuals with PEs and PDs as well as individuals with no psychotic symptoms in order to investigate gene-environment interactions in the extended and trans-diagnostic psychosis phenotype. In this subgroup, catechol-O-methyltransferase (*COMT*) val158met (rs4680) and brain-derived neurotrophic factor (*BDNF*) val66met (rs6265) polymorphisms were assessed besides the clinical re-appraisals and exposures, mentioned above. At $T_{2,}$ environmental exposures for the last six years were assessed followed by clinical re-appraisals in eligible individuals (n=254).

At T_2, data subjects were selected for a second nested case-control study (*stage 5*) using the results of both T_1 and T_2. First, 200 individuals with any psychotic symptoms (either PE or PD) at either T_1 or T_2 were randomly selected. Then, these individuals were matched with 200 individuals who participated in both T_1 and T_2, and had no psychotic symptoms (neither PE nor PD) during the follow–up period. Matching variables were age, gender and neighborhood. The selected individuals were asked to provide a blood sample for further genetic analysis as well as clinical re-appraisals. A total of 174 individuals with any psychotic symptom (61 with PD; 113 with PE) and 151 individuals with no psychotic symptoms during follow-up provided a blood sample. In these samples, *BDNF* and Neuregulin 1 (*NRG1*) whole gene sequence analysis procedure was conducted. Results were evaluated considering the environmental exposure results at both T_1 and T_2.

Statistical Analysis

In order to evaluate differential attrition over time, a two-step analysis was performed. First, a multinomial logistic regression model was performed (dependent variable with 3 categories: 0 = respondent, 1 = noncontact, 2 = refusal) in order to examine the role of baseline socio-demographics, psychopathology and environmental exposure variables on the association with the two types of attrition, separately. These associations were expressed as relative risk ratios (RRR) and their 95% confidence intervals. Then, the overall effects of the abovementioned vari-

ables on attrition were tested using chi-squared tests and the relevant effect size measure (Cramer's *V*). Cramer's *V* equals 0 when there is no relationship between the two variables, and has a maximum value of 1. A larger value for Cramer's *V* indicated a stronger relationship between the variables.

Results

Data collection results

At T_2, 954 individuals from the baseline sample could not be contacted (i.e. after at least three consecutive attempts to contact anyone at the address), and 386 individuals were lost to follow-up because of moving to a residency in a remote area. Forty-four individuals were deceased or imprisoned and 24 addresses were demolished. Furthermore, 418 individuals refused to participate in the follow-up assessment. As a result, a total of 2185 individuals were successfully re-interviewed at T_2. Figure 1 shows details of the data collection results at T_2 stratified by the baseline position across the extended psychosis phenotype. Dynamic transitions over time in the extended psychosis phenotype are presented in Figure 2.

Associations with the two types of attrition (non-contact and refusal)

Attrition due to non-contact was significantly higher in individuals who were younger, non-married, more highly educated,

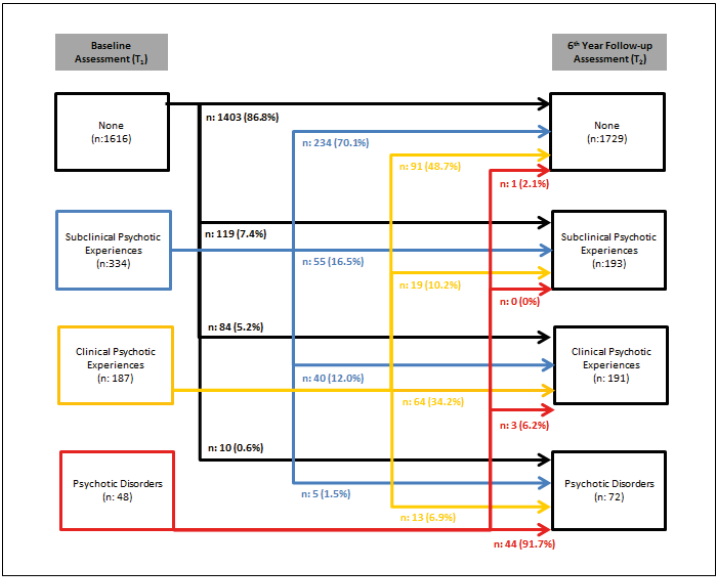


Figure 2: Dynamic transitions over time in the extended psychosis phenotype

non-helpseeking, without a valid health insurance and using cannabis and regular alcohol. The probability of *refusal* was significantly higher in individuals who were in paid employment, single, more educated and with higher socioeconomic status. Furthermore, *refusal* was lower in individuals with a baseline mood disorder, a baseline clinical PE, a history of a traumatic event, and a family history of a severe mental illness (table 1). However, analysis of overall effect on attrition showed that the

Table 1: Association between the Two Types of Attrition (Refusal/Noncontact) and Baseline Characteristics

	Respondents	Non-Contact		Refusal		Overall Effect on Attrition	
	n (%)	**n (%)**	**RRR (95%CI)**	**n (%)**	**RRR (95%CI)**	**χ^2 (df)**	**Cramer's *V***
Sociodemographic Characteristics							
Sex							
Male	890 (52.9)	612 (36.4)	1	181 (10.7)	1	3.0 (2)	0.03
Female	1295 (55.6)	796 (34.2)	0.89 (0.78-1.02)	237 (10.2)	0.89 (0.72-1.11)		
Age							
46-65	699 (49.0)	591 (41.5)	1	135 (9.5)	1	48.9 (4)**	0.08
31-45	750 (54.7)	468 (34.1)	1.31** (1.10-1.56)	153 (11.2)	1.15 (0.89-1.49)		
15-30	736 (60.6)	349 (28.7)	1.78** (1.50-2.10)	130 (10.7)	1.09 (0.84-1.42)		
Educational Level							
Basic	966 (58.2)	543 (32.7)	1	151 (9.1)	1	17.9 (4)**	0.05
High School	360 (52.0)	261 (37.7)	1.28** (1.06-1.56)	71 (10.3)	1.26 (0.92-1.71)		
University	859 (51.8)	604 (36.4)	1.25** (1.07-1.45)	196 (11.8)	1.45** (1.15-.1.83)		
Marital Status							
Married	1638 (57.7)	912 (32.1)	1	289 (10.2)	1	52.0 (4)**	0.08
Single	458 (47.0)	400 (41.0)	1.56** (1.34-1.83)	117 (12.0)	1.44** (1.14-1.83)		
Divorced	89 (45.2)	96 (48.7)	1.93** (1.43-2.61)	12 (6.1)	0.76 (0.41-1.41)		
Ethnicity							
Turkish	1840 (54.6)	1175 (34.8)	1	358 (10.6)	1	1.2 (2)	0.02
Non-Turkish	345 (54.1)	233 (36.5)	1.05 (0.88-1.26)	60 (9.4)	0.89 (0.66-1.20)		
Employment Status							
In paid employment	1020 (54.4)	639 (34.0)	1	218 (11.6)	1	5.9 (2)	0.04
Not in paid employment	1165 (54.6)	769 (36.0)	1.05 (0.92-1.21)	200 (9.4)	0.80* (0.65-0.99)		
Health Insurance							
Present	1949 (55.6)	1174 (33.5)	1	381 (10.9)	1	32.3 (2)**	0.09
Absent	236 (46.6)	234 (46.1)	1.64** (1.35-2.00)	37 (7.3)	0.80 (0.55-1.15)		
Socioeconomic status							
1	466 (54.4)	280 (32.7)	1	111 (12.9)	1	17.6 (6)**	0.05
2	585 (54.1)	382 (35.3)	1.08 (0.89-1.32)	115 (10.6)	0.82 (0.61-1.10)		
3	352 (51.9)	246 (36.3)	1.16 (0.93-1.44)	80 (11.8)	0.95 (0.69-1.10)		
4	782 (56.1)	500 (35.9)	1.06 (0.88-1.28)	112 (8.0)	0.60** (0.45-0.80)		

Baseline Clinical Characteristics							
Mental help-seeking							
None	1872 (53.7)	1242 (35.7)	1	370 (10.6)	1	5.9 (2)	0.04
Yes	313 (59.4)	166 (31.5)	0.79* (0.65-0.97)	48 (9.1)	0.77 (0.56-1.07)		
Baseline Mood Disorder							
None	1783 (54.2)	1143 (34.8)	1	363 (11.0)	1	7.5 (2)*	0.04
Yes	402 (55.7)	265 (36.7)	1.02 (0.86-1.22)	55 (7.6)	0.67** (0.49-0.91)		
Baseline Cannabis							
None	2161 (54.7)	1377 (34.8)	1	413 (10.5)	1	7.4 (2)*	0.04
>5 times	24 (40.0)	31 (51.7)	2.02** (1.18-3.46)	5 (8.3)	1.09 (0.41-2.87)		
Baseline Alcohol							
< Once a week	2055 (55.2)	1285 (34.5)	1	383 (10.3)	1	11.0 (2)**	0.05
At least once a week	130 (45.1)	123 (42.7)	1.51** (1.17-1.95)	35 (12.2)	1.44 (0.97-2.13)		
Traumatic event							
None	1383 (53.5)	903 (34.9)	1	298 (11.5)	1	9.9 (2)**	0.05
At least one	802 (56.2)	505 (35.4)	0.96 (0.83-1.10)	120 (8.4)	0.69** (0.55-0.87)		
Family History							
None or unknown	1903 (54.0)	1245 (35.3)	1	379 (10.7)	1	9.4 (4)	0.03
Common mental disorder	222 (56.8)	132 (33.8)	0.90 (0.72-1.14)	37 (9.5)	0.83 (0.58- 1.20)		
Severe Mental Illness	60 (64.5)	31 (33.3)	0.78 (0.50-1.22)	2 (2.2)	0.16* (0.04-0.68)		
Extended Psychosis Phenotype							
No PE	1616 (54.2)	1026 (34.4)	1	338 (11.4)	1	19.1 (6)**	0.05
Subclinical PE	334 (53.4)	238 (38.1)	1.12 (0.93- 1.34)	53 (8.5)	0.75 (0.55-1.03)		
Clinical PE	187 (60.9)	99 (32.3)	0.83 (0.64-1.07)	21 (6.8)	0.53** (0.33-0.85)		
Psychotic Disorder	48 (48.5)	45 (45.4)	1.47 (0.97-2.23)	6 (6.1)	0.59 (0.25-1.40)		
Baseline Clinical Characteristics							
Mental help-seeking							
None	1872 (53.7)	1242 (35.7)	1	370 (10.6)	1	5.9 (2)	0.04
Yes	313 (59.4)	166 (31.5)	0.79* (0.65-0.97)	48 (9.1)	0.77 (0.56-1.07)		
Baseline Mood Disorder							
None	1783 (54.2)	1143 (34.8)	1	363 (11.0)	1	7.5 (2)*	0.04
Yes	402 (55.7)	265 (36.7)	1.02 (0.86-1.22)	55 (7.6)	0.67** (0.49-0.91)		
Baseline Cannabis							
None	2161 (54.7)	1377 (34.8)	1	413 (10.5)	1	7.4 (2)*	0.04
>5 times	24 (40.0)	31 (51.7)	2.02** (1.18-3.46)	5 (8.3)	1.09 (0.41-2.87)		
Baseline Alcohol							
< Once a week	2055 (55.2)	1285 (34.5)	1	383 (10.3)	1	11.0 (2)**	0.05
At least once a week	130 (45.1)	123 (42.7)	1.51** (1.17-1.95)	35 (12.2)	1.44 (0.97-2.13)		
Traumatic event							
None	1383 (53.5)	903 (34.9)	1	298 (11.5)	1	9.9 (2)**	0.05
At least one	802 (56.2)	505 (35.4)	0.96 (0.83-1.10)	120 (8.4)	0.69** (0.55-0.87)		
Family History							
None or unknown	1903 (54.0)	1245 (35.3)	1	379 (10.7)	1	9.4 (4)	0.03
Common mental disorder	222 (56.8)	132 (33.8)	0.90 (0.72-1.14)	37 (9.5)	0.83 (0.58- 1.20)		
Severe Mental Illness	60 (64.5)	31 (33.3)	0.78 (0.50-1.22)	2 (2.2)	0.16* (0.04-0.68)		
Extended Psychosis Phenotype							
No PE	1616 (54.2)	1026 (34.4)	1	338 (11.4)	1	19.1 (6)**	0.05
Subclinical PE	334 (53.4)	238 (38.1)	1.12 (0.93- 1.34)	53 (8.5)	0.75 (0.55-1.03)		
Clinical PE	187 (60.9)	99 (32.3)	0.83 (0.64-1.07)	21 (6.8)	0.53** (0.33-0.85)		
Psychotic Disorder	48 (48.5)	45 (45.4)	1.47 (0.97-2.23)	6 (6.1)	0.59 (0.25-1.40)		

*p<0.05, **p<0.001
Abbreviations: CI, confidence interval; RRR, relative risk ratio

associations with any independent variable had a Cramer's *V* value lower than 0.09, indicating very small effect sizes.

Discussion

The TürkSch study was conducted in a general population sample, representative of the urban and rural areas of the city of Izmir, representing the third most industrialized area of Turkey. The primary focus of the study was the *extended and transdiagnostic psychosis phenotype*, which was prospectively evaluated. Therefore, risk factors were chosen for their association with psychosis. Furthermore, the design of the study enabled us to assess the different symptom dimensions of psychosis (positive/ negative/ disorganization/ affective). The sample size was relatively large and included both helpseeking and non-helpseeking individuals, so we were able to prevent helpseeking bias (van Os and Guloksuz 2017). Furthermore, diagnostic interviews were performed by psychiatrists with individuals with positive screening results. Therefore, we could assess psychotic outcomes along a spectrum including both clinical and subclinical levels in the same sample. The assessments included family history as well as environmental exposures both at the individual and the neighborhood level. The inclusion of candidate gene-based genetic analysis provided the opportunity to longitudinally evaluate specific gene-environment interactions in psychosis along a spectrum of severity. In summary, design of the study enabled evaluation of the multidimensional etiological and phenomenological nature of the extended and transdiagnostic psychosis phenotype.

In spite of the strengths, the following limitations of the study should be noted. First, the relatively long period of time between the two data collection points (six years) might have decreased our ability to establish the course of psychosis in detail (Schlenger *et al.* 2015). Second, as with most longitudinal studies with general population-based samples, the possibility of bias caused by differential attrition over time was a limitation. However, the drop-out rate of participants in the current study is similar to studies using similar methodology (Domin-

guez *et al.* 2009;Zammit *et al.* 2013). Furthermore, the comparison of baseline characteristics between respondents, refusals and non-contacts showed no large differences. Third, the two nested case-control studies (stages 3 and 5) in which gene-environment interactions were investigated had small sample sizes and lack of genome-wide genetic summary measures. However, nested case-control studies are most optimal in case data can only be collected in a small subsample because a sufficient number of cases can be included. In addition, the broader outcome variable including the subclinical phenotypes and the longitudinal design may help to detect smaller effect sizes. Fourth, general population-based cohort studies represent the naturalistic course of illnesses. It cannot be ruled out that among other variables, treatment modifies the course of an illness. Although we obtained information about the treatment, we cannot rule out that this limitation impacted the results. Finally, as a consequence of the sampling method, both homeless and institutionalized persons could not be included, which may have affected the level of representativeness. However, as both groups are relatively small, effects would be negligible (Binbay *et al.* 2011).

Analyses of attrition showed interesting results. Unlike what we expected, individuals with a mental health problem at baseline had lower refusal rates at follow-up. Furthermore, there was a difference in the sociodemographic correlates of attrition compared to studies of similar design conducted in western countries, as these studies showed higher attrition rates in individuals with a lower SES and a lower educational level (Dominguez *et al.* 2009;de Graaf *et al.* 2013). It may be important to make special efforts to contact individuals who are younger, more educated, non-married, having regular alcohol and cannabis use and no history of mental health problems in future prospective studies.

Abbreviations

PE: Psychotic experience, PD: Psychotic disorder

References

- Alptekin K, Ulas H, Akdede BB, Tümüklü M , Akvardar Y (2009). Prevalence and risk factors of psychotic symptoms: in the city of Izmir, Turkey. *Social psychiatry and psychiatric epidemiology* 44, 905-910.

- Andrade L, Caraveo-anduaga JJ, Berglund P, *et al.* (2003). The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) surveys. *International Journal of Methods in Psychiatric Research* 12, 3-21.

- Andrews G , Peters L (1998). The psychometric properties of the Composite International Diagnostic Interview. *Social psychiatry and psychiatric epidemiology* 33, 80-88.

- Binbay T, Drukker M, Alptekin K, *et al.* (2012a). Evidence that the wider social environment moderates the association between familial liability and psychosis spectrum outcome. *Psychological Medicine* 42, 2499-2510.

- Binbay T, Drukker M, Elbi H, *et al.* (2012b). Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophrenia bulletin* 38, 992-1002.

- Binbay T, Elbi H, Alptekin K, *et al.* (2011). Izmir Mental Health Survey for Gene-Environment in Psychoses (TurkSch): Objectives and Methodology. *Turkish Journal of Psychiatry*.

- Brugha TS , Cragg D (1990). The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta psychiatrica Scandinavica* 82, 77-81.

- Buckner JC (1988). The development of an instrument to measure neighborhood cohesion. *American Journal of Community Psychology* 16, 771-791.

- Cilli AS , Kaya N (2003). [Nicotine dependence and psychiatric comorbidity

among university students]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 14, 42-49.

- Collip D, Myin-Germeys I , Van Os J (2007). Does the Concept of "Sensitization" Provide a Plausible Mechanism for the Putative Link Between the Environment and Schizophrenia? *Schizophrenia bulletin* 34, 220-225.

- Cooper L, Peters L , Andrews G (1998). Validity of the Composite International Diagnostic Interview (CIDI) psychosis module in a psychiatric setting. *Journal of psychiatric research* 32, 361-368.

- de Graaf R, van Dorsselaer S, Tuithof M , ten Have M (2013). Sociodemographic and psychiatric predictors of attrition in a prospective psychiatric epidemiological study among the general population. Result of the Netherlands Mental Health Survey and Incidence Study-2. *Comprehensive psychiatry* 54, 1131-1139.

- Deveci A, Taskin O, Dinc G, *et al.* (2007). Prevalence of pseudoneurologic conversion disorder in an urban community in Manisa, Turkey. *Social psychiatry and psychiatric epidemiology* 42, 857-864.

- Dominguez MDG, Wichers M, Lieb R, Wittchen HU , van Os J (2009). Evidence That Onset of Clinical Psychosis Is an Outcome of Progressively More Persistent Subclinical Psychotic Experiences: An 8-Year Cohort Study. *Schizophrenia bulletin* 37, 84-93.

- Fonseca Pedrero E , Debbane M (2017). Schizotypal traits and psychotic-like experiences during adolescence: An update. *Psicothema* 29, 5-17.

- Goldthorpe JH (2016). Social class mobility in modern Britain: changing structure, constant process. *Journal of the British Academy* 4, 89-111.

- Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen HU , 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* 45, 2389-2401.

- Hanssen M, Bak M, Bijl R, Vollebergh W , Os J (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *British Journal of Clinical Psychology* 44, 181-191.

- Kaymaz N , van Os J (2010). Extended psychosis phenotype – yes: single continuum – unlikely. *Psychological Medicine* 40, 1963-1966.

- Kelleher I, Devlin N, Wigman JTW, *et al.* (2013). Psychotic experiences in a mental health clinic sample: implications for suicidality, multimorbidity and functioning. *Psychological Medicine* 44, 1615-1624.

- Kelleher I, Harley M, Murtagh A , Cannon M (2011). Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophrenia bulletin* 37, 362-369.

- Kessler RC, Berglund P, Chiu WT, *et al.* (2004). The US National Comorbidity Survey Replication (NCS-R): design and field procedures. *International Journal of Methods in Psychiatric Research* 13, 69-92.

- Kessler RC, Green JG, Gruber MJ, *et al.* (2010). Screening for serious mental illness in the general population with the K6 screening scale: results from the WHO World Mental Health (WMH) survey initiative. *International Journal of Methods in Psychiatric Research* 19, 4-22.

- Kish L (1949). A Procedure for Objective Respondent Selection within the Household. *Journal of the American Statistical Association* 44, 380-387.

- Linney YM, Murray RM, Peters ER, MacDonald AM, Rijsdijk F , Sham PC (2003). A quantitative genetic analysis of schizotypal personality traits. *Psychological Medicine* 33, 803-816.

- Linscott RJ , van Os J (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine* 43, 1133-1149.

- McCulloch A (2003). An examination of social capital and social disorganisation in neighbourhoods in the British household panel study. *Social Science & Medicine* 56, 1425-1438.

- McGrath JJ, Saha S, Al-Hamzawi A*, et al.* (2016). The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *American Journal of Psychiatry* 173, 997-1006.

- Mortensen PB, Pedersen MG , Pedersen CB (2010). Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychological Medicine* 40, 201-210.

- NIMH (1992). *NIMH Genetics Initiative: Family Interview for Genetic Studies (FIGS).* MD National Institute of Mental Health: Rockville.

- Polanczyk G, Moffitt TE, Arseneault L*, et al.* (2010). Etiological and Clinical Features of Childhood Psychotic Symptoms. *Archives of general psychiatry* 67, 328.

- Rezaki M, Ozgen G, Kaplan I, Gursoy B, Sagduyu A , Ozturk O (1995). Results from Ankara center. In *Mental Illness in General Health Care: An International Study* (ed. T. B. Ustun and N. Sartorius), pp. 39-56. John Willey & Sons: Chichester.

- Robins LN (1988). The Composite International Diagnostic Interview. *Archives of general psychiatry* 45, 1069.

- Sampson RJ (1997). Collective Regulation of Adolescent Misbehavior:Validation Results from Eighty Chicago Neighborhoods. *Journal of Adolescent Research* 12, 227-244.

- Schlenger WE, Corry NH, Kulka RA, Williams CS,

Henn-Haase C , Marmar CR (2015). Design and methods of the national Vietnam veterans longitudinal study. *International Journal of Methods in Psychiatric Research* 24, 186-203.

- Spitzer RL (1992). The Structured Clinical Interview for DSM-III-R (SCID). *Archives of general psychiatry* 49, 624.

- Ulaş H, Binbay T, Kırlı U, Elbi H , Alptekin K (2017). The epidemiology of alcohol use in Izmir, Turkey: drinking pattern, impairment and help-seeking. *Social Psychiatry and Psychiatric Epidemiology* 52, 887-899.

- van Nierop M, van Os J, Gunther N, *et al.* (2011). Phenotypically Continuous With Clinical Psychosis, Discontinuous in Need for Care: Evidence for an Extended Psychosis Phenotype. *Schizophrenia bulletin* 38, 231-238.

- van Os J , Guloksuz S (2017). A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry* 16, 200-206.

- van Os J , Linscott RJ (2012). Introduction: The Extended Psychosis Phenotype--Relationship With Schizophrenia and With Ultrahigh Risk Status for Psychosis. *Schizophrenia bulletin* 38, 227-230.

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

- van Os J , Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* 15, 118-124.

- Wigman JTW, van Nierop M, Vollebergh WAM, *et al.* (2012). Evidence That Psychotic Symptoms Are Prevalent in Disorders of Anxiety and Depression, Impacting on Illness Onset, Risk, and Severity--Implications for Diagnosis and Ultra-High Risk

Research. *Schizophrenia bulletin* 38, 247-257.

- Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD , Regier D (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British journal of psychiatry : the journal of mental science* 159, 645-653, 658.

- Zammit S, Kounali D, Cannon M, *et al.* (2013). Psychotic Experiences and Psychotic Disorders at Age 18 in Relation to Psychotic Experiences at Age 12 in a Longitudinal Population-Based Cohort Study. *American Journal of Psychiatry* 170, 742-750.

CHAPTER 3

Psychotic experiences and mood episodes predict each other bidirectionally: a 6-year follow-up study in a community-based population

Umut Kırlı [1, 2]

Tolga Binbay [3]

Marjan Drukker [2]

Jim van Os[2, 4, 5]

Köksal Alptekin [3]

Bülent Kayahan [6]

Hayriye Elbi [6]

Social Psychiatry and Psychiatric Epidemiology 2019; 54 (3): 331-341

[1] Van Education and Research Hospital, Psychiatry Unit, Van, Turkey

[2] Maastricht University Medical Centre, School of Mental Health and Neuroscience, Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, PO Box 616, Vijverdal, 6200 MD, Maastricht, The Netherlands

[3] Dokuz Eylul University, Faculty of Medicine, Department of Psychiatry, 35340, Izmir, Turkey

[4] King's College, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, UK

[5] Dept. Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre, PO BOX 85500, 3508 GA Utrecht, The Netherlands.

[6] Ege University, Faculty of Medicine, Department of Psychiatry, 35140, Izmir, Turkey

Abstract

Background: Psychotic experiences (PEs) are not exclusive to psychotic disorders and highly correlated with mood episodes. In this representative general population-based study, longitudinal bidirectional associations between the extended psychosis phenotype and mood episodes were investigated, accounting for other possible causes.

Methods: Households were contacted in a multistage clustered probability sampling frame covering 11 districts and 302 neighbourhoods at baseline (n=4011) and at 6-year follow-up (n=2185). Participants were interviewed with the relevant sections of the Composite International Diagnostic Interview (CIDI) both at baseline and at follow-up. Socio-demographic, familial and environmental risk factors associated with the extended psychosis phenotype and mood episodes were assessed. Logistic regression and cross-lagged panel correlation models were used for the associations between the extended psychosis phenotype and mood episodes

Results: PEs were associated with subsequent depressive and manic episodes. There was bidirectionality in that mood episodes were associated with subsequent PEs, and PEs were associated with subsequent mood episodes. The associations occurred in a sub-additive pattern. There were substantial synchronous and cross-lagged correlations between these psychopathology domains, with reciprocally similar cross-lagged correlations. Familial risk and adverse life events were associated with both psychopathology domains whereas some sociodemographic risk factors and alcohol/cannabis use were associated with only one domain.

Conclusion: The subadditive bidirectional associations between PEs and mood episodes over time and the similarity of cross-lagged correlations are suggestive of mutually causal connections between affective and psychotic domains of psychopathology.

Introduction

An extensive volume of literature suggests that psychotic experiences (PEs) are not exclusive to, and more common than psychotic disorders in the general population (van Os *et al.* 2009;Nuevo *et al.* 2012;Linscott and van Os 2013;McGrath *et al.* 2015).Cross-sectional studies have demonstrated high prevalence of PEs in individuals with mood disorders (Hanssen *et al.* 2003;Varghese *et al.* 2011;Kelleher *et al.* 2012;Saha *et al.* 2012). Conversely, mood disorders are prevalent in individuals with PEs (Armando *et al.* 2010;Kelleher *et al.* 2012). For example, among respondents with lifetime PEs, major depressive disorder was reported to be the most common disorder (25.4%) of the 21 DSM-IV mental disorders examined in the World Health Organization World Mental Health (WMH) Surveys (McGrath *et al.* 2016). Furthermore, research has shown that PEs and mood episodes may represent markers of severity of each other, bidirectionally driving poor outcome (Perlis *et al.* 2011;van Rossum *et al.* 2011;Kelleher *et al.* 2012;Wigman *et al.* 2012;Guloksuz *et al.* 2015a;Stochl *et al.* 2015). Despite these clues, few studies have examined the longitudinal associations between PEs and mood episodes and these studies have produced conflicting results. PEs have been associated with subsequent mood episodes among both adolescent (Dhossche *et al.* 2002;De Loore *et al.* 2011;Sullivan *et al.* 2014;Zavos *et al.* 2016) and adult populations (Rossler *et al.* 2011). However, a study with an adult sample found no association between PEs and subsequent depression (Fowler *et al.* 2012). Furthermore, mood episodes have been associated with subsequent PEs among both adolescent (Zavos *et al.* 2016) and adult populations (Fowler *et al.* 2012). However, another study with an adolescent sample found no association in this direction (Sullivan *et al.* 2014). The majority of the above-mentioned studies did not take familial liability and social/environmental covariates into account and this can be the reason for the observed inconsistency in results.

It has been suggested that psychopathology may be represented by overlapping and reciprocally impacting dimension-

al liabilities (e.g. psychotic, affective) (van Os and Linscott 2012). Phenomenologically, one of these dimensions might emerge, increasing the risk of the other. Given strong evidence linking the lifetime prevalence of PEs with high prevalence of mood episodes, we hypothesized that PEs and mood episodes would predict each other, bidirectionally over time. Furthermore, given evidence that co-occurrence of psychotic and affective domains may reflect general severity of multidimensional psychopathology, building up over time (van Rossum *et al.* 2011;van Os and Guloksuz 2017), the risk of subsequent psychopathology after PEs or mood episodes may be additive. Finally, meta-analysis of risk factors identified age, sex, education, marital status, alcohol use, cannabis use, life events, childhood adversity and family history of mental illness as important predictors of PEs (van Os *et al.* 2009;Linscott and van Os 2013). We hypothesized that a substantial part of these risk factors would be shared between PEs and mood episodes.

The first aim of this paper was to analyse the bidirectional associations between PEs and mood episodes; over a 6 years period, in a general population sample. The second aim was to analyse if baseline PEs would combine synergistically (on an additive scale) with baseline mood episodes to increase odds of subsequent PEs and mood episodes. The third aim was to evaluate the differential effect of risk factors on PEs and mood episodes.

Methods

Sample and Study Design

The TürkSch, Izmir Mental Health Survey for Gene-Environment Interaction in Psychosis is a longitudinal, general population-based study covering a time frame of approximately 6 years. The main objective of the TürkSch is to assess prevalence, incidence, risk factors, comorbidity and course of mental disorders (Binbay *et al.* 2011;Binbay *et al.* 2012a;Binbay *et al.* 2012b).

The baseline (T_1) sample was randomly selected from the wider Izmir metropolitan area using a multistage sampling procedure, stratified by urbanicity covering 11 districts and 302 neighbourhoods. Izmir is the third most urban area of Turkey with approximately 2.6 million residents in 2007 (TurkStat 2008). Addresses were provided by The Turkish Institute of Statistics (TurkStat) and the households were visited in person by trained lay interviewers between 2007 and 2009. One household member aged between 15 and 64 years was randomly selected using the Kish within-household sampling method (Kish 1949). A total of 4011 participants were interviewed at baseline. Full details on the Izmir metropolitan area, sampling, representativeness, instruments and procedures of this assessment (T_1) have been published previously (Binbay *et al.* 2011). At follow-up (T_2), addresses of all T_1 participants were re-visited in person six years after the baseline assessment in average (years 2013-2015). Several attempts were made to reduce the number of non-respondents from the baseline sample. The study team telephoned the T_1 participants to make appointments for interviews. Any contact information for T_1 participants who could not be reached was collected by asking neighbours in the area or the neighbourhood authorities. If additional information was obtained on the T_1 respondent, the person was contacted at the new contact address. At T_2, 954 individuals from the baseline sample could not be contacted (i.e. after at least three consecutive attempts to contact anyone at the address), and 386 individuals were lost due to residency in a remote area. Forty-four individuals were found to be deceased or imprisoned and 24 addresses were demolished. Furthermore, 418 individuals refused to participate in the follow-up assessment. As a result, a total of 2185 individuals were successfully re-interviewed at T_2. Baseline and follow-up TürkSch assessments were approved by the Ege University ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Interviewers, Interviewer Training and Quality Control

At T_1, lay interviewers had at least high school education, a health-related profession, and/or were experienced in doing field surveys. At T_2, lay interviewers were psychology graduates. In both assessments, lay interviewers had a two-week formal training which included basic information on common mental disorders, symptom dimensions in psychosis, and ethical aspects of the project, as well as practical training on CIDI interviews. The field work was closely monitored by the study team (UK, TB, HE, BK, KA). Each interview at T_1 and T_2 was conducted according to a standard procedure, with recording and quality coding (Binbay *et al.* 2011). If the quality of the interview was considered low, a phone call (T_1 n= 234; T_2 n=156) or a second visit (T_1 n= 392; T_2 n= 560) was planned by the study team (Binbay *et al.* 2011).

Assessments

Both at baseline and at follow-up participants were screened using the Composite International Diagnostic Interview (CIDI) 2.1 (Andrews and Peters 1998). The CIDI is a fully structured interview developed by the World Health Organization (Robins *et al.* 1988) and has been used in various surveys around the world including Turkey (Cilli and Kaya 2003;Deveci *et al.* 2007;Alptekin *et al.* 2009). Primarily designed for use in epidemiological studies of mental disorders, the CIDI can be used by both clinicians and trained lay interviewers. CIDI was found to have excellent inter-rater reliability in general population based samples in almost all sections with kappa values ranging from 0.67 to 0.97 (Wittchen *et al.* 1991).

CIDI-based screening of symptoms provides information on frequency, duration, help-seeking, severity of symptoms and psychosocial impairment. In both assessments of TürkSch, the CIDI assessment included screening sections on alcohol and substance-related disorders, depressive and dysthymic disorders, manic and bipolar affective disorders, schizophrenia and other psychotic disorders and two final sections with concluding questions, interviewer observations, and interviewer ratings (Binbay *et al.* 2011).

Assessment of Mood Episodes

In order to assess depressive and hypo/manic episodes, the same case identification procedure was applied at baseline and follow-up. For depression (CIDI section E), participants were asked if they had experienced an episode lasting at least two weeks during which they felt depressed, or had a lack of interest. If endorsed, participants were asked if, during this period, they had experienced lack of energy, appetite change, sleep problems, being slow or restless, feelings of worthlessness or guilt, decreased self-esteem, trouble thinking or indecisiveness, and thoughts of death. For manic and hypomanic episodes (CIDI section F), participants were asked whether they had experienced elevated mood or irritability for a period of at least four consecutive days either noticed by others or causing problems. If this was the case, participants were asked if, during this period, they had experienced excessive goal-directed activity, psychomotor agitation, spending sprees, sexual indiscretions, increased talkativeness, flight of ideas, loss of normal social inhibitions, increased self-esteem or grandiosity, decreased need for sleep, and distractibility. For both depressive and manic episodes, the final assessment included questions on probable association of symptoms with substance use or physical illness, help-seeking due to symptoms, the route of help-seeking, clinician diagnosis, and treatment history. All responses were re-evaluated by a team of clinicians. *Depressive episode* and *hypomanic/manic episode* was coded positive in accordance with the definitions and criteria of DSM-IV. Furthermore, any *mood episode* variable was constructed and coded positive if there was either a depressive or a hypomanic/manic episode. Time frame was the past year at T_1 and the last six years at T_2 (since baseline).

Assessment of Psychotic Experiences

In order to assess PEs, the same case identification procedure was applied both at T_1 and T_2. PEs were rated using 14 CIDI delusions items (G1, G2, G3, G4, G5, G7, G8, G9, G10, G11, G12, G13, G13b and G14) and 5 CIDI hallucinations items (G17, G18,

G20, G20C, and G21). All items were rated dichotomously indicating presence or absence. Kappa for agreement between clinicians for delusions and hallucinations was found to be 0.85 and 0.87, respectively (Cooper *et al.* 1998).

Rating of PE can be difficult because sometimes individuals can be describing a plausible event or a religious or superstitious belief that in the CIDI may be rated as a PE. Therefore, the following procedure was followed. First, during the interview, each time a participant endorsed a CIDI PE, the participant was asked to give an example, which was written down verbatim by the interviewer for later review with the mental health clinician on the team. All CIDI interviews were reviewed by the study team. When it was not clear whether or not the participant had truly endorsed a positive PE, the participant was re-contacted by a clinician over the telephone to confirm the PE (n= 156). Thus, delusional and hallucinatory experiences were coded positive if the team clinician confirmed the PE at review.

Using CIDI items G25 (duration of the PE: between 1 day and 6 months or more), G26, G28, G29 and G29A (level of dysfunction), G16 and G23 (told doctor about psychotic beliefs), a *measure of impairment associated with PEs* was defined (Binbay *et al.* 2012b;Binbay *et al.* 2012c). In addition, all individuals endorsing at least one CIDI psychosis item associated with help-seeking or, if there was no help-seeking, occurring with a frequency of at least once per week, were re-contacted by the study team and invited for a clinical evaluation with the Structured Clinical Interview for DSM-IV (SCID) by the team psychiatrist. Thus, 225 participants at T_1 and 263 participants at T_2 were clinically re-interviewed in order to identify participants with psychotic disorder. Using the *measure of impairment associated with PEs* and the SCID results, an *extended psychosis phenotype* variable was constructed including 4 categories. *The psychotic disorder group* included all individuals diagnosed with any DSM-IV disorder with psychotic features. The *clinical PE* group included individuals who had a CIDI PE leading to any

of the 7 CIDI impairment items but who did not have a diagnosis of psychotic disorder. The *subclinical PE* group included individuals with a CIDI PE not leading to any distress, impairment or help-seeking. All other individuals were included in the '*no psychosis'* category. The time frame for PEs was lifetime at baseline assessment (T_1) and the last six years at follow-up assessment (T_2).

In order to analyse the longitudinal bidirectional associations between PEs and mood episodes, an independent variable combining baseline PEs and mood episodes was constructed (baseline mental status) (0: *no PE, no mood episodes*; 1: *PE, no mood episodes* 2: *no PE, mood episodes*; 3: *both PE and mood episodes*). This variable was used in logistic regression models of the dichotomous outcome variables "*any follow-up PE*", "*any follow-up mood episodes*", *"follow-up depressive episode*", "*follow-up hypomanic/manic episode*".

Other Assessments

The baseline and follow-up assessments included a sociodemographic questionnaire and additional questions to define patterns of help-seeking (the route of help-seeking, diagnosis, prescribed medication and hospitalization). *Educational achievement* was defined based on last graduated school including five categories (University or higher, high school, secondary school, primary school, non-graduate). *Marital status* was recoded into (living as) married and non-married (single, divorced or widowed). *Socioeconomic status* was based on profession and recoded into 4 ordinal categories (1: I and II professional and IIIA non manual high employees, 2: IIIB non manual low employee and V and VI skilled workers and technicians, 3: IVA, IVB, and IVC owners of small businesses, and 4: VIIA and B manual workers) (Goldthorpe 1987). *The status of psychotropic medication use at baseline and follow-up* was recoded into 4 categories (0: never 1: use at baseline, no use at follow-up 2: no use at baseline, use at follow-up 3: use at both assessments).

Using questions derived from the Family Interview for Genetic Studies (NIMH.Genetics.Initiative 1992), history of mental disorders in the father, mother, siblings, and offspring was assessed. Thus, guided by previous works (Mortensen *et al.* 2010) a *family history of mental disorders* variable was defined and coded as "0" no or undefined family history of mental disorders,"1" common mental disorder (non-psychotic disorders of depression/anxiety, conversion, somatoform etc. in at least one family member), and "2" severe mental illness (bipolar disorder/ psychotic disorder/ hospitalization/completed suicide) in at least one family member (Binbay *et al.* 2012c).

Alcohol and cannabis use were assessed using screening questions on CIDI sections of alcohol and substance-related disorders. Conform previous CIDI-based research (Henquet *et al.* 2005;Binbay *et al.* 2012c) and using information from both T_1 and T_2, cannabis use of 5 times or more was defined as exposure status for cannabis. Regular alcohol use was defined as use of alcohol at least once a week. Using information from both T_1 and T_2, alcohol use was recoded into three variables: "0" *never used*, "1" *non-regular user* (history of alcohol use at any level but no regular use at follow-up assessment), and "2" *regular user* at follow-up assessment (Ulas *et al.* 2017). *Life events* were assessed using the List of Threatening Life Events (Brugha and Cragg 1990). The events were a serious illness, injury or an assault (suffering or happening to a close relative); death of a relative or a close friend, divorce, separation, serious problems with a relative/ neighbour/ close friend, being dismissed from the job, unemployment, major financial problems, police/ court appearance. Time frame was the last six years. The number of life events was a continuous variable with a minimum of 0 and maximum of 12. Childhood adversity between age 0-5 years and between age 6-15 years were death of any parent, divorce of parents and separation from parents for at least for 3 months and dichotomized to none or at least one (Binbay *et al.* 2012c).

Statistical Analyses

All analyses were conducted using the software package STATA, version 13 (StataCorp, 2013). In order to evaluate the possibility of bias caused by differential attrition over time, we compared the participants at T_2 with the individuals who participated at T_1 and not at T_2 on sociodemographic characteristics using the chi-squared tests. Results were presented showing the p values and effect size measures *(Cramer's V).*

To analyse the longitudinal bidirectional associations between PEs and mood episodes (first aim); crude associations were analysed between PEs at T_1 and mood episodes at T_2, and vice versa. Subsequently, results were adjusted for socio-demographics, familial and environmental risk factors. Furthermore, considering the possible influence on expression of both PEs and mood episodes, models additionally included *psychotropic medication use* (reference category: none at T_1 or at T_2).

Besides the model with the binary PEs variable, we modelled PEs as a continuum stratified by the severity (the extended psychosis phenotype variable). Using a cross-lagged panel design, polychoric correlations between the extended psychosis phenotype and mood episodes at both time points were computed.

For the second aim, interaction contrast ratios (ICRs) were used to test departure from additivity (Knol *et al.* 2007). Using the odds ratios (OR) derived from the previous logistic regression models of the dichotomous outcome variables "*any follow-up PE*" and "*any follow-up mood episodes*", we calculated ICRs using the formula (i.e. ICR =$OR_{\textit{both PE and mood episodes}}$ - $OR_{\textit{PE, no mood episodes}}$ – $OR_{\textit{no PE, mood episodes}}$ + 1). Confidence intervals and p-values for ICRs were generated using the nlcom procedure in Stata version 13.2 (StataCorp 2013).

For the third aim, logistic regression was used to assess the associations between risk factors and presence of mood episodes and PEs, separately. In all analyses, alpha was set at 0.05.

Results

Participant Characteristics

The average age of the participants at T_1 was 44.7 years (range= 21–71; SD = 13.3). Details of the sociodemographic, clinical and diagnostic characteristics of participants at T_1 and T_2 were presented in *table 1*. Attrition was slightly higher in males, and the difference between participants and non-participants was below the significance level (*males: non-participants 43.4% male vs. participants 40.6%; x^2= 3.28, df=1, p=0.07, Cramer's V= 0.02*). Attrition was higher in the younger age group (*15-29 years: non participants 39.8% vs. participants 32.0%; x^2= 35.16, df=2, p<0.01, Cramer's V = 0.09*); in non-married participants (*non-married: non-participants 34.2% vs. participants 25.0%; x^2= 40.6,df=1, p<0.01, Cramer's V= 0.10*) and in participants with higher educational achievement (*at least high school: non-participants 43.8% vs. participants 39.3%; x^2= 8.29, df=1, p=0.004, Cramer's V = 0.04*) with small effect sizes.

Table 1: Sociodemographic and Clinical Characteristics of Participants at Baseline and Follow-up Assessments

	Baseline n (%)	Follow-up n (%)
Age Categories		
15-30	699 (32.0)	354 (16.2)
31-45	750 (34.3)	844 (38.6)
46-71	736 (33.7)	987 (45.2)
Sex		
Male	887 (40.6)	887 (40.6)
Female	1298 (59.4)	1298 (59.4)
Education		
Non-Graduate	155 (7.1)	106 (4.9)
Primary School	811 (37.1)	845 (38.7)
Secondary School	360 (16.5)	278 (12.7)
High School	539 (24.7)	499 (22.8)
University or Higher	320 (14.6)	457 (20.9)
Marital Status		
Married	1638 (75.0)	1741 (79.7)
Non-married	547 (25.0)	444 (20.3)
Socioeconomic Status		
1	466 (21.3)	160 (7.3)
2	585 (26.8)	415 (19.0)
3	352 (16.1)	273 (12.5)
4	782 (35.8)	1337 (61.2)
Contact with a Mental Health Service		
None	1872 (85.7)	1788 (81.8)
At least once	313 (14.3)	397 (18.2)
Use of psychotropic medication		
None	1899 (86.9)	1798 (82.3)
At least once	286 (13.1)	387 (17.7)
Extended Psychosis Phenotype		
No PE	1616 (73.9)	1729 (79.1)
Subclinical PE	334 (15.3)	193 (8.8)
Clinical PE	187 (8.6)	191 (8.7)
Psychotic Disorder	48 (2.2)	72 (3.3)
Mood Episodes		
None	1783 (81.6)	1984 (90.8)
Present	402 (18.4)	201 (9.2)
Total	2185 (100)	2185 (100)

Table 2: Differential Effect of Sociodemographic, Familial and Environmental Factors on Presence of Follow-up Mood Episodes and Psychotic Experiences

Sample		Psychotic Experience Present at T_2		Mood Episode Present at T_2	
Categories	N (%)	n (%)	OR (CI)	**n** (%)	OR (CI)
Age Categories (at T_1)					
46-65	987 (45.2)	173 (37.9)	1 (ref)	83 (41.3)	1 (ref)
15-45	1198 (54.8)	283 (62.1)	1.5*** (1.2 - 1.8)	118 (58.7)	1.2 (0.9 – 1.6)
Sex					
Male	887 (40.6)	192 (42.1)	1 (ref)	53 (26.4)	1 (ref)
Female	1298 (59.4)	264 (57.9)	0.9 (0.7 - 1.1)	148 (73.6)	2.0*** (1.5 – 2.8)
Education					
University or Higher	457 (20.9)	67 (14.7)	1 (ref)	34 (16.9)	1 (ref)
High School	499 (22.8)	107 (23.5)	1.6** (1.1 - 2.2)	45 (22.4)	1.2 (0.8 – 2.0)
Secondary School	278 (12.7)	65 (14.2)	1.7** (1.2 – 2.6)	24 (11.9)	1.2 (0.7 – 2.0)
Primary School	845 (38.7)	193 (42.3)	1.7*** (1.3 – 2.3)	89 (44.3)	1.5 (1.0 – 2.2)
Non-Graduate	106 (4.9)	24 (5.3)	1.7* (1.1 – 2.9)	9 (4.5)	1.2 (0.5 – 2.5)
Marital Status					
Married	1741 (79.7)	310 (68.0)	1 (ref)	147 (73.1)	1 (ref)
Non-married	444 (20.3)	146 (32.0)	2.3*** (1.8 – 2.8)	54 (26.9)	1.5* (1.1 – 2.1)
Family History Of Mental Disorder					
None/Undefined	1789 (81.9)	331 (72.6)	1 (ref)	121 (60.2)	1 (ref)
Common Mental Disorder	336 (15.4)	102 (22.4)	1.9*** (1.5 – 2.5)	68 (33.8)	3.4*** (2.5 – 4.8)
Severe mental Illness	60 (2.7)	23 (5.0)	2.7*** (1.6 – 4.7)	12 (6.0)	3.4*** (1.8 – 6.7)
Alcohol Use					
Never used	1090 (49.9)	204 (44.8)	1 (ref)	98 (48.8)	1 (ref)
Non-regular user	723 (33.1)	157 (34.4)	1.2 (0.9 – 1.5)	71 (35.3)	1.1 (0.8 – 1.5)
Regular user	372 (17.0)	95 (20.8)	1.5** (1.3 – 2.0)	32 (15.9)	0.9 (0.6 – 1.4)
Cannabis Use					
None	2122 (97.1)	418 (91.7)	1 (ref)	192 (95.5)	1 (ref)
At least five times	63 (2.9)	38 (8.3)	6.2*** (3.7 – 10.4)	9 (4.5)	1.7 (0.8 – 3.4)
Life Events for the last 6 years					
None	482 (22.1)	53 (11.6)	1 (ref)	17 (8.5)	1 (ref)
At least one	1703 (77.9)	403 (88.4)	2.5*** (1.8 – 3.4)	184 (91.5)	3.3*** (2.0 – 5.5)
Childhood Adversity					
None	1870 (85.6)	375 (82.2)	1 (ref)	162 (80.6)	1 (ref)
At least one	315 (14.4)	81 (17.8)	1.4* (1.1 – 1.8)	39 (19.4)	1.5* (1.1 – 2.2)
Status of psychotropic medication use					
None	1644 (75.2)	244 (53.5)	1 (ref)	30 (14.9)	1 (ref)
T_1 (+) T_2 (-)	154 (7.1)	28 (6.2)	1.3 (0.8-2.0)	5 (2.5)	1.8 (0.7-4.7)
T_1 (-) T_2 (+)	255 (11.7)	110 (24.1)	4.4*** (3.3-5.8)	108 (53.7)	39.5 (25.5-61.3)
T_1 (+) T_2 (+)	132 (6.0)	74 (16.2)	7.3*** (5.1-10.6)	58 (28.9)	42.2 (25.6-69.4)
	Mean (SD)	Mean (SD)	OR (CI)	Mean (SD)	OR (CI)
Number Of Life Events For The Last 6 Years	1.6 (1.5)	2.5 (1.9)	1.6*** (1.5 – 1.7)	2.6 (1.8)	1.5*** (1.4 – 1.6)

*p < .05, **p < .01, ***p < .001

About one-fourth of the sample (n: 578; 26.4%) reported contact with a mental health service at least once in their lifetime. Furthermore, 541 participants (24.8%) reported psychotropic medication use (table 1). About one third of subclinical PEs persisted (29.1%) and a small proportion (1.5%) evolved into psychotic disorder expression at T_2. Of the clinical PEs, a higher proportion persisted (51.3%) and evolved into psychotic disorder expression (6.9%).

Main effects of socio-demographics, familial and environmental risk factors on the presence of psychotic experiences and mood episodes at follow-up assessments

Non-married marital status, family history of mental disorders (both common and severe), childhood adversity and number of life events exposed to for the last six years were significantly associated with both PEs and mood episodes at follow-up. Female sex was significantly associated with mood episodes but not with PEs. Younger age (≤ 45 years), lower educational achievement and alcohol/cannabis use were significantly associated with PEs but not with mood episodes. As expected, the status of psychotropic medication use was associated with both follow-up PEs and mood episodes (table 2).

Longitudinal bidirectional associations between psychotic experiences and mood episodes

In comparison with the reference category of *no PE, no mood episodes*, the baseline group of *mood episodes in isolation was* significantly associated with the *follow-up PEs*. Bidirectionally, the baseline category of *PE in isolation was* significantly associated with *follow-up mood episodes* (table 3). Furthermore, the association was significant with both follow-up depressive (*unadjusted OR: 2.0, 95% confidence interval [CI]: 1.3 to 3.2; adjusted OR: 1.5, 95% CI: 1.1 to 2.5*) and hypomanic/manic episodes (*unadjusted OR: 4.8, 95% CI: 1.6 to 14.2; adjusted OR: 3.2, 95% CI: 1.1 to*

Table 3: Longitudinal Bidirectional Associations between Extended Psychosis Phenotype and Mood Episodes

Baseline Mental Status[a]		Extended Psychosis Phenotype Present at T_2			Mood Episode Present at T_2		
Category	n (%)	n (%)	OR (CI)	OR[b] (CI)	N (%)	OR (CI)	OR[b] (CI)
PE (-) Mood (-)	1427 (65.3)	168 (36.8)	1 (ref)	1 (ref)	68 (33.8)	1 (ref)	1 (ref)
PE (-) Mood (+)	189 (8.6)	45 (9.9)	2.3*** (1.6-3.4)	1.8** (1.2-2.7)	39 (19.4)	5.2*** (3.4-8.0)	3.4*** (2.2-5.4)
PE (+) Mood (-)	356 (16.3)	143 (31.4)	5.0*** (3.9-6.6)	3.9*** (3.0-5.2)	33 (16.4)	2.0** (1.3-3.1)	1.6* (1.1-2.4)
PE (+) Mood (+)	213 (9.8)	100 (21.9)	6.6*** (4.8-9.0)	4.3*** (3.1-6.1)	61 (30.4)	8.0*** (5.5-11.8)	5.1*** (3.4-7.7)

*p < .05, **p < .01, ***P < .001

[a] PE: Presence of baseline extended psychosis phenotype; Mood: Presence of baseline mood episode

[b] Adjusted for age, sex, marital status, educational level, family history of mental disorders, childhood adversity, number of life events for the last 6 years, alcohol and cannabis use

10.1). The baseline category of *PE and mood episodes combined* was the strongest predictors of both *follow-up PE* and *mood episodes* (Table 3). However, there was no significant evidence that baseline PEs combined synergistically (on an additive scale) with baseline mood episodes to increase odds of subsequent PEs (ICR: 0.3, 95% CI -2.0 to 2.5, p= 0.82) and mood episodes (ICR = 1.8, 95% CI -1.3 to 4.8, p= 0.26). Finally, the bidirectional associations between PEs and mood episodes were attenuated, when adjusted for the status of psychotropic medication use (data not shown).

Polychoric correlations between mood episodes and the extended psychosis phenotype (stratified by severity) at T_1 and T_2 were demonstrated in *figure 1*. The synchronous correlations (r) between mood episodes and the extended psychosis phenotype were 0.48 at baseline and 0.51 at follow-up. The cross-lagged correlations (r) were 0.34 and 0.32.

Discussion

Findings

In this representative general population-based study, we mainly investigated the longitudinal bidirectional associations between mood episodes and PEs. Mood episodes were associated with subsequent PEs and, bidirectionally, PEs were associated with

subsequent mood episodes after accounting for other possible causes. Furthermore, in comparison with either PEs or mood episodes in isolation, the combined group had the higher odds for both subsequent PEs and mood episodes. However, no evidence was found that the latter associations are additive. Therefore, we assume that PEs and mood episodes had sub-additive bidirectional associations over the follow-up period. The bidirectional associations between PEs and mood episodes were attenuated, when adjusted for psychotropic medication use. Considering that the decision of either prescribing or using a psychotropic medication is likely associated with impairment and severity of the psychopathology, adjustment for these can be expected to result in attenuation of reciprocal associations of mood episodes and PEs, representing an adjustment for the severity driving the association itself. Finally, mood episodes were correlated with the severity of the extended psychosis phenotype. In light of these results, PEs may be conceptualised as a marker for the severity of affective psychopathology, as argued elsewhere (van Os and Reininghaus 2016). Similarly, these results are in agreement with reports that affective dysregulation may be a marker for dysfunction associated with PE (van Rossum *et*

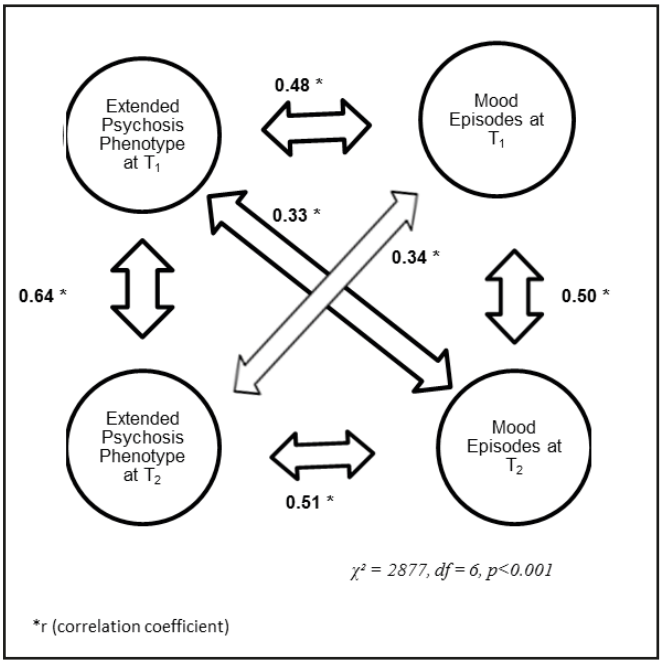


Figure 1: Polychoric correlations between mood episodes and the extended psychosis phenotype phenotype

al. 2011;Wigman *et al.* 2012;Guloksuz *et al.* 2015b;van Os and Guloksuz 2017).

The cross-lagged correlations between the extended psychosis phenotype and mood episodes were reciprocally similar (0.34 and 0.32), suggesting mutual causal connections between affective and psychotic domains of psychopathology (Anderson and Kida 1982). While some sociodemographic risk factors such as non-married marital status were associated with both psychopathology domains, some other factors were associated with only one domain. In line with previous epidemiological results (Regier *et al.* 1988;Linscott and van Os 2013), female sex was associated with mood episodes whereas no significant sex differences were found for the extended psychosis phenotype. Conversely, younger age (≤ 45 years) was significantly associated with the extended psychosis phenotype but not with mood episodes, in agreement with previous findings (Regier *et al.* 1988;Bijl *et al.* 1998;van Os *et al.* 2000b;Verdoux and van Os 2002;van Os *et al.* 2009). Furthermore, educational achievement was significantly associated with the extended psychosis phenotype, but not with mood episodes. Familial risk (both common mental disorders and severe mental illness) were associated with both psychopathology domains, in agreement with previous evidence (Bijl *et al.* 1998;van Os *et al.* 2009;Linscott and van Os 2013). Some environmental exposures such as life events over the last six years and childhood adversity were associated with both psychopathology domains at follow up. However, alcohol and cannabis use were associated with the extended psychosis phenotype, but not with mood episodes.

Our results demonstrated substantial synchronous and cross-lagged correlations between mood episodes and the extended psychosis phenotype. There is growing evidence that affective and psychotic domains of psychopathology have strong overlap in terms of symptom dimensions (van Os *et al.* 2000a;van Rossum *et al.* 2011;Reininghaus *et al.* 2016). Similar to the epidemiological results, there are grey areas between the boundaries

of psychotic and affective disorders in the current classification systems (Kelleher and Cannon 2014). A transdiagnostic approach based on the dimensional scores of both psychotic and affective domains (i.e. positive, negative, disorganisation, manic, depressive) may be useful to represent common 'psycho-affective' psychopathology more accurately (van Os and Reininghaus 2016). Such an approach might be effective to determine the place of psychopathology in the psychosis spectrum (i.e. affective/non-affective; clinical/subclinical) (van Os and Reininghaus 2016). Keeping in mind the proposed sub-additive bidirectional associations between the psychotic and affective dimensions, future research on the reciprocal influences of these dimensions, and the underlying factors moderating these, might provide a useful framework for the clinical delineation of the spectrum of affective and psychotic psychopathology.

Methodological Issues

As far as we are aware, this is the first longitudinal study in a large community-based population that examines the bidirectional associations between PEs and mood episodes controlling for common risk factors. The longitudinal design enabled us to measure non-lifetime clinical features which were subject to change in time. Furthermore, adjustment addressed some other causes of psychopathology, like socio-demographic features, familial risk, alcohol and substance use, and adverse life events.

In spite of the strengths, the results need to be considered in the light of the following limitations. First, as with most longitudinal studies, our initial sample size was reduced because of the attrition. The comparison of baseline characteristics between non-participants and participants showed that attrition was higher in younger, non-married and higher-educated individuals. However, differences between participants and non-participants were quite small (Cramer's $V \leq 0.1$). In addition, associations between PEs and mood episodes would only be confounded by non-response if this was differential with regard to the two dimensions in the association, and this is unlikely. However, results of the study should be interpreted in the light of a degree of underlying selective drop-out.

Second, despite the quality checks of the interviews using a standard procedure for formal consistency, appropriate recording and coding which was described above and in more detail elsewhere (Binbay *et al.* 2011), the assessment of PEs and mood episodes in the general population inevitably is associated with a degree of misclassification (false positives and false negatives) (Linscott and van Os 2010). However, there is little reason to assume that misclassification was differential with regard to PEs on the one hand and mood episodes on the other. Therefore, it is unlikely that findings are biased. Third, while clinical re-interviews were conducted to identify participants with psychotic disorders, the definitions of depressive and manic/hypomanic episodes were based on the CIDI results. Fourth, we only considered positive dimensions of PEs. However, negative and disorganized dimensions were also found to be predictive of later psychopathology (van Os and Reininghaus 2016). Thus, these results cannot be generalized to negative and disorganised dimensions.

Sensitivity analyses in younger age group

It is well-known that the incidence of psychosis is higher in younger age groups (Regier *et al.* 1988;Kirkbride *et al.* 2006) and may be of different origin than psychotic syndromes observed in older age groups. Thus, the associations studied in the present paper may be different in the youngest age group with the highest incidence. A sensitivity analysis was performed including participants aged 45 years or younger. Correlations were similar or a little stronger in this age group. The synchronous correlations (r) between mood episodes and the extended psychosis phenotype were 0.53 at baseline and 0.58 at follow-up. The cross-lagged correlations (r) were 0.34 and 0.36.

References

- Alptekin K, Ulas H, Akdede BB, Tumuklu M , Akvardar Y (2009). Prevalence and risk factors of psychotic symptoms: in the city of Izmir, Turkey. *Social psychiatry and psychiatric epidemiology* 44, 905-910.

- Anderson T , Kida T (1982). The Cross-Lagged Research Approach: Description and Illustration. *J. Account. Res.* 20, 403-414.

- Andrews G , Peters L (1998). The psychometric properties of the Composite International Diagnostic Interview. *Social psychiatry and psychiatric epidemiology* 33, 80-88.

- Armando M, Nelson B, Yung AR*, et al.* (2010). Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. *Schizophrenia research* 119, 258-265.

- Bijl RV, Ravelli A , van Zessen G (1998). Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social psychiatry and psychiatric epidemiology* 33, 587-595.

- Binbay T, Alptekin K, Elbi H*, et al.* (2012a). [Lifetime prevalence and correlates of schizophrenia and disorders with psychotic symptoms in the general population of Izmir, Turkey]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 23, 149-160.

- Binbay T, Drukker M, Alptekin K*, et al.* (2012b). Evidence that the wider social environment moderates the association between familial liability and psychosis spectrum outcome. *Psychological medicine* 42, 2499-2510.

- Binbay T, Drukker M, Elbi H*, et al.* (2012c). Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophrenia bulletin* 38, 992-1002.

- Binbay T, Elbi H, Alptekin K*, et al.* (2011). Izmir mental

health survey for gene-environment interaction in psychoses (TurkSch): objectives and methodology. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 22, 65-76.

- Brugha TS , Cragg D (1990). The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta psychiatrica Scandinavica* 82, 77-81.

- Cilli AS , Kaya N (2003). [Nicotine dependence and psychiatric comorbidity among university students]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 14, 42-49.

- Cooper L, Peters L , Andrews G (1998). Validity of the Composite International Diagnostic Interview (CIDI) psychosis module in a psychiatric setting. *Journal of psychiatric research* 32, 361-368.

- De Loore E, Gunther N, Drukker M*, et al.* (2011). Persistence and outcome of auditory hallucinations in adolescence: a longitudinal general population study of 1800 individuals. *Schizophrenia research* 127, 252-256.

- Deveci A, Taskin O, Dinc G*, et al.* (2007). Prevalence of pseudoneurologic conversion disorder in an urban community in Manisa, Turkey. *Social psychiatry and psychiatric epidemiology* 42, 857-864.

- Dhossche D, Ferdinand R, Van der Ende J, Hofstra MB , Verhulst F (2002). Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychological medicine* 32, 619-627.

- Fowler D, Hodgekins J, Garety P*, et al.* (2012). Negative cognition, depressed mood, and paranoia: a longitudinal pathway analysis using structural equation modeling. *Schizophrenia bulletin* 38, 1063-1073.

- Goldthorpe J (1987). *Social mobility and class structure in modern Britain*. Clarendon Press: New York.

- Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen HU , van Os J (2015a). Evidence that the presence of psycho-

sis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. *Psychological medicine* 45, 2389-2401.

- Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen HU , van Os J (2015b). Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. *Psychological medicine* 45, 2389-2401.

- Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H , van Os J (2003). How psychotic are individuals with non-psychotic disorders? *Social psychiatry and psychiatric epidemiology* 38, 149-154.

- Henquet C, Krabbendam L, Spauwen J*, et al.* (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* 330, 11.

- Kelleher I , Cannon M (2014). Whither the psychosis-neurosis borderline. *Schizophrenia bulletin* 40, 266-268.

- Kelleher I, Keeley H, Corcoran P*, et al.* (2012). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *The British journal of psychiatry : the journal of mental science* 201, 26-32.

- Kirkbride JB, Fearon P, Morgan C*, et al.* (2006). Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Archives of general psychiatry* 63, 250-258.

- Kish L (1949). A procedure for objective respondent selection withinthe household. *J Am Stat Assoc* 44, 380–387.

- Knol MJ, van der Tweel I, Grobbee DE, Numans ME , Geerlings MI (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *International journal of epidemiology* 36, 1111-1118.

- Linscott RJ , van Os J (2010). Systematic reviews of categorical versus continuum models in psychosis: evidence for discontinuous subpopulations underlying a psychometric continuum. Implications for DSM-V, DSM-VI, and DSM-VII. *Annual review of clinical psychology* 6, 391-419.

- Linscott RJ , van Os J (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine* 43, 1133-1149.

- McGrath JJ, Saha S, Al-Hamzawi A*, et al.* (2015). Psychotic Experiences in the General Population: A Cross-National Analysis Based on 31,261 Respondents From 18 Countries. *JAMA psychiatry* 72, 697-705.

- McGrath JJ, Saha S, Al-Hamzawi A*, et al.* (2016). The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *The American journal of psychiatry*, appiajp201615101293.

- Mortensen PB, Pedersen MG, Pedersen CB (2010). Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychological medicine* 40, 201-210.

- NIMH.Genetics.Initiative (1992). *Family Interview for Genetic Studies (FIGS)*. MD National Institute of Mental Health: Rockville.

- Nuevo R, Chatterji S, Verdes E, Naidoo N, Arango C , Ayuso-Mateos JL (2012). The continuum of psychotic symptoms in the general population: a cross-national study. *Schizophrenia bulletin* 38, 475-485.

- Perlis RH, Uher R, Ostacher M*, et al.* (2011). Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. *Archives of general psychiatry* 68, 351-360.

- Regier DA, Boyd JH, Burke JD, Jr.*, et al.* (1988). One-

month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. *Archives of general psychiatry* 45, 977-986.

- Reininghaus U, Bohnke JR, Hosang G*, et al.* (2016). Evaluation of the validity and utility of a transdiagnostic psychosis dimension encompassing schizophrenia and bipolar disorder. *The British journal of psychiatry : the journal of mental science* 209, 107-113.

- Robins LN, Wing J, Wittchen HU*, et al.* (1988). The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of general psychiatry* 45, 1069-1077.

- Rossler W, Hengartner MP, Ajdacic-Gross V, Haker H, Gamma A , Angst J (2011). Sub-clinical psychosis symptoms in young adults are risk factors for subsequent common mental disorders. *Schizophrenia research* 131, 18-23.

- Saha S, Scott J, Varghese D, McGrath J (2012). Anxiety and depressive disorders are associated with delusional-like experiences: a replication study based on a National Survey of Mental Health and Wellbeing. *BMJ open* 2.

- StataCorp (2013). Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

- Stochl J, Khandaker GM, Lewis G*, et al.* (2015). Mood, anxiety and psychotic phenomena measure a common psychopathological factor. *Psychological medicine* 45, 1483-1493.

- Sullivan SA, Wiles N, Kounali D*, et al.* (2014). Longitudinal associations between adolescent psychotic experiences and depressive symptoms. *PloS one* 9, e105758.

- TurkStat (2008). *The results of address based population registration system.* Turkish Statistical Institute: Ankara.

- Ulas H, Binbay T, Kirli U, Elbi H , Alptekin K (2017). The epidemiology of alcohol

use in Izmir, Turkey: drinking pattern, impairment and help-seeking. *Social psychiatry and psychiatric epidemiology*.

- van Os J, Gilvarry C, Bale R*, et al.* (2000a). Diagnostic value of the DSM and ICD categories of psychosis: an evidence-based approach. UK700 Group. *Social psychiatry and psychiatric epidemiology* 35, 305-311.

- van Os J , Guloksuz S (2017). A critique of the "ultra-high risk" and "transition" paradigm. *World psychiatry : official journal of the World Psychiatric Association* 16, 200-206.

- van Os J, Hanssen M, Bijl RV , Ravelli A (2000b). Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophrenia research* 45, 11-20.

- van Os J , Linscott RJ (2012). Introduction: The Extended Psychosis Phenotype--Relationship With Schizophrenia and With Ultrahigh Risk Status for Psychosis. *Schizophrenia bulletin* 38, 227-230.

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

- van Os J , Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World psychiatry : official journal of the World Psychiatric Association* 15, 118-124.

- van Rossum I, Dominguez MD, Lieb R, Wittchen HU , van Os J (2011). Affective dysregulation and reality distortion: a 10-year prospective study of their association and clinical relevance. *Schizophrenia bulletin* 37, 561-571.

- Varghese D, Scott J, Welham J*, et al.* (2011). Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. *Schizophrenia bulletin* 37, 389-393.

- Verdoux H , van Os J (2002). Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophrenia research* 54, 59-65.

- Wigman JT, van Nierop M, Vollebergh WA*, et al.* (2012). Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity--implications for diagnosis and ultra-high risk research. *Schizophrenia bulletin* 38, 247-257.

- Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD , Regier D (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British journal of psychiatry : the journal of mental science* 159, 645-653, 658.

- Zavos HM, Eley TC, McGuire P*, et al.* (2016). Shared Etiology of Psychotic Experiences and Depressive Symptoms in Adolescence: A Longitudinal Twin Study. *Schizophrenia bulletin* 42, 1197-1206.

CHAPTER 4

DSM outcomes of psychotic experiences and associated risk factors: 6-year follow-up study in a community-based sample

Umut Kırlı [1, 2]

Tolga Binbay [3]

Marjan Drukker [2]

Hayriye Elbi [4]

Bülent Kayahan [4]

Duygu Keskin Gökçelli [4]

Ferda Özkınay [5]

Hüseyin Onay [5]

Köksal Alptekin [3]

Jim van Os [2, 6, 7]

Psychological Medicine 2019; 49 (8): 1346-1356

1 Van Education and Research Hospital, Psychiatry Unit, Van, Turkey

2 Maastricht University Medical Centre, School of Mental Health and Neuroscience, Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, PO Box 616, Vijverdal, 6200 MD, Maastricht, The Netherlands

3 Dokuz Eylul University, Faculty of Medicine, Department of Psychiatry, 35340, Izmir, Turkey

4 Ege University, Faculty of Medicine, Department of Psychiatry, 35140, Izmir, Turkey

5 Ege University, Faculty of Medicine, Department of Medical Genetics, 35140, Izmir, Turkey

6 King's College, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, UK

7 Dept. Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre, PO BOX 85500, 3508 GA Utrecht, The Netherlands.

Abstract

Background: Psychotic experiences (PE) may predict a range of common, non-psychotic disorders as well as psychotic disorders. In this representative, general population-based cohort study, both psychotic and non-psychotic disorder outcomes of PE were analysed, as were potential moderators.

Methods: Addresses were contacted in a multistage clustered probability sampling frame covering 11 districts and 302 neighbourhoods at baseline (n=4011). Participants were interviewed with the Composite International Diagnostic Interview (CIDI) both at baseline and at 6 year follow-up. Participants with PE at baseline were clinically re-interviewed with the SCID-I at follow-up. The role of socio-demographics, characteristics of PE, co-occurrence of mood disorders and family history of mental disorders were tested in the association between baseline PE and follow-up diagnosis.

Results: In the participants with baseline PE, the psychotic disorder diagnosis rate at follow up was 7.0% - much lower than the rates of DSM-IV mood disorders without psychotic features (42.8%) and other non-psychotic disorders (24.1%). Within the group with baseline PE, female sex, lower socioeconomic status, co-occurrence of mood disorders, family history of a mental disorder and persistence of PE predicted any follow-up DSM diagnosis. Furthermore, onset of psychotic versus non-psychotic disorder was predicted by younger age (15-30 years), co-presence of delusional and hallucinatory PE and family history of severe mental illness.

Conclusion: The outcome of PE appears to be a consequence of baseline severity of multidimensional psychopathology and familial risk. It may be useful to consider PE as a risk indicator that has trans-diagnostic value.

Introduction

Previous research has demonstrated that expression of the psychosis phenotype extends from subclinical psychotic experiences (PE) to clinical psychotic disorders (van Os *et al.* 2009;Linscott and van Os 2013;Fonseca Pedrero and Debbane 2017). Furthermore, individuals who report PE have elevated risk for later psychotic disorders in comparison with those who do not (Poulton *et al.* 2000;Hanssen *et al.* 2005;Dominguez *et al.* 2011;Werbeloff *et al.* 2012;Zammit *et al.* 2013). However, most PE are self-limiting and the predictive value of PE for subsequent psychotic disorders is typically low at less than 1% per year in previous community-based studies (Hanssen *et al.* 2005;Kaymaz *et al.* 2012;Linscott and van Os 2013;Zammit *et al.* 2013). Transition rates are higher in clinical studies of individuals with affective disorder and substance use disorders with a degree of psychosis admixture, considered at ultra-high risk (UHR) (Fusar-Poli *et al.* 2012;Schmidt *et al.* 2015;Schultze-Lutter *et al.* 2015;Fusar-Poli and Schultze-Lutter 2016). However, these were conducted in help-seeking samples and generating risk-enrichment, making it difficult to compare results to longitudinal studies of PE in the general population (van Os and Guloksuz 2017).

PE were associated with increased risk of later non-psychotic disorders as well as psychotic disorders among different age groups (McGrath *et al.* 2016). First, studies assessing outcomes of PE in adolescents found associations with later depression, suicide attempts, substance use disorders and PTSD (Dhossche *et al.* 2002;De Loore *et al.* 2011;Fisher *et al.* 2013;Sullivan et al. 2014;Zavos et al. 2016). Second, PE at age 19/20 years predicted dysthymia, bipolar disorder, social phobia, and obsessive–compulsive disorder by age 49/50 years (Rossler *et al.* 2011). Finally, PE were related to increased risk of later service use (Bhavsar *et al.* 2017) and hospitalization for non-psychotic disorders (Werbeloff *et al.* 2012).

Definitions of PE and type of screening instruments used varied across studies (Kelleher *et al.* 2011), contributing to the heterogeneity of results in this area. Definitions of PE were mainly based on attenuated forms of delusional thinking and hallucinatory perceptions (van Os *et al.* 2009;Linscott and van Os 2013;Fonseca Pedrero and Debbane 2017), similar to those used in the current paper. However, negative, disorganization and affective dimensions were identified in addition to the positive dimension (van Os and Reininghaus 2016). It was suggested that positive and negative dimensions of PE might be associated with emergence of different types of psychopathology (Debbane *et al.* 2015).Moreover, many factors such as comorbid non-psychotic symptoms (Yung *et al.* 2003;Hanssen *et al.* 2005;Perlis *et al.* 2011;van Rossum *et al.* 2011;Kelleher *et al.* 2012;Wigman *et al.* 2012;Smeets *et al.* 2013;Falkenberg *et al.* 2015;Guloksuz *et al.* 2015;Honings *et al.* 2016;Salokangas *et al.* 2016), persistence (Poulton *et al.* 2000;Yung *et al.* 2003;Dominguez *et al.* 2011;Nelson *et al.* 2013), cognitive impairment (Shah *et al.* 2012;Carrion *et al.* 2013;Kelleher *et al.* 2015), familial risk (Cannon *et al.* 2008;Shah *et al.* 2012;Smeets *et al.* 2015) and environmental exposures (Cougnard *et al.* 2007;Cannon *et al.* 2008;Collip *et al.* 2008;Dragt *et al.* 2011;Smeets *et al.* 2013;Guloksuz *et al.* 2015;Smeets *et al.* 2015;van Dam *et al.* 2015) were shown to impact on outcome of PE (Fonseca Pedrero and Debbane 2017).

The above studies demonstrate that PE indexes risk for a variety of common mental disorders as well as psychotic disorder. However, this research has some limitations. Diagnoses at follow-up, with one notable exception (Werbeloff *et al.* 2012), were mostly based on lay-interviewer assessments and re-interviews were not performed by clinicians. Furthermore, research on follow-up DSM diagnoses in community-based populations with baseline PE, and the role of baseline differences thereof, remains limited.

The aims of this paper were to analyse, over a 6 year period, in a general population sample,

i) The follow-up diagnostic status of participants with baseline PE,

ii) To explore the role of socio-demographics, characteristics of PE, co-occurrence of mood disorders and family history of mental disorders in the association between baseline PE and presence of any follow-up DSM diagnosis.

iii) To explore the role of the same factors in discriminating between the outcome of psychotic and non-psychotic outcome in those with baseline PE.

Methods

Sample and Study Design

Data came from the TürkSch (Izmir Mental Health Survey for Gene-Environment Interaction in Psychosis) study which collected longitudinal data on the prevalence, incidence, risk factors, comorbidity, and course of mental disorders in a random, representative community-based sample covering a time frame of approximately 6 years(Binbay *et al.* 2011;Binbay *et al.* 2012a;Binbay *et al.* 2012b). The sample of the baseline assessment (T_1) was randomly selected from the wider Izmir metropolitan area using a multistage sampling procedure, stratified by urbanicity covering 11 districts and 302 neighbourhoods. The households were visited in person by trained lay interviewers between 2007 and 2009. One household member aged between 15 and 64 years was randomly selected using the Kish within-household sampling method (Kish 1949). A total of 4011 participants were interviewed with the Composite International Diagnostic Interview (CIDI) (Andrews and Peters 1998). Of those 4011 participants, 406 (10.1%) endorsed a PE either with a duration of at least "1 week" or with a frequency of at least "sometimes" or associated with help-seeking/ interference with functioning or enjoying relationships (Binbay *et al.* 2012b). Those 406 participants were re-contacted and the Structured Clinical Interviews for DSM-IV (SCID) (Spitzer *et al.* 1992) were conducted (Binbay *et al.* 2012b). Of the 406 participants, 99 were diagnosed with

a DSM-IV disorder with psychotic features (baseline psychotic disorder- PD group), and thus excluded from the sample of the current analysis. The remaining participants (baseline PE group, n=307) were included in the current analyses (Fig. 1). Full details on the Izmir metropolitan area, sampling, representativeness, instruments and procedures of T_1 have been published previously (Binbay *et al.* 2011).

At follow-up assessment (T_2), addresses of all T_1 participants were re-visited in person by trained lay interviewers 6 years after the baseline assessments (years 2013-2015). Attempts were made to reduce the number of non-respondents from the baseline sample (Binbay *et al.* 2011). 187 of the 307 individuals within the baseline PE group were successfully interviewed with CIDI (response rate: 60.9%; sample and results of the visits were presented in Fig. 1). All of these 187 participants were re-interviewed with SCID by the team psychiatrist (122 interviews at the hospital and 65 at the participants' residence). Both assessments of TürkSch study were approved by the Ege University ethics committee and participants provided written informed consent.

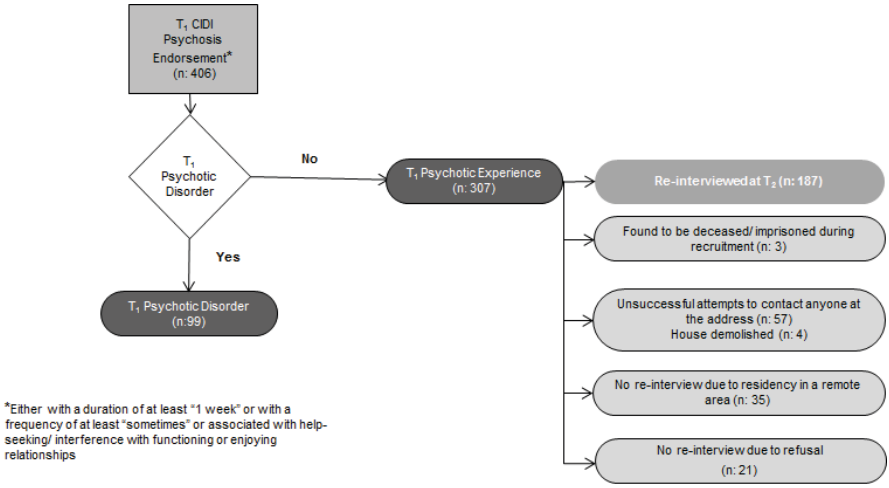


Figure 1: General design and T2 outcome of participants with psychosis endorsement at T1.

Interviewers and Quality Control

At T_1, lay interviewers had at least high school education, a health-related profession, and/or were experienced in doing field surveys. At T_2, lay interviewers were psychology graduates. At T_2, both the lay interviewers and the psychiatrist who conducted the SCID interviews (UK) had not participated in T_1, and thus were blind to baseline results. At both assessments, lay interviewers had a two-week formal training. Each CIDI interview was conducted according to a standard procedure, with recording and quality coding (Binbay *et al.* 2011).When the quality of the interview was considered low or if any missing value was present, a second visit was planned by a different lay-interviewer (n= 65). The missing values still present after the second visit (n= 18) were assessed by the psychiatrist following the clinical interview. The inter-rater reliability of the CIDI psychosis section had a kappa value of 0.45 at T_1 (Binbay *et al.* 2011) and 0.67 at T_2.

Assessments

Composite International Diagnostic Interview (CIDI)

The CIDI is a fully structured interview developed by the World Health Organization (Robins *et al.* 1988). The CIDI can be used by both clinicians and trained lay interviewers. CIDI was found to be appropriate for use in different countries and cultures (Wittchen 1994) and was used in various epidemiological surveys around the world including Turkey (Cilli and Kaya 2003;Deveci *et al.* 2007;Alptekin *et al.* 2009).The reliability and validity functions of the Turkish version of the CIDI were studied as part of an international study (Rezaki *et al.* 1995). The CIDI was found to have excellent inter-rater reliability in almost all sections with kappa values ranging from 0.67 to 0.97 (Wittchen *et al.* 1991). In particular, kappa for agreement between clinicians for delusions and hallucinations was found to be 0.85 and 0.87, respectively. Furthermore, the sensitivity of the CIDI was found to be higher than its specificity for both delusions (0.93 vs. 0.55) and hallucinations (0.86 vs. 0.50) (Cooper *et al.* 1998).

Assessment of Psychotic Experiences

PE were rated using 14 CIDI delusions items (G1, G2, G3, G4, G5, G7, G8, G9, G10, G11, G12, G13, G13b and G14) and 5 CIDI hallucinations items (G17, G18, G20, G20C, and G21). All items were rated dichotomously indicating presence or absence. The time frame for PE was lifetime at T_0 and the last six years at T_1.

The rating of PE can be difficult because sometimes individuals can be describing a plausible event that in the CIDI may be rated as a psychotic experience. Therefore, the following procedures were followed. First, during the interview, each time a participant endorsed a CIDI psychotic experience, the participant was asked to give an example, which was written down verbatim by the interviewer for later review with the team psychiatrist and/or senior psychologist. When it was not clear whether or not the participant had truly endorsed a positive psychotic experience, the participant was re-contacted by the team psychiatrist over the telephone to confirm the experience.

Persistence of PE was recoded into transient or persistent according to presence at follow-up assessment. Co-presence of delusional and hallucinatory PE was recoded into a dummy variable: 0=delusional or hallucinatory 1=combined delusional and hallucinatory

Assessment of Baseline (T_1) Mood Disorders

In order to evaluate the presence of any mood disorder at baseline assessment, a binary variable was constructed and coded positive if there was either a CIDI depressive or a hypomanic/manic episode, as described below.

For depression, participants were asked if they had experienced an episode lasting at least two weeks during which they felt depressed, or had a lack of interest. Depressive symptoms were only rated if any of the core items (depressed mood and loss of interest) were endorsed as having been present for 2 weeks. If endorsed, participants were asked if, during this period, they had

experienced lack of energy, appetite change, sleep problems, being slow or restless, feelings of worthlessness or guilt, decreased self-esteem, trouble thinking or indecisiveness, and thoughts of death. For a manic/hypomanic episode, participants were asked whether they had experienced elevated mood or irritability for a period of at least 4 consecutive days either noticed by others or causing problems. If this was the case, participants were asked if, during this period, they had experienced excessive goal-directed activity, psychomotor agitation, spending sprees, sexual indiscretions, increased talkativeness, flight of ideas, loss of normal social inhibitions, increased self-esteem or grandiosity, decreased need for sleep, and distractibility. For both depressive and manic symptoms, association with substance use or physical conditions; help-seeking, clinician diagnosis and treatment history were assessed. Depressive and hypomanic/manic episode was coded positive in accordance with the definitions and criteria of DSM-IV. Time frame for baseline mood disorders was the past year.

Other Assessments

The baseline and follow-up assessments included a sociodemographic questionnaire in order to determine various risk factors and background characteristics. In guidance of the previous literature revealing that onset of psychotic disorders occurs usually in late adolescence and progresses over time (Fusar-Poli *et al.* 2014), age (in years in 2008) was recoded into 15-30 and >30. Level of education was defined in regard to last graduated school. Socioeconomic status (SES proxy) was based on the profession of the participant (if the participant had no profession, father/husband's profession was used instead) and recoded into 3 ordinal categories: 1=Professional and non-manual employees, 2=Owners of small businesses, 3=Manual workers (Goldthorpe 1987).

Using questions derived from the Family Interview for Genetic Studies (NIMH 1992), history of mental disorders in the father, mother, siblings, and offspring was assessed. Thus, a 'family history of mental disorders' variable was defined and coded guided by previous literature (Mortensen *et al.* 2010): 0=No or undefined fami-

ly history of mental disorders; 1=Common mental disorder (depression/anxiety disorders) in at least one family member but no severe mental illness; 2=Severe mental illness (bipolar disorder/ psychotic disorder/hospitalization/completed suicide) in at least one family member (Binbay *et al.* 2012b).

Alcohol and cannabis use were assessed using screening questions on CIDI alcohol and substance-related disorders sections. Conform previous CIDI-based research, cannabis use of 5 times or more was defined as exposure status for cannabis. Regular alcohol use was defined as use of alcohol at least once a week. Using information from both T_1 and T_2, alcohol use was recoded into 3 variables: 0=Never used; 1=History of alcohol use at any level but no regular use at follow-up assessment; 2=Regular alcohol use at follow-up assessment.

Life events were assessed at follow-up using the List of Threatening Life Events Questionnaire (Brugha and Cragg 1990). Time frame was the last six years. The number of life events was a continuous variable with a minimum of 0 and maximum of 12.

Dependent Variable

The main outcome of the study was follow-up diagnosis of participants based on the SCID-I. Guided by previous research (Kessler *et al.* 2005), standardized diagnostic hierarchy rules among the disorders were applied when there was more than one diagnosis. Follow-up diagnostic outcomes were also categorised into two groups according to the psychotic features: the *psychotic disorder (PD)* group included participants who had any DSM-IV diagnosis with clinical psychotic features (including schizophrenia and other psychotic disorders; mood disorders with psychotic features; psychotic disorder due to general medical condition; substance-induced psychotic disorder). The *non-psychotic disorders* group included participants who had any DSM-IV disorder without psychotic features (e.g. mood disorders without psychotic features, anxiety disorders, somatoform disorders, substance use disorders, impulse control disorders, dementia, primary insomnia).

Statistical Analyses

All analyses were conducted using the software package STATA, version 13.1. First, we performed the analysis to explore the role of factors in the association between baseline PE and presence of any DSM diagnoses at follow-up. In these analyses, logistic regression was used with the dependent variable *any/no follow-up DSM-IV diagnosis*.

Table 1: Baseline characteristics and comparison of those participated with lost to follow-up

	Participated at Follow-up (n:187) n (%)	Lost to Follow-up (n:120) n (%)	χ^2	Df	p	Cramer's *V*
Age Categories (Year 2008)						
>30	113 (60.4)	63 (52.5)	1.88	1	0.2	0.08
15-30	74 (39.6)	57 (47.5)				
Sex						
Female	129 (31.0)	45 (37.5)	1.38	1	0.2	0.07
Male	58 (69.0)	75 (62.5)				
Education						
Higher	51 (27.3)	42 (35.6)	2.36	1	0.1	0.09
Lower	136 (72.7)	78 (64.4)				
Marital Status						
Married	122 (65.2)	70 (57.6)	1.78	1	0.2	0.08
Non-married	65 (34.8)	50 (42.4)				
SES Proxy						
Professional	52 (27.8)	38 (32.2)	1.52	2	0.5	0.07
Owner of Small Business	28 (15.0)	21 (17.8)				
Manuel Workers	107 (57.2)	61 (50.0)				
Ethnicity						
Turkish	149 (79.7)	100 (83.3)	0.64	1	0.4	0.04
Non-Turkish	38 (20.3)	20 (16.7)				
Contact with a Mental Health Service						
None	138 (73.8)	90 (75.0)	0.05	1	0.8	0.01
At least once	49 (26.2)	30 (25.0)				
Comorbid Mood Disorder						
None	89 (47.6)	60 (50)	0.17	1	0.7	0.02
Present	98 (52.4)	60 (50)				
Co-presence of Delusional and Hallucinatory PE						
Delusional or Hallucinatory	104 (55.6)	62 (51.7)	0.46	1	0.5	0.04
Combined Delusional & Hallucinatory	83 (44.4)	58 (48.3)				
Cannabis Use						
None	177 (94.6)	110 (91.7)	1.07	1	0.3	0.06
Yes	10 (5.4)	10 (8.3)				

We explored the role of factors in developing a psychotic disorder in comparison with non-psychotic disorder. Participants with a follow-up DSM diagnosis were included, logistic regression was performed with the dependent variable *psychotic versus non-psychotic follow-up DSM-IV disorder*. Associations were presented both without adjustment and also adjusted for other variables such as socio-demographic factors (age, sex, SES proxy and marital status), presence of baseline mood disorder, family history of mental disorders, alcohol/cannabis use and number of life events. Multicollinearity was assessed using correlation matrix and variance inflation factor (VIF).

Results

Participant Characteristics

Detailed characteristics of the sample were depicted in table 1. There were no large or significant differences between participants and non-participants at follow-up according to socio-demographic and clinical characteristics (table 1). Sixty-seven participants (35.8%) reported use of psychotropic medication and thirteen (7.0%) reported antipsychotic use.

Follow-up DSM Outcomes of Participants with Baseline Psychotic Experiences

Of the participants with baseline PE (n=187), 7.0% (n=13) transitioned to psychotic disorder at follow-up (6 with DSM-IV schizophrenia and related disorder; 7 with DSM-IV mood disorders with psychotic features; Table 1). Of non-transitioned participants (n=174); 70.7% (n=123) had at least one DSM-IV diagnosis at follow-up (46.0% DSM-IV mood disorder without psychotic features, 24.7% other non-psychotic DSM-IV disorder). Details of the follow-up DSM diagnoses are presented in table 2.

Table 2: DSM-IV diagnoses at 6-year follow-up in respondents with baseline PE

Diagnostic Category	Cases (n)	%
Schizophrenia and Related Disorders	6	3.2
Schizophrenia	3	1.7
Schizoaffective Disorder	1	0.5
Substance-Induced Psychotic Disorder	1	0.5
Psychotic Disorder Due to General Medical Conditions	1	0.5
Mood Disorders	87	46.5
Bipolar Disorder with Psychotic Features	5	2.7
Bipolar Disorder without Psychotic Features	9	4.8
Major Depressive Dis. with Psychotic Features	2	1.1
Major Depressive Dis. without Psychotic Features	68	36.3
Dysthymic Disorder	3	1.6
Anxiety Disorders	26	13.9
Generalized Anxiety Disorder	18	9.6
Obsessive-Compulsive Disorder	3	1.6
Panic Disorder	3	1.6
Posttraumatic Stress Disorder	2	1.1
Other Non-Psychotic Disorders	17	9.1
Somatoform Disorders	8	4.3
Substance-Related Disorders	6	3.2
Dementia	1	0.5
Impulse Control Disorder Not Otherwise Specified	1	0.5
Primary Insomnia	1	0.5
No diagnosis	51	27.3
Total	187	100

Factors associated with presence of any follow-up DSM diagnosis in participants with baseline PE

Of participants with baseline PE (n=187), 72.7% (n=136) had a DSM-IV diagnosis (psychotic or non-psychotic) at follow-up. Female sex, co-occurrence of mood disorders and persistence of PE predicted any follow-up DSM diagnosis outcome. Family history of any mental disorder was also associated with presence of follow-up DSM diagnosis although this association was attenuated on inclusion of other factors (Table 3).

Table 3: Factors associated with any DSM diagnosis at 6-year follow-up in respondents with baseline PE

Variables			Presence of Any Follow-up DSM Diagnosis					Presence of Any Follow-up DSM Diagnosis Adjusted [a]			
			Prevalence		Logistic Regression			Logistic Regression			
	N	%	N	%	OR	95% CI	p	OR	95%CI	P	Mean VIF
Sociodemographic Variables											
Age Categories (Year 2008)											
>30	113	60.4	83	73.4	Ref	-	-	Ref	-	-	
15-30	74	39.6	53	71.6	0.9	0.5-1.7	0.8	0.6	0.3-1.3	0.2	1.77
Sex											
Male	58	31.0	38	65.5	Ref	-	-	Ref	-	-	
Female	129	69.0	98	76.0	1.7	0.8-3.3	0.1	**3.1**	**1.2-7.8**	**<0.05**	2.25
Education											
Higher	70	37.4	51	72.8	Ref	-	-	Ref	-	-	
Lower	117	62.6	85	72.6	0.9	0.5-1.9	0.9	1.3	0.6-3.0	0.5	2.52
Marital Status											
Married	125	66.8	87	69.6	Ref	-	-	Ref	-	-	
Non-married	62	33.2	49	79.0	1.6	0.8-3.4	0.2	1.1	0.4-2.7	0.9	2.25
Baseline Psychopathology											
Comorbid Mood Disorder											
None	89	47.6	52	58.4	Ref	-	-	Ref	-	-	
Present	**98**	**52.4**	**84**	**85.7**	**4.3**	**2.1-8.6**	**<0.001**	**4.7**	**2.1-10**	**<0.001**	2.25
Co-presence of Delusional and Hallucinatory PE											
Delusional or Hallucinatory	104	55.6	70	67.3	Ref	-	-	Ref	-	-	
Combined Delusional &Hallucinatory	83	44.4	66	79.5	1.9	0.9-3.7	0.06	1.9	0.9-4.2	0.1	2.24
Persistence of PE											
Transient PE	91	48.7	53	58.2	Ref	-	-	Ref	-	-	
Persistent PE	96	51.3	**83**	**86.5**	**4.6**	**2.2-9.4**	**<0.001**	**5.2**	**2.2-12**	**<0.001**	2.28
Family History											
Disorder in 1 family member											
No or undefined	137	73.3	94	68.6	Ref	-	-	Ref	-	-	
A defined mental disorder	**50**	**27.7**	**42**	**84.0**	**2.4**	**1.1-5.5**	**<0.05**	2.1	0.8-5.3	0.1	2.37
Type of family history											
No or undefined	137	73.3	94	68.6	Ref	-	-	Ref	-	-	
Common mental disorders	37	19.8	30	81.1	1.9	0.8-4.8	0.1	1.9	0.7-5.3	0.2	2.25
Severe mental illness	13	6.9	12	92.3	5.5	0.7-43.5	0.1	2.9	0.3-25.8	0.3	
Baseline PE group	187	100	136	72.7	-	-	-	-	-	-	-

[a] Adjusted for age, gender, marital status, SES proxy, presence of baseline mood disorder, family history of mental disorders, alcohol use, cannabis use and number of life events

Factors associated with developing a psychotic disorder in comparison with non-psychotic disorder

Of the participants with any DSM diagnosis at follow-up (n=136), 9.6% (n=13) had a psychotic disorder. Participants in the age range of adolescence or early adulthood (15-30 years old) had more risk to develop a psychotic disorder in comparison with older participants. Furthermore, participants with combined delusional and hallucinatory PE at baseline were more likely to develop a psychotic disorder than participants with only delusional or hallucinatory PE. However these latter associations were attenuated when adjusted for other factors. Family history of severe mental illness was significantly associated with developing a psychotic disorder in comparison with non-psychotic disorder (Table 4). Tests indicated that no significant multicollinearity was present (Table 3 and 4).

Discussion

Follow-up DSM-IV Diagnoses in Participants with Baseline Psychotic Experiences

The six-year transition to PD rate in this study of 7.0% (i.e. around 1% per year) is consistent with the previous community-based findings (Kaymaz *et al.* 2012;Linscott and van Os 2013). 70.7% of non-transitioned participants with baseline PE had a DSM-IV diagnosis at follow-up. Forty-six percent of the non-transitioned participants had a mood disorder. Although any comparison with the UHR literature is problematic, as mentioned earlier, this proportion is similar to a recent UHR study showing that 68.1% of non-transitioned high-risk participants met criteria for at least one disorder and 48.7% met criteria for a mood disorder (Lin *et al.* 2015). The prevalence of non-psychotic disorders in participants with baseline PE was higher than the estimates of these disorders in the general population (Topuzoglu *et al.* 2015). Furthermore, the follow-up psychotic disorder rate was much lower than the rate of non-psychotic disorders. These findings are in line with previous evidence linking PE with

Table 4: Factors associated with developing a psychotic DSM disorder versus a non-psychotic DSM disorder at 6-year follow-up in respondents with baseline PE

			Psychotic Disorder Outcome					Psychotic Disorder Outcome Adjusted[a]			
			Incidence		Logistic Regression			Logistic Regression			
	N	%	N	%	OR	95% CI	p	OR	95%CI	p	Mean VIF
Socio-demographics											
Age Categories (2008)											
>30	83	61.0	4	4.8	Ref	-	-	Ref	-	-	
15-30	53	39.0	9	17.0	**4.0**	**1.2-13.9**	**<0.05**	3.3	0.7-16.0	0.1	1.94
Sex											
Male	38	27.9	4	10.5	Ref	-	-	Ref	-	-	
Female	98	72.1	9	9.2	0.8	0.2-3.0	0.8	4.1	0.6-29.2	0.2	2.48
Education											
Higher	51	37.5	4	7.8	Ref	-	-	Ref	-	-	
Lower	85	62.5	9	10.6	1.4	0.4-4.8	0.6	2.2	0.4-13.8	0.4	2.80
Marital Status											
Married	87	64.0	6	6.9	Ref	-	-	Ref	-	-	
Non-married	49	36.0	7	14.3	2.2	0.7-7.1	0.2	0.8	0.1-4.5	0.8	2.48
Baseline Psychopathology											
Comorbid Mood Disorder											
None	52	38.2	6	11.5	Ref	-	-	Ref	-	-	
Present	84	61.8	7	8.3	0.7	0.2-2.2	0.5	0.5	0.1-2.1	0.3	2.48
Co-presence of Delusional and Hallucinatory PE											
Delusional or Hallucinatory	70	51.5	3	4.3	Ref	-	-	Ref	-	-	
Combined Delusional &Hallucinatory	**66**	**48.5**	**10**	**15.2**	**4.0**	**1.1-15.2**	**<0.05**	3.2	0.6-16.5	0.2	2.47
Family History											
Disorder in one family member											
No or undefined	94	69.1	6	6.4	Ref	-	-	Ref	-	-	
A defined mental disorder	42	30.9	7	16.7	2.9	0.9-9.3	0.06	3.1	0.8-12.6	0.1	2.62
Type of Family History											
No or undefined	94	69.1	6	6.4	Ref	-	-	Ref	-	-	
Common mental disorders	30	22.1	4	13.3	2.2	0.6-8.6	0.2	2.0	0.4-10.2	0.4	2.48
Severe mental illness	**12**	**8.8**	**3**	**25.0**	**4.9**	**1.1-22.9**	**<0.05**	**7.4**	**1.1-50.0**	**<0.05**	
Baseline PE group with any diagnoses at follow-up	136	100	13	9.6	-	-	-	-	-	-	-

[a] Adjusted for age, gender, marital status, SES proxy, presence of baseline mood disorder, family history of mental disorders, alcohol use, cannabis use and number of life events.

increased risk of later non-psychotic psychopathology (Chapman *et al.* 1994;Dhossche *et al.* 2002;Addington *et al.* 2011;De Loore *et al.* 2011;Rossler *et al.* 2011;Kaymaz *et al.* 2012;Werbeloff *et al.* 2012;Kelleher *et al.* 2014;Sullivan *et al.* 2014;McGrath *et al.* 2016;Bhavsar *et al.* 2017). Majority of individuals with PE in the general population does not develop a psychotic disorder but still need care for non-psychotic disorders. Outcome of PE over

follow-up in the general population appears to take the form of a wide range of mental disorders including bipolar disorder, depression, anxiety disorder, somatoform disorder and impulse control disorder as well as psychotic disorders. It may be useful to consider PE as a risk indicator that has trans-diagnostic value (van Os and Reininghaus 2016).

Factors Associated with the Follow-up Outcomes of Baseline Psychotic Experiences

The follow-up outcome of baseline PE may be usefully divided into three types (i) no clinical disorder; (ii) non-psychotic disorder (trans-diagnostic phenotype) and (iii) psychotic disorder (psychotic outcome). In addition, a range of moderators may be relevant.

Participants in the adolescent or early adulthood age range had a similar risk of developing a follow-up DSM disorder as older participants. However, they were more likely to a psychotic disorder outcome of baseline PE than older participants. This finding is in line with previous studies showing associations between younger age and different levels of the extended psychosis phenotype (van Os *et al.* 2000;Verdoux and van Os 2002;van Os *et al.* 2009). Developmental maturation of the frontal cortex and synaptic pruning accelerate during adolescence (Fatemi and Folsom 2009).The normal neurobiology of the adolescent and early adult human brain may have a unique sensitivity for manifesting psychosis in comparison with older individuals (Hyde *et al.* 1992;Paus *et al.* 2008). However, as psychotic disorders often emerge around the third decade, it should be kept in mind that in excluding the baseline 'psychosis caseness' the age-of-onset curve in the remaining sample may have been shifted to the right, resulting in relatively low rates. Therefore, this particular factor might have impacted on the analysis of the effect of age.

Women had a greater risk to develop a follow-up DSM disorder than men, adjusting for other variables. This finding is in line with a recent study, albeit in a help-seeking sample, reporting

higher rates of persistent or recurrent non-psychotic disorder in women in a follow-up of a UHR sample (Lin *et al.* 2015). However, no significant differences between the sexes were found in risk of developing a psychotic disorder in comparison with non-psychotic disorder. A male excess in psychotic disorder is seen with narrow definitions, whereas broader definitions show a female excess (Castle *et al.* 1993). Our psychotic disorder outcome variable (including both non-affective and affective psychosis) thus may explain why no significant sex difference was found. Participants displaying both delusional and hallucinatory PE at baseline were more prone to psychotic disorder outcome of PE in comparison with participants having only delusional or hallucinatory PE. It has been shown that more severe genetic and environmental risk may underlie the co-presence of delusional and hallucinatory PE at baseline (Smeets *et al.* 2013), which the current result may predict poorer transition outcomes. The fact that the association between baseline co-presence of delusional and hallucinatory experiences and psychotic outcome was weakened after adjustment for other causes confirms the hypothesis that co-presence of delusional and hallucinatory experiences reflects greater exposure to risk.

PE at the population level are known to be closely associated with non-psychotic disorders (Linscott and van Os 2013). Our results demonstrated that more than half of participants with baseline PE had a concurrent mood disorder. Participants with both baseline PE and mood disorders had more risk to develop a follow-up DSM diagnosis than participants with PE in isolation. This result is line with epidemiological studies reporting that greater degree of affective dysregulation predicts help-seeking behaviour and dysfunction associated with PE (van Rossum *et al.* 2011;Wigman *et al.* 2012;Guloksuz *et al.* 2015). Nevertheless, baseline co-occurrence of mood disorders with PE was not associated with developing a psychotic disorder in comparison with non-psychotic disorder. This result is in line with a previous finding reporting that mania and depression have a stronger impact below the psychotic disorder end of the spectrum (Bin-

bay *et al.* 2012b). However, the non-significance of the association might also be explained by the fact that the psychotic disorder group was not restricted to non-affective psychosis. A recent study with a clinical sample reported that co-occurrence of depression with PE predicts persistence of PE (Salokangas *et al.* 2016). Persistence of PE can be considered as a significant marker of emerging psychotic impairment (Dominguez *et al.* 2011). Furthermore, our results showed that persistence also increases the risk of non-psychotic disorders.

Having a family history of mental disorder significantly increased the risk of having a follow-up DSM diagnosis in participants with baseline PE, however this association was basically attenuated on inclusion of presence of baseline mood disorders. A plausible explanation is that genetic risk also impacts the risk of baseline mood disorder and can thus be considered on the same causal pathway. Furthermore, participants with a family history of severe mental illness were more prone to psychotic disorder outcome of PE in comparison with participants with no such family history. This result is in line with a previous finding reporting that loading with more severe mental illness was associated with increased risk of the disorder end of the psychosis spectrum (Binbay *et al.* 2012b).Thus, it may be hypothesized that 'severity' of familial risk translates to 'severity' of the transition outcome.

Strengths and Limitations

As far as we know, this is the first longitudinal study in a community-based population that examines follow-up 'any' clinical diagnosis of baseline PE based on interviews performed by psychiatrists. The design and the fact that the study was conducted in a representative population-based sample enabled us to include non-help-seeking individuals and so prevent potential help-seeking bias and increased transition rates due to sample enrichment (van Os and Guloksuz 2017). Furthermore, we were able to take baseline differences in multidimensional psychopathology, socio-demographic features and familial risk may into account.

Moreover, the design of the study enabled us to adjust the results for other causes of psychopathology including life events and substances. Nevertheless, the results need to be considered in the light of the following limitations. First, as with most longitudinal studies with general population-based samples, a limitation is the possibility of selection bias caused by differential attrition over time. The comparison of baseline socio-demographic and clinical characteristics between non-participants and participants showed no large or significant differences. Furthermore, the six-year transition rate from PE to psychotic disorders found in our sample (7.0%) is consistent with previous meta-analytical findings (Kaymaz *et al.* 2012;Linscott and van Os 2013), supporting the present conclusions. Therefore, it is unlikely that attrition would have created bias in results. Second, the low number of participants who transitioned from PE to PD (n=13) resulted in less than five participants in some subgroups of participants with follow-up psychotic disorder (age categories, sex, education, co-presence of delusional and hallucinatory PE, type of family history; table 4). Therefore, the analyses with the dependent variable *psychotic vs. non-psychotic disorder* may have insufficient statistical power. Results of these analyses are explorative and need to be replicated. Third, our baseline PE group consisted of individuals with PE either with a duration of at least "1 week" or with a frequency of at least "sometimes" or associated with help-seeking/interference with functioning or enjoying relationships. Thus, these results cannot be generalized to individuals with less severe forms of PE. Furthermore, we considered only the positive dimension of PE, whereas negative and disorganized dimensions are also relevant (van Os and Reininghaus 2016). Therefore, these results cannot be generalized to negative and disorganised dimensions. Fourth, as we do not have follow-up SCID data of the participants who did not have PE at baseline, we unfortunately cannot introduce control comparisons. Therefore, we compared the prevalence of disorders in participants with baseline PE with the estimates of the disorders in the general population. Fifth, the baseline diagnostic interviews were conducted with a view to identify participants

with psychotic disorder (Binbay *et al.* 2011). Thus, the baseline DSM-IV diagnoses of some participants were missing. Therefore, we were not able to define the rate of incident common mental disorders in participants with baseline PE. Finally, women were overrepresented which may bias toward higher levels of mood and anxiety disorders.

Conclusion

This longitudinal epidemiological study with clinical diagnostic interviews showed that the majority of participants with baseline PE develop a non-psychotic DSM disorder (particularly mood and anxiety disorders) rather than a psychotic disorder. Sociodemographic factors, genetic risk and baseline severity of multidimensional psychopathology may impact on course and outcome of PE. Results may have important implications for the conceptualisation of PE, decision-making in high risk settings and clinical care for individuals with PE seeking help at the level of health services. Future studies should take into account non-psychotic disorder outcome of PE in addition to psychotic disorder outcomes.

References

- Addington J, Cornblatt BA, Cadenhead KS, *et al.* (2011). At clinical high risk for psychosis: outcome for nonconverters. *The American journal of psychiatry* 168, 800-805.

- Alptekin K, Ulas H, Akdede BB, Tumuklu M , Akvardar Y (2009). Prevalence and risk factors of psychotic symptoms: in the city of Izmir, Turkey. *Social psychiatry and psychiatric epidemiology* 44, 905-910.

- Andrews G , Peters L (1998). The psychometric properties of the Composite International Diagnostic Interview. *Social psychiatry and psychiatric epidemiology* 33, 80-88.

- Bhavsar V, Maccabe JH, Hatch SL, Hotopf M, Boydell J , McGuire P (2017). Subclinical psychotic experiences and subsequent contact with mental health services. *BJPsych open* 3, 64-70.

- Binbay T, Alptekin K, Elbi H, *et al.* (2012a). [Lifetime prevalence and correlates of schizophrenia and disorders with psychotic symptoms in the general population of Izmir, Turkey]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 23, 149-160.

- Binbay T, Drukker M, Elbi H, *et al.* (2012b). Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophrenia bulletin* 38, 992-1002.

- Binbay T, Elbi H, Alptekin K, *et al.* (2011). Izmir mental health survey for gene-environment interaction in psychoses (TurkSch): objectives and methodology. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 22, 65-76.

- Brugha TS , Cragg D (1990). The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta psychiatrica Scandinavica* 82, 77-81.

- Cannon TD, Cadenhead K, Cornblatt B*, et al.* (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of general psychiatry* 65, 28-37.

- Carrion RE, McLaughlin D, Goldberg TE*, et al.* (2013). Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry* 70, 1133-1142.

- Castle DJ, Wessely S , Murray RM (1993). Sex and schizophrenia: effects of diagnostic stringency, and associations with and premorbid variables. *British Journal of Psychiatry* 162, 658-664.

- Chapman LJ, Chapman JP, Kwapil TR, Eckblad M , Zinser MC (1994). Putatively psychosis-prone subjects 10 years later. *Journal of abnormal psychology* 103, 171-183.

- Cilli AS , Kaya N (2003). [Nicotine dependence and psychiatric comorbidity among university students]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 14, 42-49.

- Collip D, Myin-Germeys I , Van Os J (2008). Does the concept of "sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophrenia bulletin* 34, 220-225.

- Cooper L, Peters L , Andrews G (1998). Validity of the Composite International Diagnostic Interview (CIDI) psychosis module in a psychiatric setting. *Journal of psychiatric research* 32, 361-368.

- Cougnard A, Marcelis M, Myin-Germeys I*, et al.* (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychological medicine* 37, 513-527.

- De Loore E, Gunther N, Drukker M*, et al.* (2011). Persistence and outcome of auditory hallucinations

in adolescence: a longitudinal general population study of 1800 individuals. *Schizophrenia research* 127, 252-256.

- Debbane M, Eliez S, Badoud D, Conus P, Fluckiger R , Schultze-Lutter F (2015). Developing psychosis and its risk states through the lens of schizotypy. *Schizophrenia bulletin* 41 Suppl 2, S396-407.

- Deveci A, Taskin O, Dinc G*, et al.* (2007). Prevalence of pseudoneurologic conversion disorder in an urban community in Manisa, Turkey. *Social psychiatry and psychiatric epidemiology* 42, 857-864.

- Dhossche D, Ferdinand R, Van der Ende J, Hofstra MB , Verhulst F (2002). Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychological medicine* 32, 619-627.

- Dominguez MD, Wichers M, Lieb R, Wittchen HU , van Os J (2011). Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia bulletin* 37, 84-93.

- Dragt S, Nieman DH, Veltman D*, et al.* (2011). Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk. *Schizophrenia research* 125, 69-76.

- Falkenberg I, Valmaggia L, Byrnes M*, et al.* (2015). Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? *Psychiatry research* 228, 808-815.

- Fatemi SH , Folsom TD (2009). The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophrenia bulletin* 35, 528-548.

- Fisher HL, Caspi A, Poulton R*, et al.* (2013). Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychological medicine* 43, 2077-2086.

- Fonseca Pedrero E , Debbane M (2017). Schizotypal traits and psychotic-like experiences during adolescence: An update. *Psicothema* 29, 5-17.

- Fusar-Poli P, Bonoldi I, Yung AR*, et al.* (2012). Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of general psychiatry* 69, 220-229.

- Fusar-Poli P, Carpenter WT, Woods SW , McGlashan TH (2014). Attenuated psychosis syndrome: ready for DSM-5.1? *Annual review of clinical psychology* 10, 155-192.

- Fusar-Poli P , Schultze-Lutter F (2016). Predicting the onset of psychosis in patients at clinical high risk: practical guide to probabilistic prognostic reasoning. *Evidence-based mental health* 19, 10-15.

- Goldthorpe J (1987). *Social mobility and class structure in modern Britain*. Clarendon Press: New York.

- Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen HU , 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* 45, 2389-2401.

- Hanssen M, Bak M, Bijl R, Vollebergh W , van Os J (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *The British journal of clinical psychology* 44, 181-191.

- Honings S, Drukker M, van Nierop M*, et al.* (2016). Psychotic experiences and incident suicidal ideation and behaviour: Disentangling the longitudinal associations from connected psychopathology. *Psychiatry research* 245, 267-275.

- Hyde TM, Ziegler JC , Weinberger DR (1992). Psychiatric disturbances in metachromatic leukodystrophy. Insights into the neurobiology of psychosis. *Archives of neurology* 49, 401-406.

- Kaymaz N, Drukker M, Lieb R, *et al.* (2012). Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychological Medicine* 42, 2239-2253.
- Kelleher I, Cederlof M , Lichtenstein P (2014). Psychotic experiences as a predictor of the natural course of suicidal ideation: a Swedish cohort study. *World psychiatry : official journal of the World Psychiatric Association* 13, 184-188.
- Kelleher I, Harley M, Murtagh A , Cannon M (2011). Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophrenia bulletin* 37, 362-369.
- Kelleher I, Keeley H, Corcoran P, *et al.* (2012). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *The British journal of psychiatry : the journal of mental science* 201, 26-32.
- Kelleher I, Wigman JT, Harley M, *et al.* (2015). Psychotic experiences in the population: Association with functioning and mental distress. *Schizophrenia research* 165, 9-14.
- Kessler RC, Chiu WT, Demler O, Merikangas KR , Walters EE (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry* 62, 617-627.
- Kish L (1949). A procedure for objective respondent selection withinthe household. *Journal of the American Statistical Association* 44, 380–387.
- Lin A, Wood SJ, Nelson B, Beavan A, McGorry P , Yung AR (2015). Outcomes of nontransitioned cases in

a sample at ultra-high risk for psychosis. *The American journal of psychiatry* 172, 249-258.

- Linscott RJ , van Os J (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine* 43, 1133-1149.

- McGrath JJ, Saha S, Al-Hamzawi A*, et al.* (2016). The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *The American journal of psychiatry*, appiajp201615101293.

- Mortensen PB, Pedersen MG , Pedersen CB (2010). Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychological Medicine* 40, 201-210.

- Nelson B, Yuen HP, Wood SJ*, et al.* (2013). Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA psychiatry* 70, 793-802.

- NIMH (1992). *NIMH Genetics Initiative: Family Interview for Genetic Studies (FIGS)*. MD National Institute of Mental Health: Rockville.

- Paus T, Keshavan M , Giedd JN (2008). Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci* 9, 947-957.

- Perlis RH, Uher R, Ostacher M*, et al.* (2011). Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. *Archives of general psychiatry* 68, 351-360.

- Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R , Harrington H (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Archives of general psychiatry* 57, 1053-1058.

- Rezaki M, Ozgen G, Kaplan I, Gursoy B, Sagduyu A , Ozturk O (1995). Results from Ankara center. In *Mental Illness in General Health Care: An International Study* (ed. T. B. Ustun and N. Sartorius), pp. 39-56. John Willey & Sons: Chichester.

- Robins LN, Wing J, Wittchen HU*, et al.* (1988). The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of general psychiatry* 45, 1069-1077.

- Rossler W, Hengartner MP, Ajdacic-Gross V, Haker H, Gamma A , Angst J (2011). Sub-clinical psychosis symptoms in young adults are risk factors for subsequent common mental disorders. *Schizophrenia research* 131, 18-23.

- Salokangas RK, Schultze-Lutter F, Hietala J*, et al.* (2016). Depression predicts persistence of paranoia in clinical high-risk patients to psychosis: results of the EPOS project. *Social psychiatry and psychiatric epidemiology* 51, 247-257.

- Schmidt SJ, Schultze-Lutter F, Schimmelmann BG*, et al.* (2015). EPA guidance on the early intervention in clinical high risk states of psychoses. *European psychiatry : the journal of the Association of European Psychiatrists* 30, 388-404.

- Schultze-Lutter F, Michel C, Schmidt SJ*, et al.* (2015). EPA guidance on the early detection of clinical high risk states of psychoses. *European psychiatry : the journal of the Association of European Psychiatrists* 30, 405-416.

- Shah J, Eack SM, Montrose DM*, et al.* (2012). Multivariate prediction of emerging psychosis in adolescents at high risk for schizophrenia. *Schizophrenia research* 141, 189-196.

- Smeets F, Lataster T, van Winkel R, de Graaf R, ten Have M , van Os J (2013).

Testing the hypothesis that psychotic illness begins when subthreshold hallucinations combine with delusional ideation. *Acta psychiatrica Scandinavica* 127, 34-47.

- Smeets F, Lataster T, Viechtbauer W , Delespaul P (2015). Evidence that environmental and genetic risks for psychotic disorder may operate by impacting on connections between core symptoms of perceptual alteration and delusional ideation. *Schizophrenia bulletin* 41, 687-697.

- Spitzer RL, Williams JB, Gibbon M , First MB (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of general psychiatry* 49, 624-629.

- Sullivan SA, Wiles N, Kounali D*, et al.* (2014). Longitudinal associations between adolescent psychotic experiences and depressive symptoms. *PloS one* 9, e105758.

- Topuzoglu A, Binbay T, Ulas H*, et al.* (2015). The epidemiology of major depressive disorder and subthreshold depression in Izmir, Turkey: Prevalence, socioeconomic differences, impairment and help-seeking. *Journal of affective disorders* 181, 78-86.

- van Dam DS, van Nierop M, Viechtbauer W*, et al.* (2015). Childhood abuse and neglect in relation to the presence and persistence of psychotic and depressive symptomatology. *Psychological medicine* 45, 1363-1377.

- van Os J , Guloksuz S (2017). A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry* 16, 200-206.

- van Os J, Hanssen M, Bijl RV , Ravelli A (2000). Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophrenia research* 45, 11-20.

- van Os J, Linscott RJ, Myin-Germeys I, Delespaul P , Krabbendam L (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for

a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological medicine* 39, 179-195.

- van Os J , Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World psychiatry : official journal of the World Psychiatric Association* 15, 118-124.

- van Rossum I, Dominguez MD, Lieb R, Wittchen HU , van Os J (2011). Affective dysregulation and reality distortion: a 10-year prospective study of their association and clinical relevance. *Schizophrenia bulletin* 37, 561-571.

- Verdoux H , van Os J (2002). Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophrenia research* 54, 59-65.

- Werbeloff N, Drukker M, Dohrenwend BP*, et al.* (2012). Self-reported attenuated psychotic symptoms as forerunners of severe mental disorders later in life. *Archives of general psychiatry* 69, 467-475.

- Wigman JT, van Nierop M, Vollebergh WA*, et al.* (2012). Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity--implications for diagnosis and ultra-high risk research. *Schizophrenia bulletin* 38, 247-257.

- Wittchen HU (1994). Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *Journal of psychiatric research* 28, 57-84.

- Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD , Regier D (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British journal of psychiatry : the journal of mental science* 159, 645-653, 658.

- Yung AR, Phillips LJ, Yuen HP*, et al.* (2003). Psychosis

prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia research* 60, 21-32.

- Zammit S, Kounali D, Cannon M, *et al.* (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *The American journal of psychiatry* 170, 742-750.

- Zavos HM, Eley TC, McGuire P, *et al.* (2016). Shared Etiology of Psychotic Experiences and Depressive Symptoms in Adolescence: A Longitudinal Twin Study. *Schizophrenia bulletin* 42, 1197-1206.

CHAPTER 5

Is BDNF-Val66Met Polymorphism Associated with Psychotic Experiences and Psychotic Disorder Outcome? Evidence from a 6 Years Prospective Population-based Cohort Study

Umut Kırlı [1, 2]

Tolga Binbay [3]

Marjan Drukker [2]

Hayriye Elbi [4]

Bülent Kayahan [4]

Duygu Keskin Gökçelli [4]

Ferda Özkınay [5]

Hüseyin Onay [5]

Köksal Alptekin [3]

Jim van Os [2, 6, 7]

American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 2019; 180 (2), 113-121

1 Van Education and Research Hospital, Psychiatry Unit, Van, Turkey

2 Maastricht University Medical Centre, School of Mental Health and Neuroscience, Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, PO Box 616, Vijverdal, 6200 MD, Maastricht, The Netherlands

3 Dokuz Eylul University, Faculty of Medicine, Department of Psychiatry, 35340, Izmir, Turkey

4 Ege University, Faculty of Medicine, Department of Psychiatry, 35140, Izmir, Turkey

5 Ege University, Faculty of Medicine, Department of Medical Genetics, 35140, Izmir, Turkey

6 King's College, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, UK

7 Dept. Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre, PO BOX 85500, 3508 GA Utrecht, The Netherlands.

Abstract

There is little research on genetic risk for the extended psychosis phenotype ranging from psychotic experiences to psychotic disorders. In this general population-based prospective cohort study, the longitudinal associations between BDNF-Val66Met polymorphism and the different levels of the extended psychosis phenotype were investigated. Addresses were contacted in a multistage clustered probability sampling frame covering 11 districts and 302 neighborhoods at baseline (n=4011). A nested case-control study (n=366) recruited individuals with psychotic experiences and psychotic disorders as well as individuals with no psychotic symptoms. In this subgroup, blood sampling for genetic analysis and assessment of environmental exposures were carried out, followed by clinical re-appraisal at follow-up six years later (n=254). The BDNF Val66Met polymorphism was significantly associated with the extended psychosis phenotype. The pattern of the association was that the BDNF Val66Met polymorphism impacted in a dose-response but extra-linear fashion, with stronger impact at the psychotic disorder end of the extended psychosis phenotype. Associations were still significant after adjusting for socio-demographic factors and environmental exposures including life events, childhood adversity, socioeconomic status, urbanicity and cannabis use. The BDNF Val66Met polymorphism may index susceptibility to expression of psychosis along a spectrum.

Introduction

Epidemiological studies have provided robust evidence that attenuated forms of delusional thinking and hallucinational perception are not exclusive to psychotic disorders in the general population (Linscott and van Os 2013). A wide range of literature suggests that psychotic experiences (PE) and psychotic disorders (PD) share both genetic and non-genetic features (van Os and Reininghaus 2016). In addition, the underlying biological mechanisms may be similar (van Os and Linscott 2012). Furthermore, dynamic transitions over time from PE to PD occur, as a result of the interaction between environmental exposure and genetic risk (Linscott and van Os 2013). Thus, the *extended psychosis phenotype* is comprised of PE gradually blending into PD (Kaymaz *et al.* 2012).

BDNF influences dopaminergic (Guillin *et al.* 2001), glutamatergic (Levine and Kolb 2000), serotonergic (Martinowich and Lu 2008) and cholinergic systems (Auld *et al.* 2001). Aberrant dopaminergic (Gourion *et al.* 2005), serotonergic (Vollenweider *et al.* 1998), cholinergic (Buckley *et al.* 2007) and glutamatergic function (Coyle 2012) have been characterized as some molecular phenotypes of psychosis. Therefore, BDNF gene variations may constitute risk factors for psychosis. However, there is distinct inconsistency in results between studies linking BDNF genotype and psychosis. These inconsistent results may be due to some design issues (Notaras *et al.* 2015b). First, an important proportion of studies did not take background characteristics into account as well as differential exposure to environmental factors. Second, most of the studies in the literature have been conducted with an approach based on searching for variation only between individuals with PD (e.g. schizophrenia) and the rest of the 'healthy population'. However, in the 'healthy population' PE are prevalent and thus possible shared genetic variation may have masked some of the associations (Kelleher *et al.* 2010). Furthermore, the symptoms that hallmark these disorders are heterogeneous. It is suggested that more studies should focus their attention on the effects of BDNF gene variants on clinical features of the disorders as opposed to merely exploring single

syndromes (Notaras *et al.* 2015b). Finally, the majority of studies had a cross-sectional design which could not accurately measure the modulatory effects of BDNF genotype on symptom presence and severity that might change over time. Therefore, the cross-sectional design might not be sufficient to detect diminutive effect sizes (Numata *et al.* 2007).

Using data from a general population cohort that was followed for six years, the present paper has 3 aims:

i) To explore the role of BDNF Val66Met polymorphism in presence of any psychotic symptoms (PE or PD) during follow-up.

ii) To test the associations between different levels of the extended psychosis phenotype and BDNF Val66Met polymorphism if characterized by either graded linear or more discontinuous extra-linear relationships.

iii) To explore the role of BDNF Val66Met polymorphism in transition from PE to PD.

Methods

Sample and Study Design

The present paper uses longitudinal data of a nested case-control sample recruited from the TürkSch cohort. The TürkSch is a prospective study consisting of several data collection stages to assess genetic and environmental factors underlying the extended psychosis phenotype in a representative general population sample. The TürkSch study was described in more detail in previous papers (Binbay *et al.* 2011;Binbay *et al.* 2012a;Binbay *et al.* 2012c). Baseline sample (n=4011) was randomly selected representing the wider Izmir metropolitan area (population approximately 2.650.000) (Binbay *et al.* 2011) using a multistage sampling procedure, stratified by urbanicity covering 11 districts and 302 neighborhoods. Trained lay interviewers visited those addresses in person between November 2007 and October

2008. One household member aged between 15 and 64 years was randomly selected using the Kish within-household sampling method (Kish 1949). PE were assessed using the Composite International Diagnostic Interview (CIDI) (Andrews and Peters 1998). Socio-demographic and environmental exposure variables were also assessed, as described below. The nested case-control study selected individuals with PE and PD from the baseline sample and matched those individuals with individuals with no psychotic symptoms from the same sample (*Fig. 1*). In this subgroup, blood samples were collected for genetic analysis and individuals were reappraised by a psychiatrist (n=366). 6 years after the baseline assessment (years 2013-2015), a follow-up assessment was set to assess the mental health outcomes and

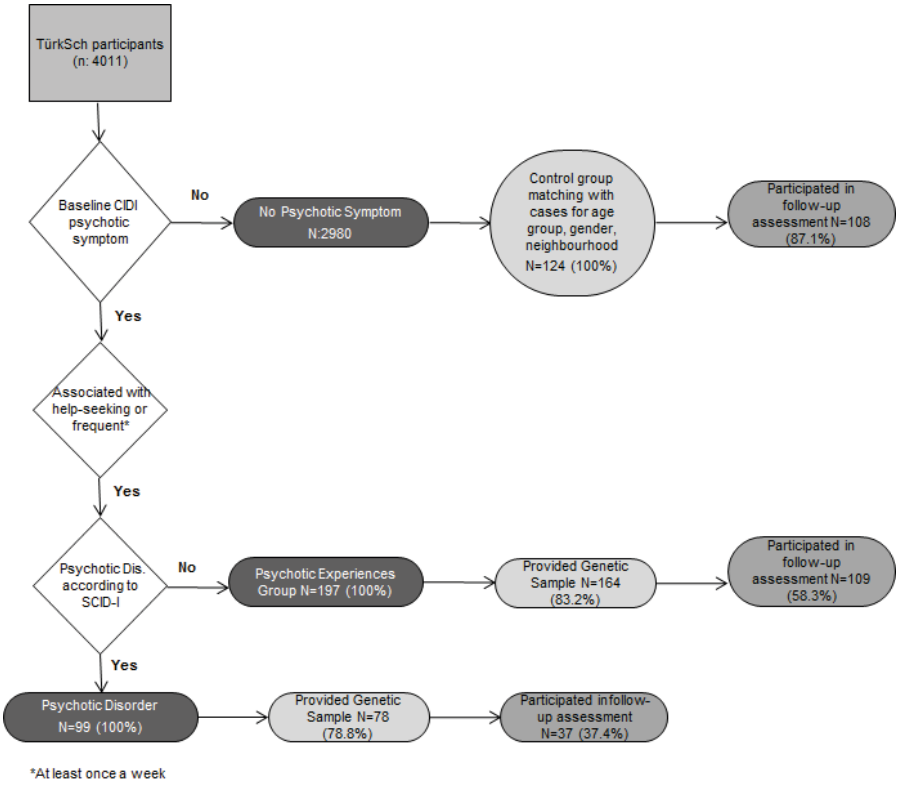


Figure 1: Recruitment to the nested case-control study and attrition

environmental exposures of the baseline sample. Addresses of baseline participants were re-visited in person by trained interviewers (psychology graduates) with several attempts to reduce the number of non-respondents from the baseline sample (Binbay *et al.* 2011). As a result of the follow-up visits; 55 individuals could not be contacted because of unsuccessful attempts (at least three consecutive) to contact anyone at the address (15.0%). 3 individuals were found to be deceased or prisoned during recruitment (0.8%) and 3 addresses were demolished and no new address could be found (0.8%). Among the subjects that were contacted (n= 305, 83.3%); interview was impossible with 33 individuals due to residency in a remote area (9.0%) and with 18 individuals due to refusal (4.8%). Consequently, 254 participants from the baseline nested case-control sample were successfully re-interviewed with CIDI at follow-up (response rate: 69.4%). Furthermore, these participants were re-contacted for a clinical re-evaluation with the Structured Clinical Interview for DSM-IV (SCID-I) (Spitzer *et al.* 1992) by a psychiatrist (145 interviews at the hospital and 109 at the participants' residence). At the follow-up assessment, SCID was conducted by a psychiatrist (UK) who had not participated in the baseline assessment and was blind to the diagnostic status at baseline. Each participant provided written informed consent for examination and procedures. The TürkSch study was approved by the Institutional Ethics Review Board of Ege University, Turkey, and is compliant with the precepts of Declaration of Helsinki.

Composite International Diagnostic Interview (CIDI)

The CIDI is a fully structured interview developed by the World Health Organization (Robins *et al.* 1988) and has been used in various epidemiological surveys around the world including Turkey (Cilli and Kaya 2003;Deveci *et al.* 2007;Alptekin *et al.* 2009). The CIDI can be used by both clinicians and trained lay interviewers. In the current study, assessments included screening sections on alcohol and substance-related disorders, depressive

and dysthymic disorders, manic and bipolar affective disorders, schizophrenia and other psychotic disorders, and 2 final sections containing interviewer observations, and interviewer ratings. Each CIDI interview at baseline and follow-up was conducted according to a standard procedure, with recording and quality coding (Binbay *et al.* 2011). If the quality of the interview was considered low by the team psychiatrist, a phone call or a second visit was planned.

Assessment of Psychotic Experiences and Disorders

In order to assess PE and PD, the same case identification procedure was applied at baseline and at follow-up. PE was rated using 14 CIDI delusions items (G1, G2, G3, G4, G5, G7, G8, G9, G10, G11, G12, G13, G13b and, G14) and 5 CIDI hallucinations items (G17, G18, G20, G20C, and G21). The time frame was lifetime at baseline assessment and the last six years at follow-up assessment. CIDI-based screening of PE provided information on frequency, duration, help-seeking, severity of symptoms and psychosocial impairment. In order to diagnose PD, participants endorsing a PE associated with help-seeking or, if there was no help-seeking, occurring with a frequency of at least once a week were re-contacted for a clinical re-evaluation with the SCID-I by the team psychiatrist.

Other Assessments

Level of education was defined in regard to last graduated school and recoded into lower than high school and at least high school. Marital status was recoded into married and non-married. Socioeconomic status was based on the profession of the participant (if the participant had no profession, father/husband's profession was used instead) and recoded into 3 ordinal categories: 1=professional and non-manual employees, 2=owners of small businesses, 3=non-professional workers (Goldthorpe 1987). Cannabis use was assessed using screening questions on CIDI substance-related disorders sec-

tions. Conform previous CIDI-based research, cannabis use of 5 times or more was defined as exposure status for cannabis. Life events were assessed at follow-up using the List of Threatening Life Events Questionnaire (Brugha and Cragg 1990). The time frame was last six years. The number of life events was a continuous variable with a minimum of 0 and maximum of 12. Childhood adversities were death of any parent, divorce of parents and separation from parents for at least for 3 months. The childhood adversities variable was dichotomized to none or at least one (Binbay *et al.* 2012c). Urbanicity was defined using the classification of the Turkish Institute of Statistics (TURKSTAT). Classification depends on the level of organized features of streets and buildings (regularity of sidewalks, status of road, completeness of drainage system, and quality of outer paintings of buildings, etc.) and includes four categories (Binbay *et al.* 2012b).

Genetic Analyses

Samples of peripheral venous blood (2 mL) with ethylenediaminetetraacetic acid (EDTA) were taken and directed to the Medical Genetics Department, Molecular Genetics Laboratory for the investigation of BDNF-Val66Met polymorphism (rs6265) (PCR and agarose gel imaging). Genomic DNA was extracted from peripheral blood cells then sequestered with the MagNa Pure LC DNA Isolation Kit I (Roche, USA). The localized gene regions for this single nucleotide polymorphism (SNP) were amplified by polymerase chain reaction (PCR). Restriction Fragment Length Polymorphism (RFLP) technique was conducted to reveal fragments relevant to SNP region. Obtained fragments were separated according to their lengths by agarose gel electrophoresis. The genotype of the BDNF (rs6265) SNP was identified (Val/Val, Val/Met, Met/Met). Since the Met/Met genotype had a much lower frequency than the Val/Met and Val/Val genotypes, the genotypes for this SNP were included in the analyses as a binary variable (Met allele carriers and Val homozygotes).

Dependent Variable

The main outcome of the study was the *extended psychosis phenotype* variable ranging from *PE* to *PD*, derived from CIDI and SCID results in both baseline and follow-up assessments. *Psychotic disorder (PD)* included participants with a DSM-IV diagnosis of any disorder with psychotic features either at baseline or at follow-up assessment, based on diagnosis at clinical re-evaluation with the SCID. *Psychotic experiences (PE)* included participants who endorsed a CIDI PE either at baseline or at follow-up assessments but did not have PD during follow-up. All other individuals were included in the *no psychotic symptoms* category.

Secondary outcome variable was *transition from PE to PD. Transition* was a binary variable and coded: 1) if the participant with baseline PE had a PD at follow-up assessment 0) if the participant with baseline PE did not have a PD at follow-up assessment (*Fig. 2*).

Statistical Analyses

All analyses were conducted using the software package STATA, version 13.1. In order to evaluate issues of bias due to the loss at follow-up, the participants (n = 254) were compared with the non-participants (n =112) in terms of baseline clinical and demographic characteristics using chi-squared tests. Furthermore, in order to provide background information, differences in socio-demographic and environmental exposure variables between participants with and without *any psychotic symptoms (PE or PD) during follow-up* were assessed using chi-squared test or t-test as appropriate. To analyze the first research question, differences in BDNF-Val66Met genotypes between those with versus without *any psychotic symptom (PE or PD) during follow-up* were assessed using the chi-squared test and logistic regression. To assess the second research question, associations between different levels of the *extended psychosis phenotype* and BDNF-Val66Met genotypes were analyzed using logistic regression analy-

sis. Because psychosis phenotype had 3 categories, this variable could not be analyzed as the dependent variable. For this reason, we reversed the dependent and the independent variable. The *psychosis phenotype* thus was modelled as an independent variable, allowing analysis of deviation from linearity. Continuity and discontinuity in the pattern of associations were tested by modelling *psychosis phenotype* spectrum as linear effect and assessing the effect of adding a squared term of psychosis phenotype. A nonsignificant squared term suggests continuity (no deviation from linearity), a negative squared term suggests a qualitatively stronger association at the lower end of the psychosis phenotype, and a positive squared term suggests a qualitatively stronger association at the disorder end of the psychosis phenotype. The odds ratios (OR) were presented both without adjustment and after adjusting for age, sex, marital status, urbanicity, socioeconomic status, childhood adversity, number of life events for the last 6 years and cannabis use. *No psychotic symptoms* was the reference group (i.e. OR=1). Due to multiple comparisons at different levels of the extended psychosis phenotype, the Bonferroni correction was applied. To assess the third research question, the association between the secondary outcome variable *transition from PE to PD* and the BDNF-Val66Met genotypes were analyzed. Given low numbers of participants who transitioned from PE to PD (n=9), Fisher's exact test was used.

Results

Sample

The average age of participants at follow-up was 46.2 years (range= 22–71; SD = 13.3). 45.2% were male. The proportion that finished high school was 39.4%; 40.1% were non-married, 72.8% were of Turkish origin and 27.2 were of non-Turkish origin. Eighty-seven participants (34.3%) reported using psychiatric medication during follow-up period. Nineteen participants (7.5%) reported having five or more standard alcoholic drinks on five or more occasions per month. Eleven participants (4.3%) reported using cannabis more than five times and five participants

(2.0%) reported using other substances during follow-up period. Detailed group characteristics of those with *any psychotic symptoms (PE or PD)* and those with *no psychotic symptoms* during follow-up were presented in *Table 1*.

The sex distribution (non-participants: 38.4% male; x^2= 1.5, df=1, p=0.2), age (non-participants mean age: 44.8; t= 0.8; p=0.4), baseline marital status (non-married: non-participants 42.0% vs. participants 38.6%; x^2= 0.3, df=1, p=0.5) and baseline

Table 1: Comparison of those with any psychotic symptom to those with no psychotic symptom during follow-up, according to sociodemographic factors, environmental exposure variables and BDNF genotypes

Risk Factor	No Psychotic Symptoms During Follow-up (n:97) n (%)	Any Psychotic Symptoms During Follow-up (n:157) n (%)	χ^2	p	Cramer's *V*
Sex					
Female	47 (48.4)	91 (58.0)	2.18	0.139	0.09
Male	50(51.6)	66 (42.0)			
Education					
Higher	40 (43.0)	57 (37.3)	0.80	0.37	0.06
Lower	53 (57.0)	96 (62.7)			
Marital Status					
Married	70 (72.2)	96 (61.2)	**3.21**	**0.073**	**0.11**
Non-married	27 (27.8)	61 (38.8)			
Socioeconomic Status					
Professional	23 (23.7)	25 (15.9)	**4.99**	**0.082**	**0.14**
Owner of Small Business	16 (16.5)	17 (10.8)			
Non-professional	58 (59.8)	115 (73.3)			
Cannabis Use					
No	94 (96.9)	149 (94.9)	0.58	0.446	0.05
Yes	3 (3.1)	8 (5.1)			
Urbanicity					
I	13 (13.4)	5 (3.2)	**13.9**	**0.003**	**0.23**
II	57 (58.8)	89 (56.7)			
III	24 (24.7)	46 (29.3)			
IV	3 (3.1)	17 (10.8)			
Childhood Adversity					
None	81 (83.5)	122 (77.7)	1.25	0.262	0.07
At least one	16 (16.5)	35 (22.3)			
BDNF Genotype					
Met carrier	42 (43.3)	45 (28.7)	**5.7**	**0.017**	**0.15**
Val-Val	55 (56.7)	112 (71.3)			
	Mean (SD)	**Mean (SD)**	***t***	**p**	**Cohen's *d***
Age	47.2 (12.9)	44.0 (13.4)	1.87	0.03	0.24
Number of life events	1.6 (1.4)	2.4 (1.9)	**-3.49**	**0.0003**	**-0.45**

SD: standard deviation, bold values are the values which have effect sizes > 0.1.

educational status (at least high school graduates: non-participants 26.8% vs. participants 36.6%; $x^2 = 3.4$, df=1, p=0.07) did not significantly differ between participants and non-participants. Attrition was higher in individuals with baseline any psychotic symptoms (PE or PD) in comparison with individuals with no baseline psychotic symptoms (baseline any psychotic symptoms; non participants 85.7% vs. participants 57.5%; $x^2 = 27.7$, df= 1, $p<0.01$).

The genotype frequencies for the BDNF-Val66Met polymorphism were: Val/Val: 65.7% (n =167), Val/Met: 28.4% (n = 72) and Met/Met: 5.9% (n = 15). These frequencies did not differ from others described in previous studies conducted in white individuals (Egan *et al.* 2003;Alemany *et al.* 2011). Hardy–Weinberg equilibrium was verified for the present population ($x^2 = 3.4$, df= 2, $p>0.05$).

Dynamic Transitions over Time in the Extended Psychosis Phenotype

Of those in the nested case-control sample who were successfully interviewed both at baseline and at follow-up (n= 254), 37 participants (14.6%) had PD and 109 participants (30.8%) had PE at baseline. Nine of the 109 participants with baseline PE (8.2%) transitioned to PD during follow-up. Therefore, a total of 46 participants (18.1%) were in the *PD group*. 111 participants were in the *PE group* (43.7%). 97 participants (38.2%) had neither PE nor PD at baseline and at follow-up (*no psychotic symptoms group*). Details of dynamic transitions over time in the extended psychosis phenotype are presented in *Fig. 2*.

Main Effects of Socio-demographics, Environmental Exposure and BDNF Val66Met Genotype

Urbanicity, age and number of life events for the last six years were significantly associated with any psychotic symptoms (PE or PD) during follow-up (Table 1). BDNF-Val-Val genotype was significantly associated with presence of any psychotic symp-

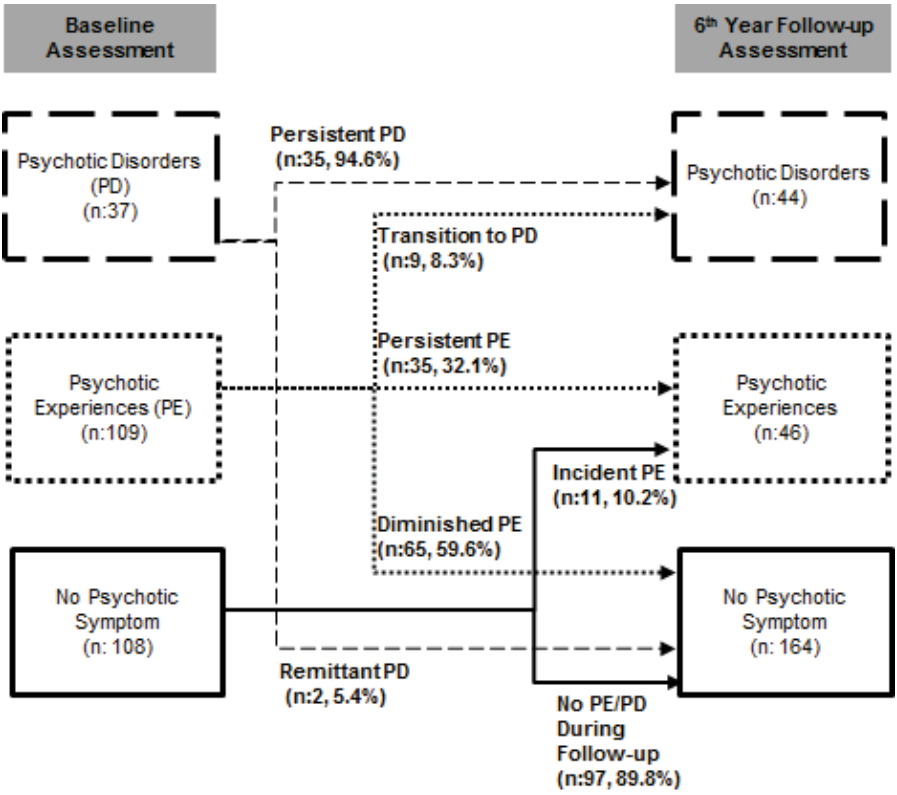


Figure 2: Dynamic transitions over time in the nested case-control sample

toms (PE or PD) during follow-up (OR= 1.9, 95% CI = 1.12- 3.23), and also after adjusting for socio-demographic features and environmental exposure variables (OR= 1.9, 95% CI = 1.05- 3.46). The association between BDNF-Val-Val genotype and the extended psychosis phenotype showed a dose-response association, but it was extra-linear (x^2 for deviation from linearity: 2.50, df= 2, p=0.0032). Thus, OR were disproportionately stronger at the psychotic disorder end of the extended psychosis phenotype (adjusted OR=2.7, table 2) than at the PE section of the phenotype (OR=1.7) or at the no psychotic symptoms end (OR=1, reference category). The corrected level of significance when the Bonferroni correction was applied remained marginally significant in the association between PD and BDNF-Val-Val genotype (the correct-

ed p-value = 0.034). Finally, BDNF-Val66Met polymorphism was not significantly associated with transition from PE to PD (transition; Val-Val 9/78 vs. Met Carrier 0/31; p=0.058, two-tailed Fisher's exact test, df= 1, Cramer's V = 0.19).

Table 2: Distribution of BDNF Val66Met genotypes per category of extended psychosis phenotype and regression results

	No psychotic symptom (n: 97)		Psychotic Experiences (n: 111)			Psychotic Disorder (n:46)		
	n (%)	OR (%95 CI)	n (%)	OR (%95 CI)	OR† (%95 CI)	n (%)	OR (%95 CI)	OR† (%95 CI)
BDNF Val66Met Val-Val Genotype	**55 (56)**	1 (ref)	77 (69)	1.73 (0.98-3.05)	1.7 (0.9-3.21)	35 (76)	2.43* (1.11-5.34)	2.7* (1.12-6.47)

*p<0.05

†Adjusted for age, sex, marital status, socioeconomic status, urbanicity, childhood adversity, number of life events for the last 6 years, cannabis use

Discussion

Findings

In this 6 years prospective population-based cohort study, the BDNF-Val-Val genotype was found to be associated with the extended psychosis phenotype. The association was in a dose-response but extra-linear fashion, with a stronger impact at the psychotic disorder end. This is in agreement with a previous work which reported positive extra-linear associations between proxy variables of genetic risk and extended psychosis phenotype in TürkSch sample at baseline (Binbay *et al.* 2012c).

As far as we are aware, there are no studies to date investigating the association between the BDNF Val66Met polymorphism and the extended psychosis phenotype including both clinical and subclinical levels that we can directly compare with the results of this paper. However, significant associations between BDNF Val66Met polymorphism and psychosis expression at different levels of the extended psychosis phenotype have been presented. These results are in agreement with our results. First, the Val allele of the BDNF Val66Met polymorphism was associated with

PD (including both affective and non-affective), and also all symptom dimensions of psychosis except the negative dimension (Rosa *et al.* 2006). Furthermore, the Val allele was associated with both affective PD (Neves-Pereira *et al.* 2002;Sklar *et al.* 2002;Geller *et al.* 2004;coLohoff *et al.* 2005), and also with schizophrenia (Neves-Pereira *et al.* 2005;Golimbet *et al.* 2008) separately. In addition, a recent study documented a gene-environment interaction involving BDNF-Val-Val genotype and PE (de Castro-Catala *et al.* 2016). Finally, there are studies which suggest that prognosis of PD is poorer in individuals with the BDNF-Val-Val genotype (Numata *et al.* 2006;Golimbet *et al.* 2008;Chang *et al.* 2009;Suchanek *et al.* 2013).

BDNF and Psychosis as a Transdiagnostic and Extended Phenotype

To date, studies assessing associations between BDNF Val66Met polymorphism and schizophrenia – the traditional poor outcome formulation of PD – have produced inconsistent results (Notaras *et al.* 2015b). Furthermore, BDNF has generally not transpired in GWAS as increasing risk for schizophrenia (Collins *et al.* 2012). While the BDNF Val66Met polymorphism may not be consistently associated with schizophrenia, there is substantial evidence that at least some of the clinical features of schizophrenia are modulated by the polymorphism (Notaras *et al.* 2015b). Furthermore, a growing number of studies have demonstrated the modulating role of the polymorphism on the association between social environmental stress and PE (Simons *et al.* 2009;Alemany *et al.* 2011;de Castro-Catala *et al.* 2016). In addition, BDNF Val66Met polymorphism has also been associated with a range of common mental disorders including mood, eating and some anxiety disorders (Gratacos *et al.* 2007;Hong *et al.* 2011;Notaras *et al.* 2015a). There is robust evidence that the risk of PE is significantly higher in individuals who have common mental disorders in comparison with individuals who do not (Kaymaz *et al.* 2012;McGrath *et al.* 2016;van Os and Reininghaus 2016). In addition, a cross-twin analysis indicated that PE might be genet-

ically continuous with psychotic disorders (Lataster *et al.* 2009). In light of the previous results linking BDNF-Val66Met polymorphism with both non-psychotic and psychotic disorders, and the present result suggesting a dose-response association between the polymorphism and the extended psychosis phenotype including both subclinical and clinical expressions of psychosis; it may be suggested that BDNF-Val66Met polymorphism indexes susceptibility to expression of psychosis along a spectrum. Further research with the extended psychosis phenotype cutting across boundaries of diagnostic categories is needed to evaluate this hypothesis.

Strengths and Limitations

The current study, to our knowledge, is the first longitudinal study that investigates the associations between BDNF Val66Met polymorphism and the extended psychosis phenotype including both subclinical and clinical expressions of psychosis in a representative population-based sample. Longitudinal design enabled us to measure non-lifetime clinical features which were subject to change over time, such as symptom presence and severity. Furthermore, the main outcome variable *extended psychosis phenotype* enabled us to include the more common phenotype *PE* next to *PD*. In addition, we were able to adjust the associations for socio-demographic features and environmental exposure variables including life events, childhood adversity, SES, urbanicity and, cannabis use.

Nevertheless, the results need to be considered in the light of the following limitations. First, as with most longitudinal studies, our initial sample size was reduced through attrition. The comparison of baseline socio-demographic characteristics between non-participants and participants showed no large or significant differences. However, in line with a simulation study of attrition (Wolke *et al.* 2009), the comparison of clinical characteristics between non-participants and participants showed that attrition was higher in individuals with any psychotic symp-

toms at baseline. Furthermore, selective attrition of those who have transitioned to PD is possible, mainly because of refusal to participate (Williams and Macdonald 1986). Therefore, this may have impacted upon the findings. However, the number of those who have refused to participate in follow-up assessment is small (n: 18, 4.8%) and the transition rate from PE to PD found in the current sample (8.2%) is consistent with previous meta-analytical findings (Linscott and van Os 2013). Second, although the sample size is similar to previous studies with a similar design (Ramsay *et al.* 2013), it can be still considered relatively small. However, the broader outcome variable including the subclinical phenotypes, the longitudinal design, and the epidemiological sample of the study including the non-helpseeking individuals next to the help-seeking individuals enabled us to detect smaller effect sizes. Third, the assessment of psychosis in the general population inevitably is associated with a degree of misclassification (false positives and false negatives). In order to reduce the risk of misclassification, gold-standard clinical interviews (SCID) were performed by a psychiatrist. Finally, as with the other candidate gene studies, we were not able to correct our results for other possible genetic variations. As BDNF has generally not transpired in GWAS as increasing risk for schizophrenia (Collins *et al.* 2012), the findings need replication in larger samples.

References

- Alemany S, Arias B, Aguilera M, *et al.* (2011). Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences. *The British journal of psychiatry : the journal of mental science* 199, 38-42.

- Alptekin K, Ulas H, Akdede BB, Tumuklu M , Akvardar Y (2009). Prevalence and risk factors of psychotic symptoms: in the city of Izmir, Turkey. *Social psychiatry and psychiatric epidemiology* 44, 905-910.

- Andrews G , Peters L (1998). The psychometric properties of the Composite International Diagnostic Interview. *Social psychiatry and psychiatric epidemiology* 33, 80-88.

- Auld DS, Mennicken F, Day JC , Quirion R (2001). Neurotrophins differentially enhance acetylcholine release, acetylcholine content and choline acetyltransferase activity in basal forebrain neurons. *Journal of neurochemistry* 77, 253-262.

- Binbay T, Alptekin K, Elbi H, *et al.* (2012a). [Lifetime prevalence and correlates of schizophrenia and disorders with psychotic symptoms in the general population of Izmir, Turkey]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 23, 149-160.

- Binbay T, Drukker M, Alptekin K, *et al.* (2012b). Evidence that the wider social environment moderates the association between familial liability and psychosis spectrum outcome. *Psychological medicine* 42, 2499-2510.

- Binbay T, Drukker M, Elbi H, *et al.* (2012c). Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophrenia bulletin* 38, 992-1002.

- Binbay T, Elbi H, Alptekin K, *et al.* (2011). Izmir mental health survey for gene-environment in-

teraction in psychoses (TurkSch): objectives and methodology. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 22, 65-76.

- Brugha TS , Cragg D (1990). The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta psychiatrica Scandinavica* 82, 77-81.

- Buckley PF, Mahadik S, Pillai A , Terry A, Jr. (2007). Neurotrophins and schizophrenia. *Schizophrenia research* 94, 1-11.

- Chang HA, Lu RB, Shy MJ, Chang CC, Lee MS , Huang SY (2009). Brain-derived neurotrophic factor Val66Met polymorphism: association with psychopathological symptoms of schizophrenia? *The Journal of neuropsychiatry and clinical neurosciences* 21, 30-37.

- Cilli AS , Kaya N (2003). [Nicotine dependence and psychiatric comorbidity among university students]. *Turk psikiyatri dergisi = Turkish journal of psychiatry* 14, 42-49.

- Collins AL, Kim Y, Sklar P, O'Donovan MC , Sullivan PF (2012). Hypothesis-driven candidate genes for schizophrenia compared to genome-wide association results. *Psychological medicine* 42, 607-616.

- coLohoff FW, Sander T, Ferraro TN, Dahl JP, Gallinat J , Berrettini WH (2005). Confirmation of association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 139B, 51-53.

- Coyle JT (2012). NMDA receptor and schizophrenia: a brief history. *Schizophrenia bulletin* 38, 920-926.

- de Castro-Catala M, van Nierop M, Barrantes-Vidal N, *et al.* (2016). Childhood trauma, BDNF Val66Met and subclinical psychotic experiences. Attempt at replication in two independent samples. *Journal*

of psychiatric research 83, 121-129.

- Deveci A, Taskin O, Dinc G, *et al.* (2007). Prevalence of pseudoneurologic conversion disorder in an urban community in Manisa, Turkey. *Social psychiatry and psychiatric epidemiology* 42, 857-864.

- Egan MF, Kojima M, Callicott JH, *et al.* (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112, 257-269.

- Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K , Cook EH, Jr. (2004). Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *The American journal of psychiatry* 161, 1698-1700.

- Goldthorpe J (1987). *Social mobility and class structure in modern Britain*. Clarendon Press: New York.

- Golimbet VE, Korovaitseva GI, Abramova LI, Kasparov SV , Uvarova LG (2008). [Association between the Val66Met polymorphism of brain-derived neurotrophic factor gene and schizophrenia in Russians]. *Molekuliarnaia biologiia* 42, 599-603.

- Gourion D, Goldberger C, Leroy S, Bourdel MC, Olie JP , Krebs MO (2005). Age at onset of schizophrenia: interaction between brain-derived neurotrophic factor and dopamine D3 receptor gene variants. *Neuroreport* 16, 1407-1410.

- Gratacos M, Gonzalez JR, Mercader JM, de Cid R, Urretavizcaya M , Estivill X (2007). Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biological psychiatry* 61, 911-922.

- Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P (2001). BDNF

controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature* 411, 86-89.

- Hong CJ, Liou YJ , Tsai SJ (2011). Effects of BDNF polymorphisms on brain function and behavior in health and disease. *Brain research bulletin* 86, 287-297.

- Kaymaz N, Drukker M, Lieb R, *et al.* (2012). Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychological Medicine* 42, 2239-2253.

- Kelleher I, Jenner JA , Cannon M (2010). Psychotic symptoms in the general population - an evolutionary perspective. *The British Journal of Psychiatry* 197, 167-169.

- Kish L (1949). A procedure for objective respondent selection within the household. *Journal of the American Statistical Association* 44, 380–387.

- Lataster T, Myin-Germeys I, Derom C, Thiery E , van Os J (2009). Evidence that self-reported psychotic experiences represent the transitory developmental expression of genetic liability to psychosis in the general population. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 150B, 1078-1084.

- Levine ES , Kolb JE (2000). Brain-derived neurotrophic factor increases activity of NR2B-containing N-methyl-D-aspartate receptors in excised patches from hippocampal neurons. *Journal of neuroscience research* 62, 357-362.

- Linscott RJ , van Os J (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine* 43, 1133-1149.

- Martinowich K , Lu B (2008). Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 33, 73-83.

- McGrath JJ, Saha S, Al-Hamzawi A*, et al.* (2016). The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *The American journal of psychiatry*, appiajp201615101293.

- Neves-Pereira M, Cheung JK, Pasdar A*, et al.* (2005). BDNF gene is a risk factor for schizophrenia in a Scottish population. *Molecular psychiatry* 10, 208-212.

- Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F , Kennedy JL (2002). The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *American journal of human genetics* 71, 651-655.

- Notaras M, Hill R , van den Buuse M (2015a). The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: progress and controversy. *Molecular psychiatry* 20, 916-930.

- Notaras M, Hill R , van den Buuse M (2015b). A role for the BDNF gene Val66Met polymorphism in schizophrenia? A comprehensive review. *Neuroscience and biobehavioral reviews* 51, 15-30.

- Numata S, Ueno S, Iga J*, et al.* (2007). Interaction between catechol-O-methyltransferase (COMT) Val108/158Met and brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in age at onset and clinical symptoms in schizophrenia. *Journal of neural transmission* 114, 255-259.

- Numata S, Ueno S, Iga J*, et al.* (2006). Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in schizophrenia is associated with age at onset and symptoms. *Neuroscience letters* 401, 1-5.

- Ramsay H, Kelleher I, Flannery P*, et al.* (2013). Relationship between the COMT-Val158Met and BDNF-Val66Met polymorphisms, childhood trauma and psychotic experiences in an adolescent general population sample. *PloS one* 8, e79741.

- Robins LN, Wing J, Wittchen HU*, et al.* (1988). The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of general psychiatry* 45, 1069-1077.

- Rosa A, Cuesta MJ, Fatjo-Vilas M, Peralta V, Zarzuela A , Fananas L (2006). The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with risk for psychosis: evidence from a family-based association study. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 141B, 135-138.

- Simons CJ, Wichers M, Derom C*, et al.* (2009). Subtle gene-environment interactions driving paranoia in daily life. *Genes, brain, and behavior* 8, 5-12.

- Sklar P, Gabriel SB, McInnis MG*, et al.* (2002). Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. *Molecular psychiatry* 7, 579-593.

- Spitzer RL, Williams JB, Gibbon M , First MB (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of general psychiatry* 49, 624-629.

- Suchanek R, Owczarek A, Paul-Samojedny M, Kowalczyk M, Kucia K , Kowalski J (2013). BDNF val66met polymorphism is associated with age at onset and intensity of symptoms of paranoid schizophrenia in a Polish population. *The*

Journal of neuropsychiatry and clinical neurosciences 25, 88-94.

- van Os J , Linscott RJ (2012). Introduction: The Extended Psychosis Phenotype--Relationship With Schizophrenia and With Ultrahigh Risk Status for Psychosis. *Schizophrenia bulletin* 38, 227-230.

- van Os J , Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World psychiatry : official journal of the World Psychiatric Association* 15, 118-124.

- Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H , Hell D (1998). Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* 9, 3897-3902.

- Williams P , Macdonald A (1986). The effect of non-response bias on the results of two-stage screening surveys of psychiatric disorder. *Social psychiatry. Sozialpsychiatrie. Psychiatrie sociale* 21, 182-186.

- Wolke D, Waylen A, Samara M*, et al.* (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *The British journal of psychiatry : the journal of mental science* 195, 249-256.

CHAPTER 6

Discussion

For a long time, it was widely held that threshold psychotic experiences are dimensional. In the article on "the diagnosis and prognosis of dementia praecox", Kraepelin addressed the role of nonsensical delusions, dull mood and lack of interest, enduring mannerisms, negativism, stereotypy, and recurring changes of mood in bringing about the "peculiar state of mental impairment". Furthermore, he concluded that: "despite all efforts, no sharp boundaries between the individual clinical manifestations of dementia praecox could be determined" (Kraepelin 1899;Kendler 2020). Kraepelin's statements included four domains of threshold psychotic states: Positive, negative, disorganisation and affective. Furthermore, despite the distinct definitions of "neurosis and psychosis" in the psychoanalytic literature, common phenomenological (e.g. anhedonia) and etiological features (e.g. frustration of childhood desires) have also been reported since the age of Freud (Freud 1924;Dereboy 2000). These common features are represented in the current classification systems (Häfner *et al.* 2005;American Psychiatric Association 2013;Szczypiński and Gola 2018).

An earlier edition of DSM (3rd edition) proposed a "symptom list of the pre-active or prodromal phase of the psychotic disorders" which is composed of symptoms from multiple domains including subthreshold psychotic experiences (PEs) (Table 1) (American Psychiatric Association 1987). Although this list was not included in the fourth and the fifth editions, recent evidence supports the notion that subthreshold psychotic states are also dimensional, and referred to as subthreshold psychotic experiences, (Dominguez *et al.* 2009;Rössler *et al.* 2011;Binbay *et al.* 2012b;Guloksuz *et al.* 2015), subthreshold negative and disorganization symptoms (van Os *et al.* 2000b;Krabbendam *et al.* 2004a;Dominguez *et al.* 2010;Walss-Bass *et al.* 2015;van Os and Reininghaus 2016;Sauvé *et al.* 2019), and affective dysregulation (van Os and Linscott 2012;Fusar-Poli *et al.* 2014;Pries *et al.* 2019b).

Table 1: Symptom List of the Pre-active or Prodromal Phase of the Psychotic Disorders Included in DSM-III

Social isolation or withdrawal
Marked impairment in role functioning as wage-earner, student, or homemaker
Markedly peculiar behaviour (e.g. collecting garbage, talking to self in public or hoarding food)
Marked impairment in personal hygiene and grooming
Blunted, flat, or inappropriate affect
Digressive, vague, over-elaborate, circumstantial, or metaphorical speech
Odd or bizarre ideation, or magical thinking, e,g. superstitiousness, clairvoyance, telepathy, "sixth sense" / "others can feel my feelings," overvalued ideas, ideas of reference
Unusual perceptual experiences, e.g., recurrent illusions, sensing the presence of a force or person not actually present

Evaluating dynamic transitions over time within the full spectrum of psychosis

Longitudinal data collection in a representative community-based population

The second chapter of this thesis covers the general outline, methods and details of attrition during the follow-up period. The detailed efforts to capture the full spectrum of psychosis expression and to evaluate multidimensional outcomes over time in the representative community-based population were also reported in this chapter (Kirli *et al.* 2019d).

Baseline characteristics of responders did not show large differences from characteristics of subjects who dropped out. In addition, the dropout rate of participants and the relevant socio-demographic characteristics were similar to studies with a similar design (Dominguez *et al.* 2009;Zammit *et al.* 2013b). However, there were also some differences in the sociodemographic correlates of attrition because these studies showed higher refusal rates in individuals with a baseline mental health problem, with a lower socioeconomic status and a lower educational level (Dominguez *et al.* 2009;de Graaf *et al.* 2013). These individuals showed lower refusal rates at follow-up in the TürkSch study (Kirli *et al.* 2019d).

In this thesis, the positive domain of psychosis was evaluated from the perspective of a spectrum framework that encompassed subclinical, subthreshold and threshold states in order to generate evidence for research on the multidimensional liabilities underlying psychosis expression.

Graded Nature of Risk Associated with Subthreshold Psychosis

The results presented in the second chapter of this thesis showed that increasing severity of subthreshold psychosis at baseline was associated with the increasing rates of persistence and psychotic disorder outcome over the follow-up period (Kirli *et al.* 2019d). However, for the last decades, a series of attempts have classified subthreshold psychosis in 'high risk' or 'prodromal psychosis' concepts. The summary of symptom domains on which these classifications are mainly based on are shown in table 2 (Klosterkötter *et al.* 1996;Miller *et al.* 2003;Schultze-Lutter *et al.* 2008;Yung and Nelson 2011;American Psychiatric Association 2013;Schultze-Lutter *et al.* 2017). Among these symptom domains, the subjective cognitive disturbances were demonstrated to be the most common in the community (Schultze-Lutter *et al.* 2017). However, psychosis-risk studies have mainly targeted the attenuated positive or disorganisation symptoms, as the great majority of individuals had been referred to high risk centre through this domain (Fusar-Poli *et al.* 2016).

Table 2: High Risk for Psychosis Categories and Associated Symptom Domains

High Risk Category	Symptom Domain
DSM-5 Attenuated Psychosis Syndrome-APS	Attenuated positive or disorganisation symptoms
At Risk Mental States- ARMS Ultra-High Risk-UHR Clinical High Risk-CHR	**Presence of any of the following domains:** Attenuated positive or disorganisation symptoms Transient threshold positive or disorganisation symptoms Genetic risk and deterioration in functioning
Basic Symptoms-BS	Subjective cognitive disturbances

When compared with individuals with subthreshold PEs in general, non-clinical populations, individuals meeting the high risk criterion have higher 'transition to frank psychosis' rates (van Os and Linscott 2012;Fusar-Poli *et al.* 2014;Lin *et al.* 2015;Polari *et al.* 2018;Radua *et al.* 2018;Oliver *et al.* 2019). The highest 'transition' rates among high risk samples were shown for individuals with 'transient threshold positive or disorganisation symptoms' which actually includes the most severe psychosis expression (Chan *et al.* 2019). These results are in line with studies in the general population, demonstrating that the severity of the baseline psychosis expression translates to 'transition' rates (Hanssen *et al.* 2005;van Os and Linscott 2012;Linscott and van Os 2013;Zammit *et al.* 2013b). Furthermore, emerging evidence from twin and molecular genetic studies showed that increasing frequency of PEs and associated distress may index increasing genetic liability to threshold psychotic disorders (Zavos *et al.* 2014;Martin *et al.* 2017;Legge *et al.* 2019). Robust evidence from epidemiological research and preliminary evidence from genetic studies suggest a graded nature of risk associated with subthreshold psychosis rather than categories with and without risk.

Bidirectional associations between the extended psychosis phenotype and affective psychopathology over time

Affective Psychopathology and the Psychosis Spectrum Predict Each Other over Time

The results in the third chapter of this thesis showed that baseline PEs were associated with both subsequent depressive and hypomanic/manic episodes. The association with subsequent hypomanic/manic episodes was stronger (Kirli *et al.* 2019c). In line with this result, recent studies linked both depression and mania with the positive dimension of psychosis, demonstrating relatively stronger associations with mania (Zavos *et al.* 2016;Anttila *et*

al. 2018;Xia *et al.* 2018;Baker *et al.* 2019;Legge *et al.* 2019;Stahl *et al.* 2019;Kotov *et al.* 2020).

Cross-sectional studies showed high comorbidity rates between psychotic and affective psychopathology at threshold level (Tsuang 1979;Buckley *et al.* 2008;McMillan *et al.* 2009;Dean *et al.* 2010;Mortensen *et al.* 2010;DeVylder and Lukens 2013), and also at subthreshold level (van Os *et al.* 1999;Verdoux *et al.* 1999;Hanssen *et al.* 2003;Stefanis *et al.* 2004;van Rossum *et al.* 2009;van Os and Linscott 2012;McGrath *et al.* 2016). A recent population-based cohort study of 5 940 778 individuals, followed up for 83.9 million person-years showed that mood disorders predicted psychotic disorders (i.e. schizophrenia) over time, and vice-versa (Plana-Ripoll *et al.* 2019). Findings from the present thesis suggest that these bidirectional associations over time also exist at the subthreshold level (Kirli *et al.* 2019c).

Shared Etiopathogenesis across Affective Psychopathology and the Psychosis Spectrum

An important proportion of symptoms classified in affective psychopathology overlap with threshold psychotic disorders (van Os *et al.* 2000a) and also with subthreshold psychosis (Krabbendam *et al.* 2004a;Kaymaz *et al.* 2007;Kafali *et al.* 2019). Furthermore, affective and psychotic disorders have shown common cognition dysfunction (Burdick *et al.* 2014;Owen and O'Donovan 2017;Bora *et al.* 2018;Kotov *et al.* 2020). Relatedly, childhood problems with communication, reading and mathematics predicted both subthreshold psychosis and mania symptoms in adolescence (Cederlöf *et al.* 2013).

Recent preliminary results suggest that dysregulation in tonic dopamine signalling (including lower and higher states) and the interactions with glutamatergic system may be common in both depression and psychosis (Szczypiński and Gola 2018). Similar electrophysiological alterations were reported in subthreshold psychosis as well as threshold psychotic and affective disorders (Hazlett *et al.* 2015;Wan *et al.* 2017;Hermens *et*

al. 2018;Javitt *et al.* 2018). Furthermore, studies assessing pro-inflammatory markers reported no distinguishing pathways (Goldsmith *et al.* 2016). Finally, familial co-aggregation (Cardno *et al.* 2002;Lichtenstein *et al.* 2009;Chou *et al.* 2017), numerous shared molecular genetic (van Os *et al.* 2017;Anttila *et al.* 2018;Ronald and Pain 2018;Sullivan *et al.* 2018;Cross-Disorder Group of the Psychiatric Genomics Consortium 2019;Legge *et al.* 2019;Stahl *et al.* 2019) and post-mortem gene expression findings (Chen *et al.* 2012;Zhao *et al.* 2014) were reported across these states (albeit with different effect sizes). These results accord with the view that affective and psychotic disorders form a spectrum of severity (Mancuso *et al.* 2015;Guloksuz and van Os 2017). However, these results should be treated with caution because of the dissimilarities across the methodology of the studies, the presence of plausible unconsidered confounders, and low replicability of biological findings in psychosis (Ioannidis 2005;Ioannidis 2011), particularly in the area of neuroimaging (Botvinik-Nezer *et al.* 2020;Elliott *et al.* 2020). Therefore, these results need further replication.

Numerous studies reported shared socio-demographic and environmental factors across affective disorders and threshold psychotic disorders (Carpenter *et al.* 2009;van Os *et al.* 2010;Zhu *et al.* 2019). The results presented in chapter three of this thesis showed that a part of these factors are also shared across the extended psychosis phenotype and affective psychopathology (Kirli *et al.* 2019c). Childhood adversity and recent stressful life events were significantly associated with both the extended psychosis phenotype and affective psychopathology (Kirli *et al.* 2019c). This is in line with previous studies demonstrating shared associations across threshold psychotic and affective disorders (Matheson *et al.* 2012;Varese *et al.* 2012;Morgan and Gayer-Anderson 2016;Palmier-Claus *et al.* 2018), and subthreshold PEs and affective dysregulation (Fisher *et al.* 2012;Linscott and van Os 2013;van Nierop *et al.* 2014;Duhig *et al.* 2015;Misiak *et al.* 2017). Furthermore, non-married marital status has been associated with both dimensions (Kirli *et al.* 2019c), in

line with earlier studies (Linscott and van Os 2013;Walker *et al.* 2019;Lunde *et al.* 2020;Narita *et al.* 2020b). Finally, family history of a mental illness was a very strong predictor of both dimensions (Kirli *et al.* 2019c), also in line with numerous studies (Dean *et al.* 2010;Mortensen *et al.* 2010;Linscott and van Os 2013). Stress and reward sensitivity refer to negative and positive affect in response to environmental stimulus. Stress and reward sensitivity were associated with both the affective and the psychotic spectrum in previous studies (Myin-Germeys and van Os 2007;Lataster *et al.* 2009b;Heinz *et al.* 2013;Gevonden *et al.* 2014;Misiak *et al.* 2017;Pries *et al.* 2019b). This is in accordance with the aforementioned shared risk factors.

Results in the third chapter of this thesis showed that the associations between cannabis/ heavy alcohol use and the extended psychosis phenotype were significant (Kirli *et al.* 2019c). These results are in line with robust evidence linking the extended psychosis phenotype with cannabis use, and less consistent evidence with heavy alcohol use (Alptekin *et al.* 2009;Kuepper *et al.* 2011;Linscott and van Os 2013;Marconi *et al.* 2016;Ragazzi *et al.* 2018). However, the associations with affective psychopathology were weaker and below the significance level (Kirli *et al.* 2019c), also in line with previous studies (Addington and Addington 2007;Degenhardt *et al.* 2007;Foti *et al.* 2010;Ringen *et al.* 2016;Quattrone *et al.* 2019b). The extended psychosis phenotype was not associated with gender in this thesis (Kirli *et al.* 2019c), parallel to previous studies (Beauchamp and Gagnon 2004;Binbay *et al.* 2011a;Linscott and van Os 2013;Ringen *et al.* 2016;Castle *et al.* 2018). In contrast, the increased risk of affective psychopathology in females presented in this thesis has been consistently demonstrated (Regier 1988;Bijl *et al.* 1998;van Os *et al.* 2010;Sadock 2015). Younger individuals showed higher risk of the extended psychosis phenotype (Kirli *et al.* 2019c), in accordance with meta-analytical evidence (Linscott and van Os 2013). However, the association with affective psychopathology was below the significance level (Kirli *et al.* 2019c). Previous studies also showed weak associations between age and affective

psychopathology and these associations did not shown a linear pattern (Regier 1988;Bijl *et al.* 1998;Pakriev *et al.* 1998;Kebede and Alem 1999;Mohammadi *et al.* 2005;Bradley *et al.* 2011). Furthermore, educational level was associated with the extended psychosis phenotype in this thesis (Kirli *et al.* 2019c). Previous reports linking educational level and the extended psychosis phenotype were not consistent, but a meta-analysis reported significant associations with subthreshold psychosis when outlier results were removed (Linscott and van Os 2013). The association with affective psychopathology was weaker and below the conventional significance level (Kirli *et al.* 2019c), but showed similar odds with previous studies (Bijl *et al.* 1998;Pakriev *et al.* 1998;Schoeyen *et al.* 2011). In summary, an important proportion of the associations with sociodemographic and environmental factors are in the same direction across the extended psychosis phenotype and affective psychopathology. Finally, based on the similar cross-legged correlations between these dimensions over time, shown in the third chapter of this thesis (Kirli *et al.* 2019c), common causal pathways may be suggested across the extended psychosis phenotype and affective psychopathology (de Jonge *et al.* 2017;Kotov *et al.* 2017;Pries *et al.* 2018).

Outcomes of Co-occurrence of the Affective Psychopathology and the Psychosis Spectrum

The baseline cross-sectional analysis of the TürkSch cohort showed significant associations between affective dysregulation and the severity of the extended psychosis phenotype (Binbay *et al.* 2012b). This thesis provided longitudinal evidence for this proposition (Kirli *et al.* 2019b;Kirli *et al.* 2019c). Co-occurrence of affective psychopathology with subthreshold PEs showed poorer outcomes than subthreshold PEs in isolation. Previous studies showed similar results (Kelleher *et al.* 2013;Guloksuz *et al.* 2015;McGrath *et al.* 2016;Navarro-Mateu *et al.* 2017;Pries *et al.* 2018). Conversely, co-occurring psychosis with affective psychopathology was associated with poorer outcomes of the index psychopathology over time, also in line with the previ-

ous evidence (Kaymaz *et al.* 2007;Wigman *et al.* 2009;Perlis *et al.* 2010;Kelleher *et al.* 2011;Rössler *et al.* 2011;Wigman *et al.* 2011;Kaymaz *et al.* 2012;Wigman *et al.* 2012a;Kelleher *et al.* 2018b). A remarkable amount of evidence has demonstrated that greater exposure to risk factors additively drives greater co-occurrence of the positive and affective domains, which together predict poorer long-term outcomes (Cougnard *et al.* 2007;Guloksuz *et al.* 2015;Salokangas *et al.* 2015;Pries *et al.* 2018).

Associations between clinically relevant subthreshold psychotic experiences and subsequent psychopathology

Follow-up Diagnoses of Individuals with Baseline Subthreshold Psychosis

The results presented in the fourth chapter of this thesis showed that the majority of participants with baseline clinically relevant subthreshold psychosis develop a common non-psychotic DSM disorder rather than a psychotic disorder. Furthermore, the follow-up diagnoses are included in various chapters of the DSM including bipolar and related disorders, depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma and stressor-related disorders, somatic symptom disorders, substance-related disorders, sleep-wake disorders, and impulse control disorders as well as schizophrenia spectrum disorders (Kirli *et al.* 2019b).

The main motivation driving the high risk for psychosis concepts (i.e. UHR, CHR, ARMS) has been to stimulate early intervention strategies and thus prevent '*transition to frank psychosis*' (Srihari *et al.* 2012;van Os and Guloksuz 2017;Correll *et al.* 2018;McGorry and Mei 2018). However, research in the area has consistently shown that only a minority of the individuals with subthreshold PEs subsequently meet the diagnostic criteria of a psychotic dis-

order. The majority has a diagnosis of a non-psychotic disorder with a degree of concurrent psychosis: i.e. anxiety, depression, bipolar, substance use disorders (Rössler *et al.* 2011;Kaymaz *et al.* 2012;Fisher *et al.* 2013;McGrath *et al.* 2016). However, a recent meta-analysis evaluating the longitudinal outcomes of subthreshold psychosis concluded that further longitudinal research was needed to precisely determine the associations with non-psychotic disorders. The reason was that most of the studies had a cross-sectional design or a retrospective cohort design, and the few prospective studies were lacking clinician-based diagnoses (Healy *et al.* 2019). Through the prospective evaluations in a representative community-based population and the clinical re-interviews performed in households when necessary, the design of the TürkSch study was able to meet these challenges.

The follow-up diagnoses of baseline clinically relevant subthreshold PEs, which were obtained from a general population sample (Kirli *et al.* 2019b), were similar to the previously reported follow-up diagnoses of the baseline high risk populations (Simon and Umbricht 2010;Addington *et al.* 2011;Ziermans *et al.* 2011;American Psychiatric Association 2013;Lin *et al.* 2015;Rutigliano *et al.* 2016;Guloksuz and van Os 2017;McGorry *et al.* 2018;McGorry and Mei 2018;Chan *et al.* 2019). Results from both the general population and the high-risk populations showed higher rates of subsequent non-psychotic disorders in individuals with subthreshold PEs. Therefore, subthreshold PEs (including high risk or prodromal psychosis concepts) should be treated in the context of multidimensional psychopathology rather than the mere consideration of a 'pre-psychotic' phase.

Baseline Characteristics Associated with the Follow-up Diagnoses of Individuals with Subthreshold Psychosis

The results presented in the fourth chapter of this thesis showed that affective psychopathology co-occurring with subthreshold PEs yielded significantly higher rates of subsequent

mental disorders. However, the co-occurrence of affective psychopathology with subthreshold psychosis was not associated with subsequent psychotic disorder in comparison with subsequent non-psychotic disorder (Kirli *et al.* 2019b). This result was in agreement with the baseline cross-sectional results of the TürkSch cohort demonstrating a disproportionate shift towards the non-psychotic disorder end of the psychosis spectrum in relation to affective dysregulation (Binbay *et al.* 2011a). However, the results comparing the follow-up subsequent psychotic disorders versus non-psychotic disorders should be interpreted considering two issues: First, the low number of participants with a subsequent psychotic disorder might result in false negative results when analysing psychotic disorders because of the low power. Second, this analysis comprised a baseline sample which already had distress associated with the subthreshold PEs. Therefore, the comparisons were between subthreshold PEs plus distress with and without affective disorder. This is the reason that these associations can be different in subclinical-subthreshold PEs, and results might be different if the whole spectrum of subthreshold psychosis was covered. In conclusion, these results showed that affective dysregulation co-occurring with PEs might be linked to higher impairment levels in line with numerous studies (Krabbendam *et al.* 2005;Krabbendam and van Os 2005;van Rossum *et al.* 2009;Salokangas *et al.* 2015).

The results in the fourth chapter demonstrated that co-occurrence of delusional and hallucinatory PEs was associated with a subsequent psychotic disorder (Kirli *et al.* 2019b). This result is in line with previous results (Krabbendam *et al.* 2004b;Smeets *et al.* 2010;Smeets *et al.* 2013;Smeets *et al.* 2015) and the baseline cross-sectional analysis of the TürkSch cohort, demonstrating associations between the degree of delusional and hallucinatory comorbidity of PEs and increased risk of the threshold psychotic disorder end of the extended psychosis phenotype (Binbay *et al.* 2011a). With these results, it can be suggested that comorbidity of symptoms within the same domain, as well as from different

domains, is associated with poorer long term outcomes (Isvoranu *et al.* 2017;Isvoranu *et al.* 2019b).

Numerous studies reported graded associations between the severity of co-occurring common-nonpsychotic disorders and the severity of subthreshold PEs (DeVylder *et al.* 2014a;Guloksuz *et al.* 2015). The results in high risk samples were also in the same direction, as an important proportion of cases with transition consisted of individuals with affective dysregulation (Addington *et al.* 2007). Therefore, one of the most recent high risk for psychosis concepts (i.e. the Clinical High at Risk Mental State-CHARMS) have been updated to include affective dysregulation and some personality traits in addition to subthreshold PEs (Hartmann *et al.* 2019). Furthermore, a recent study reported that the population attributional fractions (PAF) for incident threshold psychotic disorders were higher for affective disorders than the high risk concepts (66.2 vs. 36.9) (Guloksuz *et al.* 2020). Although the high-risk concepts are associated with subsequent threshold psychotic disorders, the sensitivity of high risk concepts is relatively low due to the low prevalence in general populations (Schultze-Lutter *et al.* 2017). Therefore, the screening of positive PEs (and high risk concepts) may cause a high false negative rate with regard to the early expression of multidimensional psychopathology (Guloksuz and van Os 2017). A broader strategy taking the severity of several dimensions into account may represent a more sensitive and specific prevention strategy (van Os *et al.* 2019a).Results presented in chapter four of this thesis showed that a defined mental disorder in the family and persistence of subthreshold PEs were associated with a follow-up mental disorder in individuals with baseline PEs (Kirli *et al.* 2019b). These results are in line with the previous findings (Poulton *et al.* 2000;Yung *et al.* 2003;Dominguez *et al.* 2009;De Loore *et al.* 2011;Linscott and van Os 2013;Nelson *et al.* 2013;Fonseca Pedrero and Debbané 2017). Furthermore, younger age and family history of severe mental illness were associated with the follow-up psychotic disorders in comparison with the follow-up non-psychotic

disorders (Kirli *et al.* 2019b). These variables also occasioned a disproportional shift in risk at the psychotic disorder end of the extended psychosis phenotype in the baseline cross-sectional analysis of the cohort (Binbay *et al.* 2011a). However, many sociodemographic factors did not significantly predict the follow-up psychotic disorders in comparison with the follow-up non-psychotic disorders in individuals with subthreshold PEs, also in line with the baseline cross-sectional analyses showing linear associations and no significant shift in risk across the extended psychosis phenotype (Binbay *et al.* 2011a). The dopamine and other neurobiological systems underlying different types of psychopathology may have the capacity to become sensitised over time (Boileau *et al.* 2006;van Os *et al.* 2009). Gradual exposure to risk might lead to gradual development from subthreshold psychosis to both common non-psychotic disorders and threshold psychotic disorders (Howes *et al.* 2020). Although many studies to date evaluated the risk factors associated with psychotic disorders, research on the determinants of the prospective outcomes of subthreshold PEs is limited, and further studies are needed.

Assessment of risk factors from a dynamic and dimensional perspective

BDNF and the Positive Spectrum of Psychosis

The results presented in the fifth chapter of this thesis showed the association of a priori hypothesized single nucleotide polymorphism (SNP) (BDNF Val66Met) with the positive spectrum of psychosis covering subthreshold and threshold levels. The pattern of the association was that the SNP impacted in a dose-response but extra-linear fashion, with stronger impact at the threshold end. The associations were significant when adjusted for socio-demographics and common environmental exposures (Kirli *et al.* 2019a).

BDNF plays a crucial role in dopaminergic signalling in the mesolimbic pathway (Hyman *et al.* 1991;Spencer *et al.* 1995). Dopamine neurons in the ventral tegmental area (VTA)–nucleus accumbens (NAc) pathway express substantial levels of BDNF protein, mRNA, and TrkB mRNA (the receptor of BDNF) (Hung and Lee 1996;Conner *et al.* 1997;Eisch *et al.* 2003). Altered dopamine signalling and dopamine-related behaviours were demonstrated as a result of BDNF infusion into to subcortical areas of adult rats (Altar *et al.* 1992;Altar *et al.* 1994;Siuciak *et al.* 1996). The Val allele of the BDNF Val66Met polymorphism has been associated with higher BDNF secretion in response to neuronal stimulation in comparison with the Met allele. Altered BDNF signalling in the VTA–NAc pathway, interacting with environmental factors, potently regulate dopaminergic signalling (Horger *et al.* 1999;Guillin *et al.* 2001;Nestler *et al.* 2002).

The aberrant salience theory refers to altered dopamine functioning in incentive salience of reward (Berridge and Robinson 1998;Radua *et al.* 2015;Howes *et al.* 2020). According to this theory, misattributions of thought, and blurred boundaries between internal and external experiences lead to expression of the positive domain of psychosis (Frith 1997;Buckner *et al.* 2008). Aforementioned effects of BDNF signalling on the mesolimbic dopaminergic pathway may impact on attribution of salience, mood and motivational states (Horger *et al.* 1999;Guillin *et al.* 2001;Nestler *et al.* 2002). It was proposed that increased BDNF activity in the mesolimbic (VTA-NAc) pathway has a "prolearning" effect (Eisch *et al.* 2003), which could then be associated with the positive domain of psychosis.

The increased activity of BDNF has been suggested in mania pathogenesis (Neves-Pereira *et al.* 2002;Tsai 2004), which has hypothesised neurobiological links with the positive domain (Kotov *et al.* 2020). In accordance, chronic administration of haloperidol in rats significantly decreased BDNF concentrations (Angelucci *et al.* 2000). The increased activity of BDNF has also been associated with increased anxiety-like traits in mice (Papa-

leo *et al.* 2011). Finally, altered BDNF levels have been associated with the positive domain more consistently than the negative domain (Munkholm *et al.* 2015;Kotov *et al.* 2020;Lin and Huang 2020). However, further consistent replication is required before definitive conclusions can be drawn in this regard.

Dimensional Genetic Risk Assessment in Psychosis

Risk factors in psychosis are pluripotent in nature (McGorry *et al.* 2018).This pluripotency brings the need for a closer examination of individual symptom domains (van Os and Reininghaus 2016). Different symptoms of psychotic disorders, even taking part in the same disorder, might be associated with different biological pathways, thus with different genetic and environmental risk factors (van Winkel *et al.* 2008;Dominguez *et al.* 2010;Varese *et al.* 2012;Fried *et al.* 2013;Ruderfer *et al.* 2013;Isvoranu *et al.* 2017;Elliott *et al.* 2018;Baker *et al.* 2019). Therefore, individuals with psychosis considered in single categories in previous studies may actually have difference in associated risk factors. It was proposed that genetic risk might predominantly have an impact on the liability to develop the positive domain while environmental exposure might be predominantly related to symptoms of general psychopathology (Isvoranu *et al.* 2019a). These clues highlight the need for cross-disorder and dimensional assessments of genetic risk, particularly in the positive domain.

Threshold psychotic disorders are consistently associated with family history of psychotic disorders. Furthermore, these disorders are also associated with the family history of common non-psychotic disorders. A large register-based family history study showed interesting results on this topic. The family history of schizophrenia and related disorders accounted for a much lower population attributable risk of schizophrenia in comparison with the family history of mental disorders in general (9.8% vs. 27.1) (Mortensen *et al.* 2010). Conversely, parental psychotic disorders were associated with both psychotic and non-psychotic disorders in the offspring (Dean *et al.* 2010;DeVylder and Lukens

2013). These results clearly demonstrate the transdiagnostic nature of the genetic effects.

Similar to threshold psychotic disorders, the heritability of subthreshold psychosis was demonstrated using cross-twin analysis (Linney *et al.* 2003;Lataster *et al.* 2009a;Polanczyk *et al.* 2010;Zavos *et al.* 2014;Ronald 2015;Ronald and Pain 2018). A meta-analysis of general population-based studies reported that having a family history of mental illness was among the most important predictors of subthreshold psychosis. However, this meta-analysis did not report whether psychotic or common non-psychotic disorders contributed to the risk of PEs (Linscott and van Os 2013). There is consistent evidence from cross-twin and family history analysis linking the risk with the parental psychotic disorders (Lataster *et al.* 2009a;Polanczyk *et al.* 2010). Conversely, a family history of PEs was associated with the individuals' risk of psychotic disorders (van Os *et al.* 2003). Furthermore, there is preliminary evidence from family history studies linking the risk of PEs with non-psychotic family history. A general-population based birth cohort study reported that adolescents with a family history of a common mental disorder had 1.20 times higher risk of PEs, but this association was below the conventional significance level (Jeppesen *et al.* 2015). The baseline cross-sectional results of our cohort showed that the family history of common non-psychotic mental disorders was significantly associated with the different positions of the extended psychosis phenotype, including subthreshold psychosis (Binbay *et al.* 2012b). Results from other general-population based studies also showed significant associations between the risk of PEs and non-psychotic family history (Zammit *et al.* 2008;Wigman *et al.* 2012b;Zammit *et al.* 2013a).

Recent molecular genetic studies suggested modest SNP heritability (SNP-h^2) for subthreshold psychosis (3%-9% in adolescence, 20%-27% in adults) (Ortega-Alonso *et al.* 2017;Pain *et al.* 2018). A recent study using psychological network analysis between positive, negative, depressive symptoms showed that

the polygenic risk score (PRS) for schizophrenia was directly connected to the spectrum of positive and depressive symptoms (Isvoranu *et al.* 2019a). Although recent studies showed significant associations between PRS for schizophrenia and the risk of PEs (Pain *et al.* 2018;Taylor *et al.* 2019), other studies did not (Potash *et al.* 2012;Zammit *et al.* 2013a;Potash *et al.* 2014;Jones *et al.* 2016;Ronald and Pain 2018). Another study showed an association only for those at higher than average risk such as relatives of patients (van Os *et al.* 2019b). The discrepancies in these results might be due to differences in phenotypes, in particular the severity of the phenotypes used (i.e. schizotypy, psychotic experiences and negative symptoms-PENS, PEs etc.), the sample sizes, the age range of the samples (adolescent or adults) and power of the versions of the PRS (van Os and Linscott 2012;van Os and Reininghaus 2016;Pries *et al.* 2019a). The largest GWAS with PEs to date showed significant genetic correlations with a wide range of disorders including psychotic disorders (schizophrenia), non-psychotic disorders (major depressive disorder, bipolar disorder, attention-deficit hyperactivity disorder), and neurodevelopmental disorders (Legge *et al.* 2019). Furthermore, two loci were genome-wide significant. Interestingly, the most significant gene (ANK3) was previously significant in the Psychiatric Genomics Consortium cross-disorder GWAS (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). This result is consistent with previous epidemiological results, as the PEs are strongly associated with a range of common non-psychotic mental disorders besides psychotic disorders (van Os *et al.* 1999;Verdoux *et al.* 1999;Hanssen *et al.* 2003;Stefanis *et al.* 2004;van Rossum *et al.* 2009;van Os and Linscott 2012;McGrath *et al.* 2016;Kirli *et al.* 2019b;Kirli *et al.* 2019c). In summary, there is emerging evidence from molecular genetic studies suggesting shared genetic influences along the extended and transdiagnostic psychosis phenotype.

Cross-twin and family history analyses consistently demonstrated the heritability of threshold psychotic disorders. However, few molecular genetic findings, if any, have been consistent (Par-

diñas *et al.* 2018). One of the possible explanations why the molecular genetic studies have failed to generate replicated findings might be suboptimal phenotypes (Isvoranu *et al.* 2019a). The phenotypes used in previous case-control designs were embracing a polythetic approach, which might cause much heterogeneity from sample to sample. Actually, symptoms from different domains might have different genetic liabilities (Isvoranu *et al.* 2019a;Isvoranu *et al.* 2019b). Furthermore, phenotypes in most of the studies did not include subthreshold psychosis which may share genetic variations with threshold psychosis (van Os *et al.* 2003;Lataster *et al.* 2009a;Polanczyk *et al.* 2010;Binbay *et al.* 2012b). Including subthreshold psychosis could have increased power and precision. Additionally, the associations were not adjusted for socio-environmental factors. Finally, the phenotypes used in the majority of studies were not assessed longitudinally. Therefore, possible fluctuating manifestations might have been missed. Along with other methodological issues in the area (Sullivan 2008;Isvoranu *et al.* 2019a), a novel dynamic and dimensional perspective is needed. The phenotype used in the study presented in the fifth chapter of this thesis was dimensional including subthreshold phenotypes, and longitudinally evaluated. Furthermore, the socio-environmental factors were taken into account. Albeit several limitations discussed below, this design was able to meet some challenges of previous genetic studies in the area of psychosis, and might stimulate further studies with a dimensional perspective in the future (Kirli *et al.* 2019a).

The analysis of the association between the positive spectrum of psychosis and BDNF Val66Met SNP in the fifth chapter of this thesis has important limitations. BDNF did not give a significant signal in GWAS in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) and subthreshold PEs (Legge *et al.* 2019). However, previous GWAS in subthreshold PEs identified only two significantly associated loci (Legge *et al.* 2019). Many gene-gene interactions were previously reported for BDNF (Tsai 2018). The genetic analysis in this thesis included a priori hypothesized gene variations

(BDNF), and lacking genome-wide associations, which is an important limitation while investigating genetic factors. Furthermore, while the positive spectrum of psychosis (including threshold and subthreshold levels) was significantly associated with BDNF Val66Met variation, the association with subthreshold PEs was close but below the conventional significance level (95% Confidence Interval: 0.98-3.05). Probably this analysis suffered from the relatively small sample size in the nested case-control study. Because of these important limitations, this study should be considered as an explorative attempt which assesses a genetic variation for the positive spectrum of psychosis including subthreshold levels. In conclusion, the findings on BDNF warrant caution and need replication in larger samples with more comprehensive genetic analyses.

Methodological issues

The large and representative population-based sample, inclusion of subthreshold phenotypes in non-help seeking individuals, independent data collection at different time-points over six years and clinical re-interviews were the major strengths. Furthermore, parallel data collection on different phenomenology; sociodemographic, environmental, familial and genetic measures in a single sample brought some advantages to take a bigger part of the clinical picture of psychosis into account. However, the limitations of the study, introduced below, should be considered while interpreting the results.

A longitudinal design with a general population-based sample commonly brings the disadvantage of the possibility of bias caused by differential attrition over time. The TürkSch cohort was conducted in the third most populated city of Turkey, and one of the major cities in Europe (Binbay *et al.* 2011b;Turkish Statistical Institute 2019). As Turkey is a country with rapid migration, intra-city residency changes and urbanization for the last four decades (Guresci 2010;Binbay *et al.* 2011b;Ünal *et al.*

2018;Turkish Statistical Institute 2019), this design required detailed preparation, education, supervision, monitoring and optimization of the use of resources. However, the dropout rate was similar to studies with a similar design (Dominguez *et al.* 2009;Zammit *et al.* 2013b), with satisfactory results on analysis of attrition, as described in detail in the second chapter of this thesis (Kirli *et al.* 2019d).

Evaluation of the full spectrum of psychosis in community-based populations, and particularly the subthreshold phenotypes, has methodological difficulties. The spectrum of psychosis may be conceptualized in various ways (Linscott and van Os 2013). There are lots of terms/definitions of subthreshold psychosis in the area: i.e. high risk, prodromal state, schizotypy, schizotaxia, psychotic experiences and negative symptoms (PENS), psychotic (like) experiences etc. Those terms indeed indicate different positions along the spectrum. Furthermore, phenomenological screening was conducted complemented by the frequency, associated distress, impairment and help-seeking (Binbay *et al.* 2011a;Binbay *et al.* 2011b). Then, these measures were also combined with DSM diagnoses as outcome variables (Kirli *et al.* 2019b). This type of consideration might lead to a degree of conceptual complexity. In order to be consistent, and for international comparisons of the results in the area, an international consortium on the operational definitions of the constructs pertaining to subthreshold psychosis is needed. Methodological uncertainties are still open with regard to defining and measuring psychosis expression (Nuevo *et al.* 2012;Linscott and van Os 2013).

Any screening tool may generate many false-positive and false-negative reports (van Os *et al.* 2009;Nuevo *et al.* 2012;Kelleher *et al.* 2018a). Although the sensitivity of lay-interviewer assessments is relatively high, the specificity may be scant. Therefore, confirmation of the lay-interviewer assessments is of high importance (Kline and Schiffman 2014). The two-stage screening procedure comprised of fully structured lay-interviewer assess-

ments and clinician based-diagnoses in the field, and accessing multiple sources of information at both time points were the major advantages to overcome this issue. Furthermore, collecting data on admission to outpatient mental health services, lifetime use of psychotropic medication, lifetime diagnoses, and psychiatric hospitalisation probably helped to reduce the false-negative rates.

Detailed evaluation of environmental exposure is crucial in epidemiological research in order to make causality more plausible (van Os *et al.* 2010;Pries *et al.* 2019a). Although socio-environmental variables were measured at both time points, some limitations still exist. First, the childhood adversity assessments used in the analyses were predominantly capturing childhood neglect. However, different types of adversity may lead to different consequences as a recent study linked childhood emotional neglect to increased suspiciousness/persecutory ideas whereas the childhood sexual abuse to disorganized communication (Ered and Ellman 2019). Second, as childhood adversity was obtained retrospectively, these assessments may have suffered from the limitations of recall bias. Third, some of the socio-environmental measures were proxy variables, not the exposure per se (e.g. socioeconomic status). Furthermore, the impact of some environmental exposures on the longitudinal outcome of subthreshold PEs was not analysed in the present thesis (i.e. urbanicity, alcohol-substance use, individual social adversities, neighbourhood-level exposure variables etc.). However, additional data on these measures was obtained (detailed in the second chapter of this thesis). These data will be analysed in the near future.

Clinical re-interviews were not possible for the entire sample, as the households were placed around a 900 km^2 of area including urban and rural wards (Binbay *et al.* 2011b;Turkish Statistical Institute 2019). The baseline clinical re-interviews were performed with a priority to recognize the threshold psychotic disorder cases among the psychosis spectrum. The follow-up cli-

nician-based diagnoses were possible for a subgroup of individuals: (i). individuals with baseline clinically relevant subthreshold PEs; (ii). individuals with follow-up probable threshold psychotic disorder cases based on a systematic case assortment strategy (Kirli *et al.* 2019d). Lack of clinical re-interviews with the entire sample caused some limitations. First, the baseline co-occurrence of affective psychopathology with subthreshold PEs was based on lay-interviewer assessments. Hence, results on the incidence of common mental disorders associated with subthreshold PEs could not be obtained. Second, non-psychotic disorders at follow-up could not be compared between individuals who have baseline subthreshold PEs and who do not. Therefore, the non-psychotic disorder risk attributable to subthreshold PEs could not be analysed. Third, the analyses of subsequent psychotic disorders versus non-psychotic disorders covered only the baseline clinically relevant subthreshold PEs. Therefore, these results cannot be referred to the full spectrum of subthreshold psychosis. Furthermore, the low number of individuals with a subsequent threshold psychotic disorder caused low power in these analyses. Therefore, these results need to be replicated.

Directions for future research

To date, the majority of studies on phenomenology, risk factors as well as the neurobiological correlates of psychotic illness have focused on single syndromal states (Isvoranu *et al.* 2019b). However, it has been observed that these underlying factors do not comply well with existing mental disorders, but rather are associated with individual symptom domains across diagnostic categories (van Os and Reininghaus 2016;McGorry *et al.* 2018;Xia *et al.* 2018;Baker *et al.* 2019). Therefore, it is essential to identify dimensions of mental states in graded fashion in order to generate more accurate assumptions (Cuthbert and Insel 2013;van Os *et al.* 2019a; Beauchaine and Hinshaw 2020;Kotov *et al.* 2020). As stated earlier in this thesis, different domains of psychosis have different aspects in brain structure, neurotransmission,

co-occurring psychopathology, and risk factors (van Winkel *et al.* 2008;Dominguez *et al.* 2010;Varese *et al.* 2012;Fried *et al.* 2013;Ruderfer *et al.* 2013;Corlett *et al.* 2016;Isvoranu *et al.* 2017;Elliott *et al.* 2018;Baker *et al.* 2019). There is an important need for further cross-disorder investigations to identify shared variables throughout the domains of psychosis and non-shared variables which may be specific to some disorder states (van Os and Reininghaus 2016;Walss-Bass *et al.* 2017;Quattrone *et al.* 2019a). These efforts may facilitate the attempts converging dimensional and categorical measures and definitions of cut-off points for dimensional measures in clinical decision making (Guloksuz *et al.* 2020;Kotov *et al.* 2020).

Substantial evidence demonstrating the relevance of subthreshold negative and disorganisation phenotypes on psychotic states is present (Bedwell *et al.* 2009;Cohen and Davis 2009;Dominguez *et al.* 2010;Fett and Maat 2011;Fonseca-Pedrero *et al.* 2011;DeVylder *et al.* 2014b;Korponay *et al.* 2014;Engel *et al.* 2015;Walss-Bass *et al.* 2015;Duman *et al.* 2017;Jones *et al.* 2017;Mekori-Domachevsky *et al.* 2017;Pelletier-Baldelli *et al.* 2017;Riehle and Lincoln 2017;Unterrassner *et al.* 2017;Acosta *et al.* 2019;Ered and Ellman 2019;Schultze-Lutter *et al.* 2019). Furthermore, baseline cross-sectional analyses of the TürkSch study showed the associations of the negative and disorganisation domains with the positive spectrum. The TürkSch study and literature studying similar research questions has generated substantial evidence for the graded fashion of the positive domain encompassing subclinical, clinically relevant subthreshold and threshold phenotypes across different disorders based on demographic variables, environmental risk factors, family traits, predictive power, neurobiological similarities and the associations with distress and functional impairment (van Os *et al.* 2009;Binbay *et al.* 2011a;American Psychiatric Association 2013;Linscott and van Os 2013;Unterrassner *et al.* 2017). Furthermore, evidence on the longitudinal bidirectional associations between the positive and the affective domain has been generated (McGrath *et al.* 2016;Kirli *et al.* 2019c;Plana-Ripoll *et al.* 2019). However, more research is

necessary to generate evidence for a similar type of graded pattern for negative and disorganisation phenotypes in the community, as well as the associations with and between other dimensions. Data on these measures has been collected in the TürkSch study (detailed in the second chapter of this thesis), which are going to be analysed as a next step.

Although the prospective unidimensional assessments to capture the subsequent threshold psychotic disorders made important contributions to the area, these efforts did not generate specific and comprehensive results (van Os and Guloksuz 2017;McGorry *et al.* 2018;Guloksuz *et al.* 2020). The priority in the next years should be to understand the pathways from multidimensional liabilities of psychosis to specific forms of threshold disorder states (van Os 2013). The prospective evaluation of baseline subthreshold levels of dimensions in interaction with each other may generate essential findings (Kotov *et al.* 2017;Kotov *et al.* 2020). Studies have shown that exposure to risk factors leads to increasing interconnectivity across dimensions (Guloksuz *et al.* 2016;Pries *et al.* 2018). More research on this novel area is needed to evaluate how risk exposure impacts on the interconnectivity. Furthermore, the integration of neurodevelopmental alterations to dimensional measures (by early life epigenetic variations) would promisingly contribute to our understating of the gradual impairment (Pries *et al.* 2019b).

Associations between different dimensions of psychopathology may reflect the impact of various symptoms on each other in addition to shared etiological risk (Isvoranu *et al.* 2017;van den Heuvel and Sporns 2019;Taquet *et al.* 2020). Investigation of the longitudinal effects of symptoms on each other may enhance individual-based formulations as well as intervention strategies (van Os 2013;van Os *et al.* 2013). Despite the growing evidence, the symptom by symptom causal interactions are predominantly based on clinical observations. Further evidence is needed to identify which symptom domain commonly impacts on which, as well as the directions of the effects.

To date, most of the studies suggestive for gene-environment interactions in psychosis (including the TürkSch study) have used proxy measures for genetic vulnerability such as family history of mental disorders or a priori hypothesized genetic variations (e.g. SNPs). Furthermore, these analyses were predominantly performed with single environmental measures. Recently, promising attempts were made to evaluate cumulative environmental risk based on the meta-analytical associations with psychosis (Padmanabhan *et al.* 2017;Pries *et al.* 2019a). As the additive impact of environmental exposures on the outcome of psychosis has been shown (Cougnard *et al.* 2007;Guloksuz *et al.* 2015;Pries *et al.* 2018), one of the future directions of TürkSch is to include "polyenvironmental risk score (PERS)" when analysing longitudinal data. The quality of the data enables to assess the associations with the threshold psychotic disorder outcome over time, as well as the associations with the extended psychosis phenotype. To further investigate the gene-environment interactions in psychosis, research in the upcoming period should focus on generating a graded measure of socio-environmental loading, interacting with stronger versions of PRS for psychosis, with dependent variables comprising dimensional measures (Pries *et al.* 2018).

Substantial evidence has demonstrated the impact of neighbourhood environment on various mental outcomes including the extended and transdiagnostic psychosis phenotype (Drukker and van Os 2003;Schneiders *et al.* 2003;Allardyce and Boydell 2006;Drukker *et al.* 2006;Drukker *et al.* 2007;Kirkbride *et al.* 2007;Keraite *et al.* 2016;O'Donoghue *et al.* 2016;Wilson *et al.* 2016;Narita *et al.* 2020b). The baseline cross-sectional analysis of the TürkSch study also showed that the impact of family history of severe mental illness on the extended psychosis phenotype was stronger in neighbourhoods with higher levels of socioeconomic disadvantage, and with higher levels of social control (Binbay *et al.* 2012a). Furthermore, recent studies proposed the perceived neighbourhood change as a contributing factor in psychosis expression (Hastings *et al.* 2019;Narita *et al.* 2020a).

Further longitudinal studies are needed to examine the associations between neighbourhood change and psychosis expression in the community (Narita *et al.* 2020a). Additional data has been collected on these measures throughout the TürkSch study (detailed in the second chapter of this thesis). In the near future, the longitudinal associations between neighbourhood-contextual measures and the psychosis spectrum in the TürkSch data will be analysed.

To date, a remarkable number of studies have generated results on the odds of etiological factors and phenomenological states for particular psychotic states. However, for a community-based view of prevention, the population attributable fraction (PAF) is also important to comprehensively plan screening and intervention strategies. These measures in the current literature are somewhat scarce. Some recent studies started generating novel and important results on this issue (Di Forti *et al.* 2019;Guloksuz *et al.* 2020). As the TürkSch study prospectively evaluated risk factors in a representative-community based population, one of the future directions is to generate further findings on population attributable risk of clinical psychotic states.

Recent meta-analyses showed that early intervention in subthreshold psychosis might be beneficial in terms of treatment discontinuation and psychiatric hospitalization (van der Gaag *et al.* 2013;Correll *et al.* 2018). However, there are many open questions on how to intervene. As the current evidence for the available intervention methods is insufficient (Davies *et al.* 2018a;Davies *et al.* 2018b;Howes *et al.* 2020), further research to form evidence-based interventions in different dimensions of subthreshold psychopathology is necessary. Furthermore, some concerns are to be solved on the comprehensiveness of the early-intervention centre (van Os and Guloksuz 2017;Guloksuz *et al.* 2020).

In conclusion, the TürkSch study consisted of several multilevel data collection stages in a representative-community based

population, and covered the full spectrum of psychosis including subclinical, subthreshold and threshold phenotypes. Therefore, the TürkSch study provided a comprehensive data set on the multidimensional nature of the extended and transdiagnostic psychosis phenotype. Through the analyses in the present thesis as well as the analyses which will be conducted in the future, the study may shed light to several etiological and phenomenological aspects of psychosis in the community. Future assessments of the cohort, with more comprehensive genetic analysis and broader clinical interviews, may answer some open questions on gene-environment interactions in psychosis, may provide important clues to improve screening strategies, and may further generate evidence for the socio-environmental factors that adversely affect public mental health.

References

- Acosta H, Straube B , Kircher T (2019). Schizotypy and mentalizing: An fMRI study. *Neuropsychologia* 124, 299-310.
- Addington J , Addington D (2007). Patterns, predictors and impact of substance use in early psychosis: a longitudinal study. *Acta psychiatrica Scandinavica* 115, 304-309.
- Addington J, Cadenhead KS, Cannon TD*, et al.* (2007). North American Prodrome Longitudinal Study: A Collaborative Multisite Approach to Prodromal Schizophrenia Research. *Schizophrenia bulletin* 33, 665-672.
- Addington J, Cornblatt BA, Cadenhead KS*, et al.* (2011). At Clinical High Risk for Psychosis: Outcome for Nonconverters. *American Journal of Psychiatry* 168, 800-805.
- Allardyce J , Boydell J (2006). Review: the wider social environment and schizophrenia. *Schizophrenia Bulletin* 32, 592-598.
- Alptekin K, Ulas H, Akdede BB, Tümüklü M , Akvardar Y (2009). Prevalence and risk factors of psychotic symptoms: in the city of Izmir, Turkey. *Social psychiatry and psychiatric epidemiology* 44, 905-910.
- Altar CA, Boylan CB, Fritsche M, Jackson C, Hyman C , Lindsay RM (1994). The Neurotrophins NT-4/5 and BDNF Augment Serotonin, Dopamine, and GABAergic Systems during Behaviorally Effective Infusions to the Substantia Nigra. *Experimental Neurology* 130, 31-40.
- Altar CA, Boylan CB, Jackson C*, et al.* (1992). Brain-derived neurotrophic factor augments rotational behavior and nigrostriatal dopamine turnover in vivo. *Proceedings of the National Academy of Sciences* 89, 11347-11351.
- American Psychiatric Association (1987). *Diagnostic and statistical manual*

of mental disorders, -3rd edition-revised: DSM-III-R. American Psychiatric Association: Washington, DC.

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

- Angelucci F, Mathe AA , Aloe L (2000). Brain-derived neurotrophic factor and tyrosine kinase receptor TrkB in rat brain are significantly altered after haloperidol and risperidone administration. *Journal of Neuroscience Research* 60, 783-794.

- Anttila V, Bulik-Sullivan B, Finucane HK*, et al.* (2018). Analysis of shared heritability in common disorders of the brain. *Science* 360, eaap8757.

- Baker JT, Dillon DG, Patrick LM*, et al.* (2019). Functional connectomics of affective and psychotic pathology. *Proceedings of the National Academy of Sciences* 116, 9050-9059.

- Beauchaine TP , Hinshaw SP (2020). RDoC and Psychopathology among Youth: Misplaced Assumptions and an Agenda for Future Research. *Journal of Clinical Child & Adolescent Psychology* 49, 322-340.

- Beauchamp G , Gagnon A (2004). Influence of diagnostic classification on gender ratio in schizophrenia. *Social psychiatry and psychiatric epidemiology* 39, 1017-1022.

- Bedwell JS, Kamath V , Compton MT (2009). The relationship between interview-based schizotypal personality dimension scores and the continuous performance test. *Schizophrenia Research* 108, 158-162.

- Berridge KC , Robinson TE (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews* 28, 309-369.

- Bijl RV, Ravelli A , van Zessen G (1998). Prevalence of psychiatric disorder in the general population:

results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social psychiatry and psychiatric epidemiology* 33, 587-595.

- Binbay T, Drukker M, Alptekin K*, et al.* (2012a). Evidence that the wider social environment moderates the association between familial liability and psychosis spectrum outcome. *Psychological Medicine* 42, 2499-2510.

- Binbay T, Drukker M, Elbi H*, et al.* (2011a). Testing the Psychosis Continuum: Differential Impact of Genetic and Nongenetic Risk Factors and Comorbid Psychopathology Across the Entire Spectrum of Psychosis. *Schizophrenia Bulletin* 38, 992-1002.

- Binbay T, Drukker M, Elbi H*, et al.* (2012b). Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophrenia bulletin* 38, 992-1002.

- Binbay T, Elbi H, Alptekin K*, et al.* (2011b). Izmir Mental Health Survey for Gene-Environment in Psychoses (TurkSch): Objectives and Methodology. *Turkish Journal of Psychiatry*.

- Boileau I, Dagher A, Leyton M*, et al.* (2006). Modeling Sensitization to Stimulants in Humans. *Archives of general psychiatry* 63.

- Bora E, Yucel M , Pantelis C (2018). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *British Journal of Psychiatry* 195, 475-482.

- Botvinik-Nezer R, Holzmeister F, Camerer CF*, et al.* (2020). Variability in the analysis of a single neuroimaging dataset by many teams. *Nature* 582, 84-88.

- Bradley B, DeFife JA, Guarnaccia C*, et al.* (2011). Emotion Dysregulation and Negative Affect. *The Journal of clinical psychiatry* 72, 685-691.

- Buckley PF, Miller BJ, Lehrer DS , Castle DJ (2008). Psychiatric Comorbidities and Schizophrenia. *Schizophrenia Bulletin* 35, 383-402.

- Buckner RL, Andrews-Hanna JR , Schacter DL (2008). The Brain's Default Network. *Annals of the New York Academy of Sciences* 1124, 1-38.

- Burdick KE, Russo M, Frangou S*, et al.* (2014). Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. *Psychological Medicine* 44, 3083-3096.

- Cardno AG, Rijsdijk FV, Sham PC, Murray RM , McGuffin P (2002). A Twin Study of Genetic Relationships Between Psychotic Symptoms. *American Journal of Psychiatry* 159, 539-545.

- Carpenter WT, Bustillo JR, Thaker GK, van Os J, Krueger RF , Green MJ (2009). The psychoses: Cluster 3 of the proposed meta-structure for DSM-V and ICD-11. *Psychological Medicine* 39, 2025-2042.

- Castle DJ, Wessely S , Murray RM (2018). Sex and Schizophrenia: Effects of Diagnostic Stringency, and Associations with Premorbid Variables. *British Journal of Psychiatry* 162, 658-664.

- Cederlöf M, Östberg P, Pettersson E*, et al.* (2013). Language and mathematical problems as precursors of psychotic-like experiences and juvenile mania symptoms. *Psychological Medicine* 44, 1293-1302.

- Chan CT, Abdin E, Subramaniam M, Tay SA, Lim LK , Verma S (2019). Two-Year Clinical and Functional Outcomes of an Asian Cohort at Ultra-High Risk of Psychosis. *Frontiers in psychiatry* 9.

- Chen C, Cheng L, Grennan K*, et al.* (2012). Two gene co-expression modules differentiate psychotics and controls. *Molecular psychiatry* 18, 1308-1314.

- Chou IJ, Kuo C-F, Huang Y-S, *et al.* (2017). Familial Aggregation and Heritability of Schizophrenia and Co-aggregation of Psychiatric Illnesses in Affected Families. *Schizophrenia bulletin* 43, 1070-1078.
- Cohen AS , Davis TE (2009). Quality of life across the schizotypy spectrum: findings from a large non-clinical adult sample. *Comprehensive Psychiatry* 50, 408-414.
- Conner JM, Lauterborn JC, Yan Q, Gall CM , Varon S (1997). Distribution of Brain-Derived Neurotrophic Factor (BDNF) Protein and mRNA in the Normal Adult Rat CNS: Evidence for Anterograde Axonal Transport. *The Journal of Neuroscience* 17, 2295-2313.
- Corlett PR, Honey GD , Fletcher PC (2016). Prediction error, ketamine and psychosis: An updated model. *Journal of Psychopharmacology* 30, 1145-1155.
- Correll CU, Galling B, Pawar A, *et al.* (2018). Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis. *JAMA Psychiatry* 75, 555.
- Cougnard A, Marcelis M, Myin-Germeys I, *et al.* (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness–persistence model. *Psychological Medicine* 37, 513.
- Cross-Disorder Group of the Psychiatric Genomics Consortium (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet* 381, 1371-1379.
- Cross-Disorder Group of the Psychiatric Genomics Consortium (2019). Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* 179, 1469-1482 e1411.
- Cuthbert BN , Insel TR (2013). Toward the future of psychiatric diagnosis: the

seven pillars of RDoC. *BMC Medicine* 11.

- Davies C, Cipriani A, Ioannidis JPA, *et al.* (2018a). Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. *World Psychiatry* 17, 196-209.

- Davies C, Radua J, Cipriani A, *et al.* (2018b). Efficacy and Acceptability of Interventions for Attenuated Positive Psychotic Symptoms in Individuals at Clinical High Risk of Psychosis: A Network Meta-Analysis. *Frontiers in psychiatry* 9.

- de Graaf R, van Dorsselaer S, Tuithof M , ten Have M (2013). Sociodemographic and psychiatric predictors of attrition in a prospective psychiatric epidemiological study among the general population. Result of the Netherlands Mental Health Survey and Incidence Study-2. *Comprehensive psychiatry* 54, 1131-1139.

- de Jonge P, Wardenaar KJ, Lim CCW, *et al.* (2017). The cross-national structure of mental disorders: results from the World Mental Health Surveys. *Psychological Medicine* 48, 2073-2084.

- De Loore E, Gunther N, Drukker M, *et al.* (2011). Persistence and outcome of auditory hallucinations in adolescence: A longitudinal general population study of 1800 individuals. *Schizophrenia research* 127, 252-256.

- Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E , Pedersen CB (2010). Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Archives of General Psychiatry* 67, 822-829.

- Degenhardt L, Tennant C, Gilmour S, *et al.* (2007). The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic disorders: findings from a 10-month prospective study. *Psychological Medicine* 37, 927-934.

- Dereboy F (2000). Şizofreniye İlişkin Psikanalitik

Yaklaşımlar (Psychanalytical Approach to Schizophrenia). Şizofreni Dizisi 3, 11-19.

- DeVylder JE, Burnette D , Yang LH (2014a). Co-occurrence of psychotic experiences and common mental health conditions across four racially and ethnically diverse population samples. *Psychological Medicine* 44, 3503-3513.

- DeVylder JE , Lukens EP (2013). Family history of schizophrenia as a risk factor for axis I psychiatric conditions. *Journal of psychiatric research* 47, 181-187.

- DeVylder JE, Muchomba FM, Gill KE*, et al.* (2014b). Symptom trajectories and psychosis onset in a clinical high-risk cohort: The relevance of subthreshold thought disorder. *Schizophrenia Research* 159, 278-283.

- Di Forti M, Quattrone D, Freeman TP*, 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* 6, 427-436.

- Dominguez M-d-G, Saka MC, Lieb R, Wittchen H-U , van Os J (2010). Early Expression of Negative/Disorganized Symptoms Predicting Psychotic Experiences and Subsequent Clinical Psychosis: A 10-Year Study. *American Journal of Psychiatry* 167, 1075-1082.

- Dominguez MDG, Wichers M, Lieb R, Wittchen HU , van Os J (2009). Evidence That Onset of Clinical Psychosis Is an Outcome of Progressively More Persistent Subclinical Psychotic Experiences: An 8-Year Cohort Study. *Schizophrenia bulletin* 37, 84-93.

- Drukker M, Gunther N , van Os J (2007). Disentangling associations between poverty at various levels of aggregation and mental health. *Epidemiologia e psichiatria sociale* 16, 3-9.

- Drukker M, Krabbendam L, Driessen G , van Os J (2006). Social disadvantage and schizophrenia. *Social Psychiatry and Psychiatric Epidemiology* 41, 595-604.

- Drukker M , van Os J (2003). Mediators of neighbourhood

socioeconomic deprivation and quality of life. *Social psychiatry and psychiatric epidemiology* 38, 698-706.

- Duhig M, Patterson S, Connell M*, et al.* (2015). The prevalence and correlates of childhood trauma in patients with early psychosis. *Australian & New Zealand Journal of Psychiatry* 49, 651-659.

- Duman B, Sedes N , Baskak B (2017). Additive Effects of Former Methylenedioxymethamphetamine and Cannabis Use on Subclinical Psychotic Symptoms. *Noro psikiyatri arsivi* 54, 38-42.

- Eisch AJ, Bolaños CA, de Wit J*, et al.* (2003). Brain-derived neurotrophic factor in the ventral midbrain–nucleus accumbens pathway: a role in depression. *Biological psychiatry* 54, 994-1005.

- Elliott ML, Knodt AR, Ireland D*, et al.* (2020). What Is the Test-Retest Reliability of Common Task-Functional MRI Measures? New Empirical Evidence and a Meta-Analysis. *Psychological Science* 31, 792-806.

- Elliott ML, Romer A, Knodt AR , Hariri AR (2018). A Connectome-wide Functional Signature of Transdiagnostic Risk for Mental Illness. *Biological psychiatry* 84, 452-459.

- Engel M, Fritzsche A , Lincoln TM (2015). Subclinical negative symptoms and the anticipation, experience and recall of emotions related to social interactions: An experimental study. *Psychiatry research* 230, 350-356.

- Ered A , Ellman LM (2019). Specificity of Childhood Trauma Type and Attenuated Positive Symptoms in a Non-Clinical Sample. *Journal of Clinical Medicine* 8, 1537.

- Fett AKJ , Maat A (2011). Social Cognitive Impairments and Psychotic Symptoms: What Is the Nature of Their Association? *Schizophrenia Bulletin* 39, 77-85.

- Fisher HL, Caspi A, Poulton R*, et al.* (2013). Specificity of childhood psychotic symptoms for predicting

schizophrenia by 38 years of age: a birth cohort study. *Psychological medicine* 43, 2077-2086.

- Fisher HL, Schreier A, Zammit S*, et al.* (2012). Pathways Between Childhood Victimization and Psychosis-like Symptoms in the ALSPAC Birth Cohort. *Schizophrenia bulletin* 39, 1045-1055.

- Fonseca-Pedrero E, Paino M, Lemos-Giráldez S , Muñiz J (2011). Schizotypal traits and depressive symptoms in nonclinical adolescents. *Comprehensive Psychiatry* 52, 293-300.

- Fonseca Pedrero E , Debbané M (2017). Schizotypal traits and psychotic-like experiences during adolescence: An update. *Psicothema* 29, 5-17.

- Foti DJ, Kotov R, Guey LT , Bromet EJ (2010). Cannabis Use and the Course of Schizophrenia: 10-Year Follow-Up After First Hospitalization. *American Journal of Psychiatry* 167, 987-993.

- Freud S (1924). *Neurosis and psychosis*. Hogarth Press: London.

- Fried EI, Nesse RM, Zivin K, Guille C , Sen S (2013). Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. *Psychological medicine* 44, 2067-2076.

- Frith C (1997). The role of the prefrontal cortex in self-consciousness: the case of auditory hallucinations. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* 351, 1505-1512.

- Fusar-Poli P, Cappucciati M, Borgwardt S*, et al.* (2016). Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk: A Meta-analytical Stratification. *JAMA Psychiatry* 73, 113-120.

- Fusar-Poli P, Nelson B, Valmaggia L, Yung AR , McGuire PK (2014). Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental

state: impact on psychopathology and transition to psychosis. *Schizophr Bull* 40, 120-131.

- Gevonden MJ, Myin-Germeys I, van den Brink W, van Os J, Selten JP , Booij J (2014). Psychotic reactions to daily life stress and dopamine function in people with severe hearing impairment. *Psychological Medicine* 45, 1665-1674.

- Goldsmith DR, Rapaport MH , Miller BJ (2016). A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Molecular psychiatry* 21, 1696-1709.

- Guillin O, Diaz J, Carroll P, Griffon N, Schwartz J-C , Sokoloff P (2001). BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature* 411, 86-89.

- Guloksuz S, Pries LK, Have M*, et al.* (2020). Association of preceding psychosis risk states and non-psychotic mental disorders with incidence of clinical psychosis in the general population: a prospective study in the NEMESIS-2 cohort. *World Psychiatry* 19, 199-205.

- Guloksuz S, van Nierop M, Bak M*, et al.* (2016). Exposure to environmental factors increases connectivity between symptom domains in the psychopathology network. *BMC psychiatry* 16.

- Guloksuz S, van Nierop M, Lieb R, van Winkel R, Wittchen HU , 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* 45, 2389-2401.

- Guloksuz S , van Os J (2017). The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological medicine* 48, 229-244.

- Guresci E (2010). The phenomenon of the urban - rural migration in Turkey. *Journal of Dogus University* 11, 77-86.

- Häfner H, Maurer K, Trendler G, an der Heiden W, Schmidt M , Könnecke R (2005). Schizophrenia and depression: Challenging the paradigm of two separate diseases—A controlled study of schizophrenia, depression and healthy controls. *Schizophrenia research* 77, 11-24.

- Hanssen M, Bak M, Bijl R, Vollebergh W , Os J (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *British Journal of Clinical Psychology* 44, 181-191.

- Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H , van Os J (2003). How psychotic are individuals with non-psychotic disorders? *Social Psychiatry and Psychiatric Epidemiology* 38, 149-154.

- Hartmann JA, Nelson B, Spooner R, *et al.* (2019). Broad clinical high-risk mental state (CHARMS): Methodology of a cohort study validating criteria for pluripotent risk. *Early Intervention in Psychiatry* 13, 379-386.

- Hastings PD, Serbin LA, Bukowski W, *et al.* (2019). Predicting psychosis-spectrum diagnoses in adulthood from social behaviors and neighborhood contexts in childhood. *Development and psychopathology*, 1-15.

- Hazlett EA, Rothstein EG, Ferreira R, Silverman JM, Siever LJ , Olincy A (2015). Sensory gating disturbances in the spectrum: Similarities and differences in schizotypal personality disorder and schizophrenia. *Schizophrenia research* 161, 283-290.

- Healy C, Brannigan R, Dooley N, *et al.* (2019). Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. *Psychological medicine* 49, 1589-1599.

- Heinz A, Deserno L , Reininghaus U (2013). Urbanicity, social adversity and psychosis. *World Psychiatry* 12, 187-197.

- Hermens DF, Chitty KM , Kaur M (2018). Mismatch negativity in bipolar disor-

der: A neurophysiological biomarker of intermediate effect? *Schizophrenia research* 191, 132-139.

- Horger BA, Iyasere CA, Berhow MT, Messer CJ, Nestler EJ , Taylor JR (1999). Enhancement of Locomotor Activity and Conditioned Reward to Cocaine by Brain-Derived Neurotrophic Factor. *The Journal of Neuroscience* 19, 4110-4122.

- Howes OD, Hird EJ, Adams RA, Corlett PR , McGuire P (2020). Aberrant Salience, Information Processing, and Dopaminergic Signaling in People at Clinical High Risk for Psychosis. *Biological psychiatry*.

- Hung H-C , Lee EHY (1996). The mesolimbic dopaminergic pathway is more resistant than the nigrostriatal dopaminergic pathway to MPTP and MPP+ toxicity: role of BDNF gene expression. *Molecular Brain Research* 41, 16-26.

- Hyman C, Hofer M, Barde Y-A*, et al.* (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature* 350, 230-232.

- Ioannidis JP (2005). Why most published research findings are false. *PLoS Med* 2, e124.

- Ioannidis JPA (2011). Excess Significance Bias in the Literature on Brain Volume Abnormalities. *Archives of general psychiatry* 68, 773.

- Isvoranu A-M, Guloksuz S, Epskamp S, van Os J , Borsboom D (2019a). Toward incorporating genetic risk scores into symptom networks of psychosis. *Psychological medicine*, 1-8.

- Isvoranu A-M, van Borkulo CD, Boyette L-L, Wigman JTW, Vinkers CH , Borsboom D (2017). A Network Approach to Psychosis: Pathways Between Childhood Trauma and Psychotic Symptoms. *Schizophrenia Bulletin* 43, 187-196.

- Isvoranu AM, Boyette LL, Guloksuz S , Borsboom D (2019b). Symptom network models of psychosis. In *Psychotic Disorders: Compre-*

hensive Conceptualization and Treatments (ed. J. van Os, U. Reininghaus, E. I. Ivleva and C. A. Tamminga). Oxford University Press: Oxford.

- Javitt DC, Lee M, Kantrowitz JT , Martinez A (2018). Mismatch negativity as a biomarker of theta band oscillatory dysfunction in schizophrenia. *Schizophrenia research* 191, 51-60.

- Jeppesen P, Larsen JT, Clemmensen L*, et al.* (2015). The CCC2000 Birth Cohort Study of Register-Based Family History of Mental Disorders and Psychotic Experiences in Offspring. *Schizophrenia Bulletin* 41, 1084-1094.

- Jones HJ, Stergiakouli E, Tansey KE*, et al.* (2016). Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population. *JAMA psychiatry* 73, 221.

- Jones JD, Calkins ME, Scott JC, Bach EC , Gur RE (2017). Cannabis Use, Polysubstance Use, and Psychosis Spectrum Symptoms in a Community-Based Sample of U.S. Youth. *Journal of Adolescent Health* 60, 653-659.

- Kafali HY, Bildik T, Bora E, Yuncu Z , Erermis HS (2019). Distinguishing prodromal stage of bipolar disorder and early onset schizophrenia spectrum disorders during adolescence. *Psychiatry research* 275, 315-325.

- Kaymaz N, Drukker M, Lieb R*, et al.* (2012). Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychological Medicine* 42, 2239-2253.

- Kaymaz N, van Os J, de Graaf R, ten Have M, Nolen W , Krabbendam L (2007). The impact of subclinical psychosis on the transition from subclinicial mania to bipolar disorder. *Journal of affective disorders* 98, 55-64.

- Kebede D , Alem A (1999). Major mental disorders in

Addis Ababa, Ethiopia. II. Affective disorders. *Acta psychiatrica Scandinavica* 100, 18-23.

- Kelleher I, Devlin N, Wigman JTW*, et al.* (2013). Psychotic experiences in a mental health clinic sample: implications for suicidality, multimorbidity and functioning. *Psychological Medicine* 44, 1615-1624.

- Kelleher I, Jenner JA , Cannon M (2018a). Psychotic symptoms in the general population – an evolutionary perspective. *British Journal of Psychiatry* 197, 167-169.

- Kelleher I, Keeley H, Corcoran P*, et al.* (2018b). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *British Journal of Psychiatry* 201, 26-32.

- Kelleher I, Murtagh A, Molloy C*, et al.* (2011). Identification and Characterization of Prodromal Risk Syndromes in Young Adolescents in the Community: A Population-Based Clinical Interview Study. *Schizophrenia bulletin* 38, 239-246.

- Kendler KS (2020). The Development of Kraepelin's Concept of Dementia Praecox. *JAMA Psychiatry*.

- Keraite A, Sumathipala A, Siriwardhana C, Morgan C , Reininghaus U (2016). Exposure to conflict and disaster: A national survey on the prevalence of psychotic experiences in Sri Lanka. *Schizophrenia research* 171, 79-85.

- Kirkbride JB, Morgan C, Fearon P, Dazzan P, Murray RM , Jones PB (2007). Neighbourhood-level effects on psychoses: re-examining the role of context. *Psychological medicine* 37, 1413-1425.

- Kirli U, Binbay T, Drukker M*, et al.* (2019a). Is BDNF-Val66Met polymorphism associated with psychotic experiences and psychotic disorder outcome? Evidence from a 6 years prospective population-based cohort study. *American journal of*

medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 180, 113-121.

- Kirli U, Binbay T, Drukker M*, et al.* (2019b). DSM outcomes of psychotic experiences and associated risk factors: 6-year follow-up study in a community-based sample. *Psychological Medicine* 49, 1346-1356.

- Kirli U, Binbay T, Drukker M*, et al.* (2019c). Psychotic experiences and mood episodes predict each other bidirectionally: a 6-year follow-up study in a community-based population. *Social psychiatry and psychiatric epidemiology* 54, 331-341.

- Kirli U, Binbay T, Elbi H*, et al.* (2019d). Izmir Mental Health Cohort for Gene-Environment Interaction in Psychosis (TürkSch): Assessment of the Extended and Transdiagnostic Psychosis Phenotype and Analysis of Attrition in a 6-Year Follow-Up of a Community-Based Sample. *Frontiers in psychiatry* 10, 554.

- Kline E , Schiffman J (2014). Psychosis risk screening: A systematic review. *Schizophrenia research* 158, 11-18.

- Klosterkötter J, Ebel H, Schultze-Lutter F , Steinmeyer EM (1996). Diagnostic validity of basic symptoms. *European Archives of Psychiatry and Clinical Neuroscience* 246, 147-154.

- Korponay C, Nitzburg GC, Malhotra AK , DeRosse P (2014). Positive and negative subclinical symptoms and MCCB performance in non-psychiatric controls. *Schizophrenia Research: Cognition* 1, 175-179.

- Kotov R, Jonas KG, Carpenter WT*, et al.* (2020). Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum. *World Psychiatry* 19, 151-172.

- Kotov R, Krueger RF, Watson D*, et al.* (2017). The Hierar-

chical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of abnormal psychology* 126, 454-477.

- Krabbendam L, Myin-Germeys I, De Graaf R, *et al.* (2004a). Dimensions of depression, mania and psychosis in the general population. *Psychological Medicine* 34, 1177-1186.

- Krabbendam L, Myin-Germeys I, Hanssen M, *et al.* (2004b). Hallucinatory experiences and onset of psychotic disorder: evidence that the risk is mediated by delusion formation. *Acta psychiatrica Scandinavica* 110, 264-272.

- Krabbendam L, Myin-Germeys I, Hanssen M, *et al.* (2005). Development of depressed mood predicts onset of psychotic disorder in individuals who report hallucinatory experiences. *British Journal of Clinical Psychology* 44, 113-125.

- Krabbendam L , van Os J (2005). Affective processes in the onset and persistence of psychosis. *European Archives of Psychiatry and Clinical Neuroscience* 255, 185-189.

- Kraepelin E (1899). Zur Diagnose und Prognose der Dementia praecox. In *Allgemeine Zeitschrift für Psychiatrie*, pp. 254-264.

- Kuepper R, van Os J, Lieb R, Wittchen HU, Hofler M , Henquet C (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *Bmj* 342, d738-d738.

- Lataster T, Myin-Germeys I, Derom C, Thiery E , van Os J (2009a). Evidence that self-reported psychotic experiences represent the transitory developmental expression of genetic liability to psychosis in the general population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 150B, 1078-1084.

- Lataster T, Wichers M, Jacobs N, *et al.* (2009b). Does reactivity to stress cosegregate with subclinical psychosis? A general

population twin study. *Acta psychiatrica Scandinavica* 119, 45-53.

- Legge SE, Jones HJ, Kendall KM*, et al.* (2019). Association of Genetic Liability to Psychotic Experiences With Neuropsychotic Disorders and Traits. *JAMA Psychiatry* 76, 1256.

- Lichtenstein P, Yip BH, Björk C*, et al.* (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *The Lancet* 373, 234-239.

- Lin A, Wood SJ, Nelson B, Beavan A, McGorry P , Yung AR (2015). Outcomes of Nontransitioned Cases in a Sample at Ultra-High Risk for Psychosis. *American Journal of Psychiatry* 172, 249-258.

- Lin C-C , Huang T-L (2020). Brain-derived neurotrophic factor and mental disorders. *Biomedical Journal* 43, 134-142.

- Linney YM, Murray RM, Peters ER, MacDonald AM, Rijsdijk F , Sham PC (2003). A quantitative genetic analysis of schizotypal personality traits. *Psychological Medicine* 33, 803-816.

- Linscott RJ , van Os J (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine* 43, 1133-1149.

- Lunde KB, Mehlum L, Melle I , Qin P (2020). Deliberate self-harm and associated risk factors in young adults: the importance of education attainment and sick leave. *Social psychiatry and psychiatric epidemiology*.

- Mancuso SG, Morgan VA, Mitchell PB, Berk M, Young A , Castle DJ (2015). A comparison of schizophrenia, schizoaffective disorder, and bipolar disorder: Results from the Second Australian national psycho-

sis survey. *Journal of affective disorders* 172, 30-37.

- Marconi A, Di Forti M, Lewis CM, Murray RM , Vassos E (2016). Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophrenia bulletin* 42, 1262-1269.

- Martin J, Taylor MJ , Lichtenstein P (2017). Assessing the evidence for shared genetic risks across psychiatric disorders and traits. *Psychological Medicine* 48, 1759-1774.

- Matheson SL, Shepherd AM, Pinchbeck RM, Laurens KR , Carr VJ (2012). Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychological Medicine* 43, 225-238.

- McGorry PD, Hartmann JA, Spooner R , Nelson B (2018). Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry* 17, 133-142.

- McGorry PD , Mei C (2018). Ultra-high-risk paradigm: lessons learnt and new directions. *Evidence Based Mental Health* 21, 131-133.

- McGrath JJ, Saha S, Al-Hamzawi A*, et al.* (2016). The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *American Journal of Psychiatry* 173, 997-1006.

- McMillan KA, Enns MW, Cox BJ , Sareen J (2009). Comorbidity of Axis I and II Mental Disorders with Schizophrenia and Psychotic Disorders: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *The Canadian Journal of Psychiatry* 54, 477-486.

- Mekori-Domachevsky E, Guri Y, Yi J*, et al.* (2017). Negative subthreshold psychotic symptoms distinguish 22q11.2 deletion syndrome from other neurodevelopmental disorders: A two-site study. *Schizophrenia Research* 188, 42-49.

- Miller TJ, McGlashan TH, Rosen JL*, et al.* (2003). Prodromal Assessment With

the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms: Predictive Validity, Interrater Reliability, and Training to Reliability. *Schizophrenia Bulletin* 29, 703-715.

- Misiak B, Krefft M, Bielawski T, Moustafa AA, Sąsiadek MM , Frydecka D (2017). Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neuroscience & Biobehavioral Reviews* 75, 393-406.

- Mohammadi M-R, Davidian H, Noorbala A*, et al.* (2005). An epidemiological survey of psychiatric disorders in Iran. *Clinical Practice and Epidemiology in Mental Health* 1, 16.

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

- Mortensen PB, Pedersen MG , Pedersen CB (2010). Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychological Medicine* 40, 201-210.

- Munkholm K, Vinberg M , Kessing LV (2015). Peripheral blood brain-derived neurotrophic factor in bipolar disorder: a comprehensive systematic review and meta-analysis. *Molecular psychiatry* 21, 216-228.

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

- Narita Z, Knowles K, Fedina L*, et al.* (2020a). Neighborhood change and psychotic experiences in a general population sample. *Schizophrenia research* 216, 316-321.

- Narita Z, Stickley A , DeVylder J (2020b). Loneliness and psychotic experiences in a general population sample. *Schizophrenia research* 218, 146-150.

- Navarro-Mateu F, Alonso J, Lim CCW, *et al.* (2017). The association between psychotic experiences and disability: results from the WHO World Mental Health Surveys. *Acta psychiatrica Scandinavica* 136, 74-84.

- Nelson B, Yuen HP, Wood SJ, *et al.* (2013). Long-term Follow-up of a Group at Ultra High Risk ("Prodromal") for Psychosis. *JAMA Psychiatry* 70, 793.

- Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ , Monteggia LM (2002). Neurobiology of Depression. *Neuron* 34, 13-25.

- Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F , Kennedy JL (2002). The Brain-Derived Neurotrophic Factor Gene Confers Susceptibility to Bipolar Disorder: Evidence from a Family-Based Association Study. *The American Journal of Human Genetics* 71, 651-655.

- Nuevo R, Chatterji S, Verdes E, Naidoo N, Arango C , Ayuso-Mateos JL (2012). The continuum of psychotic symptoms in the general population: a cross-national study. *Schizophrenia bulletin* 38, 475-485.

- O'Donoghue B, Roche E , Lane A (2016). Neighbourhood level social deprivation and the risk of psychotic disorders: a systematic review. *Social Psychiatry and Psychiatric Epidemiology* 51, 941-950.

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

- Ortega-Alonso A, Ekelund J, Sarin A-P, *et al.* (2017). Genome-Wide Association Study of Psychosis Proneness in the Finnish Population. *Schizophrenia Bulletin* 43, 1304-1314.

- Owen MJ , O'Donovan MC (2017). Schizophrenia and the neurodevelopmental continuum:evidence from genomics. *World Psychiatry* 16, 227-235.

- Padmanabhan JL, Shah JL, Tandon N , Keshavan MS (2017). The "polyenviromic risk score": Aggregating environmental risk factors predicts conversion to psychosis in familial high-risk subjects. *Schizophrenia research* 181, 17-22.

- Pain O, Dudbridge F, Cardno AG*, et al.* (2018). Genome-wide analysis of adolescent psychotic-like experiences shows genetic overlap with psychiatric disorders. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 177, 416-425.

- Pakriev S, Vasar V, Aluoja A, Saarma M , Shlik J (1998). Prevalence of mood disorders in the rural population of Udmurtia. *Acta psychiatrica Scandinavica* 97, 169-174.

- Palmier-Claus JE, Berry K, Bucci S, Mansell W , Varese F (2018). Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *British Journal of Psychiatry* 209, 454-459.

- Papaleo F, Silverman JL, Aney J*, et al.* (2011). Working memory deficits, increased anxiety-like traits, and seizure susceptibility in BDNF overexpressing mice. *Learning & Memory* 18, 534-544.

- Pardiñas AF, Holmans P, Pocklington AJ*, et al.* (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature genetics* 50, 381-389.

- Pelletier-Baldelli A, Strauss GP, Visser KH , Mittal VA (2017). Initial development and preliminary psychometric properties of the Prodromal Inventory of Negative Symptoms (PINS). *Schizophrenia Research* 189, 43-49.

- Perlis RH, Uher R, Ostacher M*, et al.* (2010). Association Between Bipolar Spectrum Features and Treatment Outcomes in Outpatients With Major Depressive Disorder. *Archives of general psychiatry* 68, 351.

- Plana-Ripoll O, Pedersen CB, Holtz Y, *et al.* (2019). Exploring Comorbidity Within Mental Disorders Among a Danish National Population. *JAMA Psychiatry* 76, 259.
- Polanczyk G, Moffitt TE, Arseneault L, *et al.* (2010). Etiological and Clinical Features of Childhood Psychotic Symptoms. *Archives of general psychiatry* 67, 328.
- Polari A, Lavoie S, Yuen HP, *et al.* (2018). Clinical trajectories in the ultra-high risk for psychosis population. *Schizophrenia Research*.
- Potash JB, Derks EM, Vorstman JAS, Ripke S, Kahn RS , Ophoff RA (2012). Investigation of the Genetic Association between Quantitative Measures of Psychosis and Schizophrenia: A Polygenic Risk Score Analysis. *PloS one* 7, e37852.
- Potash JB, Sieradzka D, Power RA, *et al.* (2014). Are Genetic Risk Factors for Psychosis Also Associated with Dimension-Specific Psychotic Experiences in Adolescence? *PloS one* 9, e94398.
- Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R , Harrington H (2000). Children's Self-Reported Psychotic Symptoms and Adult Schizophreniform Disorder. *Archives of general psychiatry* 57, 1053.
- Pries L-K, Guloksuz S, ten Have M, *et al.* (2018). Evidence That Environmental and Familial Risks for Psychosis Additively Impact a Multidimensional Subthreshold Psychosis Syndrome. *Schizophrenia bulletin* 44, 710-719.
- Pries L-K, Lage-Castellanos A, Delespaul P, *et al.* (2019a). Estimating Exposome Score for Schizophrenia Using Predictive Modeling Approach in Two Independent Samples: The Results From the EUGEI Study. *Schizophrenia bulletin* 45, 960-965.
- Pries L-K, Snijders C, Menne-Lothmann C, *et al.* (2019b). TwinssCan — Gene-Environment Interaction in Psychotic and

Depressive Intermediate Phenotypes: Risk and Protective Factors in a General Population Twin Sample. *Twin Research and Human Genetics* 22, 460-466.

- Quattrone D, Di Forti M, Gayer-Anderson C*, et al.* (2019a). Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study. *Psychological medicine* 49, 1378-1391.

- Quattrone D, Ferraro L, Tripoli G*, et al.* (2019b). Cannabis associated symptom profiles in patients with first episode psychosis and population controls. *bioRxiv 2019:577932*.

- Radua J, Ramella-Cravaro V, Ioannidis JPA*, et al.* (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry* 17, 49-66.

- Radua J, Schmidt A, Borgwardt S*, et al.* (2015). Ventral Striatal Activation During Reward Processing in Psychosis. *JAMA Psychiatry* 72, 1243.

- Ragazzi TCC, Shuhama R, Menezes PR , Del-Ben CM (2018). Cannabis use as a risk factor for psychotic-like experiences: A systematic review of non-clinical populations evaluated with the Community Assessment of Psychic Experiences. *Early intervention in psychiatry* 12, 1013-1023.

- Regier DA (1988). One-Month Prevalence of Mental Disorders in the United States. *Archives of general psychiatry* 45, 977.

- Riehle M , Lincoln TM (2017). Social consequences of subclinical negative symptoms: An EMG study of facial expressions within a social interaction. *Journal of behavior therapy and experimental psychiatry* 55, 90-98.

- Ringen PA, Nesvåg R, Helle S*, et al.* (2016). Premorbid cannabis use is associated with more symptoms and poorer functioning in schizophrenia spectrum disorder. *Psychological Medicine* 46, 3127-3136.

- Ronald A (2015). Recent quantitative genetic research on psychotic experiences: new approaches to old questions. *Current Opinion in Behavioral Sciences* 2, 81-88.

- Ronald A , Pain O (2018). A systematic review of genome-wide research on psychotic experiences and negative symptom traits: new revelations and implications for psychiatry. *Human molecular genetics*.

- Rössler W, Hengartner MP, Ajdacic-Gross V, Haker H, Gamma A , Angst J (2011). Sub-clinical psychosis symptoms in young adults are risk factors for subsequent common mental disorders. *Schizophrenia research* 131, 18-23.

- Ruderfer DM, Fanous AH, Ripke S*, et al.* (2013). Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Molecular Psychiatry* 19, 1017-1024.

- Rutigliano G, Valmaggia L, Landi P*, et al.* (2016). Persistence or recurrence of non-psychotic comorbid mental disorders associated with 6-year poor functional outcomes in patients at ultra high risk for psychosis. *Journal of Affective Disorders* 203, 101-110.

- Sadock B, Sadock, VA. (2015). *Kaplan & Sadock's synopsis of psychiatry : behavioral sciences/clinical psychiatry*. Wolters Kluwer: Philadelphia

- Salokangas RKR, Schultze-Lutter F, Hietala J*, et al.* (2015). Depression predicts persistence of paranoia in clinical high-risk patients to psychosis: results of the EPOS project. *Social Psychiatry and Psychiatric Epidemiology* 51, 247-257.

- Sauvé G, Brodeur MB, Shah JL , Lepage M (2019). The Prevalence of Negative Symptoms Across the Stages of the Psychosis Continuum. *Harvard Review of Psychiatry* 27, 15-32.

- Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights

from 108 schizophrenia-associated genetic loci. *Nature* 511, 421-427.

- Schneiders J, Drukker M, van der Ende J, Verhulst FC, van Os J , Nicolson NA (2003). Neighbourhood socioeconomic disadvantage and behavioural problems from late childhood into early adolescence. *Journal of epidemiology and community health* 57, 699-703.

- Schoeyen HK, Birkenaes AB, Vaaler AE*, et al.* (2011). Bipolar disorder patients have similar levels of education but lower socio-economic status than the general population. *Journal of affective disorders* 129, 68-74.

- Schultze-Lutter F, Michel C, Ruhrmann S , Schimmelmann BG (2017). Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychological medicine* 48, 1167-1178.

- Schultze-Lutter F, Nenadic I , Grant P (2019). Psychosis and Schizophrenia-Spectrum Personality Disorders Require Early Detection on Different Symptom Dimensions. *Frontiers in psychiatry* 10.

- Schultze-Lutter F, Ruhrmann S, Berning J, Maier W , Klosterkotter J (2008). Basic Symptoms and Ultra-high Risk Criteria: Symptom Development in the Initial Prodromal State. *Schizophrenia Bulletin* 36, 182-191.

- Simon AE , Umbricht D (2010). High remission rates from an initial ultra-high risk state for psychosis. *Schizophrenia Research* 116, 168-172.

- Siuciak JA, Boylan C, Fritsche M, Altar CA , Lindsay RM (1996). BDNF increases monoaminergic activity in rat brain following intracerebroventricular or intraparenchymal administration. *Brain Research* 710, 11-20.

- Smeets F, Lataster T, Dominguez MdG*, et al.* (2010). Evidence That Onset of Psychosis in the Population Reflects Early Hallucinatory Experiences

That Through Environmental Risks and Affective Dysregulation Become Complicated by Delusions. *Schizophrenia bulletin* 38, 531-542.

- Smeets F, Lataster T, van Winkel R, de Graaf R, ten Have M , van Os J (2013). Testing the hypothesis that psychotic illness begins when subthreshold hallucinations combine with delusional ideation. *Acta psychiatrica Scandinavica* 127, 34-47.

- Smeets F, Lataster T, Viechtbauer W , Delespaul P (2015). Evidence That Environmental and Genetic Risks for Psychotic Disorder May Operate by Impacting on Connections Between Core Symptoms of Perceptual Alteration and Delusional Ideation. *Schizophrenia bulletin* 41, 687-697.

- Spencer C, Hyman C, Studer L*, et al.* (1995). Effect of BDNF on Dopaminergic, Serotonergic, and GABAergic Neurons in Cultures of Human Fetal Ventral Mesencephalon. *Experimental Neurology* 133, 50-63.

- Srihari VH, Shah J , Keshavan MS (2012). Is Early Intervention for Psychosis Feasible and Effective? *Psychiatric Clinics of North America* 35, 613-631.

- Stahl EA, Breen G, Forstner AJ*, et al.* (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nature genetics* 51, 793-803.

- Stefanis NC, Delespaul P, Smyrnis N*, et al.* (2004). Is the excess risk of psychosis-like experiences in urban areas attributable to altered cognitive development? *Social Psychiatry and Psychiatric Epidemiology* 39, 364-368.

- Sullivan PF (2008). Schizophrenia genetics: the search for a hard lead. *Current opinion in psychiatry* 21, 157-160.

- Sullivan PF, Agrawal A, Bulik CM*, et al.* (2018). Psychiatric Genomics: An Update and an Agenda. *American Journal of Psychiatry* 175, 15-27.

- Szczypiński JJ , Gola M (2018). Dopamine dysregulation hypothesis: the common basis for motivational anhedonia in major depressive disorder and schizophrenia? *Reviews in the Neurosciences* 29, 727-744.
- Taquet M, Smith SM, Prohl AK*, et al.* (2020). A structural brain network of genetic vulnerability to psychiatric illness. *Molecular psychiatry*.
- Taylor MJ, Martin J, Lu Y*, et al.* (2019). Association of Genetic Risk Factors for Psychiatric Disorders and Traits of These Disorders in a Swedish Population Twin Sample. *JAMA psychiatry* 76, 280.
- Tsai S-J (2004). Is mania caused by overactivity of central brain-derived neurotrophic factor? *Medical Hypotheses* 62, 19-22.
- Tsai S-J (2018). Critical Issues in BDNF Val66Met Genetic Studies of Neuropsychiatric Disorders. *Frontiers in Molecular Neuroscience* 11.
- Tsuang MT (1979). Long-term Outcome of Major Psychoses. *Archives of general psychiatry* 36, 1302.
- Turkish Statistical Institute (2019). Population of Province/District Centers, Towns/Villages by Provinces and Districts and Annual Growth Rate of Population. 26 April 2019, http://www.turkstat.gov.tr/PreIstatistikTablo.do?istab_id=2305
- Unterrassner L, Wyss TA, Wotruba D, Ajdacic-Gross V, Haker H , Rössler W (2017). Psychotic-Like Experiences at the Healthy End of the Psychosis Continuum. *Frontiers in psychology* 8.
- Ünal HE, Birben Ü , Bolat F (2018). Rural population mobility, deforestation, and urbanization: case of Turkey. *Environmental Monitoring and Assessment* 191.
- van den Heuvel MP , Sporns O (2019). A cross-disorder connectome landscape of brain dysconnectivity. *Nature Reviews Neuroscience* 20, 435-446.

- van der Gaag M, Smit F, Bechdolf A, *et al.* (2013). Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. *Schizophrenia research* 149, 56-62.

- van Nierop M, Viechtbauer W, Gunther N, *et al.* (2014). Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries. *Psychological Medicine* 45, 1277-1288.

- van Os J (2013). The Dynamics of Subthreshold Psychopathology: Implications for Diagnosis and Treatment. *American Journal of Psychiatry* 170, 695-698.

- van Os J, Delespaul P, Wigman J, Myin-Germeys I , Wichers M (2013). Beyond DSM and ICD: introducing "precision diagnosis" for psychiatry using momentary assessment technology. *World Psychiatry* 12, 113-117.

- van Os J, Gilvarry C, Bale R, *et al.* (2000a). Diagnostic value of the DSM and ICD categories of psychosis: an evidence-based approach. UK700 Group. *Social psychiatry and psychiatric epidemiology* 35, 305-311.

- van Os J , Guloksuz S (2017). A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry* 16, 200-206.

- van Os J, Guloksuz S, Vijn TW, Hafkenscheid A , Delespaul P (2019a). The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: time for change? *World Psychiatry* 18, 88-96.

- van Os J, Hanssen M, Bak M, Bijl RV , Vollebergh W (2003). Do Urbanicity and Familial Liability Coparticipate in Causing Psychosis? *American Journal of Psychiatry* 160, 477-482.

- van Os J, Hanssen M, Bijl RV , Ravelli A (2000b). Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophrenia Research* 45, 11-20.

- van Os J, Kenis G , Rutten BPF (2010). The environment and schizophrenia. *Nature* 468, 203-212.

- van Os J , Linscott RJ (2012). Introduction: The Extended Psychosis Phenotype--Relationship With Schizophrenia and With Ultrahigh Risk Status for Psychosis. *Schizophrenia bulletin* 38, 227-230.

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

- van Os J, Pries LK, Delespaul P*, et al.* (2019b). Replicated evidence that endophenotypic expression of schizophrenia polygenic risk is greater in healthy siblings of patients compared to controls, suggesting gene-environment interaction. The EUGEI study. *Psychological Medicine*, 1-14; doi: 10.1017/S003329171900196X. Online ahead of print.

- van Os J , Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* 15, 118-124.

- van Os J, van der Steen Y, Islam MA, Guloksuz S, Rutten BP , Simons CJ (2017). Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. *Psychological medicine* 47, 2421-2437.

- van Os J, Verdoux H, Maurice-Tison S*, et al.* (1999). Self-reported psychosis-like symptoms and the continuum of psychosis. *Social Psychiatry and Psychiatric Epidemiology* 34, 459-463.

- van Rossum I, Dominguez MdG, Lieb R, Wittchen HU , van Os J (2009). Affective Dysregulation and Reality Distortion: A 10-Year Prospective Study of Their Association and Clinical

Relevance. *Schizophrenia Bulletin* 37, 561-571.

- van Winkel R, Stefanis NC , Myin-Germeys I (2008). Psychosocial Stress and Psychosis. A Review of the Neurobiological Mechanisms and the Evidence for Gene-Stress Interaction. *Schizophrenia Bulletin* 34, 1095-1105.

- Varese F, Smeets F, Drukker M*, et al.* (2012). Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies. *Schizophrenia bulletin* 38, 661-671.

- Verdoux H, Van Os J, Maurice-Tison S, Gay B, Salamon R , Bourgeois ML (1999). Increased occurrence of depression in psychosis-prone subjects: A follow-up study in primary care settings. *Comprehensive Psychiatry* 40, 462-468.

- Walker S, Mackay E, Barnett P*, et al.* (2019). Clinical and social factors associated with increased risk for involuntary psychiatric hospitalisation: a systematic review, meta-analysis, and narrative synthesis. *The Lancet Psychiatry* 6, 1039-1053.

- Walss-Bass C, Forstner AJ, Hecker J*, et al.* (2017). Identification of shared risk loci and pathways for bipolar disorder and schizophrenia. *PloS one* 12, e0171595.

- Walss-Bass C, Werbeloff N, Dohrenwend BP*, et al.* (2015). The Association between Negative Symptoms, Psychotic Experiences and Later Schizophrenia: A Population-Based Longitudinal Study. *PloS one* 10, e0119852.

- Wan L, Thomas Z, Pisipati S, Jarvis SP , Boutros NN (2017). Inhibitory deficits in prepulse inhibition, sensory gating, and antisaccade eye movement in schizotypy. *International Journal of Psychophysiology* 114, 47-54.

- Wigman JTW, van Nierop M, Vollebergh WAM*, et al.* (2012a). Evidence That Psychotic Symptoms Are Prevalent in Disorders of

Anxiety and Depression, Impacting on Illness Onset, Risk, and Severity--Implications for Diagnosis and Ultra-High Risk Research. *Schizophrenia bulletin* 38, 247-257.

- Wigman JTW, van Winkel R, Ormel J, Verhulst FC, van Os J , Vollebergh WAM (2012b). Early trauma and familial risk in the development of the extended psychosis phenotype in adolescence. *Acta psychiatrica Scandinavica* 126, 266-273.

- Wigman JTW, van Winkel R, Raaijmakers QAW*, et al.* (2011). Evidence for a persistent, environment-dependent and deteriorating subtype of subclinical psychotic experiences: a 6-year longitudinal general population study. *Psychological Medicine* 41, 2317-2329.

- Wigman JTW, Vollebergh WAM, Raaijmakers QAW*, et al.* (2009). The Structure of The Extended Psychosis Phenotype in Early Adolescence--A Cross-sample Replication. *Schizophrenia bulletin* 37, 850-860.

- Wilson C, Smith ME, Thompson E*, et al.* (2016). Context matters: The impact of neighborhood crime and paranoid symptoms on psychosis risk assessment. *Schizophrenia Research* 171, 56-61.

- Xia CH, Ma Z, Ciric R*, et al.* (2018). Linked dimensions of psychopathology and connectivity in functional brain networks. *Nature Communications* 9.

- Yung AR , Nelson B (2011). Young people at ultra high risk for psychosis: a research update. *Early Intervention in Psychiatry* 5, 52-57.

- Yung AR, Phillips LJ, Yuen HP*, et al.* (2003). Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia research* 60, 21-32.

- Zammit S, Hamshere M, Dwyer S*, et al.* (2013a). A Population-Based Study of Genetic Variation and Psychotic Experiences in Adolescents. *Schizophrenia Bulletin* 40, 1254-1262.

- Zammit S, Horwood J, Thompson A, *et al.* (2008). Investigating if psychosis-like symptoms (PLIKS) are associated with family history of schizophrenia or paternal age in the ALSPAC birth cohort. *Schizophrenia Research* 104, 279-286.

- Zammit S, Kounali D, Cannon M, *et al.* (2013b). Psychotic Experiences and Psychotic Disorders at Age 18 in Relation to Psychotic Experiences at Age 12 in a Longitudinal Population-Based Cohort Study. *American Journal of Psychiatry* 170, 742-750.

- Zavos HMS, Eley TC, McGuire P, *et al.* (2016). Shared Etiology of Psychotic Experiences and Depressive Symptoms in Adolescence: A Longitudinal Twin Study. *Schizophrenia bulletin* 42, 1197-1206.

- Zavos HMS, Freeman D, Haworth CMA, *et al.* (2014). Consistent Etiology of Severe, Frequent Psychotic Experiences and Milder, Less Frequent Manifestations. *JAMA Psychiatry* 71, 1049.

- Zhao Z, Xu J, Chen J, *et al.* (2014). Transcriptome sequencing and genome-wide association analyses reveal lysosomal function and actin cytoskeleton remodeling in schizophrenia and bipolar disorder. *Molecular psychiatry* 20, 563-572.

- Zhu K, Ou Yang T-H, Dorie V, Zheng T , Anastassiou D (2019). Meta-analysis of expression and methylation signatures indicates a stress-related epigenetic mechanism in multiple neuropsychiatric disorders. *Translational Psychiatry* 9.

- Ziermans TB, Schothorst PF, Sprong M , van Engeland H (2011). Transition and remission in adolescents at ultra-high risk for psychosis. *Schizophrenia Research* 126, 58-64.

CHAPTER7

Summary

In **Chapter 1,** a background was provided on the conceptualization of psychosis as laid out in current classification systems. In addition, the concept of an extended psychosis phenotype in the general population was described, as was the notion that there is a distribution or spectrum of psychosis across current psychiatric nosology. Evidence on the transdiagnostic nature of the psychosis spectrum was discussed, and a multidimensional view of psychosis was introduced. Research describing a network of overlapping and interacting dimensions across the psychosis spectrum was reviewed. Finally, the aims and the outlines of the thesis were described.

In **Chapter 2**, the design of the TurkSch study was presented. This included the assessment of the different dimensions of the extended and transdiagnostic psychosis phenotype, as well as the description of the multilevel data collection including socio-environmental exposures and blood sampling in a representative community-based population. Outcomes of household visits and analysis of attrition, based on noncontacts and refusals in the longitudinal arm were introduced. Finally, dynamic transitions over time, within the spectrum of the extended psychosis phenotype, were demonstrated. Results showed that attrition over time showed no large differential effect sizes as a function of important variables. Furthermore, increasing severity of subthreshold psychosis at baseline was associated with increasing rates of persistence and psychotic disorder outcomes over the follow-up period. However, an even higher proportion of clinically relevant subthreshold psychosis did not persist over time.

In **Chapter 3,** longitudinal bidirectional associations between the spectrum of the positive psychosis domain and affective psychopathology were evaluated, accounting for other possible influences. The analyses revealed reciprocal sub-additive longitudinal associations between these domains, as well as similar cross-lagged correlations over time. Finally, there was considerable sharing of socio-environmental and familial risk factors

across these domains. These results suggest mutually causal connections between the affective and positive domains.

In **Chapter 4**, clinician-based longitudinal diagnoses of clinically relevant subthreshold psychosis were presented as well as moderating factors. Results showed that the psychotic disorder diagnosis rate at follow up was 7.0%. This is much lower than the rates of mood disorders without psychotic features (42.8%) and other non-psychotic disorders (24.1%). Female sex, lower socio-economic status, co-occurrence of mood disorders, family history of a mental disorder, and persistence of psychotic experiences predicted any follow-up DSM diagnosis. Furthermore, follow-up psychotic versus non-psychotic disorder outcome was predicted by younger age (15–30 years), co-presence of delusional and hallucinatory PE and family history of severe mental illness. The results demonstrated the importance of subthreshold psychosis as a marker of transdiagnostic risk.

In **Chapter 5**, the association of a priori hypothesized SNP (rs6265) with a longitudinally assessed dimensional phenotype covering subthreshold and threshold levels of the positive psychosis domain was investigated. The SNP was significantly associated with the positive spectrum of psychosis. The pattern of the association was that the SNP impacted in a dose-response but extra-linear fashion, with stronger impact at the threshold end. Associations were still significant when adjusted for sociodemographic factors and environmental exposures including life events, childhood adversity, socioeconomic status, urbanicity, and cannabis use. The results potentially indicate the relevance of dimensional risk assessment in relation to genetic association.

In **Chapter 6**, the results of the studies in this thesis were summarized, discussed and integrated in light of the current literature. Strengths and limitations were stated. Finally, future directions were provided.

CHAPTER 8

Impact

Main objectives, results and conclusions

The assessment of the different dimensions of psychosis in a graded fashion is progressively replacing the classification of threshold phenotypes in the form of distinct categories. Examples are the release of the National Institute of Mental Health, Research Domain Criteria and Clinician-Rated Dimensions of Psychosis Symptom Severity in the Emerging Measures and Models section of the DSM-5. This paradigm shift is supported by 'grey areas' between illness and normality, lack of zones of relative rarity, high rates of comorbidity, shared ethiopathogenesis, heterogeneity within disorders, and diagnostic instability. Longitudinal assessment of the extended and transdiagnostic psychosis phenotype in general populations is a productive way to generate evidence for the expression of psychosis as multidimensional psychopathology. In this thesis, psychosis was assessed along a spectrum of severity including both helpseeking and non-helpseeking individuals in a representative community-based population of Izmir, which is one of the major cities in Europe and the Middle East, with around three million residents. Etiological and phenomenological associations (within the same domain and across different domains of psychopathology) over a six year follow-up period were the major focus of attention.

The summary of the main results described in different chapters of this thesis is as follows:

Results in chapter 2 showed that baseline characteristics of responders did not show large differences from characteristics of subjects who dropped out. In addition, socio-demographic characteristics were similar to studies with a similar design, but also had differences. Thus, results are sufficiently representative of the Izmir population. Furthermore, the spectrum of the positive psychosis domain showed a fluctuating phenotype over time. Chapter 3 demonstrated that affective psychopathology and the spectrum of the positive domain of psychosis were bi-directionally associated with each other over

time, in a sub-additive pattern. A remarkable number of socio-environmental and familial risk factors were shared across these domains. Similar cross-lagged correlations over time were demonstrated across these domains, suggesting mutually causal connections. In chapter 4, the prospective diagnostic evaluation of clinically relevant subthreshold psychosis showed that subsequent psychotic disorder diagnoses represented only a minority of outcomes whereas the majority had diagnoses of common non-psychotic disorders at follow-up. Furthermore, baseline characteristics of individuals (e.g. age range, sex, familial risk, socioeconomic status, comorbidity of symptoms, and persistence of subthreshold psychosis) were predictive of the longitudinal diagnostic outcome (i.e. any mental disorder and psychotic vs. non-psychotic disorder). The results of chapter 5 showed that an SNP (rs6265), hypothesized a priori, was significantly associated with the longitudinally assessed spectrum of the positive domain, including subthreshold and threshold phenotypes, adjusting for socio-environmental factors. The associations were in a dose-response but extra-linear fashion with stronger associations at the threshold level.

RELEVANCE

Scientific Impact

To date, few longitudinal community-based studies on the extended psychosis phenotypes have been performed, and they were conducted predominantly in western populations. Cultural and socio-economic characteristics of populations across geographical regions may lead to differences in findings. The TurkSch study is a unique example of a longitudinal community-based study conducted at the cross-border between Europe and the Middle-East. Hence, the design of the TurkSch study has the potential to stimulate similar studies in other regions in this part of the world. Furthermore, the sociodemographic correlates of attrition may guide future studies to make special efforts to include these particular groups.

There are a number of terms/definitions used in research in the area of subthreshold psychosis (i.e. schizotypy, schizotypal traits, schizotaxia, psychotic (like) experiences, psychotic symptomatology, attenuated psychotic symptoms, prodromal psychotic symptoms, high risk for psychosis) and associated outcomes (i.e. psychotic impairment, transition, clinical psychosis, psychotic disorders, first episode psychosis, affective psychosis, non-affective psychosis, schizophrenia spectrum). These terms usually differ based on aspects of the particular sample (i.e. general population-based, early intervention centre-based, help seeking, non-help seeking, presence of co-occurring distress and common mental disorder), and the outcome measures used (DSM diagnoses, questions on help seeking and dysfunction, Comprehensive Assessment of At-risk Mental State-CAARMS, Scale of Psychosis-Risk Symptoms-SOPS). These definitions indicate different positions within the psychosis spectrum. Standardized terms/definitions are necessary for the area to progress, for example in an international consortium testing the reliability and validity of these operational definitions. This thesis and the previous results of the TurkSch study demonstrated that clinical and general-population phenotypes in this research area have important similarities with regard to risk factors and longitudinal outcomes. Given the fact that the TurkSch study covered the full spectrum of psychosis from subclinical phenotypes gradually blending into clinically-relevant subthreshold phenotypes, threshold psychosis outside schizophrenia spectrum disorders and finally schizophrenia spectrum disorders, as well as associated risk factors, co-occurring dimensions and longitudinal outcomes, it may be used as an initial step towards the standardization efforts of psychosis spectrum terminology.

Subthreshold psychosis is represented in current classification systems as categorical entity, based on positive psychosis phenomena. For instance, the attenuated psychosis syndrome, classified under subheadings of both ‘other specified schizophrenia spectrum and other psychotic disorder’ and ‘conditions for further study’ in DSM 5, is characterized by clinically relevant

subthreshold delusions, hallucinations and disorganized speech. Results in this thesis and previous results in the TurkSch study question the validity of this type of classification and demonstrates the need for multidimensional assessments and dynamic interplay between affective and psychosis domains.

The results on dynamic transitions over time in the extended psychosis phenotype in this thesis showed that a high proportion of clinically relevant subthreshold psychosis does not persist over time. These results demonstrate the need to reconsider the view that psychosis itself is 'toxic' for the brain and/or part of a phenotype that progresses through stages. Research in the area of high-risk for psychosis predominantly leans on unidimensional assessment strategies with a reliance on positive phenotypes. However, this strategy unintentionally may set a self-limiting barrier for research in this area. Results described in this thesis clearly show that the subthreshold positive domain usually co-occurs with symptoms from other domains. The outcomes are also heterogeneous and dependent on the degree of interplay between dimensions. Through unidimensional assessment strategies, the associations between emerging outcomes and prior symptom domains outside the positive domain (or the interconnectivity between domains) are missed. Furthermore, various outcomes outside the positive domain are overlooked. Therefore, this thesis may contribute to the methodology of future prospective research to include broader phenotypes of psychopathology in order to evaluate different pathways to psychotic impairment.

Studies designed to investigate etiological associations predominantly compare 'cases' that have distinct categories of mental disorders with 'healthy' controls. However, this methodology has some limitations. Different domains of psychopathology, even as they are co-occurring in the same disorder, may be associated with different pathways, thus with different genetic and environmental risk factors, which may cause much heterogeneity from sample to sample. Furthermore, controls may share some

phenotypes with cases, in particular subthreshold phenotypes, which could cause loss of power and precision. Additionally, data is usually collected on a single factor (e.g. molecular data only, socioenvironmental exposure only etc.) which hampers insight into confounding, moderation, mediation and moderated mediation for many other influences. Finally, the descriptions of 'caseness' are mostly based on a single assessment, not taking into account fluctuating manifestations over time. However, case-control studies have advantages of getting more rapid results and being cheaper. Therefore, integrating dimensional assessments of psychopathology as well as cumulative measures of different risk factors can add extra value. The design of risk assessment in this thesis is dimensional and longitudinal, providing opportunity to adjust for other factors. This design may stimulate further research on risk assessment in the future.

Socioeconomic Impact

Meta-analyses have reported that dimensional measures have increased validity, explaining more variance in risk factors, neurophysiological markers, and functioning in comparison with categorical measures. The perspective of research on dimensional assessments and the interconnectivity between dimensions in this thesis, along with other studies with similar research questions, can accelerate the rise of personalised medicine in psychiatry with enhanced diagnostic and prognostic accuracy. Furthermore, this framework may improve the search for biomarkers in psychiatry.

Screening psychosis risk in the community through a unidimensional assessment strategy has two major limitations. First, most of the individuals with this 'risk state' do not develop a psychotic disorder, but rather develop a common non-psychotic disorder. Furthermore, some individuals even do not develop any mental disorder over time. Second, a high proportion of individuals who develop psychotic disorders does not meet the criteria of risk categories. Along with other studies with similar research questions, the results of this thesis showed that early expres-

sions of psychotic psychopathology comprise multiple signs and symptoms from multiple domains. The results on the characteristics of individuals with subthreshold psychosis (e.g. age range, sex, familial risk, socioeconomic status, comorbidity of symptoms, persistence of subthreshold psychosis) who develop psychotic disorders as well as common-non psychotic disorders over time may help to plan personalized early intervention strategies. Therefore, these results contribute to the growing evidence for ways to improve screening strategies.

The traditional consideration of psychosis as a dichotomous event, in some degree, may add to the stigmatization of individuals with psychosis. The TurkSch study evaluated psychosis as a common phenomenon lying on a spectrum from illness to normal mentation, and showed substantial shared aspects across these ends. Furthermore, the longitudinal results show that the majority of individuals with baseline clinically relevant subthreshold psychosis do not develop 'schizophrenia'. Therefore, psychosis over time does not concur with the social image of schizophrenia as a 'devastating progressive and desperate mental illness'. These results might be an important basis for the fight against stigmatization of psychosis in society.

Target Groups

Academic community in other disciplines

This thesis provides an advanced design to meet the challenges of longitudinal data collections in representative-community-based populations. Furthermore, genetic analyses within a general population-based sample were performed. Therefore, the results may be of interest not only for psychiatrists and psychologists, but also for geneticists, physicians from various disciplines working in the area of epidemiology as well as social scientists. A multidisciplinary perspective within an epidemiological framework can productively bring together different areas of research that sometimes have difficulties finding each other.

Patients and their relatives

For patients with psychosis, the results of the TurkSch study demonstrate that the condition they experience has shared aspects, or connectedness, with experiences of a substantial part of the general population. For any person with psychotic experiences, and particularly for relatives of individuals with subthreshold psychosis, it is a vital question if a psychotic disorder may arise in the future. The answer is that the majority is not going to be diagnosed with a psychotic disorder, although there is an apparent risk for mental disorders in general, with an increasing risk if they have persistent psychotic experiences, co-occurring mental distress, low socioeconomic status, substance use, and family history of mental disorders. Therefore, a devastating worry for a future psychotic disorder is not useful. However, the modifiable risk factors among these, such as substance use, may be targeted to reduce the risk of impairment.

Society at large

Stigmatization of psychosis is common in society. The results of the TurkSch study have shown that psychosis is a much more common phenomenon than is generally assumed, lying on a spectrum from normal mentation to need for care. Furthermore, psychotic experiences are generally transient, and not antecedents of 'devastating' mental illness, so these experiences may be considered as part of human variation with deep roots in evolution of mind.

Policy makers

The findings in this thesis support the view that psychotic experiences may be a useful marker for mental distress that has transdiagnostic value. Furthermore, psychotic experiences have close associations with socio-environmental exposures, which are therefore associated with the longitudinal outcomes of individuals' mental states. Community-based prevention strategies should be organised taking into account a multidimensional perspective, prioritizing the impact of socio-environmental expo-

sures in order to reduce the burden of mental problems. Furthermore, efforts to fight against stigmatization of psychosis in society are of value.

Mental health care providers

The results of this thesis provide an important base for physicians and other professionals working in the area of mental health. Subthreshold psychosis should not be considered merely as the 'pre-psychotic' phase. However, considering frequency and distress associated with the experiences, socio-environmental and genetic risk of individuals, and interactions with other dimensions of psychopathology, may result in more precise predictions of transdiagnostic outcomes over time. Therefore, avoiding 'schizo'-discourse when considering psychosis phenotypes is required. Rather, follow-up of these individuals in a supportive environment, treatment of co-occurring disorders leading to impairment in social, occupational, or other important areas of functioning, and psychoeducation on plausible socio-environmental risk may be of value.

Network Product

The TurkSch study was based on interdepartmental and international collaborations. Results of the study have been presented in many national and international conferences. A new assessment of the cohort (T_3) is being planned. Furthermore, a PhD thesis at Maastricht University, focussing on the longitudinal neighbourhood-contextual measures of the TurkSch study is in progress.

Summary and Conclusion

The results of this thesis have several scientific and social impacts. First, the assessments covered the full spectrum of psychosis, as well as the dynamic interplay between symptom domains. Therefore, results may contribute to the efforts to achieve a consistent terminology for multidimensional psychotic pheno-

types as well as more comprehensive and precise classification of psychosis. Second, the results on longitudinal outcomes of subthreshold psychosis as well as the moderating factors were presented. These results may have impact on clinical practice when considering individuals with subthreshold psychosis. Furthermore, these results may help to improve screening strategies in order to provide more comprehensive community-based prevention strategies. Third, the methodology may stimulate further research on assessment of risk factors with more accurate results. Finally, the consideration of psychosis as a common phenomenon lying on a spectrum from illness to normal mentation as well as the longitudinal outcomes of these phenotypes may be an important basis for the fight against stigmatization of psychosis in society.

ACKNOWLEDGEMENT

Life is the time passing while waiting for the inspiring moments. This thesis actually started in a very stressful moment which then turned into one of the most inspiring moments of my life… I was at the early times of my psychiatry training in Ege University. A patient burned himself at the inpatient unit… I was in a desperate mood. After the emergency treatment of the patient and transfer to a burn unit, following a deep breath, my professor **Hayriye Elbi** asked me to plan and coordinate the longitudinal arm of a unique epidemiological project, which I would learn the name "TürkSch" after. I remember the words "you look like a swift and bright person. I trust you, you can manage". It was unexpected for me, but also very inspiring, encouraging and honouring… That was also one of the exceptional opportunities of my life. My aim to be in medical school and in psychiatry was to touch humans' lives. This was a great opportunity to touch thousands of individuals' lives maybe whom I would not meet at any times. Throughout the project I always felt the encouraging trust of Professor Elbi. I will be grateful to her throughout my life…

The baseline wave of the TürkSch project was coordinated by **Tolga Binbay**. I first met him when he was a psychiatric trainee and I was a medical student in Ege University. I remember talking on student organisations. We did not meet for several years after. However, I remember to be impressed by his calm and wise attitude. Professor Elbi told me to contact him, which was a very nice surprise. He has been very helpful and desiring to teach till this moment. Both an older brother and a sophisticated teacher… Also, a role model… He also introduced me to Jim van Os, so my collaboration with Maastricht University started. Then he introduced me to MheNs. Since the time in Maastricht, many storms have broken out around, but he has always been nearby. I will be grateful to him throughout my life, too.

While preparing the details of the TürkSch, I met Prof. **Köksal Alptekin**, who has been the mentor of the project since the be-

ginning. He is one of the greatest scientists to be met for a young trainee who wants to take part in science. And a great mentor to think wider. I would like to thank to him for the scientific identity borrowed, for many things learnt and to be learnt.

One of the most inspiring moments of my life was the moment I first met **Jim van Os**. I talked about the TürkSch project, and he suddenly asked if I would like to do a PhD in Maastricht. It was a great chance to learn the subtleties of epidemiology from one of the most outstanding scientists and centres of the world. His view, which combines both being practical and also achieving to miss no details, is one of the most inspiring experiences of my life. I'm sure that this view has contributed a lot to my way of thinking. Furthermore, I would like to thank **Marjan Drukker** as a great scientist for her excellent guidance. Her detailed and educative comments importantly contributed to my scientific view. Furthermore, she taught me to use STATA that now I can help my colleagues. They are both Pole Stars of my scientific journey.

The TürkSch project was conducted under the sustained supportive environment of Ege University Department of Psychiatry. It is a warm place to be a psychiatric trainee. You better understand how a precious department it is after a piece of time you work outside. I would like to thank Prof. **Şebnem Pırıldar** for teaching what to do with your anxiety as well as with the patients'... And also my professors **Simavi Vahip, Yusuf Alper, Baybars Veznedaroğlu, Fisun Akdeniz, Hakan Coşkunol, Ali Saffet Gönül, Ayşin Noyan, Özen Önen Sertöz, Ender Altıntoprak, and Çağdaş Eker** who have great signs on my understanding of the human mind. They provided knowledge, skills and confidence as a physician as well as the scientific way of thinking. I would also like to thank Prof. **Bülent Kayahan** for his mentorship and encouragement in the TürkSch project and the great contribution to my psychiatric training. I am also grateful to the co-senior residents and all my colleagues for the warm environment in Ege University.

I would like to thank Prof. **Hüseyin Onay** and Prof. **Ferda** Özkınay from Ege University, Department of Genetics for their collaboration in the project. Furthermore, I would like to thank **Nesli Zagli, Kübra Yıldırım, Bertan Turgut, Duygu Keskin Gökçelli** and **many others** to be shoulder to shoulder on various streets of Izmir during the project, for about three years. I also would like to thank the **great people residing in urban and rural areas of Izmir**, who opened their doors, lives and souls many times for the TürkSch project…

I am also grateful to my family for supporting me to decide the things I desire and work hard for them … I can never forget preparing my father's talks to be read in special days of his school, when I was a primary school kid. Now i understand how big gifts those preparations are. Esteem and confidence by your **father**… And my **mother**… When I feel stressed, just drawing on her imagination has always made me feel that it is going to be over. This is what connects one to life…. And **Fatoş**… She has always been the naughty and sweet piece of my life, bringing curiosity and joy. Thank you all for your existence and love…

And **Melike**… The moment I first met in a class for the preparation of TUS (medical specialty entrance exam), I felt that it was the exceptional turning point of my life. Despite the short time to that 'hard' exam, I could never stop thinking her for a moment. She has been the unconditional peace in my soul which is described to be in the womb… Besides many things, I also would like to thank her for her patience during the preparation of this thesis. During this project we had our baby, **Ekin**. She is now three years old. With her 'unstoppable' curiosity, i everyday review my views about life. Thank you for your great existence and love…

Life is the time passing while waiting for inspiring moments. And this thesis is one of the most inspiring experiences of my life…

Curriculum Vitae

Umut Kırlı was born in September, 1986 in Manisa, Turkey. He attended to medical school at Ege University, Izmir, Turkey (2004-2010), and was an exchange medical student in Lund University, Sweden (2008). During these years, he completed the international project “the same differently” on the social disadvantages of migrants funded by the European Union Youth in Action commission. After finishing medical education, he worked as a general practitioner in the emergency department of Erzurum Karayazi State Hospital. Then he got trained in psychiatry in Ege University between 2011 and 2015. Starting from his residency in psychiatry, he attended to analytically oriented group therapy for 7 years. Then, he completed supportive psychotherapy theoretical educations and supervisions. After completing his residency, he worked in Hakkari State Hospital for 2 years, followed by working in Van Training and Research Hospital for 1 year as a psychiatrist. He has been working in Yuzuncu Yil University, School of Medicine, Department of Psychiatry as an assistant professor since 2019.

His research interest has started in early years of his medical education. At the early years of his residency in psychiatry, he started to coordinate the longitudinal arm of the TurkSch project, which is one of the leading projects about psychiatric epidemiology and gene-environment interactions in Turkey. The TürkSch project was supported by 1001 programme of the Scientific and Technological Research Council of Turkey with two separate funds as well as research funds of Ege University. With this project, his research interest focused on psychosis epidemiology, gene-environment interactions in psychosis and dimensional approach in psychiatry. He was awarded in European Psychiatric Association (EPA) Annual Forum of European Federation of Psychiatric Trainees (2012) as best poster presenter, in 23rd World Congress of Psychiatric Genetics (WCPG) Early Career Investigator Programme as travel award (2015), in Psychiatric Association of Turkey (PAT) 51st National Psychiatry Congress as best research award (2015), and in the European College of Neuropsychopharmacology (ECNP) Workshop for Junior Scientists in Europe participation funds (2016).

He became a non-residential PhD candidate at the School of Mental and Neuroscience (MHeNS) at the Maastricht University, the Netherlands in 2016. He was an observer at MHeNS in July 2016. He is a member of International Society of Psychiatric Genetics (ISPG), Psychiatric Association of Turkey (PAT) and was a board member of PAT Izmir Branch (2013-2015).

Publications

- **Kırlı U**, Binbay T, Drukker M et al. (2019). DSM outcomes of psychotic experiences and associated risk factors: six year follow-up study in a community-based sample. Psychological Medicine, 49 (8), 1346-1356 DOI: 10.1017/S0033291718001964

- **Kırlı U**, Binbay T, Drukker M et al. (2019). Is BDNF-Val-66Met Polymorphism Associated with Psychotic Experiences and Psychotic Disorder Outcome? Evidence from a 6 Years Prospective Population-based Cohort Study. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 180 (2), 113-121, DOI: 10.1002/ajmg.b.32641

- **Kırlı U**, Binbay T, Drukker M, van Os J, Alptekin K, Kayahan B, Elbi H (2019). Psychotic experiences and mood episodes predict onset of each other bi-directionally: six years follow-up study in a community-based population. Social Psychiatry and Psychiatric Epidemiology 54 (3): 331-341 DOI: 10.1007/s00127-018-1641-8

- **Kırlı U**, Binbay T, Elbi H et al. (2019). Izmir Mental Health Cohort for Gene-Environment Interaction in Psychosis (TürkSch): Assessment of the Extended and Transdiagnostic Psychosis Phenotype and Analysis of Attrition in a Six Years Follow-up of a Community-based Sample. Frontiers in Psychiatry. 10, 554 DOI: 10.3389/fpsyt.2019.00554

- **Kırlı U**, Binbay T (2019). Pre-psychosis: symptoms leading to prodrome and psychotic disorder. Update in Psychiatry, 9(4), 284-294

- **Kırlı U**, Binbay T, Elbi H, Alptekin K (2020). COVID-19 Pandemic and Psychotic Symptoms. Journal of Clinical Psychiatry 23(1): 81-85, DOI: 10.5505/kpd.2020.27122

- **Kırlı U**, Alptekin K. (2020). Acute and Maintenance Pharmacotherapy of Schizophrenia (Review). Archieves of Neuropsychiatry (in press)

- Özdemir PG, **Kırlı U**, Işık M et al. (2020). The role of thought suppression in conversion disorder in relation to depression, symptom interpretation, and sleep hygiene: A case-control study. Archives of Clinical Psychiatry. 47(3):59-64. DOI: 10.1590/0101-60830000000233

- Ulas H, Binbay T, **Kırlı U** et al. (2017). The epidemiology of alcohol use in Izmir, Turkey: drinking pattern, impairment and help-seeking. Social Psychiatry Psychiatric Epidemiology. 52 (7), 887-899. DOI 10.1007/s00127-017-1345-5

- Zai G, **Kırlı U,** Alberry B et al. (2016). Rapporteur summaries of plenary, symposia, and oral sessions from the XXIIIrd World Congress of Psychiatric Genetics Meeting in Toronto, Canada, 16-20 October 2015.. Psychiatric Genetics. 26(6):229-257 DOI: 10.1097/YPG.0000000000000148

Book Sections

- **Kırlı U**, Binbay T. Epidemiology of Psychosis and Schizophrenia: in Şchizophrenia and other Psychotic Disorders 2nd Edition Editors: Ayşen Esen-Danacı, Ömer Böke, Meram Can Saka, Almıla Erol, Semra Ulusoy Kaymak, Ankara: Psychiatric Association of Turkey: 2018.29-51

- Kayahan B, Elbi H, **Kırlı U** (2018) Attenuated Psychotic Symptoms in Adolescence: in Adolescence and Mental Disorders Editor: Tezan Bildik, Ankara: Turkish Clinics: 2018. 180-186.

- **Kırlı U**. The Effects of COVİD-19 Pandemic on Mental Health: in Current Approach to Covid-19, Editors: Ümit Haluk İliklerden, Kamuran Karaman, Nurettin Yüzkat, Ali İrfan Baran, Hanifi Yıldız. Ankara: Akademisyen Press: 2020. 165-169

- **Kırlı U**, Akgül Ö, Alptekin K. Neurodevelopmental Roots of Schizophrenia: in Şchizophrenia and other Psychotic Disorders 3rd Edition, Editors: Ayşen Esen-Danacı, Ömer Böke, Meram Can Saka, Almıla Erol, Semra Ulusoy Kaymak, Ankara: Psychiatric Association of Turkey (in press)

- **Kırlı U**, Akgül Ö, Alptekin K. The Biochemistry of Schizophrenia (Dopamine and Others): in Şchizophrenia and other Psychotic Disorders 3rd Edition, Editors: Ayşen Esen-Danacı, Ömer Böke, Meram Can Saka, Almıla Erol, Semra Ulusoy Kaymak, Ankara: Psychiatric Association of Turkey (in press)

Abstracts

- **Kırlı U**, Binbay T, Elbi H, Alptekin K et al. (2019). Outcome of DSM-5 attenuated psychosis syndrome over follow-up: Six years follow-up study in a large general population-based population. European Neuropsychopharmacology. 29: 73-74. doi:10.1016/j.euroneuro.2019.09.138

- **Kırlı U**, Binbay T, Elbi H, Kayahan B et al. (2016). Psychotic experiences convert not only to psychotic disorders; also to depression and anxiety disorders: Evidence from a 6 years follow-up of a large general population sample. 5th Biennial Schizophrenia International Research Society (SIRS) Conference, Florence, İtaly; Nature Partner Journals Schizophrenia, doi:10.1038/npjschz.2016.10

- **Kırlı U**, Binbay T, Elbi H, Kayahan B et al. (2016) Psychotic experiences, alcohol-cannabis abuse, stressful events and familial risk is associated with onset of clinical psychosis: Evidence from a 6 years longitudinal population-based cohort. European Psychiatry 33: 256-257, http://dx.doi.org/10.1016/j.eurpsy.2016.01.526

- **Kırlı U**, Binbay T, Elbi H, Kayahan B et al. (2016) Quitting cannabis decreases but does not eliminate psychosis risk: evidence from a 7 years large population-based cohort. European Neuropsychopharmacology 26: 53-54

- **Kırlı** U, Binbay T, Elbi H, Alptekin K et al. (2015) Are BDNF-Val66Met and COMT-Val158Met polymorphisms associated with psychotic experiences and clinical psychotic outcome? Evidence from a prospective population-based cohort, 2008-2015. European Neuropsychopharmacology doi:10.1016/j.euroneuro.2015.09.009

- **Kırlı U**, Binbay T, Elbi H, Alptekin K et al. (2015). TurkSCH II: Evaluation of psychotic experiences, onset of clinical psychosis and associated risk factors in a 6 years prospective community-based follow-up. Turkish Journal of Psychiatry, 26 (Suppl. 2): 4-5

- **Kırlı U**, Parildar S, Cakir M (2014) Low quality sleep , general psychopathology and association with quality of life in cases with bruxism. Turkish Journal of Psychiatry 25 (Suppl. 1): 40

- **Kırlı U**, Çiftci S (2014) Bipolar Disorder and Multiple Sclerosis. Etiological Association? Coincidence? Turkish Journal of Psychiatry 25 (Suppl. 1): 40-41

- **Kırlı U**, Aydogdu I (2014) Interictal psychosis Turkish Journal of Psychiatry 25 (Suppl. 2): 116

- **Kırlı U** (2012) Psychotic like experiences, risk factors for conversion to psychotic disorders, gene-environment interactions: A follow-up study on a community based population;, New Directions In Psychiatry, Annual Forum of European Federation of Psychiatric Trainees, Sorrento- İtaly, Congress Book 206-208

- Binbay T, **Kırlı U**, Elbi H, Alptekin K et al. (2016). Exploring the impact of catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) polymorphisms on association between psychotic experiences and depression-suicidal ideation in a six-year follow-up of general population based sample. Nature Partner Journals Schizophrenia, doi:10.1038/npjschz.2016.10

- Binbay T, **Kırlı U**, Elbi H, Alptekin K et al. (2016). Which Social Environment Is More Important In Persistence Of Psychotic Experiences? Differential Impact of Neighborhood and Family Context In a Six Year Longitudinal Population Based Cohort. European Psychiatry 33: 202-203

- Elbi H, **Kırlı U**, Binbay T, Alptekin K et al. (2015). Extended Psychosis Phenotype, Gene-Environment Interactions. A Follow-up Study on a Community Based Population. European Neuropsychopharmacology doi:10.1016/j.euroneuro.2015.09.009

- Atan YS, **Kırlı U** (2019). Fahr syndrome diagnosed with first episode psychosis. Turkish Journal of Psychiatry 30 (Suppl. 2): 76

- Elbi H, Binbay T, **Kırlı U**, Kayahan B et al. (2016). Subthreshold Depression As A Predictor of Emergence and Persistence of Psychotic Experiences: A Six Years Longitudinal Population Based Cohort. European Psychiatry 33: 268-269

- Alptekin K, Binbay T, **Kırlı U**, Elbi H et al. (2016). A Six-Year Longitudinal Population-Based Cohort for the Extended Psychosis Phenotype: An Epidemiological Study of the Gene-Environment Interactions (TürkSch). European Psychiatry 33: 284-285

The PhD ceremonies of the last year in MHeNs*

- Shenghua Zong. Autoantibodies in disorders of the brain: expanding the spectrum. Supervisor: prof.dr. P. Marinez; co-supervisor: dr. M. Losen; dr. R. Rouhl.

- Jan-Willem Kallewaard. Diagnosis and minimally invasive treatment of chronic discogenic low back pain. Supervisor: prof.dr. M. van Kleef; co-supervisors: prof. dr. H. van Santbrink; dr. P. Willems.

- Simone M. Crivelli. Sphingolipid metabolism in the pathophysiology and treatment of Alzheimer's disease. Supervisors: prof.dr. P. Martinez-Martinez; prof.dr. E. de Vries, VUmc. Co-supervisors: dr. M. Losen; dr. M. Mulder, Rotterdam.

- Natasha Pahuja. Etiopathogenesis, advanced imaging and treatment outcomes in Asian Indians with keratoconus. Supervisor: prof.dr. R. Nuijts, co-supervisor: dr. R. Shetty, Bengaluru. Pooja Khamar Mayur Raksha.

- Clinical, Molecular and Biomechanical outcomes of SMILE (small incision lenticule extraction) and other refractive surgery techniques. Supervisor: prof.dr. R. Nuijts, co-supervisor: dr. R. Shetty, Bengaluru.

- Niels Janssen. Patterns and pathways. Indicators for potential improvements of dementia care. Supervisors: prof.dr. F. Verhey; prof.dr.mr. S. Evers; Co-supervisor: dr. R. Handels.

- Giovanni Mansueto. Childhood adversities and Psychosis: investigation of the potential aetio-pathogenetic mechanisms. Supervisor: prof.dr. K. Schruers; co-supervisors: prof.dr. F. Cosci, University of Florence, It; prof.dr. R. van Winkel, KU Leuven.

- Joke Debruyne. Cochlear implantation in adults with early-onset deafness. Supervisors: prof.dr. B. Kremer; prof.dr.ir. T. Francart, KU Leuven; Co-supervisor: dr.ir. J. Brokx.

- Koenraad Meuwissen, Burst Spinal Cord Stimulation in a Rat Model of Chronic Neuropathic Pain: Spinal and Supraspinal Mechanisms. Supervisors: prof. dr. E.A.J. Joosten; prof. dr. M. van Kleef.

- Lisa Schmiedek, Episodic memory in ageing and AD: a possible target for electrical stimulation ? Supervisors: prof. dr. F.R.J. Verhey; prof. dr. A.T. Sack; co-supervisor: dr. H.I.L. Jacobs

- Paolo Maino, Implantable Intrathecal Drug Delivery in Treatment of Chronic Intractable Pain and Spasticity: Improvement of Safety and the Use of Imaging Techniques. Supervisors: prof. dr. E.A. Joosten; prof. dr. M. van Kleef.

- José Geurts, Chronic Pain; Impact of Chronic Pain on a Societal, Personal, and Treatment Level. Supervisors: prof. dr. C.D. Dirksen; prof.dr. M. van Kleef; co-supervisor: dr. P.C. Willems.

- Brigitte Brouwer, Painful Small Fiber Neuropathy; Symptoms, assessments and interventions. Supervisor: prof. dr. C.F. Faber; co-supervisors: dr. I.S.J. Merkies, Willemstad, Curaçao; dr. J.G.J. Hoeijmakers.

- Ruth Gussenhoven, Antenatal inflammatory insults and preterm brain injury: Pathophysiology and therapeutic strategies. Supervisors: prof. dr. B.W. Kramer; prof. dr. L.J.I. Zimmermann; Dr. T.G.A.M. Wolffs.

- Adriana (Janine) Collet, Specific Care on the Interface of Mental health and Nursing home “SpeCIMeN”.

Supervisors: prof. dr. M.E. de Vugt; prof. dr. J.M.G.A. Schols; Prof. dr. F.R.J. Verhey.

- Fares Nigim, Glioblastoma and Meningioma Biology, Targeted Therapy and Oncolytic Virus Therapy. Supervisors: prof. dr. Y. Temel; prof. dr. S.D. Rabkin, Harvard; cosupervisors: dr. H. Wakimoto, Harvard; dr. L. Ackermans.

- Leonie Banning, Neuropsychiatric symptoms in Alzheimer's disease; Associations with biomarkers. Supervisor: prof. dr. F.R.J. Verhey; co-supervisors: dr. P. Aalten; Dr. I.H.G.B. Ramakers.

- Johan Haumann, Prevalence and pharmacological treatment of pain in patients with cancer; The role of opioids with and without NMDA receptor affinity. Supervisor: prof.dr. E.A. Joosten; co-supervisors: Prof. dr. M.H.J. van den Beuken-van Everdingen; dr. S.M.J. Van Kuijk.

- Joost Riphagen, Vascular matters in aging and dementia. Supervisor: prof.dr. F.R.J. Verhey; co-supervisor: Dr. H.I.L. Jacobs. Nikos Priovoulos, Structural and functional imaging of the locus coeruleus at 7T: from methodological to clinical application. Supervisor: prof.dr. F.R.J. Verhey; co-supervisors: Dr. H.I.L. Jacobs; dr. B.A. Poser.

- Simone Verhagen, The power of individual landscapes; A clinical exploration of personal experience sampling and new horizons. Supervisors: prof.dr. P.A.E.G. Delespaul; prof.dr. J.J. van Os, UM/UU; co-supervisor: dr. C.J.P. Simons.

- Nagy Youssef, Epigenetics, resilience and brain stimulation: advances in the mechanistic and therapeutic utility in patients with affective (PTSD and mood) dis-

orders. Supervisor: Prof.dr. B.P.F. Rutten; co-supervisor: Prof. dr. P. Sienaert, KU Leuven.

- Abhishek Appaji, Retinal vascular features as a biomarker for psychiatric disorders. Supervisor: Prof. Dr. C.A.B. Webers; co-supervisor: Dr. T.T.J.M. Berendschot, Dr. Naren P. Rao.

- Koos Hovinga, Angiogenesis Inhibition in Glioblastoma. Supervisor: prof. dr. Y. Temel; co-supervisor: Prof. V. Tabar, New York, USA.

- Gerhard Drenthen, Myelin and networks, Magnetic Resonance Imaging in Epilepsy. Supervisors: prof. dr.ir. W.H. Backes; Prof.dr. A.P. Aldenkamp; co-supervisor: dr. J.F.A. Jansen.

- Anna Gorlova, Understanding the Molecular Mechanisms of Aggression in BALB/C and TPH2-Deficient Mice. Supervisor: prof.dr. K. Lesch, Universitätsklinikum Würzburg, cosupervisors: dr. T. Strekalova; prof.dr. L. Bettendorff, University of Liège.

- Ekaterina Veniaminova, The impact of the 'Western Diet' on Emotional, Social and Cognitive Behaviours as revealed by a study on conventional and serotonin Transporter-Deficient Mice. Supervisor: prof.dr. K. Lesch, Universitätsklinikum Würzburg, co-supervisors: dr. T. Strekalova; prof. D.C. Anthony, Oxford.

- Dmitrii Pavlov, The contribution of CNS inflammation and Glycogen Synthase Kinase-3 (GSK-3)-cascades on adverse memory learning on mouse models of emotional stress. Supervisor: prof.dr. K. Lesch, Universitätsklinikum Würzburg, co-supervisors: dr. T. Strekalova; prof.dr. L. Bettendorff, University of Liège.

- Eric Fonseca Wald, Absence Epilepsy and Panayiotopoulos Synrome: Neurocognition and Brain Development. Supervisor: prof.dr. R.J. Vermeulen; co-supervisors: Dr. S. Klinkenberg; dr. M.J.A. Debeij-van Hall; Dr. J.G.M. Hendriksen, Epilepsiecentrum Kempenhaeghe.

- Kimberley S. Noij, Cervical vestibular evoked myogenic potentials; Toward optimizing clinical use. Supervisors: prof.dr. H. Kingma; prof. S.D. Rauch, MD, Massachusetts Eye and Ear, Harvard; co-supervisor: Dr. R. van de Berg.

- Mark J. van Tilburg, Advancement in cVEMP's. Supervisors: prof.dr. H. Kingma; prof.dr. S. Rauch, Harvard; co-supervisors: dr. R. van de Berg; dr. B. Herrmann, Boston.

- Nalini Atcharayam, Duchenne Muscular Dystrophy: The NIMHANS Experience. Supervisors: prof.dr. T. Delhaas; prof.dr. B.W. Kramer.

- Murat L Atagün, Cognitive neurophsysiology and neurochemistry in bipolar disorder. Supervisor: Prof. Dr. Therese van Amelsvoort; co-supervisors: Dr. Sinan Guloksuz; Dr. Marian Drukker.

- Majed Aldehri, Deep brain stimulation, memory functions and mechanisms. Supervisor: Prof. dr. Y. Temel; co-supervisors: dr. S. Hescham; dr. A. Jahanshahianvar.

- Printha Kentheeswaran-Wijesinghe, Age-related cytoskeletal pathologies: A study on elderly brains to investigate the extent of neuropathological and cerebrovascular changes at death ad their risk factors. Supervisor: Prof. dr. H. Steinbusch, Prof. dr. R. De Silva - (University of Sri Jayewardenepura), Prof. dr. D. Shankar - (NIMHANS Bangalore).

- Mahmoud Elbatrik, Network pharmacology for mechanistically redefined comorbidities. Supervisor: Prof. dr. H.H.H.W. Schmidt; co-supervisors: Dr. A.I. Casas Guijarro.

- Alexander Grønning, Big Data Analytics in Bioinformatics. Supervisors: Prof. dr. J. Baumbach - (University of Southern, Denmark), Prof. dr. H.H.H.W. Schmidt; co-supervisor: Dr. R. Röttger.

- Britta Nijsse, Cognition after stroke; various perspectives. Supervisors: Prof. dr. C.M. van Heugten, Prof. dr. J.M.A. Visser/Meily, Prof. dr. J.M. Spikman; co-supervisor: Dr. P.L.M. de Kort.

- Eva Koetsier. Dorsal Root Ganglion Stimulation for Pain Relief in Painful Polyneuropathy: Efficacy and Mechanism of Action. Supervisors: Prof. dr. E.A.J Joosten Prof. dr. J.A.M. van Zundert; co-supervisor: Dr. S.M.J. van Kuijk.

- Youssef Yakkioui, Molecular biomarkers in skull base chordoma. Supervisors: Prof. dr. Y. Temel, Prof. dr. M. van Engeland.

- Sascha Meyer, Visual Associative Learning in Alzheimer's Disease and Performance Validity. Supervisor: Prof. dr. R.W.H.M. Ponds; co-supervisor: Dr. J.F.M. de Jonghe.

- Daniël Verberne, Psychosocial outcome after stroke and traumatic brain injury - Longitudinal perspectives and recommendations for aftercare. Supervisors: Prof. dr. C.M. van Heugten, Prof. dr. R.W.H.M. Ponds; co-supervisor: Dr. M.E.A.L. Kroese.

- Britt van Hagen, Improving Pattern Separation and Cognition: Effects of Pharmacological Interventions

on Rodent Behavior and Neuroplasticity. Supervisors: Prof. dr. J. Prickaerts, Prof. dr. H. Schmidt.

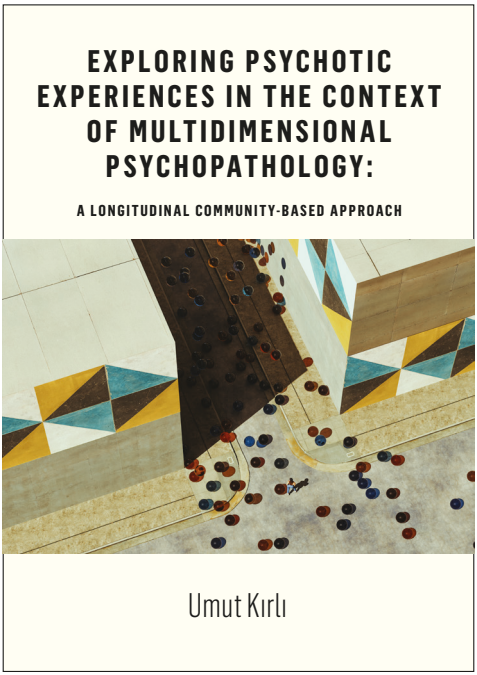
- Sara Bartels, Monitoring Everyday Life in Aging & Dementia – Perspectives from Experience Sampling and Technology Use. Supervisors: Prof. dr. F.R.J. Verhey, Prof. dr. M.E. de Vugt; co-supervisors: Dr. R.J.M. van Knippenberg, Dr. C. Malinowsky - (Karolinska Institutet, Sweden).

- Roel van Reij, Genetic Risk Factors in prediction and treatment of Chronic Post-Surgical Pain. Supervisor: Prof. dr. E.A.J. Joosten; co-supervisor: Dr. N.J. van den Hoogen.

- Hannah Christie, The Implementation of EHealth in Dementia Care: Lessons Learned. Supervisors: Prof. dr. M.E. de Vugt, Prof. dr. F.R.J. Verhey; co-supervisor: Dr. H.J. Tange.

- Antoine Bernas, Resting-state fMRI neurodynamics in neuropsychiatric disorders. Supervisors: Prof.dr. A.P. Aldenkamp Dr. ir. S. Zinger, TUE Gwendoline Montes Diaz, Immune regulation by mimethyl fumarate (DMF) in relapsingremitting multiple sclerosis patients. Supervisors: prof.dr. R. Hupperts, prof.dr. V. Somers, Hasselt, Dr. J. Fraussen, Hasselt

* Full list of PhD ceremonies in MHeNs can be found in the following website: https://mhens.mumc.maastrichtuniversity.nl/sites/intranet.mumc.maastrichtuniversity.nl/files/mhens_mumc_maastrichtuniversity_nl/public_article/phd_theses_-_tot_okt_2020.pdf



The extended and transdiagnostic psychosis phenotype represents an excellent framework from which to study the psychosis expression in the context of multidimensional psychopathology. In this dissertation, some results of a cohort project are presented which is conducted in a community-based population, representative of the Izmir metropolitan area. Psychosis is assessed across a spectrum of severity including experiences in healthy individuals, in individuals with non-psychotic disorders and in individuals with psychotic disorders. The associations with multidimensional psychopathology, genetic and socio-environmental factors are assessed based on a six-year follow-up.