From the Max Plank Institute of Psychiatry and the SGDP Centre at King's College London

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From Urbanicity to Genes: Transdiagnostic Approaches for Understanding Psychopathology

Dissertation

zum Erwerb des Doctor of Philosophy (Ph.D.)

an der Medizinischen Fakultät der Ludwig-Maximilians-Universität zu München

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aus:

Mexiko-Stadt, Mexiko

Jahr:

2023

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

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Datum der Verteidigung:

March 27th, 2023

To my grandmas, and to the little girl that dared to go beyond what she knew, in search of kindness and truth

ABSTRACT

The main classification systems of mental health that guide diagnosis and treatment rely on outdated conceptualizations of psychopathology, which view disorders as clearly distinguishable from each other and from mental wellness. Transdiagnostic approaches present an alternative, where processes and factors shared across diagnostic categories are investigated, and where clinical reality can be better represented. Through the use of such approaches, the goal of this thesis was to examine psychopathology symptoms and their interactions with environmental risk factors and biological factors, and to identify transdiagnostic symptoms and risk factors that could present targets for prevention or intervention. This was achieved by analysing data from large community cohorts from the United Kingdom.

The first study identified associations between mental health symptoms (specifically, symptoms of depression, mania and neuroticism), urban environment features and brain volume in a middle-aged cohort. The second study used a network approach to detect symptoms involved in the co-occurrence of depression and psychosis symptoms in the same cohort. This study also examined the influence of environmental risk factors (including trauma and urbanicity factors) and genetic risk factors on symptom associations. The third study evaluated the genetic structure of the general psychopathology factor (i.e. the *p* factor), and it examined whether genetic risk for the *p* factor and for other psychiatric traits can predict baseline levels and trajectories of psychopathology symptoms during childhood and early adolescence.

Depression (both on a symptom level and in terms of its genetic predisposition) was found to have the strongest and most widespread associations with the psychopathology symptoms evaluated in these studies, which included symptoms of mania, psychosis, anxiety, ADHD and conduct disorder. These results indicate that both depression symptoms and genetic predisposition to depression could be viewed as transdiagnostic factors, and that identified depression symptoms could be considered as transdiagnostic targets for intervention.

Among urban environment factors, socioeconomic deprivation had the strongest associations with psychopathology symptoms, which predominantly included symptoms of depression and psychosis. Deprivation was also associated with lower grey matter volume in brain areas involved in cognition and emotion processing, and was linked with the cumulative experience of traumatic events, which in turn was linked to

depression and psychosis symptoms. These findings suggest that, among modifiable environmental risk factors, targeting socioeconomic deprivation should be a priority for improving mental health.

Finally, genetic risk for psychopathology was associated with both functional impairment associated with the experience of psychopathology symptoms, and with psychopathology symptom levels in childhood. Pending future improvements in the predictive value of polygenic risk scores, these measures have potential utility as biomarkers to help prioritise support and interventions in individuals at higher risk of experiencing severe levels of psychopathology symptoms.

This thesis contributes to a more comprehensive and dimensional understanding of mental health, shedding light on transdiagnostic aspects of psychopathology. Specifically, key mental health symptoms, environmental and genetic risk factors and biological mechanisms are elucidated.

ACKNOWLEDGEMENTS

The journey to complete this doctoral thesis has shaped me, not just as a researcher, but more importantly, as a person. The people I have interacted and worked with during this time have played a significant part in this journey, and it is thanks to their support and guidance that I have been able to get this far.

I first want to thank Prof. Edward Barker for welcoming me to his research group and giving me access to the resources to carry out my PhD research, for supporting me in developing as a researcher and for his guidance and feedback on both methodological and practical research aspects.

I thank Prof. Elisabeth Binder and Prof. Cathryn Lewis; their meaningful support and their strong and empathetic leadership allowed me to continue with the PhD, and they served to me as confirmation of the kind of researcher I want to be.

I also want to thank Prof. Nikolaos Koutsouleris, for his useful scientific and methodological advice, and for the encouraging feedback he provided as a member of my thesis advisory committee.

I thank the coordinators of the International Max Planck School for Translational Psychiatry, particularly Bettina Schönherr, for their continued support and guidance during the PhD. I also want to thank the Max Planck of Psychiatry, the International Max Planck School for Translational Psychiatry and King's College London for providing me with the opportunity, the structure and the resources to carry out my PhD.

Moreover, I thank the participants and research staff involved in the UK Biobank and ALSPAC studies, whose participation and work has greatly contributed to advancing research, including my own. Thank you also to Kayla Friedman and Malcolm Morgan of the Centre for Sustainable Development, University of Cambridge, UK for their thesis template, which was used to produce this document.

I am also very grateful for my friends, colleagues and collaborators, both the ones that were with me for a small part of the journey and the ones that have been there for longer. Being able to learn with each other, to share laughs and lean on each other has made a meaningful difference to me during the PhD. I especially want to thank the members of the Developmental Psychopathology Lab, including Yi An, Deniz and Alex, as well as Kai and Anna, members of the IMAGEN Lab, including Alex, Xiao and Zuo, and Alison, Marlon, Simone and Marie.

Finally, I want to thank my family, especially my mom, my dad and my brother. I could not have achieved this without them.

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ACC	Anterior cingulate cortex
AIC	Akaike Information Criterion
ALSPAC	Avon Longitudinal Study of Parents and Children
ADHD	Attention deficit hyperactivity disorder
BIC	Bayesian Information Criterion
CD	Conduct disorder
CFI	Comparative Fit Index
CIDI-SF	Composite International Diagnostic Interview Short Form
CS	Correlation stability
CTS	Childhood Trauma Screener
DAWBA	Development and Wellbeing Assessment
dLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPIN-R	Eysenck Personality Inventory Neuroticism scale
ESCAPE	European Study of Cohorts for Air Pollution Effects
FDR	False Discovery Rate
GWAS	Genome-wide association study
HRC	Haplotype Reference Consortium
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQ	Intelligence quotient
LSOA	Lower-layer Super Output Area
LUR	Land Use Regression
M	Mean
MAF	Minor allele frequency
MGM	Mixed graphical model
MHQ	Mental health questionnaire
MRI	Magnetic resonance imaging
msCCA	Multiple sparse canonical correlation analysis
NO2	Nitrogen dioxide
ODD	Oppositional defiant disorder
PCA	Principal component analysis
PHQ-9	Patient Health Questionnaire-9
PRS	Polygenic risk score

PTSD	Post-traumatic stress disorder
RMSEA	Root Mean Square Error of Approximation
ROI	Region of interest
sCCA	Sparse canonical correlation analysis
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SEM	Structural equation modelling
SD	Standard deviation
SLE	Stressful life event
SNP	Single nucleotide polymorphism
SRMR	Standardized Root Mean Square
TLI	Tucker-Lewis Index
UK	United Kingdom
UKBUMP	UK Biobank Urban Morphometric Platform

PUBLICATION STATEMENT

The work presented in this PhD thesis is part of one first-author peer-reviewed research article (Garcia-Mondragon et al., *Translational Psychiatry*, 2022), which is attached in the Appendix and which corresponds to the content of Study 2 in this thesis. The work in this thesis is also part of one first-author manuscript in preparation for submission to a peer-reviewed journal, which is titled "Prediction of Child and Adolescent Psychopathology: Examining the Genetic P-factor", and which corresponds to Study 3 in this thesis. The majority of the content in the Material and Methods section and in the Results section for Study 2 and Study 3 was adapted from these pieces of work.

Lastly, part of a co-authored peer-reviewed research article (Xu et al., *Nature Medicine*, in press) closely follows the methodology used in Study 1, as the article originated from this study. The Material and Methods section and the Results section for these pieces of work have been independently written.

1 INTRODUCTION

1.1 Current Challenges in The Understanding of Psychopathology

The importance of mental health is increasingly recognized in the global health agenda, and in society as a whole. However, mental health disorders continue to represent one of the most challenging global issues of our time. This is evidenced in the high prevalence rates of mental health disorders worldwide (Steel et al., 2014) and in their global burden of disease, which surpasses that of cardiovascular disease and cancer, and which accounts for 7~13% of disability-adjusted life-years worldwide (Vigo et al., 2016; World Health Organization, 2008). Despite continued research into the causes, biomarkers and treatments for mental health disorders, the disease burden of these disorders has shown no significant decreases in the past 20 years (GBD 2019 Mental Disorders Collaborators, 2022).

Progress in this area of health has been partly hampered by a suboptimal understanding and conceptualization of psychopathology, which has in turn hindered advances in the prevention, diagnosis and treatment of mental health difficulties. Current conceptual models of psychopathology are heavily focused on individual disorders, and classify mental illness into distinct categories (e.g. major depressive disorder, bipolar disorder, general anxiety disorder). Mental illness in these models is considered to be clearly separated from mental wellness, and categories of mental illness are also considered to be clearly distinguishable from each other. The Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) and the International Classification of Diseases (ICD) (World Health

Organization, 2019) both embody these conceptual models of mental health, and they are the main classification systems of mental illness. Although historically useful for guiding and framing clinical practice and research, these manuals have fallen behind on current psychopathology knowledge, and they may be reaching the limits of their research and clinical utility (Reed, 2010).

There are four main ways in which these prevailing models of mental health fail to represent clinical reality. Firstly, clinical evidence shows that the boundaries between mental wellness and mental illness, and between different clinical diagnoses, are not precise. In fact, there are no clear-cut natural boundaries between these categories (Widiger, 2005). Rather, the number and intensity of mental health symptoms that can be experienced in a population exist on a continuum, where one end is characterised by an absence or low intensity of symptoms, and the other end, by a high number of symptoms or by significant functional impairment associated with the experience of these symptoms (Bosman et al., 2019; Fergusson et al., 2005; Lahey et al., 2018). Moreover, comorbidity in psychopathology is the rule rather than the exception: more than 50% of individuals diagnosed with a mental disorder in a given year also meet diagnostic criteria for another disorder (Demyttenaere et al., 2004; Kessler et al., 2005).

Secondly, there is high heterogeneity within mental health disorders. Patients with the same diagnosis can present with very different constellations of symptoms, and they may even have no symptoms in common (Olbert et al., 2014). This high variability in clinical profiles has been observed across a range of disorders, including depression (Fried & Nesse, 2015a), PTSD (Young et al., 2014) and ADHD (Luo et al., 2019).

Thirdly, symptoms are often shared across different mental health conditions. There are in fact few symptoms that are unique to any mental health diagnosis; a single symptom can contribute to multiple disorders, and it can therefore act as a common comorbidity across disorders (Sprooten et al., 2022). For instance, insomnia is commonly present across disorders spanning major depression, generalized anxiety disorder and schizophrenia (Dolsen et al., 2014)). Feelings of guilt, anhedonia, impulsivity and intrusive thoughts are additional examples of symptoms that can be found across depression, anxiety, ADHD, drug addiction and schizophrenia (Capone et al., 2021; Guineau et al., 2022; Harvey et al., 2004; S. L. Johnson et al., 2013).

Fourthly, environmental and biological risk factors, such as the experience of traumatic events (Hovens et al., 2012; Moustafa et al., 2021; Nierop et al., 2015),

exposure to urbanicity (Galea et al., 2011; Peen et al., 2010) and genetic predisposition (Kreek et al., 2005; P. H. Lee et al., 2021; Smoller et al., 2019), have shown to overlap among a wide range of mental health disorders, spanning depression, anxiety, schizophrenia and externalizing disorders such as drug addiction.

Collectively, these well-documented observations call into question the current boundaries between traditional diagnostic categories, and between mental health and mental illness. These observations also point to a need to consider alternative approaches to psychopathology that are better grounded in clinical reality, and that can therefore provide a more complete understanding of mental health. Transdiagnostic perspectives provide a promising approach in this regard, as they place traditional diagnostic boundaries aside and instead use dimensional conceptualizations of psychopathology that focus on common processes and factors shared across diagnostic categories (Harvey et al., 2004).

Transdiagnostic approaches are in line with a dimensional view of mental health, where mental health is considered to exist on a continuum from normal functioning to disorder (Krueger & Eaton, 2010), and where individuals diagnosed with a condition differ from normality only in the frequency and/or severity in which they experience symptoms (Brown, 1996). Individual symptoms, environmental and biological risk factors that are shared across disorders are among the factors investigated by these approaches, as this information has large implications for understanding the aetiology and mechanisms of psychopathology.

The goal of the present thesis will be to investigate symptoms and their interactions with environmental and biological risk factors through the lens of transdiagnostic frameworks of psychopathology, in order to achieve a more complete and dimensional understanding of mental health. Transdiagnostic approaches also offer a greater transfer of theoretical and treatment advances between disorders, and research into these mechanisms can help identify new targets for prevention and intervention that are effective across disorders. In the rest of this chapter, three transdiagnostic frameworks will be explored, comprised by symptomics, network approaches and latent approaches, and we will then explore the role of environmental risk factors and biological factors that are shared among mental health disorders. Lastly, we will approach pending research questions on these topics, which will be addressed in the aims and the empirical work of this thesis.

1.1.1 Transdiagnostic Approaches to Psychopathology

Over the last decades, research studies and transdiagnostic approaches have increasingly examined psychopathology in terms of its basic units: individual symptoms. While a large portion of medical conditions (such as diabetes, cancer and heart disease) has identifiable causes, and can be diagnosed based on clinical tests and biomarkers, the root causes of most mental health disorders are yet to be fully ascertained. Currently, mental health disorders can only be diagnosed based on experienced symptoms (Borsboom & Cramer, 2013). Symptoms thus play an essential role in mental health diagnosis and treatment, and consequently, they have been assigned a central role by transdiagnostic approaches to psychopathology.

1.1.1.1 Symptomics

Symptomics is a recently proposed framework that aims to examine causal relationships among symptoms. Instead of examining symptoms in an unspecific and general manner (i.e. as sum scores or severity scores), this framework investigates the properties by which individual symptoms associate and differ from each other, and the relation of symptom profiles with risk factors and with functional outcomes (Fried, 2017).

In terms of symptom associations, and in support of the symptomics approach, specific symptoms have been found to be strongly associated with each other. For instance, among symptoms of depression, strong associations have been found between symptoms of hopelessness and suicidal ideation (Beck et al., 1990). Relatedly, and as previously indicated, symptoms belonging to different disorder categories have shown relevant associations with each other. For example, symptoms of rumination and insomnia have shown strong correlations between them (Carney et al., 2013); these symptoms can be observed both in depression and anxiety (E. O. Johnson et al., 2006; Neckelmann et al., 2007), and they are also associated with additional symptoms of depression and anxiety, such as concentration difficulties (Moul et al., 2002).

Also in line with the symptomics framework, symptoms have been found to be differentially linked to biological correlates, to predisposing risks and to functional impairment (Fried & Nesse, 2014, 2015b). For example, the experience of specific symptoms such as sleep problems, increased appetite and weight gain, has been associated with higher levels of inflammation in the context of depression (Duivis et al., 2013). Additionally, specific life events have been associated with the experience of

distinct depression symptoms (e.g. depressed mood and feelings of guilt are more common after a relationship breakup, in contrast with fatigue and hypersomnia after chronic stress) (Keller et al., 2007), and sad mood has been found to have a stronger association with functional impairment, compared to other symptoms such as hypersomnia (Fried & Nesse, 2014).

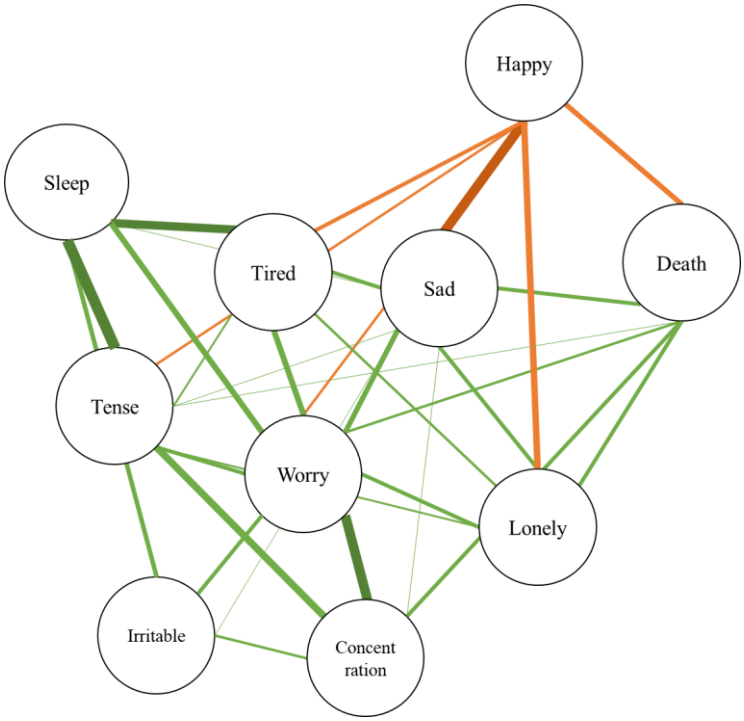
Investigating individual symptoms can thus shed light on differences between symptoms that have traditionally belonged to the same disorder categories, and help elucidate relationships between symptoms that belong to different disorder categories but that may have similar underlying causes, mechanisms and risk factors. In turn, investigating associations between symptoms, potential risk factors, biological correlates and functional impairment can provide valuable information related to mechanisms and potential targets for treatment and prevention.

1.1.1.2 Network approaches

A transdiagnostic approach that derives from symptomics and that has also allowed to empirically evaluate this framework, is the network approach to psychopathology. This approach considers that the relationships between symptoms are the causal agents for psychopathology (Borsboom, 2008; McNally et al., 2015); rather than reflecting underlying mental disorders, symptoms and their interplay *constitute* these disorders (Fried et al., 2017). In network approaches, vulnerability is represented by the pattern and strength of connections between symptoms (Borsboom, 2017); by reinforcing each other, interactions between mental health symptoms can give rise to self-perpetuating cycles that trigger and maintain psychopathology (Kappelmann et al., 2021). Conversely, the mutual deactivation of symptoms can lead to recovery.

The formulation of the network approach to psychopathology has been accompanied by the development of statistical models for estimating psychopathology networks based on empirical data (Epskamp et al., 2018). With network analysis, visual representations of associations among symptoms can be obtained (see Figure 1.1); these associations can be understood as partial correlations (Beard et al., 2016). Central symptoms can be identified through network analysis; these are defined by strong and/or widespread associations with other symptoms. Central symptoms are theoretically more likely to influence symptom interactions within a network due to their degree of interconnectedness, and are therefore considered to play a key role in the development and maintenance of mental health disorders (Beard et al., 2016).

Figure 1.1. Illustration of a symptom network that includes depression and anxiety symptoms.



Note. Green edges depict positive associations, while red edges depict negative associations.

Network analysis also allows the detection of bridge symptoms, which can be particularly relevant for understanding comorbidity. Bridge symptoms connect clusters of symptoms corresponding to different psychopathology disorders, and thus may play an important role in spreading symptom activation from one disorder to another (Castro et al., 2019; Fried et al., 2017). For example, the experience of insomnia in the context of post-traumatic stress disorder may lead to fatigue and concentration problems; as these symptoms can also be present in major depression and generalized anxiety disorder, they could act as bridge symptoms for the experience of additional depression and anxiety symptoms (Borsboom, 2017).

Thus, network approaches to psychopathology consider that individual symptoms are not interchangeable, as they can have unique contributions to psychopathology and to the experience of subsequent symptoms. This is also supported by evidence presented previously: symptoms can be differentially associated with biological correlates, risk factors and functional impairment.

The potential clinical utility of identifying central and bridge symptoms lies in the consideration of these symptoms as targets for prevention and clinical interventions. Targeting these symptoms could prevent or reduce symptom activation overall,

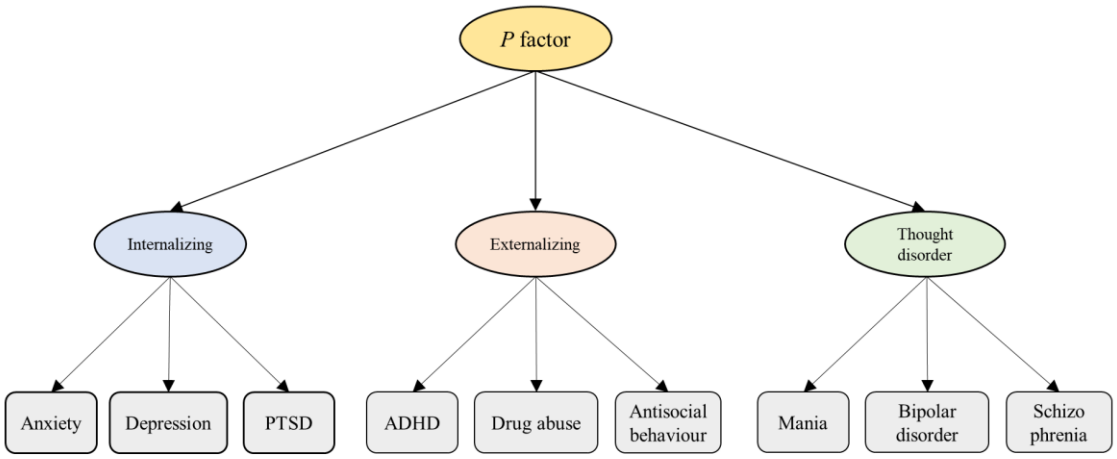
including self-reinforcing feedback loops (van Rooijen et al., 2018). The network approach to psychopathology has produced a growing body of empirical research, and emergent findings have shown to be potentially useful for representing and predicting psychopathology. For example, symptoms identified as central in symptom networks have been observed to better predict later diagnosis of depression and of PTSD (Boschloo et al., 2016; Haag et al., 2017).

1.1.1.1 Latent factor approaches

Another transdiagnostic approach that has increasingly received theoretical and empirical support is the latent factor approach. This approach considers that the high co-occurrence and cross-disorder associations between mental health diagnoses can be explained by underlying latent dimensions, which represent a general vulnerability to psychopathology. In more detail, this approach proposes there is a single underlying factor that represents an individuals' propensity to develop any mental health disorder (Lahey et al., 2012). This factor has been termed the general psychopathology factor or *p* factor, and it has been extracted from correlations between psychopathology symptoms.

Across latent factor studies, a hierarchical structure for psychopathology has been observed, where the *p* factor represents a broad general predisposition to psychopathology, and where two or more specific psychopathology domains can be observed, as represented in Figure 1.2. These domains capture the shared variance of disorders that tend to be comorbid, and they can be comprised by internalizing and externalizing domains. Some studies have also examined a domain for thought disorder. The internalizing domain accounts for the propensity to experience unipolar mood and anxiety disorders, including major depression, generalized anxiety disorder, specific phobias and post-traumatic stress disorder (Keyes et al., 2013; Krueger & Eaton, 2015). In turn, the externalizing domain accounts for the propensity to experience disinhibitory disorders that include impulsivity, disruptive conduct, antisocial and substance use symptoms (Krueger et al., 2002; Krueger & Eaton, 2015), such as ADHD, conduct disorder and drug addiction. Finally, the thought disorder domain is characterized by the propensity to experience mania, bipolar disorder and schizophrenia (Keyes et al., 2013).

Figure 1.2. Representation of the *p* factor and its psychopathology domains.



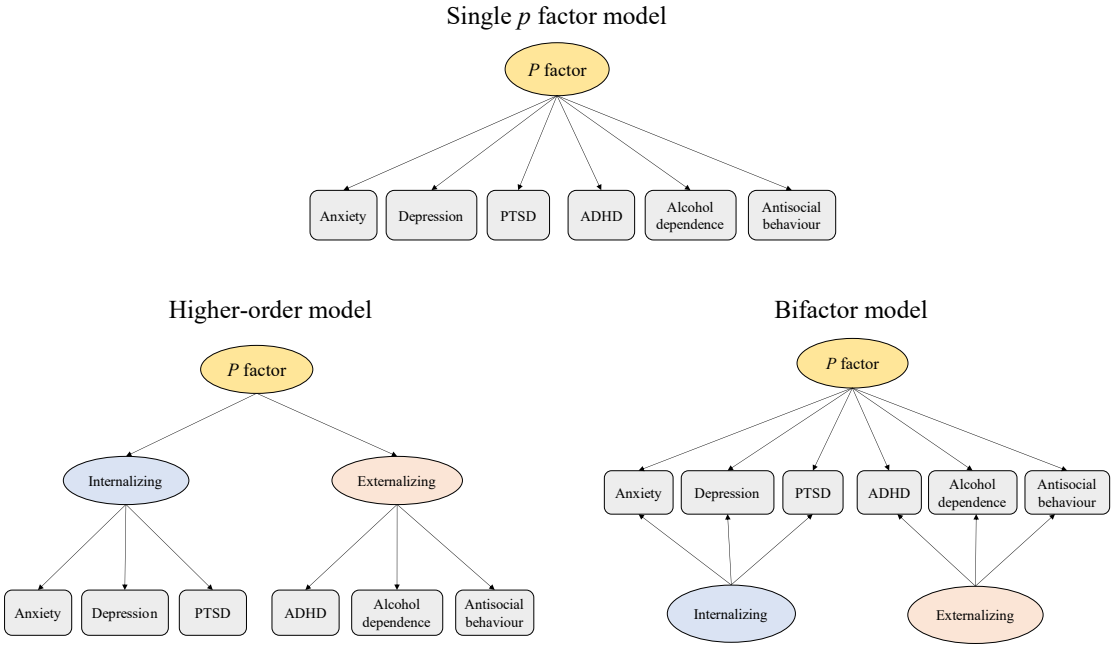
The hierarchical structure of psychopathology has been examined through three main models, which vary in the way they represent this structure and in their implications for the potential aetiology of psychopathology (Caspi & Moffitt, 2018) (see Figure 1.3). Firstly, in the single *p* factor model, all disorders load onto a single common psychopathology factor. This is the simplest model that has been formulated, and in line with the concept of the *p* factor, the implication of this model is that one single underlying factor accounts for the propensity to develop any and every common psychopathological disorder (Cortese et al., 2021).

Secondly, in the higher-order model, a general psychopathology factor is placed at the top level of the model, and psychopathology domains (e.g. internalizing and externalizing) are placed at a lower level. The *p* factor in this model is estimated from the correlations among such lower-level domains. This model allows to represent the hierarchy of psychopathology with a single integrated model. However, the fact that the *p* factor and its lower-level domains are not statistically independent limits the potential of discovering unique causes and mechanisms for the *p* factor and its domains (Lahey et al., 2021).

Thirdly, in the bifactor model, a general *p* factor and lower-level domains (e.g. internalizing, externalizing) also form part of this model, with the distinction that these domains are uncorrelated to each other (Martel et al., 2017). In this model, all disorders load onto the general *p* factor as in the single *p* factor model, while the lower-level psychopathology domains capture the remaining covariance not accounted by the *p* factor. Such a model allows to account for common variance (i.e. the *p* factor) across a range of correlated disorders or mental health problems, while allowing for unique

variance (i.e. that not accounted by the *p* factor) in its respective domains. As the lower-order domains account for unique domains of psychopathology, they can potentially have distinct aetiology (Haltigan et al., 2018). Bifactor models can thus be more readily used to identify psychological and biological processes that may underlie these dimensions of psychopathology.

Figure 1.3. Illustration of three main model structures to estimate the *p* factor.



General and specific factors of psychopathology have shown to be replicable in the same individuals over time, including child and adolescent samples (Carragher et al., 2016; Class et al., 2019; McElroy et al., 2018; Snyder et al., 2017). Moreover, the *p* factor has been associated with greater life impairment, family psychiatric history and altered brain integrity (Caspi et al., 2014); this factor and lower-level domain factors have also been shown to predict functional outcomes, such as self-harm and suicidal behaviour (Haltigan et al., 2018; Hoertel et al., 2015), criminal behaviour and academic attainment (Patalay et al., 2015; Sallis et al., 2019). From this information, it follows that the *p* factor has a heuristic value, as it could provide a concise predictor for a range of outcomes. Relatedly, this factor could potentially be considered as a therapeutic target to decrease psychopathology, as interventions at the level of more global psychopathological processes are likely to have larger effects (Hoertel et al., 2015).

Altogether, the transdiagnostic approaches to psychopathology covered in this section provide potential explanations for the observed high comorbidity between

mental health disorders, strong associations between mental health symptoms across clinical diagnoses and non-interchangeable nature of symptoms. They also lay the foundation for future research, as more extensive explorations are required to elucidate mechanisms shared across disorders, and to identify causes underlying dimensions of psychopathology. Investigating associations of psychopathology symptoms with environmental and biological risk factors can be key to this endeavour, and to generating knowledge of theoretical and clinical relevance.

1.2 Transdiagnostic Environmental Risk Factors

As previously mentioned, and in line with transdiagnostic and dimensional perspectives to psychopathology, mental health disorders have been found to have overlapping environmental risk factors. Environmental factors can act as predisposing and causal drivers for the emergence and maintenance of a range of mental health disorders and difficulties, hence the relevance of investigating them within a transdiagnostic perspective. Both proximal and distal environmental risk factors have been implicated in the experience of a range of mental health disorders.

On the one hand, proximal environmental factors involve social and physical experiences that have a direct effect on individuals' life and health (Moffitt et al., 2006). These can include the home environment, close relationships and the experience of stressful life events and of traumatic events. There is a wealth of knowledge on the influence of these risk factors on psychopathology. In particular, traumatic experiences, which involve the experience of intense or chronic events that are distressing in nature, have been consistently associated with increased risks for the presentation of mental health disorders that include depression, anxiety, post-traumatic stress disorder, psychosis and externalizing disorders such as substance use disorders and conduct disorder (Carliner et al., 2017; Gracie et al., 2007; Hovens et al., 2012; Karam et al., 2014; Nierop et al., 2015). Cumulative experiences of trauma have shown particularly strong associations with psychopathology, where the higher the number of experienced traumatic events, the higher the likelihood of experiencing mental health difficulties and of suffering from greater severity and functional impairment (Follette et al., 1996; Layne et al., 2014; Turner & Lloyd, 1995).

On the other hand, distal environmental factors involve cultural, demographic and geographic aspects of the environment that can have an indirect effect on

psychopathology, potentially by altering the likelihood of being exposed to proximal environmental risk factors (Moffitt et al., 2006). In the past years there has been an increased recognition of the role of these risk factors on psychopathology. One such factor that is being increasingly acknowledged as relevant to the susceptibility and experience of psychopathology, is urbanicity. This will be the main environmental risk factor of focus in this thesis, due to its potential of uncovering novel risk factors involved in psychopathology that have only recently started to be explored.

Urban areas are home to more than 50% of the world's population, and by 2050, it is predicted that 68% of the world population will reside in urban zones (Heilig, 2012). Although urban life can bring about benefits such as better access to health services, education and wealth (Dye, 2008; van Maarseveen, 2021), individuals living in urban areas can also be exposed to higher density residential and commercial buildings, and can face a reduced access to green areas. People living in cities also tend to be more exposed to harmful substances and factors (e.g. air pollution, sound pollution, pesticides) and to stressful social conditions, including inequality and social isolation (Hidaka, 2012; Lederbogen et al., 2011; van den Bosch & Meyer-Lindenberg, 2019).

In line with these potentially challenging conditions, emerging research has found evidence for a role of urbanicity in mental health disorders. Studies have consistently found increased prevalence rates and risk for schizophrenia in individuals living in urban areas, compared to individuals living in rural or less populated areas (J. McGrath et al., 2004; Vassos et al., 2012). The prevalence of other mental health disorders has also shown to differ between urban and rural areas. For instance, residents of urban areas have been observed to be on average 20 to 40% more likely to experience anxiety or mood disorders, compared with rural areas (Pedersen, 2001; Peen et al., 2010). The presence of substance abuse is also higher in urban areas (Penkalla & Kohler, 2014). Moreover, a possible causal role of the urban environment in mental health has been suggested by the presence of dose-dependent effects. For example, the longer individuals have lived in areas with higher degree of urbanization, the higher their risk is for experiencing mental health conditions such as schizophrenia (Pedersen, 2001).

Studies in this research area have also started investigating mental health-urbanicity associations on a more fine-grained level. Firstly, studies have started to examine these associations in a more dimensional manner by going beyond the assessment of disorders and instead focusing on the symptom level. Secondly, specific

elements of the urban environment have started to be evaluated in their associations with mental health. In line with transdiagnostic perspectives of psychopathology, urbanicity exposure has been found to represent a risk not only for increased rates of disorders and clinical diagnoses, but also for increased symptomatology in the general population. For example, the experience of psychosis symptoms has been observed to be positively associated with population density in community samples (van Os et al., 2001, 2002).

There is also growing evidence of associations between specific urbanicity factors and psychopathology, including socioeconomic deprivation, air pollution and greenspace availability (Dowdall et al., 2017; Gao et al., 2017; Henson et al., 2020; Lim Youn-Hee et al., 2012; O'Donoghue et al., 2016; Sarkar et al., 2018). However, a consensus on the specific features of the urban environment that have the strongest influence on mental health has not been reached thus far.

Moreover, potential mechanisms through which urbanicity factors may influence mental health are still largely unexplored. Elements associated with the urban environment, such as stress (on a social and physical level), may increase the vulnerability to develop mental health disorders by altering brain activity and structure (Spauwen et al., 2004), and by increasing the risk of being exposed to proximal environmental risk factors.

There is emerging research on the role of brain structure and function in psychopathology-urbanicity associations, but these biological mechanisms are yet to be fully determined. There are also only a few studies that have jointly considered the influence and interaction between proximal and distal risk factors in the context of psychopathology. It could be particularly useful to examine interactions between the exposure to urbanicity and the experience of traumatic experiences, as the urban environment may provide a background of social adversity, against which traumatic experiences may further increase the risk of developing psychopathology (Frissen et al., 2015). More research is needed to gain information about these complex associations.

In summary, research has shown the involvement of proximal and distal environmental risk factors in a range of mental health disorders. There is a need to further investigate the influence of environmental risk factors on mental health at a symptom-level, as this will allow a more dimensional and empirically-grounded understanding of these associations and potential mechanisms. To advance knowledge

in this emerging research area, identification of specific features of the urban environment that may act as risk and protective factors for mental health disorders is also particularly relevant, as information derived from this research could inform the design of policies and interventions targeting specific aspects of the urban environment that can benefit mental health. Finally, the examination of interactions between distal and proximal environmental risk factors within the context of psychopathology can further provide information about mechanisms involved in the emergence and maintenance of mental health difficulties. These investigations can provide a more complete understanding of the links between environmental risk and mental health, and of the mechanisms involved in these associations.

1.3 Transdiagnostic Biological Mechanisms and Risk Factors

Mental health disorders not only share environmental risk factors; they also share biological mechanisms and risk factors. On the one hand, structural and functional alterations in the brain have been found across a range of mental health disorders, with a convergence of alterations in brain areas involved in the processing and regulation of emotion, cognition and reward-related behaviour. On the other hand, the genetics of psychopathology have shown to transcend traditional diagnostic boundaries, as substantial shared genetic risk and high genetic correlations have been observed across disorders such as schizophrenia, depression, anxiety, PTSD, ADHD and addiction.

1.3.1 Brain Alterations

Research in the last years has started to integrate findings of brain alterations shared across mental health disorders, and it has found a considerable amount of evidence for alterations that overlap across conditions. Firstly, overall reduced cortical thickness and global reductions in grey matter volume have been identified across internalizing disorders (including depression, anxiety and PTSD), externalizing disorders (including ADHD, conduct disorder and drug addiction) and thought disorders (including mania and schizophrenia). These patterns have been suggested to reflect a transdiagnostic feature of psychopathology, and in more detail, to potentially reflect non-specific risk factors for the experience of psychopathology in general.

Secondly, and in addition to global brain volume alterations, reduced grey matter volume has been consistently identified for specific areas in a variety of mental

health disorders. Indeed, a reduced volume in brain areas involved in emotion processing and regulation, in cognitive control and in motivation and reward-related behaviour has been found in patients with schizophrenia, depression, anxiety, bipolar disorder and substance use disorder. In relation to emotion processing, a reduced volume in the amygdala and the insula has been found in mental health disorders that include anxiety, depression, schizophrenia and bipolar disorder (Goodkind et al., 2015). Both the amygdala and the insula are part of the limbic system, which is in charge of the processing of emotion. These findings are in line with the observation that symptoms associated with emotional regulation including rumination, anxiety, irritability and hypervigilance are common in the conditions mentioned above (Goldberg & Fawcett, 2012; McLaughlin & Nolen-Hoeksema, 2011; Moustafa et al., 2021; Richards et al., 2014; Temmingh & Stein, 2015).

Another relevant brain area that is also involved in emotional regulation, as well as cognitive control, is the anterior cingulate cortex (ACC). This area regulates activity in the amygdala (Devinsky et al., 1995), and as it would be expected, alterations in its brain volume have been extensively documented in a range of mental health conditions, including anxiety, bipolar disorder, schizophrenia and addiction (Goodkind et al., 2015; Shang et al., 2014; Wise et al., 2017). Moving on to cognitive control, a decreased volume in the prefrontal cortex, which has connections to the ACC and which plays a key role in attention, reasoning and executive functions such as working memory, has been found in patients with schizophrenia, bipolar disorder, depression, anxiety, addiction and ADHD (Fusar-Poli et al., 2012; Koenigs & Grafman, 2009; Liu et al., 2009; Shad et al., 2004; Shang et al., 2014; Valera et al., 2007; Wise et al., 2017). These results are in line with cognitive symptoms (e.g. cognitive biases) observed in these disorders.

As for motivation and reward processing, volume alterations in the striatum – which forms part of the main circuit in charge of these functions – have been found across ADHD, drug addiction, depression and schizophrenia (Barrós-Loscertales et al., 2011; Castellanos et al., 2002; Ellison-Wright et al., 2008; Gaser et al., 2004; Matsuo et al., 2008). The striatum includes the caudate nucleus, the putamen and the nucleus accumbens, and these brain areas have relevant connections with the prefrontal cortex and the ACC (Alexander et al., 1986; Haber, 2011). The disorders mentioned above can exhibit symptoms related to impaired reward-related processes, such as impulsivity,

compulsivity and anhedonia (Lubman et al., 2004; Wolf, 2006; Zisner & Beauchaine, 2016), which is congruent with volume alterations in the striatum.

Recent findings have shown that even sensory and motor brain areas may be affected across mental health disorders; some examples of this include observations of 1) a reduced volume in the thalamus (which is heavily involved in relaying sensory information to the cortex) in patients with schizophrenia and depression (Bora et al., 2012; Gaser et al., 2004), 2) a reduced volume in motor cortex in ADHD and schizophrenia (Exner et al., 2006; Mostofsky et al., 2002), and 3) volume alterations in the somatosensory cortex for bipolar disorder, depression and schizophrenia (Kropf et al., 2018; Minuzzi et al., 2018). This evidence indicates that even more basic functions related to the integration of sensory information (and potentially, of early-stage attentional processes) as well as motor control (including coordination of thought and action) may be altered in psychopathology (Ahrendts et al., 2011; Exner et al., 2006).

Thirdly, and in line with known interactions between the brain areas covered above, brain alterations across mental health disorders have been detected not only in relation to brain volume, but also in terms of brain function and connectivity. For example, deficits in functional connectivity between the nucleus accumbens, the insula and the prefrontal cortex have been observed across patients with depression, bipolar disorder and schizophrenia (Sharma et al., 2017). Across patients with bipolar disorder, ADHD and schizophrenia, alterations in functional connectivity within brain networks containing motor and sensory brain areas have been observed, as well as between sensory-motor networks and subcortical brain regions (including the striatum and areas from the limbic system) (Kebets et al., 2019).

Psychopathology at the brain level thus mirrors observations made at the symptom level, where overlaps between mental health disorders are common. This indicates that different disorders may have similar biological mechanisms, and it again supports the use of transdiagnostic approaches that evaluate cross-disorder mechanisms and risk factors to better understand psychopathology.

1.3.2 Genetic Risk Factors

Studies in the last decades have shown that psychopathology disorders are influenced by a large number of genetic risk factors that are shared across disorders, and that these shared genetic factors contribute to the observed co-occurrence of mental

health disorders and traits (Plomin et al., 2016). Family studies and twin studies provided the first indications that genetics do not follow diagnostic categories of psychopathology, as they have revealed familial overlaps and shared heritability for all major psychopathology disorders, including depression, bipolar disorder, schizophrenia, anxiety, ADHD, alcohol dependence and drug abuse (Domschke, 2013; Smoller et al., 2019). In simple terms, these studies have found that a range of mental health disorders cluster together in families and in twins, which indicates that there are heritable factors that overlap between mental health disorders.

Genome-wide association studies (GWASs) have provided complementary evidence to these findings at the level of DNA variation, as they have found a substantial shared genetic risk among mental health disorders through the investigation of pleiotropy. GWASs are designed to detect genetic variants that are associated with complex traits in population samples (Visscher et al., 2012); it is expected that the identification of these variants and associated genes and biological pathways will lead to a better understanding of the biology and aetiology of diseases, including mental health disorders. GWASs are able to examine pleiotropy, which refers to the observation of a single variant or gene influencing the genetic risk for multiple disorders/traits (He & Zhang, 2006). This phenomenon has found to be highly widespread among complex human traits; accordingly, it has shown to be the rule rather than the exception in psychopathology (P. H. Lee et al., 2021). For example, hundreds of common variants that increase the risk for schizophrenia have also been found to be involved in the genetic risk for bipolar disorder and major depression (S. H. Lee et al., 2013; Purcell et al., 2009), and to a lower extent, ADHD (Hamshere et al., 2013).

GWASs have also found that psychiatric disorders are highly polygenic and thus more genetically complex than initially expected. Indeed, sets of thousands of common DNA variants (typically single nucleotide polymorphisms, SNPs) with individual small effects have been found to account for a large portion of the genetic risk for psychiatric diseases and traits (Smoller et al., 2019). Genetic correlations based on SNPs shared across disorders have been able to quantify average effects of pleiotropy; for instance, genetic correlations between schizophrenia and bipolar disorder amount to 0.68, correlations between major depressive disorder and schizophrenia equal 0.43, and correlations between ADHD and major depressive disorder amount to 0.32 (S. H. Lee et al., 2013). Moreover, personality traits such as neuroticism have been shown to be genetically correlated with psychopathology traits, and to have variants in common with

these traits (Hettema et al., 2004; Nagel et al., 2018; Okbay et al., 2016). This indicates that just as psychopathology is characterized by dimensional variation in symptoms, the genetic structure of psychopathology also exhibits dimensional variation. Altogether, the observed shared genetic liability across disorders, ubiquitous pleiotropy and genetic correlations between mental health disorders speak to the transdiagnostic nature of mental health difficulties on a genetic level.

Polygenic risk scores (PRSs) constitute another recently developed tool that allows to examine shared genetic effects across traits. PRSs can index the genetic predisposition that a person carries for a specific disorder or trait (Allegrini et al., 2020; Lambert et al., 2019), by leveraging knowledge about variants associated with psychiatric disorders or traits. Results from GWASs (i.e. identified genetic variants associated with a trait) can be used to calculate PRSs, by aggregating into a single score the genetic risk across thousands of variants in the human genome.

The introduction of PRSs to psychiatric genetics has opened new avenues of research and of gaining knowledge in this area, as it has allowed to evaluate associations between individual-level genetic vulnerability for specific psychopathology traits and health/life outcomes. The use of PRSs can also allow to examine interactions between environmental and genetic risk factors involved in psychopathology on an individual level.

Moreover, the investigation of PRSs has provided further empirical evidence on the genetic dimensionality of psychopathology, and on the lack of genetic boundaries between normality and pathology. For example, PRSs for ADHD have been able to predict attention problems in community samples of children, and PRSs for schizophrenia have demonstrated predictive ability for social cognition in healthy individuals (Germine et al., 2016; Groen-Blokhuis et al., 2014). Research on PRSs has also demonstrated cross-disorder genetic overlaps for a range of psychopathology traits, including significant associations between PRSs for schizophrenia, depression, PTSD, ADHD, conduct disorder and oppositional defiant disorder (L. E. Duncan et al., 2018; H. J. Jones et al., 2016; Nivard et al., 2017). Investigations on the potential causes for these genetic cross-disorder associations are currently underway, as they could help elucidate the structure and biological origins of psychopathology.

1.4 Pending Questions in Transdiagnostic Psychopathology

As previously mentioned, an important research area within transdiagnostic approaches to psychopathology involves the interactions of environmental and biological risk factors with mental health symptoms. Considering both types of factors jointly, instead of evaluating their associations with mental health in an isolated manner, can lead to a more complete understanding of psychopathology and its mechanisms. Another relevant pending question involves the causes for the genetic cross-disorder associations observed for psychopathology traits and disorders, as this could help shed light on the biological mechanisms of psychopathology. A potential explanation for these observations is the presence of a genetic general factor of psychopathology, akin to the phenotypic *p* factor.

In this section, we will first introduce outstanding research gaps related to associations between the urban environment, mental health symptoms and brain features. We will then address pending research questions about interactions between depression and psychosis symptoms with genetic risk and urbanicity factors. Finally, we will introduce research questions related to the genetic nature of the *p* factor, and the potential of this genetic *p* factor to predict psychopathology.

1.4.1 Associations between Psychopathology, Urban Environment and Brain Features

As previously highlighted, there are knowledge gaps about the relationship between psychopathology and the urban environment, particularly in terms of the specific features of the urban environment that have the strongest influence on mental health, and of the brain mechanisms involved in these mental health-environment associations.

On the one hand, urbanicity factors that include socioeconomic deprivation, neighbourhood quality, greenspace access, land use mix, industry activity and traffic volume have been individually linked to psychopathology and psychological distress (Gong et al., 2016). However, there are few studies that have comprehensively examined a range of urbanicity factors in relation to mental health symptoms. This lack of detailed knowledge on the specific elements of the urban environment that are more influential on mental health is an obstacle to the design and implementation of effective public health interventions that can promote mental health.

On the other hand, initial studies on potential biological mechanisms involved in these associations have suggested that urban life – and the potential stress associated with it – can affect brain structure and function. For instance, one of the first studies in this research area found that living in a city was associated with increased activity in the amygdala, and with activity in the ACC, during the exposure to socially stressful stimuli (Lederbogen et al., 2011). Other studies have started to detect links between urban living and the structural alteration of brain areas. For example, studies in healthy participants have found that early life urbanicity is negatively associated with grey matter volume and cortical thickness in the dorsolateral prefrontal cortex (dLPFC), in the inferior parietal lobe and in temporal cortices that include the left superior temporal and left parahippocampal cortex (Besteher et al., 2017; Haddad et al., 2015; Lammeyer et al., 2019).

Collectively, these findings suggest that urbanicity as an environmental risk factor can significantly impact brain structure and function. Further research is still required to comprehensively evaluate how the urban environment can impact brain volume, as this gap in knowledge has only recently started to be addressed. Most studies on this research area have been carried out on young participants and have examined upbringing (e.g. the first 15 years of life), hence there is information lacking beyond young life. Studies have also generally evaluated small sample sizes ($n < 100$), which may prevent the elucidation of smaller but relevant effects.

In summary, there is a need for investigating associations between the urban environment, mental health and brain volume, in order to shed light on potential mechanisms for psychopathology. An approach such as symptomics can provide a theoretical framework for examining these links between mental health, environmental risk and biological mechanisms, and through related methods of analysis, it can allow to identify symptom profiles associated to specific urban environment features and to brain volume. Specifically, a method that would be suitable for this investigation is sparse canonical correlation analysis (sCCA); this is a method that allows to identify sets of variables that are maximally associated with each other. Previous studies have successfully used sCCA to identify symptom groups associated with specific structural and functional brain features (Ing et al., 2019).

For this investigation, the examination of symptoms related to mood disorders, including symptoms of depression, mania and negative emotionality (i.e. neuroticism) could be useful. On the one hand, the association of the urban environment with mood

disorders has been examined in a range of studies (Hoare et al., 2019; Peen et al., 2010; Weaver et al., 2015), especially in relation to depression, but these associations have not been extensively characterized on a symptom level. There are only a few studies that have examined links between urbanicity and symptoms of mania, for instance (Kaymaz et al., 2006; Sundquist et al., 2004). On the other hand, neuroticism has been found to be linked with psychopathology in general (Lahey, 2009), and although it has been traditionally considered as a personality trait, it has found to measure items similar to anxiety and depression (Nagel et al., 2018), and to be related to mania as well (Jylhä et al., 2010; Kirkland et al., 2015). The evaluation of these symptoms in relation to the urban environment and brain volume would allow a more dimensional examination of psychopathology.

1.4.2 Interactions of Psychopathology with Environmental and Genetic Risk Factors

The joint influence of environmental risk (including proximal and distal factors) and genetic risk factors on mental health symptoms is another topic that requires further research. Although these sets of risk factors are expected to play a significant role in symptom interactions, their joint influence has not been examined in detail at a symptom-based level, and there is a lack of integrative models that consider both risk factors in the context of mental health. For instance, network studies have only recently started to incorporate risk factors into network models (Kappelmann et al., 2021; Konac et al., 2021), and there is a scarcity of studies that simultaneously examine environmental and genetic risk factors in symptom networks.

By comprehensively evaluating interactions between environmental and genetic risk factors with symptoms, key bridge symptoms and associated risk factors can be identified. Such an investigation can also allow to evaluate whether environmental and genetic risk factors have similar or differential associations with mental health symptoms, and to examine the interactions of proximal and distal environmental risk factors in the context of psychopathology.

An area of psychopathology that can particularly benefit from the evaluation of these symptom and risk factor associations involves the relationship between depression and psychosis symptoms. The comorbidity of psychosis and depression is quite high; there are estimates that comorbid depression is present in about 50% of patients with

schizophrenia (Buckley et al., 2009). It is no surprise that when depressive and psychotic disorders are comorbid, disease and treatment burdens are exacerbated (Herz & Lamberti, 1995; Sim et al., 2004).

As previously mentioned, depression and psychotic disorders such as schizophrenia also have a shared genetic predisposition, which has been demonstrated by findings of familial aggregation (i.e. the clustering of these conditions in families), of significant shared heritability and of strong genetic correlations (r = 0.43) between these conditions (Domschke, 2013; S. H. Lee et al., 2013; Maier et al., 1993). Moreover, these conditions have shared environmental risk factors. On the one hand, the experience of trauma – especially cumulative trauma – has shown relevant associations both with depression and psychosis (Gracie et al., 2007; Nierop et al., 2015). On the other hand, factors related to urbanicity, including neighbourhood deprivation, greenspace exposure and air pollution have shown links with depression and with psychosis (Dowdall et al., 2017; Gao et al., 2017; Henson et al., 2020; Lim Youn-Hee et al., 2012; O'Donoghue et al., 2016; Sarkar et al., 2018).

Despite known genetic and environmental overlaps between depression and psychosis, little is known about their interplay at a symptom-based level. Recent network studies have started to investigate these symptom associations, and they have evaluated symptom networks that include depression, disorganization, negative, positive and motor symptoms, as well as factors related to internal resources, functional capacity and cognition (Belvederi Murri et al., 2020; Galderisi et al., 2018; Griffiths et al., 2021; Moura et al., 2021). These studies have identified symptoms including low mood, delusions, suspiciousness, and hallucinations as central in such symptom networks.

There is also a handful of recent studies that have incorporated either environmental or genetic risk factors into the evaluation of depression and psychosis symptom interactions. For example, a study that evaluated a symptom network including traumatic life events, depression symptoms, psychosis symptoms and biases in cognition identified central symptoms to these interactions, which consisted of depression feelings, persecutory delusions and cognitive biases associated with external attributions (Gawęda et al., 2020). Another network study evaluated associations between polygenic risk for schizophrenia and psychosis symptoms, and it identified associations of this genetic risk factor with symptoms of paranoia and conspiracy beliefs (Isvoranu et al., 2020).

Network analysis can thus allow to simultaneously evaluate the influence of environmental and genetic risk factors in the experience of psychosis and depression symptoms, particularly in relation to cumulative trauma, urbanicity factors and genetic risk. A comprehensive examination of symptom and risk factor associations could allow to identify bridge symptoms between lifetime symptoms of depression and psychosis and associated functional impairment, and to detect key links between these symptoms and risk factors. The clinical relevance of such investigation lies in the potential for detected symptoms and risk factors to be considered as targets for intervention and prevention strategies. Indeed, targeting key symptoms and factors is expected to lead to decreases in overall symptom activation (Borsboom & Cramer, 2013).

1.4.3 The Genetic *P* Factor and its Prediction of Psychopathology

Finally, a previously mentioned gap in psychopathology knowledge and its mechanisms involves the genetic causes for the transdiagnostic nature of mental health difficulties. A potential explanation for the shared heritability, ubiquitous pleiotropy and moderate to high genetic correlations observed across mental health traits lies in the existence of a genetic *p* factor that mirrors the phenotypic *p* factor. Analogous to its phenotypic counterpart, the genetic *p* factor would represent an underlying latent genetic factor that confers general vulnerability towards the experience of mental health difficulties.

Research in recent years has started to examine the potential existence of a genetic *p* factor. For instance, findings from twin and sibling studies have found evidence that supports a common origin for psychopathology disorders, as they have found shared sources of genetic predisposition for disorders that include depression, anxiety, schizophrenia, ADHD, conduct disorder, bipolar disorder and drug abuse (Lahey et al., 2011; Pettersson et al., 2016). Twin studies allow to evaluate the relative contributions of genetic and environmental influences on specific traits, by conducting comparisons between identical and fraternal twins. However, the methods used in these studies have not allowed to systematically examine potential causes for genetic associations observed between psychopathology traits.

A method that can more directly test the presence of the *p* factor on a genetic level is genomic structural equation modelling (Genomic SEM). This method can model the joint genetic architecture of complex traits with the use of GWAS summary statistics (Grotzinger et al., 2019). By combining information across genetically

associated traits, Genomic SEM can specify and compare a range of multivariate genetic models, which can help elucidate the potential causes of genetic correlations between traits. This method can also aid in the discovery of variants that are involved in cross-trait vulnerability.

With the use of Genomic SEM, Grotzinger and collaborators (Grotzinger et al., 2019) recently modelled a genetic *p* factor from genetic correlations between five psychiatric traits: schizophrenia, bipolar disorder, major depression, anxiety and PTSD. A PRS obtained from this *p* factor was able to predict a range of psychopathology measures in a cross-sectional, middle-aged sample (Grotzinger et al., 2019).

Investigating the *p* factor at the genetic level could shed light on the biological underpinnings of this factor, and it could further evaluate the validity of the *p* factor by examining it at different levels (e.g. phenotypic, genetic). The use of Genomic SEM could allow to explicitly examine the structure of the *p* factor on a genetic level, and it could specifically allow to evaluate the potential hierarchical structure of the genetic *p* factor, which remains a knowledge gap. Such knowledge could have implications for the aetiology and pathology of mental health difficulties, and it could inform our current conceptualizations of psychopathology.

Relatedly, as in the 2019 study by Grotzinger and collaborators, investigating the genetic *p* factor could allow to obtain a single measure that indexes general genetic vulnerability towards experiencing mental health difficulties. This could be particularly useful for evaluating the prediction of psychopathology in childhood and adolescence by the genetic *p* factor, which has only started to be addressed in recent years (Allegrini et al., 2020).

Previous research has assessed the potential of PRSs for psychiatric traits (including PRSs for depression, schizophrenia, anxiety and ADHD) to predict general and specific factors of psychopathology (Neumann et al., 2021). There are also previous studies that have identified associations of PRSs for psychiatric traits (including PRSs for depression, neuroticism and anxiety) with trajectories of psychopathology in adolescence and early adulthood (Kwong et al., 2021). However, there is a lack of research into the potential use of the genetic *p* factor for predicting trajectories of psychopathology. Moving beyond disorder-specific genetic information by identifying genetic risk variants that have a role on all forms of psychopathology could indeed provide useful information for the assessment and prediction of psychopathology.

Overall, analysing the genetic *p* factor can help shed light on the structure of psychopathology, and on its biological mechanisms. Moreover, examining associations between genetic risk (including risk for the *p* factor) and developmental trajectories of psychopathology can help predict psychopathology, and elucidate its developmental origins.

1.5 Aims of Thesis

The overarching aim of this thesis was to gain a more comprehensive understanding of mental health by examining the interplay between psychopathology symptoms, environmental risk factors and biological factors within a transdiagnostic context. In more detail, this thesis aimed to identify symptoms and risk factors that could eventually be considered as transdiagnostic targets for psychopathology prevention or intervention, and to gain insights into possible psychological, environmental and biological mechanisms of psychopathology. To achieve these aims, multivariate approaches were applied to data from large, predominantly urban population-based cohorts from the United Kingdom. The evaluation of large community samples allowed to implement a dimensional examination of mental health that is in line with transdiagnostic perspectives, and it provided power to detect small but significant effects in the associations of interest.

The first study used a symptomics approach to characterize associations between mental health symptoms, a comprehensive range of urban environment features and brain volume in a middle-aged community cohort. In more detail, this study used sparse canonical association analysis (sCCA) to identify a set of mental health symptoms (among symptoms related to depression, mania and neuroticism) and urban environment features that were maximally associated with each other. Multiple sparse canonical correlation analysis (msCCA, which is an extension of sCCA) was then used to evaluate potential biological mechanisms underlying these mental health–urban environment associations. Specifically, msCCA allowed to find brain volume areas that were simultaneously associated with the previously identified mental health symptoms and urban environment features.

The second study used a network approach in a middle-aged community cohort to examine interactions between lifetime symptoms of depression and psychosis, and to evaluate the joint influence of environmental and genetic risk factors in these symptom

associations. In a first step, associations between depression and psychosis symptoms were examined, and bridges that connect these symptom communities were identified. In a second step, proximal and distal environmental risk factors and genetic risk factors were incorporated into the symptom network, to evaluate the interplay of depression and psychosis symptoms with these risk factors. The cumulative lifetime exposure to trauma was assessed as a proximal risk factor, and the exposure to urbanicity factors of deprivation, air pollution and greenspace availability were examined as distal risk factors. In turn, depression PRSs and schizophrenia PRSs were evaluated as genetic risk factors.

Finally, the third study used a latent factor approach to examine the genetic structure of the *p* factor, and to evaluate whether genetic risk for the *p* factor can predict psychopathology symptoms during late childhood and early adolescence. The study investigated the potential hierarchical structure of the *p* factor on a genetic level by estimating different *p* factor models with the use of Genomic SEM. Baseline levels and linear trajectories of internalizing and externalizing psychopathology symptoms were then assessed in a community-based child sample, and their associations with PRSs calculated for the *p* factor and for individual psychiatric traits were evaluated. The predictive ability of the *p* factor PRS was compared against single-trait PRSs, in order to evaluate the specificity and the power of PRSs for predicting psychopathology.

2 MATERIAL AND METHODS

2.1 General Methods

The studies in this thesis used data from two large community-based cohorts: the UK Biobank study and the Avon Longitudinal Study of Parents and Children (ALSPAC) study. Further details on these cohorts are presented below.

2.1.1 UK Biobank Cohort

UK Biobank is a population-based, observational cohort study that has collected data from an initial sample of over 500,000 participants aged 40-70 years that lived in the United Kingdom. The UK Biobank study was designed to examine the lifestyle, environmental and biological determinants of a range of adult diseases. The study received ethical approval by The North West Multi-Centre Ethics Committee, and all its participants gave informed consent. Details on the setting and study design for the UK Biobank study can be found elsewhere (Sudlow et al., 2015).

Individuals were invited to the study if they were registered with the National Health Service and if they lived within a 35 km radius of one of the 22 assessment centres located across the UK at the time of recruitment. This recruitment strategy allowed to include participants that lived in a range of urban areas and beyond urban fringes. The UK Biobank study recruited participants and carried out baseline assessments between the years 2007 and 2010; these assessments included the completion of questionnaires on medical history, sociodemographic, lifestyle, occupational, psychosocial and environmental aspects, in addition to the collection of

physical measures and biological samples (N. Allen et al., 2012). Genome-wide genotype data has also been collected on all UK Biobank participants, and the study has collected detailed measures of urban environment exposures linked to the residential addresses of participants, including measures of air and sound pollution, access to greenspaces, neighbourhood deprivation and land use density (Sarkar et al., 2015).

Follow-up assessments for the UK Biobank study have been carried out, which have included online questionnaires that evaluate specific health factors in more detail, such as diet, cognitive function, occupational history and mental health (Sudlow et al., 2015). Follow-up information has also been acquired through linkage to health and medical records (Bycroft et al., 2018). Additionally, data from physical activity monitors and from multi-modal imaging assessments that includes magnetic resonance imaging (MRI) of the brain, heart and abdomen have been collected in a subsample of participants (Sudlow et al., 2015). The brain imaging assessment is composed of structural, diffusion and functional data.

Access to the UK Biobank resource for this thesis was possible under UK Biobank project number 63994.

2.1.2 ALSPAC Cohort

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal cohort study that recruited pregnant women living in the former county of Avon, UK, who had expected delivery dates between Apr. 1st, 1991 and Dec. 31st, 1992 (Boyd et al., 2013). The study was created to investigate the influence of genetic and environmental characteristics in the health and development of parents and their offspring. The initial cohort included 14,062 live births, and it was increased to 14,899 children who were alive at one year of age after additional recruitment efforts (Northstone et al., 2019).

The study received ethical approval from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Further details about the study and recruitment can be found elsewhere (Boyd et al., 2013), and information on all the data available from this study can be accessed through the study website, which includes a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

Participants in the study were generally representative of the United Kingdom's population at the time the data was collected, as compared to data from the 1991 National Census (Boyd et al., 2013; Fraser et al., 2013). The ALSPAC study has collected an extensive range of genetic, environmental and phenotypic data on children and their parents (including mothers and their partners). Regular assessments have been carried out in children and parents, starting with pregnancy and continuing with follow-up assessments to this day, with the latest measures collected when participants were 28 years old (Smith et al., 2021).

Phenotype measures collected by the ALSPAC study include information about demographics, physical health, psychological and social factors, development, education and school performance, physiological and cognitive measures. Collected environmental measures include information about diet, housing, social background, stressful conditions, physical activity, medications, air pollutants, noise and physical environment measures (Boyd et al., 2013). The study has collected multi-informant data related to the children participating in the study, with the use of reports from caregivers, the child themselves and assessments at clinic visits. Moreover, follow-up assessments have included questionnaires and clinical assessment visits which have collected biological samples, genetic and epigenetic data (including genome-wide data on 8,365 children), as well as linkage to health and administrative records and information about psychological, social and other environmental exposures (Boyd et al., 2013).

Access to the ALSPAC cohort for this thesis was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R01HD068437, and by the Economic and Social Research Council under Grant ES/R005516/1 to Dr Edward D. Barker.

2.2 Study 1 Methods

Study 1 used a symptomics approach to investigate associations between mental health symptoms of depression, mania and neuroticism, a comprehensive set of urban environment measures and brain volume in a middle-aged population-based cohort. Details on the measures and analyses carried out for this study are presented below.

2.2.1 Study Sample

This study used data from the UK Biobank study. Participants were included in the study if they had data available for a mental health questionnaire that was completed at the time of recruitment, and if they had urban environment data linked to their residential address available. To ensure the reliability of urban environment measures used in this study, participants also had to reside in England and to have lived at their residential address for at least 3 years at the time of recruitment. Finally, to avoid confounding factors related to ethnic background heterogeneity in the studied sample, only participants of white European origin were selected for the study. The sample for this study included 91,629 participants that fulfilled these inclusion criteria.

Analyses that evaluated associations between mental health symptoms, urban environment features and brain volume included an additional selection criterion: only participants who had brain volume measures available, in addition to fulfilling the above requirements, were selected. The sample for these analyses included 7,517 participants.

2.2.2 Measures

Mental Health Symptoms. A set of nineteen measures were used to assess mental health symptoms in this study. These measures were obtained from a standardised mental health questionnaire that participants answered at the time of recruitment. The measures assessed symptoms related to depression, mania and neuroticism.

Questions assessing depression symptoms were based on the depression module of the Patient Health Questionnaire (PHQ-9), which is a self-administered instrument to assess common mental disorders (Kroenke et al., 2001). Four questions from this questionnaire evaluated the experience of depression symptoms (i.e. depressed mood, unenthusiasm, tiredness, restlessness) in participants over the past two weeks, and items were rated on a four-point scale, from “not at all” (0) to “nearly every day” (3). Questions evaluating manic symptoms were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996). Two questions from this questionnaire evaluated the lifetime experience of manic symptoms (“Ever highly irritable/argumentative for 2 days” and “Ever manic/hyper for 2 days”), and items were rated on a binary scale (0 = no; 1 = yes). Finally, neuroticism was assessed with the use of twelve questions from the Eysenck Personality Inventory Neuroticism scale (EPIN-

R) (Eysenck & Eysenck, 1975), a self-rated test to evaluate this personality trait. The Neuroticism scale includes items such as "Are you often troubled by feelings of guilt?", "Does your mood often go up and down?", "Are you a worrier?", which are rated on a binary scale (0 = no; 1 = yes).

A full list of the items used to assess mental health in this study is available in Table A.1. in the Appendix.

Urban Environment Measures. Urban environment measures for this study were derived from participants' living addresses and made available through the UK Biobank Urban Morphometric Platform (UKBUMP). UKBUMP is a high-resolution spatial database that contains objective measures of the physical and socioeconomic environment surrounding the living addresses of UK Biobank participants (Sarkar et al., 2015). This database was generated to allow the investigation of links between the built urban environment and health and wellbeing in the UK Biobank study. UKBUMP modelled and compiled a wide range of individual-level urban measures linked to each participant through a series of spatial and network analyses based on UK-wide spatial databases (Sarkar et al., 2015).

A set of 275 urban environment measures was selected for this study, which covered a broad range of urban environment qualities including air and sound pollution, greenspace availability, socioeconomic deprivation, land use density (e.g. density of commercial, residential and factory facilities) and slope.

Since various of these measures examined similar aspects of the urban environment (e.g. average daytime noise pollution, average evening noise pollution), principal component analysis (PCA) was used to summarize the urban environment measures into a smaller set of categories. A set of 44 categories of urban environment measures was defined based on the different aspects of the urban environment that were examined. These included categories related to traffic, air pollution, sound pollution, greenspace, deprivation in terms of income, employment and education, deprivation in terms of crime, living environment and housing, slope, and categories related to distance and density to facilities. Generation of distance and density to facilities categories was also guided by codes provided by the UK Biobank study, which in turn were based on Address Base Premium land use classification codes and descriptions. A full list of the categories and the measures included in each category can be found in Table A.2 in the Appendix.

In more detail, after z-normalizing individual urban environment measures, a PCA was carried out for each category. Only variables with a positive loading equal to or greater than 0.3 in the first component were retained, and the first component was used as the summary score for each category. This allowed to obtain a single measure for each category of urban environment features.

Brain Volume Measures. Grey volume measures examined in this study were made available by the UK Biobank team and were obtained from brain data collected for a set of ~10,000 participants between 2014 and 2017. T1-weighted brain images (i.e. structural brain data) were obtained in a 3T scanner (standard Siemens Skyra 3T running VD13A SP4), with the use of a 3D MPRAGE sequence (repetition time = 2000 ms, resolution = 1 mm^3). The brain data was processed and segmented with the use of FAST FSL (Zhang et al., 2001), and grey matter volume estimates were obtained by a) summing the grey matter partial volume estimates within 139 regions of interest (ROI's) and by b) the use of FSL FIRST, which allows to obtain volume estimates from subcortical regions (Patenaude et al., 2011). The ROI's were based on a combined parcellation from three different atlases: the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006), and the Diedrichsen cerebellar atlas (Diedrichsen et al., 2009). Grey matter volume estimates from 154 cortical and subcortical ROI's were thus obtained (Alfaro-Almagro et al., 2018). Additional information on the collection, image processing and quality control of brain data from UK Biobank participants can be found elsewhere (Alfaro-Almagro et al., 2018; Miller et al., 2016).

2.2.3 Statistical Analysis

Data analysis for this study was performed in two steps. In Step 1, associations between mental health symptoms and urban environment features were examined to obtain and identify a set of mental health symptoms and urban environment features that were strongly associated with each other. In Step 2, the association of brain volume with the identified mental health-urban environment relationships was examined, in order to find brain volumes that are simultaneously associated with the previously identified mental health symptoms and urban environment features.

Data preparation. Since the methods used in the present study (namely, sparse canonical correlation analysis (sCCA), and multiple sparse canonical correlation analysis (msCCA)) required the use of standardized data (Ing et al., 2019), the mental health symptom measures and the urban environment measures were z-standardized

once age, gender and assessment centre were regressed out from these measures. Grey matter volume measures were also corrected for sex, age, scanning site and head size, and they were z-standardized. Data preparation and the rest of the analyses for this study were carried out with the use of the Matlab software (MathWorks, version R2018a).

Step 1: Sparse Canonical Correlation Analysis (sCCA). sCCA is a multivariate, data-driven method that can be considered as a generalization of multiple linear regression. This method allows to identify linear relationships between two sets of variables, where there is no distinction between which variables are considered independent and which ones are considered dependent (Ing et al., 2019). In more detail, sCCA maps linear associations between sets of variables, by identifying weights for each variable that will result in a weighted sum of variables in each set that is maximally correlated with the weighted sum of variables from the opposite set (Ing et al., 2019). sCCA uses an L1 regularization that forces variables with negligible contributions to the variance explained between the sets of variables to take an exact value of zero, which enhances the interpretability of the results obtained with this method (Ing et al., 2019; Witten et al., 2009).

sCCA was used in this study to identify a set of mental health symptoms and urban environment measures that are most strongly associated to each other. A train/test design was used to ensure the validity of the findings. Participants were randomly allocated to either a training set that included 80% of the study sample, or to a test set that comprised 20% of the study sample. The training set was used to 1) carry out a variable selection step, and 2) to implement a model-fitting step that would result in weighted sets of measures maximally associated with each other. The test set was used to validate the model fitted in the training set.

The variable selection step was carried out to enhance model stability, and it involved resampling the data in the training set for 1000 times, implementing the sCCA in the resampled data and considering variables as stable only if they showed non-zero loadings for above 75% of the resampling trials. In more detail, 50% of the training data was randomly drawn in each trial, and sCCA was carried out with a randomly chosen sparsity, which could range from 0.1 to 1, in increments of 0.1. The resulting weights for each mental health and urban environment variable were recorded for each of the 1000 trials, and the variables that were present in > 75% of the trials were considered to be stable (Meinshausen & Bühlmann, 2010). This step allowed to identify a set of stable

mental health symptom variables and urban environment that are consistently associated with each other.

After the variable selection step, the sCCA algorithm was applied to the full training set with the use of the stable variables in a model-fitting step, without imposing any sparsity. This step allowed to obtain weights for each stable variable, as well as a correlation coefficient (termed canonical correlation) that describes the association between the sets of mental health symptoms and urban environment variables. The weights obtained in this model-fitting step where then applied to the test set for validation, and the canonical correlation coefficient for the test set was recorded as well.

Permutation tests (consisting of 1000 permutations) were carried out to assess the significance of the obtained correlation coefficients in the training set and the test set; the canonical correlations were considered significant at an alpha level of 0.05. An in-house Matlab script based on the algorithm described by Witten (Ing et al., 2019; Witten et al., 2009) was used to perform the sCCA.

Step 2: Multiple Sparse Canonical Correlation Analysis (msCCA). Once associations between mental health symptoms and urban environment measures were characterized, msCCA was performed on grey matter volume measures and on the previously identified weighted sets of mental health symptoms and urban environment features. This analysis allowed to examine potential brain mechanisms involved in the relationship between mental health symptoms and the urban environment.

msCCA is an extension of sCCA that allows to examine associations between more than two sets of variables. This method can optimize the correlation between a weighted sum of variables in a target set with weighted sums of variables of additional sets (Ing et al., 2019). In this study, msCCA was used to maximize the correlation between brain volume measures and the previously identified weighted sets of mental health symptom and urban environment variables, allowing to identify a stable and select set of brain areas whose volume was associated to both of these sets of variables.

The design for the msCCA was analogous to the sCCA; a train/test design was used, with 80% of the sample used as training set and 20% of the sample used as test set. This analysis also included a variable selection step and a model-fitting step in the training set. As in the sCCA, 1000 resampling trials were used for the variable selection step, where msCCA was repeatedly implemented, and variables were considered to be stable if they had non-zero loadings for above 75% of the resampling trials. Permutation tests

with 1000 permutations were also used to evaluate the significance of the obtained correlation coefficients in the training set and the test set. An in-house Matlab script (Ing et al., 2019) was used to implement the msCCA.

2.3 Study 2 Methods

Study 2 used a network approach to identify key symptoms involved in the lifetime co-occurrence of depression and psychosis symptoms, and to examine the association of environmental (specifically, cumulative trauma and urbanicity factors) and genetic risk factors (specifically, depression and schizophrenia polygenic risk scores; PRSs) with these symptoms in a middle-aged urban population-based cohort. Information about the measures and analyses implemented in this study are presented in the following section.

2.3.1 Study Sample

Data from the UK Biobank cohort was used in this study. Participants were included in the study if they had data available for an online mental health questionnaire (MHQ) that assessed lifetime symptoms of depression, psychosis and traumatic events, if they had genetic data available and if they had data available on urbanicity factors linked to their residential address. Further inclusion criteria are indicated below.

Inclusion to the study was restricted to participants of white European ancestry, given that the GWASs that were used to calculate PRSs were from participants with this ancestry. Finally, in order to improve reliability of data from urbanicity factors, participants were also required to have lived at the same residential address for at least a period of five years to be included in this study. The study sample that fulfilled these criteria consisted of 77,650 participants.

2.3.2 Measures

Depression Symptoms. Lifetime symptoms of depression and related functional impairment were evaluated with self-reported items from the MHQ, which was completed by 157,348 participants at a follow-up assessment for the UK Biobank study that took place between 2016-2017. Specifically, depression symptoms were assessed based on the lifetime version of the Composite International Diagnostic Interview Short Form (CIDI-SF), which consists of a series of screening scales for the assessment of mental disorders (Davis et al., 2020; Kessler et al., 1998). The presence of lifetime

depression symptoms (0 = no; 1 = yes) was thus evaluated: primary symptoms of depression ("Ever had prolonged feelings of sadness or depression" [low mood] and "Ever had prolonged loss of interest in normal activities" [anhedonia]) were examined, and if participants confirmed they experienced at least one of these during their lifetime, secondary symptoms of depression (feelings of worthlessness, feelings of tiredness, sleep change, weight change, thoughts of death and difficulty concentrating during the worst period of depression) were assessed.

Functional impairment for depression was examined on a binary scale based on the answers to two items from the MHQ: "Impact on normal roles during worst period of depression" and "Professional informed about depression". These items were presented only to participants that reported the experience of at least one primary symptom of depression. Further details on this measure are available in the Appendix.

Psychosis Symptoms. Lifetime symptoms of psychosis and related functional impairment were evaluated based on items from the MHQ. In more detail, psychosis symptoms were assessed with the lifetime version of the CIDI Psychosis module (Davis et al., 2020; J. J. McGrath et al., 2015). This questionnaire examined the presence of lifetime psychosis symptoms (0 = no; 1 = yes), through the following items: "Ever believed in an unreal conspiracy against self", "Ever believed in unreal communications or signs", "Ever heard an unreal voice" and "Ever seen an unreal vision".

Functional impairment for psychosis was examined on a binary scale based on two items from the MHQ: "Distress caused by unusual or psychotic experiences" and "Ever talked to health professional about unusual or psychotic experiences". These items were presented only to participants that reported the experience of at least one symptom of psychosis. Additional details on this measure can be found in the Appendix.

Traumatic Events. Lifetime experience of traumatic events was assessed through items from the MHQ. This assessment included items related to the experience of childhood trauma, adult trauma and of trauma related to post-traumatic stress disorder. In more detail, childhood trauma was examined by five items from the Childhood Trauma Screener (CTS), a shortened version of the Childhood Trauma Questionnaire (Glaesmer et al., 2013), and adult trauma was examined by an equivalent 5-items screener (Davis et al., 2020). These two sets of items evaluated the experience of emotional neglect, emotional abuse, physical neglect, physical abuse and sexual

abuse. Finally, the experience of events that commonly elicit PTSD symptoms was evaluated by five items that included the experience of accidents, violence and assault (Davis et al., 2020). A list with the specific items evaluating the lifetime experience of traumatic events for this study can be found in Table 2.1.

Table 2.1. Items assessing traumatic events.

Child trauma	Adult trauma	PTSD-related trauma
Someone to take to doctor* when needed as a child	Able to pay rent/mortgage as an adult*	Witnessed sudden violent death
Felt loved as a child*	Been in a confiding relationship as an adult*	Been in serious accident believed to be life threatening
Felt hated by family member as child	Belittlement by partner or ex-partner as an adult	Been involved in combat or exposed to war zone
Sexually molested as a child	Sexual interference by partner or ex-partner without consent as an adult	Victim of sexual assault
Physically abused by family as child	Physical violence by partner or ex-partner as adult	Victim of physically violent crime

**These items were reverse-coded.*

Child and adult trauma items were evaluated on a five-point scale, from "never true" (0) to "very often true" (4), while PTSD-related trauma items were originally evaluated on a three-point scale (0 – never; 1 – yes, but not in the last 12 months; 2 – yes, within the last 12 months). PTSD-related trauma items were recoded to a two-point scale (0 – never; 4 – yes) to ensure all trauma measures would have the same range for calculating cumulative trauma. Some child and adult trauma items were also reverse coded (as observed in Table 2.1) to ensure that higher scores for all items would represent a stronger degree of experienced trauma. Cumulative trauma experience was calculated by summing the scores for all trauma questions.

Urbanicity factors. Measures of urbanicity involving socioeconomic deprivation, air pollution and greenspace availability were obtained from the UKBUMP database, which is composed of high-resolution measures of the physical and socioeconomic environment surrounding the living addresses of UK Biobank's participants. Urbanicity factors were available for two time points: 2007 and 2010, which covered the period through which baseline data was collected in the UK Biobank study. Since the measures from 2010 were collected at a timepoint closer to the

completion of the MHQ in 2016-2017, measures from this timepoint were selected for the present study. Urbanicity factors showed high correlations across the two available timepoints, which showed their stability and lent support to their use in this study (see Table 2.2).

Table 2.2. Correlations of urbanicity factors between 2007 and 2010.

Measure	*r* coefficient
Index of Multiple Deprivation	0.99*
Nitrogen dioxide air pollution	0.79*
Greenspace percentage	0.97*

**Correlation is significant at a $p < 1x10^{-3}$*

Neighbourhood deprivation was measured by the English Index of Multiple Deprivation (IMD) which is a global measure that represents small-area deprivation. The IMD is calculated as a continuous measure based on the weighted combination of seven indicators, which are in turn generated based on national census data. These indicators include education skills and training deprivation, employment deprivation, income deprivation, barriers to housing and services, health deprivation and disability and living environment and crime. IMD scores are calculated at the level of Lower-layer Super Output Areas (LSOA's), which are small geographic areas with average populations of 1,500. The UK Biobank team used LSOA's corresponding to UK Biobank participants' residential addresses to allocate IMD scores to each participant.

In turn, air pollution was indexed by nitrogen dioxide [NO2] levels, which were modelled for UK Biobank participants' addresses with the use of a Land Use Regression (LUR) model. This model was developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE), and it was based on pollutant concentrations measured at monitoring sites and on measures of traffic, topography and land use (Beelen et al., 2013). NO2 levels were quantified as annual average values in $\mu g/m^3$.

Finally, greenspace availability was measured as the percentage of land classed as 'greenspace' surrounding participants' living addresses. In more detail, greenspace was estimated with the use of the Generalised Land Use database for England (Office of the Deputy Prime Minister, 2005), which contains information on land use distribution and which includes 'greenspace' as one of its simplified land categories. A 1-km buffer area from participants' addresses was considered for estimating greenspace availability.

Polygenic Risk Scores. PRSs for depression and schizophrenia were calculated on an individual level in the UK Biobank sample. To generate PRSs, data from a GWAS study (i.e. "base" data) is required, which consists of summary statistics that contain effect sizes and *p* values for genotype-phenotype associations at genetic variants (i.e. SNPs) (Choi et al., 2020). PRSs are calculated for each individual in a sample, usually referred to as the "target" data, which consists of genotypes from individuals in a sample that is independent from the sample used in the GWAS study of interest.

In more detail, PRSs are generated by calculating the sum of risk variants present in an individual's genotyped data, which are weighted by the risk variant's association effect sizes previously estimated in a GWAS (Choi et al., 2020). This weighted sum is usually performed with the use of a "clumping and thresholding" approach, which restricts summary statistics to SNPs that are not in linkage disequilibrium with one another (i.e. SNPs that are statistically independent), and which then applies one or multiple thresholds (usually based on *p* values) to restrict the weighted sum to SNPs that have been statistically associated with the trait of interest (Choi et al., 2020; Kappelmann et al., 2021). The calculation of PRSs therefore results in a single value per subject that provides an estimate of that individual's genetic liability for a trait.

Genetic data for UK Biobank participants was collected via two very similar genotyping arrays: the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix and the Applied Biosystems UK Biobank Axiom Array, which covered ~800,000 SNPs (Bycroft et al., 2018). The raw genome-wide data acquired from 488,377 participants went through a quality control procedure carried out by the UK Biobank team, which excluded participants if they had gender mismatches, unusual levels of missingness or heterozygosity, or if they had withdrawn their consent for analysis of their data. Imputation of the genotyped data was carried out with the use of the Haplotype Reference Consortium (HRC) and the UK10K reference panels (Bycroft et al., 2018). Additional quality control for the genetic data comprised the exclusion of participants who were related to another individual in the dataset, as well as the restriction of SNPs to common variants (i.e. SNPs with minor allele frequency (MAF) > 0.01) with a call rate > 98% that were in approximate Hardy-Weinberg equilibrium ($p > 10^{-8}$) and that were either directly genotyped or imputed from the HRC with high confidence (IMPUTE INFO metric > 0.4).

The PRSs for depression and for schizophrenia were calculated in the UK Biobank sample with the use of PRSice-2 (Euesden et al., 2015). The base data for computing the PRSs consisted of GWAS summary statistics for depression (Wray et al., 2018) and for schizophrenia (Pardiñas et al., 2018). The target data for calculating the PRS was comprised of the UK Biobank sample, which was independent from the samples used to calculate the GWAS summary statistics. Clumping parameters to identify index SNPs and delete SNPs in linkage disequilibrium were set to $r^2 > 0.1$ over 250kb sliding windows. PRSs were calculated at a GWAS *p* value threshold of 0.1, and they were adjusted for the first five genetic principal components to account for population stratification.

2.3.3 Statistical Analysis

Data analysis for this study was performed in two main steps. In Step 1, a network model was estimated to evaluate the network structure of symptoms of depression and psychosis, and associated functional impairment. In Step 2, environmental risk factors (i.e. cumulative trauma and urbanicity factors) and genetic risk factors (i.e. depression and schizophrenia PRSs) were incorporated into the depression-psychosis network to investigate the interplay of depression and psychosis symptoms with these risk factors. Bridge nodes were identified in both networks, in order to gain insights into the co-occurrence between symptom categories of depression and psychosis and the examined risk factors.

Network analysis allows to model complex patterns of relationships, and to obtain graphical representations of the associations between a set of variables (Hevey, 2018). In network analysis, the variables in a network are termed nodes, and the connections between nodes are termed edges. Edges represent statistical relationships between nodes (most commonly, partial correlations), and they can provide information about the direction and strength of associations between nodes (Hevey, 2018). Once a network has been estimated, it can be further analysed in terms of its core features, such as its global density/sparsity, the centrality of its nodes and the clustering of nodes into communities. In particular, centrality indices can provide information about the relative importance of a node compared with the remaining nodes in a network (Borgatti, 2005). In turn, communities can be considered as groups of nodes measuring similar concepts, which can be connected to each other through bridge nodes (P. J. Jones et al., 2019).

Data preparation. Data types for this study consisted of a mixture of binary, ordinal and continuous measures. Network methods that work with continuous measures assume normally distributed measures, which is unlikely to be the case in community health-related data (van Borkulo et al., 2014). For this reason, a binary network approach was chosen for this study, as this method does not assume normally distributed measures, and it has been used in previous network studies that examined a mixture of data types (McElroy et al., 2019; Wigman et al., 2017). This method generates weighted undirected networks from binary measures.

To implement the binary network approach, ordinal and continuous measures were dichotomized. Specifically, cumulative trauma measures were dichotomized at the 75th centile of each measure's distribution, which allowed to capture increased non-linear severity of exposure to traumatic events. Urbanicity factors and PRSs were dichotomized in the same way, in order to capture increased exposure to neighbourhood deprivation, air pollution, greenspace availability and increased genetic risk, respectively. Data preparation and the analyses for this study were performed with the use of the R-statistical software (R Core Team, 2013), version 3.6.3.

Node Selection. A node selection step was performed prior to network estimation, in order to avoid redundancy in the constructs examined by individual items in the networks. This step was implemented with the use of the goldbricker function from the *networktools* R software package (P. J. Jones, 2018), which allows to compare correlations between each pair of items of interest. Node pairs with less than 25% of significantly different correlations and with a zero-order correlation of 0.5 or above ($p < .01$) were set to be identified as redundant. No pair of items examined was identified as redundant, hence all measures of interest were carried forward in the following analyses and were represented as individual nodes in the estimated networks.

Network Estimation. The networks from Step 1 and Step 2 were estimated with the use of Ising network models and with the R software packages *bootnet* (Epskamp et al., 2018) and *IsingFit* (van Borkulo et al., 2014). An elasso regularization technique was used in the calculation of these networks, which sets estimated small edges to zero in order to reduce the possibility of estimating false positive associations. This regularization technique involves a model selection based on the extended Bayesian Information Criterion (BIC), which aims to detect an optimal network structure with a balance between parsimony and goodness of fit. The resulting network includes edges that can be interpreted similarly to partial correlations, where an edge that links two

items indicates a statistically significant association after controlling for the remaining items in the network. To visualize the calculated networks, the *qgraph* package (Epskamp et al., 2012) was employed. This package makes use of the Fruchterman Reingold algorithm to place nodes closer together and in the centre of the network when they are strongly related, while placing nodes that are weakly connected in the network periphery (Fruchterman & Reingold, 1991).

Centrality Estimates. To assess the structure of the estimated networks and identify nodes with high centrality, which are more likely to influence network dynamics, indices of strength, closeness, expected influence and betweenness were calculated. As its name indicates, strength evaluates direct connections between nodes in terms of their strength; closeness assesses the strength of indirect connections between nodes; expected influence examines the strength of direct connections between nodes while considering the direction of these associations (i.e. positive or negative), and betweenness measures the importance of a node in terms of its average path between other node pairs (Epskamp et al., 2018; Hevey, 2018; Robinaugh et al., 2016).

To identify bridge nodes, bridge expected influence (Step 2) metrics were calculated with the package *networktools*. This metric considers both direct and indirect effects of a node on other communities; higher levels of this metric indicate nodes that are more strongly connecting multiple node communities. The top 25% scoring nodes on this metric were identified as bridges. For bridge estimations, symptoms of depression and depression impairment were considered as a single "depression" community; symptoms of psychosis and psychosis impairment were specified as a "psychosis" community; environmental risk factors were specified as belonging to a single "environmental risk" community, and genetic risk factors were also specified as a single "genetic risk" community.

Network Stability and Node Centrality. The stability of centrality indices calculated for the estimated networks was assessed with the use of the *bootnet* package. This package was used to obtain bootstraps (i.e. subsets of data) to evaluate if the order of centrality indices remained the same after re-estimating networks which less cases. Specifically, case-dropping bootstrapped centrality indices were obtained based on 1,000 bootstrapped samples. The *bootnet* package was also used to test the accuracy of estimated network edges by calculating confidence intervals for their estimates, specifically by generating bootstrapped 95% confidence intervals based on 1,000

bootstrapped samples. Only network edges that were present in at least 70% of these bootstrapped samples were reported in the present study.

Sensitivity Analyses. Given that the lifetime rate of some of the psychosis symptoms was very low (as observed in Table 3.2 in the Results section), symptom networks were recalculated in a sensitivity analysis to evaluate the possible impact of an imbalanced rate of psychopathology symptoms in the estimated networks. In more detail, the networks from Step 1 and Step 2 were recalculated in a down-sampled cohort that included all participants that had experienced at least one psychosis symptom in their lifetime, and a matched number of randomly-selected participants that had never experienced any psychosis symptom in their lifetime. This down-sampled cohort included 6,222 participants.

An additional sensitivity analysis was also carried out to assess the possible impact of dichotomizing continuous measures that were included in the Step 2 network. This network was recalculated in the original sample of participants by including the environmental and genetic risk factors in their original continuous scale, along with binary symptom measures. This network estimation was carried out with the use of a mixed graphical model (MGM), which can accommodate for a range of data types. The *mgm* package (Haslbeck & Waldorp, 2020) was used for the estimation of this network, which uses a regularized model selection based on the extended BIC.

2.4 Study 3 Methods

Study 3 aimed to examine the hierarchical structure of the genetic *p* factor, and to evaluate whether genetic risk for the *p* factor and for other psychiatric traits can predict baseline levels and trajectories of child and early adolescent psychopathology in a community-based cohort. This study was pre-registered (https://osf.io/6v5zj/). Details on the measures and analyses involved in the study are presented in the section below.

2.4.1 Study Sample

This study used data from the ALSPAC cohort. Participants were included if they had genetic data available, if they were unrelated to each other and if they had data available for all evaluated psychopathology symptoms for at least one of the three time points of interest in this study: ages 7, 10 and 13. The study sample that fulfilled these

criteria included 6,339 individuals, with data available for 5,386 participants at age 7, for 5,143 participants at age 10 and for 4,797 participants at age 13.

2.4.2 Measures

Psychopathology Symptoms. Maternal reports on the Development and Wellbeing Assessment (DAWBA) (Goodman et al., 2000) were used to evaluate symptoms of psychopathology in ALSPAC participants at ages 7, 10 and 13. DAWBA is a well-validated, semi-structured interview-based questionnaire which assesses the presence, severity and duration of a range of psychopathology symptoms.

Symptoms from internalizing and externalizing domains were evaluated for this study. For the internalizing domain, three symptom categories were examined: generalised anxiety, depression and post-traumatic stress disorder. For the externalizing domain, four symptom categories were assessed: inattention (from the component in ADHD problems), hyperactivity/impulsivity (from the component in ADHD problems), conduct disorder (CD) and oppositional defiant disorder (ODD).

Psychopathology symptoms were assessed based on a series of questions that evaluated the presence (e.g. 0 = no; 1 = yes) and severity of symptoms (e.g. 0 = no; 1 = a little; 2 = yes, a lot). A list of the DAWBA items included in each psychopathology category that were examined at age 7 can be found in Table A.4 in the Appendix (questionnaires examined analogous items at all time points). Individual symptom scores from each psychopathology category were combined into sum scores for each category, and they were prorated to account for missing item data. Symptom scores were prorated if participants had less than 30% missing data for each symptom category; if participants presented more than 30% missing data for a symptom category, the sum score was recorded as missing. The R-package PROscorerTools version 0.0.1 (Baser, 2017) was used to prorate the data.

GWAS Data. Summary statistics from seven recent European-only GWASs were used for this study, as participants from the study were of European origin. Internalizing traits/disorders included major depressive disorder (Howard et al., 2019), PTSD (Nievergelt et al., 2019) and anxiety disorder (Purves et al., 2020). Externalizing traits/disorders included ADHD (Demontis et al., 2019), risk-taking (Karlsson Linnér et al., 2019), which aimed to mirror the hyperactivity/impulsivity symptoms evaluated by DAWBA, antisocial behaviour (Tielbeek et al., 2021), which aimed to mirror the CD

symptoms assessed by DAWBA, and childhood aggression (Ip et al., 2021), which aimed to mirror the ODD symptoms examined by DAWBA.

Genetic Data. Genetic data in ALSPAC children were acquired with the Illumina HumanHap550 quad genome-wide SNP genotyping platform. The resulting raw genome-wide data with 550,000 SNPs from 9,115 participants were subjected to standard quality control by the ALSPAC team. This included the exclusion of participants from analysis in the case of gender mismatches, minimal or excessive heterozygosity, high levels of individual missingness (>3%), insufficient sample replication (IBD < 0.8), evidence of cryptic relatedness (measured as proportion of identity by descent; IBD > 0.1) and non-European ancestry, which was assessed by multidimensional scaling analysis. Moreover, SNPs were excluded if they had a MAF of < 1%, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium ($p < 5e^{-7}$). After the QC, imputation of the genotyped data was performed by the ALSPAC team with the use of Impute V2.2.2 against the 1000 genomes reference panel (Phase 1, Version 3: all polymorphic SNPs excluding singletons), utilizing all 2,186 reference haplotypes (including non-Europeans).

2.4.3 Statistical Analysis

Data analysis for this study was conducted in three main steps. In Step 1, the structure of the genetic *p* factor was modelled in three ways: as a single *p* factor, as a higher-order model and as a bifactor model. The above-mentioned GWAS summary statistics for internalizing and externalizing traits were used to model the genetic *p* factor. After selecting a *p* factor model that had a suitable model fit and theoretical plausibility, PRSs for the *p* factor and for individual psychopathological traits were calculated in the ALSPAC sample. In Step 2, longitudinal trajectories of internalizing and externalizing psychopathology symptoms through ages 7, 10 and 13 were estimated in the ALSPAC sample. Finally, Step 3 examined associations of the *p* factor PRS and the single-trait PRSs with baseline levels and trajectories of psychopathology symptoms.

Step 1: Genomic SEMs For The *p* Factor and Calculation of PRSs. Genomic structural equation modelling (Genomic SEM) was used to estimate the structure of the genetic *p* factor. This method allows to model multivariate genetic associations among phenotypes, and to identify variants that have effects on general dimensions of cross-trait vulnerability, which can potentially lead to the calculation of more predictive

polygenic scores (Grotzinger et al., 2019). As the name suggests, Genomic SEM is based on structural equation modelling (SEM), a statistical technique that allows to measure and examine multivariate causal relationships, and to analyse the strength of associations between observed and latent variables (i.e. unobserved variables that cannot be directly measured, but rather represent the shared variance between observed variables) (Beran & Violato, 2010; Fan et al., 2016).

In more detail, SEM allows to test the validity of theoretical models ("structural models") by comparing them to empirical data ("measurement models", which usually consist of data in the form of correlations and covariances) (Beran & Violato, 2010). Structural models can represent hypothesized causal relationships between variables with the use of equations, which can be solved to estimate the relationships of interest in real data (Kline, 2011). Goodness-of-fit statistics can be used to determine if a theoretical model adequately explains the examined data, and they can also be used to compare different structural models to determine the model that best represents the data.

Genomic SEM uses GWAS summary statistics from different traits as input to estimate the genetic covariance structure of these traits. A range of structural models that can account for the genetic correlations between these traits can then be estimated, evaluated against the genetic covariance and compared, which can aid in better understanding the potential causes of observed genetic correlations between traits (Grotzinger et al., 2019).

Estimation of Genomic SEMs. For this study, summary statistics for the traits/disorders of interest (major depressive disorder, PTSD, anxiety disorder, ADHD, risk-taking, antisocial behaviour and childhood aggression) were used as input for the Genomic SEM analysis. The summary statistics were formatted for pre-processing and subsequently, the genetic covariance of these traits was estimated. Single *p* factor, higher-order and bifactor models were estimated based on these genetic covariances. Genomic SEM analyses for the study were run with the use of the *GenomicSEM* R package (Grotzinger et al., 2019).

A model that would be considered as having acceptable fit should have the following goodness-of-fit statistics, according to our pre-registered criteria: Root Mean Square Error of Approximation (RMSEA) and Standardized Root Mean Square Residual (SRMR) < .08 (excellent fit < .05); Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) > .90 (excellent fit > .95). Models were considered untenable if they

had factor loadings that were out of bounds (e.g. negative factor loadings), if factor loadings were not significantly different from zero or if they had very large standard errors.

In line with our preregistered analyses, we first aimed to model a single common genetic *p factor*, i.e., a latent factor that would summarize the genetic variance shared between the traits/disorders of interest. However, the Genomic SEMs based on the seven phenotypes of interest did not converge. This was due to strong genetic correlations ($r > 0.89$) identified between the summary statistics of externalizing traits, specifically between ADHD, aggression and antisocial behaviour. Genetic correlations between these phenotypes can be found in Figure 3.9 in the Results section.

In order to prevent issues with multicollinearity and model fitting, we restricted the traits that were included in the Genomic SEMs to the following internalizing phenotypes: major depressive disorder, PTSD and anxiety disorder, and to the following externalizing phenotypes: risk-taking and childhood aggression. ADHD and antisocial behaviour were excluded from the models as they had high genetic correlations with childhood aggression, which indicated an overlap in variance ranging from very high to unity (specifically, a variance overlap in a range of 89% to 100% of variance). Nevertheless, since these phenotypes were of interest to our study, we evaluated them individually in relation to their associations with other traits and as PRSs in subsequent analyses.

After estimating a single *p* factor model with Genomic SEM, we attempted to fit a higher-order *p* factor model based on the same traits/disorders included in the single *p* factor model. In the higher-order model, the *p* factor would index shared variance between a latent internalising and a latent externalising psychopathology factor. Finally, we aimed to estimate a bifactor model, in which the *p* factor indexing shared variance across all examined traits/disorders is accompanied by orthogonal domains that index internalizing and externalizing psychopathology.

However, higher-order and bifactor models did not converge due to negative loadings for externalizing traits and for the externalizing factors. Since the single common *p* factor model showed adequate model fit, as described in the Results, and since the estimates associated with this model were theoretically plausible, the single common *p* factor model was taken forward for the remaining analyses. Once this model was estimated with Genomic SEM, a multivariate genome-wide association analysis

was conducted for the latent *p* factor extracted from this model, which allowed to estimate SNP associations with the *p* factor. This analysis was done with the use of Genomic SEM, and it used the SNPs available in the HapMap 3 Consortium consensus set (International HapMap 3 Consortium, 2010) to generate summary statistics that contained association results between SNPs and the latent *p* factor.

Calculation of Polygenic Risk Scores. Psychopathology PRSs were calculated on an individual level in the ALSPAC sample by using PRSice-2 (Euesden et al., 2015). The base data for the calculation of PRSs consisted of summary statistics for internalizing and externalizing traits/disorders that were previously mentioned (major depressive disorder, PTSD, anxiety disorder, ADHD, risk-taking, antisocial behaviour and childhood aggression) and of summary statistics for the *p* factor that were previously generated with Genomic SEM. The target data for the PRS calculation consisted of the ALSPAC sample, which was independent from the samples used to calculate the GWAS summary statistics. Clumping parameters were set to $r^2 > 0.25$ over 250 kb sliding windows to obtain SNPs in linkage equilibrium, and PRSs were calculated at a GWAS *p* value threshold of 1 (i.e. the weightings of all available SNPs in the summary statistics were included in the PRS calculation). The PRSs were adjusted for the first 11 genetic principal components, in order to account for population structure.

Step 2: Longitudinal Trajectories of Psychopathology Symptoms. We estimated the latent structure and longitudinal trajectories of internalizing and externalizing symptoms of psychopathology in the ALSPAC sample, with the use of a SEM framework. In line with our pre-registered analyses, we planned on using a "factors of curves" model (McArdle, 1988) to evaluate symptom changes over time for the *p* factor. This model allows to assess whether higher-order "causes" or factors can account for associations among lower-order developmental trajectories (e.g. longitudinal trajectories of internalizing and externalizing symptoms).

To estimate a factor of curves model, latent growth curve models for each category of psychopathology symptoms (generalised anxiety, depression, PTSD, inattention, hyperactivity/impulsivity, CD and ODD) through ages 7, 10 and 13 were estimated. Latent indicators of baseline levels and of longitudinal trajectories in psychopathology symptoms would be obtained through these models.

Latent growth curve modelling is an application of SEM, and it allows to analyse means from repeated measures to characterize the change over time for a variable in a given sample (T. E. Duncan & Duncan, 2004). In a latent growth curve model, change is modelled as a function of time and it is represented by latent variables that are estimated based on individual-level data. These variables are referred to as growth factors, and they consist of a latent intercept, which represents the baseline levels of a variable, and a latent slope, which represents the change of the variable over time (Felt et al., 2017). Growth factors provide an estimate of the average trajectory and individual variation around that trajectory over time, and model fit indices can be obtained to determine if the latent growth curve model provides an adequate fit to the longitudinal data at hand (T. E. Duncan & Duncan, 2004).

After estimating growth factors for each category of psychopathology symptoms, the organization of these growth factors into higher-order factor structures (both in terms of their intercepts and slopes) would then be evaluated; specifically, the organization of the growth factors into a single common *p factor*, a higher-order *p factor* model and a bifactor model would be assessed. Finally, baseline levels and trajectories of individual symptom categories and of the best-fitting *p* factor model would be used to analyse their associations with the previously calculated PRSs.

Latent growth curve modelling was carried out with the *lavaan* package for R (Rosseel, 2012). Full information maximum likelihood estimation (Enders & Bandalos, 2001) was used for the analysis, which allowed to estimate parameters for the growth curve models using all available data from ALSPAC participants, including participants who had missing data for some of the examined timepoints. The intercept loadings for the latent growth curve models were all set to 1 to define baseline scores, and slope loadings to describe a linear change over time were set to 0, 3 and 6, respectively, in order to represent the time interval between measures.

Once latent growth curve models were estimated for psychopathology symptoms in the ALSPAC sample, some of the externalizing symptoms were observed to have differing slopes (i.e. some increased over time, others decreased over time). Due to these different slopes, the modelling of intercepts and slopes into an externalizing factor did not converge, and a factor-of-curves could therefore not be properly fit to the data. Consequently, the rest of the analyses for this study were done on the intercepts and slopes of individual psychopathology symptoms.

Step 3: Associations Between PRSs and Psychopathology Symptoms. The *p* factor PRS and the individual-trait PRSs were used as predictors for each of the intercepts and slopes of the examined psychopathology symptoms, in order to examine associations between the PRSs and the symptoms. This analysis was done by individually entering each PRS as a regressor in the latent growth curve models. In order to evaluate the differences in predictive value between the *p* factor PRSs and individual PRSs, we compared their associations with psychopathology symptoms with the use of Williams's Test. This test allows to evaluate if two dependent correlations (i.e. correlations that share one variable) are significantly different from each other. In more detail, factor scores corresponding to the intercepts and slopes of the psychopathology symptoms were extracted from the latent growth curve analysis, and the correlations of these factor scores with the single *p* factor PRSs were compared with the correlations of factor scores with single-trait PRSs via Williams's Tests. We used the *psych* package for R (*Psych*, 2017) to carry out these tests.

The associations between PRSs and psychopathology symptoms, and the differences in dependent correlations, were considered significant at a p value < 0.05, which was corrected for multiple comparisons with the use of the False Discovery Rate (FDR) (Benjamini & Hochberg, 1995). The latent growth curve analysis that examined associations between PRSs and psychopathology symptoms involved 112 tests: eight PRSs x two latent variables (i.e. intercept and slope) x seven psychopathology symptom categories. The Williams's Tests that assessed differences in dependent correlations (i.e. *p* factor PRS-symptom associations vs individual PRSs-symptom associations) involved 98 tests: seven PRSs x two latent variables (i.e. intercept and slope) x seven psychopathology symptom categories. Psychopathology symptoms were adjusted for sex and within-wave age in all performed tests.

Sensitivity Analyses. We performed a sensitivity analysis to evaluate the influence of child IQ, financial difficulties and exposure to stressful life events (SLE's) on the associations between the PRSs and the psychopathology symptoms. Child IQ was evaluated in ALSPAC participants at 8 years of age with the use of the Wechsler Intelligence Scale for Children, 3rd UK edition (Wechsler, 1991). The presence of financial difficulties was self-reported by mothers when children were 2 to 4 years old, based on a questionnaire on difficulties to afford food, heating, clothing, rent/mortgage and things for the child. In turn, exposure to SLE's was evaluated with the use of a life event questionnaire that was completed by mothers when children were aged 11 years

old (Jensen et al., 2015). A sum score for the exposure to SLE's was computed by summing the scores from 33 items in this questionnaire that reflected negative life events, including events related to interpersonal loss, abuse and family instability. Information about the specific items included in this questionnaire is available in the Appendix.

To carry out this sensitivity analysis, we regressed scores for child IQ, financial difficulties and the sum score for exposure to SLE's on the intercepts and slopes of the latent growth curves. As in the main analyses, we corrected *p* values for multiple comparisons with the use of FDR. This involved 112 tests: eight PRSs x two latent variables (i.e. intercept and slope) x seven psychopathology symptom categories.

3 RESULTS

3.1 Study 1 Results

The sample for this study comprised 91,629 white British participants with complete data (53% females, mean age at recruitment [SD] = 57.33 [7.89]).

3.1.1 Step 1: Associations Between Mental Health Symptoms and Urban Environment

The results from the sCCA revealed a significant association between a set of mental health symptoms and a set of urban environment measures (r = 0.12, n = 73,304, $p < 0.001$). The set of mental health symptoms was composed of four symptoms predominantly related to depression, including feelings of unenthusiasm and disinterest, fed up feelings, loneliness and tiredness and lethargy, as shown in Figure 3.1. The model was also significant when it was applied to the test dataset (r = 0.11, n = 18,325, $p < 0.001$).

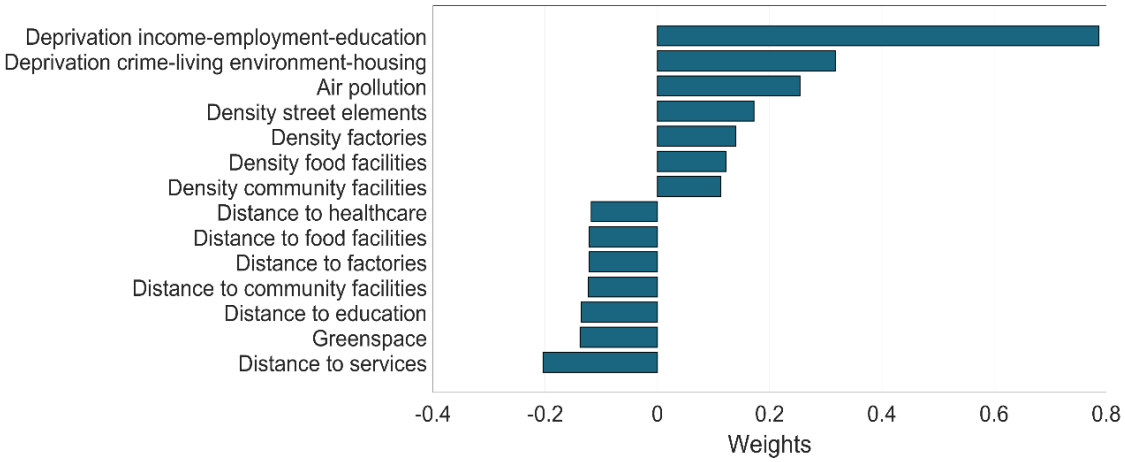
Figure 3.1. Set of mental health symptoms significantly associated with urban environment measures in the UK Biobank sample.

Note. Bars show canonical weights resulting from the sCCA.

The set of depressive symptoms was positively associated with measures of neighbourhood socioeconomic deprivation, air pollution and with the density of various facilities and urban elements (including street elements and factories) (Figure 3.2). In turn, this set of symptoms was negatively associated with measures of greenspace and with the distance to various facilities (which included food facilities, community facilities and education spaces). Among the identified urban environment measures, deprivation related to income, employment and education was found to have the strongest association with depressive symptoms, followed by deprivation related to crime, living environment and housing, and by air pollution and greenspace measures.

Identified associations indicate that higher levels of depressive symptoms are linked to living in environments with higher socioeconomic deprivation, higher air pollution, and higher density of urban facilities, while higher levels of greenspace and of distance to facilities are linked to lower levels of depressive symptoms.

Figure 3.2. Set of urban environment measures significantly associated with mental health symptoms in the UK Biobank sample.

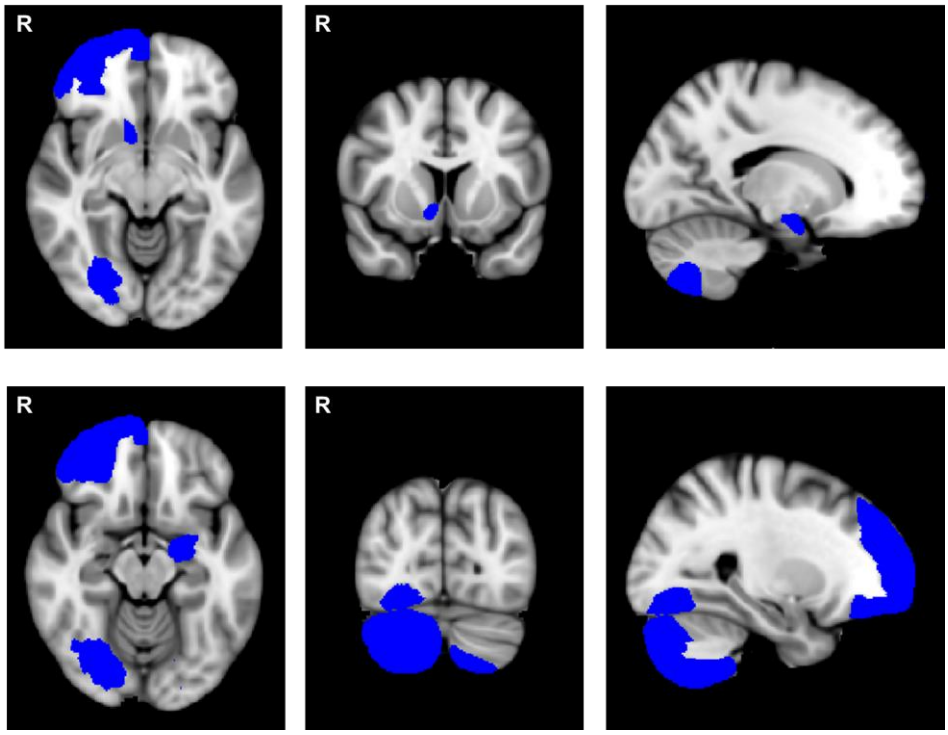


Note. Bars show canonical weights resulting from the sCCA.

3.1.2 Step 2: Associations of Brain Volume with Mental Health and Urban Environment

A significant association was found between a set of 11 brain volumes, the weighted set of depressive symptoms and the weighted set of urban environment measures that were previously identified (r = 0.05, n = 6,014, p = 0.01). This set of brain volumes included unilateral and bilateral cerebellar lobules that spanned lobules VIIIa, VIIb and VIIIa, as well as the cerebellum crus. The brain volume set also included the right frontal pole, the right occipital fusiform gyrus, the left amygdala and the right accumbens (see Figure 3.3).

Figure 3.3. Brain volumes simultaneously associated with depressive symptoms and with 'depression-related' urban environment features.



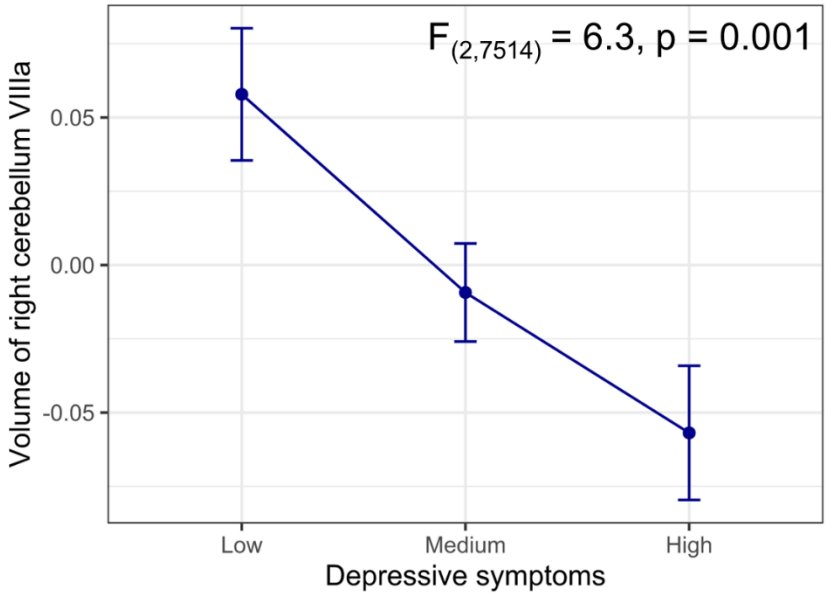
The negative weights identified for all brain areas in the set (see Table 3.1) indicate that a lower grey matter volume in these areas was associated with a higher degree of depressive symptoms and of 'depression-related' urban environment features.

Table 3.1. msCCA weights for brain volumes associated with depressive symptoms and with 'depression-related' urban environment features.

Brain area	Weight
Right Cerebellum VIIIa	-0.438
Right Cerebellum VIIb	-0.332
Right Cerebellum VIIIb	-0.328
Right Crus I Cerebellum	-0.319
Left Cerebellum VIIIa	-0.296
Right Crus II Cerebellum	-0.287
Left Amygdala	-0.278
Left Cerebellum VIIb	-0.256
Right Accumbens	-0.246
Right Occipital Fusiform Gyrus	-0.242
Right Frontal Pole	-0.239

The negative association between these brain areas and depressive symptoms is illustrated in Figure 3.4, which shows the average right cerebellum VIIIa volume in participants with low, medium and high levels of depressive symptoms. The msCCA model also showed to be significant when applied to the test dataset (r = 0.04, n = 1,503, p = 0.02).

Figure 3.4. Associations between volume of right cerebellum VIII and depression symptoms.



Note. Dots and bars represent means and standard errors, respectively, of right cerebellum VIIIa volume in participants with low, medium and high levels of depressive symptoms.

3.2 Study 2 Results

The sample for this study consisted of 77,650 white British participants with complete data (53% females, mean age at recruitment [SD] = 56.48 [7.52]). The labels assigned to each node included in the evaluated networks, as well as item frequencies, can be observed in Table 3.2 (Garcia-Mondragon et al., 2022, p. 4).

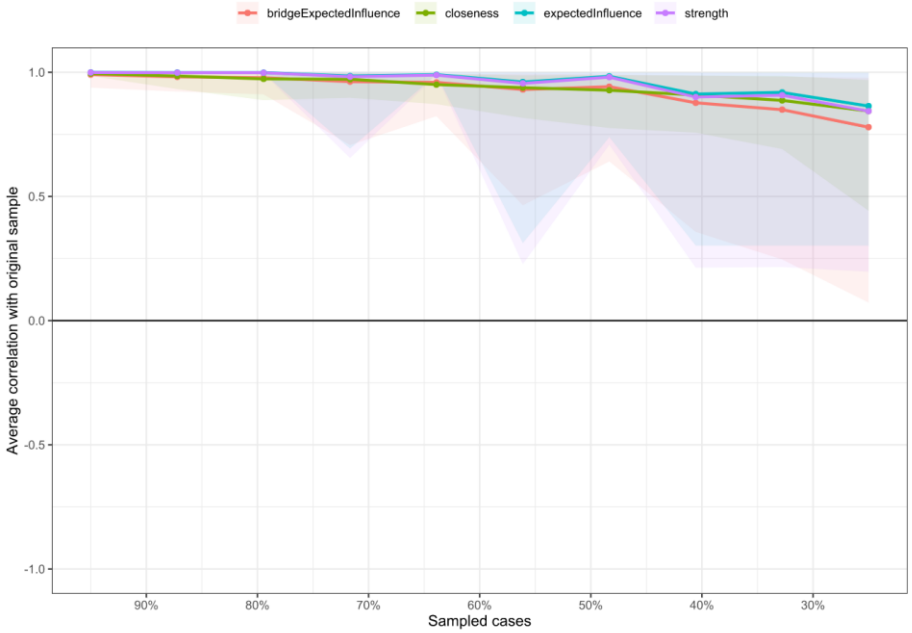
Table 3.2. Labels, descriptions and item frequencies for nodes included in symptom networks.

Node	Description	Item frequency (percentage)
Sad	Feelings of sadness or depression	31,489 (40.6%)
Anh	Anhedonia	23,170 (29.8%)
Wor	Feelings of worthlessness	16,548 (21.3%)
Tir	Feelings of tiredness	26,402 (34.0%)
Sle	Sleep changes	25,819 (33.3%)
Wei	Weight change	19,702 (25.4%)
Dea	Thoughts of death	17,374 (22.4%)
Cnc	Difficulty concentrating	25,289 (32.6%)
Dei	Depression impairment	23,009 (29.6%)
Con	Beliefs in unreal conspiracy against self	467 (0.6%)
Com	Beliefs in unreal communications or signs	435 (0.6%)
Voi	Hearing unreal voices	1,043 (1.3%)
Vis	Seeing unreal visions	2,075 (2.7%)
Psi	Psychosis impairment	951 (1.2%)
Trau	Cumulative trauma	23,346 (30.1%)
IMD	Index of Multiple Deprivation	19,429 (25.0%)
Pol	Air pollution	19,415 (25.0%)
Gre	Greenspace	19,416 (25.0%)
PRd	Depression PRS	19,442 (25.0%)
PRs	Schizophrenia PRS	19,484 (25.1%)

Note. Total N = 77,650. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, p. 4. CC BY-NC.

Case-dropping bootstrapped centrality indices for the Step 1 and the Step 2 networks were highly stable and therefore reliable. In more detail, for the Step 1 network, correlation stability (CS) coefficients were equal to 0.75 for betweenness, 0.75 for closeness, 0.75 for strength, 0.75 for expected influence and 0.67 for bridge expected influence (see Figure 3.5).

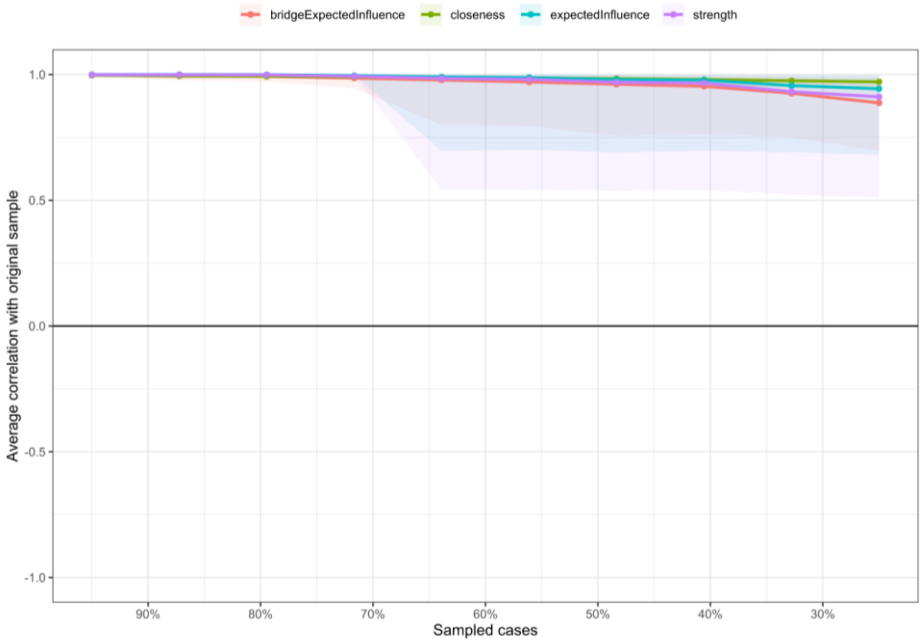
Figure 3.5. Case-dropping bootstrapped centrality indices for Step 1 network.



Note. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, Supplementary Materials. CC BY-NC.

For the Step 2 network, CS coefficients were equal to 0.59 for betweenness, 0.44 for closeness, 0.44 for strength, 0.59 for expected influence and 0.75 for bridge expected influence (see Figure 3.6).

Figure 3.6. Case-dropping bootstrapped centrality indices for Step 2 network.



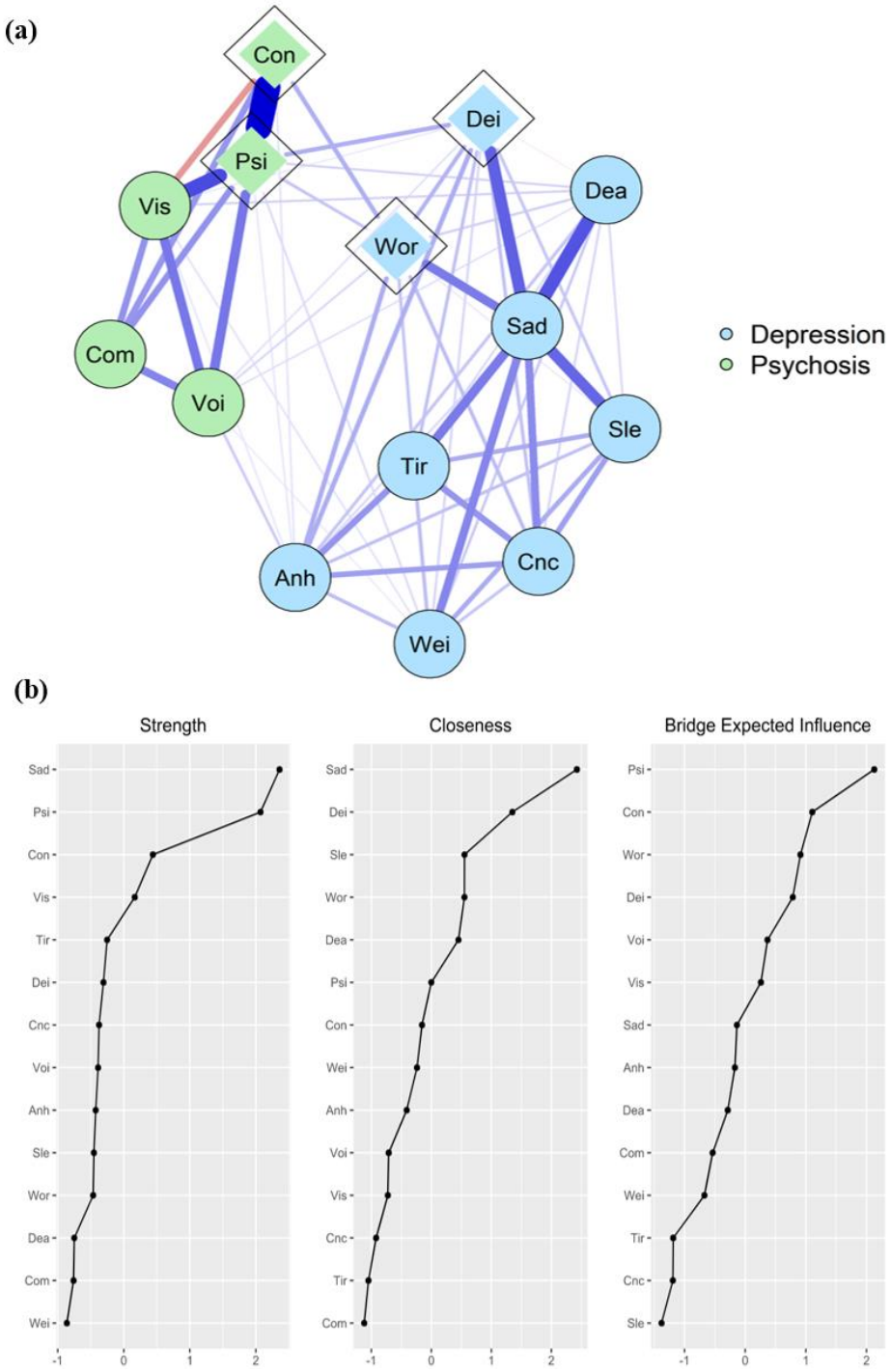
Note. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, Supplementary Materials. CC BY-NC.

In turn, edge weight accuracy tests showed overall narrow confidence intervals that indicated a generally stable estimation of edge weights for both networks (see Figure A.1 and Figure A.2 in the Appendix). Edges that were present in at least 70% of the bootstrapped samples can be found in Table A.5. in the Appendix. These are the only edges that are reported in the present study.

3.2.1 Step 1: Depression-Psychosis Symptom Network

Symptoms and associations within communities. Symptoms of depression were shown to be strongly connected to each other, while symptoms of psychosis were also strongly associated with each other. The symptom with the highest node strength and the highest closeness across the whole network was *feelings of sadness or depression* (see Figure 3.7; Garcia-Mondragon et al., 2022, p. 5). This result indicates that *feelings of sadness or depression* could activate large sections of the symptom network; this symptom had strong connections with most symptoms of depression. Relatedly, the strongest connection of *depression impairment* was with *feelings of sadness or depression*. The *depression impairment* node was also strongly linked with *anhedonia* and with *psychosis impairment*. As for the community of symptoms of psychosis, *psychosis impairment* emerged as the most central node, which had a high node strength and strong associations with symptoms of psychosis. The strongest link of this node was with *beliefs in unreal conspiracy against self*. Most of the edges in the symptom network had positive weights, which indicates a predominance of positive relationships between symptoms.

Figure 3.7. Symptom network in the UK Biobank sample, including symptoms of depression and psychosis.



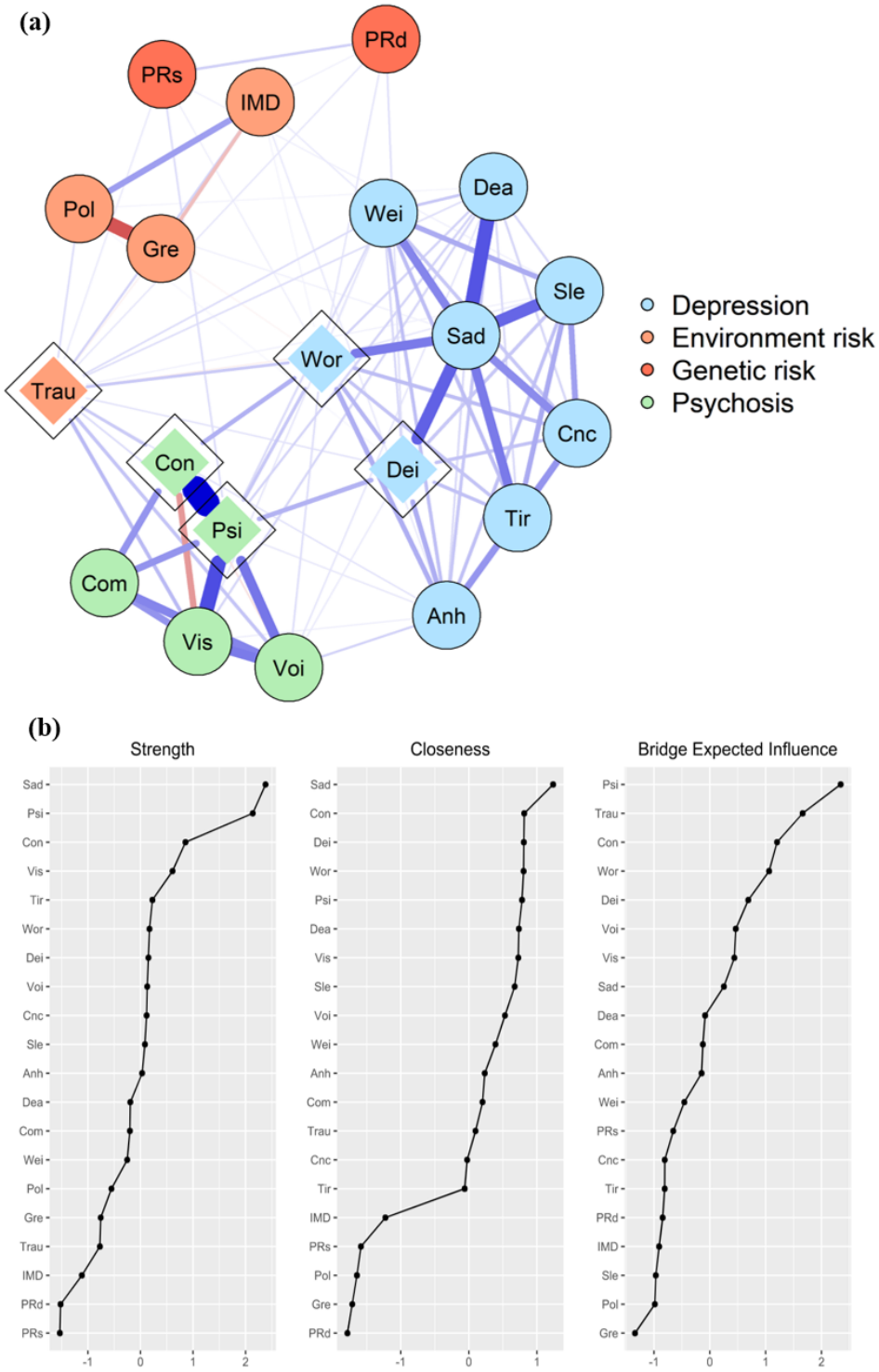
(a) Symptom network of depression symptoms (in blue) and psychosis symptoms (in green). Bridge nodes are shown with a diamond shape. Line thickness reflects the degree of (partial) correlations between nodes. Blue lines depict positive associations, while red lines depict negative associations. **(b)** Indices of centrality and of bridge expected influence for Step 1 network. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, p. 5. CC BY-NC.

Associations between communities: bridge nodes. As seen in Figure 3.7, four nodes were identified as bridge nodes that connected depression and psychosis symptoms: *feelings of worthlessness*, *beliefs in unreal conspiracy against self*, *depression impairment* and *psychosis impairment*. *Feelings of worthlessness* and *beliefs in unreal conspiracy against self* had strong associations with each other, while *depression impairment* and *psychosis impairment* were strongly linked to each other.

3.2.2 Step 2: Interplay of Environmental and Genetic Risk Factors with Symptom Network

As seen in Figure 3.8 (Garcia-Mondragon et al., 2022, p. 6), the incorporation of environmental and genetic risk factors to the symptom network did not lead to changes in associations between symptoms of depression and psychosis. Rather, the addition of risk factors revealed associations between these factors and symptoms.

Figure 3.8. Symptom network in the UK Biobank sample, including symptoms of depression and psychosis, genetic risk factors and environmental risk factors.



(a) Symptom network of depression symptoms (in blue), psychosis symptoms (in green), genetic risk factors (in red) and environmental risk factors (in orange). Bridge nodes are shown with a diamond shape. Line thickness reflects the degree of (partial) correlations between nodes. Blue lines depict positive associations, while red lines depict negative associations. **(b)** Indices of centrality and of bridge expected influence for Step 2 network. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, p. 6. CC BY-NC.

Environmental risk factors. *Cumulative trauma,* which was examined as a proximal environmental risk factor, had a strong positive association with *neighbourhood deprivation* and a positive relationship with *air pollution,* along with a weak and negative association with *greenspace percentage*. As expected, distal environmental risk factors (i.e. the urbanicity factors) were closely related to each other: *neighbourhood deprivation* had a strong and positive link with *air pollution*, and greenspace percentage had negative associations with *neighbourhood deprivation* and with *air pollution*. As for centrality indices of strength and closeness, environmental risk factors were located midway between symptom nodes, which continued to be strongly linked to each other, and PRSs.

Out of the examined environmental risk factors, *cumulative trauma* had the highest number of links with depression and psychosis symptoms. This risk factor was particularly associated with the following symptoms of psychosis: *seeing unreal visions*, *hearing unreal voices*, and *beliefs in unreal conspiracy against self*, and its strongest link with depression symptoms was with *feelings of worthlessness*. Weaker associations for *cumulative trauma* were also observed with *depression impairment* and with *psychosis impairment.* Among the distal environmental risk factors, *neighbourhood deprivation* displayed stronger associations with symptoms of depression, followed in strength by *air pollution*. *Greenspace percentage* did not have any notable links with symptoms of depression or psychosis, which was in line with its observed low centrality indices.

Genetic risk factors. The *depression PRS* and the *schizophrenia PRS* were linked with each other, and they displayed sparse relationships with the rest of the network. The PRSs had low centrality indices in terms of strength and closeness, which indicates that these risk factors had a small influence on the symptom network overall. The *depression PRS* showed an association with *depression impairment*; similarly, the *schizophrenia PRS* was linked with *psychosis impairment*. Both PRSs had weak associations with *cumulative trauma* and with *feelings of worthlessness*; the *depression PRS* showed slightly stronger associations with these nodes compared to the *schizophrenia PRS*. The *depression PRS* also had a weak link with *neighbourhood deprivation*.

Bridge nodes. With the addition of environmental and genetic risk factors to the symptom network, *cumulative trauma* emerged as a new bridge node that predominantly linked symptoms of depression and symptoms of psychosis. Particularly,

cumulative trauma linked to *feelings of worthlessness* and *beliefs in unreal conspiracy*, which had been identified as bridge symptoms in Step 1. The four nodes that were identified as bridge symptoms in Step 1 remained as bridges in Step 2; this included *feelings of worthlessness*, *beliefs in unreal conspiracy against self*, *depression impairment* and *psychosis impairment*. As can be seen in Figure 3.8, *cumulative trauma* had the second highest bridge expected influence, falling just below *psychosis impairment*.

3.2.3 Sensitivity Analyses

To evaluate the possibility that an imbalanced rate of presence/absence of psychosis symptoms in the sample could impact network results, symptom networks were recalculated in a down-sampled cohort based on the presence of psychosis symptoms (n = 6,222). This recalculated network led to the same pattern of results observed for the original sample; identified bridge nodes remained the same, and most of the network edges observed in the original sample remained. The only exception to this were two edges that were not present in the down-sampled cohort, specifically associations of the *schizophrenia PRS* with *cumulative trauma* and with *feelings of worthlessness*. Visualizations of the down-sampled networks and their centrality estimates are presented in Figure A.3 and Figure A.4 in the Appendix.

Finally, the Step 2 MGM network recalculated with genetic and environmental risk factors in their continuous scale produced the same pattern of results as the original Step 2 network, which was calculated on binary measures. Identified bridge nodes remained the same, along with most of the network edges observed in the original network. Detailed results for this network can be found in Table A.5 and Table A.6 in the Appendix.

3.3 Study 3 Results

The sample for this study included 6,339 participants (50.8% females) who had genetic and psychopathology data available for at least one time point. Table 3.3 shows descriptive statistics for the measures included in the main analyses. Measures for IQ (M = 105.5; SD = 16.29, range = 45 - 151), financial difficulties (M = 0.09, SD = 0.29, range = 0 - 1) and stressful life events (M = 2.95, SD = 2.68, range = 0 - 21) were used in sensitivity analyses.

Table 3.3. Descriptive statistics of psychopathology symptoms examined in the ALSPAC sample.

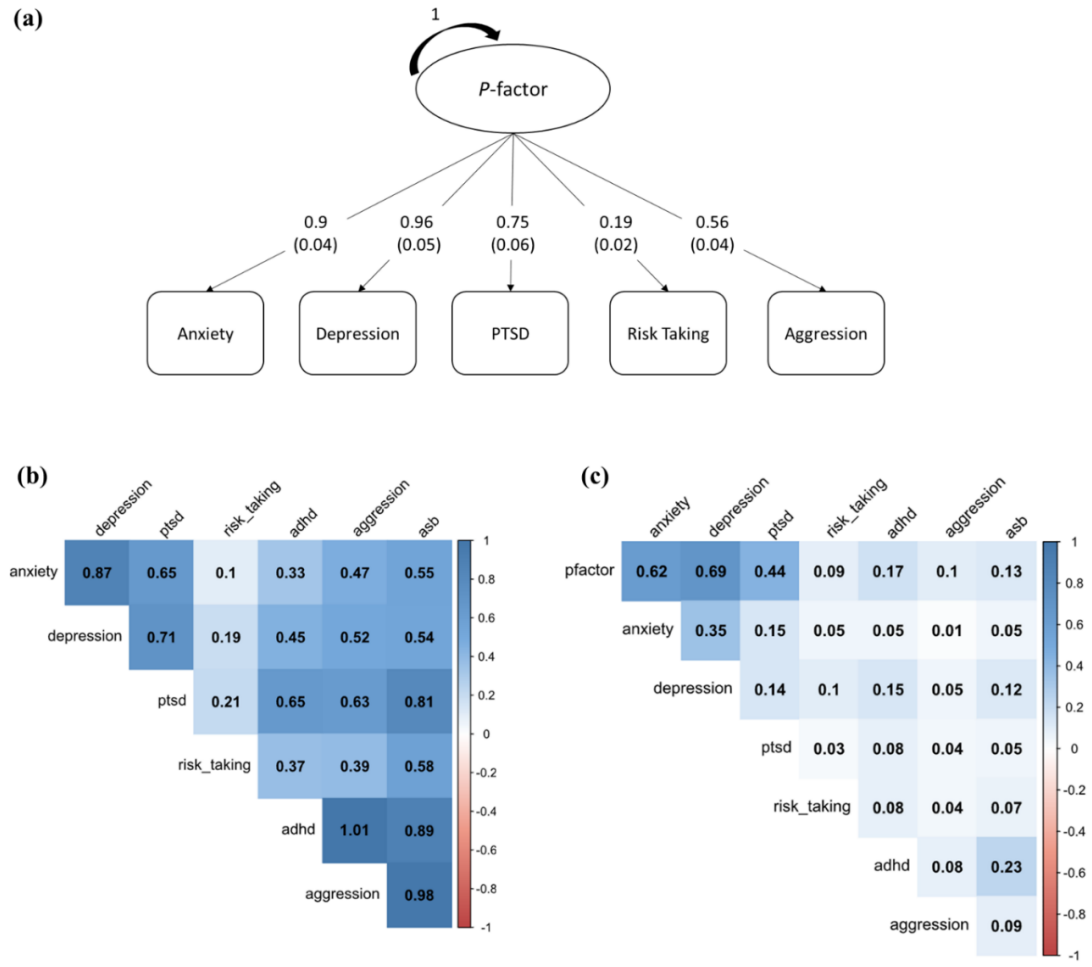
	Age 7	**Age 10**	**Age 13**
	M (SD), range	M (SD), range	M (SD), range
Anxiety	9.99 (2.26), 8 - 23	10.67 (2.69), 8 - 22	10.37 (2.63), 8 - 23
Depression	12.48 (1.33), 12 - 23	12.52 (1.42), 12 - 23	12.59 (1.61), 12 - 24
PTSD	14.48 (1.79). 14 -35	14.58 (2.02), 14 -38	14.64 (2.14), 14-35
Impulsivity	11.4 (3.58), 9 - 27	10.83 (3.2), 9 -27	10.39 (2.77), 9 -27
Inattention	11.45 (3.69), 9 -27	11.65 (3.84), 9 -27	11.61 (3.89) - 9 -27
ODD	12.06 (3.16), 10 - 30	11.89 (3.1), 10 - 30	11.61 (2.9), 10 - 30
CD	7.55 (1.03), 7 - 17	7.47 (0.98), 7 - 19	7.57 (1.26). 7 - 21

Note. M = mean, SD = standard deviation, ODD = oppositional defiant disorder, CD = conduct disorder.

3.3.1 Step 1: Genomic SEM For the *P* Factor and Calculation of PRSs

Figure 3.9 presents the structure of the single *p* factor model estimated with Genomic SEM. Model fit for the single *p* factor was adequate (Akaike Information Criterion (AIC) = 84.75, CFI = 0.958, SRMR = 0.094). Standardized estimates for this model, which can be observed in Figure 3.9, showed that internalizing traits loaded strongly onto the genetic *p* factor, with the highest loadings observed for depression (standardized loading = 0.96) and anxiety (standardized loading = 0.9).

Figure 3.9. Genomic SEM for single *p* factor model and PRSs in the ALSPAC sample.



(a) Standardized estimates for single *p factor* Genomic SEM. SEs are shown in parentheses. **(b)** Genetic correlations among psychopathological traits. **(c)** Correlations between PRSs in ALSPAC. *Note.* Asb = antisocial behaviour.

Genetic correlations between psychopathology traits that were included in the Genomic SEMs are shown in Figure 3.9. Correlations between PRSs for these traits and for the *p* factor, which were calculated in the ALSPAC sample, are also shown in Figure 3.9. In line with observed standardized estimates for the single *p* factor model, PRSs for the *p* factor had strong associations with PRSs for internalizing traits (particularly with depression and anxiety PRSs; r = 0.69 and r = 0.62, respectively), and weaker associations with PRSs for externalizing traits (PRSs correlations ranged from 0.09 – 0.17). PRSs for internalizing traits had stronger associations with each other than the PRSs for externalizing traits had with each other. In general, PRSs for externalizing traits had low correlations with each other (except for a moderate correlation between the PRS for ADHD and the PRS for antisocial behaviour; r = 0.23), and they also had low correlations with internalizing PRSs.

3.3.2 Step 2: Longitudinal Trajectories of Psychopathology Symptoms

Univariate latent growth curves for the seven examined categories of psychopathology symptoms showed overall acceptable model fit for linear trajectories. Model fit statistics for the latent growth curves of all evaluated symptoms can be found in Table 3.4, along with their corresponding mean estimates. For all internalizing symptoms, the fitted latent growth curves showed significant increases in symptom levels over time: depression scores increased at a rate of 0.02 units per year ($p < 0.001$), while anxiety scores increased at a rate of 0.08 units per year ($p < 0.001$) and PTSD scores increased at a rate of 0.03 units per year ($p < 0.001$). Among externalizing symptoms, inattention symptoms showed a significant increase over time, at a rate of 0.04 units per year ($p < 0.001$), while two of the externalizing symptoms showed significant decreases over time: symptoms of hyperactivity/impulsivity decreased at a rate of 0.16 units per year ($p < 0.001$), and symptoms of ODD decreased at a rate of 0.06 units per year ($p = < 0.001$). Symptoms of CD were the only symptom category that showed no significant change in symptom levels over time, with $p = 0.3$.

Table 3.4. Latent growth curve models of psychopathology symptoms: model fit statistics and mean estimates of parameters.

	RMSEA	CFI	SRMR	TLI	Parameter	Estimate	Std. error	*p* value
Anxiety	0.19	0.91	0.05	0.74	Intercept	10.07	0.03	<0.001*
					Slope	0.08	0.01	<0.001*
Depression	0.00	1.00	0.00	1.00	Intercept	12.48	0.02	<0.001*
					Slope	0.02	0.00	<0.001*
PTSD	0.00	1.00	0.00	1.00	Intercept	14.50	0.02	<0.001*
					Slope	0.03	0.01	<0.001*
Impulsivity	0.03	1.00	0.01	1.00	Intercept	11.42	0.05	<0.001*
					Slope	-0.16	0.01	<0.001*
Inattention	0.04	1.00	0.01	1.00	Intercept	11.52	0.05	<0.001*
					Slope	0.04	0.01	<0.001*
ODD	0.00	1.00	0.00	1.00	Intercept	12.08	0.04	<0.001*
					Slope	-0.06	0.01	<0.001*
CD	0.09	0.97	0.03	0.92	Intercept	7.53	0.01	<0.001*
					Slope	0.00	0.00	0.34

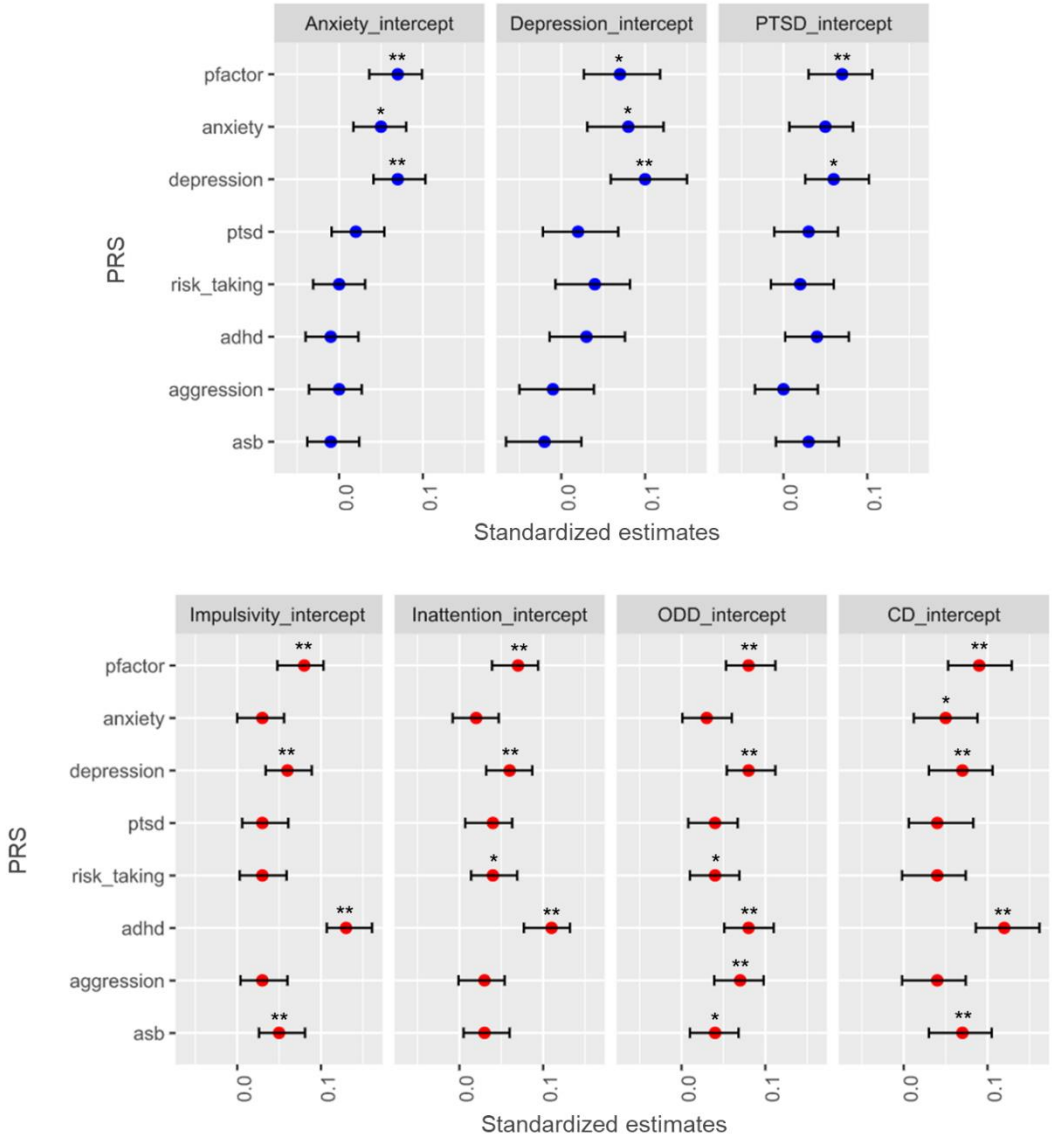
Note. * represents $p < 0.05$ (FDR corrected). ODD = oppositional defiant disorder, CD = conduct disorder, RMSEA = Root Mean Square Error of Approximation, CFI = Comparative Fit Index, SRMR = Standardized Root Mean Square, TLI = Tucker-Lewis Index.

3.3.3 Step 3: Associations Between PRSs and Psychopathology Symptoms

In terms of associations between PRSs and baseline levels (i.e. intercepts) of psychopathology symptoms in the ALSPAC sample, the *p* factor PRS and the depression PRS showed significant relationships with baseline levels of all examined symptoms (see Figure 3.10 and Table A.7 in the Appendix). In turn, the anxiety PRS had significant associations with baseline levels of depression, anxiety and CD (β = standardised regression coefficients; $\beta_{depression}$ = 0.08, p = 0.01; $\beta_{anxiety}$ = 0.05, p = 0.01; β_{CD} = 0.05, p = 0.04), and the PTSD PRS showed no significant associations with baseline levels of psychopathology symptoms. In terms of PRSs for externalizing traits, the ADHD PRS was significantly associated with baseline levels of all externalizing symptoms ($\beta_{hyperactivity/impulsivity}$ = 0.13, p < 0.001; $\beta_{inattention}$ = 0.11, p < 0.001; β_{ODD} = 0.08, p < 0.001; β_{CD} = 0.12, p < 0.001), and the antisocial behaviour PRS was significantly associated with baseline levels of most externalizing symptoms (hyperactivity/impulsivity, ODD and CD), except for inattention. Finally, the risk-taking PRS had significant associations with baseline levels of inattention (β = 0.04, p = 0.01) and ODD (β = 0.04, p = 0.03), and the aggression PRS was significantly related to baseline levels of ODD (β = 0.07, p = < 0.001).

Conversely, there were very few significant associations between PRSs and the trajectories (i.e. slopes) of psychopathology symptoms in the ALSPAC sample, and these associations were observed only for externalizing symptoms (see Table A.7 in the Appendix). In more detail, the *p* factor PRS and the ADHD PRS were the only PRSs that were significantly related to the impulsivity linear trajectory ($\beta_{p\text{-}factor}$ = -0.06 p = 0.01; β_{ADHD} = -0.06 p = 0.01).

Figure 3.10. Regression coefficients of PRSs on baseline levels of psychopathology symptoms.



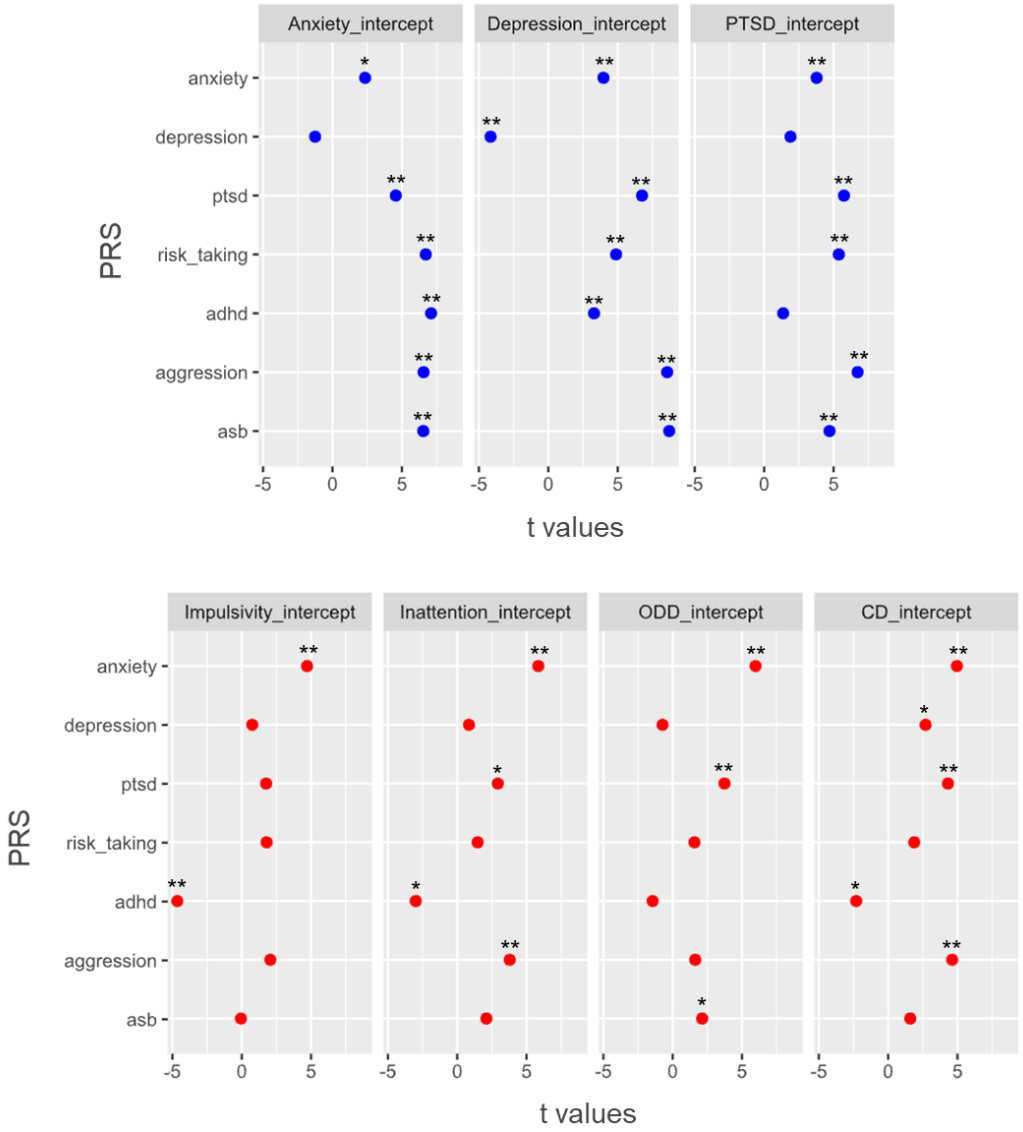
Note. Associations are corrected for age and sex. * represents p < 0.05, ** represents p < 0.001 (FDR corrected). Error bars indicate 95% confidence intervals. Asb = antisocial behaviour, ODD = oppositional defiant disorder, CD = conduct disorder.

Lastly, we present results from Williams's test, which were carried out to evaluate the predictive value of the *p* factor PRS compared with single-trait PRSs, in relation to baseline levels and trajectories of psychopathology symptoms. For internalizing symptoms, the *p* factor PRS was found to be significantly more strongly associated with baseline levels of all examined symptoms (anxiety, depression and PTSD) compared with the PTSD PRS and with most of the single-trait externalizing PRSs. The *p* factor PRS was also significantly more strongly linked with baseline levels of depression and PTSD when compared with the anxiety PRS.

However, there were a few notable exceptions to the observed predictive superiority by the *p* factor PRS. Firstly, the *p* factor PRS was not significantly different from the anxiety PRS in its prediction of anxiety baseline levels. Secondly, the *p* factor PRS was not significantly different from the depression PRS in its prediction of the majority of psychopathology symptom baseline levels, including anxiety, PTSD, impulsivity, inattention and ODD. Moreover, the depression PRS was found to provide a significantly stronger prediction of depression baseline levels, compared with the *p* factor PRS.

As for externalizing symptoms, the *p* factor PRS was significantly more strongly associated with baseline levels of all evaluated symptoms (impulsivity, inattention, ODD and CD symptoms) when it was compared with the anxiety PRS. The *p* factor PRS was also significantly more strongly related to baseline levels of inattention, ODD and CD when compared with the PTSD PRS. Moreover, the *p* factor PRS was significantly more strongly linked with baseline levels of CD compared with the depression PRS, and it was also significantly more strongly associated with baseline levels of inattention and CD when it was compared with the aggression PRS. However, the ADHD PRS showed significantly stronger associations with baseline levels of most externalizing symptoms (specifically, impulsivity, inattention and CD) when it was compared with the *p* factor PRS. These results can be visualized in Figure 3.11 and in Table A.8 in the Appendix.

Figure 3.11. Williams's tests: differences in predictive value between *p* factor PRS and single-trait PRSs for predicting baseline levels of psychopathology symptoms.



Note. Associations are corrected for age and sex. * p represents < 0.05, ** represents p < 0.001 (FDR corrected). Asb = antisocial behaviour, ODD = oppositional defiant disorder, CD = conduct disorder.

3.3.4 Sensitivity Analyses

The majority of identified associations between PRSs and psychopathology symptoms declined slightly, but remained, once the influence of IQ, financial difficulties and exposure to stressful events were taken into account in these associations (see Table A.9 in the Appendix). Nonetheless, some associations diverged from this general observation. In the case of associations between the *p* factor PRS and baseline levels of psychopathology symptoms, once the mentioned covariates were accounted for, the PRS was no longer significantly associated with baseline levels of

depression symptoms, nor with baseline levels of PTSD symptoms. The depression PRS was also no longer significantly linked with baseline levels of PTSD symptoms once the covariates were accounted for, hence none of the evaluated PRSs were significantly associated with PTSD symptoms anymore after accounting for the covariates. Symptoms of PTSD were the only symptom category that was not associated with any PRS once covariates were accounted for.

4 DISCUSSION

The present thesis used transdiagnostic approaches to psychopathology to evaluate 1) symptoms from a range of mental health categories, 2) environmental risk factors and 3) biological factors in large community samples, with the use of multivariate statistical methods. This research aimed to shed light on psychopathology and to identify mental health symptoms and risk factors that are associated with each other, and that could be used as targets for promoting mental health and preventing mental health difficulties.

The first study used a symptomics approach to uncover associations between a range of mental health symptoms and features in the urban environment, and to identify brain volume areas associated with these identified mental health symptoms and urban environment features. The second study applied network analysis to investigate the lifetime co-occurrence of symptoms of depression and psychosis, and the associations of these symptoms with environmental and genetic risk factors. The third study used a latent factor approach to 1) investigate the genetic structure of the *p* factor, 2) evaluate the relationship of this genetic *p* factor with baseline levels and trajectories of psychopathology symptoms in childhood and early adolescence, and 3) compare the predictive value of the genetic *p* factor with single-trait PRSs in its association with psychopathology symptoms.

Among the strengths of the studies included in this thesis, the sample size of the assessed community samples can be noted. The examination of large samples allowed for an unprecedent power to examine links between symptom, environmental and biological levels, and to detect small but significant and potentially relevant effects and associations. The evaluation of joint associations between mental health symptoms,

environmental and biological factors which characterized the studies in this thesis also represents a strength by itself, as it allowed a more holistic examination of psychopathology.

The richness of urban environment measures evaluated in the first study also deserves mention. This study allowed for a comprehensive examination of urban environment features in their association with mental health symptoms. This contrasts with the majority of previous empirical studies that examined a smaller set of urban environment measures in an isolated manner (Gao et al., 2017; Sarkar et al., 2018). Furthermore, the investigation of brain features involved in mental health-urban environment associations in this study allowed to gain insights within this largely unexplored area of research.

In turn, the second study included one of the largest community samples analysed in network studies thus far. There is only one other network study that we are aware of that evaluated associations between both genetic and environmental risk factors with psychopathology symptoms (van Loo et al., 2018). The study by van Loo and collaborators examined a much smaller sample and it used a methodology that could not directly reveal associations between symptoms and risk factors, as it relied on the comparison of symptom networks from samples with different levels of genetic predisposition and exposure to adversity.

Finally, for the third study, the ability to maximize information from available GWASs through the use of Genomic SEM can be noted as a strength, as it allowed to examine genetic correlations between a set of traits that would otherwise be complicated to assess in a single sample. Moreover, this study performed a comprehensive evaluation of associations between PRSs and psychopathology symptoms, which included direct comparisons of the predictive power of a *p* factor PRS against single-trait PRSs. These explicit comparisons were lacking in previous studies (Grotzinger et al., 2019), and they allowed to investigate whether the *p* factor PRS can significantly inform on the level and trajectories of psychopathology symptoms beyond the information that single-trait PRSs can provide.

In the remainder of this section, we discuss the findings of each study, followed by a general discussion that integrates results across these studies, as well as study limitations and future directions.

4.1 Study 1

This study examined associations between mental health symptoms, urban environment features and brain volume areas in a predominantly urban-based, middle-aged population cohort. Three main findings are discussed here. Firstly, among the symptoms of depression, mania and neuroticism that were examined, depression symptoms showed the strongest association with urban environment features.

In contrast with previous studies that considered psychopathology as a single entity when examining its link with the urban environment (e.g. through the use of sum scores or based on clinical diagnosis for specific disorders) (J. L. Wang, 2004; R. Wang et al., 2019; Weaver et al., 2015), the present study was able to uncover specific symptoms related to depression that were associated with specific elements in the urban environment. Specifically, a symptom profile consisting of feelings of unenthusiasm and disinterest, tiredness and lethargy, loneliness/isolation and fed-up feelings was linked to urban environment features in this study. Of note, these symptoms were all associated to a similar degree with the urban environment features. This finding is in agreement with previous studies that found a link between clinical depression and urbanicity (Generaal, Hoogendijk, et al., 2019; Wiens et al., 2017).

Secondly, among a comprehensive set of urban environment features that were assessed in this study, a profile of urban environment features composed of high neighbourhood deprivation, high air pollution, low access to greenspace areas and high density/proximity to a range of urban facilities (including factories, food and community facilities) was associated with the identified set of depression symptoms. In particular, neighbourhood deprivation related to economic factors (i.e. deprivation related to income and employment inequality) was the feature most strongly linked with the set of identified depression symptoms. This was followed by neighbourhood deprivation related to physical factors (including the quality of the living environment and housing), air pollution and access to greenspace.

The present study contrasts with previous research that examined urbanicity as a single entity in its associations with mental health; by evaluating a range of urban environment features and being able to identify the features with the strongest associations with mental health symptoms, the study corroborated and unified previously isolated findings relating to associations between specific elements of the urban environment and depression. For instance, previous studies identified links

between neighbourhood deprivation and depression symptoms (Cohen-Cline et al., 2018; Dowdall et al., 2017); the present study extended those findings by identifying specific aspects of neighbourhood deprivation that have stronger links to the experience of depression symptoms. Previous research has also identified links between higher neighbourhood greenness and a lower prevalence of major depression (Sarkar et al., 2018), and of links between air pollution and depressive symptomatology (Lim Youn-Hee et al., 2012; van den Bosch & Meyer-Lindenberg, 2019).

In line with the overall findings from this study, emerging research has found that the quality of socioeconomic and physical characteristics at the neighbourhood level, such as low socioeconomic status, air and noise pollution, are associated with the presence of depressive disorders, rather than urbanization level alone (Generaal, Timmermans, et al., 2019). The present study added knowledge to previous research by identifying a specific depression symptom profile associated with these urban environment features.

The third and most novel finding from this study relates to the identified set of brain features that were simultaneously associated with depression symptoms and urban environment features. Specifically, a decreased grey matter volume in the cerebellum, the frontal pole, the amygdala, the nucleus accumbens and the occipital fusiform gyrus was linked to depressive symptoms and to depression-related urban environment features. Cerebellum volume showed the strongest associations with the identified symptoms and urban environment features.

The role of the cerebellum has been traditionally linked to motor coordination and basic motor processing, but its involvement in higher-order cognitive and emotional processes is being increasingly recognized (Buckner, 2013; D'Angelo & Casali, 2013). Reduced grey matter in the cerebellum has also been recently found in a range of mental health disorders, including depressive disorder (Peng et al., 2011). The present study therefore added to existing knowledge by identifying a link between lower cerebellum volume, depression symptoms and a specific set of urban environment features in a community sample.

Moreover, several of the remaining brain areas that were found to be associated with depression symptoms and depression-related urban environment features have connections with the cerebellum, such as the prefrontal cortex (Buckner et al., 2011), which is part of the frontal pole and is involved in cognitive control, the amygdala

(Farley et al., 2016), which has a key role in emotional processing, and the nucleus accumbens, which is involved in reward processing (Blatt et al., 2013). Through its connections with the cerebral cortex, the cerebellum has been hypothesized to be in charge of integrating information, and of calculating mental models that represent future thoughts, action plans and emotions to guide behaviour (Romer et al., 2018). Structural and functional alterations in the cerebellum and connected brain areas might thus lead to an altered integration of information and calculation of mental models, which may impact on mental health.

Finally, for the case of the occipital fusiform gyrus, this brain area has mostly been associated with face detection and face processing (Rossion et al., 2003). However, recent findings have pointed to a decreased volume and to an altered function of this area in patients with depression; these results has been hypothesized to indicate alterations in social perception (J. S. Lee et al., 2021; Schmaal et al., 2017).

While the specific set of brain areas identified in this study is novel, results of this study are generally in line with previous studies that found a link between reduced volume in a range of brain areas and exposure to urban environments (Besteher et al., 2017; Haddad et al., 2015; Lammeyer et al., 2019). As previously mentioned, prolonged exposure to stress has been postulated as the main potential mechanism for associations between urbanicity and psychopathology; stress originating from distant sources such as the urban environment may thus have long-lasting effects on mental health and on the brain. This includes social stress, which is likely to be present in neighbourhoods characterized by socioeconomic deprivation.

Indeed, prolonged stress can alter the biological stress response and lead to a higher susceptibility for developing mental health disorders, likely through alterations in brain function and structure, and in cognition and emotion processing (Lupien et al., 2018). Furthermore, air pollution might lead to inflammatory processes in the brain, which may also affect brain integrity. For example, in animal models, there is evidence that ultrafine particles of similar size as airborne particles present in the urban air can translocate into the brain, including the striatum, frontal cortex and cerebellum (Elder et al., 2006). The role of these potential mechanisms still remains to be further investigated and explicitly addressed in future research.

In conclusion, this study integrated findings from previous urbanicity-mental health studies and provided more in-depth knowledge about these associations by identifying

specific depression symptoms of low mood, unenthusiasm, tiredness and loneliness that were associated with the experience of living in areas characterized by socioeconomic deprivation, air pollution and low access to greenspaces. Moreover, this study is among the first to provide insights into brain features involved in associations between the urban environment and mental health, and it thus contributes to this emerging research area. Specifically, the study found that lower grey matter volume in brain areas involved in cognitive and emotion processing, including the cerebellum, is associated with these depression symptoms and urban environment features. The results from the present study suggest that policies and efforts to target identified urban environment features (e.g. policies aimed at decreasing socioeconomic deprivation and increasing access to greenspaces) could have a positive impact on depression symptoms. Additional investigations will be necessary to further investigate the biological mechanisms involved in the link of the urban environment with mental health and brain integrity, for example by evaluating the role of stress and inflammation.

4.2 Study 2

This study evaluated the co-occurrence of depression and psychosis symptoms in the general population, and the relationship of these symptoms with genetic and environmental risk factors. The main contributions made by this study are discussed in the following. Firstly, the study added to the literature on network studies that have assessed lifetime symptoms of psychopathology (Isvoranu et al., 2020), by identifying bridges between clusters of lifetime depression and psychosis symptoms, which consisted of feelings of worthlessness, beliefs in unreal conspiracy against oneself, depression impairment and psychosis impairment. These results mean that individuals who have experienced negative self-beliefs throughout their lives are more likely to have also experienced symptoms of paranoia (i.e. beliefs in an unreal conspiracy against themselves).

These findings are in agreement with previous studies that have found that negative perceptions about the self and others can play a key role in the experience and maintenance of symptoms of depression and psychosis, including paranoid beliefs (Fowler et al., 2012; Gracie et al., 2007; Mills et al., 2007). The findings are also in line with theories that consider cognitive alterations, such as negative self-beliefs and negative beliefs about others, as maladaptive processes that can lead to alterations in

emotional processing and to the development and maintenance of psychosis symptoms (Garety et al., 2001).

Identified symptom associations highlight the importance of negative beliefs in the lifetime co-occurrence of depression and psychosis symptoms, and these results support their consideration as potential intervention targets to lessen or prevent these symptoms. The fact that psychosis impairment had its strongest connection with beliefs in unreal conspiracy against oneself further supports the key role of this symptom in the symptom network assessed in this study.

Secondly, the results from this study suggested that instead of having a direct influence on the development of specific symptoms of depression and psychosis, genetic predisposition has a largely broad and non-specific influence on the development of these symptoms (by potentially affecting the number, frequency or intensity of experienced symptoms). Specifically, depression and schizophrenia PRSs were related to functional impairment for depression and psychosis symptoms, respectively, rather than specific symptoms. These findings align with previous studies in clinical samples that showed depression and schizophrenia PRSs correlate with clinical severity and chronicity of depression and schizophrenia, respectively (Halldorsdottir et al., 2019; Meier et al., 2016; Wray et al., 2018), and the present study is one of the first to demonstrate similar results in a community sample. These results also extend findings from earlier population-based studies that did not find any significant links between schizophrenia PRSs and psychosis symptoms (H. J. Jones et al., 2016; Sieradzka et al., 2014).

Thirdly, of the environmental risk factors that were examined, cumulative trauma showed the most widespread and the strongest associations with symptoms of depression and psychosis. Of note, this proximal risk factor was found to act as a bridge between deprivation (i.e. one of the evaluated distal risk factors) and the bridge symptoms of feelings of worthlessness and beliefs in unreal conspiracy. This result indicates that individuals that live in deprived areas are more likely to have gone through traumatic experiences over their lifetime, and to have experienced these particular symptoms. Previous research has found that cumulative trauma exposure is a key risk factor for the experience of depression and psychosis symptoms (Tanskanen et al., 2004). Moreover, the amount of experienced traumatic events has indicated to be more predictive of psychopathology than the specific type of trauma experienced (Cloitre et al., 2009; Gracie et al., 2007).

Indeed, alterations in mood and cognition can follow the experience of trauma, especially when a traumatic event is connected with intentions to harm (such as physical and emotional abuse). These experiences can lead to distorted cognitive representations of oneself and the world. Relatedly, such negative representations and beliefs can make individuals more likely to hold suspicions about the intention of others (American Psychiatric Association, 1980; Moriyama et al., 2018). The experience of traumatic events has also been previously associated with neighbourhood social disorganization and deprivation (Beyer et al., 2015; Butcher et al., 2015), in agreement with the fact that these conditions are related to higher social stress, and a higher risk of violence and crime.

Also in line with this result, a prior study that evaluated a psychopathology network found that paranoia symptoms were related to psychopathology symptoms in individuals residing in areas characterized by high deprivation (McElroy et al., 2019). Additionally, previous research has indicated that associations between traumatic experiences and paranoia can be partially explained by the presence of negative self-beliefs (Fisher et al., 2012; Gracie et al., 2007).

Findings from this study and previous literature therefore indicate that cumulative trauma can play a significant role in associations between neighbourhood deprivation, depression and psychosis symptoms. Further research on this area will allow to gain an understanding of the directionality of these relationships, and also of potential mechanisms involved in these associations, such as alterations in stress regulation and brain integrity.

To conclude, this study allowed to gain insights on key symptoms and risk factors involved in the lifetime co-occurrence of symptoms of depression and psychosis through a network approach. The experience of symptoms associated with negative self-beliefs and negative perceptions of others, as well as the cumulative exposure to traumatic events, were identified as particularly influential for the co-occurrence of depression and psychosis symptoms. Interventions to reduce the experience of these symptoms and of traumatic events could thus help prevent or decrease depression and psychosis symptoms. Further replication of these results in additional clinical studies will help ascertain the usefulness of targeting these factors.

This study also showed that genetic and environmental risk factors have distinct associations with depression and psychosis symptoms; genetic risk was mainly related

to psychopathology symptoms through its association with functional impairment, while the lifetime experience of trauma had associations with specific symptoms. Genetic and environmental risk factors may thus differentially influence the experience of symptoms of depression and psychosis. Further research will be required to ascertain this possibility.

Finally, results from this study suggest that programs aimed at promoting social equality and reducing neighbourhood deprivation (e.g. by allocating more resources to deprived areas) can potentially benefit mental health, for instance by reducing the likelihood of individuals being exposed to multiple traumatic experiences. If the predictive value of PRSs continues to increase over time (e.g. aided by increases in power by GWASs), and in line with the results from this study, PRSs may potentially be used in the future to guide the prioritization of support and care for individuals who are at higher risk of experiencing functional impairment associated to mental health symptoms.

4.3 Study 3

The main findings of this study, which examined the genetic structure of the *p* factor and the prediction of psychopathology symptoms in late childhood by genetic risk for the *p* factor, are discussed in the following. Firstly, results from this study indicated that the single *p* factor model is the most plausible model for representing the underlying genetic architecture of the *p* factor, lending support to the notion that genetic mechanisms involved in individual psychiatric disorders operate through a general factor of psychological vulnerability. This finding was derived from Genomic SEM analyses that modelled the *p* factor from genetic correlations of internalizing (anxiety, depression and PTSD) and externalizing (risk taking and aggression) traits, as the single *p* factor model showed the best data fit in these analyses.

In contrast, higher-order *p* factor and bifactor models suffered from inadequate model fit associated to negative loadings on the externalizing domain. In line with these results, previous studies that evaluated the genetic *p* factor and associated domains reported that bifactor models do not provide the best model fit (Karlsson Linnér et al., 2021; Waldman et al., 2020). These studies have also shown that bifactor models may lead to problematic model properties, such as overfitting and non-parsimonious data structures.

The findings mentioned above collectively indicate that simple accounts of the genetic *p* factor may be sufficient to characterize genetic correlations between psychiatric traits. These findings also contrast with results from phenotypic studies that have showed model fit indices can be skewed in favour of bifactor models (Bonifay et al., 2017; Greene et al., 2019). It is therefore valuable to study the *p* factor at different levels (e.g. genetic, phenotypic, neural) to ascertain the structure and validity of this general vulnerability factor.

Secondly, PRSs for the single *p* factor were associated with baseline levels of all evaluated internalizing and externalizing symptoms in the late childhood sample. This result adds to the childhood literature linked to the *p* factor, and it extends findings from adult samples that showed PRSs representing individual-level predisposition to the genetic *p* factor can predict psychopathology phenotypes (Grotzinger et al., 2019). However, genetic risk for the *p* factor was not informative for the prediction of trajectories of psychopathology over late childhood and early adolescence, as only one significant association was found between the *p* factor PRSs and psychopathology symptom trajectories (specifically, with linear changes in impulsivity symptoms from ages 7 to 13).

Of note, previous studies have shown that phenotypic and genetic predictors can explain more variance when predicting levels of traits compared to slopes; this has been observed across a range of samples and contexts that include psychopathology and cognition (Kwong et al., 2021; Ritchie et al., 2016, 2020). Moreover, psychopathology can be heterogeneous in its trajectories, as observed in the mixture of increasing and decreasing slopes for externalizing symptoms in this study. Heterogeneous trajectories have been found for ADHD, CD and ODD in previous studies (Larsson et al., 2011; van Lier et al., 2007); the prediction of developmental trajectories of psychopathology is therefore likely to be hindered by this heterogeneity.

Thirdly, and in contrast with previous studies that did not explicitly compare the predictive power of the *p* factor PRS against single-trait PRS, this study revealed that the *p* factor PRSs was not a significantly stronger predictor of psychopathology symptom baseline levels, compared with two single-trait PRSs. In fact, depression PRSs showed significant associations with all evaluated psychopathology symptoms, and almost no significant differences were found between the *p* factor and the depression PRSs in their associations with psychopathology symptoms. Compared with the *p* factor

PRSs, the ADHD PRSs also showed significantly stronger associations with most externalizing symptoms.

Previous studies have demonstrated that on both a genetic and a phenotypic level, depression and ADHD have relevant associations with a number of psychopathology traits. For example, depression has shown high factor loadings in genetic and phenotypic *p* factor models (Caspi et al., 2014; Grotzinger et al., 2022; Selzam et al., 2018), which provides indications of its relevance for general psychopathology. This information is also consistent with findings from this study, as depression was the psychiatric trait with the strongest loading on the estimated genetic *p* factor. In the case of ADHD, previous research has suggested that genes linked to ADHD and other neurodevelopmental disorders may render individuals more susceptible to psychopathology in general (Waldman et al., 2020). On a phenotypic level, both depression and ADHD are linked to a range of mental health difficulties that include anxiety and externalizing disorders, such as substance abuse, and both of them have heterogeneous clinical profiles, developmental trajectories and comorbidities (Goldberg, 2011; Hamdi & Iacono, 2014; Luo et al., 2019). Overall, findings from this and previous studies indicate that depression and ADHD may already index a significant amount of transdiagnostic variance that is comparable to the *p* factor, both on a genetic and a phenotypic level. Hence, these traits could potentially be considered as markers of general psychopathology.

As a final insight, the sensitivity analysis from the present study revealed that once the effect of IQ, stressful life events and financial difficulties was taken into account, most psychopathology symptoms could still be predicted by PRSs. The only exception to this result were PTSD symptoms, which could no longer be predicted by PRSs after accounting for these covariates. This finding suggests that in addition to the predisposition brought on by genetic risk, environmental influences are particularly influential on the experience of PTSD symptoms. Nevertheless, gene-environment interactions are expected to also play a role in the presentation of symptoms of PTSD (Pitman et al., 2012; Rothbaum et al., 2014) and other symptoms of psychopathology, hence further research sensitive to these interactions will be necessary.

To conclude, the present study shed light on the genetic structure of the *p* factor, and thus on potential biological mechanisms involved in psychopathology. The study also provided insights on the capacity of the genetic *p* factor to predict levels and trajectories of psychopathology symptoms in late childhood and early adolescence.

Three main findings were derived from this study. First, a parsimonious model of the genetic *p* factor best explained genetic relationships between internalizing and externalizing traits. Second, childhood levels of internalizing and externalizing symptoms were predicted by genetic vulnerability to the *p* factor, but symptom changes from late childhood to early adolescence could not be predicted by this genetic vulnerability. Finally, genetic vulnerability to depression and to ADHD was found to be equally predictive of psychopathology symptom levels as genetic vulnerability to the *p* factor. On a genetic level, depression and ADHD could thus be considered as transdiagnostic markers of general psychopathology. It is expected that the predictive ability of the genetic *p* factor will increase as the power and phenotypic characterization of psychopathology traits in GWASs improve.

4.4 General Discussion

As previously mentioned, this thesis aimed to gain insights into possible psychological, environmental and biological mechanisms of psychopathology, and to identify symptoms and risk factors that could eventually be evaluated as transdiagnostic targets for psychopathology prevention or intervention.

Across the studies included in this thesis, three main findings can be noted. Firstly, depression symptoms and genetic predisposition to depression were found to be key in the experience of a range of mental health symptoms, as they were both related to a wide range of psychopathology symptoms, and to a stronger and more widespread degree compared with other examined symptoms (which included symptoms of mania, anxiety, psychosis, PTSD, CD and ODD). The results from the studies in this thesis suggest that depression symptoms, as well as genetic liability to depression, could potentially be considered as transdiagnostic factors by themselves – specifically, as general markers of psychopathology. This is supported by the fact that clinical depression has high rates of comorbidity with other mental health disorders, including anxiety (Sartorius et al., 1996), PTSD (Campbell et al., 2007) and schizophrenia (Buckley et al., 2009). Symptoms of depression, including negative affect and rumination, have also been found to be present in a range of mental health disorders (Kreminski et al., 2022; McLaughlin et al., 2014; McLaughlin & Nolen-Hoeksema, 2011; Sauer-Zavala et al., 2012).

The experience of depression symptoms could act as a gateway for the development of symptoms from other psychopathology categories, although the presence of other mental health disorders may also precipitate the experience of depression symptoms. Overall, the key role of depression in psychopathology has implications for the conceptualization of mental health disorders, and for mental health interventions. Efforts to prevent or decrease depression symptoms could potentially help prevent or reduce symptoms of psychopathology in general. In turn, pending further replication of findings from this thesis and increases in the predictive power of PRSs, genetic liability for depression could be used as a marker to prioritize resources and interventions for individuals at higher risk of experiencing depression and more generally, mental health difficulties.

Secondly, among the environmental risk factors examined in this thesis, which mainly comprised urban environment factors and the experience of traumatic life events, socioeconomic deprivation showed the strongest and most widespread associations with psychopathology symptoms (predominantly, with depression and psychosis symptoms). The impact of socioeconomic deprivation on mental health is being increasingly recognized (Cohen-Cline et al., 2018; Generaal, Timmermans, et al., 2019); as previously mentioned, living in a socially and economically disadvantaged environment has been associated with more adverse life conditions, including more difficulties in building and maintaining supportive social relationships (Gruebner et al., 2017; Stafford et al., 2003) and a higher likelihood of exposure to crime and violence (Kawachi et al., 1999; Sampson et al., 1997).

Studies from the present thesis expanded on existing knowledge by showing specific links between neighbourhood deprivation, the experience of trauma and the experience of specific mental health symptoms, and by demonstrating that neighbourhood deprivation has a stronger association with mental health symptoms compared with other features in the urban environment, including access to greenspaces, air and sound pollution and land use density. As previously mentioned, these results indicate that interventions and policies addressing deprivation at the neighbourhood level could have a positive impact on mental health symptoms, both through direct associations with mental health and indirectly, through the reduction of the potential exposure to traumatic life events. Indeed, greater social equality has been suggested to be one of the most important factors for ensuring better social and health outcomes in society (Wilkinson & Pickett, 2009).

Thirdly, biological factors consisting of brain volume and genetic risk were found to have significant associations with mental health symptoms examined in the studies from this thesis. In more detail, these studies found that 1) brain areas related to emotion and cognitive regulation (including previously neglected brain areas in this research area, such as the cerebellum) are involved in depression symptoms-urban environment associations, potentially through stress and inflammation mechanisms, 2) the main influence of genetic predisposition on mental health difficulties (specifically on the experience of depression and psychosis symptoms) seems to take place through functional impairment, and 3) genetic predisposition to mental health difficulties is positively associated with baseline levels of childhood psychopathology, but not with trajectories of late-childhood psychopathology. Studies in this thesis thus allowed to gain insights about potential biological mechanisms involved in psychopathology, and this information could be translated into targets for interventions or personalized treatments in the future.

As more insights are gained from biological data, including brain volume and genetic data, and as the power of genetic studies increases, biological information is expected to play a larger role towards targeting, tailoring and stratifying mental health interventions. For example, the use of biomarkers might enable the prioritization of support to individuals at risk of experiencing mental health difficulties in the future, or the prescription of specific interventions to individuals who are more likely to benefit from them.

A potential account of psychopathology that integrates the results from the studies in this thesis and the potential mechanisms at play is presented as follows: socioeconomic deprivation may lead to stress and inflammatory mechanisms; which may lead to alterations in grey matter volume of brain areas involved in cognitive and emotional processing; deprivation can also lead to an increased risk of experiencing traumatic events. All of these factors can trigger the experience of mental health symptoms, and particularly, of depression symptoms, which may trigger or maintain the presence of symptoms from other psychopathology categories. Moreover, individuals with high genetic predisposition towards mental illness may experience an elevated intensity or number of symptoms in response to environmental pressures, and may thus experience a greater degree of related functional impairment. Further research will be needed to directly evaluate these potential interactions and mechanisms.

4.5 Limitations

The studies carried out as part of this thesis are not absent of limitations. One of the most notable ones relates to the representativeness of the samples evaluated in these studies, which could impact the generalizability of results from the studies to the general population. This is a common issue in community-based cohort studies and it is partly due to selection bias, as individuals with lower socioeconomic status and poorer health are less likely to participate in research (Galea & Tracy, 2007). In the case of the UK Biobank study, even though its recruitment strategy aimed to achieve a sample representative of the general population, individuals that consented to participate have shown to be healthier and better-off socioeconomically, compared to the general population (Fry et al., 2017).

In the case of the ALSPAC study, although the initial cohort of expecting mothers was representative of its recruitment area (i.e. the Avon catchment area) as well as the British population, mothers that remained in the study at eight months post-childbirth were also more likely to be better-off socioeconomically, compared to the general British population (Fraser et al., 2013). The representativeness of this sample and of the UK Biobank sample have further decreased in follow-up assessments, as individuals with poorer health and lower socioeconomic levels have been more likely to drop out of these studies (Davis et al., 2020; Howe et al., 2013). This has led to an over-representation of more affluent groups within these population-based cohorts. Results observed in the studies from this thesis may therefore not fully generalize to the general population.

Despite these limitations, there are several points that support the validity of results from the studies in this thesis. Even though studies such as UK Biobank are not the most suitable for estimating prevalence or incidence rates of illness, the large sample size of this study and the variety of exposure measures that have been collected have been found to be robust enough to enable valid inferences on associations between exposures and health conditions (Fry et al., 2017). Similarly, studies examining the influence of selective drop-out in the ALSPAC sample with the use of simulations have found that drop-outs may lead to underestimates for the prevalence of mental health disorders, but that observed associations between risk factors and mental health outcomes may be only marginally affected by this. More specifically, in studies where

underestimates of prevalence are present, the strength of identified associations may be attenuated compared to true population effects (Wolke et al., 2009).

The above information suggests that associations detected in the studies from this thesis are more likely to represent true effects, and potentially underestimates of true effects. For studies that examined genetic data within this thesis, links identified between PRSs and mental health symptoms (and potentially environmental risks as well) are also more likely to represent underestimates of true associations between genetic factors, symptoms and environmental factors. This is because PRSs for psychiatric traits are currently limited by the low variance that they account for; these scores only partially capture genetic risk.

On a related note, and as previously indicated, the studies included in this thesis were carried out on samples of White European ethnicity living in the UK. The study of individuals from a single ethnic group ensured homogeneity of results, particularly for analyses of genetic data, as ethnicity can act as a confounding variable in genetic analyses and it can lead to inaccurate results (Choi et al., 2020). However, the potential generalizability of results from these studies to other ethnicities and geographical locations remains an open question.

On the one hand, most PRSs that can be currently calculated are more accurate for individuals of European ancestry, compared to other ancestries. This disparity is a consequence of ancestry biases in GWASs (A. R. Martin et al., 2019), as the majority of these studies have analysed data from White or European individuals. The prioritization of these samples in genetic studies can lead to ethical and scientific challenges involved in the clinical implementation of PRSs. The genetic analyses carried out in the present thesis suffered from and maintained these biases.

On the other hand, since the studies in this thesis only evaluated samples from the UK, the generalizability of results to other geographical locations would require further investigation. Previous studies investigating links between urbanicity or urban environment factors and mental health have shown some consistency across geographical locations, including Europe, America and Africa (Caspi et al., 2000; Dowdall et al., 2017; Generaal, Hoogendijk, et al., 2019; Wiens et al., 2017). Nonetheless, there is a paucity of studies that directly evaluate the robustness of urban environment-psychopathology findings across geographical locations. The study of

additional regions would allow to evaluate the generalizability of results from the studies included in this thesis.

Another relevant limitation present in the studies of this thesis relates to the correlational and cross-sectional nature of most evaluated associations between symptoms and risk factors. Results from correlational analyses preclude making causal claims from the findings observed in these studies, hence longitudinal designs will be required to gain insights on the directionality of associations between mental health symptoms, environmental risk factors and biological factors.

In terms of notable limitations specific to each study, for the first study we note that the study was not able to isolate the association of specific urban environment features with mental health symptoms or with brain volume. Although the main goal of this study was to examine these associations in a holistic manner, by identifying a profile of urban environment features that were maximally linked with mental health symptoms and brain volume, future studies will be needed to further untangle such associations and their directionality. Moreover, brain data analysed in this study was acquired several years after urban environment and mental health data were collected, which may have impacted the results identified in the study.

For the second study, mood-congruent recall (Singer & Salovey, 1988) and recall biases may have altered the identified symptom-environment associations, as the mental health symptoms examined in this study were based on retrospective reports. The evaluation of these symptom-risk factor interactions in a shorter timeframe – potentially in clinical samples – would help assess the robustness of the findings from this study. The possible examination of a broader set of psychosis symptoms, of post-traumatic stress symptoms and of specific trauma categories in future research will also be needed to enable a richer characterization of associations between depression symptoms, psychosis symptoms and the experience of traumatic events.

Finally, the third study was potentially limited by the quality of GWAS summary statistics, as models estimated with Genomic SEM rely on the quality and power of evaluated GWASs. Externalizing GWASs are more likely to be hindered by low power due to smaller sample sizes and to a higher variability on the definition of target phenotypes (Barr et al., 2020; Tielbeek et al., 2017). Even though Genomic SEM is meant to be robust against sample size differences (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), it is possible that a lower power present in

externalizing GWASs could have impacted the loadings estimated for externalizing traits on the genetic *p* factor. The structure of the *p* factor has also been found to vary depending on the specific traits that are used to measure this factor (Watts et al., 2020), hence the traits evaluated in this study may have had an impact on the model structure results. Finally, the lack of available measures for the experience of thought disorder symptoms for the assessed age ranges precluded the potential examination of thought disorders as a *p* factor domain. Overall, the stability and validity of the genetic *p* factor will need to be evaluated in additional studies.

In the following section, we lay out potential future research directions that can help overcome relevant limitations, and that can further advance knowledge on the topics addressed in this thesis.

4.6 Future Directions

To continue gaining a more complete understanding of psychopathology, directions for future research are discussed. Firstly, the investigation of more diverse samples will be an important step towards generating psychopathology knowledge that is more representative of the general population, and more likely to be generalizable. In line with this, there is an emerging effort in GWASs and in psychiatric genetics studies to diversify the populations studied. These actions will ensure that findings and outcomes derived from genetic studies, such as PRSs, can be as representative and predictive as possible for the general population, thereby preventing health disparities from being exacerbated and ensuring that any potential clinical value generated from these studies can benefit populations as a whole. To promote representativeness, the consideration of inclusive strategies throughout the whole research process will be required, including research design, recruitment, data collection and data analysis.

Secondly, and as previously mentioned, more in-depth investigations into mechanisms and etiological pathways involved in the results from this thesis will also be valuable, both on a psychological and a biological level. Explicitly testing mechanisms proposed in these studies, such as the role of stress on associations between identified urban environment factors and mental health symptoms – for example, with the use of network analysis – will allow to gain more robust insights that can be used for the development of therapeutic approaches and for personalizing interventions. As another example, genetic variants identified in the risk for mood disorders and

schizophrenia have pointed out biological pathways implicated in synaptic function and immune function, which may underlie these conditions (Devlin et al., 2015). These genetic variants could be considered as potential therapeutic targets that can have a cross-diagnostic impact, and the information they provide may help improve the prediction of diagnosis treatment responses and potentially, personalize treatments (Breen et al., 2016).

Thirdly, the joint examination of environmental and biological factors on a fine-grained level (i.e. at the level of symptoms instead of diagnoses) will continue to provide more relevant insights on psychopathology, especially if genetic studies increase in power (e.g. by the inclusion of larger sample sizes and the use of meta-analyses). In more detail, future psychopathology studies will benefit by evaluating the unique contributions of environmental and biological factors on the one hand, and their interactions on the other hand. On a broad level, genetics may predispose individuals to the development of psychopathology, and while environmental risk factors may trigger the development of symptoms, persistent psychopathology can also change gene expression. Through subsequent changes in brain function and structure, and through alterations in decision-making, psychopathology can in turn lead to changes in individuals' environments (Borsboom & Cramer, 2013). Although complex, accounting for these interactions will be required for gaining a more complete understanding of mental health and its mechanisms.

Fourthly, the implementation of causal and longitudinal studies will be required to untangle the directionality, temporality and individual contributions of environmental and biological influences on mental health. Longitudinal studies can allow to better identify and eventually target causal factors involved in psychopathology. For instance, in relation to the first study from this thesis, the longitudinal evaluation of brain volume and of the exposure to urban environment features would allow to understand causal interactions between these variables. In relation to the second study, the implementation of longitudinal analyses could allow to evaluate the role of identified bridge symptoms and risk factors on clinical outcomes, and the potential causal interactions between neighbourhood deprivation, the experience of traumatic events and the development of psychopathology symptoms. These examinations would also allow to ascertain whether identified symptoms and risk factors can be used as prevention or treatment targets. Relatedly, and as done in the third study, the collection and analysis of prospective data

would allow to continue shedding light into the development of psychopathology, and it would reduce potential biases present in retrospective data, such as recall biases.

As a fifth point, and in the spirit of more holistic and comprehensive research, the use of hybrid models that consider both common causes (e.g. latent factors) and symptom network structures in their conceptualization of psychopathology could help achieve a better characterization of mental health and its mechanisms (Fried & Cramer, 2017). These models can be particularly useful for representing disorders where a defined cause may be responsible for the onset of a set of symptoms, and where symptoms may subsequently start to interact with and reinforce each other. For example, trauma may be the initial trigger for the development of PTSD symptoms, but interactions between these symptoms, such as feelings of social disconnection and anhedonia, can contribute to symptom maintenance (McNally et al., 2015). Depression could also be represented with such a model, as the majority of patients that first experience an episode of major depression do so after being exposed to a stressful life event, or to chronic stress. Latent models and network models could therefore complement, rather than exclude, one another (Epskamp et al., 2017). Ongoing work in this area, including the implementation of longitudinal assessments, will be needed to evaluate the usefulness of such hybrid models for elucidating the causes and mechanisms involved in psychopathology.

A final direction for future research involves the consideration of transdiagnostic approaches not only for investigating psychopathology, but also for the design and evaluation of prevention and treatment interventions in mental health. In particular, insights gained from transdiagnostic research can be applied to the design of more holistic and efficient interventions that target shared factors and mechanisms; these treatment approaches may offer advantages in communities with lower resources (e.g. in neighbourhoods characterized by socioeconomic deprivation) (P. Martin et al., 2018). The potential value of such approaches has been supported by findings that different disorders can respond to the same treatments (L. B. Allen et al., 2010; Barlow et al., 2010; Hersh et al., 2016). The use of transdiagnostic approaches to psychopathology can also have added benefits in clinical practice, as these approaches are better suited for acknowledging and accommodating the complexity of individuals' experiences. Indeed, using these approaches can prevent potential burdens or stigma due to the assignment of multiple diagnostic labels to patients, which is not uncommon in traditional approaches.

4.7 Conclusion

The studies in this thesis shed light on transdiagnostic aspects of psychopathology, including key mental health symptoms, environmental risk factors, biological mechanisms and genetic risk factors that are significantly associated with each other. Depression symptoms and the genetic liability to depression were found to have widespread associations with a range of mental health symptoms. In turn, socioeconomic deprivation was found to have significant links with mental health symptoms that included symptoms of depression and schizophrenia, and it was also associated with a lower grey matter volume of brain areas involved in cognition and emotion, including the cerebellum, and with the cumulative experience of traumatic events. Finally, genetic predisposition towards psychopathology was associated with functional impairment related to the experience of psychopathology symptoms, and with levels of psychopathology symptoms in childhood.

This thesis contributed to a growing evidence base that is moving beyond traditional and categorical mental health conceptualizations, and into the investigation of cross-disorder symptom associations and shared environmental and biological risk factors. This work holds the promise of achieving an understanding of mental health that better represents clinical reality. Through unveiling key mechanisms and causes of psychopathology with the use of transdiagnostic approaches, the design of more effective and comprehensive interventions that target shared factors and mechanisms can take place. For example, results from this thesis indicate that interventions tackling inequalities and socioeconomic deprivation could prevent or reduce a range of mental health symptoms.

A long journey remains before symptom, environmental and biological levels involved in psychopathology are better integrated, and before the causes and mechanisms of psychopathology are more comprehensively understood. Nonetheless, it is only through interdisciplinary and integrative work that a field as complex as mental health can eventually be understood. The potential rewards, including a better understanding of mental health from both an academic and a societal perspective – with individuals being better able to understand themselves and others, and to receive the support that they need to flourish – are more than worth the continued efforts.

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6 APPENDIX

6.1 Supplementary Information: Materials And Methods

Study 1

Table A.1. Items evaluating mental health symptoms.

Item	Question	Coding
Mood swings	Does your mood often go up and down?	Yes (1) / No (0)
Miserableness	Do you ever feel 'just miserable' for no reason?	Yes (1) / No (0)
Irritability	Are you an irritable person?	Yes (1) / No (0)
Sensitivity / hurt feelings	Are your feelings easily hurt?	Yes (1) / No (0)
Fed-up feelings	Do you often feel 'fed-up'?	Yes (1) / No (0)
Nervous feelings	Would you call yourself a nervous person?	Yes (1) / No (0)
Worrier / anxious feelings	Are you a worrier?	Yes (1) / No (0)
Tense / 'highly strung'	Would you call yourself tense or 'highly strung'?	Yes (1) / No (0)
Worry too long after embarrassment	Do you worry too long after an embarrassing experience?	Yes (1) / No (0)
Suffer from 'nerves'	Do you suffer from 'nerves'?	Yes (1) / No (0)
Loneliness, isolation	Do you often feel lonely?	Yes (1) / No (0)
Guilty feelings	Are you often troubled by feelings of guilt?	Yes (1) / No (0)
Risk taking	Would you describe yourself as someone who takes risks?	Yes (1) / No (0)

Frequency of depressed mood in last 2 weeks	Over the past two weeks, how often have you felt down, depressed or hopeless?	Not at all (0) / Several days (1) /More than half the days (2) / Nearly every day (3)
Frequency of unenthusiasm / disinterest in last 2 weeks	Over the past two weeks, how often have you had little interest or pleasure in doing things?	Not at all (0) / Several days (1) /More than half the days (2) / Nearly every day (3)
Frequency of tenseness / restlessness in last 2 weeks	Over the past two weeks, how often have you felt tense, fidgety or restless?	Not at all (0) / Several days (1) /More than half the days (2) / Nearly every day (3)
Frequency of tiredness / lethargy in last 2 weeks	Over the past two weeks, how often have you felt tired or had little energy?	Not at all (0) / Several days (1) /More than half the days (2) / Nearly every day (3)
Ever manic/hyper for 2 days	Have you ever had a period of time lasting at least two days when you were feeling so good, "high", excited or "hyper" that other people thought you were not your normal self or you were so "hyper" that you got into trouble?	Yes (1) / No (0)
Ever highly irritable/argumentative for 2 days	Have you ever had a period of time lasting at least two days when you were so irritable that you found yourself shouting at people or starting fights or arguments?	Yes (1) / No (0)

Table A.2. Urban environment categories and variables included in each category.

Urban environment category	Variable names
Traffic	Close_to_major_road
	Inverse_distance_nearest_major_road
	Sum_of_road_length_major_roads_within_100m
	Traffic_intensity_nearest_road
Air pollution	Nitrogen_dioxide_air_pollution_2010
	Nitrogen_oxides_air_pollution_2010
	PM2_5_air_pollution_2010
	PM10_air_pollution_2010
Sound pollution	Average_daytime_sound_level_of_noise_pollution
	Average_evening_sound_level_of_noise_pollution

	Average_night_time_sound_level_of_noise_pollution
Greenspace	Greenspace_percentage_buffer_1000m
	Natural_environment_percentage_buffer_1000m
Deprivation income-employment-education	IMD_score
	Income_score
	Employment_score
	Education_skills_and_training_score
	Children_Young_People_Sub_domain_score
	Income_Deprivation_Affecting_Children_Index_(IDACI)_score
Deprivation-crime-living environment-housing	Crime_and_disorder_score
	Living_environment_score
	Indoors_Sub_domain_Score
	Outdoors_Sub_domain_Score
	Wider_Barriers_Sub_domain_Score
Slope	Slope500m_Mean
	Slope500m_Maximum
	Slope500m_STD
Distance to education	ND_CE01_College
	ND_CE02_Childrens_Nursery_Creche
	ND_CE03_Preparatory_First_Primary_Infant_Junior_M
	ND_CE04_Secondary_High_School
	ND_CE05_University
Distance to factories	ND_CI01_Factory_Manufacturing
	ND_CI02_Mineral_Ore_Working_Quarry_Mine
	ND_CI03_Workshop_Light_Industrial
	ND_CI04_Warehouse_Store_Storage_Depot
Distance to community facilities	ND_CC04_Public_Village_Hall_Other_Community_Facility
	ND_CL03_Library
	ND_CL07_Cinema_Conf_Exhib_Centre_Theatre_Concert_Hall
	ND_ZW_Places_of_Worship
Distance to healthcare	ND_CM01_Dentist
	ND_CM02_GP_Practice_Surgery_Clinic
	ND_CM03_Hospital_Hospice
Distance to services	ND_CC12_Job_Centre
	ND_CO01GV_Central_Government_Service
	ND_CO01LG_Local_Government_Service
	ND_CR01_Bank_Financial_Service
	ND_CR02_Retail_Service_Agent

	ND_CR02PO_Post_Office
Distance to waste and energy	ND_CU02_Landfill
	ND_CU03_Power_Station_Energy_Production
	ND_CU07_Water_Waste_Water_Sewage_Treatment_Works
	ND_Recycling_Recycling
Distance to transport	ND_CT03_Parking_Park_and_Ride_Site
	ND_CT08_Station_Interchange_Terminal_Halt
Distance to emergency services	ND_CX01_Police_Transport_Police_Station
	ND_CX02_Fire_Station
	ND_CX03_Ambulance_Station
Distance to food	ND_CR06_Public_House_Bar_Night_Club
	ND_CR07_Restaurant_Cafeteria
	ND_CR10_Fast_Food_Outlet_Takeaway
Density agricultural facilities	Den_CA01_Farm_Non_Residential_Associated_Building
	Den_CA02_Fishery
	Den_CA03_Horticulture
Density education	Den_CE_Education
	Den_CE02_Childrens_Nursery_Creche
	Den_CE03_Preparatory_First_Primary_Infant_Junior_Middle_School
	Den_CE03NP_Non_State_Primary_Preparatory_School
	Den_CE04_Secondary_High_School
	Den_CE05_University
Density accommodation	Den_CH01_Boarding_Guest_House_Bed_And_Breakfast_Youth_Hostel
	Den_CH02_Holiday_Let_Accommodation_Short_Term_Let
	Den_CH03_Hotel_Motel
Density factories	Den_CI01_Factory_Manufacturing
	Den_CI03_Workshop_Light_Industrial
	Den_CI04_Warehouse_Store_Storage_Depot
Density physical activity1	Den_CL06_Indoor_Outdoor_Leisure_Sporting_Activity_Centre
	Den_CL06CK_Cricket_Facility
	Den_CL06QS_Racquet_Sports_Facility
	Den_CL06WA_Water_Sports_Facility
Density physical activity2	Den_CL06FB_Football_Facility
	Den_CL06LS_Activity_Leisure_Sports_Centre
	Den_CL06RF_Rugby_Facility
Density	Den_CM_Medical

healthcare	
	Den_CM01_Dentist
	Den_CM02_General_Practice_Surgery_Clinic
	Den_CM02HC_Health_Centre
	Den_CM02HL_Health_Care_Services
	Den_CM05_Prof_Medical_Service_Assessment_Developm_Services
Density hospital	Den_CM03_Hospital_Hospice
	Den_CM03HI_Hospice
	Den_CM03HP_Hospital
	Den_CM04_Medical_Testing_Research_Laboratory
Density animal centre	Den_CN02_Animal_Services_Animal_Quarantining
	Den_CN04_Vet_Animal_Medical_Treatment
Density food	Den_CR06_Public_House_Bar_Nightclub
	Den_CR07_Restaurant_Cafeteria
	Den_CR09_Other_Licensed_Premise_Vendor
	Den_CR10_Fast_Food_Outlet_Takeaway_Hot_Cold
Density emergency services	Den_CX01_Police_Transport_Police_Station
	Den_CX02_Fire_Station
	Den_CX03_Ambulance_Station
Density street elements	Den_CZ01_Advertising_Hoarding
	Den_CR11_Automated_Teller_Machine_ATM
	Den_CU11_Telephone_Box
	Den_Bstops_Density_of_bus_stops
Density maintained areas	Den_LM01_Landscaped_Roundabout
	Den_LM02_Verge_Central_Reservation
	Den_LM03_Maintained_Amenity_Land
	Den_LM04_Maintained_Surfaced_Area
Density parks	Den_LM_Amenity_Open_areas_not_attracting_visitors
	Den_LP01_Public_Park_Garden
	Den_LP02_Public_Open_Space_Nature_Reserve
	Den_LP03_Playground
Density unused land	Den_LL_Allotment
	Den_LU01_Vacant_Derelict_Land
Density water	Water_percentage_buffer_1000m
	Den_LW01_Lake_Reservoir
	Den_LW02_Named_Pond
Density military	Den_M_Military
	Den_MA_Army
Density residence-general	Den_R_Residential

	Den_RB_Ancillary_Building
	Den_RC01_Car_Park_Space
	Den_RD_Dwelling
Density residence-HMO	Den_RH01_HMO_Parent
	Den_RH02_HMO_Bedsit_Other_Non_Self_Contained_Accommodation
	Den_RH03_HMO_Not_Further_Divided
Density residence-detached	Den_RD02_Detached
	Den_RD03_Semi_Detached
	Den_RD04_Terraced
	Den_RD06_Self_Contained_Flat_Includes_Maisonette_Apartment
Density residence-communal	Den_RI01_Care_Nursing_Home
	Den_RI02_Communal_Residence
	Den_RI03_Residential_Education
Density monuments	Den_ZM01_Obelisk_Milestone_Standing_Stone
	Den_ZM02_Memorial_Market_Cross
	Den_ZM03_Statue
	Den_ZM05_Other_Structure_Art_Display_Cascade_Fountain_Windmill
Density underground features	Den_Z_Object_of_Interest
	Den_ZS_Stately_Home
	Den_ZU_Underground_Feature
	Den_ZV_Other
Density worship places	Den_ZW_Place_Of_Worship
	Den_ZW99CH_Church
	Den_ZW99MQ_Mosque
	Den_ZW99TP_Temple
Density transport	Den_CT_Transport
	Den_CT02_Bus_Shelter
	Den_CT07_Railway_Asset
	Den_CT08_Station_Terminal_Halt_Bus_Coach_Railway_Station
	Den_CT09_Transport_Track_Way
	Den_CT10_Vehicle_Storage
	Den_CT11_Transport_Related_Infrastructure
Density waste and energy	Den_CC10_Recycling_Site
	Den_CU_Utility
	Den_CU01_Electricity_Sub_Station
	Den_CU06_Telecommunication
Density community facilities	Den_CC04_Community_Facility_Youth_Recreat_Social_Club

	Den_CC07_Church_Hall_Religious_Meeting_Place_Hall
	Den_CL01_Amusements_Leisure_Pier
	Den_CL03_Library
	Den_CL04_Museum_Gallery
	Den_CL07_Cinema_Conference_Exhib_Centre_Theatre_Concert_Hall
	Den_CL10_Licensed_Private_Members_Club_Recreational_Social_Club
Density services	Den_CC05_Public_Convenience
	Den_CO01_Office_Work_studio
	Den_CR01_Bank_Financial_Service
	Den_CR02_Retail_Service_Agent_Post_Office
	Den_CR08_Shop_Showroom_Garden_Centre

Note. Adapted from "Nighttime lights, urban features, household poverty, depression, and obesity" by Y. Liao et al., 2022, *Current Psychology*, *12*, Supplementary Materials. CC BY-NC.

Study 2

Definition of Functional Impairment for Depression. Functional impairment associated with depression symptoms was evaluated with the use of two questions from the MHQ: "Impact on normal roles during worst period of depression" and "Professional informed about depression". The specific questions used to assess functional impairment were:

1. "Think about your roles at the time of this episode, including study/employment, childcare and housework, leisure pursuits. How much did these problems interfere with your life or activities?". The original coding of this item was: 0 – not at all; 1 – a little; 2 – somewhat; 3 – a lot.
2. "Did you ever tell a professional about these problems (medical doctor, psychologist, social worker, counsellor, nurse, clergy, or other helping professional)?". The original coding of this item was: 0 – no; 1 – yes.

These items were presented to participants if they had previously reported experiencing at least one core depression symptom (i.e. anhedonia and low mood) in their lifetime. Functional impairment was considered to be present (i.e. it was coded as 1) if participants answered "somewhat" or "a lot" to the first question, or if they answered "yes" to the second question. If this was not the case, functional impairment was considered to be absent (i.e. it was coded as 0).

Definition of Functional Impairment for Psychosis. Functional impairment associated with psychosis symptoms was evaluated with the use of two questions from

the MHQ: “Distress caused by unusual or psychotic experiences” and “Ever talked to health professional about unusual or psychotic experiences”. The specific questions used to assess functional impairment were:

1. "How distressing did you find having any of these experiences (seeing a vision, hearing a voice, or believing that something strange was trying to communicate with you, or there was a plot against you)?". The original coding of this item was: 0 – not distressing at all, it was a positive experience; 1 – not distressing, a neutral experience; 2 – a bit distressing; 3 – quite distressing; 4 – very distressing.
2. Did you ever talk to a doctor, counsellor, psychiatrist or other health professional about any of these experiences (seeing a vision, hearing a voice, or believing that something strange was trying to communicate with you, or there was a plot against you)?". The original coding of this item was: 0 – no; 1 – yes.

These items were presented to participants if they had previously reported experiencing at least one symptom of psychosis (i.e. beliefs in unreal communications or signs, beliefs in unreal conspiracy against self, seeing an unreal vision or hearing unreal voices) in their lifetime. Functional impairment was considered to be present (i.e. it was coded as 1) if participants answered “quite distressing” or “very distressing” to the first question, or if they answered “yes” to the second question. If this was not the case, functional impairment was considered to be absent (i.e. it was coded as 0).

Study 3

Table A.4. DAWBA items for each psychopathology category examined at age 7.

Psychopathology category	Item	Coding		
Anxiety	Study child ever worries	1 = Yes	2 = No	
	Frequency child worries about past behaviour	1 = No, not at all	2 = Sometimes	3 = Often
	Frequency child worries about schoolwork/homework	1 = No, not at all	2 = Sometimes	3 = Often
	Frequency child worries about disasters	1 = No, not at all	2 = Sometimes	3 = Often
	Frequency child worries	1 = No, not	2 =	3 = Often

	about health	at all	Sometimes	
	Frequency child worries about bad things happening to others	1 = No, not at all	2 = Sometimes	3 = Often
	Frequency child worries about the future	1 = No, not at all	2 = Sometimes	3 = Often
	Frequency child worries about other things	1 = No, not at all	2 = Sometimes	3 = Often
Depression	Child has been miserable, irritable or suffered from interest-loss in past month	1 = Yes	2 = No	
	Child lacked energy in past month	1 = Yes	2 = No	3 = Don't know
	Child ate much more/less than usual in past month	1 = Yes	2 = No	3 = Don't know
	Child lost/gained a lot of weight in past month	1 = Yes	2 = No	3 = Don't know
	Child found it hard to get to sleep in past month	1 = Yes	2 = No	3 = Don't know
	Child slept too much in past month	1 = Yes	2 = No	3 = Don't know
	Child was frequently agitated for a period in past month	1 = Yes	2 = No	3 = Don't know
	Child frequently felt worthless/guilty for a period in past month	1 = Yes	2 = No	3 = Don't know
	Child found it unusually hard to concentrate for a period in past month	1 = Yes	2 = No	3 = Don't know
	Child thought about death a lot in past month	1 = Yes	2 = No	3 = Don't know
	Child talked about harming/killing self in past month	1 = Yes	2 = No	3 = Don't know
	Child tried to harm/kill self in past month	1 = Yes	2 = No	3 = Don't know
PTSD	Child has experienced exceptionally stressful event	1 = Yes	2 = No	
	Degree to which child relived stressful event	1 = No	2 = A little	3 = Yes, a lot

	with vivid memories in past month			
	Degree to which child had repeated bad dreams of stressful event in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child got upset by reminders of stressful event in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child avoided talking about stressful event in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child avoided activities/places/people related to stressful event in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child blocked out details of stressful event from memory in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child had reduced interest in activities in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child expressed reduced range of feelings in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child had problems sleeping in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child seemed irritable/angry in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child had difficulty concentrating in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child was always alert for possible dangers in past month	1 = No	2 = A little	3 = Yes, a lot
	Degree to which child was easily startled in past month	1 = No	2 = A little	3 = Yes, a lot

Impulsivity	Degree to which child often fidgeted in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child found it hard to sit down for long in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child ran or climbed about illicitly in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child found it hard to play quietly in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child found it hard to calm down in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often blurted out answers in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child found it hard to wait own turn in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often butted into conversations/games in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often went on talking when asked to stop in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
Inattention	Degree to which child often made careless mistakes in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often lost interest in activities in past 6	1 = No	2 = A little more than others	3 = A lot more than others

	months relative to peers			
	Degree to which child often didn't listen when addressed in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often didn't finish a job properly in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often found it hard to get organised in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often tried to get out of activities involving thought in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child often lost things needed for school in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child was easily distracted in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
	Degree to which child was often forgetful in past 6 months relative to peers	1 = No	2 = A little more than others	3 = A lot more than others
ODD	Degree of child's awkward behaviour in past 6 months relative to peers	1 = Less troublesome than average	2 = About average	3 = More troublesome than average
	Degree to which child has had severe temper tantrums in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
	Degree to which child has been easily annoyed in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others

	Degree to which child has been angry & resentful in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
	Degree to which child has argued with grown-ups in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
	Degree to which child has ignored rules / been disobedient in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
	Degree to which child has deliberately annoyed people in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
	Degree to which child has blamed others for own mistakes in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
	Degree to which child has been spiteful in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
	Degree to which child has tried to get revenge on people in past 6 months relative to peers	1 = No more than others	2 = A little more than others	3 = A lot more than others
CD	Child has told lies to obtain objects/favours or to avoid duties in past 12 months	1 = No	2 = Perhaps	3 = Definitively
	Frequency child has started fights with non-siblings in past 12 months	1 = No	2 = Sometimes	3 = Often
	Frequency child has bullied/threatened people in past 12 months	1 = No	2 = Sometimes	3 = Often
	Frequency child has stayed out later than allowed in past 12 months	1 = No	2 = Sometimes	3 = Often

	Child has stolen things in past 12 months	1 = No	2 = Perhaps	3 = Definitively
	Frequency child has run away / stayed away all night without permission in past 12 months	1 = No	2 = Yes, once only	3 = Yes, more than once
	Child has often played truant in past 12 months	1 = No	2 = Perhaps	3 = Definitively

Stressful life events considered to calculate the stressful life events sum score

1. Mother's husband/partner died since study child's 9th birthday.
2. One of mother's children has died since study child's 9th birthday.
3. Mother's friend/relative has died since study child's 9th birthday.
4. One of mother's children was been ill since study child's 9th birthday.
5. Mother's husband/partner has been ill since study child's 9th birthday.
6. Mother has been admitted to hospital since study child's 9th birthday.
7. Mother has been in trouble with the law since study child's 9th birthday.
8. Mother has been divorced since child's 9th birthday.
9. Mother's husband/partner didn't want their child since study child's 9th birthday.
10. Mother has been very ill since the study child's 9th birthday.
11. Mother's husband/partner lost his job since study child's 9th birthday.
12. Mother's husband/partner had problems at work since the study child's 9th birthday.
13. Mother had problems at work since study child's 9th birthday.
14. Mother lost their job since study child's 9th birthday.
15. Mother's husband/partner went away since study child's 9th birthday.
16. Mother's husband/partner was in trouble with the law since study child's 9th birthday.
17. Mother separated from husband/partner since the study child's 9th birthday.
18. Mother's income was reduced since study child's 9th birthday.
19. Mother argued with their husband/partner since study child's 9th birthday.
20. Mother's husband/partner was physically cruel to them since study child’s 9th birthday.
21. Mother became homeless since study child's 9th birthday.
22. Mother had a major financial problem since study child's 9th birthday.
23. Mother's husband/partner was physically cruel to their children since study child’s 9th birthday.
24. Mother was physically cruel to their children since the study child's 9th birthday.

25. Mother attempted suicide since the study child's 9th birthday.

26. Mother was convicted of an offence since study child's 9th birthday.

27. Mother had a miscarriage since study child's 9th birthday.

28. Mother's husband/partner was emotionally cruel to them since study child's birthday.

29. Mother's husband/partner has been emotionally cruel to their children since study child's 9th birthday.

30. Mother has been emotionally cruel to their children since study child's 9th birthday.

31. Mother's house/car was burgled since study child's 9th birthday.

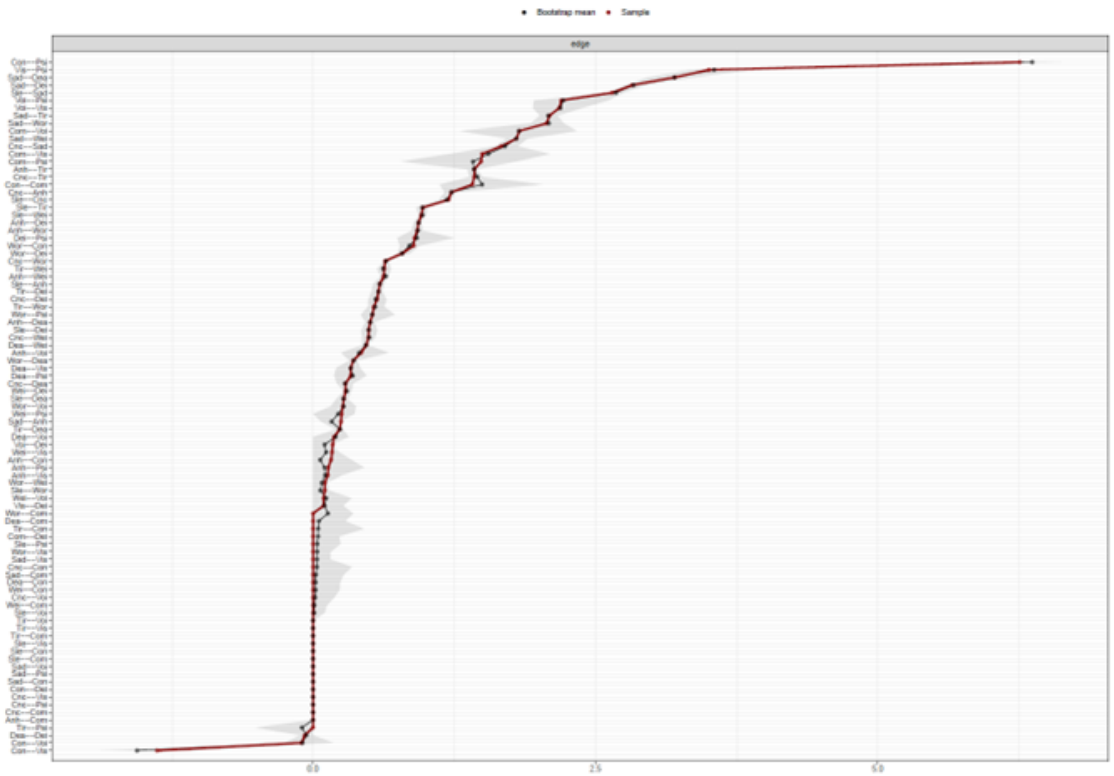
32. Mother's pet died since study child's 9th birthday.

33. Mother had an accident since study child's 9th birthday.

6.2 Supplementary Information: Results

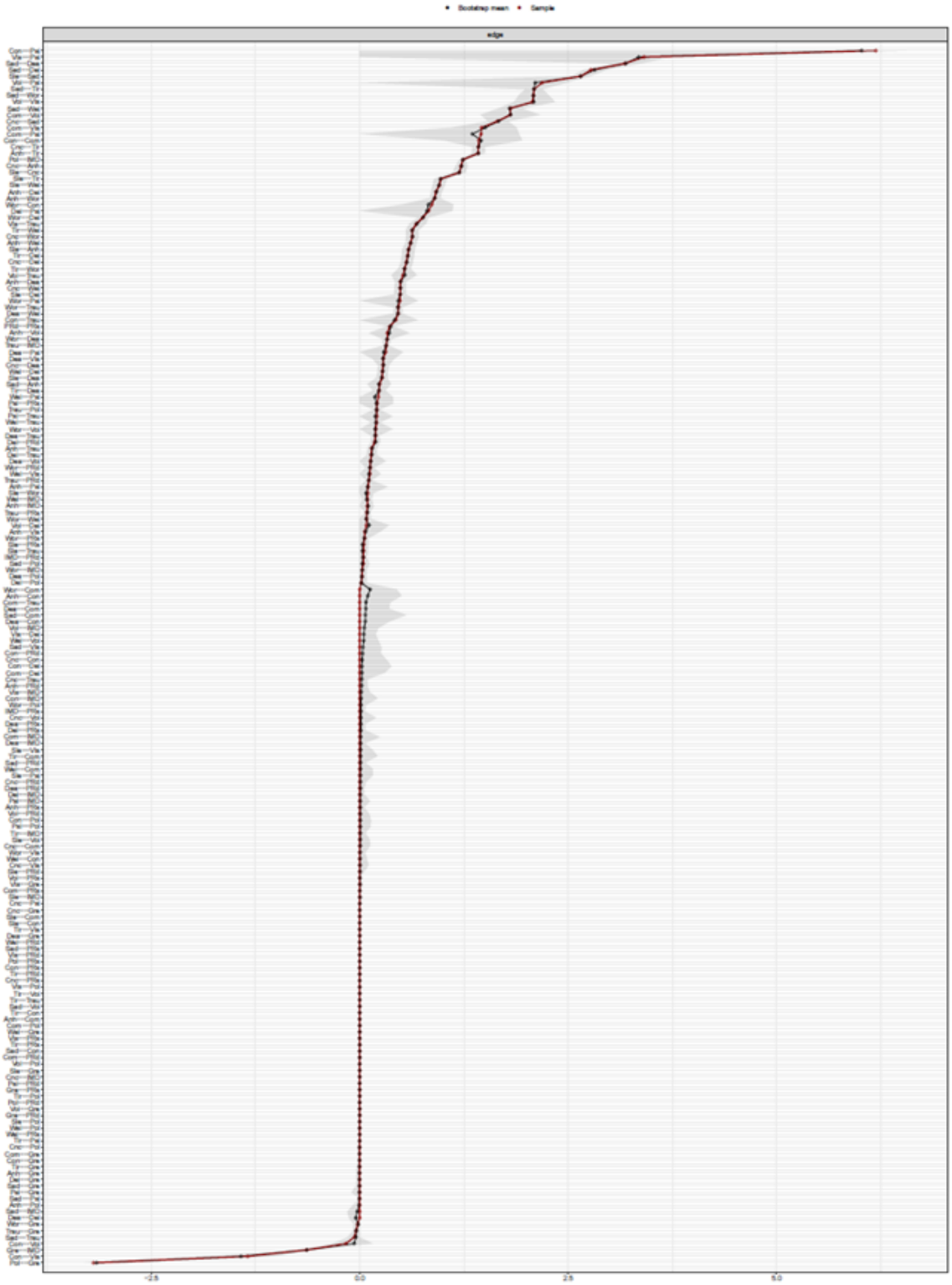
Study 2

Figure A.1. Bootstrapped 95% confidence intervals for edge weights in Step 1 network.



Note. Red dots depict the value of edge weights; grey lines depict bootstrapped 95% confidence intervals for edge weights. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, Supplementary Materials. CC BY-NC.

Figure A.2. Bootstrapped 95% confidence intervals for edge weights in Step 2 network.



Note. Red dots depict the value of edge weights; grey lines depict bootstrapped 95% confidence intervals for edge weights. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, Supplementary Materials. CC BY-NC.

Table A.5. Significant network edges: non-zero edges present in at least 70% of bootstrapped samples in Step 1 and Step 2 networks, and non-zero edges present in Step 2 MGM network.

Step 1 Network			Step 2 Network			
Edge	Edge weight	Presence in bootstrapped samples (%)	Edge	Edge weight	Presence in bootstrapped samples (%)	Presence in MGM network (edge weight)
Anh--Dea	0.507	100	Anh--Dea	0.492	100	Y (0.246)
Anh--Dei	0.935	100	Anh--Dei	0.921	100	Y (0.456)
Anh--Tir	1.424	100	Anh--IMD	0.101	95.6	Y (0.044)
Anh--Voi	0.407	100	Anh--Tir	1.422	100	Y (0.704)
Anh--Wei	0.645	100	Anh--Trau	0.148	100	Y (0.078)
Anh--Wor	0.929	100	Anh--Voi	0.355	98.5	Y (0.157)
Cnc--Anh	1.227	100	Anh--Wei	0.611	100	Y (0.302)
Cnc--Dea	0.283	100	Anh--Wor	0.901	100	Y (0.441)
Cnc--Dei	0.553	100	Cnc--Anh	1.221	100	Y (0.603)
Cnc--Sad	1.7	100	Cnc--Dea	0.284	100	Y (0.152)
Cnc--Tir	1.454	100	Cnc--Dei	0.565	100	Y (0.29)
Cnc--Wei	0.498	100	Cnc--Sad	1.667	100	Y (0.828)
Cnc--Wor	0.646	100	Cnc--Tir	1.425	100	Y (0.713)
Com--Psi	1.417	100	Cnc--Wei	0.487	100	Y (0.252)
Com--Vis	1.552	100	Cnc--Wor	0.632	100	Y (0.32)
Com--Voi	1.823	100	Com--Psi	1.35	97.1	Y (0.745)
Con--Com	1.498	100	Com--Vis	1.506	100	Y (0.692)
Con--Psi	6.368	100	Com--Voi	1.809	100	Y (0.895)
Con--Vis	-1.558	100	Con--Com	1.458	100	Y (0.708)
Con--Voi	-0.094	90	Con--Psi	6.021	97.2	Y (3.019)
Dea--Dei	-0.058	70	Con--Trau	0.416	89.8	Y (0.241)
Dea--Psi	0.353	100	Con--Vis	-1.426	100	Y (0.656)
Dea--Vis	0.334	100	Dea--Psi	0.287	93.2	Y (0.151)
Dea--Voi	0.2	90	Dea--Trau	0.185	100	Y (0.093)
Dea--Wei	0.467	100	Dea--Vis	0.279	100	Y (0.134)
Dei--Psi	0.92	100	Dea--Voi	0.133	78.2	Y (0.068)
Sad--Anh	0.164	100	Dea--Wei	0.459	100	Y (0.23)
Sad--Dea	3.2	100	Dei--PRd	0.191	100	Y (0.081)
Sad--Dei	2.839	100	Dei--Psi	0.807	97.2	Y (0.405)
Sad--Tir	2.082	100	Dei--Trau	0.144	100	Y (0.07)
Sad--Wei	1.799	100	Gre--IMD	-0.633	100	Y (0.064)
Sad--Wor	2.088	100	IMD--PRd	0.041	83.5	Y (0.013)
Sle--Anh	0.591	100	Pol--Gre	-3.158	100	Y (-0.722)
Sle--Cnc	1.183	100	Pol--IMD	1.236	100	Y (0.304)
Sle--Dea	0.269	100	PRd--PRs	0.37	100	Y (0.139)
Sle--Dei	0.493	100	Psi--PRs	0.201	79.2	Y (0.017)
Sle--Sad	2.682	100	Psi--Trau	0.187	83.5	Y (0.147)
Sle--Tir	0.968	100	Sad--Anh	0.229	100	Y (0.393)

Sle--Wei	0.97	100	
Tir--Dea	0.239	100	
Tir--Dei	0.578	100	
Tir--Wei	0.62	100	
Tir--Wor	0.551	100	
Vis--Dei	0.103	70	
Vis--Psi	3.551	100	
Voi--Dei	0.102	80	
Voi--Psi	2.216	100	
Voi--Vis	2.191	100	
Wei--Dei	0.3	100	
Wei--Psi	0.222	80	
Wei--Vis	0.117	90	
Wor--Con	0.854	100	
Wor--Dea	0.361	100	
Wor--Dei	0.788	100	
Wor--Psi	0.523	100	
Wor--Voi	0.272	100	
Wor--Wei	0.078	90	
Sad--Dea	3.191	100	Y (1.612)
Sad--Dei	2.818	100	Y (1.413)
Sad--Tir	2.09	100	Y (1.044)
Sad--Wei	1.797	100	Y (0.886)
Sad--Wor	2.084	100	Y (1.058)
Sle--Anh	0.586	100	Y (0.297)
Sle--Cnc	1.194	100	Y (0.6)
Sle--Dea	0.265	100	Y (0.144)
Sle--Dei	0.485	100	Y (0.255)
Sle--Sad	2.649	100	Y (1.305)
Sle--Tir	0.969	100	Y (0.493)
Sle--Wei	0.949	100	Y (0.479)
Tir--Dea	0.231	100	Y (0.128)
Tir--Dei	0.577	100	Y (0.299)
Tir--Wei	0.629	100	Y (0.323)
Tir--Wor	0.537	100	Y (0.277)
Trau--Gre	-0.041	90.6	N
Trau--IMD	0.315	100	Y (0.103)
Trau--Pol	0.202	100	Y (0.031)
Trau--PRd	0.108	100	Y (0.036)
Trau--PRs	0.093	100	Y (0.034)
Vis--Psi	3.346	97.2	Y (1.662)
Vis--Trau	0.687	100	Y (0.283)
Voi--Psi	2.105	97.2	Y (1.072)
Voi--Trau	0.542	100	Y (0.262)
Voi--Vis	2.088	100	Y (1.004)
Wei--Dei	0.275	100	Y (0.142)
Wei--IMD	0.084	98.1	Y (0.023)
Wei--Psi	0.18	78.1	Y (0.105)
Wei--Trau	0.194	100	Y (0.106)
Wei--Vis	0.11	87.6	Y (0.049)
Wor--Con	0.824	100	Y (0.37)
Wor--Dea	0.328	100	Y (0.161)
Wor--Dei	0.761	100	Y (0.378)
Wor--IMD	0.03	71.6	N
Wor--PRd	0.121	100	Y (0.034)
Wor--PRs	0.055	92.6	Y (0.009)
Wor--Psi	0.462	97.2	Y (0.229)
Wor--Trau	0.459	100	Y (0.22)
Wor--Voi	0.184	92.7	Y (0.081)
Wor--Wei	0.078	94.3	Y (0.034)

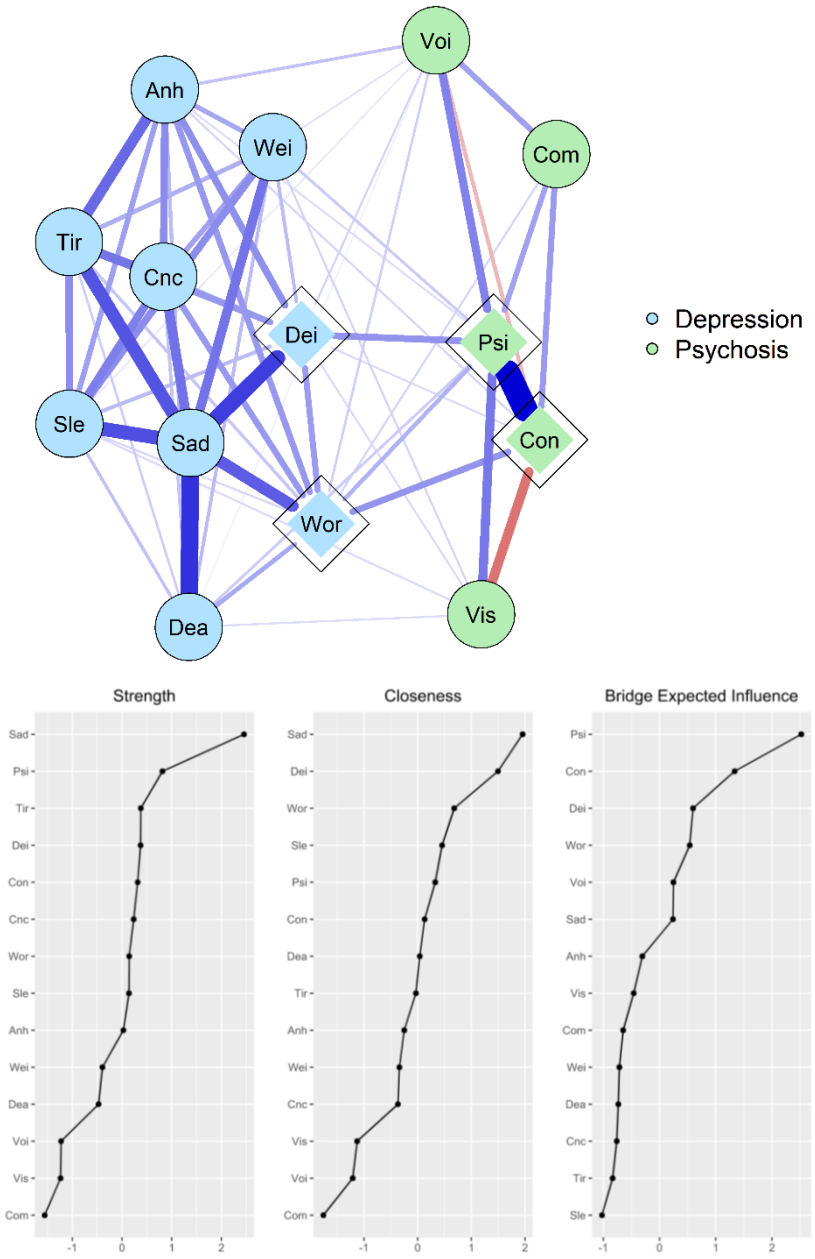
Note. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, Supplementary Materials. CC BY-NC.

Table A.6. Bridge nodes identified in Step 2 MGM network.

Node	Bridge expected influence	Bridge nodes
Sad	3.900	
Anh	3.089	
Tir	1.220	
Wor	5.527	X
Dea	3.333	
Wei	1.967	
Sle	0.908	
Cnc	1.566	
Dei	5.109	X
Con	6.848	X
Com	2.447	
Voi	4.185	
Vis	5.082	
Psi	8.555	X
Trau	8.734	X
IMD	0.905	
Pol	0.092	
Gre	0.009	
PRd	0.922	
PRs	0.364	

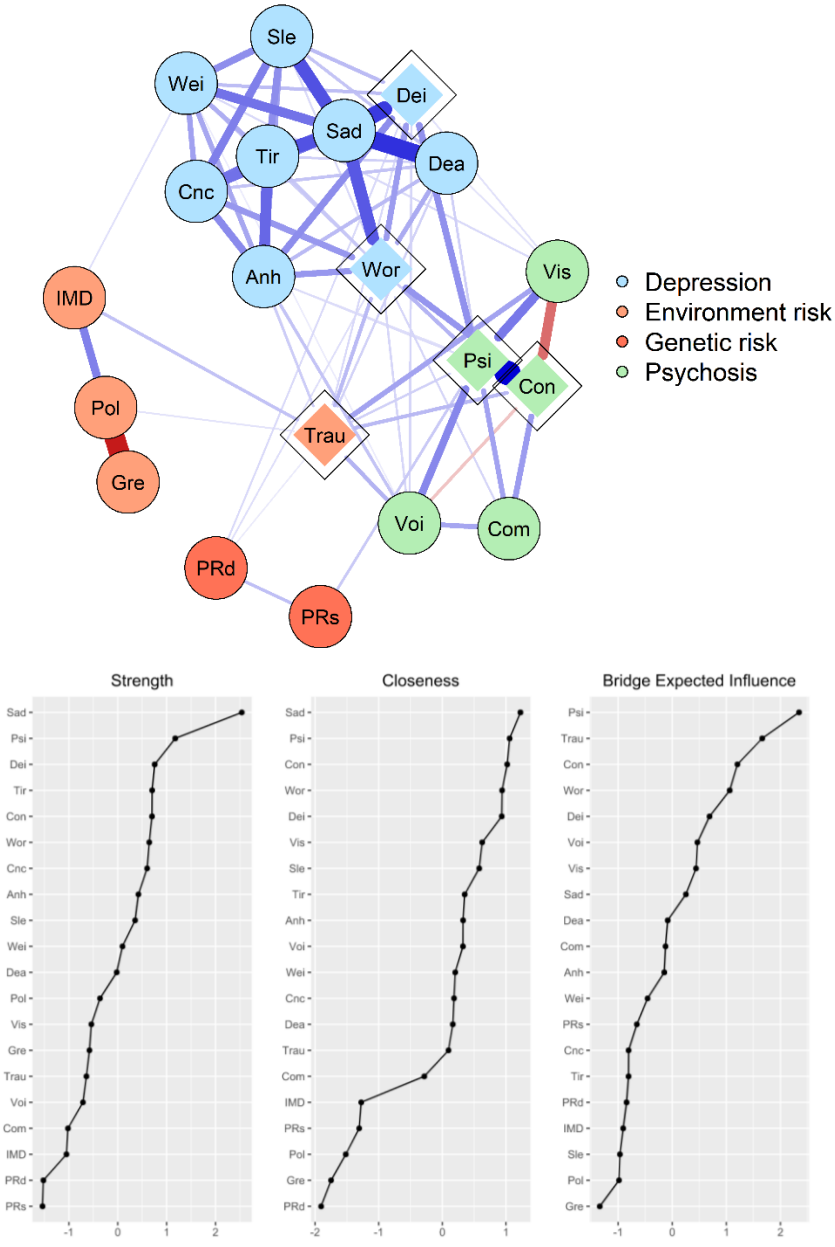
Note. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry, 12*, Supplementary Materials. CC BY-NC.

Figure A.3. Down-sampled Step 1 network with centrality indices and bridge expected influence index.



Note. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, Supplementary Materials. CC BY-NC.

Figure A.4. Down-sampled Step 2 network with centrality indices and bridge expected influence index.



Note. From "Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis" by L. Garcia-Mondragon et al., 2022, *Translational Psychiatry*, *12*, Supplementary Materials. CC BY-NC.

Study 3

Table A.7. Regression coefficients of PRSs on latent linear models of psychopathology symptoms.

PRS		Anxiety		Depression		PTSD		Impulsivity		Inattention		ODD		CD	
		Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value
***p* factor**	Intercept	0.07	<0.001*	0.07	0.01*	0.07	<0.001*	0.08	<0.001*	0.07	<0.001*	0.08	<0.001*	0.09	<0.001*
	Slope	-0.01	0.90	0.05	0.41	0.01	0.84	-0.06	0.01*	0.03	0.24	-0.04	0.16	0.05	0.42
anxiety	Intercept	0.05	0.01*	0.08	0.01*	0.05	0.06	0.03	0.12	0.02	0.31	0.03	0.12	0.05	0.04*
	Slope	0.00	1.00	-0.05	0.41	0.01	0.90	-0.03	0.17	0.02	0.53	-0.01	0.63	0.04	0.45
depression	Intercept	0.07	<0.001*	0.10	<0.001*	0.06	0.01*	0.06	<0.001*	0.06	<0.001*	0.08	<0.001*	0.07	<0.001*
	Slope	0.01	0.88	0.03	0.62	-0.01	0.90	-0.04	0.15	0.02	0.41	-0.03	0.36	0.05	0.40
ptsd	Intercept	0.02	0.29	0.02	0.48	0.03	0.31	0.03	0.06	0.04	0.05	0.04	0.05	0.04	0.07
	Slope	-0.01	0.92	0.02	0.74	0.00	0.99	0.00	0.93	0.03	0.24	-0.01	0.70	0.06	0.33
risk-taking	Intercept	0.00	1.00	0.04	0.22	0.02	0.41	0.03	0.08	0.04	0.01*	0.04	0.03*	0.04	0.15
	Slope	-0.04	0.23	0.00	1.00	-0.01	0.90	-0.02	0.53	0.03	0.24	0.02	0.51	0.15	0.01*
adhd	Intercept	-0.01	0.75	0.03	0.31	0.04	0.11	0.13	<0.001*	0.11	<0.001*	0.08	<0.001*	0.12	<0.001*
	Slope	-0.02	0.54	0.07	0.24	0.05	0.15	-0.06	0.01*	0.03	0.24	0.01	0.74	0.03	0.63
aggression	Intercept	0.00	0.90	-0.01	0.90	0.00	0.92	0.03	0.07	0.03	0.15	0.07	<0.001*	0.04	0.16
	Slope	-0.03	0.42	0.01	0.92	0.01	0.90	-0.02	0.51	-0.01	0.75	-0.05	0.07	0.03	0.62
asbo	Intercept	-0.01	0.80	-0.02	0.51	0.03	0.26	0.05	<0.001*	0.03	0.07	0.04	0.03*	0.07	<0.001*
	Slope	0.00	1.00	0.06	0.31	0.00	0.94	-0.01	0.85	0.03	0.17	0.01	0.90	0.05	0.41

Note. Associations are corrected for age and sex. * represents p < 0.05 (FDR corrected). Std. est. = standardized estimate, Asb = antisocial behaviour, ODD = oppositional defiant disorder, CD = conduct disorder.

Table A.8. William's tests: differences in predictive value between *p* factor PRS and single-trait PRSs for predicting psychopathology symptoms.

PRS		**Anxiety**		**Depression**		**PTSD**		**Impulsivity**		**Inattention**		**ODD**		**CD**	
		t	*p* value	t	*p* value	t	*p* value	t	*p* value	t	*p* value	t	*p* value	t	*p* value
anxiety	Intercept	2.35	0.03*	3.97	<0.001*	3.78	<0.001*	4.71	<0.001*	5.85	<0.001*	5.98	<0.001*	4.96	<0.001*
	Slope	-0.27	0.49	2.11	0.05	0.13	0.50	1.31	0.18	0.69	0.36	-1.08	0.24	0.03	0.50
depression	Intercept	-1.25	0.19	-4.16	<0.001*	1.90	0.08	0.76	0.35	0.85	0.31	-0.73	0.35	2.70	0.01*
	Slope	-0.68	0.36	0.39	0.46	0.71	0.35	1.11	0.23	0.62	0.38	-0.60	0.39	-0.13	0.50
ptsd	Intercept	4.56	<0.001*	6.75	<0.001*	5.75	<0.001*	1.76	0.09	2.93	0.01*	3.74	<0.001*	4.32	<0.001*
	Slope	-0.10	0.50	0.42	0.45	0.30	0.48	2.59	0.02*	0.00	0.50	-0.96	0.27	-0.15	0.50
risk-taking	Intercept	6.72	<0.001*	4.88	<0.001*	5.38	<0.001*	1.80	0.09	1.47	0.15	1.57	0.12	1.88	0.08
	Slope	0.97	0.27	0.73	0.35	0.46	0.43	1.22	0.19	-0.01	0.50	-1.71	0.10	-1.65	0.11
adhd	Intercept	7.10	<0.001*	3.29	<0.001*	1.37	0.16	-4.65	<0.001*	-2.99	0.01*	-1.45	0.15	-2.30	0.03*
	Slope	0.21	0.49	-0.34	0.47	-1.03	0.25	-0.08	0.50	-0.01	0.50	-1.76	0.09	0.25	0.49
aggression	Intercept	6.56	<0.001*	8.56	<0.001*	6.73	<0.001*	2.06	0.05	3.79	<0.001*	1.63	0.11	4.62	<0.001*
	Slope	0.49	0.42	0.57	0.39	0.09	0.50	1.44	0.15	1.37	0.16	0.22	0.49	0.22	0.49
asb	Intercept	6.54	<0.001*	8.71	<0.001*	4.71	<0.001*	-0.06	0.50	2.11	0.05	2.13	0.05	1.60	0.12
	Slope	-0.12	0.50	-0.12	0.50	0.35	0.47	1.69	0.10	-0.19	0.50	-1.27	0.19	-0.01	0.50

Note. Associations are corrected for age and sex. * represents $p < 0.05$ (FDR corrected). Asb = antisocial behaviour, ODD = oppositional defiant disorder, CD = conduct disorder.

Table A.9. Regression coefficients of PRSs on latent linear models of psychopathology, additionally corrected for control measures.

PRS		Anxiety		Depression		PTSD		Impulsivity		Inattention		ODD		CD	
		Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value	Std. est.	*p* value
***p* factor**	Intercept	0.06	0.01*	0.05	0.12	0.05	0.06	0.05	<0.001*	0.04	0.04*	0.06	<0.001*	0.06	0.02*
	Slope	-0.01	0.76	0.04	0.64	-0.01	0.89	-0.05	0.04*	0.03	0.42	-0.04	0.16	0.03	0.68
anxiety	Intercept	0.04	0.04*	0.07	0.02*	0.04	0.18	0.02	0.40	0.01	0.68	0.02	0.36	0.04	0.16
	Slope	0.00	0.94	-0.06	0.42	0.00	0.99	-0.03	0.28	0.02	0.64	-0.02	0.64	0.03	0.64
depression	Intercept	0.06	<0.001*	0.08	<0.001*	0.05	0.07	0.04	0.02*	0.04	0.04*	0.06	<0.001*	0.04	0.13
	Slope	0.00	0.94	0.02	0.81	-0.02	0.61	-0.03	0.29	0.02	0.58	-0.03	0.38	0.04	0.58
ptsd	Intercept	0.02	0.53	0.01	0.81	0.01	0.65	0.02	0.48	0.02	0.51	0.02	0.32	0.02	0.42
	Slope	-0.01	0.81	0.01	0.89	-0.01	0.86	0.01	0.82	0.03	0.37	-0.02	0.64	0.04	0.52
risk-taking	Intercept	0.00	0.89	0.03	0.40	0.02	0.58	0.03	0.16	0.04	0.02*	0.04	0.06	0.03	0.28
	Slope	-0.04	0.30	0.00	0.98	-0.01	0.81	-0.02	0.61	0.03	0.35	0.02	0.58	0.15	0.02*
adhd	Intercept	-0.01	0.65	0.02	0.58	0.02	0.47	0.11	<0.001*	0.07	<0.001*	0.06	<0.001*	0.10	<0.001*
	Slope	-0.03	0.48	0.06	0.40	0.05	0.28	-0.05	0.04*	0.03	0.35	0.01	0.82	0.01	0.89
aggression	Intercept	-0.01	0.86	-0.01	0.82	0.00	0.95	0.02	0.28	0.02	0.49	0.06	<0.001*	0.03	0.37
	Slope	-0.03	0.49	0.01	0.90	0.01	0.90	-0.01	0.65	-0.01	0.81	-0.05	0.11	0.03	0.65
asb	Intercept	-0.01	0.79	-0.03	0.42	0.02	0.58	0.04	0.04*	0.01	0.64	0.03	0.23	0.05	0.04*
	Slope	0.00	0.96	0.07	0.37	0.00	0.94	0.00	0.99	0.04	0.23	0.01	0.89	0.04	0.58

Note. Associations are corrected for age, sex, IQ, presence of financial difficulties and exposure to stressful life events. * represents $p < 0.05$ (FDR corrected). Asb = antisocial behaviour, ODD = oppositional defiant disorder, CD = conduct disorder.

6.3 Published first-author article

Translational Psychiatry www.nature.com/tp

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Role of polygenic and environmental factors in the co-occurrence of depression and psychosis symptoms: a network analysis

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Depression and psychosis are often comorbid; they also have overlapping genetic and environmental risk factors, including trauma and area-level exposures. The present study aimed to advance understanding of this comorbidity via a network approach, by (1) identifying bridge nodes that connect clusters of lifetime depression and psychosis symptoms and (2) evaluating the influence of polygenic and environmental risk factors in these symptoms. This study included data from European ancestry participants in UK Biobank, a large population-based sample ($N = 77{,}650$). In Step 1, a network model identified bridge nodes between lifetime symptoms of depression and psychosis and functional impairment. In Step 2, genetic and environmental risk factors were incorporated to examine the degree to which symptoms associated with polygenic risk scores for depression and schizophrenia, lifetime exposure to trauma and area-level factors (including deprivation, air pollution and greenspace). Feelings of worthlessness, beliefs in unreal conspiracy against oneself, depression impairment and psychosis impairment emerged as bridges between depression and psychosis symptoms. Polygenic risk scores for depression and schizophrenia were predominantly linked with depression and psychosis impairment, respectively, rather than with specific symptoms. Cumulative trauma emerged as a bridge node associating deprivation with feelings of worthlessness and beliefs in unreal conspiracy, indicating that the experience of trauma is prominently linked with the co-occurrence of depression and psychosis symptoms related to negative views of oneself and others. These key symptoms and risk factors provide insights into the lifetime co-occurrence of depression and psychosis.

Translational Psychiatry (2022)12:259 ; https://doi.org/10.1038/s41398-022-02022-9

INTRODUCTION

Mental health disorders constitute one of the most challenging global issues of current times, and their impact on society is only expected to increase in coming years [1]. In particular, depression is one of the most prevalent psychiatric disorders worldwide [2], while psychotic disorders are among the most debilitating [3]. When psychosis and depression co-occur, which is quite common [4], treatment and disease burden are further increased [5, 6].

Consistent with high rates of comorbidity, there is common genetic liability underlying both psychosis and depression. Evidence highlights familial aggregation and shared heritability among conditions that include psychotic depression, affective disorders, schizoaffective disorder and schizophrenia [7]. Genome-wide association studies (GWAS) have also shown a substantial shared genetic risk (with a genetic correlation of 0.43) among major depressive disorder and schizophrenia [8].

This observed co-occurrence and shared genetic influence suggests that categorical boundaries between depression and psychosis in current diagnostic classification systems do not fully reflect clinical reality [9, 10], which is further supported by the fact that depression and psychosis have overlapping environmental risk factors. Notable examples include traumatic experiences—in particular the cumulative experience of trauma, which has been consistently associated with increased risk for depression and psychosis [11, 12]—and area-level factors related to urbanicity. In reference to the latter, multiple studies have found increased prevalence of depression and schizophrenia in individuals living in urban areas compared to rural or less populated areas [13, 14], and there is growing evidence of associations between area-level factors that include socioeconomic deprivation, air pollution and greenspace availability with depression and psychosis [15–20].

To advance understanding of the comorbidity between depression and psychosis, alternative views of psychopathology may be warranted. The network approach to psychopathology posits that comorbidities emerge from the interplay between symptoms [9]. Indeed, individual symptoms have been differentially linked to functional impairment and to predisposing risks [21, 22], suggesting that sum scores may obfuscate the

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Received: 27 December 2021 Revised: 29 May 2022 Accepted: 8 June 2022
Published online: 22 June 2022

understanding of comorbidity. Network analysis allows identification of central and bridge symptoms; central symptoms highlight the interconnectedness within a disorder or symptom network, whereas bridge symptoms can be particularly relevant for explaining comorbidity. These are defined as symptoms that connect clusters of symptoms corresponding to different mental disorders, and thus may play a key role in spreading activation from one disorder to another [9, 23].

Although risk factors are also expected to play an influential role on symptom interactions, only a handful of studies have incorporated them into network models so far [24–26]. In the case of depression and psychosis symptoms, recent network studies have found depressed mood, suspiciousness, delusions, and hallucinations to act as central nodes across symptom networks that include negative, positive, depression and disorganization symptoms and factors related to functional capacity, cognition, motor symptoms, and personal resources [27–30].

Emerging research has also started to uncover the individual influence of genetic and environmental risk factors on depression and psychosis symptoms. For instance, in patients seeking treatment after exposure to psychological trauma, symptoms related to social isolation and negative perceptions of self-worth were identified as bridges between prolonged grief disorder, post-traumatic stress disorder (PTSD) and major depression symptoms [31]. Another recent study found a central role for persecutory-like ideations, feelings of depression and cognitions related to external attribution within a network of traumatic life events, cognitive biases, depression symptoms and psychotic-like experiences in young adults [32]. Finally, an additional network study found associations between a genetic risk score for schizophrenia, notions of conspiracy and paranoia [26].

To our knowledge, there is a scarcity of studies that simultaneously evaluate genetic and environmental risk factors in symptom networks of depression and psychosis. Treating symptoms together with genetic and environmental factors as a dynamic system would enable the detection of clinically relevant bridge symptoms and risk factors linked to them. Identified symptoms and factors could potentially be used as targets for prevention and clinical interventions in the future, as bridge symptoms are expected to play a key role in symptom networks by spreading symptom activation from one disorder to another and potentially generating self-reinforcing feedback loops [33]. Therefore, targeting these symptoms may prevent or reduce symptom activation overall.

The aims of the present study were to identify bridge symptoms connecting lifetime symptoms of depression and psychosis and associated functional impairment in a community sample via a network approach, and to evaluate the influence of polygenic and environmental risk factors in these bridge symptoms. Network models were computed in participants with European ancestry from the UK Biobank study, a large population-based cohort of participants in the United Kingdom aged 40–70 years at the time of the recruitment. UK Biobank contains the largest nationwide urban morphometric database with detailed measures of area-level exposures, as well as one of the largest genotyped cohorts worldwide.

Examining lifetime symptoms in a middle-aged sample enabled a comprehensive evaluation of symptom, functional impairment and risk factor associations in this study, including depression polygenic risk scores (PRS), schizophrenia PRS, cumulative lifetime exposure to trauma and area-level factors consisting of measures of deprivation, air pollution and greenspace availability.

Based on previous research, we hypothesized that feelings of sadness and feelings of worthlessness would be identified as central symptoms in the network [27, 31] and potentially as bridges between depression and psychosis symptoms and risk factors. We also hypothesized that hallucinations and thoughts of conspiracy against oneself would similarly be identified as central symptoms [29, 30] and potentially as bridges in the symptom network. We expected that both genetic risk [34, 35] and the lifetime experience of traumatic events [36, 37] would be associated with functional impairment, and that among the area-level risk factors evaluated, neighborhood deprivation [15, 18] would have the strongest links with depression and psychosis symptoms.

METHODS

Study sample

UK Biobank is a population-based, observational cohort study that has collected data from ~500,000 participants aged 40–70 years living in the United Kingdom. The UK Biobank study investigates the lifestyle, environmental and biological determinants of a range of adult diseases, and it acquired baseline data between 2007–2010. The study received ethical approval by The North West Multi-Centre Ethics Committee, and all its participants gave informed consent. Details on the setting and study design for the UK Biobank study can be found elsewhere [38].

Participants were selected for the present study if they had completed an online mental health questionnaire (MHQ), which measures the lifetime experience of symptoms of depression, psychosis and traumatic events, had area-level data linked to their residential address available and had genetic data available. Participants who answered "I don't know" or "I prefer not to answer" to any of the selected questions from the MHQ were excluded from the study.

The MHQ was answered by 157,348 participants at a follow-up assessment completed during 2016–2017. To improve reliability of area-level data, participants were also required to have lived at their address for at least 5 years at baseline to be included in the present study. The sample was further restricted to participants of white European ancestry, as the GWAS used to compute PRS were primarily performed on this ancestry. The final study sample consisted of 77,650 participants.

Power and sample size calculations to estimate appropriate sample sizes for network analyses are not readily available, but preliminary research has found that sample sizes of 250 to 350 tend to produce moderate sensitivity, high specificity and high edge weight correlations in networks with 20 items or less [39]. The considerably large sample available for this study and the number of items included (20 items at most) in our network analyses indicate that our sample size was well-suited for this study.

Measures

Depression symptoms. Self-reported lifetime depression symptoms and related functional impairment were assessed based on items from the MHQ. Evaluation of depression symptoms was based on the lifetime version of the Composite International Diagnostic Interview Short Form (CIDI-SF) [40, 41]. Core lifetime symptoms of depression ("Ever had prolonged feelings of sadness or depression" [low mood] and "Ever had prolonged loss of interest in normal activities" [anhedonia]) were assessed, and if participants endorsed at least one of these, questions related to non-core depressive symptoms (feelings of tiredness, feelings of worthlessness, thoughts of death, weight change, sleep change and difficulty concentrating during the worst period of depression) were queried. Answers to these seven items indicated either the presence (1) or absence (0) of ever having a symptom.

Functional impairment for depression was assessed on a binary scale based on two items from the MHQ: "Impact on normal roles during worst period of depression" and "Professional informed about depression", which were presented only to participants reporting at least one core lifetime depression symptom. Further details on this measure are presented in the Supplementary Methods.

Psychosis symptoms. Self-reported lifetime psychosis symptoms and related functional impairment were also assessed based on items from the MHQ. Evaluation of psychotic experiences was based on the CIDI Psychosis module in its lifetime version [40, 42]. Items included: "Ever believed in an unreal conspiracy against self", "Ever believed in unreal communications or signs", "Ever heard an unreal voice" and "Ever seen an unreal vision". Answers to these four items were also binary (presence = 1; absence = 0).

Functional impairment for psychosis was assessed on a binary scale based on two items from the MHQ: "Distress caused by unusual or psychotic experiences" and "Ever talked to health professional about

unusual or psychotic experiences", which were presented only to participants reporting at least one lifetime psychosis symptom. Further details on this measure are presented in the Supplementary Methods.

Traumatic events. Lifetime experience of traumatic events, including childhood trauma, adult trauma and post-traumatic stress disorder (PTSD)-relevant trauma was examined with items from the MHQ. Childhood trauma was assessed by five questions from the Childhood Trauma Screener (CTS), a shortened version of the Childhood Trauma Questionnaire [43], and adult trauma was assessed with an equivalent screener [40]. Both sets of questions evaluated the experience of physical abuse, emotional abuse, physical neglect, emotional neglect and sexual abuse. The experience of events that commonly trigger PTSD was assessed by five items encompassing experiences of violence, accidents, and assault [40].

Items for child and adult trauma were rated on a five-point scale, from "never true" to "very often true". Items for PTSD-relevant trauma were originally rated on a three-point scale (0—never; 1—yes, but not in the last 12 months; 2—yes, within the last 12 months). As the interest of the present research was on lifetime experience of trauma, and to ensure that the scale of the different trauma measures would have the same range when calculating cumulative trauma, items for PTSD-relevant trauma were recoded to a two-point scale (0—never; 4—yes). Some items on child and adult trauma were also reverse coded so that higher scores represented more severe experience of trauma for all items (Supplementary Table S1). Cumulative trauma experience was computed by summing scores of all trauma questions.

Area-level factors. Area-level measures of neighborhood deprivation (measured by the English Index of Multiple Deprivation), air pollution (nitrogen dioxide [NO_2]) and greenspace availability (measured as the percentage of the living address classed as "greenspace" within a buffer area of 1000 m) were obtained from UKBUMP, a high-resolution spatial database of objective measures of the physical environment surrounding UK Biobank participants' living addresses [44]. These measures were available on a continuous scale. Further details are presented in the Supplementary Methods.

Area-level factors were available for two timepoints covering the acquisition period of baseline data in the UK Biobank study: 2007 and 2010. Measures from 2010 were selected for this study, as they were acquired at a closer timepoint to the completion of the MHQ in 2016–2017. Within-area-level factor correlations between 2007 and 2010 were highly stable across these timepoints (Supplementary Table S2), lending support to the use of the measures in the present study.

Polygenic risk scores. PRS for major depressive disorder and for schizophrenia were generated from UK Biobank genetic data with the use of PRSice [45]. GWAS summary statistics for depression [46] and schizophrenia [47] were obtained from publicly available datasets and used as the base dataset, with UK Biobank genetic data as the target dataset. PRS were created for a *p*-value threshold of 0.1; clumping was set to identify index SNPs and remove SNPs in linkage disequilibrium by using a threshold of $r^2 > 0.1$ within a 250 kb window. The resulting PRS were on a continuous scale, and each PRS was adjusted for the first five genetic principal components to correct for population stratification.

Data preparation

Considering available data types for this study (a mixture of binary, ordinal and continuous measures), a binary Ising network approach was chosen, as implemented in previous network studies with a mixture of data types [25, 48]. In contrast with network methods that use continuous measures, this approach does not assume normally distributed measures, which is unlikely to be the case in community mental health data [49]. Cumulative trauma measures were dichotomized at the 75th centile of each measure's distribution, in the interest of capturing increased non-linear severity of exposure to traumatic events. Each area-level measure and PRS was dichotomized in the same manner. This allowed us to capture increased exposure to neighborhood deprivation, air pollution, greenspace availability and increased genetic risk, respectively.

Statistical analysis

Two main network models were estimated to examine the interplay of depression and psychosis symptoms with risk factors in an incremental manner. *Step 1* examined the network structure of symptoms of depression and psychosis and associated functional impairment, with 14 items included in the network. *Step 2* incorporated polygenic factors (i.e., depression and schizophrenia PRS) and environmental risk factors (i.e., cumulative trauma and area-level measures) into the depression-psychosis network, with 20 items included in the network. Bridge nodes were identified in both networks. For bridge estimations, depression symptoms and depression impairment were specified as a single community (i.e., a group of predefined nodes measuring similar concepts [50]); psychosis symptoms and psychosis impairment were specified as another separate community, and polygenic factors and environmental risk factors were specified as distinct communities. All analyses were performed with the R-statistical software [51], version 3.6.3.

Node selection. To avoid redundancy in the constructs examined by individual nodes (i.e., items in the networks), a node selection step was carried out. The goldbricker function from the *networktools* R software package [52] was used to compare correlations between each pair of variables; node pairs with less than 25% of significantly different correlations and a zero-order correlation of 0.5 or above ($p < 0.01$) would be flagged as redundant. Since no pair of items was identified as such, all measures of interest were represented as individual nodes in the network analyses.

Network estimation. Ising network models were used to estimate each of the two networks with the use of the R software packages *bootnet* [53] and *IsingFit* [49]. Ising models generate weighted undirected networks from binary measures. The *IsingFit* package uses an elasso regularization technique that includes model selection based on the extended Bayesian Information Criterion, aiming to identify an optimal network structure that reaches a balance between parsimony and goodness of fit. The product of *IsingFit* is a network whose edges can be interpreted similarly to partial correlations, where an edge/line linking two nodes reflects a statistically significant association after controlling for the remaining nodes in the network. Networks were visualized with the *qgraph* package [54], which uses the Fruchterman Reingold algorithm to place strongly associated nodes closer together and in the center of the network, with weakly connected nodes on the periphery [55].

Centrality estimates. Centrality indices of strength, closeness, betweenness and expected influence were computed to evaluate each network and identify nodes with high centrality, which are more theoretically likely to influence network dynamics. Strength measures how strongly a node is directly connected to other nodes, while closeness evaluates how strongly a node is indirectly connected to other nodes, and betweenness quantifies how important a node is in the average path between other pairs of nodes [53, 56]. Similarly to strength, expected influence measures the strength of connections between a node and other nodes, while taking into account the direction of associations between nodes (i.e., positive/negative associations) [57].

In turn, bridge expected influence (Step 2) metrics were calculated to identify bridge nodes, as this metric considers both direct and indirect effects of a node on other communities; nodes with higher levels of this metric most strongly connect multiple communities of nodes. The package *networktools* was used to calculate bridge expected influence (Step 2), and the top 25% scoring nodes on this metric were determined as bridges.

Network stability and node centrality. The stability of centrality estimates was evaluated for each network by obtaining case-dropping bootstrapped centrality indices with the *bootnet* package, based on 1000 bootstrapped samples. The *bootnet* package was also used to test the accuracy of network edges with the generation of bootstrapped 95% confidence intervals, and with the use of 1000 bootstrapped samples as well. Only network edges that were present in at least 70% of the bootstraps were reported in this study.

Sensitivity analyses. As the lifetime occurrence of some psychosis symptoms had rates that were very low (Table 1), with 96% of the sample reporting no lifetime symptoms of psychosis, networks were recalculated using a down-sampled cohort ($n = 6222$) to assess the possible impact of an imbalanced rate of psychopathology in the network results. This cohort was generated by selecting all participants that had experienced at least one psychosis symptom in their lifetime ($n = 3111$; equivalent to 4% of the total sample), and a matched number of random participants who had never experienced any psychosis symptom in their lifetime. Networks from Step 1 and Step 2 were thus recalculated with data from this down-sampled cohort.

Finally, to evaluate the possible impact of dichotomization of continuous measures in the Step-2 network, this network was recalculated by including the polygenic and environmental risk factors in their continuous scale and the binary symptom measures in a mixed graphical model (MGM). The *mgm* package [58] was employed for the estimation of this network, which produces a regularized model based on extended Bayesian Information Criterion model selection.

RESULTS

The study sample consisted of 77,650 white European participants with complete data (53% females, mean age at recruitment [SD] = 56.48 [7.52]). Four percent of participants experienced at least one symptom of psychosis during their lifetime, and 1.2% of participants reported significant functional impairment associated with experienced psychosis symptoms. In turn, 42% of participants experienced at least one symptom of depression during their lifetime, and 30% of participants reported significant functional impairment associated with depression symptoms. Table 1 presents the labels assigned to each network node and item frequencies.Network centrality indices were shown to be overall highly stable and therefore reliable in both networks, with most correlation stability (CS) coefficients exceeding the recommended threshold of 0.5 for stable estimation [53]. CS-coefficients for both networks can be found in Supplementary Figs. S1 and S2. In turn, the overall narrow confidence intervals from the edge weight accuracy tests indicated that the estimation of edge weights was generally stable across networks (Supplementary Figs. S3 and S4). Supplementary Table S3 shows the edges that were present in at least 70% of the bootstrapped samples, and which are reported in this study.

Step 1: Depression-psychosis network

Of the 91 possible edges in the network, 62 (68%) were estimated to be above zero, indicating that the network was highly connected. The mean edge weight in the network was 0.64 units.

Table 1. Node labels and node descriptions used in estimated networks, along with item frequencies.

Node	Node description	Item frequency (percentage)
Sad	Feelings of sadness or depression	31,489 (40.6%)
Anh	Anhedonia	23,170 (29.8%)
Tir	Feelings of tiredness	26,402 (34.0%)
Wor	Feelings of worthlessness	16,548 (21.3%)
Dea	Thoughts of death	17,374 (22.4%)
Wei	Weight change	19,702 (25.4%)
Sle	Sleep changes	25,819 (33.3%)
Cnc	Difficulty concentrating	25,289 (32.6%)
Dei	Depression impairment	23,009 (29.6%)
Con	Beliefs in unreal conspiracy against self	467 (0.6%)
Com	Beliefs in unreal communications or signs	435 (0.6%)
Voi	Hearing unreal voices	1,043 (1.3%)
Vis	Seeing unreal visions	2,075 (2.7%)
Psi	Psychosis impairment	951 (1.2%)
Trau	Cumulative trauma	23,346 (30.1%)
IMD	Index of multiple deprivation	19,429 (25.0%)
Pol	Air pollution	19,415 (25.0%)
Gre	Greenspace	19,416 (25.0%)
PRd	Depression PRS	19,442 (25.0%)
PRs	Schizophrenia PRS	19,484 (25.1%)

Total$N$ = 77,650.

Symptoms and links within communities. Depression symptoms were strongly connected to each other, and the same was observed for psychosis symptoms. As shown in Fig. 1, *feelings of sadness or depression* had the highest node strength and closeness across the whole network, and it was strongly connected with most depression symptoms. This symptom was also the node with the highest betweenness and expected influence in the network, indicating that this node may activate large portions of the symptom network. *Depression impairment* had its strongest connection with *feelings of sadness or depression*, followed by *anhedonia* and *psychosis impairment*. In turn, *psychosis impairment* was the most central node within the community of psychosis symptoms, showing a high node strength, betweenness and expected influence. This node had strong links with other psychosis symptoms, particularly with *beliefs in unreal conspiracy against self*. Most edges had positive weights, indicating positive associations between symptoms.

Links between communities: bridge nodes. As observed in Fig. 1, four nodes were identified as bridge nodes connecting depression and psychosis symptoms: *feelings of worthlessness*, *beliefs in unreal conspiracy against self*, *depression impairment* and *psychosis impairment*. *Feelings of worthlessness* and *beliefs in unreal conspiracy against self* were strongly linked to each other, while the impairment nodes showed strong associations with each other.

Step 2: Interplay of polygenic and environmental risk factors with depression-psychosis network

Of the 190 possible edges in the network, 116 (61%) were calculated to be above zero, and the mean edge weight in the network corresponded to 0.29 units, indicating a lower degree of network connectivity and edge strength compared with the previous network, which did not include genetic and environmental risk factors. As observed in Fig. 2, the addition of genetic and environmental risk factors did not alter relationships within and between depression and psychosis symptoms; rather, it uncovered connections between risk factors and symptoms.

Polygenic factors. The *depression* and *schizophrenia PRS* were associated with each other and had sparse associations with the rest of the network; these nodes had low centrality indices in terms of strength, closeness, betweenness and expected influence, which indicates that overall they had a small influence on the symptom network. The *depression PRS* was linked with *depression impairment*, while the *schizophrenia PRS* was connected with *psychosis impairment*. Both PRS were weakly associated with *cumulative trauma* and *feelings of worthlessness* (with stronger links for the *depression PRS*). The *depression PRS* was also weakly linked with *deprivation*.

Environmental risk factors. *Cumulative trauma* showed a strong positive connection with *deprivation*, was also positively linked with *air pollution* and it showed a weak and negative connection with *greenspace percentage*. Area-level factors were closely linked to each other, with strong and positive associations between *deprivation* and *air pollution*, and with negative links of *greenspace percentage* with *deprivation* and with *air pollution*. In terms of strength, closeness, betweenness and expected influence, environmental risk factors generally fell midway between symptom nodes (which remained strongly connected to each other) and PRS.

Cumulative trauma was the environmental risk factor with the highest centrality indices and with the highest number of links across the network; it was particularly linked with psychosis (*seeing unreal visions*, *hearing unreal voices*, *beliefs in unreal conspiracy against self*) and depression symptoms (displaying its strongest association with *feelings of worthlessness*), and it displayed weaker

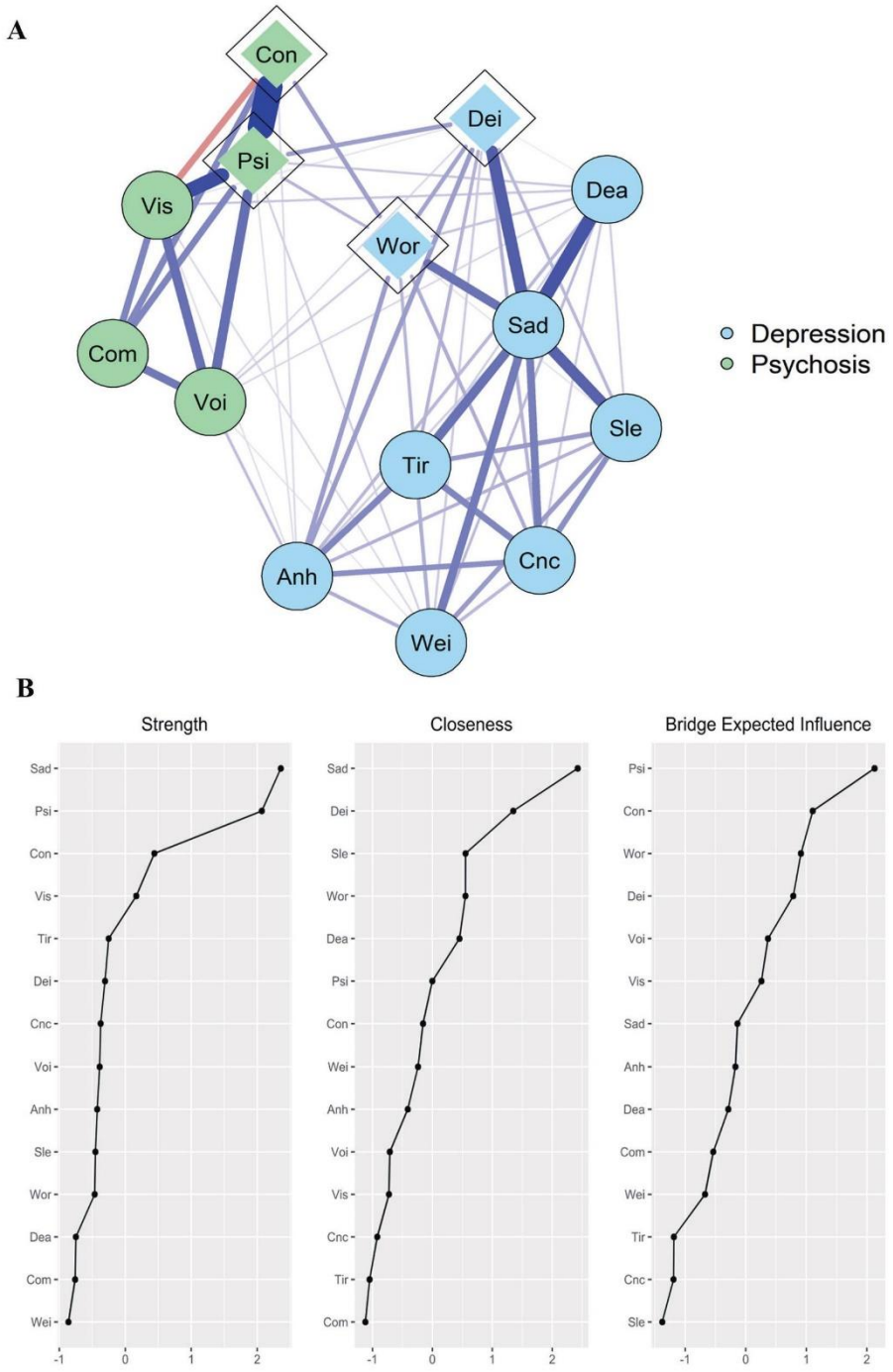

Fig. 1 Network of depression and psychosis symptoms in the UK Biobank study. A Symptom groups are represented with different colors; bridge nodes are depicted with a diamond shape. Edges (lines) can be interpreted as partial correlations, with edge thickness representing the strength of the correlation. Blue edges represent positive associations; red edges represent negative associations. **B** Centrality indices and bridge expected influence index for Step-1 network. *Anh = anhedonia; Cnc = difficulty concentrating; Com = beliefs in unreal communications; Con = beliefs in unreal conspiracy against self; Dea = thoughts of death; Dei = depression impairment; Psi = psychosis impairment; Sad = feelings of sadness/depression; Sle = sleep changes; Tir = feelings of tiredness; Vis = seeing unreal visions; Voi = hearing unreal voices; Wei = weight change; Wor = feelings of worthlessness.*

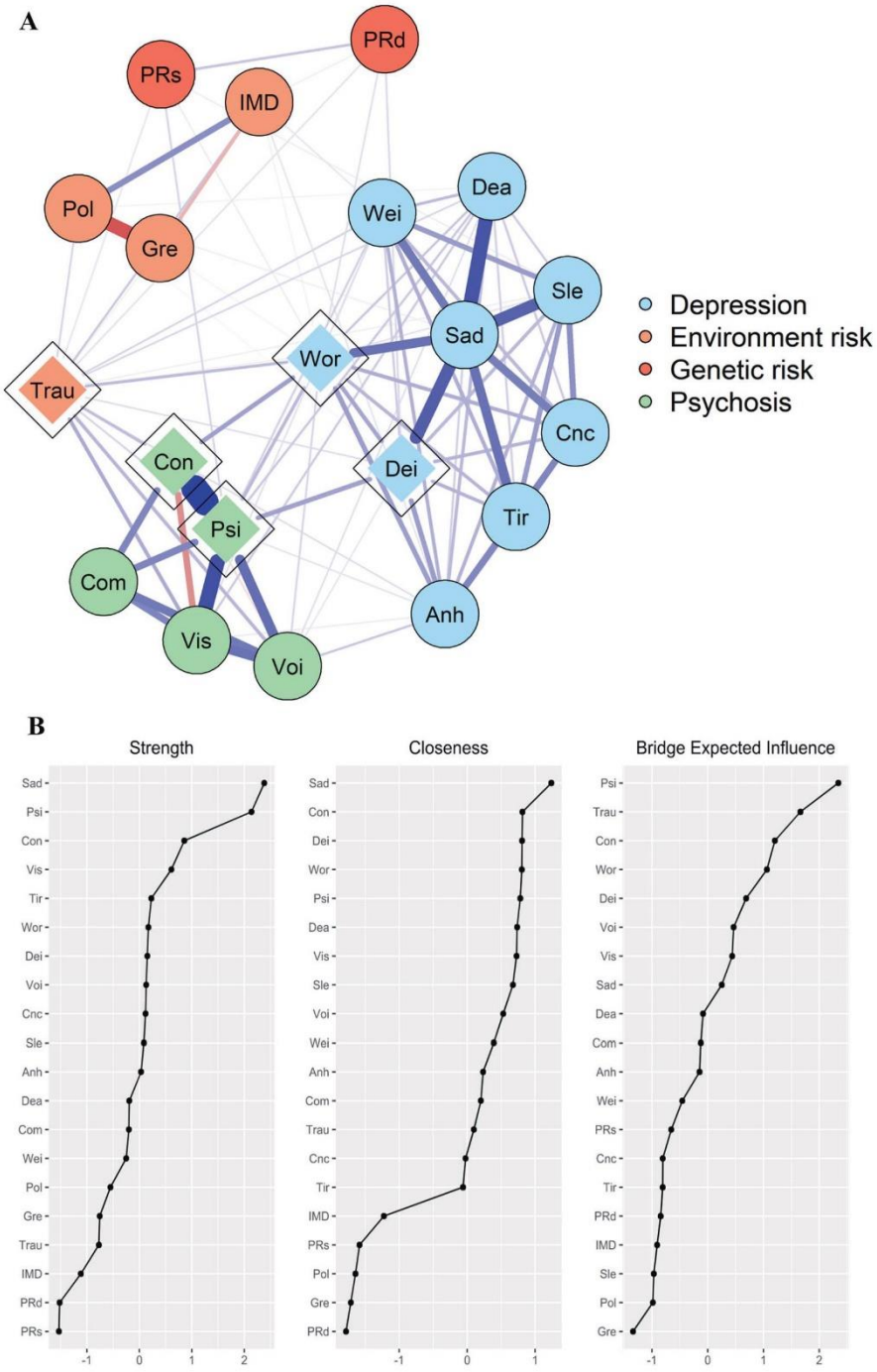

Fig. 2 Network of depression and psychosis symptoms with polygenic and environmental risk factors in the UK Biobank study. **A** Symptom groups, polygenic factors, and environmental risk factors are represented with different colors; bridge nodes are depicted with a diamond shape. Edges (lines) can be interpreted as partial correlations, with edge thickness representing the strength of the correlation. Blue edges represent positive associations; red edges represent negative associations. **B** Centrality indices and bridge expected influence index for Step-2 network. *Anh = anhedonia; Cnc = difficulty concentrating; Com = beliefs in unreal communications; Con = beliefs in unreal conspiracy against self; Dea = thoughts of death; Dei = depression impairment; Gre = greenspace; IMD = Index of Multiple Deprivation; Pol = air pollution; PRd = depression PRS; PRs = schizophrenia PRS; Psi = psychosis impairment; Sad = feelings of sadness/depression; Sle = sleep changes; Tir = feelings of tiredness; Trau = cumulative trauma; Vis = seeing unreal visions; Voi = hearing unreal voices; Wei = weight change; Wor = feelings of worthlessness.*

links with *depression impairment* and *psychosis impairment*. Among the area-level factors, *deprivation* showed stronger connections with depression symptoms, followed in strength by *air pollution*. *Greenspace percentage* lacked any notable associations with depression or psychosis symptoms, in line with its low centrality indices.

Bridge nodes. *Cumulative trauma* was identified as a new bridge node that mainly linked depression symptoms and psychosis symptoms, including the previously identified bridge symptoms of *feelings of worthlessness* and *beliefs in unreal conspiracy*. The four nodes identified as bridge symptoms in Step 1 (*feelings of worthlessness*, *beliefs in unreal conspiracy against self*, *depression impairment* and *psychosis impairment*) remained as bridges in Step 2. As observed in Fig. 2, *cumulative trauma* showed the second highest bridge expected influence, just below *psychosis impairment*.

Sensitivity analyses

To evaluate the possibility that an imbalanced rate of presence/absence of psychosis symptoms in the sample could impact network results, symptom networks were recalculated with a down-sampled cohort based on the presence/absence of psychosis symptoms ($n = 6222$). This led to the same pattern of results as in the original sample; the identified bridge nodes remained the same, and most of the network edges observed in the original sample remained. The only exception to this were two edges that were not present in the down-sampled cohort, specifically the links of the *schizophrenia PRS* with *cumulative trauma* and with *feelings of worthlessness*. Visualizations of the down-sampled networks and their centrality estimates are presented in Supplementary Figs. S5 and S6.

Finally, the Step-2 MGM network recalculated with polygenic and environmental risk factors in their continuous scale produced the same pattern of results as the original Step-2 network with binary measures. The identified bridge nodes remained the same, along with most of the network edges observed in the original network. Detailed results for this network can be found in Supplementary Tables S3 and S4.

DISCUSSION

The present study applied network analysis to investigate the lifetime co-occurrence of individual symptoms of depression and psychosis, and their associations with both genetic and environmental risk factors in a large community sample—one of the largest used in network research to date. To our knowledge, only one other network study has included both genetic and environmental risk factors to investigate psychopathology, albeit in a much smaller sample and with a methodology that could not directly uncover links between symptoms and risk factors [24]. Our study extends current knowledge of the co-occurrence of depression and psychosis symptoms in three main ways.

First, feelings of worthlessness, beliefs in unreal conspiracy against oneself, depression impairment and psychosis impairment emerged as bridges between clusters of depression and psychosis symptoms. This aligns with previous evidence that negative beliefs about the self and others contribute to depression and psychosis symptoms [12, 59, 60], and more generally, with cognitive theories on the role of negative thoughts about the self and others in psychosis [61]. Since the evaluated symptoms in this study are lifetime symptoms, these results mean that individuals who experienced negative beliefs about themselves over their lifetime were more likely to have also had beliefs in an unreal conspiracy against themselves over their lifetime. This study therefore contributes to network studies examining lifetime symptoms [26].

The fact that these symptoms linked depression and psychosis symptom clusters highlights their relevance in lifetime symptom co-occurrence, and places them as possible targets for interventions to reduce or prevent depression and psychosis symptomatology. The relevance of beliefs in unreal conspiracy against oneself in the examined symptom network is further supported by the fact that psychosis impairment had its strongest association with this symptom.

Second, depression and schizophrenia PRS were predominantly associated with functional impairment for depression and psychosis symptoms, respectively, rather than specific symptoms. Of interest, depression and schizophrenia PRS in clinical samples have been correlated with clinical severity and chronicity for depression and schizophrenia, respectively [34, 35, 46]. This is among the first studies to show similar results on a community sample, and it extends findings from previous population-based studies that found no associations between a schizophrenia PRS and symptoms of psychosis [62, 63]. These results suggest that genetic predisposition to depression and to schizophrenia predominantly influences the liability to develop symptoms in a broad, non-specific manner that may affect the frequency, number or intensity of symptoms rather than by influencing the liability to develop specific symptoms.

Third, of the evaluated environmental risk factors, cumulative trauma had the strongest and most extensive connections with depression and psychosis symptoms. Cumulative exposure to traumatic events has been indicated as a key risk factor in the experience of symptoms of depression and psychosis [64], and the number of experienced traumatic events has been suggested to be more important than the specific type of experienced trauma for predicting psychopathology [12, 65]. Interestingly, this risk factor emerged as a bridge node that linked neighborhood deprivation to the bridge symptoms of feelings of worthlessness and beliefs in unreal conspiracy, meaning that individuals living in deprived areas are more likely to have had traumatic experiences over their lifetime, and to have experienced these specific symptoms. In support to this finding, a previous network study found that symptoms of paranoia (i.e., suspicions about others' intentions) were linked with mental health symptoms in participants living in highly deprived areas [25]. Previous studies have also shown that negative beliefs about the self may partially account for associations between traumatic experiences and paranoia [12, 66].

The experience of trauma, especially when associated with intentions to harm (e.g., physical and emotional abuse), has indeed shown to lead to alterations in cognition and mood such as distorted and long-lasting negative beliefs about oneself and the world, which may make individuals more susceptible to being suspicions about the intention of others [67, 68]. In turn, neighborhood social disorganization and deprivation have been linked with increases in the experience of traumatic events [69, 70], as these contexts are associated with higher social stress, crime and risk of violence. Thus, cumulative trauma may be an important mediator for the relationships between neighborhood deprivation, depression and psychosis symptoms, though prospective studies will be required to disentangle the directionality in these associations.

The results from this study showed distinct associations of genetic and environmental risk factors with depression and psychosis symptoms, with polygenic risk mainly presenting associations with symptomatology through functional impairment, and with cumulative trauma showing specific associations with symptoms related to negative beliefs about oneself and others. These risk factors may therefore confer differential risks for the experience of depression and psychosis symptoms, although additional studies will be needed to further investigate this.

The evaluation of lifetime symptoms of depression and psychosis symptoms allowed to investigate the co-occurrence of these symptoms in a population-based sample, as evaluations over a shorter timeframe (e.g., symptoms experienced within the

previous month) may not have been informative enough in this context, given the low incidence of psychosis symptoms in the general population. The application of a regularized network approach in this study allowed to obtain an interpretable network, which is likely to better extrapolate to new samples and which ensures the reduction of false positives [71]. The use of a bootstrapping procedure to evaluate the validity of edge weights across networks and the implemented sensitivity analyses also aided in evaluating the robustness of the results identified in this study. Additionally, the inclusion of a node selection step allowed to identify and remove any pair of nodes that would correlate too highly, which circumvented issues related to potential variance overlap between symptoms and between risk factors included in the networks. The fact that the network approach allows to identify associations between nodes that are present after controlling for the remaining nodes in the network contributed as well to circumventing potential biases in the estimation of symptom-symptom associations and risk factor-symptom associations.

This study is however not absent of limitations. UK Biobank participants who completed the MHQ were on average healthier and of higher socioeconomic status compared with the general population and with the initial cohort of UK Biobank participants [40]. Results from this study may therefore not be fully representative of the general population. Of note, this study evaluated participants with European ancestry only, which may preclude the generalization of results to individuals with a different ancestry. Mood-congruent recall [72] and recall biases in general are another possible source of bias in the identified symptom-environment associations, hence the corroboration of these symptom-risk factor interactions in a shorter timeframe—particularly in clinical samples—will aid in examining the robustness of the results from this study. Overall, research in clinical samples will be needed to evaluate the generalizability of results from this community-sample study, and to determine whether relevant symptoms and risk factors can eventually serve as useful targets for prevention or treatment.

Moreover, studies based on longitudinal data will be necessary to examine whether our results also apply to intra-individual psychological processes over time [73]. Analyses using repeated assessments, such as ecological momentary assessments, will allow to determine the directionality of interactions between symptoms and risk factors identified in this study (e.g., do symptoms related to negative perceptions of oneself activate symptoms related to negative perceptions towards others?) and will aid in assessing whether targeting key symptoms and risk factors have a positive impact on clinical outcomes.

Another potentially relevant limitation of this study relates to our assessment of functional impairment, which was based on two measures: the distress/impact on normal life caused by the experience of depression or psychosis symptoms, and the consultation with a health professional about experienced symptoms. Our choice of evaluating functional impairment by combining these two items could have impacted the observed associations in this study, as results of network analysis depend heavily on the items included. Future studies evaluating functional impairment in alternative ways will be needed to further assess the robustness of results from the present study.

Finally, although the majority of results remained in sensitivity analyses performed on a subsample of participants, a few associations between the schizophrenia PRS and other network nodes were no longer present, indicating that observation of some of these links may be dependent on larger sample sizes (such as our original sample). A broader limitation of the field relates to the low variance that PRS currently explain; as these only partially capture genetic risk, identified associations between PRS and symptoms (and possibly environmental risks) are likely to be underestimates of true genetic-symptom-environment links.

The possible examination of a broader set of psychosis symptoms in future research will also enable a richer characterization of associations between depression and psychosis symptoms. Relatedly, future studies should consider incorporating post-traumatic stress symptoms into the examination of these symptom-risk factor interactions, given the close links between the experience of traumatic life events and of post-traumatic stress symptoms, and the known comorbidity between PTSD, depression [74] and psychosis [75]. The present study was not able to explore the influence of post-traumatic stress symptoms in the examined associations, as information on the lifetime experience of these symptoms was not available in the UK Biobank study. Finally, as specific categories of trauma may be differently associated with psychopathology symptoms [76], relevant insights will be gained if future studies evaluate associations of specific trauma types with depression and psychosis symptoms. For example, there are indications that the exposure to traumatic life events with intention to harm have stronger associations with psychosis symptoms, compared to other traumas (such as accidents) [77].

In conclusion, the present study identified key symptoms and risk factors that give insights into the lifetime co-occurrence of depression and psychosis with the use of a network approach. Present findings point to the experience of symptoms related to negative views of oneself and others and to the cumulative experience of traumatic events as relevant in the co-occurrence of such symptoms. Therefore, pending replication of these results in further clinical studies, efforts to diminish these experiences could potentially aid in reducing or preventing symptoms of depression and psychosis. Policies tackling deprivation at the neighborhood level may also have a positive impact on these symptoms by reducing residents' cumulative exposure to trauma. Our findings also suggest that in the future, as the predictive capacity of PRS increases, their clinical value might include an ability to prioritize treatment for individuals at highest risk of experiencing functional impairment.

DATA AVAILABILITY

Access to UK Biobank data is available to bona fide researchers through a procedure described at https://www.ukbiobank.ac.uk/enable-your-research.

CODE AVAILABILITY

Computer code used to generate results for this study can be made available from the corresponding author upon reasonable request.

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ACKNOWLEDGEMENTS

This research was conducted with the use of the UK Biobank resource, under UK Biobank project number 63994. We would like to thank the UK Biobank participants and coordinators for this dataset. This research was supported by the Economic and Social Research Council under Grant ES/R005516/1 (to EDB). LGM is supported by the International Max Planck Research School of Translational Psychiatry (IMPRS-TP).

AUTHOR CONTRIBUTIONS

LGM and EDB conceptualized and designed the study; DK, JBN, KSY, AEF, and AI provided advice on methodology; LGM performed the analysis and interpretation of data; DK provided assistance in data analysis and interpretation; LGM wrote original manuscript; all authors provided critical revisions of the manuscript; EDB provided supervision.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-022-02022-9.

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