Towards Understanding the Role of Environmental Risk Factors in Psychosis and Beyond: A Data-Driven Network Approach

Inaugural Dissertation

zur

Erlangung des Doktorgrades
philosophiae doctor (PhD) in Health Sciences
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von

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aus Neumarkt in der Oberpfalz

2022

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Datum der Mündlichen Prüfung:	09.06.2022

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1. General Introduction

1.1 Clinical features and burden of psychotic disorders

Diagnostic manuals, such as the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, define psychotic disorders as mental disorders characterized by fundamental disturbances in thinking, perception, and emotions; including, for example, delusions, hallucinations, and diminished emotional expression (Guloksuz & van Os, 2018; Loch, 2019; van Os & Kapur, 2009). Schizophrenia is the most common diagnosis within this broader diagnostic group of psychotic disorders, accounting for the 30% with the poorest outcomes (Guloksuz & van Os, 2018; Perälä et al., 2007). In the general population, pooled cross-national data shows an average lifetime prevalence of 0.8% for meeting the diagnostic criteria for a psychotic disorder (Moreno-Küstner et al., 2018). Despite their low prevalence, psychotic disorders represent a high and multifaceted burden both for those affected and for society (Rössler et al., 2005). This high burden can be attributed in part to the fact that psychotic disorders typically first occur in early adulthood (Solmi et al., 2021), a critical period for development in education, work, and personal relationships. Specifically, psychotic disorders are often associated with decreased psychosocial functioning, such as detachment from family and peers and loss of productivity in work-related activities (Penn et al., 2005), lower quality of life (Leendertse et al., 2018), stigmatization (Doll et al., 2021), increased risk for criminal activity (Yee et al., 2020), and even premature death. The life expectancy of people diagnosed with a psychotic disorder is shortened by an average of 12 to 15 years compared to the general population (Chang et al., 2011; Druss et al., 2011; Laursen, 2011; Saha et al., 2007), resulting in more lives lost than from most types of cancer and physical illnesses (van Os & Kapur, 2009). In parallel to this immense personal burden, psychotic disorders are also the most expensive mental illnesses in terms of societal cost-of-illness per patient worldwide (Christensen et al., 2020).

Unfortunately, there is still a lack of effective preventive interventions (Fusar-Poli et al., 2020; Mei et al., 2021) and quite a few patients do not respond to or relapse following 'gold standard treatments' (Ceraso et al., 2020; Griffiths & Birchwood, 2020). Thus, there is an urgent need for improved prevention and clinical management of psychosis, which can be achieved through a better understanding of its etiology.

1.2 The environment and psychotic disorders

Findings from twin studies had long suggested that genetic factors contribute substantially to the etiology of psychotic disorders, with heritability estimated to be as high as 79% for schizophrenia, for example (Hilker et al., 2018). However, recent large genome wide association studies in unrelated individuals show much lower estimates of heritability (7%; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). At the same time, epidemiological research has documented strong and consistent associations between environmental risk factors and psychotic disorders; including childhood trauma (Sideli, Murray, et al., 2020; Varese et al., 2012), stressful life events (Beards et al., 2013), cannabis use (Marconi et al., 2016; Moore et al., 2007; Sideli, Quigley, et al., 2020), ethnic minority status (Radua et al., 2018; van Os et al., 2010), and urbanicity (Vassos et al., 2012). Collectively, these results provide a strong indication that environmental risk factors play a more prominent role in the etiology of psychotic disorders than previously assumed (Isvoranu, Boyette, et al., 2020; Zwicker et al., 2018).

Thus, the etiological model best supported by empirical research to date suggests that the risk for developing psychotic disorders increases with the aggregation of numerous influences from both the genetic and environmental domain and their interaction (Murray et al., 2017; Radua et al., 2018;

Zwicker et al., 2018). Specifically, under the cumulative influence of a multitude of genetic factors, a small proportion of individuals may become more susceptible to the effects of environmental influences and eventually develop full-blown psychotic psychopathology (Cougnard et al., 2007; Guloksuz et al., 2019; Linscott & van Os, 2013; Stepniak et al., 2014; Zwicker et al., 2018).

Some of the risk factors associated with the development of psychotic disorders – such as childhood trauma – include interacting environmental and genetic components that may be difficult to separate (Radua et al., 2018; Zwicker et al., 2018). In the present thesis, I take a pragmatic approach and conceptualize the term *environmental risk factor* as any "non-purely genetic factor[]" (Radua et al., 2018, p. 49). Another important observation relevant to the analysis of the effects of environmental factors on psychosis risk is that many people experience more than one environmental risk factor (Stepniak et al., 2014). Thus, environmental risk factors do typically not occur in isolation; rather, there is evidence of complex patterns of interaction among them (Guloksuz et al., 2018; Isvoranu et al., 2016). For example, the effects of urbanicity on psychosis risk may be largely mediated by its association with cannabis use (Isvoranu et al., 2016). Thus, in order to comprehensively represent pathways to psychosis, it has been argued that ideally the exposome should be modeled, i.e., the totality of environmental exposures, or at least multiple, plausibly related exposures, rather than single risk factors (Guloksuz et al., 2018; Zwicker et al., 2018). By concurrent modeling of a set of relevant environmental exposures, different sources of heterogeneity in psychosis etiology can be dissected.

Research on environmental risk factors and their distinct pathways to psychosis is pivotal from a clinical perspective. First, some of these risk factors, such as cannabis use, bear an inherent preventive potential at the population level (e.g., in public outreach campaigns) that may be refined through insights into their ways of action (Murray et al., 2017; Radua et al., 2018). Second, knowledge of etiological pathways may help to tailor preventive interventions at the level of each individual, depending on the environmental exposures reported (Radua et al., 2018). Finally, an improved etiological understanding may ultimately help develop more effective treatments that can improve outcomes in psychotic disorders (Garety et al., 2007).

To date, however, the pathways through which environmental risk factors increase the risk for psychotic disorders have remained poorly understood. The following sections outline reasons for lack of knowledge in this area, which impedes advances in the prevention and treatment of psychotic disorders.

1.3 The essentialist view on psychotic disorders

A key obstacle to progress in understanding the etiology of psychotic disorders lies in the persistent presence of essentialist conceptions of mental disorders in psychiatric research and practice (Isvoranu, Boyette, et al., 2020). Essentialism entails the notion that mental disorders, such as schizophrenia, exist as natural kinds with necessary and sufficient intrinsic essences that uniquely define and distinguish them from other kinds (Haslam, 2000; Kendler, 2016; Kendler et al., 2011; Kotov et al., 2017). The assumed essence of a mental disorder, also referred to as the underlying disorder entity (Borsboom, 2017a; Borsboom et al., 2019; Isvoranu et al., 2016; McHugh & Slavney, 1998; McNally, 2021), is the common cause that leads to the observed symptoms of a disorder. In other words, essentialist thinking about psychotic disorders involves the notion that all individuals diagnosed with schizophrenia share a common essence, i.e., the 'schizophrenia' disorder entity, that is responsible for a similar clinical presentation and prognosis in these individuals; similar to how the atomic number uniquely identifies elements in the periodic table and allows further properties of a particular element to be lawfully inferred (Haslam, 2000; Kendler et al., 2011). The expression 'suffering from schizophrenia', frequently used by

clinicians, scientists, and laypeople alike, succinctly summarizes these ideas, suggesting the presence of a causally relevant disorder entity (Isvoranu, Boyette, et al., 2020).

In the psychometric representation of this so-called *common cause model* of psychopathology, the underlying disorder entity represents a latent variable that causes the observed symptoms, rendering symptoms interchangeable, locally independent indicators of the assumed disorder entity (Borsboom, 2017a; Isvoranu et al., 2016; Schmittmann et al., 2013). In other words, relations between individual symptoms are in a nontrivial sense 'spurious' and not of interest, given that any observed covariation between symptoms can be explained by their common dependence on the underlying disorder entity (see *figure 1*; Borsboom et al., 2016; Isvoranu et al., 2016; Schmittmann et al., 2013). This psychometric representation justifies the common practice of summing the number of diagnostically equivalent symptoms to assess the severity of the disorder and ultimately to make a diagnosis by inferring a presumed underlying disorder from the observed symptoms (Borsboom, 2017a; Fried & Nesse, 2014; Haslam, 2000). The number of symptoms, rather than their nature, matters.

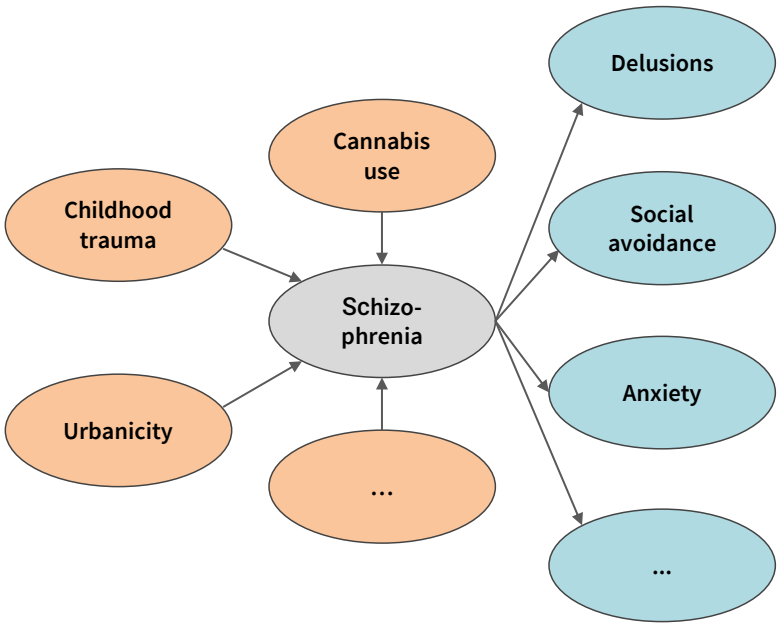

Figure 1: Simplified visualization of the common cause model of schizophrenia. According to this model, the underlying disorder entity, i.e., schizophrenia (depicted in gray), is the root cause of its symptoms (depicted in turquoise), which co-occur only because they are all caused by the same underlying disorder entity, but cannot influence each other. The effects of environmental factors, such as childhood trauma (depicted in orange), on individual symptoms are thought to be mediated by the underlying disorder entity. Thus, all symptoms should have the same or similar risk factors (Isvoranu, Boyette, et al., 2020). The symptoms represent examples extracted from the Positive and Negative Syndrome Scale (Kay et al., 1987).

Historically, essentialist conceptions of mental disorders date back to the influential work of Emil Kraepelin (Borsboom et al., 2016). Building upon advances in general medicine at the turn of the century, when bacterial infections were identified as the common cause of the symptoms observed in diseases such as tuberculosis, Kraepelin popularized the view that symptoms of mental disorders are a consequence of distinct, to-be-identified disorder entities (Borsboom, 2017a; Kendler & Engstrom, 2018; Kendler, 2019; Loch, 2019). This view – in which mental disorders are conceptualized in the

same way as medical disorders – is arguably still the (often tacitly adopted) standard view in psychiatry today and firmly entrenched in diagnostic manuals (Borsboom, 2017b; Borsboom et al., 2016; de Boer et al., 2021; Fried & Robinaugh, 2020; Isvoranu, Boyette, et al., 2020).

Typically embedded in the common cause model of psychopathology is the notion that the essence of mental disorder can be identified at the level of biology, i.e., disturbed or abnormal structures, functions, or processes in the brain (Borsboom et al., 2019; Haslam, 2000; Kendler, 2019; McHugh & Slavney, 1998). Moreover, the effects of environmental risk factors are expected to be mediated by the underlying disorder entity (see *figure 1*). Specifically, environmental risk factors are thought to contribute to the liability to develop a psychotic disorder, which in turn causes the symptoms (Isvoranu, Boyette, et al., 2020; Isvoranu et al., 2016). Consequently, all symptoms observed within the disorder should have the same or similar risk factors (Isvoranu, Boyette, et al., 2020). From an essentialist perspective, therefore, the principle aim of research into the nature of mental disorders is to reveal their biological substrates, through which also the effects of environmental risk factors should be understood (Deacon, 2013; Isvoranu et al., 2016; Kuipers et al., 2019).

1.4 Problems with the essentialist view on psychotic disorders

> "The current concept of schizophrenia, described by diagnostic guidelines and later reified, has become detrimental to progress in mental health by confining research efforts to a constantly changing construct that does not exist in Nature."
> —(Guloksuz & van Os, 2018, p. 239)

While essentialist approaches are pervasive in psychiatric research and practice owing to their practical utility and intuitivity, evidence has accumulated against the hypothesis that mental disorders represent natural kinds. In what follows, I will briefly review key findings from the field that, taken together, refute the assumption that psychotic disorders are discrete disorder entities with similar clinical presentation and prognosis. Interestingly, many of the points outlined below can be traced to early critiques of Kraepelin's application of the medical disease model to psychiatry at the turn of the century (Kendler & Engstrom, 2018).

1.4.1 The role of historical circumstances and context

First, it is useful to consider that even though essentialist conceptions of mental disorders are ubiquitous in psychiatric research and practice, diagnostic categories, such as schizophrenia, are not 'natural' (Kendler, 2008, 2016). Much rather, the design of our classification of mental disorders has been heavily shaped by historical circumstances and influential experts (Bentall et al., 1988; Deacon, 2013; Kendler, 2016; Loch, 2019; Scull, 2021). For example, Kendler (2016) argues that our classification of mental disorders would likely look quite different had Emil Kraepelin not involuntarily abandoned his career in experimental psychology: Without Kraepelin's work on psychiatric nosology, especially that of the psychoses, it appears unlikely that today's diagnostic concept of 'schizophrenia' would have emerged the way it did.

Relatedly, some aspects of psychopathology are influenced by context (Borsboom et al., 2019; Haslam, 2000; McGrath et al., 2004). For example, the distress associated with psychotic experiences that determines clinical relevance varies considerably across cultures (Garety et al., 2007; Luhrmann, 2017). Similarly, the diagnostic concept of psychotic disorders such as schizophrenia has changed on

a number of occasions over time; for example in the 1980s, when the broad schizophrenia concept in DSM-II was replaced with DSM-III's narrow definition of chronic schizophrenia (Bentall et al., 1988; Guloksuz & van Os, 2018).

Thus, our definitions of psychotic disorders are not independent of historical circumstances and contexts, in contrast to what would be expected if they were in fact natural kinds, i.e., those sufficiently characterized by a universal essence that makes them what they are (Bentall et al., 1988; Haslam, 2000; Kendler, 2016).

1.4.2 Lack of expected zones of rarity

Second, taxometric analyses have consistently demonstrated the lack of expected zones of rarity in most mental disorders, including psychotic disorders, i.e., there is no evidence for a clear dividing line that separates psychotic disorders from mental health (Haslam et al., 2020; Kotov et al., 2020). In accordance therewith, attenuated expressions of positive psychotic symptoms below the diagnostic threshold (also called *psychotic experiences*, which typically encompass delusional and hallucinatory experiences) are reported by about 5.8% of the general population in their lifetime (McGrath et al., 2015). This proportion is about 7.25 times greater than the worldwide lifetime prevalence of psychotic disorders in general population samples would suggest (Linscott & van Os, 2013; Moreno-Küstner et al., 2018; van Os & Reininghaus, 2016). Psychotic experiences are usually transient, but persist over time in about 20% of individuals and result in a psychotic disorder in about 7% of individuals who report psychotic experiences (Linscott & van Os, 2013; van Os & Reininghaus, 2016; Zammit et al., 2013).

These observations have led to a re-conceptualization of psychotic psychopathology: It is not an 'all-or-none' phenomenon that occurs only in patients diagnosed with psychotic disorders, but is distributed throughout the population along a phenomenological and temporally continuous dimension (DeRosse & Karlsgodt, 2015; Guloksuz & van Os, 2018; Haslam et al., 2020; Krabbendam et al., 2004; Linscott & van Os, 2013; Rimvall et al., 2020; van Nierop et al., 2012). The hypothesized psychosis continuum ranges from mostly transient psychotic experiences to full-blown psychotic symptoms observed in psychotic disorders, with risk factors acting in similar ways across the continuum (Cosgrave et al., 2021; DeRosse & Karlsgodt, 2015; Guloksuz & van Os, 2018; Haslam et al., 2020; Kotov et al., 2017; Krabbendam et al., 2004; Linscott & van Os, 2013; Loch, 2019; van Os & Reininghaus, 2016). This means that environmental risk factors for psychotic disorders also increase the risk for attenuated expressions of psychotic psychopathology (Cosgrave et al., 2021; Linscott & van Os, 2013). Linscott and van Os (2013), in their psychosis-proneness-persistence-impairment model, propose that environmental risk factors may increase the distress and severity associated with attenuated psychotic psychopathology, increasing the probability that it will develop into clinically relevant psychotic psychopathology.

Overall, there is ample evidence that psychopathology across the psychosis continuum differs in severity, frequency, and associated distress, but not in kind (Cosgrave et al., 2021; Krabbendam et al., 2004; Linscott & van Os, 2013; van Nierop et al., 2012; van Os & Reininghaus, 2016). In other words, differences between attenuated and full-blown psychotic symptoms are quantitative rather than qualitative (Schreuder et al., 2021). Any binary classification of naturally continuous phenomena, such as is inherent in the diagnosis of 'schizophrenia', remains arbitrary with respect to cut-off values and inevitably leads to a loss of rich clinical information (Guloksuz & van Os, 2018; Kotov et al., 2017; Rimvall et al., 2020). However, most efforts in psychosis research concentrate on the narrow 'schizophrenia' population, in keeping with an essentialist mindset (Guloksuz & van Os, 2018).

1.4.3 Fuzzy disorder boundaries

Third, it also appears that boundaries between supposedly distinct disorder entities, such as psychotic and affective disorders, are fuzzy rather than sharp (Haslam, 2000). Specifically, expression of psychopathology has been shown to be more transdiagnostic than previously thought: Psychotic experiences predict subsequent psychotic (Chapman et al., 1994; van Nierop et al., 2012) but also non-psychotic mental disorders, such as affective and substance use disorders (Kaymaz et al., 2007; Rössler et al., 2011). Attenuated and full-blown psychotic symptoms also manifest in the context of non-psychotic disorders, such as mood, anxiety, behavioral or borderline personality disorders (Hanssen et al., 2003; Kelleher et al., 2012, 2014; Slotema et al., 2018; Varghese et al., 2011; Wigman et al., 2012), and predict poorer outcomes therein (Perlis et al., 2011; Slotema et al., 2018). Thus, psychotic psychopathology has prognostic relevance for a wide range of mental disorders and its expression is likewise not restricted to psychotic disorders (Loch, 2019).

On the other hand, non-psychotic psychopathology, such as affective disturbance, may play a crucial role in progression from non-clinical to clinical levels of psychosis (Guloksuz et al., 2015, 2020; Myin-Germeys & van Os, 2007; Smeets et al., 2012; van Os & Reininghaus, 2016). Additionally, particularly in early phases of psychotic disorder, a significant proportion of patients report affective symptoms, such as depressed mood, anxiety, and suicidality, which are associated with higher severity of psychotic symptoms, distress, and poorer outcomes (Conley et al., 2007; Hartley et al., 2013; Upthegrove et al., 2010, 2020; Wilson et al., 2020). Given these key functional roles, affective psychopathology should not be considered a mere comorbidity, but rather a fundamental feature of psychotic disorders (Upthegrove et al., 2010, 2020).

Taken together, both psychotic and affective psychopathology occur irrespective of diagnostic boundaries established by essentialist approaches. These findings are difficult to reconcile with the notion that mental disorders, as currently defined, represent distinct natural kinds.

1.4.4 Heterogeneity in clinical presentation and etiology

Finally, individuals diagnosed with psychotic disorders show vast variability in their clinical presentation (Cocchi et al., 2013; Dwyer et al., 2020; Picardi et al., 2012). In fact, based on criteria set forth in diagnostic manuals, such as the DSM, two people with the diagnosis 'schizophrenia' may not have a single symptom in common (Andreasen, 1999; Bentall et al., 1988). Similarly, illness courses and outcomes are highly variable in psychotic disorders (Bentall et al., 1988; Dwyer et al., 2020). For instance, patients with psychotic disorders who report higher levels of depressive symptoms are at increased risk for a fluctuating illness course characterized by re-occurrence of functional impairments after partial recovery compared to patients with lower levels of depressive symptoms (Dwyer et al., 2020). Collectively, these findings cast doubt on the notion that symptoms act as equivalent or interchangeable indicators of a latent disorder entity that determines similar prognosis across patients (Bentall et al., 1988).

Individual environmental risk factors typically increase risk for developing specific (as opposed to all) psychotic experiences and symptoms, which contributes to the observed phenotypic heterogeneity in psychotic disorders (Bentall et al., 2012; Berg et al., 2014; Freeman et al., 2015; Garety et al., 2007). For example, cannabis use seems to primarily induce hallucinatory, but not delusional experiences (Freeman et al., 2015). These findings are at odds with what one would expect from the essentialist perspective, i.e., that there is no specificity whatsoever in the associations between risk factors and symptoms of psychosis given the mediating role of the hypothesized disorder entity (see *figure 1*). Complementing evidence for

fuzzy disorder boundaries reviewed in the previous section, many risk factors, such as childhood trauma and insecure attachment, also convey risk for multiple, putatively distinct disorders, such as psychotic and affective disorders, through transdiagnostic processes (Herstell et al., 2021; McLaughlin et al., 2020; Zwicker et al., 2018).

Overall, these observations suggest a high degree of heterogeneity in the clinical presentation, course, and etiology of psychotic psychopathology that common cause models cannot account for.

1.5 Consequences of essentialist views for psychosis research and treatment

The available evidence suggests that our current diagnostic categories for psychotic disorders are highly fuzzy, heterogeneous and strongly influenced by historical circumstances and context. Thus, the conceptualization of psychotic disorders as natural kinds with a causally acting, biologically based essence is "at best, an idealization" (Kendler et al., 2011, p. 1144). For this reasons, diagnostic labels such as 'schizophrenia' have been viewed as scientifically questionable concepts for some time now (Bentall et al., 1988). Not surprisingly, despite tremendous research efforts over the years to 'reverse-engineer' their presumed biological essence, no uniquely specific biomarker for any mental disorder, including psychotic disorders, is available to date (Adam, 2013; Borsboom, 2017b; Borsboom et al., 2019; Guloksuz & van Os, 2018; Scull, 2021).

For psychosis research, it follows that approaches based upon essentialist assumptions, e.g., linking environmental risk factors to sum scores or diagnoses, are problematic. First, these approaches rely on diagnostic categories with limited scientific support, as discussed above. Second, common cause models do not foresee specific pathways from individual environmental risk factors to particular patterns of symptom expression in psychosis (see *figure 1*), yet there is ample evidence for these (Bentall et al., 2012; Berg et al., 2014; Freeman et al., 2015; Isvoranu et al., 2016; Kendler, 2008). Thus, common cause approaches to psychosis are inherently limited in their explanatory power. Therefore, there are increasing voices arguing that further research on the etiology of diagnostic categories such as schizophrenia will likely prove futile and not help improve outcomes in psychotic disorders (Bentall et al., 1988; Fried & Robinaugh, 2020; Haslam, 2000; Kendler, 2008, 2019).

Essentialism not only hampers progress in etiological research, but also comes with direct negative consequences for the patient. Treatment approaches that focus on 'all-or-none' disorders tend to neglect evidence that significant impairments and distress can arise in the absence of a formal diagnosis at the less severe ends of the psychosis continuum (Kelleher et al., 2014; van Nierop et al., 2012; Wüsten et al., 2018). As a consequence, the potential of prevention and early intervention in psychosis is not yet sufficiently exploited (Correll et al., 2018; Drake et al., 2020; Fusar-Poli et al., 2020; Mei et al., 2021). Particularly in conjunction with the prevailing, primarily biomedical explanations of mental disorders, essentialism also exacerbates the pessimistic view that mental disorders are immutable and unlikely to remit (Lebowitz & Appelbaum, 2019). Among clinicians, reliance on an essentialist, biomedical model has been associated with lower levels of empathy, warmth, and care for their patients, thereby compromising the therapeutic alliance (Lebowitz, 2014; Lebowitz et al., 2015). In patients, it has been linked to a lower belief in their ability to overcome symptoms (Lebowitz et al., 2013).

1.6 A network approach to psychotic psychopathology

> "[D]espite thousands of new studies every year, and major technological advances, schizophrenia research is not leading to consistent improvements in the lives of people with the disorder (Insel, 2010). What might make a difference? One possibility is that a shift in the way that schizophrenia is conceptualized and approached may lead to improvements in our understanding of the condition, which could then translate into more effective methods of prevention and promotion of recovery."
> —(Silverstein et al., 2014, p. 259)

On the basis of the evidence reviewed above, it can be concluded that the common cause model does not offer the best perspective to parse etiological pathways to psychosis (Borsboom, 2017a; Isvoranu, Boyette, et al., 2020). Like most natural phenomena, psychotic psychopathology requires an explanatory framework that allows to go beyond the simplistic accounts offered by essentialism. Recent years have therefore seen growing calls for alternative conceptualizations of psychosis that embrace its heterogeneous and multifactorial nature (Guloksuz & van Os, 2018; Isvoranu et al., 2016; Kuipers et al., 2019; McGorry et al., 2018; Wigman et al., 2012).

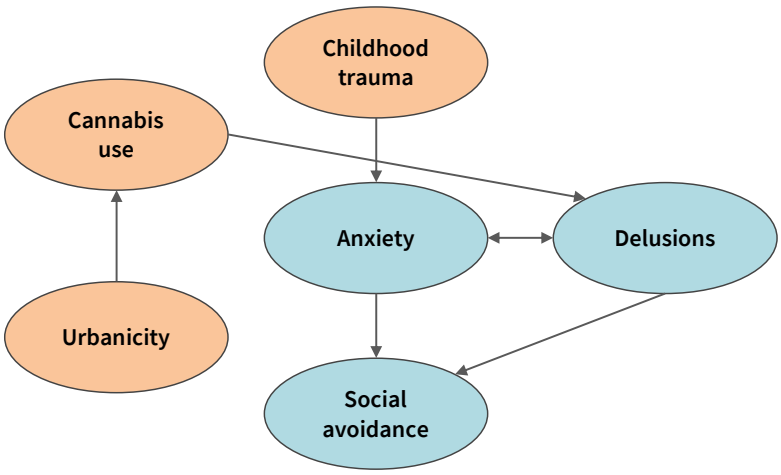

Figure 2: Simplified visualization of a hypothetical network model of schizophrenia. Following this model, the symptoms of schizophrenia (depicted in turquoise) have causal power to influence each other. Similarly, environmental factors, such as childhood trauma (depicted in orange), can trigger individual symptoms directly. The symptoms represent examples extracted from the Positive and Negative Syndrome Scale (Kay et al., 1987).

One such conceptualization is the *network approach to psychopathology*, developed in a series of papers by the psychometrician Denny Borsboom and his colleagues from 2008 on (Borsboom, 2008; Borsboom & Cramer, 2013; Cramer et al., 2010; Schmittmann et al., 2013). In this approach, individual symptoms take the stage as the central units of analysis: Mental disorders are conceived as networks of causally connected symptoms (Borsboom, 2008, 2017a; see *figure 2*). In other words, the observed patterns of covariation between symptoms are no longer explained by a latent disorder entity but are themselves thought to reflect direct relations constituting the disorder (Borsboom, 2017a; Schmittmann et al., 2013). *Direct* implies that the relation between symptoms is real, i.e., not

spurious in the sense that a common cause model assumes it to be (Borsboom et al., 2016; Cramer et al., 2010). Components other than symptoms, such as risk factors, can be explicitly integrated into network models to assess their relationship with individual symptoms (Isvoranu, Boyette, et al., 2020; see *figure 2*).

This shift in perspective promotes symptoms from passive, interchangeable indicators to active, non-interchangeable agents (Borsboom, 2017b; Robinaugh et al., 2020). The idea of causal symptom-symptom relations is intuitive and aligns well with how clinicians typically think about and aim to treat psychopathology (Hofmann & Hayes, 2019; Kendler, 2017; Kim & Ahn, 2002; McNally, 2021) – for example, experiencing delusions may trigger anxiety, which in turn may lead the patient to isolate herself at home (Isvoranu, Boyette, et al., 2020; Isvoranu, Guloksuz, et al., 2020). In other words, symptoms, and other relevant components, such as environmental risk factors, do not co-occur randomly, but because they are functionally related (McNally, 2021). From a philosophical stance, the network approach conceptualizes mental disorders as kinds unified by direct, meaningful relations among symptoms rather than a shared essence (Kendler, 2016; Kendler et al., 2011; Robinaugh et al., 2020).

In sum, mental disorders are thought to result from a complex interplay between functionally related symptoms and other relevant components rather than a central dysfunction (Isvoranu, Guloksuz, et al., 2020). Interestingly, this also reflects the state-of-the-art in disorders such as diabetes, where etiology is considered to be highly multifactorial (Kendler, 2019; Tremblay & Hamet, 2019). Some authors have therefore argued that the network view may serve as an important research approach for medicine as a whole (Guloksuz et al., 2017).

1.7 Network analysis: the statistical back-end of the network approach

Symptom networks cannot be observed directly, but need to be estimated (McNally, 2021). The term *network analysis* subsumes the statistical techniques used to generate symptom network structures from empirical data (Borsboom et al., 2021). In these network structures, *nodes* represent individual symptoms and other components of interest, and *edges* represent unique, pairwise relations between individual symptoms (Epskamp, Waldorp, et al., 2018). In the following, I will give an overview of the most important statistical techniques used for estimating networks given different types of data.

To identify the direct symptom-symptom relations of central interest in the network approach, network analysis typically involves the estimation of sparse networks of conditional dependence relationships (Robinaugh et al., 2020). These network structures represent a set of unique, pairwise relations between symptoms and other relevant components, i.e., relations that cannot be explained by any other variable under consideration. To obtain sparse network structures, regularization techniques, such as penalized maximum likelihood estimation, can be used (Abegaz & Wit, 2013; Epskamp, Waldorp, et al., 2018; Friedman et al., 2008; Haslbeck & Waldorp, 2020; van Borkulo et al., 2014). These techniques set small edges, assumed to reflect sampling variation rather than true relations, to zero (Epskamp, Waldorp, et al., 2018). Alternatively, stepwise model search can be conducted by repeatedly adding and pruning edges and fitting the corresponding network to find a parsimonious model with optimal information criterion (Epskamp, 2020; Isvoranu, Guloksuz, et al., 2020).

1.7.1 Symptom networks estimated in cross-sectional data

For cross-sectional data, network analysis typically involves the estimation of unique, undirected pairwise relations between symptoms in the form of a pairwise Markov Random Field (PMRF): the Ising Model for binary data (van Borkulo et al., 2014), the Gaussian Graphical Model for multivariate

normal data (Epskamp, Waldorp, et al., 2018), and the Mixed Graphical Model for mixed data (Haslbeck & Waldorp, 2020; Yang et al., 2014). Other modeling approaches, such as directed acyclic graphs (DAGs), can also be used to estimate cross-sectional network structures with directed relations (Moffa et al., 2017). However, DAGs place strong, clinically implausible assumptions on the structure of the generating model, such as acyclicity, and are therefore much less common (Borsboom et al., 2021; McNally, 2021; Robinaugh et al., 2020).

A PMRF estimated in cross-sectional data represents the multivariate pattern of conditional dependencies that characterize the joint distribution of the variables in the network, measured at a single time point in a large sample (Borsboom et al., 2021; Epskamp, Waldorp, et al., 2018; Hamaker, 2012). Particularly conditional independence relations reveal important information about potential etiological mechanisms: Whenever two nodes in a network are not connected by an edge, there is no direct relation between the corresponding symptoms or components of interest; rather, they affect each other only indirectly via other symptoms or components of interest (Borsboom et al., 2021; Epskamp, Waldorp, et al., 2018). Without a priori commitment to a particular data-generating mechanism, cross-sectional networks provide a valuable exploratory view on undirected functional relations between environmental risk factors and symptoms, as described in more detail below (Borsboom et al., 2021; Isvoranu et al., 2017).

1.7.2 Symptom networks estimated in longitudinal data

Cross-sectional network analysis, however, cannot provide insights into truly dynamic symptom relations as proposed in the network approach to psychopathology. Moreover, it is unclear whether relationships identified at the cross-sectional group level also hold at the individual level: Estimated edges reflect a blend of between- and within-person processes present at a single point in time (Epskamp, 2020; Hamaker, 2012).

To reveal potential dynamic relationships among the variables of interest, some form of longitudinal data are necessary (Borsboom et al., 2021). These may be panel data, i.e., a limited set of repeated measurements for a large number of participants, or a large number of repeated measurements for at least one participant, collected using, for example, experience sampling methods (ESM). Networks are typically estimated from longitudinal data using statistical techniques based on vector autoregressive (VAR) models (Epskamp, 2020; Epskamp, Waldorp, et al., 2018). These allow for the estimation of temporal relationships and contemporaneous relationships between symptoms and other components of interest (Epskamp, Waldorp, et al., 2018). Temporal relationships indicate how, on average, symptoms predict each other or themselves in the next window of measurement, potentially providing information about the direction of the effect (Jordan et al., 2020). Contemporaneous relationships indicate how symptoms, on average, relate to each other within the same window of measurement (Epskamp, Waldorp, et al., 2018).

Networks based on ESM data allow to estimate temporal and contemporaneous networks for individual participants, providing insight into symptom dynamics specific to each person (Epskamp, van Borkulo, et al., 2018; Robinaugh et al., 2020). ESM data from multiple participants additionally allow to derive temporal and contemporaneous networks on group-level, i.e., average symptom dynamics, and thus can explicitly separate within-subject and between-subject effects (Borsboom et al., 2021; Epskamp, 2020; Epskamp, Waldorp, et al., 2018).

1.7.3 Which kind of network analysis to choose?

Ultimately, the choice of analysis depends on the available data and the research question at hand. For example, some environmental risk factors, such as developmental cannabis use or exposure to childhood trauma, do not vary within an individual over time. Therefore, a longitudinal network modeling approach may not be the best choice to elucidate potential direct etiological pathways, as repeated assessment of time-invariant risk factors does not yield new information. Valuable insights can instead be gained by integrating different levels of analysis, e.g., by relying on clinician-rated symptoms from a single time point (Isvoranu et al., 2017), or by assessing how dynamic symptom-symptom relations in personalized networks differ across individuals as a function of time-invariant environmental exposure (Rosen et al., 2022). Overall, within-person dynamics and between-person differences are not entirely unrelated; rather, cross-sectional symptom networks have been shown to be of exploratory value for generating hypotheses for relations occurring within persons (von Klipstein et al., 2021). To obtain a comprehensive picture of the role of environmental exposure in psychopathological processes, ideally different levels of network analysis should be integrated (Epskamp, Waldorp, et al., 2018).

1.8 Environmental exposure in the network of psychopathology

There are two principal ways through which the effects of environmental risk factors in symptom networks may be conceived.

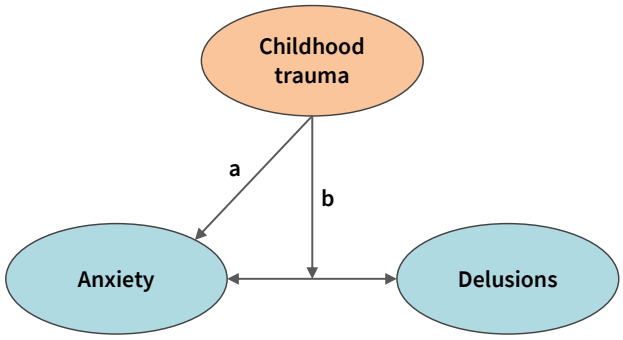

Figure 3: Simplified visualization of direct and indirect effects of environmental risk factors in symptom networks. (a) An environmental risk factor, such as childhood trauma (depicted in orange), can trigger individual symptoms observed in psychotic disorders (depicted in turquoise) directly. (b) An environmental risk factor, such as childhood trauma (depicted in orange), can shape the relation between individual symptoms observed in psychotic disorders (depicted in turquoise). The symptoms represent examples extracted from the Positive and Negative Syndrome Scale (Kay et al., 1987).

First, environmental factors may be integrated into the symptom network as nodes (see *figure 3a*), which allows to assess their direct relations with individual symptoms (Borsboom, 2017a). Within network structures derived from empirical data, the observation of such a relationship is a necessary condition for a causal relationship between a risk factor and a specific symptom, but usually not sufficient (due to the possible influence of, e.g., unmeasured confounders) (Borsboom et al., 2021; de Boer et al., 2021; Epskamp, van Borkulo, et al., 2018). Therefore, observed direct associations in symptom networks can only be interpreted as an indication of potential causal pathways from an upstream environmental

risk factor to individual symptoms (Epskamp, Waldorp, et al., 2018; Isvoranu, Boyette, et al., 2020; Isvoranu et al., 2016). For a unidirectional interpretation of the relationships between risk factors and symptoms, an appropriate temporal sequence is required (de Boer et al., 2021). This can be realized either in temporally ordered data, for instance panel or ESM data, or through inherent relationships, e.g., when examining the impact of childhood trauma on psychopathology in adulthood (Isvoranu et al., 2017). Thus, from a theoretical perspective, one mode of action of environmental exposure is that it may contribute to the probability of the occurrence of certain symptoms (Isvoranu, Boyette, et al., 2020). Activation of these symptoms could in turn trigger activation of other, neighboring symptoms in the network. By parsing unique pairwise relations between the components under consideration, network analysis enables the representation of multistep pathways from environmental risk factors to specific symptoms (Borsboom et al., 2021; Isvoranu et al., 2017, 2020).

Second, environmental factors may moderate the strength of edges between two symptoms (see *figure 3b*), i.e., shape potentially causal effects between two symptoms (Borsboom, 2017a). For example, an environmental risk factor may predispose an individual to experience greater levels of anxiety in response to delusions (Isvoranu, Boyette, et al., 2020; Isvoranu et al., 2016). Such moderation effects may be assessed in both cross-sectional and longitudinal data. Theoretically, in this mode of action, environmental risk contributes to the probability of experiencing certain symptoms in concert (Borsboom, 2017a; Isvoranu, Boyette, et al., 2020). This view concurs with findings demonstrating that the degree to which psychotic experiences co-occur with affective symptoms depends on the level of environmental exposure (Guloksuz et al., 2015; van Nierop et al., 2015).

In summary, environmental exposure contributes to etiological heterogeneity in psychosis expression in two ways: by increasing the risk to experience specific symptoms and by shaping the strength of connections between certain symptoms (Betz, Penzel, Rosen, Bhui, et al., 2021; Borsboom, 2017a).

1.9 A transdiagnostic network approach to psychosis

By shifting the focus from hypothesized disorder entities to observable individual symptoms and their connections, the network approach allows for a broad, transdiagnostic view on psychopathology that has been advocated by several leading commentators in the field for a better understanding of the etiology of psychosis (Bentall et al., 2012; DeRosse & Karlsgodt, 2015; Guloksuz & van Os, 2018; McGorry et al., 2018; Upthegrove et al., 2020; van Os & Reininghaus, 2016; Wigman et al., 2012).

First and foremost, the network approach, with its focus on specific symptoms and their interrelations, aligns well with research showing that different types of attenuated and full-blown psychotic symptoms should be treated as phenomena of interest in their own right with differentiated etiological processes (Bentall et al., 2012; Freeman, 2007; Freeman et al., 2010, 2015, 2017; Freeman & Garety, 2014; McGrath et al., 2015). When these phenomena are construed as individual nodes in symptom networks, relations can become apparent that would remain hidden if sum scores were used (McNally, 2021). Similarly, specific associations between different environmental risk factors and individual symptoms can be assessed, which may provide clues to the differential processes associated with specific environmental risk factors, which in turn has implications for prevention and treatment (Kuipers et al., 2019). Second, the network approach, quite naturally, also discontinues the rigid separation of psychotic and non-psychotic psychopathology and allows the inclusion of symptoms from different domains in the sense of a transdiagnostic perspective (Borsboom et al., 2011; Cramer et al., 2010; Kuipers et al., 2019). This concurs with a growing recognition that non-psychotic psychopathology, such as anxious and depressed mood, sleep disturbance, and increased stress reactivity, is fundamental

to the development, progression, and maintenance of specific psychotic symptoms and not merely a comorbidity phenomenon (Freeman et al., 2012; Griffiths et al., 2021; Guloksuz et al., 2020; Guloksuz & van Os, 2018; Myin-Germeys & van Os, 2007; Upthegrove et al., 2017; van Os et al., 2020; van Os & Reininghaus, 2016).

With this outlook, the network perspective has proven to be a rich source of insights into the pathways of environmental risk factors in psychosis. In a seminal paper, Isvoranu and colleagues (2017) employed a network approach to show that childhood trauma does not connect to psychotic symptoms directly, but only indirectly via pathways through general psychopathology. Thus, by incorporating symptoms from multiple domains, the network approach can reveal potential transdiagnostic processes: An affective pathway involving increased stress reactivity may be a possible route through which childhood trauma increases risk for psychopathology in general (Isvoranu et al., 2017; McLaughlin et al., 2020; Myin-Germeys & van Os, 2007; Upthegrove et al., 2015). Such results, not readily achievable with approaches targeting common causes, are of great clinical importance because non-psychotic general psychopathology may serve as a potential target for prevention and treatment, especially in early stages of psychosis (Griffiths et al., 2021; Guloksuz et al., 2020; Kuipers et al., 2019; Upthegrove et al., 2020).

Not relying on disorder entities of an 'all-or-none' nature, the network approach also allows to incorporate the assumptions of phenomenological and etiological continuity into the research agenda of psychosis (Borsboom et al., 2016). A central implication of this continuum perspective is that the study of attenuated psychotic experiences and associated risk mechanisms can inform the understanding of full-blown expressions of psychosis (Freeman, 2007). Specifically, environmental risk factors for psychotic disorders also increase the risk of psychotic experiences (Cosgrave et al., 2021; Linscott & van Os, 2013). Thus, there is a compelling case for expanding network-analytic research efforts to at-risk and general population samples to better understand the etiology of clinically relevant psychotic psychopathology.

1.10 Thesis outline

In summary, the network approach to psychopathology is a framework well-suited to accommodate the highly heterogeneous nature of psychosis, its complexity and fuzzy boundaries, and the central role of individual symptoms with distinct underlying etiological processes. In this spirit, this thesis takes a transdiagnostic network perspective to help disentangle how environmental risk factors shape the expression of psychosis in non-clinical and clinical populations. Specifically, the series of papers presented focuses on (1) pathways from recent stressful life events to psychotic psychopathology, (2) pathways from childhood trauma to perceived stress, (3) pathways from cannabis use characteristic to psychotic experiences, (4) the heterogeneity in symptom networks of psychosis as a function of environmental and demographic risk factors, and (5) the study protocol for an ESM study in a help-seeking population, which will allow to link environmental risk factors to personalized networks. Each paper is described in more detail below.

The first part of this thesis (Chapters 2.1–2.3) examines the pathways through which three known environmental risk factors for psychotic disorders, i.e., early and recent stressful life events and developmental cannabis use, increase the risk for psychotic psychopathology. Chapter 2.1 (Betz et al., 2020), presents results from an analysis conducted in patients at-risk for psychosis and recent onset psychosis from the multicentric, European Personalised Prognostic Tools for Early Psychosis Management (PRONIA) study. Building on evidence for an affective pathway from childhood trauma to psychosis shown in a network approach by Isvoranu et al. (2017), we tested whether a similar pathway applies to exposure to recent stressful life events (Beards et al., 2013). To do so, we integrated results

from network analyses based on cross-sectional and panel data. Chapter 2.2 (Betz, Penzel, Rosen, & Kambeitz, 2021) zooms into the proposed affective pathway via increased stress reactivity through which childhood trauma is thought to contribute to the liability for psychopathology at large, including psychotic disorders (McLaughlin et al., 2017, 2020; Myin-Germeys & van Os, 2007; Reininghaus et al., 2016). Specifically, this work sought to explore the potential cognitive pathways through which different domains of childhood trauma, which can be broadly categorized into abuse and neglect experiences (McLaughlin et al., 2014; Wadsworth, 2015), are associated with different facets of perceived stress. Methodologically, we constructed cross-sectional networks using data from two large, nationally representative samples from the United States. Chapter 2.3 (Betz et al., 2022) turns to another important environmental risk factor for psychotic disorders, cannabis use (Moore et al., 2007; Sideli, Quigley, et al., 2020). Building on findings of our group that highlighted the distinct effects of early initiation of cannabis use on brain development (Penzel et al., 2021), we examined the differential effects of age of initiation of cannabis use on psychopathology while controlling for the effects of lifetime cumulative cannabis use as well as early life risk factors. Specifically, we employed a network-analytic approach based on mixed cross-sectional data from a large general population sample from the United States. With this analysis, the study sought to provide a more nuanced look at the impact of developmental cannabis use on psychopathology than previous research that either aggregated different psychotic experiences into sum scores or did not model other important risk factors simultaneously (Guloksuz et al., 2018; Zwicker et al., 2018).

The second part of this thesis (Chapters 2.4–2.5) examines how environmental risk factors contribute to the heterogeneity observed in the psychosis continuum through indirect effects, i.e., by moderating the strength of edges in cross-sectional and dynamic symptom networks. Addressing this heterogeneity is critical to uncover potential differences in relevant etiological mechanisms that may be concealed in averaged network models of psychosis (Betz, Penzel, Rosen, Bhui, et al., 2021; Jones et al., 2020). Chapter 2.4 (Betz, Penzel, Rosen, Bhui, et al., 2021) reports findings from an innovative recursive partitioning approach applied to a large general population sample from England to explore moderation effects of environmental exposure on cross-sectional symptom networks of psychosis expression. The data-driven, exploratory recursive partitioning approach has the particular advantage that it can identify individual and joint moderating effects of many environmental and demographic factors on symptom networks (Betz, Penzel, Rosen, Bhui, et al., 2021; Jones et al., 2020), moving beyond problematic a priori thresholding or combination of risk factors (e.g., Guloksuz et al., 2015; Isvoranu et al., 2016; Wüsten et al., 2018). Using this approach, we were able to comprehensively explore potential etiological differences in psychosis risk (Guloksuz et al., 2018; Zwicker et al., 2018). Chapter 2.5 (Rosen et al., 2022) takes the step from cross-sectional networks to truly dynamic symptom networks, introducing the study protocol for the ESM project PhenoNetz conducted from November 2020 until November 2021 in the Early Recognition Center for Mental Disorders of the University Hospital Cologne. The PhenoNetz study aims to provide an explorative phenotyping of transdiagnostic psychopathology in a heterogeneous help-seeking population. Specifically, we propose to use multilevel VAR models to gain insight into the dynamic patterns of connectivity between a set of psychotic and non-psychotic experiences. A central goal of the study is to examine how the connectivity within these dynamic symptom networks varies as a function of environmental exposure.

Chapter 3 concludes this thesis with a synthesis of findings from theoretical and clinical perspectives and a discussion of the challenges of current approaches and future research directions for understanding the role of environmental risk factors in psychotic disorders.

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2. Original Publications

This cumulative thesis is based on the following publications:

1. **Betz, L. T.***, Penzel, N.*, Kambeitz-Ilankovic, L., Rosen, M., Chisholm, K., Stainton, A., Haidl, T. K., Wenzel, J., Betrolino, A., Borgwardt, S., Brambilla, P., Lencer, R., Meisenzahl, E., Ruhrmann, S., Salokangas, R. K. R., Schultze-Lutter, F., Wood, S. J., Upthegrove, R., Koutsouleris, N., Kambeitz, J., & PRONIA Consortium (2020). General psychopathology links burden of recent life events and psychotic symptoms in a network approach. *npj Schizophrenia, 6*(1), 1–8. https://doi.org/10.1038/s41537-020-00129-w.
2. **Betz, L. T.**, Penzel, N., Rosen, M., & Kambeitz, J. (2021). Relationships between childhood trauma and perceived stress in the general population: a network perspective. *Psychological Medicine, 51*(15), 2696–2706. https://doi.org/10.1017/S003329172000135X.
3. **Betz, L. T.**, Penzel, N., & Kambeitz, J. (2022). A network approach to relationships between cannabis use characteristics and psychopathology in the general population. *Scientific Reports, 12*(1), 1–10. https://doi.org/10.1038/s41598-022-11092-0.
4. **Betz, L. T.**, Penzel, N., Rosen, M., Bhui, K., Upthegrove, R., & Kambeitz, J. (2021). Disentangling heterogeneity of psychosis expression in the general population: sex-specific moderation effects of environmental risk factors on symptom networks. *Psychological Medicine*, 1–10. https://doi.org/10.1017/S0033291721003470.
5. Rosen, M.*, **Betz, L. T.***, Montag, C., Kannen, C., & Kambeitz, J. (2022). Transdiagnostic psychopathology in a help-seeking population of an early recognition center for mental disorders: protocol for an experience sampling study. *JMIR Research Protocols 11*(8), e35206. https://doi.org/10.2196/35206.

   * denotes shared first authorship

   The contributions of all authors to the individual publications are detailed in appendix section 6.6.

2.1 General psychopathology links burden of recent life events and psychotic symptoms in a network approach

Linda T. Betz*, Nora Penzel*, Lana Kambeitz-Ilankovic, Marlene Rosen, Katharine Chisholm, Alexandra Stainton, Theresa K. Haidl, Julian Wenzel, Alessandro Bertolino, Stefan Borgwardt, Paolo Brambilla, Rebekka Lencer, Eva Meisenzahl, Stephan Ruhrmann, Raimo K. R. Salokangas, Frauke Schultze-Lutter, Stephen J. Wood, Rachel Upthegrove, Nikolaos Koutsouleris, Joseph Kambeitz & PRONIA Consortium

* denotes shared first authorship

Published in *npj Schizophrenia*, Volume 6, Article Number 40, pp. 1–8, https://doi.org/10.1038/s41537-020-00129-w.

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General psychopathology links burden of recent life events and psychotic symptoms in a network approach

Linda T. Betz[1,18]✉, Nora Penzel[1,2,18], Lana Kambeitz-Ilankovic[1,2], Marlene Rosen[1], Katharine Chisholm[3,4], Alexandra Stainton[3,5,6], Theresa K. Haidl[1], Julian Wenzel[1], Alessandro Bertolino[7], Stefan Borgwardt[8,9], Paolo Brambilla[10], Rebekka Lencer[9,11,12], Eva Meisenzahl[13], Stephan Ruhrmann[1], Raimo K. R. Salokangas[14], Frauke Schultze-Lutter[13,15], Stephen J. Wood[3,5,6], Rachel Upthegrove[3], Nikolaos Koutsouleris[2,16,17], Joseph Kambeitz[1] and the PRONIA consortium*

Recent life events have been implicated in the onset and progression of psychosis. However, psychological processes that account for the association are yet to be fully understood. Using a network approach, we aimed to identify pathways linking recent life events and symptoms observed in psychosis. Based on previous literature, we hypothesized that general symptoms would mediate between recent life events and psychotic symptoms. We analyzed baseline data of patients at clinical high risk for psychosis and with recent-onset psychosis ($n = 547$) from the Personalised Prognostic Tools for Early Psychosis Management (PRONIA) study. In a network analysis, we modeled links between the burden of recent life events and all individual symptoms of the Positive and Negative Syndrome Scale before and after controlling for childhood trauma. To investigate the longitudinal associations between burden of recent life events and symptoms, we analyzed multiwave panel data from seven timepoints up to month 18. Corroborating our hypothesis, burden of recent life events was connected to positive and negative symptoms through general psychopathology, specifically depression, guilt feelings, anxiety and tension, even after controlling for childhood trauma. Longitudinal modeling indicated that on average, burden of recent life events preceded general psychopathology in the individual. In line with the theory of an affective pathway to psychosis, recent life events may lead to psychotic symptoms via heightened emotional distress. Life events may be one driving force of unspecific, general psychopathology described as characteristic of early phases of the psychosis spectrum, offering promising avenues for interventions.

npj Schizophrenia (2020)6:40 ; https://doi.org/10.1038/s41537-020-00129-w

INTRODUCTION

Stressful life events, such as losing a loved one, failure in an exam or change of residence, have been repeatedly linked to the onset, course and outcome of psychotic disorders[1–7]. Specifically, prior research has documented associations between recent life events and broad outcome categories, such as diagnosis of a psychotic disorder and compound measures of positive symptomatology[2,7,8]. However, the specific pathways linking recent stressful life events and expression of psychotic symptomatology in the psychosis spectrum, including early stages, i.e. at-risk stages and recent-onset psychosis, are yet to be fully understood[2,3,7,9,10].

Recent years have seen the emergence of two distinct trends in the fields of psychopathology and psychiatry that may help to address this issue. First, there is a growing awareness that domains of affective, cognitive and negative symptoms need to be considered to gain a thorough understanding of the etiology of psychosis[11–17]. Second, vital insight can be acquired when modelling psychosis via individual symptoms instead of diagnostic cut-offs and sum scores of symptoms[18]. Specifically, symptom networks may constitute an insightful way to conceive the complex dependencies between life events and symptoms in early phases of the psychosis spectrum[12,18,19]. Here, mental disorders are conceptualized as sets of interacting symptoms that show specific associations with other clinically relevant factors, such as stressful recent life events[12,19].

Adopting a network-based perspective on psychopathology allows the identification of potential psychological pathways from adverse events to psychotic symptoms[12,18,19]. For example, in a previous network analysis, childhood trauma was found to connect to positive and negative symptoms only via symptoms of general psychopathology[12]. These findings suggest that adverse events might result in psychosis through heightened emotional reactivity to stress and add to the accumulating evidence for an affective pathway to psychosis[13,20]. Corroborating this idea, recent findings suggest that the association between a range of lifetime traumatic events and psychotic-like experiences is largely mediated by general psychopathology in a sample of prisoners[21]. Overall, it seems reasonable to hypothesize that recent stressful life events may predispose expression of psychotic symptomatology by a pathway similar to childhood trauma, i.e. via

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heightened emotional distress[13,20,22]. Childhood trauma may interact with adult life events by sensitizing individuals to future stressful events and by increasing the risk of experiencing later burdensome life events[23,24].

Inherently, this reflects a within-person process: individual burden following life events is paralleled by an increase in an individual's emotional distress. Network models estimated from cross-sectional data, though valuable for deriving unique associations in high-dimensional variable spaces, do not necessarily reflect within-person dynamics over time[25]. Rather, cross-sectional networks reflect combined influences at both the within-person and the between-person level[26]. Panel data, in which many subjects are measured at multiple times, allow the examination of average within-person dynamics, i.e. temporal dependencies. To date, this possibility has not been exploited in research on the association between life events and psychopathology observed in the early psychosis spectrum.

Additionally, given large interindividual differences in the experience of the same life events, studying the subjective burden of recently experienced life events rather than the mere exposure may be most insightful[27–29]. Individuals may, for instance, perceive a given life event as less burdensome following prior exposure that allowed them to develop adaptive strategies to deal with similar future adversity[30]. Likewise, life events that are commonly perceived as positive and little stressful may evoke burden in certain individuals. Ideally, analyses should therefore not be limited to a predefined set of negative or traumatic recent life events.

In the current study, we use network analysis to investigate pathways between the cumulative burden of a comprehensive set of recent life events and individual positive, negative and general symptoms in the early psychosis spectrum. Based on previous literature[12,21,31], we hypothesize that burden of recent life events will not be connected to positive and negative symptoms directly, but indirectly via general symptoms. In a control analysis, we examine whether childhood trauma can explain links between burden of recent life events and symptoms. Additionally, we investigate the dynamic, within-person interplay between burden of recent life events and symptomatology over time by using multiwave panel data.

RESULTS

Sample characteristics

The final sample ($N = 547$) comprised 265 patients at clinical high risk for psychosis (CHR) and 282 patients with recent-onset psychosis (ROP). Overall, 47.3% of the participants were women and the average age was 24.7 years (SD = 5.6). On average, 0.3% of the baseline network variables were missing. ROP participants were significantly older and comprised more men as compared to CHR participants. Significant differences were also present in symptomatology and functioning (Table 1). Prevalence of SCID-diagnoses in the sample are available in Supplementary Table 1. Reported number of life events and mean burden did not differ between the groups. For a comparison of demographic and clinical variables in women and men, see Supplementary Table 2. The three most common life events in our sample were "significant negative incident related to partnership", "major examination successful", and "removal from living place" (for an overview of reported life events in the sample, Supplementary Fig. 1). In the longitudinal analysis, 337 participants (168 CHR, 169 ROP) were included. This sample did not differ significantly in most demographic and clinical characteristics at baseline from participants excluded due to missing data (Supplementary Table 3).

Network analysis

Figure 1a illustrates the L_1-regularized Gaussian graphical model[32,33], i.e. the regularized, undirected network of partial correlation coefficients between individual items of the Positive and Negative Syndrome Scale (PANSS[34]) and the cumulative burden of reported recent life events we estimated from the data. Of 465 possible edges, 177 were retained in the L_1-regularized partial correlation network. We identified positive relationships

Table 1. Demographic and clinical characteristics of the sample at baseline.

Variable	CHR ($n = 265$)	ROP ($n = 282$)	Whole sample ($n = 547$)	Comparison (CHR vs. ROP)
Sex (% female)	52.7	42.7	47.5	$\chi^2 = 5.40$, $p = 0.020$
Age	23.6 (5.2)	25.6 (5.9)	24.7 (5.6)	$Z = -4.08$, $p < 0.001$
PANSS (subscale scores)				
Positive	11.2 (3.6)	18.5 (6.1)	15.0 (6.2)	$Z = -13.7$, $p < 0.001$
Negative	13.6 (6.6)	16.1 (7.6)	14.9 (7.2)	$Z = -4.09$, $p < 0.001$
General	29.3 (8.1)	34.7 (10.7)	32.1 (9.9)	$Z = -6.39$, $p < 0.001$
Total	54.1 (15.4)	69.3 (20.4)	62.0 (19.7)	$Z = -9.02$, $p < 0.001$
Number of recent life events (median, range)	3 (0–10)	3 (0–10)	3 (0–10)	$Z = 0.63$, $p = 0.532$
Burden of recent life events	6.6 (6.2)	6.4 (6.6)	6.5 (6.4)	$Z = 0.32$, $p = 0.748$
CTQ-SF (subscale scores)				
Emotional abuse	10.4 (4.5)	9.7 (4.4)	10.0 (4.5)	$Z = 1.65$, $p = 0.101$
Physical abuse	6.5 (2.9)	6.5 (3.1)	6.5 (3.0)	$Z = -0.19$, $p = 0.857$
Sexual abuse	6.0 (2.7)	6.1 (3.0)	6.1 (2.9)	$Z = -0.68$, $p = 0.504$
Emotional neglect	11.9 (4.0)	11.4 (4.1)	11.7 (4.1)	$Z = 1.17$, $p = 0.255$
Physical neglect	7.4 (2.6)	7.6 (3.0)	7.5 (2.8)	$Z = -0.71$, $p = 0.477$
GAF-disability (past month)	52.3 (13.0)	45.0 (14.1)	48.6 (14.1)	$Z = 6.06$, $p < 0.001$
GAF-symptoms (past month)	52.1 (11.3)	41.0 (14.3)	46.4 (14.1)	$Z = 9.22$, $p < 0.001$
BDI-II (total score)	26.3 (12.2)	21.6 (13.1)	23.9 (12.9)	$Z = 3.95$, $p < 0.001$

Means (SD) unless stated otherwise.
BDI Beck Depression Inventory, *CHR* clinical high risk, *CTQ-SF* Childhood Trauma Scale-Short Form, *GAF* global assessment of functioning, *PANSS* Positive and Negative Syndrome Scale, *ROP* recent-onset psychosis.

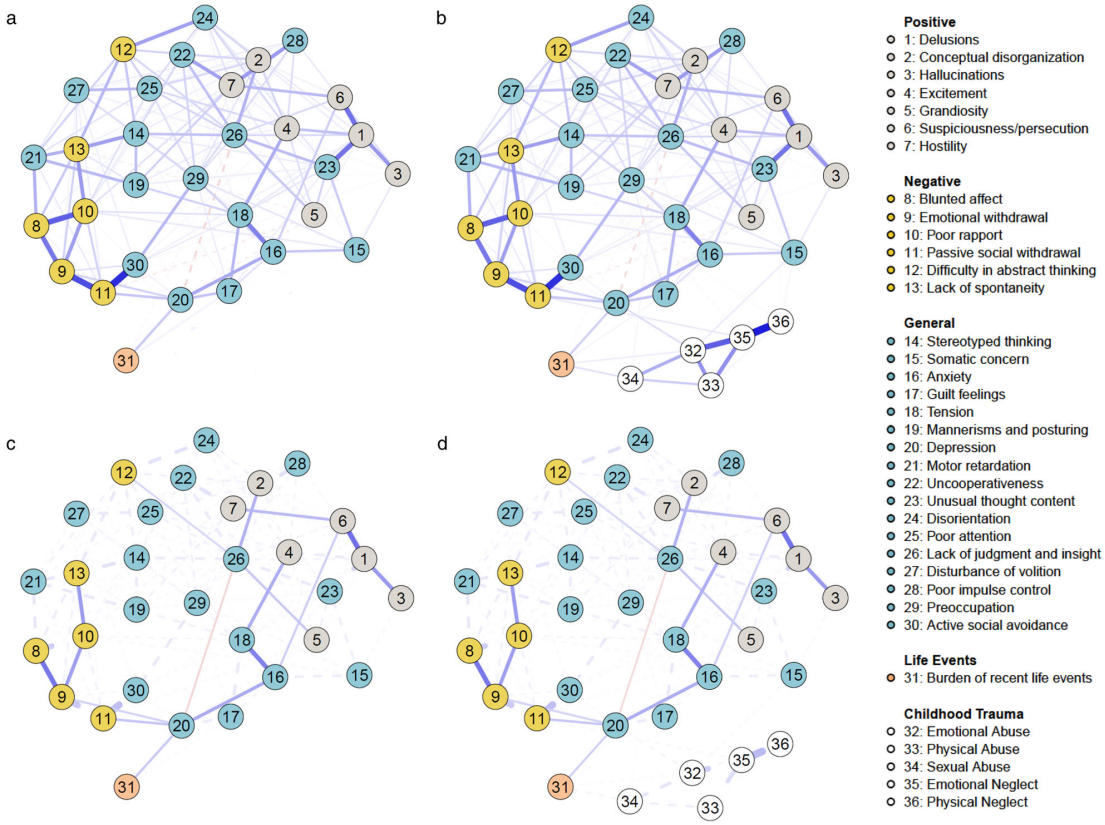

Fig. 1 Cross-sectional network of relationships between burden of recent life events and symptomatology assessed with the Positive and Negative Syndrome Scale (PANSS[34]) in the early psychosis spectrum ($n = 547$). Upper panel: Network depicting unique associations between burden of recent life events and individual symptoms. **a** before and **b** after controlling for different childhood trauma types as covariates. The wider the edge, the stronger the association. Blue (red) edges reflect positive (negative) connections. Lower panel: Network highlighting shortest paths between burden of recent life events and the positive and negative symptom domain of the PANSS. **c** before and **d** after controlling for different childhood trauma types as covariates. Solid lines represent shortest paths, dashed lines represent connections that do not lie on the shortest paths. The wider the edge, the stronger the association. Blue (red) edges reflect positive (negative) connections.

between burden of recent life events (node 31) and the PANSS items depression (node 20) as well as guilt feelings (node 17). Additionally, there was a small negative association between burden of recent life events (node 31) and lack of judgment and insight (node 26). The shortest paths (Fig. 1c) display the shortest routes that connect burden of recent life events (node 31) to each individual positive and negative symptom of the PANSS (nodes 1–13). The shortest route to reach most positive psychotic symptoms from burden of recent life events is via depression (node 20) and anxiety (node 16). Specifically, anxiety links to suspiciousness/persecution (node 6), which, in turn, connects to delusions (node 1), hallucinations (node 3) and hostility (node 7). Excitement (node 4) is reached by burden of recent life events via a path through depression (node 20) and tension (node 18). Even though the path from burden of recent life events via depression (node 20) and lack of judgment/insight (node 26) per definition constitutes the shortest route to positive symptoms conceptual disorganization (node 2) and grandiosity (node 5), the negative association between depression (node 20) and lack of judgment/insight (node 26) "disrupts" these pathways. Conversely, an extended pathway to conceptual disorganization (node 2) and grandiosity (node 5) via excitement (node 4), features positive connections only. All negative symptoms in the network can be reached via depression (node 20). Robustness analyses showed that the network was very stable and identified edges were estimated with good accuracy (Supplementary Results 1 and Supplementary Figs 2 and 3).

When corrected for the influence of different types of childhood trauma, the major pathways from burden of recent life events to positive and negative symptoms via general psychopathology remain unaffected (Fig. 1b, d). In the network, emotional and sexual abuse are positively linked to burden of recent life events. Types of childhood trauma also show several independent pathways to psychotic symptoms via general psychopathology, such as from emotional abuse via depression and anxiety to suspiciousness, and from emotional abuse via somatic concern to hallucinations, grandiose ideas and delusions. Robustness analyses showed that the network was very stable and identified edges were estimated with good accuracy (Supplementary Results 1 and Supplementary Figs 4 and 5). Networks of CHR and ROP participants differed significantly neither in network structure, global strength of connections, nor strength of any individual connections (Supplementary Results 2 and Supplementary Fig. 6). Similarly, there were no significant differences between the networks estimated separately in women and men (Supplementary Results 3 and Supplementary Fig. 7).

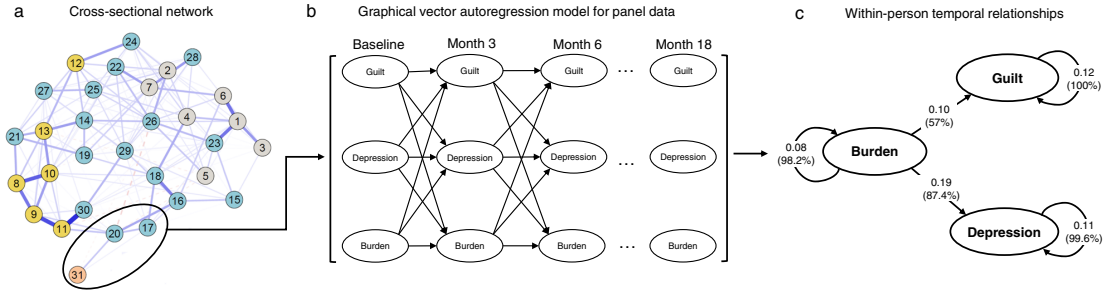

Fig. 2 Longitudinal analysis of the relationship between burden of recent life events, depression and guilt feelings in the early psychosis spectrum ($n = 337$). a Focusing on symptoms that showed connections with burden of recent life events in the cross-sectional network, modeled using 30 PANSS items and burden of recent life events, **b** up to seven equidistant, consecutive measurement occasions, each about three months apart, were used for modeling **c** the longitudinal relationships between burden of recent life events, depression, and guilt in a graphical vector autoregression model for panel data (*panelgvar*). Parameters reflecting the longitudinal relationships were standardized to partial directed correlations. All depicted parameters estimates were significant ($p < 0.001$). The percentages in brackets indicate how often each edge was included across 1000 bootstrap models.

Exploring the longitudinal relationship between burden of recent life events, depression and guilt feelings

Figure 2 shows the temporal effects, standardized to partial directed correlations, between burden of recent life events, depression and guilt feelings obtained from a graphical vector autoregression model for panel data[25]. There were positive directed associations from burden of recent life events to both depression ($\beta = 0.19$, $p < 0.001$) and from burden to guilt feelings ($\beta = 0.10$, $p = 0.002$), but not vice versa. This finding suggests that when an individual experiences higher levels of burden at one timepoint, levels of depression and guilt feeling are increased at the follow-up timepoint. Autoregressive effects for each variable were as follows: burden of recent life events = 0.08 ($p = 0.034$), depression = 0.11 ($p < 0.001$), guilt = 0.12 ($p < 0.001$), i.e. the amount of within-person carry-over effect from one timepoint to the next was about equally large for all three variables. This implies that timepoints on which a patient scored above his or her expected score are likely to be followed by timepoints on which he or she still scores above the expected score again, and vice versa. The bootstrapping analysis showed that all estimated edges were included in the majority of estimated models, suggesting a general robustness of the results to sampling variation.

DISCUSSION

In the present study, we investigated the relationship between the burden of recent life events and specific symptoms in the early psychosis spectrum. Specifically, we conducted a cross-sectional network analysis including all individual symptoms of the PANSS (positive, negative and general psychopathology symptoms) and cumulative burden of recent life events. Our results show that burden of recent life events is not directly linked to any of the positive or negative symptoms. As hypothesized, shortest pathways in the network illustrate that burden of recent life events is connected to positive and negative symptoms only via general psychopathology such as depression, guilt feelings, anxiety or tension. Importantly, these results were robust with respect to the inclusion of different types of childhood trauma. Overall, this suggests that general psychopathology symptoms mediate the relationship between life event burden and expression of psychotic symptomatology. Further, we used longitudinal modelling based on panel data to identify the temporal relationship between burden of recent life events and symptoms. Here, burden predicted depression and guilt feelings 3 months later, suggesting a specific effect of life event burden on the severity of affective symptomatology at the cross-sectional and within-person level. In summary, these findings extend previous cross-sectional evidence obtained in a sample of prisoners[21] to a clinical sample of patients in the early psychosis spectrum, including a more comprehensive set of life events and symptoms, and additionally provide a nuanced longitudinal analysis that suggested temporal priority of burden of recent life events over affective symptoms at the level of the individual.

Our results can be interpreted in light of an affective pathway to psychosis. According to this hypothesis, adverse life events lead to expression of psychotic symptomatology through heightened emotional distress[13,20,22]. Major burdensome life events result in negative affect—e.g. in the form of depression, anxiety, guilt feelings and tension, as indicated previously[6,21] and by our analysis. This in turn may increase sensitivity to minor daily hassles, potentially facilitating the development of psychotic symptomatology[20,35]. Similarly, previous work suggests that early adverse events, such as childhood trauma, may trigger a pathway to psychotic symptoms via general psychopathology, in particular anxiety, tension and depression[12,36,37]. We could replicate several of these previously identified pathways[12] in our control analysis, such as the pathway from abuse via depression and anxiety to suspiciousness, and the pathway from abuse via somatic concern to a cluster of hallucinations and delusions. One putative biological mechanism underlying this increased stress reactivity may involve alterations in the hypothalamus-pituitary-adrenal axis, which may subsequently give rise to psychotic symptoms via increased dopamine receptor densities and dopamine release[20,38]. Complementarily, heightened emotional distress can also be understood in terms of cognitive models of psychosis: Emotional changes following burdensome life events, such as depression, guilt feelings, anxiety and tension, may feed back into moment-by-moment processing of paranoid ideas and anomalous experiences and make their occurrence more likely[10].

Another important finding of our analysis is that early adverse experiences and burden of recent life events are not independent: experience of childhood abuse makes the experience of life events as burdensome more likely. This could be due to a lasting vulnerability to stress following childhood trauma, characterized by an enhanced experience of life events to be burdensome and stressful[10,20,23,39]. Likewise, a personal environment associated with adverse childhood experiences might also entail more conflicts, and thus, more burdensome life events, in adolescence and early adulthood. Importantly, our results suggest that early and recent stressful life events have similar, yet independent effects on psychotic symptoms, as pathways from recent life events to psychotic symptoms via general psychopathology were present in the network even after inclusion of childhood trauma. The interplay between early and recent stressful life events underscores the relevance of analyzing the association between

risk factors to advance the understanding of the etiology of psychotic symptomatology[18,22]. More research is necessary to work out differences in the specific mechanisms of actions of recent stressful life events and childhood trauma on general psychopathology and psychotic symptoms.

Overall, our results suggest that life events may be one driving force of unspecific, general psychopathology described as characteristic of early phases of mental disorders, corroborating previous considerations[11,14,15,19,31]. Early transdiagnostic pathways from life events to general psychopathology also align with the idea of multifinality in the emergence of psychopathology following recent stressful life events, similar to early trauma[12,22,39,40]. Accordingly, life events have been associated not only with increased risk for psychosis, but also with onset and course of other disorders, such as depressive[41,42], anxiety[43], bipolar[44,45] or obsessive-compulsive disorder[46]. In the network view, life events trigger negative affect, from which further activity may then "spread" in the network. Yet, it is still unclear when this is the case and transdiagnostic approaches might help to shed light on this question[47]. In later stages of mental illness, symptoms may then sustain each other even after cessation of external stressors such as life events[19]. From a clinical perspective, this underscores a growing consensus that general psychopathology symptoms should receive more attention in the management of patients with suspected and early psychosis[10–12,14,15], in particular given burdensome personal circumstances or affective dysregulation in early stages of psychotic disorder. One viable strategy may involve reducing certain types of burdensome life events, such as conflicts in the family or partnership, through appropriate interventions, e.g. assertive community treatment or family-focused therapy, to reduce stress in the social environment of patients[20,31,48,49].

Several limitations regarding the present results need to be taken into consideration. First, the comprehensive main network was built on cross-sectional data, allowing no conclusion about temporal priority and relationships in the individual. We aimed to clarify the directionality of the most important connections and examined averaged within-person processes by providing an additional longitudinal analysis based on panel data. Due to modeling constraints, selection of items used in this analysis was based on the connections in the more comprehensive cross-sectional network, which may not be representative of the most important longitudinal relationships. Second, we used the PANSS to assess symptomatology in an early psychosis spectrum sample including patients with ROP and CHR. It might be argued that alternative scales are more appropriate for assessment in CHR; however, we opted for the PANSS over other tools designed specifically for CHR populations as it covers a broader range of symptomatology, and generally shows good construct and convergent validity also in CHR samples[50]. Third, as sample sizes were small relative to the number of nodes in the network, statistical power in the comparison of networks of CHR and ROP, as well as those estimated separately in women and men, may have been insufficient to detect relevant differences. Larger sample sizes are likely needed to gain a better understanding of the role of life events in different stages of the psychosis spectrum. Larger sample sizes would also enable investigations of the role of specific types of life events as well as analyses in subgroups, such as affective and nonaffective psychosis, in which life events might exert different effects. Lastly, the group-level design of our analysis, focused on burden of recent life events as a generalized measure, does not allow direct conclusions for individual patients nor individual types of life events. We also implicitly assume that experiencing no life events is equivalent to experiencing life events without perceiving concomitant burden. Future studies may assess the impact of specific life events in psychosis by means of extensive longitudinal data collected in the individual, e.g. experience sampling methods (ESM). By following a group of patients longitudinally, with repeated ESM assessments, such a study design would allow to examine how life events alter the interplay between emotional reactivity to daily stressors and symptomatology at the level of the individual.

In sum, we adopted a network perspective to investigate the relationship between burden of recent life events and a comprehensive set of symptoms in a sample of patients at risk for psychosis and with recent-onset psychosis. Our findings provide further evidence for an affective pathway to psychosis[12,14,21,22] and show that unspecific, general psychopathology mediates the association between life event burden and expression of psychotic symptomatology, suggesting promising avenues for targeted interventions. These results highlight the added value of network analysis in deriving insights into psychological pathways implicated in the complex etiology of psychotic symptoms.

METHODS

Participants

We analyzed data from participants at CHR ($n = 275$) and patients with ROP ($n = 316$) of the multicentric Personalized Prognostic Tools for Early Psychosis Management study (PRONIA, https://www.pronia.eu; German Clinical Trials Register identifier DRKS00005042)[51]. Participants aged 15–40 were recruited between February 2014 and December 2017 in 10 academic early-recognition services in five European countries, i.e. Finland, Germany, Italy, Switzerland and the United Kingdom. The scheduled total follow-up period was 18 months, during which participants were assessed every three months. For the longitudinal analyses, we used data of up to month 18 past study inclusion, leading to a possible maximum of seven approximately equidistant measurement occasions for each participant. We included participants with available information on life events and the PANSS at the baseline assessment, yielding a final sample size of $N = 547$ ($n = 265$ CHR participants, $n = 282$ ROP participants). For longitudinal modeling, we used a subset of these 547 participants who had data on at least two consecutive measurement occasions available ($n = 337$). Details on inclusion and exclusion criteria have been published previously[51]. In short, the CHR state in PRONIA was defined by: (1) cognitive disturbances (COGDIS), as assessed by the Schizophrenia Proneness Instrument (SPI-A[52]); and/or (2) adapted PRONIA ultra-high-risk (UHR) criteria for psychosis, as measured by the Structured Interview for Psychosis-Risk Syndromes (SIPS[53]). Specific exclusion criteria for CHR individuals were (1) intake of antipsychotic medication for more than 30 cumulative days at or above the minimum dosage threshold defined by the DGPPN S3 Guidelines for the treatment of first-episode psychosis (https://www.dgppn.de/_Resources/Persistent/43ca38d4b003b8150b856df48211df68e412d9c9/038-009k_S3_Schizophrenie_2019-03.pdf), and (2) any intake of antipsychotic drugs within the past 3 months before psychopathological baseline assessments at or above the minimum dosage threshold. To ensure that risk symptoms were not due to drug consumption, participants had to be abstinent from illegal drugs for at least 4 weeks prior to study entry.

For ROP patients, specific inclusion criteria included meeting full DSM-IV criteria for an affective or nonaffective psychotic episode in the past three months and first onset of psychosis during the last 24 months. ROP patients were excluded if they had taken antipsychotic medication for more than 90 days (cumulative number of days) at or above minimum dosage of the first-episode psychosis range of DGPPN S3 Guidelines.

All adult participants provided their written informed consent prior to study inclusion, and minor participants (defined as those younger than 18 years) provided written informed assent and their guardians written informed consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The local research ethics committees at each study site approved the study.

Burden of recent life events

Life events were recorded with the Cologne Chart of Life Events (CoLE[54]). The CoLE was adapted from the Munich Life Event List[55] and comprises a list with 117 events from 12 domains (Supplementary Fig. 8). The interviewer asks the participant whether he or she experienced any event from these 12 domains in the last 12 months (baseline assessment) or since the least visit (at follow-up visits). For all reported events, the interviewer assigns the event to the most representative category from the list and notes duration and the participant's subjective evaluation, experienced burden and controllability of

each reported life event. For each measurement occasion, up to ten life events are recorded. For the present analyses, we focused on the burden of a given life event, which was scored on a 5-point Likert scale (0: no burden; 1: little burden; 2: moderate burden; 3: much burden; 4: very much burden). We computed the total burden of all reported life events by summing the individual burden ratings of each reported life event (maximum possible score = 40), excluding life events directly linked to the mental health status of the participants, such as hospitalization and start of psychopharmacological treatment, as these events are not commonly conceptualized as life events[56]. If a patient reported no life events, the total burden of recent life events was defined as 0.

Symptomatology

For the present analysis, we used the 30 individual items from the PANSS[34], which is a widely used, clinician-administered assessment of psychopathology typically associated with psychotic syndromes, with each item scored on a 7-point Likert severity scale from 1 (absent) to 7 (extreme). The reference period for the symptoms were the last 7 days.

Covariates: domains of childhood trauma

As covariates in a separate control analysis, we included five domains of childhood trauma, assessed by the subscales of the Childhood Trauma Questionnaire—Short Form (CTQ-SF[57]), i.e. emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse.

Data analytic strategy

We conducted all analyses in the *R* language for statistical computing, version 3.6.3[58]. Throughout, we considered a significance level of $\alpha < 0.05$, two-sided. Group comparisons for descriptive statistics were based on permutation-tests implemented in the *R* package 'coin', version 1.3-1[59].

Network estimation

We fitted a Gaussian graphical model in the form of a L_1-regularized partial correlation network to the data[32,33]. Each node in the network corresponds to one of the included PANSS items and the burden of life events. Connections between nodes reflect the partial correlation (or, equivalently, conditional dependence relation) between these items and represent the strength of the association between two items after controlling for all other variables under consideration. To account for the ordinal nature of the network items, we computed the partial correlation matrix based on Spearman's correlation coefficient. We recovered the optimal network by minimizing the extended Bayesian Information Criterion (EBIC) of a set of 100 networks estimated with the graphical lasso (glasso) algorithm that imposes L_1-regularization[60,61]. L_1-regularization ensures that small and likely spurious edges are removed from the model, leading to sparse, interpretable networks[32]. The EBIC itself has a hyperparameter that we set to 0 for the present analyses. For plotting both networks, we used a force-directed layout generated by the Fruchterman–Reingold algorithm based on the network including the covariates[62]. Additionally, we highlighted the shortest paths between the burden of life events variable and the positive and negative symptoms of the PANSS. The shortest path between two nodes represents the minimum number of steps necessary to go from one node to the other, highlighting possible pathways and mediators between life events and positive and negative symptoms[12,63]. We calculated the shortest pathways using Dijkstra's algorithm[64]. We repeated all network estimation and visualization steps in a control analysis where we included the five domains of the CTQ (i.e. emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect)[57].

Additionally, we estimated networks separately for participants with CHR and ROP, and compared the resulting network structures statistically with a permutation test (1000 permutations)[65] to formally assess whether networks of CHR and ROP participants differed from each other in (1) their network structures (i.e. the maximum of element-wise, absolute differences in edge weights), (2) global strength (i.e. the sum of all absolute edge weights) and (3) individual edge weights[65]. Due to the focus of the analysis, we restricted the comparison of individual edges to edges associated with burden of recent life events. Here, we corrected for multiple comparisons by controlling the false discovery rate[66]. Analogously, separate networks were estimated and compared for women and men (using combined data from CHR and ROP participants).

Network estimation and visualization steps were performed using the *R* package 'qgraph', version 1.6.5[67] and statistical network comparison was conducted with the *R* package 'NetworkComparisonTest', version 2.2.1[65].

Robustness analyses

As recommended, we conducted several follow-up bootstrapping analyses on the calculated networks to investigate their proneness to sampling variation and stability under case-dropping using the *R* package 'bootnet', version 1.4[32,68]. These analyses (a) show how accurately the edges in the network are estimated by constructing a 95% bootstrapped confidence interval (CI) around them, and (b) indicate how stable edges and centrality indices are estimated via the centrality-stability (CS) coefficient[69]. This coefficient indicates the maximum proportion of observations that can be dropped while confidently (95%) retaining results that correlate highly ($r > 0.7$) with the results obtained in the original sample. A CS coefficient of 0.25 or above indicates adequate stability and a coefficient of 0.50 or above indicates high stability[32]. For all robustness analyses, we used 1000 bootstrap samples.

Longitudinal relationship between burden of recent life events and symptoms

We explored longitudinal network relationships between burden of recent life events and symptoms connected to burden of recent life events in the baseline network by using a graphical vector autoregression model for panel data (panelgvar)[25]. The panelgvar-model allows to determine how these variables influence each other across the seven possible measurement occasions at the within-person, state-like level, while controlling for trait-like, between-person differences through the inclusion of a random intercept[26]. The panelgvar-model constrains the effects that variables have on each other to remain stable over the seven possible measurement occasions. In our analyses, we first fit a panelgvar-model in which all edges were included, using full information maximum likelihood estimation (FIML). Cases with missing observations are retained and the FIML estimation adjusts the likelihood function so that each participant contributes information on the variables that are observed. Second, we used a stepwise model search to find the model with optimal Bayesian information criterion (BIC), thresholding at $\alpha = 0.05$ for the addition or pruning of individual edges. In the optimal model, no edge can be added or pruned to improve fit. The resulting temporal network encodes directed predictive effects between the variables over time, which reflect the within-person temporal relationships of the average participant[25] (Fig. 2). A comprehensive explanation of the model goes beyond the scope of the present work (see the recent methodological article[25] for details). We tested the robustness of the results to sampling variation by assessing how often each edge was included across 1000 bootstrapped models. All analyses were run with the *R* package 'psychonetrics', version 0.7.1.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

Supplemental findings supporting this study are available on request from the corresponding author (LTB). The data are not publicly available due to Institutional Review Board restrictions—since the participants did not consent to their data being publicly available.

CODE AVAILABILITY

Code used for data analysis is available at: https://github.com/LindaBetz/Network_Life_Events_Psychosis.

Received: 10 August 2020; Accepted: 12 November 2020;
Published online: 15 December 2020

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ACKNOWLEDGEMENTS

PRONIA is a Collaboration Project funded by the European Union under the 7th Framework Programme (grant agreement n° 602152). J.K. has received funding from the German Research Foundation (DFG; grant agreement n° KA 4413/1-1).

AUTHOR CONTRIBUTIONS

L.T.B. and N.P. should be considered joint first authors of this manuscript. L.T.B., N.P., J.K. and L.K.-I. conceptualized the analysis and drafted the manuscript. L.T.B., N.P. and J.K. had full access to the data in the study and conducted the data analysis. L.T.B., N.P., J.K., L.K.-I., M.R., K.C., A.S., T.H., J.U., A.B., S.B., P.B., R.L., E.M., S.R., R.K.R.S., F.S.-L., S.J.W., R.U. and N.K. were involved in acquisition of data. N.K., L.K.-I., S.R., R.K.R.S., P.B., S.B., and S.J.W. were involved in obtaining funding. J.K., L.K.-I., S.R., F.S.-L., S.J.W., P.B., A.B., R.L., R.U., S.B. and N.K. were involved in supervision. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors are accountable for all aspects of the work.

FUNDING

Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information is available for this paper at https://doi.org/10.1038/s41537-020-00129-w.

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2.2 Relationships between childhood trauma and perceived stress in the general population: a network perspective

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Published in *Psychological Medicine*, Volume 51, Issue 15, pp. 2696–2706, https://doi.org/10.1017/S003329172000135X.

Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Betz LT, Penzel N, Rosen M, Kambeitz J (2020). Relationships between childhood trauma and perceived stress in the general population: a network perspective. *Psychological Medicine* 1–11. https://doi.org/10.1017/S003329172000135X

Received: 12 December 2019
Revised: 20 February 2020
Accepted: 23 April 2020

Key words:
Adverse life events; childhood trauma; early risk; network analysis; pathogenesis; perceived stress

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CAMBRIDGE UNIVERSITY PRESS

Relationships between childhood trauma and perceived stress in the general population: a network perspective

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Abstract

Background. Experiences of childhood trauma (CT) are associated with increased psychological vulnerability. Past research suggests that CT might alter stress processing with a subsequent negative impact on mental health. However, it is currently unclear how different domains of CT exert effects on specific subjective experiences of stress during adulthood.
Methods. In the present study, we used network analysis to explore the complex interplay between distinct domains of CT and perceived stress in a large, general-population sample of middle-aged adults ($N = 1252$). We used a data-driven community-detection algorithm to identify strongly connected subgroups of items within the network. To assess the replicability of the findings, we repeated the analyses in a second sample ($N = 862$). Combining data from both samples, we evaluated network differences between men ($n = 955$) and women ($n = 1159$).
Results. Results indicate specific associations between distinct domains of CT and perceived stress. CT domains reflecting a dimension of deprivation, i.e. experiences of neglect, were associated exclusively to a stress network community representing low perceived self-efficacy. By contrast, CT associated with threat, i.e. experiences of abuse, was specifically related to a stress community reflecting perceived helplessness. Our results replicated with high accordance in the second sample. We found no difference in network structure between men and women, but overall a stronger connected network in women.
Conclusions. Our findings emphasize the unique role of distinct domains of CT in psychological stress processes in adulthood, implying opportunities for targeted interventions following distinct domains of CT.

Introduction

A history of childhood trauma (CT), including experiences of neglect and abuse and other traumatic events during childhood, has been linked to a greater risk of developing mental illness and health-risk behaviors later in life (Afifi et al., 2011; Dube, Anda, Felitti, Edwards, & Croft, 2002; Grilo & Masheb, 2002; Kessler, Davis, & Kendler, 1997; Khoury, Tang, Bradley, Cubells, & Ressler, 2010; Lindert et al., 2014; Lotzin, Grundmann, Hiller, Pawils, & Schäfer, 2019; Varese et al., 2012). About half of the adult population report some form of CT (Afifi et al., 2011; Kessler et al., 1997), underscoring the importance of these experiences in shaping population-level mental health.

One way by which CT may increase the liability to mental illness is increased sensitization to stress (Dienes, Hammen, Henry, Cohen, & Daley, 2006; Hammen, 2005; Hammen, Henry, & Daley, 2000; Heim & Nemeroff, 2001; McLaughlin et al., 2017; Myin-Germeys & van Os, 2007; Read, Perry, Moskowitz, & Connolly, 2001; Reininghaus et al., 2016). As a severe early-life stressor, CT has been shown to induce enduring alterations at the neurobiological level changing the stress response, including elevated subjective experience of stress and enhanced threat anticipation (Carpenter et al., 2009; Dannlowski et al., 2012; LoPilato et al., 2019; McLaughlin, Conron, Koenen, & Gilman, 2010; Teicher & Samson, 2016). Heightened awareness of and reactivity to stressors may be conceptualized as lasting functional adaptations to childhood adversity as a chronically stressful environment (Wadsworth, 2015). Simultaneously, these adaptations of stress perception constitute one potential mechanism by which CT predisposes a broad range of psychopathological phenotypes emerging later in life, including mood and anxiety disorders, but also psychotic phenomena (Hammen, 2005; Heim & Nemeroff, 2001; Isvoranu et al., 2017; McLaughlin et al., 2010, 2017; Myin-Germeys & van Os, 2007; Reininghaus et al., 2016; Rössler, Ajdacic-Gross, Rodgers, Haker, & Müller, 2016; van Nierop et al., 2018).

Given that different domains of CT represent vastly different social experiences, it is advisable to differentiate between different types of adversity to delineate the effects of CT on the

subjective experience of stress (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014; Wadsworth, 2015). In line with this idea, a recent study showed a specific pathway from childhood abuse to a generalized measure of stress perception in the female subgroup of a cohort at-risk for psychosis (LoPilato et al., 2019). Similarly, previously undifferentiated domains of CT have been shown to exert distinct effects on neurobiological, socio-emotional and cognitive development (Busso, McLaughlin, & Sheridan, 2017; Cecil et al., 2016, 2017; Hildyard & Wolfe, 2002; Kuhlman, Geiss, Vargas, & Lopez-Duran, 2015; LoPilato et al., 2019; McLaughlin et al., 2014; Sheridan & McLaughlin, 2014; Teicher & Samson, 2016). Differential links have also been found between distinct domains of childhood adversity and symptoms in psychiatric populations (Cecil, Viding, Fearon, Glaser, & McCrory, 2017; Isvoranu et al., 2017). Overall, it seems likely that different domains of CT pose varying functional demands on the stress system, with ultimately different consequences for behavior (LoPilato et al., 2019; McLaughlin, DeCross, Jovanovic, & Tottenham, 2019; Soffer, Gilboa-Schechtman, & Shahar, 2008; Wadsworth, 2015).

However, until now little is known about the putative psychological stress-processes underlying distinct types of trauma, as prior research has assessed the impact of CT on perceived stress in adulthood in a way that restricted specificity on one side of the association: The analyses either confined to a selected, rather than a comprehensive group of experiences of CT (Soffer et al., 2008), or used a generalized, rather than a specific measure of stress perception (LoPilato et al., 2019; Rössler et al., 2016). Characterizing how distinct domains of CT influence specific aspects of perceived stress may allow to design interventions that target these mechanisms directly to reduce the intensity of psychopathological burden and, ultimately, foster resilience to mental illness (Reininghaus et al., 2016). Given the high prevalence of CT and its strong implication in mental, but also physical health (Goodwin & Stein, 2004), such targeted interventions come with the potential to reduce the negative personal and socioeconomic impact associated with CT.

In the present study, we aim to further explore how distinct domains of CT shape different aspects of subjective experiences of stress in adult life. One methodological difficulty in assessing the impact of distinct domains of CT is that they are typically highly interrelated and frequently co-occur (Baker & Festinger, 2011; Cecil et al., 2017; Dong et al., 2004). Considering one or a selected group of childhood adversities in isolation may likely result in an overestimation of their effects on adult experiences of stress, just as generalizing different domains of CT into one broad category may obscure important insights into mechanisms linking CT with developmental outcomes (Cecil et al., 2017; McLaughlin et al., 2014). To account for these difficulties, we use network analysis, a statistical framework that allows to quantify the unique associations among many variables simultaneously (Epskamp, Borsboom, & Fried, 2018a; Epskamp, Waldorp, Mõttus, & Borsboom, 2018b; Koller & Friedman, 2009). This property makes network analysis an ideal choice for assessing the specific impact of co-occurring, strongly interrelated domains of CT. Typically, researchers apply network analysis as a tool to model psychopathology from a network perspective (Isvoranu et al., 2017; Rhemtulla et al., 2016). The components of such a network are conceptualized as active components of a dynamic system of symptoms or psychobiological factors that can mutually influence and maintain each other (Borsboom, 2017; Borsboom & Cramer, 2013). In the present analysis, we model the interrelations of five domains of CT and items measuring perceived stress in a large, general-population sample in middle adulthood. Following a growing call for replicability investigations (Borsboom, Robinaugh, Rhemtulla, & Cramer, 2018; Fried et al., 2018), we assessed the replicability of the findings in a second sample. Given recent indications for sex effects in the association between CT and subjective experience of stress (LoPilato et al., 2019), we also assessed if networks of associations between CT and perceived stress differed between men and women. With the suggested network analysis, we aim to provide novel insights into the pathways by which CT impacts experiences of stress, thus paving ways to ameliorate the negative health consequences of CT.

Method

Participants

We used data from the Biomarker Project of the Midlife Development in the United States (MIDUS) Survey, a nationally representative longitudinal panel study of health and aging in the noninstitutionalized civilian population of the 48 contiguous USA (Ryff et al., 2017, 2019). The original MIDUS sample comprised English-speaking adults aged 25–74 years whose household included at least one telephone (recruited by random digit dialing), with oversampling of five metropolitan areas, twin pairs and siblings (Brim, Ryff, & Kessler, 2019). MIDUS I ($N = 7108$) was conducted from 1995 to 1996, and a follow-up study (MIDUS II) was conducted 10 years after the baseline assessment in $N = 4963$ MIDUS I respondents (70% response rate) between 2004 and 2005. Of those who participated in MIDUS II, 1255 (23% of MIDUS II) were able and willing to participate in the more comprehensive Biomarker Project Substudy, which was used for the main analysis reported in this paper (original sample). Details on the study protocol and scientific aims are available elsewhere (Dienberg Love, Seeman, Weinstein, & Ryff, 2010).

As a replication sample, we used the Refresher Biomarker Project (Weinstein et al., 2019) that emulates the original MIDUS Biomarker Project, employing the same assessments in an additional $N = 863$ participants between 2012 and 2016. The Refresher Biomarker Study was designed to parallel the five decadal age groups contained within the original MIDUS I baseline cohort. The Institutional Review Boards at the University of Wisconsin–Madison, the University of California–Los Angeles, and Georgetown University approved both Biomarker Projects. Research participants were admitted to or studied on the University of Wisconsin-Clinical and Translational Research Core (UW-CTRC).

Assessments

Childhood trauma

CT (up to age 18) was assessed with the English version of the Childhood Trauma Questionnaire-Short Form (CTQ-SF, Bernstein et al., 2003). The CTQ-SF is a self-report measure of CT, including five items within each of five different domains of CT: (1) physical neglect (failure of a caretaker to provide basic necessities for a child such as food, clothing, shelter); (2) physical abuse (bodily assault on a child posing a risk of or resulting in injury); (3) emotional neglect (failure of caretaker basic emotional and psychological needs for a child, such as love and nurturance); (4) emotional abuse (verbal assaults on a child, such as humiliation); and (5) sexual abuse (unwanted sexual

contact or conduct between a child and an adult). Responses for each item are recorded on a 5-point-Likert scale, ranging from 1 (never true) to 5 (very often true). We computed total scores for each domain that were used in the construction of the networks. Possible total scores of each domain ranged from 5 to 25.

Perceived stress

In MIDUS, perceived stress was measured using the 10-item version of the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983). Participants are asked to rate the occurrence of stress-related thoughts and feelings over the past month on a 5-point-Likert-scale, ranging from 1 (never) to 5 (very often). To facilitate interpretation in the present analysis, we reverse-coded the positive items so that higher values are indicative of more perceived stress.

Data analytic strategy

We ran all analyses in the R language for statistical computing, version 3.6.1 (R Core Team, 2019). Participants with completely missing data in the network variables of interest were excluded from the analysis. We calculated descriptive statistics for the original, replication and combined sample. To evaluate differences between the original and replication sample, we used permutation tests implemented in the R package 'coin', version 1.3 (Hothorn, Hornik, van de Wiel, & Zeileis, 2008). Throughout, we considered a significance level of $\alpha = 0.05$. Code to reproduce the analysis is available online (https://github.com/LindaBetz/Network_CT_Stress).

Network analysis

Network Estimation. We fitted networks in the form of a partial correlation network, also known as Gaussian graphical model (GGM), to the data (Epskamp et al., 2018b; Koller & Friedman, 2009). In this undirected network, the five CTQ-domains and the 10 stress-experience items from the PSS questionnaire are represented as nodes. A connection (called 'edge' in the network literature) between two nodes indicates a partial correlation between the two variables, i.e. the association between these two variables that remains after controlling for all other variables under consideration (Koller & Friedman, 2009). In other words, edges can be interpreted as predictive effects, representing the share of the pairwise association that cannot be explained by any other variables in the model (Epskamp et al., 2018b; Isvoranu et al., 2017). The stronger the partial correlation between two nodes, the thicker the edge drawn in the network. Whenever the partial correlation between two variables is exactly zero, these variables are independent after controlling for all other variables in the model, and no edge is drawn between the two corresponding nodes in the network (Epskamp et al., 2018b; Koller & Friedman, 2009).

To account for the ordinal distribution of the items and missing data, we estimated the partial correlation matrix based on Spearman correlations using pairwise complete observations (Epskamp et al., 2018a). We determined the optimal network model by using stepwise, unregularized model selection. This approach returns the best-fitting model by minimizing the Bayesian information criterion (BIC) of unregularized GGM models. In the final network model, no edge can be added or removed to improve fit. For plotting the network, we generated a force-directed layout using the Fruchterman-Reingold algorithm (Fruchterman & Reingold, 1991). To facilitate comparison, the same network layout (generated based on the original data set) was used for visualizing networks throughout the paper. We constructed and visualized the networks using the package 'qgraph', version 1.6.3 (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012). Weighted adjacency matrices containing the set of partial correlation coefficients corresponding to the depicted networks are available in the supplement and in the linked github repository.

For methodological details, we refer the interested reader to available tutorial and overview articles (Epskamp et al., 2018a, 2018b).

Community detection. For a data-driven identification of highly connected subgroups (termed 'communities') in the generated network of CT and perceived stress, we used the walktrap algorithm (Pons & Latapy, 2005) as implemented in the R package 'igraph', version 1.2.4.1 (Csardi & Nepusz, 2006). The walktrap algorithm detects communities within a network by using random walks. Results were compared to an alternative community detection approach, the spinglass algorithm (Reichardt & Bornholdt, 2006), as implemented in the R package 'igraph'.

Robustness analyses

We performed several follow-up analyses on the calculated networks to assess their robustness using the R package 'bootnet', version 1.2.4 (Epskamp et al., 2018a; Epskamp & Fried, 2015). These analyses (a) show how accurately the edges in the network are estimated by constructing a 95% bootstrapped confidence interval (CI) around them, and (b) indicate how stable centrality is estimated via the centrality-stability (CS) coefficient (Costenbader & Valente, 2003). This coefficient indicates the maximum proportion of observations that can be dropped while confidently (95%) retaining results that correlate highly ($r > 0.7$) with the results obtained in the original sample. A CS coefficient of 0.25 or above indicates adequate stability and a coefficient of 0.50 or above indicates high stability (Epskamp et al., 2018a). For all robustness analyses, we used 1000 bootstrap samples.

Replicability analyses

Using the same workflow as described above, we estimated the network of CT and perceived stress in the replication sample. Following procedures described by Fried et al. (2018), we aimed to quantify the replicability of the network. First, we correlated the individual edge weights contained within the partial correlation matrices of the two networks, which provides a coefficient of similarity (Borsboom et al., 2018; Rhemtulla et al., 2016). Second, we used permutation tests (1000 permutations) to formally assess whether the networks differed from each other in their network structures and global strength (i.e. the sum of all absolute edge values) using the R package 'NetworkComparisonTest', version 2.2.1 (van Borkulo et al., 2017). Third, based on the results from the permutation test, we examined post-hoc how many of the 105 edges differed across the networks. This was done using the false discovery rate (FDR) corrected *p*-values (Benjamini & Hochberg, 1995). Finally, we estimated and visualized the network based on the combined data set. Detailed results for this analysis are available in the supplement.

Comparison of networks in men and women

To investigate the moderating role of sex on associations between CT and perceived stress, we compared the networks of men and women using the same permutation-based approach (1000 permutations) detailed above (van Borkulo et al., 2017). When

comparing individual edges of the network of men and women, we considered FDR-corrected *p*-values (Benjamini & Hochberg, 1995). To retain a similar level of power for detection of edges in the subgroup networks, we merged data from the Biomarker Study (original sample) and the Biomarker Refresher Study (replication sample) for both analyses.

Results

Sample characteristics

Of the 1255 participants in the original sample, three had completely missing data in the variables of interest and could not be included in the analysis. Hence, the final sample comprised 1252 individuals (43.3% male), with a mean age of 57.3 (S.D. = 11.5) years. On average, 0.2% of the network variables of interest were missing. Table 1 summarizes the demographic and clinical sample characteristics. The replication sample (one participant excluded due to completely missing data, $n = 862$) was overall similar in relevant clinical characteristics, but had more males, was younger, and better educated. The average amount of missing values was 0.1%. For the subgroup analysis, the combined original and replication sample ($N = 2114$) was split into male ($n = 955$) and female ($n = 1159$) participants. Table 2 presents the demographic and clinical sample characteristics of the combined sample as well as the subgroups. Women were on average younger, less White, showed more depressive symptoms and global perceived stress, and scored higher on CT domains of emotional and sexual abuse.

Network

The network depicted in Fig. 1 illustrates the relationships between the different domains of CT and perceived stress (for the partial correlation coefficients, online Supplementary Table S1; centrality plot in online Supplementary Fig. S1). Of 105 possible edges, 35 were retained after the unregularized model selection procedure. All except one edge were positive. Sensitivity analyses suggested that the network model was very stable (all CS-coefficients $r = 0.75$, online Supplementary Figs S2–S3) and network parameters were estimated with good accuracy (online Supplementary Fig. S4).

Within the network, all CT domains, as well as items reflecting perceived stress, are highly interconnected, suggesting that the associations within each construct are larger than between the two constructs. Evidently, CT domains are differentially associated with perceived stress. Emotional neglect is positively associated with 'did not feel on top of things'. Physical neglect connects to 'not confident to handle personal problems'. Emotional abuse has an edge to 'felt nervous and stressed'. A second, smaller edge connects emotional abuse to feeling 'unable to control important things'. Physical abuse makes feeling 'upset by something unexpected' more likely. Additionally, there is a small edge from sexual abuse to 'could not cope with all things to do'. Finally, there is a small, negative edge between physical abuse and not feeling 'on top of things'. Due to its unexpected, negative sign, this edge is likely indicative of conditioning on a collider (Epskamp et al., 2018b; Koller & Friedman, 2009): in an undirected network like the one present, a negative edge is falsely introduced between two variables that have positive, directed effects on a common third variable (here, likely node 10: 'difficulties piling up can't overcome').

Community detection

The walktrap algorithm detected three communities (Fig. 1). The five domains of CT form the first, strongly interconnected community. The second and third community detected within the items of the PSS fully align with a two factor-solution identified in several healthy and clinical samples using factor analysis (Leung, Lam, & Chan, 2010; Reis, Hino, & Añez, 2010; Roberti, Harrington, & Storch, 2006). These two factors have been labelled 'perceived self-efficacy' and 'perceived helplessness' (Roberti et al., 2006), which is the labeling we will also use here. These two identified stress communities show differential associations with CT: perceived self-efficacy primarily relates to CT dimensions of neglect, and perceived helplessness exclusively relates to CT dimensions of abuse. Communities obtained with the spinglass algorithm were identical to results from the walktrap algorithm.

Replicability

Paralleling results for the original network, sensitivity analyses suggested that the network model based on the replication data was very stable (all CS-coefficients $r = 0.75$, online Supplementary Figs S6 and S7) and network parameters were estimated with good accuracy (online Supplementary Fig. S8). Pearson's correlation of the edge weights of the original and replication network was 0.92, suggesting a strong similarity between the two networks (Borsboom et al., 2018; Fried et al., 2018). Pearson's correlation between strength centrality of individual nodes was similarly high ($r = 0.96$; for centrality plots online Supplementary Figs S1 and S5). In line with this, permutation-based comparison suggested no significant differences in structure (Test statistic $M = 0.15$, $p = 0.418$) nor global strength (Test statistic $S = 0.24$, $p = 0.165$) between the original and the replication network. Post-hoc comparisons of individual edges showed that none of the 105 edges differed significantly between the two networks. In sum, we conclude that both networks are highly similar and results from the analysis reported in this paper are replicable. The replication network estimated based on the Biomarker Refresher data as well as the cross-sample network are available in online Supplementary Fig. S9, and the corresponding weighted adjacency matrices in online Supplementary Tables S2 and S3.

Comparison of networks in men and women

Figure 2 depicts the networks estimated for men and women separately (for weighted adjacency matrices, online Supplementary Tables S4 and S5). Permutation-based comparison of the networks revealed a significantly stronger connected network in women than in men (Test statistic $S = 0.35$, $p = .037$). Conversely, no differences emerged in overall network structure (Test statistic $M = 0.14$, $p = 0.595$) nor individual connections between any of the network variables when applying FDR correction for multiple comparisons (all $ps > 0.705$).

Discussion

Understanding potential mechanistic cognitive pathways by which CT impacts mental health is central to ameliorate its manifold negative consequences. To achieve this goal, it has been argued to distinguish between different types of trauma (McLaughlin et al., 2019, 2014). In this study, we estimated a network of five domains of CT and items measuring experiences of perceived stress in a large general-population sample. We found that distinct domains of CT are specifically related to two identified network communities reflecting different aspects of perceived

Table 1. Demographic and clinical characteristics of the original and replication sample

Variable	Original sample ($n = 1252$)	Replication sample ($n = 862$)	Comparison
Age (years)	57.3 (11.5)	52.7 (13.4)	$Z = 8.28$, $p < 0.001$
Sex (% male)	43.3	50.0	$\chi^2 = 4.40$, $p = 0.037$
Ethnicity (%)	White (92.9), African American (2.6), Other (4.6)	White (81.0), African American (7.6), Other (11.5)	$\chi^2 = 58.5$, $p < 0.001$
Education (%)	Less than high school (3.5), graduated at least high school or obtained GED (49.8), graduated 4-year college (46.7)	Less than high school (2.3), graduated at least high school or obtained GED (40.5), graduated 4-year college (57.2)	$\chi^2 = 19.8$, $p < 0.001$
CES-D-total	8.7 (8.2)	9.3 (7.9)	$Z = -1.48$, $p = 0.141$
PSS-total	22.2 (6.3)	22.5 (6.4)	$Z = -0.89$, $p = 0.371$
CTQ-SF			
Emotional neglect	9.8 (4.6)	9.9 (4.6)	$Z = -0.79$, $p = 0.426$
Physical neglect	6.9 (2.8)	6.9 (2.7)	$Z = 0.45$, $p = 0.651$
Emotional abuse	8.0 (4.2)	8.2 (4.2)	$Z = -1.01$, $p = 0.306$
Physical abuse	7.0 (3.1)	7.1 (3.3)	$Z = -1.12$, $p = 0.276$
Sexual abuse	6.6 (4.0)	6.7 (4.2)	$Z = -0.37$, $p = 0.720$

Means (s.d.) unless stated otherwise.
CES-D, Center for Epidemiological Studies Depression Scale; CTQ-SF, Childhood Trauma Questionnaire-Short Form; GED, General Education Diploma; PSS, Perceived Stress Scale.

Table 2. Demographic and clinical characteristics for men and women

Variable	Combined sample ($n = 2114$)	Men ($n = 955$)	Women ($n = 1159$)	Comparison (men *v.* women)
Age (years)	55.5 (12.6)	56.3 (12.9)	54.7 (12.2)	$Z = -2.85$, $p = 0.005$
Sex (% male)	45.2	100	0	na
Ethnicity (%)	White (88.0), African American (4.6), Other (7.4)	White (89.9), African American (2.8), Other (7.3)	White (86.3), African American (6.2), Other (7.5)	$\chi^2 = 11.9$, $p = 0.002$
Education (%)	Less than high school (3.0), graduated at least high school or obtained GED (46.0), graduated 4-year college (51.0)	Less than high school (3.2), graduated at least high school or obtained GED (43.1), graduated 4-year college (53.7)	Less than high school (2.9), graduated at least high school or obtained GED (48.5), graduated 4-year college (48.6)	$\chi^2 = 5.24$, $p = 0.075$
CES-D-total	8.9 (8.1)	8.4 (7.8)	9.4 (8.3)	$Z = 2.88$, $p = 0.004$
PSS-total	22.3 (6.3)	21.7 (6.1)	22.9 (6.5)	$Z = 4.39$, $p < 0.001$
CTQ-SF				
Emotional neglect	9.8 (4.6)	9.7 (4.2)	10.0 (4.8)	$Z = 1.61$, $p = 0.110$
Physical neglect	6.9 (2.8)	6.8 (2.5)	7.0 (2.9)	$Z = 1.46$, $p = 0.150$
Emotional abuse	8.1 (4.2)	7.4 (3.4)	8.7 (4.7)	$Z = 6.79$, $p < 0.001$
Physical abuse	7.1 (3.2)	6.9 (2.8)	7.2 (3.4)	$Z = 1.75$, $p = 0.078$
Sexual abuse	6.6 (4.1)	5.6 (2.0)	7.5 (5.0)	$Z = 10.9$, $p < 0.001$

Means (s.d.) unless stated otherwise.
CES-D, Center for Epidemiological Studies Depression Scale; CTQ-SF, Childhood Trauma Questionnaire-Short Form; GED, General Education Diploma, PSS, Perceived Stress Scale.

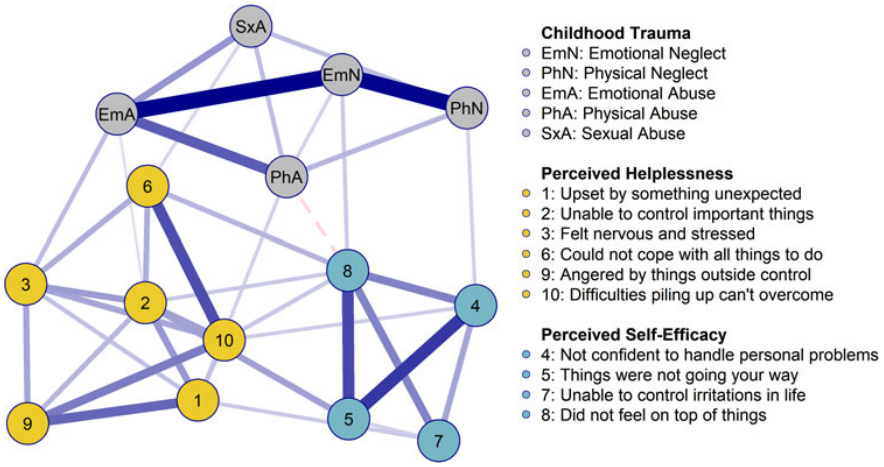

Fig. 1. Network of five domains of childhood trauma and perceived stress. Solid edges indicate positive relationships and dashed edges indicate negative relationships. The thicker the edge, the stronger the association between two variables. Node coloring represents the three communities detected with the walktrap algorithm (Pons & Latapy, 2005). The force-directed layout for plotting the network was generated by the Fruchterman-Reingold algorithm (Fruchterman & Reingold, 1991). To facilitate interpretation of connections in the network, we recoded and reworded the positive items for the present analysis.

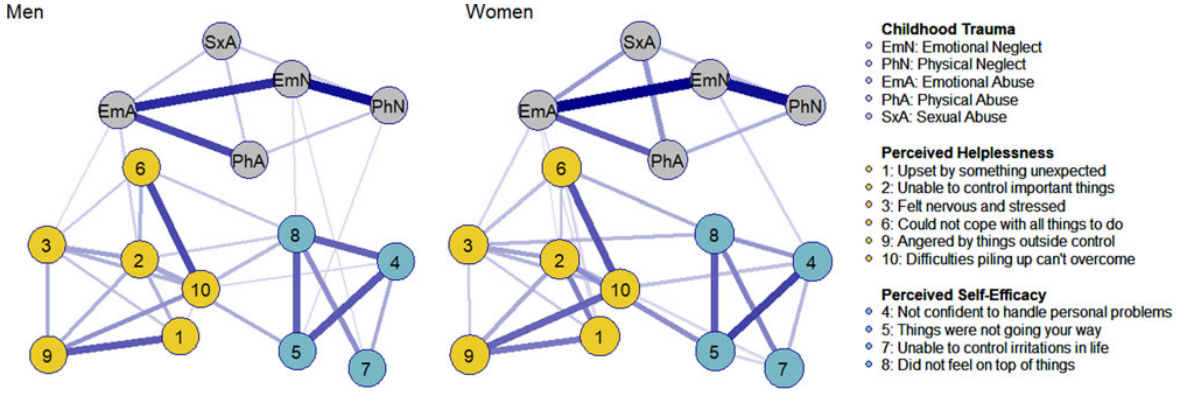

Fig. 2. Network of five domains of childhood trauma and perceived stress estimated in men ($n = 955$) and women ($n = 1159$). Solid edges indicate positive relationships. The thicker the edge, the stronger the association between two variables. Node coloring represents the three communities detected with the walktrap algorithm (Pons & Latapy, 2005). Both networks were plotted with the force-directed layout of the original network, generated by the Fruchterman-Reingold algorithm (Fruchterman & Reingold, 1991). To ease interpretation of connections in the network, we recoded and reworded the positive items for the present analysis. To facilitate visual comparison of the networks, minimum and maximum of edge weights were scaled identically across the two networks.

stress. Our results support the notion that different domains of CT represent different functional demands for the developing stress system, with differential consequences for the perception of stress in adulthood (Wadsworth, 2015): In the identified network, domains of child neglect exclusively connect to experiences of stress reflecting lowered perceived self-efficacy, i.e. reduced belief in one's competence to successfully accomplish the desired objective (Lawrance & McLeroy, 1986). All domains of child abuse, on the other hand, mainly connect to items from a community representing increased perceived helplessness. These findings add to an accumulating body of research documenting associations between CT and perceived stress in adulthood (LoPilato et al., 2019; McLaughlin et al., 2010; Rössler et al., 2016; Soffer et al., 2008), but extend the literature by delineating specific effects of core dimensions of CT on different aspects of perceived stress in a network approach. Notably, the two network communities of perceived stress fully align with factor solutions obtained in previous studies (Leung et al., 2010; Reis et al., 2010; Roberti et al., 2006). As expected based on previous work, network analysis identified one strongly connected community of CT domains suggesting high interrelatedness and co-occurrence of the different domains of CT (Baker & Festinger, 2011; Cecil et al., 2016, 2017). Overall, our findings could be replicated in an independent, large population sample which suggests that our results are robust despite several differences in demographic variables. Subgroup analysis comparing networks of men and women showed no differences in network structure, but a significantly stronger connected network of CT and perceived stress in women.

The grouping of CT into neglect and abuse by differential network associations with perceived stress resonates well with a proposed distinction of early traumatic experiences into core dimensions of deprivation and threat (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014). Based on evidence and

mechanisms derived from basic neuroscience and animal research, primarily sensory deprivation and fear learning, it has been suggested that childhood adversity dimensions of deprivation and threat have a distinct impact on neurodevelopment and ultimately behavior (McLaughlin et al., 2014). In the context of CT, the dimension of deprivation involves neglect of any form, e.g. emotional or physical neglect, experienced during childhood. Experiences of threat include events that involve verbal assaults, any harm to one's physical integrity, and sexual violation (Sheridan & McLaughlin, 2014). Our data suggest that CT domains of deprivation, represented by emotional and physical neglect, specifically connect to stress-experiences representing reduced perceived self-efficacy. CT domains of threat, represented by emotional, physical, and sexual abuse, by contrast, are primarily associated with experiences of stress reflecting perceived helplessness. This pattern of results is consistent with a previous structural equation modeling study in an Israeli college sample (Soffer et al., 2008). The study reported specific associations between emotional neglect and a measure of self-efficacy on the one hand, and emotional abuse and depressive vulnerability on the other hand. The specificity of the connections between CT and adult stress experience identified in the present study underscores the call for assessing different domains of CT simultaneously rather than in isolation or lumped under a single big category (Cecil et al., 2017; Hildyard & Wolfe, 2002; LoPilato et al., 2019; McLaughlin et al., 2014; Teicher & Samson, 2016).

Children experiencing severe deprivation have been shown to hold only very restricted positive beliefs about themselves (Hildyard & Wolfe, 2002; Toth, Cicchetti, Macfie, & Emde, 1997). Restricted positive self-representations are likely aligning with a domestic environment giving little attention to basic emotional and physical needs, offering only very few opportunities to experience the self as positive (Toth et al., 1997). Results from the present network analysis suggest that such restricted positive views following experiences of child neglect may carry over into adulthood, presenting themselves as beliefs of being less competent to successfully master demanding situations.

Experiences of abuse can be conceptualized as early exposure to a series of highly negative, uncontrollable events (McLaughlin et al., 2014; Volpicelli, Balaraman, Hahn, Wallace, & Bux, 1999). Our findings indicate that such repeated threat is linked to a perceived lack of control to be effective in other aversive situations, even extending into adulthood. This pattern of behavior is well-known as 'learned helplessness' (Foa, Zinbarg, & Rothbaum, 1992; Overmier & Seligman, 1967; Seligman & Maier, 1967; Volpicelli et al., 1999). Individuals that have experienced uncontrollable trauma may learn that their efforts will have no effect, leaving them notably passive and helpless in future aversive situations, even if they are potentially controllable (Pryce et al., 2011; Volpicelli et al., 1999). Increased perceived helplessness following experiences of uncontrollable threat, such as emotional, physical and sexual abuse, may constitute one pathway by which CT makes depressive symptoms more likely, as implicated by prominent cognitive models of depression (Abramson, Seligman, & Teasdale, 1978; Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Pryce et al., 2011; Soffer et al., 2008).

Notably, the present network analysis showed many connections between items from the two communities of stress experience, suggesting that perceived self-efficacy and perceived helplessness are not independent from each other. Some authors have suggested that low self-efficacy may be a determinant of learned helplessness (Filippello, Sorrenti, Buzzai, & Costa, 2015). Conceptually, these constructs differ in that perceived helplessness has been theorized to represent the consequences of exposure to uncontrollable events, while self-efficacy refers to one's expectation to be able to perform actions (Lawrance & McLeroy, 1986). The differential connections of perceived helplessness and self-efficacy to CT dimensions of threat and deprivation evidenced in our network support this distinction. Importantly, this observed pattern of connections also offers a first insight on how to direct preventive or therapeutic interventions towards reducing experiences of helplessness and/or improving self-efficacy, depending on the predominant domain of CT experienced. Such targeted interventions come with the potential to attenuate the personal burden and negative impact of CT on mental and physical health by disrupting pathways via increased stress perception. Given the high prevalence of CT, such measures also have economic relevance for population-level healthcare.

Our results suggest that the overall network structure of associations between CT and perceived stress does not vary as a function of sex, contrasting previous work that reported a positive association between CT domains of abuse and a generalized measure of perceived stress unique to women (LoPilato et al., 2019). However, the network of women in our sample showed stronger global connectivity than the network of men. This could suggest that in women, individual domains of CT and perceived stress may more frequently co-occur, and also more easily activate and sustain each other. Sex differences in the overall strength of associations may arise due to differences in the predominant domain of CT experienced: women reported higher levels of emotional and sexual abuse in the present sample, consistent with previous work (Tolin & Foa, 2006). Exposure to more experiences of threatful abuse during childhood may enforce stronger associations with and within perceived stress during adulthood in women. Moreover, sex differences in initial physiological and psychological appraisal processes of trauma (Irish et al., 2011; Perry, Pollard, Blakley, Baker, & Vigilante, 1995) may predispose differences in strength of the impact of CT on perceived stress in adulthood. However, with the present data, it cannot be excluded that the stronger network connectivity observed in women is an artifact of previously reported sex-specific reporting tendencies in CT and perceived stress (Davis, Matthews, & Twamley, 1999; Tolin & Foa, 2006). Thus, the need to continue the investigation on the moderating role of sex on CT-related stress experience in adulthood remains.

A limitation of the current analyses is that they are based on cross-sectional data. Hence, the identified networks do not necessarily generalize to the individual level and conclusions regarding causality of the resulting connections cannot be definite. An additional critical point is that the CTQ, as a retrospective, self-report measure of CT, may be prone to biases in memory and social desirability. Self-report questionnaires, however, also promote feelings of privacy and are generally considered less invasive than face to face interviews (Bernstein et al., 2003).

In conclusion, the present network analysis highlights the complex and specific associations between dimensions of deprivation and threat of CT and different types of stress experienced in adulthood in two large general population samples. These results may be yet another indicator for distinct developmental impact following different domains of CT (Hildyard & Wolfe, 2002; McLaughlin et al., 2014; Sheridan & McLaughlin, 2014; Teicher & Samson, 2016; Wadsworth, 2015). Even though often overlooked, subjective experiences of stress may be essential for

understanding the negative long-term impact of CT on a wide range of mental health outcomes. Future work should assess how the specific effects of distinct domains of CT on perceived stress might relate to different kinds of psychopathological expression. Further research also needs to disentangle the cognitive and biological mechanisms underlying the functional roles of distinct domains of CT in psychological stress mechanisms to pave the way for the development of targeted interventions. These may be the road to lower intensity of psychopathological burden and higher resilience to mental illness.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172000135X.

Acknowledgements. The authors would like to thank all the participants and research staff of the MIDUS Study. The authors are also grateful for the opportunity to use these publicly available data. The MIDUS study has been funded by the following: John D. and Catherine T. MacArthur Foundation Research Network, National Institute on Aging (P01-AG020166), National Institute on Aging (U19-AG051426). MIDUS Biomarker data collection was further supported by the National Institutes of Health National Center for Advancing Translational Sciences (NCATS) Clinical and Translational Science Award (CTSA) program as follows: UL1TR001409 (Georgetown), UL1TR001881 (UCLA) and 1UL1RR025011 (UW).

Conflicts of interest. None.

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2.3 A network approach to relationships between cannabis use characteristics and psychopathology in the general population

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Published in *Scientific Reports*, Volume 12, Article Number 7163, pp. 1–10, https://doi.org/10.1038/s41598-022-11092-0.

scientific reports

OPEN

A network approach to relationships between cannabis use characteristics and psychopathology in the general population

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Cannabis use characteristics, such as earlier initiation and frequent use, have been associated with an increased risk for developing psychotic experiences and psychotic disorders. However, little is known how these characteristics relate to specific aspects of sub-clinical psychopathology in the general population. Here, we explore the relationships between cannabis use characteristics and psychopathology in a large general population sample (*N* = 2,544, mean age 29.2 years, 47% women) by employing a network approach. This allows for the identification of unique associations between two cannabis use characteristics (lifetime cumulative frequency of cannabis use, age of cannabis use initiation), and specific psychotic experiences and affective symptoms, while controlling for early risk factors (childhood trauma, urban upbringing). We found particularly pronounced unique positive associations between frequency of cannabis use and specific delusional experiences (persecutory delusions and thought broadcasting). Age of cannabis use initiation was negatively related to visual hallucinatory experiences and irritability, implying that these experiences become more likely the earlier use is initiated. Earlier initiation, but not lifetime frequency of cannabis use, was related to early risk factors. These findings suggest that cannabis use characteristics may contribute differentially to risk for specific psychotic experiences and affective symptoms in the general population.

Prospective epidemiological studies have consistently reported an association between cannabis use and an increased risk for subsequent psychotic experiences and psychotic disorders[1–3]. However, only a minority of individuals who use cannabis will eventually develop a psychotic disorder. Thus, recent research efforts aim to identify aspects of exposure to cannabis that are particularly potent in increasing the risk for psychosis and psychotic experiences, including higher frequency and duration of use[4–7] and initiation at a younger age[4,8–12]. Initiation of cannabis use at a young age may be particularly harmful as adolescence is a critical period of increased vulnerability to the effects of cannabis due to developmental and maturational processes in key areas of the brain[11,13–18].

Prior investigations on the psychopathological effects of cannabis use characteristics have focused on broad mental health outcomes, such as diagnosis with a psychotic disorder or compound measures of psychopathology[1,8,9,19–22]. A first study found associations between earlier initiation of cannabis use and both positive and negative symptom dimensions of psychosis (i.e., distorted or excessive normal functions such as delusions, hallucinations, disorganized behavior vs. diminished or absent normal functions related to motivation and interest such as avolition, flattening of affect, and poverty of speech[23]), but not depressive symptoms in a large young-adult general population sample[9]. Conversely, in a nationally representative study of 19-year-olds in Greece, both lifetime frequency and earlier age of cannabis use initiation were associated with increases in psychotic clusters of hallucinations, paranoia, grandiosity, and first-rank symptoms, but not in dimensions of negative symptoms and depression[20]. In a third study, daily, compared to non-daily non-psychotic cannabis users, showed greater prevalence of symptom clusters of first-rank symptoms, hallucinations, and grandiosity, even

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after controlling for age of cannabis use initiation[22]. In a fourth study conducted in a large community sample of adolescents in Australia, higher frequency of cannabis use in the last year was associated with higher scores on subscales of perceptual abnormalities and magical thinking, but not with bizarre thinking and persecutory ideation[21]. Finally, in a population sample drawn from the UK Biobank, there was a dose-dependent relationship between frequency of cannabis use and psychotic experiences, particularly persecutory delusions[24]. Even though somewhat mixed regarding findings on negative symptoms, these studies overall suggest a certain specificity in the association between cannabis use characteristics and psychopathology in the psychosis continuum: earlier initiation and frequency of cannabis use do not appear to affect all symptom domains equally.

In line with this observation, there is increasing awareness that interactions between individual risk factors and symptoms may offer a nuanced insight into the etiology of psychosis[25–30]. More specifically, adopting a network perspective represents one promising approach to disentangle the multifaceted ways by which cannabis use characteristics relate to the occurrence of attenuated expressions of positive psychotic symptoms below the diagnostic threshold (also called *psychotic experiences*[31]). Network theory conceptualizes psychological behavior as a complex interplay between symptoms, biological, sociological, and environmental components[25,32,33]. Following this approach, the focus shifts from investigating broad outcomes, such as diagnosis with a psychotic disorder or sum scores of psychotic dimensions, to interactions between individual symptoms and other clinically relevant components, such as environmental risk factors[25,26,28,34].

Typically, statistical network models based on cross-sectional data depict unique relationships between variables, representing the share of the association between two variables that remains after controlling for all other variables in the network[35]. This allows for a simultaneous analysis of all relationships that may be important in a network of connected phenomena. Hence, network models are a suitable choice to uncover the specific relationships in the context of distinct cannabis use characteristics, such as frequency and age of cannabis use initiation, that are typically not independent: earlier initiation of use is more likely to become longstanding[8]. Assessing either aspect in isolation, without controlling for the respective other, may likely overestimate its effect on individual aspects of psychopathology. Similarly, there is evidence that cannabis use and other early environmental risk factors for psychosis, such as childhood trauma and urbanicity, are not independent[7,25,36,37]. When examining the associations between cannabis use characteristics and individual symptoms, it is therefore important to take further available cannabis use characteristics and environmental risk factors into account to derive unique associations, i.e., associations that remain even after controlling for the other factors. Such joint modeling acknowledges the complex dependencies in environmental risk[29,37,38]. Likewise, expanding focus to domains of psychopathology beyond positive psychotic experiences has proven informative for a comprehensive account of the complex etiology of psychotic experiences and full-blown psychotic disorders[25,28,29,34,39–41]. For example, the mediating role of affective psychopathology in pathways from environmental risk factors to psychotic psychopathology is increasingly recognized[28,29,40,41].

In the present work, we take a network approach to explore the unique relations between specific cannabis use characteristics, i.e., age of cannabis use initiation and lifetime cumulative frequency, a broad spectrum of psychotic experiences and affective psychopathology, as well as early environmental risk factors such as childhood trauma and urbanicity, in cannabis users of a large general population sample (i.e., those who reported having used cannabis at least once in their lifetime). With these analyses, we extend the existing literature on cannabis use characteristics and psychopathology in three ways. First, we investigate the associations between distinct cannabis use characteristics and individual aspects of psychopathology, avoiding binarized measures of cannabis use characteristics that may obscure important associations. Second, we take both the cumulative frequency and the age of cannabis use initiation into account. Third, we simultaneously model childhood trauma and urban upbringing as early environmental risk factors in the network. Using this approach, we can identify unique associations, i.e., which specific symptoms are related to cannabis use characteristics, after controlling for all other modeled symptoms, cannabis use characteristics, and environmental risk factors[42].

Method

Sample. The data used in this study come from the National Comorbidity Survey (NCS)[43], a collaborative epidemiological investigation based on a nationally representative, stratified, multistage, area probability sample of persons in the age range 15–54 in the non-institutionalized population of the 48 coterminous states of America designed to study the prevalence and correlates of psychiatric disorders between 1990 and 1992. Overall response rate was 82.4%, with a total of 8,098 participants. Informed consent was obtained from all participants. The NCS interview was administered in two parts. Part I was administered to all respondents and contained the core diagnostic interview, as well as a brief risk factor battery. A subsample of the original respondents ($N = 5877$) completed the additional NCS Part II survey that contained a more detailed risk factor battery and additional diagnostic assessments. The current study is based on respondents in the Part II subsample. We limited the Part II subsample to participants who reported any lifetime cannabis use and were aged 40 and younger at the time of assessment ($N = 2624$) to reduce the possibility to capture secondary psychosis related to (beginning) neurodegenerative disorders, and due to concerns about recall and reporting artifacts[45,46]. A full description of the NCS is available elsewhere[43].

The original NCS data collection protocol was approved by the University of Michigan's Internal Review Board (IRB). All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Measurements

Psychopathology. A modified version of the Composite International Diagnostic Interview (CIDI)[43,47,48] was used in the NCS. The CIDI is a non-clinician administered diagnostic interview developed jointly by the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and the World Health Organization (WHO) to facilitate psychiatric epidemiologic research[47]. Modifications of the CIDI for the NCS are described in detail in[48,49] and all study materials can be retrieved from https://www.hcp.med.harvard.edu/ncs/Baseline_NCS.php. The psychosis screening section of the CIDI (Section K) contained 13 items related to psychotic experiences and beliefs, all of which were included in our analyses. To represent more general dimensions of psychopathology, we included 6 items from the lifetime mood and health behaviors screening section of the CIDI (Section B), including lifetime experiences of panic, anxiety, sadness, loss of interest, mania, and irritability. All items were responded to by all participants used for the present analyses (i.e., there was no skip-structure), using a simple "yes" or "no" response format. For details on these assessments, see Supplementary Table 1.

Cannabis use characteristics. We included two available cannabis use characteristics derived from the Medication and Drugs module in the NCS: the age of cannabis use initiation (age at which cannabis was first used) and cumulative lifetime frequency of cannabis use, expressed as the total number of cannabis use occasions, which were coded in a binned format (1 or 2 times, 3 to 5 times, 6 to 10 times, 11 to 49 times, 50 to 99 times, 100 to 199 times, 200 or more times). For details on these assessments, see Supplementary Table 1.

Early risk factors. To control for exposure to early environmental risk, we included childhood trauma and urban upbringing. Information on childhood trauma was derived from the Posttraumatic Stress Disorder (PTSD) module from the modified version of the CIDI[48]. In accordance with prior analyses in the NCS[50–52], we selected five questions that represented (1) childhood neglect, (2) childhood physical abuse, (3) rape (before age 18), and (4) sexual molestation (before age 18). Items were scored with a "yes" or "no" response format. No explicit age limit was stated for "childhood" events (1, 2). Question 1 was used to represent childhood neglect. Again, following prior work in the NCS[51,52], questions 2–4 were collapsed into a binary variable representing childhood abuse, which indicated if a participant had given a "yes" response to any of these questions. The variable urban upbringing reflected whether participants had been raised in a suburb or city during most of their childhood. For details on these assessments, see Supplementary Table 1.

Covariate. To control for age-related links between cannabis use characteristics (e.g., older individuals having often used more) and psychopathology (e.g., some symptoms manifesting later than others), we additionally included age at assessment as a covariate in the network model.

Data analytic strategy

We conducted all analyses using *R*, version 4.1.0[53]. Throughout, we considered a significance level of $\alpha < 0.05$. Reporting complied with recently proposed standards for network analyses in cross-sectional data[54]. Data used in this study are available for public use via the Inter-university Consortium for Political and Social Research[44]. Code to reproduce the analyses is available at https://github.com/kambeitzlab/Network_Cannabis.

Network estimation. Because the data contained continuous, ordinal, and binary variables, we chose an undirected mixed graphical model for network estimation[55,56]. Items assessed on ordinal scales without equal spacing have typically been treated as continuous in this particular modeling context in prior work (e.g., [56,57]). Thus, lifetime cumulative frequency of cannabis use, age of cannabis use initiation, and age at assessment were treated as continuous variables, while the remaining items relating to early risk factors and psychopathology, coding the presence or absence of the respective factor, were treated as categorical variables in the estimation of the mixed graphical network model. In such a network, variables are represented by nodes, and edges between two nodes reflect the association between the corresponding variables that remains after controlling for all other variables under consideration. Edges can be interpreted as predictive effects, i.e., the share of the pairwise association between two variables that cannot be explained by any other variable in the network, also known as conditional dependence relation[35]. If two variables are independent conditioned on all other variables, no edge is drawn between them in the network. Estimation of mixed graphical models is based on a so-called pseudo-likelihood, node-wise regression approach[58], where each variable is predicted by all other variables in a L_1-regularized Generalized Linear Model (GLM) framework. The link function used in the GLM depends on the type of exponential family distribution of a given variable[59] (in the present case, Gaussian distribution for the two continuous cannabis use-related variables and Bernoulli distribution for all remaining binary variables). This node-wise regression approach leads to two estimates for each edge weight that we combined using the "OR" rule, meaning that at least one edge weight estimate had to be non-zero in order to set the edge to be present in the network[56].

L_1-regularization ensures a high specificity of the edges in the network[60]. The optimal penalty parameter used in regularization was determined by minimizing the Extended Bayesian Information Criterion (EBIC[61]). The EBIC itself has a hyperparameter, γ, that governs the amount of regularization in the network; the higher γ, the more regularization is imposed, and the higher the possibility of false negatives edges in the network[61]. The findings reported in the main paper are based on $\gamma = 0$, ensuring maximal sensitivity[57,62]. Additionally, we systematically varied γ from 0 to 0.25 in steps of 0.05 to test the impact of the amount of regularization on our findings. We constructed the networks using the *R* package 'mgm', version 1.2–12[56], and visualized them using the *R* package 'qgraph', version 1.6.9[63]. Of note, 'mgm' does currently not allow missing values. We therefore tested

Variable	
Sex, n (%)	Women: 1196 (47.0); Men: 1348 (53.0)
Age in years, mean (SD)	29.2 (6.5)
Education, n (%)	Less than high school: 385 (15.1); high school or equivalent: 857 (33.7); some college: 760 (29.9); college degree and beyond: 197 (7.7); no information: 345 (13.6)
Ethnicity, n (%)	White: 2081 (81.8); Black: 245 (9.6); Hispanic: 150 (5.9); Other: 66 (2.6); no information: 2 (0.1)
Immigration status, n (%)	U.S.-born: 2455 (96.5); foreign-born: 89 (3.5)
Age of cannabis use initiation, mean (SD)	16.7 (3.2)
Lifetime cumulative frequency of cannabis use, n (%)	1 or 2 times: 462 (18.2); 3 to 5 times: 329 (12.9); 6 to 10 times: 277 (10.9); 11 to 49 times: 438 (17.2); 50 to 99 times: 226 (8.9); 100 to 199 times: 182 (7.2); 200 or more times: 630 (24.8)
Time last used cannabis, n (%)	Past month: 348 (13.7); past six months: 234 (9.2); past year: 113 (4.4); more than a year ago: 1844 (72.5); no information: 5 (0.2)
Childhood abuse, n (% yes)	422 (16.6)
Childhood neglect, n (% yes)	116 (4.6)
Urban upbringing, n (% yes)	1181 (46.4)

Table 1. Demographics of the study sample ($N = 2{,}544$).

whether data were missing completely at random (MCAR) using the nonparametric test of homoscedasticity described by Jamshidian and Jalal[64], as implemented in the *R* package 'MissMech', version 1.0.2[65]. If the MCAR assumption is met, removal of observations with missing data is expected to produce unbiased estimates of the parameters in the network model[66,67].

For visualization, we manually placed the two nodes representing characteristics of cannabis use (age of initiation, lifetime cumulative frequency) in the center of the network, as these variables, and their association with symptoms, were the focus of the analysis. The positioning of the remaining nodes was determined using the Fruchterman-Reingold algorithm, placing more strongly connected nodes to the center and less connected nodes to the periphery of the network[68]. Additionally, we manually un-faded edges connected to the two nodes representing cannabis use characteristics. i.e., these edges were deliberately set opaque, while the other edges retained transparency depending on their respective edge weight[26]. The cut-value was set to 0, meaning that for plotting the network, no cut-off was used to curtail the scaling of edges in width and color saturation; rather, all edges were allowed to vary in width and color depending on their strength and sign (for details, see[63]).

Following recommended guidelines[42], we employed the routine implemented in the *R* package 'bootnet', version 1.4.3[69] to assess the stability and robustness of the estimated network structures with respect to proneness to sampling variation and dropping of cases with 1,000 bootstrap samples.

To assess the effect of sex on our results[29], we estimated a moderated mixed graphical model[70] via the *R* package 'mgm'[56]. Here, we focused on moderation-effects of sex on network connections related to variables of cannabis-use characteristics, i.e., age of cannabis use initiation and cumulative lifetime frequency of cannabis use. We tested the stability of the results using 1,000 bootstrap samples.

Results

Sample characteristics. Of 2,624 participants, 80 (3.0%) had to be excluded due to missing values in the network variables of interest. Missing data met the MCAR assumption ($p = 0.624$), supporting a complete case analysis. The final sample thus comprised $N = 2{,}544$ participants, 47.0% percent of whom were women, with an average age of 29.2 years ($SD = 6.5$) at assessment. Mean age of cannabis use initiation was 16.7 years ($SD = 3.2$). On average, participants had consumed cannabis 11 to 49 times in their lives. Table 1 provides details on demographic characteristics of the sample. Lifetime prevalences of the modeled affective symptoms were as follows: *panic*: 35.4%, *anxious*: 52.6%; *sad*: 54.3%; *loss interest*: 50.2%; *irritable*: 36.0%; *manic:* 11.7%. Lifetime prevalences of the modeled psychotic experiences were as follows: *spying/following you:* 14.3%; *poison/hurt you:* 3.9%; *reading your mind*: 7.8%; *hear your thoughts*: 4.5%; *hear others thought*: 7.5%; *controlled by force*: 3.8%; *others stole thoughts*: 2.7%; *special messages/tv:* 2.7%; *hypnotized/magic/force:* 1.3%*; saw visions:* 9.0%; *heard noise/voice:* 8.6%; *smells/body odors*: 5.0%; *feelings in/on body*: 8.5%.

Network. Figure 1 depicts the network illustrating unique relationships between cannabis use characteristics, early environmental risk factors, as well as psychotic experiences and affective psychopathology (for the individual edge weights, see Table 2). Of 300 possible edges, 121 (40.3%) were retained in the regularized mixed-graphical model estimation, with a mean edge weight of 0.08. Results show that *age of cannabis use initiation* is negatively related to *saw visions* (*edge weight* (w) = − 0.08), *irritable* ($w = -0.06$), and early risk factors, including *childhood neglect* ($w = -0.08$) and *abuse* ($w = -0.02$) as well as *urban upbringing* ($w = -0.02$). These results suggest that *earlier* initiation of cannabis use makes the positive endorsement of these variables more likely (e.g., younger age at first use of cannabis makes lifetime experiences of visual hallucinations more likely). *Lifetime cumulative frequency* showed positive links to *hear your thoughts* ($w = 0.05$), *spying/following you* ($w = 0.04$), and *heard noise/voice* ($w = 0.02$), indicating that the higher lifetime cumulative use, the more likely these experiences

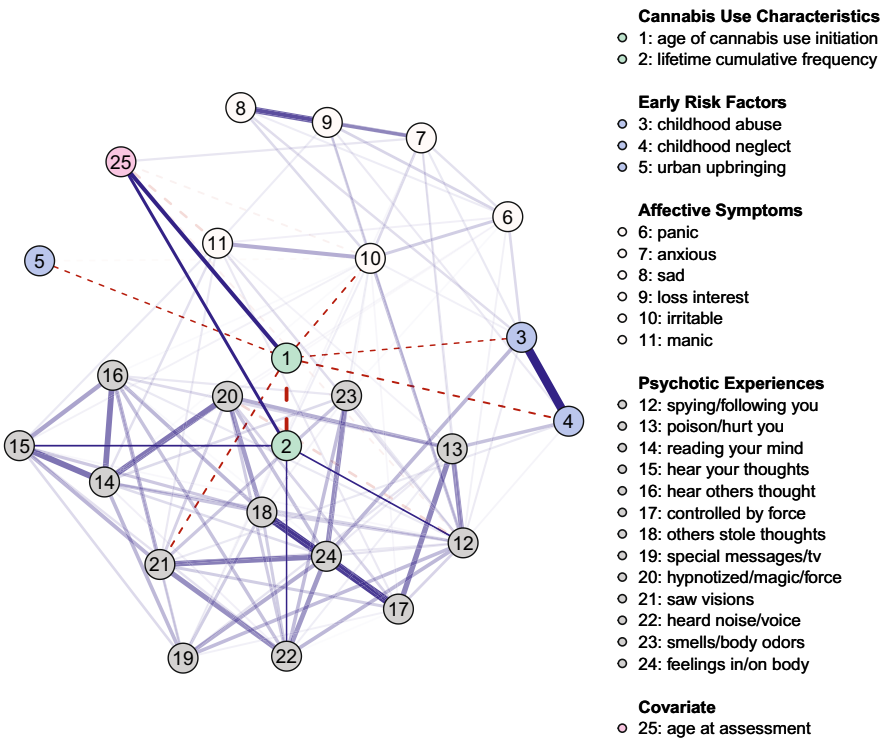

Figure 1. Network of cannabis use characteristics (age of cannabis use initiation, lifetime cumulative frequency of cannabis use), early risk factors, psychotic experiences, and affective symptoms ($N = 2{,}544$). Solid blue (dashed red) lines represent positive (negative) associations between variables and wider, more saturated edges indicate stronger associations. Given that the focus of the paper was to investigate the relations between the cannabis use characteristics and aspects of psychopathology, the edges connecting to the two relevant variables (age of cannabis use initiation, lifetime cumulative frequency of cannabis use) have been manually un-faded, i.e., these edges were deliberately set opaque, while the edges between the other nodes in the network retain transparency. Variable groups are differentiated by color.

become. The covariate *age at assessment* shows positive links to both *age of cannabis use initiation* ($w = 0.39$) and *lifetime cumulative frequency of cannabis use* ($w = 0.24$), suggesting that the older the person was at assessment, the later they started consuming cannabis on average, and the more often they had cannabis consumed in their lifetime.

Childhood abuse has positive connections with *feelings in/on body* ($w = 0.34$) and *spying/following you* ($w = 0.09$) from the psychosis dimension, and also has positive associations with the majority of affective symptoms, including *panic* ($w = 0.18$), *sad* ($w = 0.16$), *anxious* ($w = 0.11$), and *irritable* ($w = 0.07$). *Childhood neglect* connects several psychotic experiences, i.e., *poison/hurt you* ($w = 0.30$), *saw visions* ($w = 0.11$), and *spying/following you* ($w = 0.06$), as well as to *loss interest* ($w = 0.10$) from the affective dimension. Effects of urbanicity on psychopathology were fully mediated by age of cannabis use initiation.

Stability analyses suggest that the network and identified edges are overall stable. Of the 121 identified edges, 114 (94.2%) were included in at least 50% of the bootstrapped network models. Of the edges connected to *age of cannabis use initiation* and *lifetime cumulative frequency*, all edges were included in at least 50% of the bootstrapped network models, except for the edge connecting *age of cannabis use initiation* with *childhood abuse*, indicating that this association should be interpreted with caution (see Supplementary Fig. 1). For the network showing stable edges only, see Supplementary Fig. 2. 59.5% of the participants could be left out to retain a correlation of $r = 0.70$ with the edge weights in the original model (see Supplementary Fig. 3), suggesting high stability of the results to dropping of cases[42]. All network connections related to the two variables representing cannabis use characteristics were retained at higher degrees of regularization (see Supplementary Fig. 4).

In the sex-moderated mixed graphical model, there was evidence that the association between *age of cannabis use initiation* and *age at assessment* was stronger in women than in men. Moreover, the association between *lifetime cumulative frequency of cannabis use* and *urbanicity* was stronger in men. However, results from bootstrapping suggest that these moderation effects were unstable, i.e., susceptible to sampling variation, and should be interpreted with caution.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1	0	-0.35	-0.02	-0.08	-0.02	0	0	0	0	-0.06	0	0	0	0	0	0	0	0	0	0	-0.08	0	0	0	0.39
2	-0.35	0	0	0	0	0	0	0	0	0	0	0.04	0	0	0.05	0	0	0	0	0	0	0.02	0	0	0.24
3	-0.02	0	0	1.06	0	0.18	0.11	0.16	0	0.07	0	0.09	0	0	0	0	0	0	0	0	0	0	0	0.34	0
4	-0.08	0	1.06	0	0	0	0	0	0.10	0	0	0.06	0.30	0	0	0	0	0	0	0	0.11	0	0	0	0
5	-0.02	0	0	0	0	0	0	0	0	-0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0.18	0	0	0	0.15	0.09	0.20	0.24	0.07	0.06	0	0.03	0	0	0	0	0	0.04	0	0	0.03	0	0
7	0	0	0.11	0	0	0.15	0	0.38	0.31	0.18	0	0.13	0.07	0	0	0	0	0	0.04	0	0	0	0	0	0.12
8	0	0	0.16	0	0	0.09	0.38	0	0.74	0.17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0.10	0	0.20	0.31	0.74	0	0.19	0.09	0.13	0	0	0	0	0	0	0	0	0	0	0	0	0
10	-0.06	0	0.07	0	-0.03	0.24	0.18	0.17	0.19	0	0.39	0.28	0	0.02	0.07	0.03	0.04	0	0.08	0	0	0	0.09	0.03	-0.07
11	0	0	0	0	0	0.07	0	0	0.09	0.39	0	0.16	0.06	0.15	0.11	0	0.11	0	0	0	0.10	0	0	0	-0.17
12	0	0.04	0.09	0.06	0	0.06	0.13	0	0.13	0.28	0.16	0	0.53	0.21	0.04	0.11	0.20	0.2	0.32	-0.18	0.10	0.34	0.11	0.13	-0.07
13	0	0	0	0.30	0	0	0.07	0	0	0	0.06	0.53	0	0	0	0.18	0.59	0	0.13	0.38	0	0.08	0	0.10	0
14	0	0	0	0	0	0.03	0	0	0	0.02	0.15	0.21	0	0	0.67	0.64	0	0.28	0.34	0.66	0	0.07	0.17	0.17	0
15	0	0.05	0	0	0	0	0	0	0	0.07	0.11	0.04	0	0.67	0	0.44	0	0.26	0.18	0	0.36	0.14	0	0	0
16	0	0	0	0	0	0	0	0	0	0.03	0	0.11	0.18	0.64	0.44	0	0.03	0.34	0.11	0	0.38	0.29	0.11	0	0
17	0	0	0	0	0	0	0	0	0	0.04	0.11	0.20	0.59	0	0	0.03	0	0.94	0.07	0.20	0.24	0.02	0	0.26	0
18	0	0	0	0	0	0	0	0	0	0	0	0.20	0	0.28	0.26	0.34	0.94	0	0.24	0.47	0	0.24	0.06	0.30	0
19	0	0	0	0	0	0	0.04	0	0	0.08	0	0.32	0.13	0.34	0.18	0.11	0.07	0.24	0	0	0.21	0	0	0.39	0
20	0	0	0	0	0	0.04	0	0	0	0	0	-0.18	0.38	0.66	0	0	0.20	0.47	0	0	0.22	0.25	0	0.30	0
21	-0.08	0	0	0.11	0	0	0	0	0	0	0.10	0.10	0	0	0.36	0.38	0.24	0	0.21	0.22	0	0.53	0.27	0.61	0
22	0	0.02	0	0	0	0	0	0	0	0	0	0.34	0.08	0.07	0.14	0.29	0.02	0.24	0	0.25	0.53	0	0.31	0.49	0
23	0	0	0	0	0	0.03	0	0	0	0.09	0	0.11	0	0.17	0	0.11	0	0.06	0	0	0.27	0.31	0	0.54	0
24	0	0	0.34	0	0	0	0	0	0	0.03	0	0.13	0.10	0.17	0	0	0.26	0.30	0.39	0.30	0.61	0.49	0.54	0	0
25	0.39	0.24	0	0	0	0	0.12	0	0	-0.07	-0.17	-0.07	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 2. Edge weights for the network shown in Fig. 1 (obtained via mixed graphical-model estimation). *Node labels*: 1 = age of cannabis use initiation, 2 = lifetime cumulative frequency of cannabis use, 3 = childhood abuse, 4 = childhood neglect, 5 = urban upbringing, 6 = panic, 7 = anxious, 8 = sad, 9 = loss interest, 10 = irritable, 11 = manic, 12 = spying/following you, 13 = poison/hurt you, 14 = reading your mind, 15 = hear your thoughts, 16 = hear others thought, 17 = controlled by force, 18 = others stole thoughts, 19 = special messages/tv, 20 = hypnotized/magic/force, 21 = saw visions, 22 = heard noise/voice, 23 = smells/body odors, 24 = feelings in/on body, 25 = age at assessment.

Discussion

We employed a data-driven network approach to explore the complex dependencies between cannabis use characteristics, i.e., age of initiation and lifetime cumulative frequency, and a broad spectrum of psychotic experiences and affective psychopathology as well as further early risk factors, i.e., childhood trauma and urban upbringing, in a general population sample. This approach allowed us to disentangle specific effects of age of initiation and lifetime cumulative frequency of cannabis use, while controlling for all other variables under consideration. There were three key findings: First, lifetime cumulative frequency of cannabis use showed particularly pronounced positive associations with delusional experiences, i.e., thought broadcasting and persecutory delusions, and, to a smaller extent, with auditory hallucinatory experiences. Second, age of cannabis use initiation showed negative associations with visual hallucinatory experiences and irritability, suggesting that these experiences become more likely the earlier use is initiated. Third, early risk factors, i.e., urban upbringing and childhood neglect, were stably linked to an earlier initiation, but not lifetime frequency of cannabis use. Results were stable and edges were overall estimated with good accuracy, and consistent across different levels of regularization.

The present study adds to a large body of evidence showing that early and frequent cannabis use do not only increase risk for full-blown psychotic symptoms observed in psychotic disorders, but also for psychotic experiences in non-clinical populations[9,20,22,24,39,71], in line with a psychosis-proneness-persistence-impairment model of psychotic disorder[72]. Importantly, our results suggest that early and frequent cannabis use may have different relationships with different types of psychotic experiences. Replicating previous findings[24], we find particularly pronounced associations of frequency of cannabis use with delusional experiences, especially persecutory ideas. Extending previous findings, we show that these particularly pronounced associations cannot be explained by age of cannabis use initiation. Collectively, these results underscore a differential association of frequency of cannabis use with hallucinations and delusions in the longer term that mirrors findings from acute cannabis intoxication[24,73,74]. In contrast, we found earlier cannabis use to be specifically associated with visual hallucinatory experiences. There was also a strong link between the two cannabis use characteristics in the network: Earlier cannabis use was associated with more frequent lifetime cannabis use. In line with previous epidemiological research, this pattern of results suggest that earlier initiation of cannabis use appears to be a key risk factor for vulnerability to the harmful psychopathological effects of cannabis use[8,9,11,15,20,22,75] and

increased, potentially problematic cannabis use later in life[12,76–78]. Thus, our findings corroborate the notion that delaying initiation of cannabis use is an important harm reduction intervention in terms of preventing or reducing later cannabis use and psychopathology[8,9,20,76,78]. This body of evidence is highly relevant from a public health perspective as the age of cannabis use initiation decreases and jurisdictions move toward legalization of cannabis[79,80]. Cannabis use in adolescence has been suggested to alter the development of various neurobiological systems[11,13–18]. Speculatively, early cannabis use may increase the risk for visual hallucinatory experiences by inducing lasting alteration in brain structures and functioning that serve the integration process of bottom-up perceptual information and prior expectations[27,81]. In accordance with this idea, previous research has shown that in patients with psychosis, cannabis use was linked to altered functional connectivity in visual attentional brain networks, and strength of connectivity was positively associated with a history of visual hallucinations, as well as a compound measure of cannabis use behaviors featuring earlier initiation[82]. While our findings do not allow conclusions about the underlying neurobiological mechanisms involved in the links between early cannabis use and visual hallucinatory experiences, they can serve as an informative intermediate step in a larger chain of interdisciplinary research efforts.

The present analysis also suggested links between earlier initiation of cannabis use and irritability. This finding highlights the relevance of specific affective experiences in cannabis-related psychopathology that were previously either not modeled[21,22] or only assessed by sum scores[9,20]. Affective psychopathology has been suggested to play a key role in mediating between external triggers, such as cannabis use, and delusional ideas[28,40,83]. Consistent with this idea, increases in negative affect and perceptual aberrations fully explained increases in persecutory ideas following experimental administration of Δ9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis , in a previous study[73]. Future work needs to carve out mechanistic pathways that account for the association between earlier initiation of cannabis use and individual affective symptoms, as well as their role in psychotic experiences.

Moreover, only earlier initiation, but not lifetime cumulative frequency of cannabis use was linked to early risk factors included in the network, i.e., experiences of childhood neglect and urbanicity. Interestingly, earlier initiation of cannabis use mediated the influence of urbanicity, a complex proxy environmental influence, on psychopathology, extending previous research that showed that lifetime cannabis exposure mediated effects between urbanicity and psychopathology in the past two weeks[25]. Our findings add specificity to this previously identified association, suggesting that earlier initiation, but not increased lifetime cumulative frequency of cannabis use, seems to become more likely given urban upbringing. Overall, these results might imply that psychogenic effects of growing up in urban surroundings may be partially explained by an earlier age of cannabis use initiation, which could, among other factors, be attributable to greater local availability of cannabis in non-rural areas compared to rural areas in the US[84,85]. This putative mechanism has important implications for public health, pointing to urban adolescent populations as a target for preventive campaigns of early cannabis use. Mirroring previous findings[12], we also found early cannabis use to be associated with increased psychosocial risk in the form of childhood trauma, particularly neglect. It could be speculated that reduction of parental neglect might have a positive impact in terms of delaying initiation of cannabis use with the potential to prevent or reduce future cannabis use and psychotic experiences. Interestingly, cannabis use characteristics and childhood trauma showed unique as well as shared network links to specific psychotic experiences; specifically, visual hallucinatory experiences and persecutory delusions were associated with cannabis use as well as childhood trauma variables. This pattern of results may reflect both independent and additive pathways from environmental risk factors to specific psychotic experiences[36,37]. Overall, our findings underscore the complex interplay between different environmental risk factors, and that, when possible, they should be modeled jointly to assess their unique and shared effects on individual aspects of psychopathology[25,29,37,38].

There are several limitations of the present study that need to be considered. First, given the cross-sectional nature of our data, reverse mechanisms, whereby psychotic or affective experiences in adolescence drive earlier initiation of cannabis use, reflecting self-medication or inclination towards risk-behaviors, cannot be excluded. Even though converging evidence based on longitudinal and retrospective designs renders this possibility rather unlikely[2,20,75,86], analyses of prospective data are required to determine how earlier initiation of cannabis use maps onto individual affective and psychotic experiences through late adolescence and early adulthood. Similarly, inclusion of polygenic risk scores into the network may shed light on potential gene × environment interactions—for example, to assess to what extent genetic vulnerability may influence links between earlier initiation of cannabis use and psychopathology[24,26,87–91]. Second, older participants, on average, started using cannabis later than younger participants. This may reflect known historical cohort trends in age of cannabis use initiation[46,92]; however, biases in reports of early cannabis use due to recall error, social acceptance, and fear of disclosure may also play a role[46]. Third, the data used for modeling were collected in the 1990s. Since then, use patterns of cannabis have changed, especially with regard to harmful high-potency variants of cannabis products that have become increasingly available and popular in recent years[2,6,93,94]. In particular, there may be a role for frequent use of high potency variants of cannabis that we could not examine with the present data. Against the backdrop of ongoing debates[32] and methodological advances in the network community[95], the assessment of the replicability and generalizability of the present findings to diverse samples and present circumstances will be an important step for future research. Similarly, further samples may help to elucidate the role of additional factors, such as initiation age of tobacco smoking. Lastly, frequency of cannabis use was assessed in a binned format, which inevitably entails a loss of information. In general, quantification of drug use is a challenging task, with exact measures of the number of lifetime use occasions, especially in case of frequent use, likely being unreliable due to memory biases. Here, implementation of recently proposed minimum standards for quantifying cannabis use could facilitate the collection and integration of evidence on cannabis use across studies and disciplines[96].

In conclusion, we employed a network approach to comprehensively explore unique associations between cannabis use characteristics, i.e., lifetime frequency and age of cannabis use initiation, and psychotic and affective

psychopathology in a large, general population sample of cannabis users (i.e., those who reported having used cannabis at least once in their lifetime), while controlling for early risk factors and age at assessment. We found particularly pronounced associations between increased frequency of cannabis use and specific delusional experiences, i.e., persecutory delusions and thought broadcasting on the one hand, and earlier initiation of cannabis use and visual hallucinatory experiences and irritability on the other hand. Early risk factors were linked to an earlier initiation, but not frequency of cannabis use. Overall, these findings suggest that cannabis use characteristics may contribute differentially to risk for specific psychotic experiences and affective symptoms in the general population. Thus, we provide a valuable starting point for further investigation of the complex relationships between cannabis use patterns and specific symptoms.

Received: 20 September 2021; Accepted: 8 April 2022
Published online: 03 May 2022

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Author contributions
L.T.B. analyzed the data. L.T.B., N.P. and J.K. interpreted the results. L.T.B. drafted the manuscript and prepared the figures and tables. N.P. and J.K. revised the manuscript for important intellectual content. All authors agreed on the final version of the manuscript.

Funding
Open Access funding enabled and organized by Projekt DEAL.

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/s41598-022-11092-0.

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2.4 Disentangling heterogeneity of psychosis expression in the general population: sex-specific moderation effects of environmental risk factors on symptom networks

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Published in *Psychological Medicine*, First View, pp. 1–10, https://doi.org/10.1017/S0033291721003470.

Psychological Medicine

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Original Article

Cite this article: Betz LT, Penzel N, Rosen M, Bhui K, Upthegrove R, Kambeitz J (2021). Disentangling heterogeneity of psychosis expression in the general population: sex-specific moderation effects of environmental risk factors on symptom networks. *Psychological Medicine* 1–10. https://doi.org/10.1017/S0033291721003470

Received: 6 May 2021
Revised: 14 July 2021
Accepted: 4 August 2021

Key words:
Network analysis; psychopathology; environmental exposure; sex differences; affective pathway to psychosis; general population

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CAMBRIDGE UNIVERSITY PRESS

Disentangling heterogeneity of psychosis expression in the general population: sex-specific moderation effects of environmental risk factors on symptom networks

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Abstract

Background. Psychosis expression in the general population may reflect a behavioral manifestation of the risk for psychotic disorder. It can be conceptualized as an interconnected system of psychotic and affective experiences; a so-called 'symptom network'. Differences in demographics, as well as exposure to adversities and risk factors, may produce substantial heterogeneity in symptom networks, highlighting potential etiological divergence in psychosis risk.

Methods. To explore this idea in a data-driven way, we employed a novel recursive partitioning approach in the 2007 English National Survey of Psychiatric Morbidity ($N = 7242$). We sought to identify 'network phenotypes' by explaining heterogeneity in symptom networks through potential moderators, including age, sex, ethnicity, deprivation, childhood abuse, separation from parents, bullying, domestic violence, cannabis use, and alcohol.

Results. Sex was the primary source of heterogeneity in symptom networks. Additional heterogeneity was explained by interpersonal trauma (*childhood abuse* and *domestic violence*) in women and *domestic violence*, *cannabis use*, *ethnicity* in men. Among women, especially those exposed to early interpersonal trauma, an affective loading within psychosis may have distinct relevance. Men, particularly those from minority ethnic groups, demonstrated a strong network connection between hallucinatory experiences and persecutory ideation.

Conclusion. Symptom networks of psychosis expression in the general population are highly heterogeneous. The structure of symptom networks seems to reflect distinct sex-related adversities, etiologies, and mechanisms of symptom-expression. Disentangling the complex interplay of sex, minority ethnic group status, and other risk factors may help optimize early intervention and prevention strategies in psychosis.

Introduction

Recent research has advanced our understanding of psychosis through so-called 'symptom networks', i.e. causal systems of individual interacting experiences and symptoms (Betz et al., 2020; Hardy, O'Driscoll, Steel, van der Gaag, & van den Berg, 2020; Isvoranu, Borsboom, van Os, & Guloksuz, 2016; Isvoranu et al., 2019, 2017; Moffa et al., 2017; Murphy, McBride, Fried, & Shevlin, 2018; Robinaugh, Hoekstra, Toner, & Borsboom, 2020). Complex interactions between specific psychotic as well as non-psychotic experiences (e.g. depression and anxiety) in the general population may predate onset of psychosis in clinical settings (Guloksuz et al., 2016, 2015; Kelleher et al., 2012; Linscott & van Os, 2013; Murphy et al., 2018; van Os & Reininghaus, 2016). Additional lines of evidence indicate that there is considerable etiological continuity between subclinical and clinical levels of psychosis (Binbay et al., 2012; DeRosse & Karlsgodt, 2015; Kelleher & Cannon, 2011; Linscott & van Os, 2013). Thus, examining the symptom network structure of a transdiagnostic psychosis phenotype, reflecting a behavioral manifestation of risk for psychotic disorder in the general population that blends gradually into clinical syndromes, may help to better understand etiological mechanisms in psychosis and to develop prevention strategies (Bebbington, 2015; Binbay et al., 2012; DeRosse & Karlsgodt, 2015; Isvoranu et al., 2016; Kelleher & Cannon, 2011; Linscott & van Os, 2013; Robinaugh et al., 2020; van Os & Reininghaus, 2016).

Importantly, symptomatology and involved etiological mechanisms in psychosis expression are highly variable by specific at risk groups (Bentall, Wickham, Shevlin, & Varese, 2012;

Isvoranu et al., 2016; Linscott & van Os, 2013; van Os & Reininghaus, 2016). For example, in line with the theory of an affective pathway to psychosis, early traumatic events are strongly associated with connections between affective and psychotic symptomatology (Myin-Germeys & van Os, 2007; Upthegrove et al., 2015; van Nierop et al., 2015). In the presence of heterogeneity, averaged network models of psychosis may obscure important distinctions in relevant etiological mechanisms across specific risk groups (Jones, Mair, Simon, & Zeileis, 2020; Moriarity, van Borkulo, & Alloy, 2020). Thus far, however, heterogeneity in symptom networks of psychosis has been either overlooked or addressed in a partial way on a single candidate risk factor (such as sex, cannabis use, or socioeconomic background) at specific thresholds, or using summed environmental risk scores (Betz et al., 2020; Guloksuz et al., 2016; Isvoranu et al., 2016; Wüsten et al., 2018), which lose specificity and relevance for real work prevention and intervention.

The characterization of 'network phenotypes' based on a comprehensive set of environmental and demographic factors may explain heterogeneity; that is, the structure of symptomatology is a function of types, combinations, and intensity of etiological loads in psychosis expression (Jones et al., 2020; Moriarity et al., 2020). With the goal of characterization of network phenotypes in mind, the current study uses novel work on recursive partitioning, a data-driven, explorative statistical technique that can sequentially extract isolated and combined moderation effects of a large set of environmental and demographic factors on symptom networks, without a priori specification of thresholds or combinations of risk factors (Jones et al., 2020; Strobl, Malley, & Tutz, 2009). Recursive partitioning identifies network phenotypes that are maximally distinct from each other (Jones et al., 2020; Zeileis, Hothorn, & Hornik, 2008).

We used recursive partitioning to define meaningful network phenotypes of psychosis expression in the general population, using the 2007 Adult Psychiatric Morbidity in England Survey (APMS; National Centre for Social Research, University of Leicester, 2017). We hypothesized that exposure to environmental risk, if identified as defining a network phenotype, would be characteristically associated with more densely connected symptom networks when compared with samples not exposed to that specific environmental risk (Guloksuz et al., 2016, 2015; Isvoranu et al., 2016; Lin, Fried, & Eaton, 2019; Russell, Keding, He, Li, & Herringa, 2020). We also aimed to test whether the strength of connections between individual symptoms differed between network phenotypes.

Method

Data analytic strategy

We conducted all analyses in the R language for statistical computing, version 4.0.4. Throughout, we considered a significance level of $\alpha = 0.05$. Data of the 2007 APMS (National Centre for Social Research, University of Leicester, 2017) used in the analyses are available from the UK Data Service (https://ukdataservice.ac.uk/). Code to reproduce the analyses can be accessed at www.github.com/LindaBetz/APMS_NetworkTree.

Sample

We present analyses based on the 2007 APMS of adults living in private households aged 16 and above who were recruited using a stratified multistage random probability sampling strategy ($N = 7403$) (McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009; Singleton, Bumpstead, O'Brien, Lee, & Meltzer, 2003). Methods, procedures, and full details on sample characteristics have been described previously (McManus et al., 2009). For the present analyses, we excluded participants with missing values in the variables of interest, given that the methods employed do not allow missings. For comparing sample characteristics of included and excluded participants, we used permutation tests as implemented in the R package 'coin' (Hothorn, Hornik, van de Wiel, & Zeileis, 2008).

Assessment of symptomatology

Selection and definition of symptom variables followed a previously published network analysis using data from the 2007 APMS (Moffa et al., 2017), including measures from an affective domain (worry, sleep disturbance, generalized anxiety, and depression), and from a psychotic domain (persecutory ideation and hallucinatory experiences). All symptom variables in the network were coded in binary form (present or absent). For details on these assessments, see online Supplementary Method 1.

Assessment of environmental and demographic risk factors

Environmental risk factors comprised of psychosocial adversities in the form of physical abuse and sexual abuse before the age of 16, separation from parents until the age of 16 (local authority care and/or institutional care), lifetime experiences of bullying, and lifetime experiences of domestic violence. Additionally, we included sex, age, ethnic origin (White, Black, South Asian, and Mixed/Other), cannabis use in the past year, alcohol use, and socioeconomic deprivation. For details on these assessments, see online Supplementary Method 2.

Identification of network subgroups via recursive partitioning

In a first step, we estimated a partial correlation network (without regularization) based on the full sample, using the R package 'qgraph', version 1.6.5 (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012). A partial correlation network depicts unique pairwise associations between variables ('edges' in network terminology), i.e. the share of the association between two variables that remains after controlling for all other variables in the network (Epskamp, Borsboom, & Fried, 2018). We estimated the underlying zero-order correlations between the binary items using Pearson's φ, as recommended when employing recursive partitioning on binary data (Jones et al., 2020). The stronger the partial correlation between two variables, the more likely it is that they co-occur, controlling for the other variables under consideration.

Second, we used a model-based recursive partitioning approach to identify meaningful subgroups of symptom networks given the included environmental and demographic factors, as implemented in the R package 'networktree', version 1.0.1 (Jones et al., 2020). In brief, recursive partitioning sequentially creates a decision tree by either splitting or not splitting the sample along a set of potential moderating variables (Strobl et al., 2009; Zeileis et al., 2008). The 'networktree' approach (Fig. 1) determines sample splits based on significant invariance in the correlation matrix of the network variables under consideration, yielding non-overlapping partitions of the sample with maximally heterogeneous symptom networks (Jones et al., 2020). For a detailed account, we refer to online Supplementary Method 3 and available methodological articles

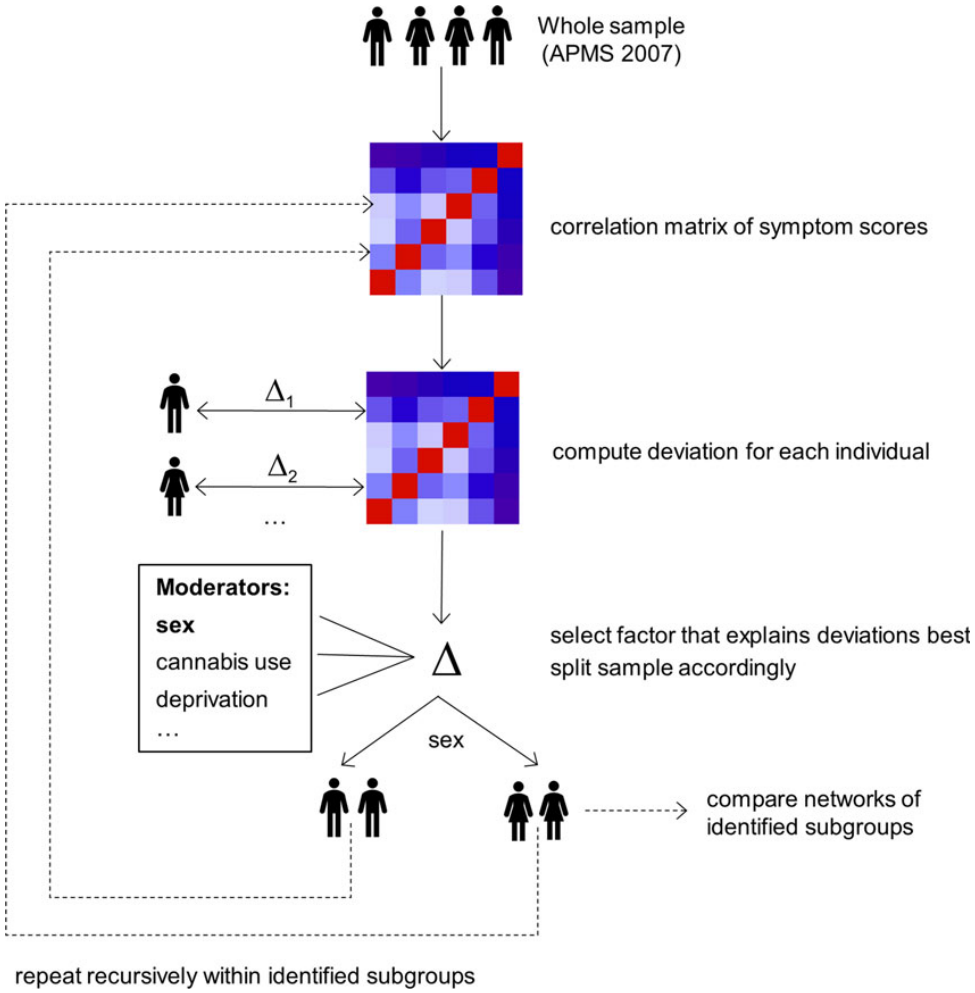

Fig. 1. Recursive partitioning for symptom networks as applied to data from the 2007 Adult Psychiatric Morbidity Survey (APMS) study. The goal is to assess which of the included demographic and risk factors capture individual deviations from the correlation matrix of symptom scores, which underlies symptom networks. Starting with the whole sample, individual deviations from the correlation matrix of symptom scores are computed via a log-likelihood-based score function. The variable that explains these deviations best, as determined by a minimum *p*-value strategy at Bonferroni-corrected α, is selected (here: sex), and the sample split accordingly. Within the identified subgroups, the procedure is repeated recursively until no significant deviations, i.e. heterogeneity, is detected. We compared symptom networks of the identified subgroups in terms of global strength and individual edge weights. For a detailed account of the method, see online Supplementary Method 3 and Jones et al. (2020).

(Jones et al., 2020; Strobl et al., 2009; Zeileis et al., 2008). For plotting, we transformed the correlation matrices to partial correlation matrices using the R package 'qgraph', such that edges reflect unique associations between two variables.

Comparison of identified subgroups

To delineate specific network differences between the identified subgroups (i.e. differences between subgroups as defined by a splitting factor in the recursive partitioning approach), we compared the overall strength of symptom connections, defined as the absolute sum of all individual partial correlation coefficients in the network (global strength; S), and differences in estimates of individual partial correlation coefficients (individual edge weights; ρ) within a Bayesian framework, using the R package 'BGGM', version 2.0.2 (Williams, 2021; Williams & Mulder, 2019; Williams, Rast, Pericchi, & Mulder, 2020). Specifically, we used posterior predictive checks for assessing differences in overall connection strength (Williams et al., 2020), and evaluated the posterior distribution for each difference in partial correlation coefficients, where we deemed a difference significant if the 95% credible interval did not contain 0 (Williams, 2021). The *p*-values derived from recursive partitioning are denoted as p_{RP}, whereas *p*-values derived from post-hoc comparisons implemented in the package 'BGGM' are denoted as p_{BGGM}.

Robustness analyses

We used the R package 'bootnet', version 1.4.3 (Epskamp et al., 2018) to conduct robustness analyses to check stability and accuracy of the results. We investigated stability of symptom networks estimated in the full sample and identified subgroups by testing

Table 1. Network variables and potential moderators with positive endorsement (%) or median (IQR) for the whole sample and disaggregated by sex

Variable Yes (%)/median (IQR)	Whole sample (*N* = 7242)	Women (*n* = 4115)	Men (*n* = 3127)
Network variables			
Worry	36.0	40.2	30.5
Sleep problems	34.6	41.4	25.8
Anxiety	17.3	19.4	14.5
Depression	22.9	25.5	19.4
Persecutory ideation	7.7	7.1	8.4
Hallucinatory experiences	0.80	1.0	0.70
Potential moderators			
Sex (% female)	56.8	100	0
Age (years)	50 (30)	50 (30)	50 (28)
Ethnic background	White: 92.7, Black: 2.6, South Asian: 2.6, Mixed/Other: 2.1	White: 93.1, Black: 2.7, South Asian: 2.1, Mixed/Other: 2.1	White: 92.1, Black: 2.4, South Asian: 3.3, Mixed/Other: 2.1
Deprivation	3 (2)	3 (2)	3 (2)
Bullying	18.9	19.0	18.8
Separation from parents	3.4	3.0	4.0
Domestic violence	9.5	12.9	5.0
Physical abuse	4.8	4.2	5.5
Sexual abuse	13.5	17.1	8.7
Cannabis use in past year	5.7	4.1	7.8
Alcohol consumption (AUDIT score)	4 (5)	3 (4)	5 (6)

sensitivity to dropping cases. Specifically, we assessed the degree to which edge weights remained the same after re-estimating the networks with less cases via the correlation stability (CS) coefficient. The CS coefficient represents the maximum proportion of cases that can be dropped, such that the correlation between original edge weights and edge weights of networks based on subsets is 0.7 or higher (95% confidence). The CS coefficient should preferably be above 0.5 (good stability), and not be below 0.25 (acceptable stability) (Epskamp et al., 2018). To investigate the accuracy of individual edge weights estimates across the networks in the full sample and identified subgroups, participants were randomly resampled 5000 times, and the bootstrapped confidence intervals (CIs) of the edge weights were estimated.

Results

Sample

Following removal of 161 participants (2.2% of the whole sample) with missing values in the variables of interest, the final sample comprised of 7242 participants, 56.8% of whom were women, with an average age of 50 (IQR = 30) years. Participants excluded due to missing data were on average older, less White and reported lower proportions of alcohol use and hallucinatory experiences, and higher proportions of depressive symptoms (online Supplementary Table S1).

Network variables and potential moderators

Table 1 presents positive endorsement and characteristics of the network variables and potential moderating risk factors in the sample. The most prevalent symptom was worry, and the most prevalent risk factor bullying.

Overall symptom network structure and subgroups

The partial correlation network estimated in the full sample suggested positive relationships between all symptoms, with a mean edge weight of 0.11. Partial correlations within each symptom domain were, on average, stronger than between the domains. Recursive partitioning revealed that six of the tested demographic and environmental risk factors were linked to significant heterogeneity in symptom networks and split the sample accordingly in a hierarchical fashion: *sex*, *childhood sexual abuse*, *childhood physical abuse*, *domestic violence*, *cannabis use*, and *ethnicity*. Partial correlation matrices for the plotted networks are available at the linked GitHub repository. Sex was the primary source of heterogeneity (Fig. 2*a*, $p_{RP} < 0.001$): the network of women was overall significantly less strongly connected ($\Delta S = -0.17$, $p_{BGGM} = 0.002$), and featured a significantly stronger connection between depression and hallucination ($\Delta\rho = 0.06$), and a significantly weaker connection between sleep problems and persecutory ideation ($\Delta\rho = -0.07$) than the network of men. This means that in women, depression and hallucination were more likely to co-occur than in men, whereas sleep problems and persecutory ideation were less likely to co-occur than in men. For networks of women and men, see Fig. 3.

Distinct risk factors explained further heterogeneity in symptom networks of women and men, yielding eight different network phenotypes in total. Among women, experiences of

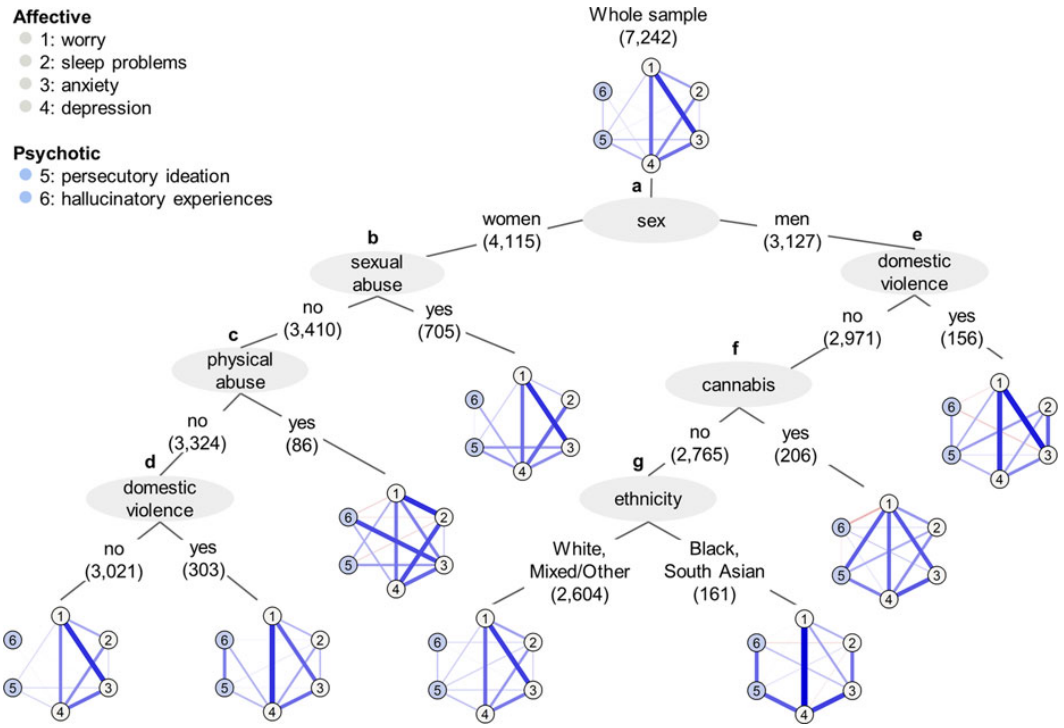

Fig. 2. Results from recursive partitioning, depicted as a decision tree of partial correlation networks. Numbers behind splitting factors give the sample size retained after the corresponding sample split. Symptom domains are differentiated by color. The thicker and less transparent the edge, the stronger the partial correlation between two symptoms. Blue (red) edges indicate positive (negative) relationships. To ensure visual comparability, edge weights were scaled identically across all networks. Only connections representing edge weights larger than 0.01 are depicted.

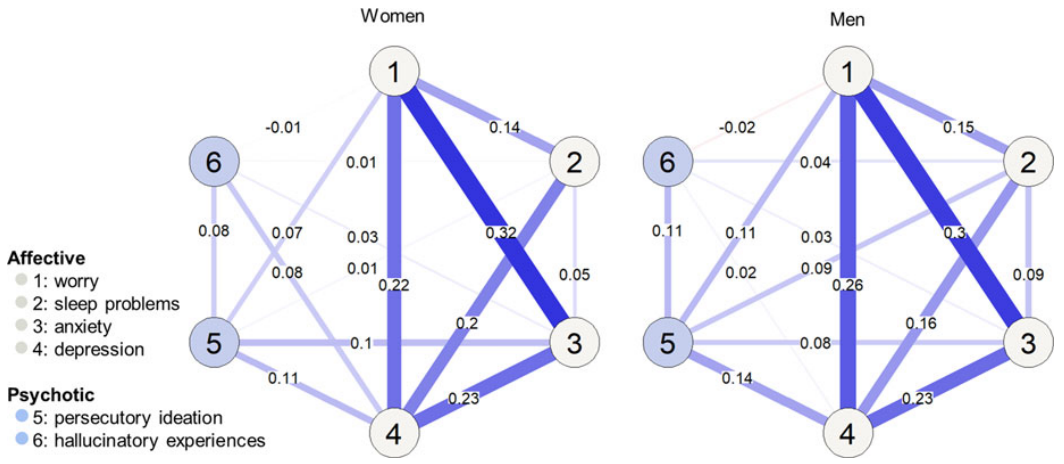

Fig. 3. Partial correlation networks estimated in women ($n = 4115$) and men ($n = 3127$). Sex was identified as the first split in the recursive partitioning approach, suggesting that sex was the primary source of heterogeneity in symptom networks. Symptom domains are differentiated by color. The thicker and less transparent the edge, the stronger the partial correlation between two symptoms. Blue (red) edges indicate positive (negative) relationships. To ensure visual comparability, edge weights were scaled identically across both networks.

childhood sexual abuse were the major source of heterogeneity in symptom networks (Fig. 2*b*, $p_{RP} = 0.016$) linked to a stronger connection between anxiety and persecutory ideation ($\Delta\rho = 0.09$). The difference in global strength of the symptom networks of women who reported sexual abuse and those who did not was not significant ($\Delta S = 0.08$, $p_{BGGM} = 0.482$). Among women who reported no childhood sexual abuse, exposure to childhood physical abuse explained further heterogeneity (Fig. 2*c*, $p_{RP} = 0.015$),

and was associated with a significantly stronger association between anxiety and hallucinations ($\Delta\rho = 0.26$). Corresponding symptom networks did not differ significantly in global strength ($\Delta S = 0.70$, $p_{BGGM} = 0.204$). Finally, among those women that reported neither sexual nor physical abuse, exposure to domestic violence (Fig. 2*d*, $p_{RP} = 0.012$) was linked to a stronger connection between worry and depression ($\Delta\rho = 0.12$), as well as persecutory ideation and hallucinations ($\Delta\rho = 0.19$). The difference in global strength of the corresponding symptom networks was not significant ($\Delta S = 0.32$, $p_{BGGM} = 0.113$).

Among men, in those who reported having experienced domestic violence (Fig. 2*e*, $p_{RP} = 0.007$) the connection between sleep problems and anxiety was significantly stronger than that in men who did not report past domestic violence ($\Delta\rho = 0.17$). Global strength was not significantly different between the corresponding networks ($\Delta S = 0.26$, $p_{BGGM} = 0.376$). Second, in men not reporting past domestic violence, cannabis use in the past year (Fig. 2*f*, $p_{RP} = 0.009$) was associated with a significantly increased connection between worry and persecutory ideation ($\Delta\rho = 0.17$), and a significantly weaker connection between hallucination and persecutory ideation ($\Delta\rho = -0.18$). Global strength of the corresponding symptom networks did not differ significantly ($\Delta S = 0.33$, $p_{BGGM} = 0.126$). Finally, men reporting neither domestic violence nor cannabis use were further split by ethnic background (Fig. 2*g*, $p_{RP} = 0.011$): the network of men with a Black or South Asian ethnic background was overall significantly more strongly connected ($\Delta S = 0.76$, $p_{BGGM} = 0.003$), and showed stronger connections between worry and depression ($\Delta\rho = 0.25$), sleep problems and anxiety ($\Delta\rho = 0.20$), anxiety and depression ($\Delta\rho = 0.16$), depression and persecutory ideation ($\Delta\rho = 0.21$), as well as persecutory ideation and hallucinatory experiences ($\Delta\rho = 0.20$), and a weaker connection between sleep problems and depression ($\Delta\rho = -0.23$) than the network of men from a White or Mixed ethnic background.

Age of the respondent, alcohol use, bullying, separation experiences, and socioeconomic deprivation were not identified as relevant sources of heterogeneity in symptom networks. Repeating analyses based on data from women and men separately yielded identical results regarding sex-specific moderators (online Supplementary Fig. S1).

Robustness analyses

The network estimated in the full sample, as well as all identified subgroup networks, showed good stability to dropping cases (online Supplementary Table S2). Accuracy analyses showed some relatively wide bootstrapped CIs in some of the identified subgroups with smaller sample sizes. In these cases, we recommend caution when interpreting the strength of weaker edges. However, the bootstrap mean was generally very close to the sample mean, indicating interpretable results (online Supplementary Figs S2–S16).

Discussion

In the current study, we employed a novel, data-driven recursive partitioning approach in a large national household survey to identify networks of psychotic and affective experiences in the population. Our findings point to considerable heterogeneity, which we explain with several phenotypic systems: six (out of 11) demographic and environmental risk factors yielded eight different network phenotypes, with sex being the primary source of heterogeneity in symptom networks. Among women and men, different risk factors were related to heterogeneity in symptom networks, suggesting potentially distinct relevance and mechanisms of these risk factors across the sexes, in line with a multidimensional model of sexual differentiation in psychosis risk (Riecher-Rössler, Butler, & Kulkarni, 2018). Overall, our findings on sex and other environmental differences illustrate that the multifactorial and heterogeneous nature of psychosis expression (Isvoranu et al., 2016; Linscott & van Os, 2013; van Os & Reininghaus, 2016) appears to be reflected in symptom networks that differed considerably depending on the type, combination, and strength of demographic and environmental risk in a large general population sample.

Differences in symptom networks of women and men

The identification of multiple network phenotypes substantiates the notion that averaged symptom network models are likely not representative of psychosis expression in the general population (Jones et al., 2020). Rather, observed differences in the strength of overall and specific symptom connections may point to diverse etiological mechanisms operating across different demographic and environmental risk factors. Corroborating a growing recognition that understanding variability by sex is central for the development of comprehensive etiological models of psychopathology (Hartung & Lefler, 2019; Hodes & Epperson, 2019; Riecher-Rössler et al., 2018; Rosen, Haidl, Ruhrmann, Vogeley, & Schultze-Lutter, 2019), the primary source of heterogeneity in symptom networks of psychosis was sex.

Specifically, our results highlight how associations between affective and psychotic experiences may be differentially expressed in women and men. Prior research indicates that, following the theory of an affective pathway to psychosis, affective alterations, in particular depression and anxiety, may be fundamental driving forces of psychotic experiences (Betz et al., 2020; Isvoranu et al., 2017; Myin-Germeys & van Os, 2007; Upthegrove et al., 2020; Upthegrove, Marwaha, & Birchwood, 2017; van Nierop et al., 2018). Present findings suggest a particularly strong association between depression and hallucinatory experiences in the network of women compared to men, corroborating the idea that such an affective pathway to psychosis involving depression may be expressed to a greater degree in women, potentially funneled by increased emotional reactivity to life events and daily hassles (Davis, Matthews, & Twamley, 1999; Hodes & Epperson, 2019; Myin-Germeys & van Os, 2007; Stainton et al., 2021). In the symptom network of men, by contrast, a previously identified link between sleep problems and persecutory ideation (Freeman et al., 2010) was stronger, and therefore, possibly more relevant, than in women. An intriguing potential clinical implication to be tested is that men may, on average, profit in particular from the use of interventions for sleep problems with demonstrated benefit for reducing persecutory ideation (Freeman et al., 2017).

Risk factors explaining heterogeneity in symptom networks of women and men

Among women, heterogeneity in symptom networks of psychosis expression was explained by exposure to interpersonal trauma, including childhood abuse and domestic violence. Specifically, exposure to childhood abuse was linked to stronger associations between anxiety and psychotic experiences. These findings are consistent with previous reports of increased proportions of

mixed symptom expression following childhood trauma (Guloksuz et al., 2015; Russell et al., 2020; Upthegrove et al., 2015; van Nierop et al., 2015), but extend the literature by highlighting how sex may be an important determinant in this relationship. Following trauma, women are more likely to blame themselves, to view the world as dangerous, and to hold more negative views of themselves (Davis et al., 1999; Tolin & Foa, 2002). This may facilitate a pathway from distressing interpretations of everyday events, including the experience of anxiety, to threat beliefs feeding into the formation of psychotic experiences, as proposed in cognitive models of psychosis (Freeman, 2007; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Hardy et al., 2020). Overall, the idea that a pathway from anxiety to psychotic experiences may be particularly relevant among women with a history of childhood abuse has potentially important repercussions for clinical practice and deserves further investigation (Bloomfield et al., 2020). Moreover, at a population level, it may well be that links between affective and psychotic experiences following childhood abuse are manifestations of personality function. The interplay between borderline personality functioning and affective instability, also involving psychosis, and subclinical and clinical levels of psychosis warrants further investigations (Barnow et al., 2010).

Among men, cannabis use and minority ethnic group status were identified as potential sources of heterogeneity in network connections between psychotic and affective symptoms. Most striking differences were evident in the symptom network of men with a minority ethnic group status reporting no domestic violence or cannabis use. Documented variations in experience and reporting of hallucinations (Vanheusden et al., 2008) and delusions (Berg et al., 2014) in minority ethnic groups seem to extend to the level of symptom networks. Here, they appear to be expressed as an increased co-occurrence of hallucinations and persecutory ideations in men from a minority ethnic background compared to men from the majority White or Mixed ethnic background. This finding agrees with the idea that, under the influence of risk factors, hallucinations and delusions can become connected, which has been linked to worse prognosis and symptom persistence (Binbay et al., 2012; Smeets et al., 2012; Smeets, Lataster, Viechtbauer, Delespaul, & G.R.O.U.P., 2014; van Os & Reininghaus, 2016). Taken together with the present results, this may reinforce evidence that demonstrates that people from a minority ethnic background, particularly men, are at increased risk for poor mental health outcomes (Morgan et al., 2017; Singh et al., 2015). With the present data, however, it cannot be excluded that ethnicity acts as a proxy measure for factors not covered by our analysis, such as specific forms of deprivation. Delineating how mental health outcomes in men from a minority ethnic background are determined is an outstanding task for future research and may help to design more effective interventions. Identifying potential commonalities underlying minority ethnic group status and domestic violence, both of which were associated with increased co-occurrence of psychotic experiences in men and women, respectively, may prove insightful in this context.

Except for domestic violence, which was a relevant moderating factor in women and men, different risk factors explained heterogeneity in symptom networks of women and men, suggesting a likely complex interplay between sex and risk factors in impacting psychosis risk. Childhood sexual and physical abuse, for instance, were sources of heterogeneity in symptom networks of women, but not men. This finding adds to previous research suggesting particularly detrimental effects of sexual and physical abuse on mental health of girls and women (Adams, Mrug, & Knight, 2018; Thompson, Kingree, & Desai, 2004). One reason for the distinct role of adversities may lie in the sex-specific effects they have on the nervous system, against the backdrop of sex differences in maturation, structure, and functioning thereof (DeSantis et al., 2011; Dow-Edwards, 2020; Hodes & Epperson, 2019; Popovic et al., 2020). Moreover, characteristics of some risk factors have been shown to differ by sex: men are more likely to engage in more escalating and chronic patterns of cannabis use than women, for example (Hawes, Trucco, Duperrouzel, Coxe, & Gonzalez, 2019; Wagner & Anthony, 2007). Girls, on the other hand, are more likely than boys to experience severe forms of sexual abuse within close victim–perpetrator relationships (Gold, Elhai, Lucenko, Swingle, & Hughes, 1998; Kendall-Tackett, Williams, & Finkelhor, 1993). Such variations may contribute to differing patterns of relationships between risk and symptom expression in women and men.

Overall, our results corroborate a growing realization that research should appraise that mechanisms contributing to psychosis expression may, at least in parts, differ by sex (Hodes & Epperson, 2019; Riecher-Rössler et al., 2018; Rosen et al., 2019; Stainton et al., 2021). As clinical research works toward early identification and individually tailored preventive interventions, the complex interplay between sex and environmental factors in impacting psychosis risk needs to be better understood to optimize these efforts (Hartung & Lefler, 2019; Riecher-Rössler et al., 2018; Rosen et al., 2019; Stainton et al., 2021). This includes disaggregating results by sex and gender in psychosis research more consistently (Hartung & Lefler, 2019), for example by documenting differences and similarities in symptom networks of women and men.

Limitations

Results from the current study should be interpreted given several limitations. First, posterior predictive checks used for comparing the overall network connectivity tend to be conservative (Williams et al., 2020), which may have resulted in low sensitivity in post-hoc comparisons. This factor, and small sample sizes in some subgroups, may explain why we found no evidence that exposure to risk factors was associated with more densely connected symptom networks compared to non-exposure, contrary to our hypothesis. Effects of risk factors on symptom networks seem to be more specific, impacting single relations between symptoms rather than connectivity between all symptoms. Second, model-based recursive partitioning identifies those variables that reduce heterogeneity in symptom networks the most. Thus, age of the respondent, alcohol use, separation experiences, bullying, and socioeconomic deprivation may explain heterogeneity in symptom networks, but not to the same extent as the other risk factors tested. Related, differential relevance of risk factors, for example within ethnic groups, may have remained undetected due to small sample sizes in some subgroups. For a better understanding of the mechanisms relevant in different minority groups, targeted investigations in these populations with larger sample sizes are needed. Third, we did not incorporate complex design features of the APMS, such as weights to take non-response into account, due to the lack of established methods to do so for network models (Lin et al., 2019). Related, recursive partitioning currently only allows for complete case analyses. Even though the percentage of excluded participants was small, they differed from included

participants in some important aspects, including hallucinatory and depressive symptoms, which may have biased our results. Although therefore not fully representative of the English population, our results are based on a large national household survey, with suitability for a data-intensive method, such as network-based recursive partitioning, unlike for smaller samples which would not offer the same opportunity. Fourth, the retrospective assessment of risk factors via self-report may be prone to memory biases and so directions of effect may be contested. Fifth, data used in the present analyses were gathered in a large epidemiological study; therefore, instruments and tools used were designed such that they were simple to understand and appropriate given their use in over 7000 people. This setting necessarily leads to less refined assessments of symptomatology and risk. Sixth, the analyses were based on cross-sectional data, meaning that the directions of interactions among the symptoms remain unknown. Longitudinal studies are therefore an important next step for this line of research, and extension of recursive partitioning methods to personalized network structures (e.g. derived from experience sampling methods) may allow for insights into how risk factors moderate dynamic associations between symptoms in individuals. Finally, some researchers have expressed concerns about stability and replicability of network models (e.g. estimates of edges; Forbes, Wright, Markon, & Krueger, 2017; for a summary of the debate, see McNally, 2021). Although our robustness analysis suggests that the networks and edge estimates are generally stable, especially weaker links in the networks of small subgroups should be interpreted with care. Given that recursive partitioning and network methodology are data-driven, replication of present findings in other samples is needed to establish generalizability (Fried et al., 2018).

Conclusion

Symptom networks of psychosis expression in the general population are highly heterogeneous. Sex was the primary source of heterogeneity, and different risk factors explained further variability in symptom networks of women and men, potentially reflecting distinct sex-specific mechanisms contributing to psychosis risk. Among women, an affective loading within psychosis, particularly following early interpersonal trauma, may have distinct importance. Among men, the symptom network of those from a minority ethnic background showed a particularly strong connection between hallucinatory experiences and persecutory ideation, which may reflect poorer outcomes including symptom resolution in this group. A better understanding and consideration of these sex differences provides an important opportunity to deliver high-quality prevention and patient-centered care in psychosis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721003470

Financial support. JK has received funding from the German Research Foundation (DFG; grant agreement no. KA 4413/1-1). MR has received funding from the Köln Fortune program (grant agreement no. 304/2020).

Conflict of interest. The authors declare no conflict of interests with relation to the work reported in this manuscript.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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2.5 Transdiagnostic psychopathology in a help-seeking population of an early recognition center for mental disorders: protocol for an experience sampling study

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Published in *JMIR Research Protocols*, Volume 11, Issue 8, e35206, https://doi.org/10.2196/35206.

Protocol

Transdiagnostic Psychopathology in a Help-Seeking Population of an Early Recognition Center for Mental Disorders: Protocol for an Experience Sampling Study

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Abstract

Background: Prevention in psychiatry provides a promising way to address the burden of mental illness. However, established approaches focus on specific diagnoses and do not address the heterogeneity and manifold potential outcomes of help-seeking populations that present at early recognition services. Conceptualizing the psychopathology manifested in help-seeking populations from a network perspective of interacting symptoms allows transdiagnostic investigations beyond binary disease categories. Furthermore, modern technologies such as smartphones facilitate the application of the Experience Sampling Method (ESM).

Objective: This study is a combination of ESM with network analyses to provide valid insights beyond the established assessment instruments in a help-seeking population.

Methods: We will examine 75 individuals (aged 18-40 years) of the help-seeking population of the Cologne early recognition center. For a maximally naturalistic sample, only minimal exclusion criteria will be applied. We will collect data for 14 days using a mobile app to assess 10 transdiagnostic symptoms (ie, depressive, anxious, and psychotic symptoms) as well as distress level 5 times a day. With these data, we will generate average group-level symptom networks and personalized symptom networks using a 2-step multilevel vector autoregressive model. Additionally, we will explore associations between symptom networks and sociodemographic, risk, and resilience factors, as well as psychosocial functioning.

Results: The protocol was designed in February 2020 and approved by the Ethics Committee of the University Hospital Cologne in October 2020. The protocol was reviewed and funded by the Köln Fortune program in September 2020. Data collection began in November 2020 and was completed in November 2021. Of the 258 participants who were screened, 93 (36%) fulfilled the inclusion criteria and were willing to participate in the study. Of these 93 participants, 86 (92%) completed the study. The first results are expected to be published in 2022.

Conclusions: This study will provide insights about the feasibility and utility of the ESM in a help-seeking population of an early recognition center. Providing the first explorative phenotyping of transdiagnostic psychopathology in this population, our study will contribute to the innovation of early recognition in psychiatry. The results will help pave the way for prevention and targeted early intervention in a broader patient group, and thus, enable greater intended effects in alleviating the burden of psychiatric disorders.

International Registered Report Identifier (IRRID): DERR1-10.2196/35206

(JMIR Res Protoc 2022;11(8):e35206) doi: 10.2196/35206

KEYWORDS

help-seeking population; phenotyping; ecological momentary assessment; symptom networks; transdiagnositc psychiatry; prevention; early intervention; psychiatry; mental health

Introduction

Background

Prevention and early intervention in psychiatry provide promising ways to address the immense burden of mental illness [1-3]. The currently established prevention approach implemented in early recognition services focuses on risk syndromes developed for predicting specific diagnoses (eg, psychosis [4,5]). However, the majority of help-seeking patients who present at early recognition services are not covered by these specific risk syndromes, as they do not fulfill the respective criteria that indicate the increased risk that qualifies them for targeted intervention [4,6]. Thus, in a sizable proportion of this population, early recognition centers for mental disorders currently miss out on a critical potential for preventive efforts. In fact, help-seeking populations present with a mixture of various symptoms [7] such as depressive, anxious, and psychotic symptoms. Depressive and anxiety symptoms have proven to be among the main reasons why individuals seek help [8,9], whereas psychotic symptoms are of interest as they are the most burdensome for the affected individuals as well as for the health care system, despite their low prevalence [10]. These symptoms are shared across different diagnoses [11-13], as well as different disorder states such as risk-syndrome, subthreshold, and full-threshold disorders [11]. Similarly, growing evidence demonstrates that distress is a mediating and triggering factor for psychopathology at large [12-16]. Taken together, help-seeking populations are much more heterogeneous than previously assumed and may develop manifold potential outcomes [17] or show other unfavorable outcomes such as persisting deficits in psychosocial functioning [18].

Thus, there is a growing call for a broader, transdiagnostic approach for prevention in psychiatry [19-22]. Although there is important data on the psychopathology of patients presenting to early recognition centers (eg, [6,8,23,24]), their interpretation is limited by the typically purely cross-sectional, retrospective, and diagnosis-specific character of the assessments. However, symptoms fluctuate over time [25-27], and important insights are missed when neglecting this dynamic component of psychopathology in help-seeking populations. Moreover, as outlined above, conventional assessments are often considered in isolation rather than in concert, neglecting the transdiagnostic, intertwined nature of psychopathology in help-seeking populations. Collectively, these observations underline the necessity to use novel methods to enrich traditional self- and observer-based reports to understand the psychopathology in help-seeking populations.

One novel method consists of integrating 2 distinct innovative ideas that have emerged in the field of psychopathology in recent years [28]. The first idea consists of intensive longitudinal measurements of symptoms and other relevant variables via the Experience Sampling Method (ESM), which has become increasingly feasible and accepted in recent years, especially with the advance of mobile technology such as smartphones [29,30]. ESM provides valid insights into psychopathology as it occurs in daily life by assessing the targeted phenomena repeatedly during the course of the day within a specific time period. ESM increases ecological validity compared to retrospective reporting, reduces biases resulting from false memory or aggregation processes of experience over a longer time period, and allows the collection of data at the within-person level [31].

The second idea is the network approach mainly put forward by Borsboom et al [32-34] (recent overview [35]), in which psychopathology is conceived as a dynamic system of connected, interacting, and maintaining symptoms and other clinically relevant variables [32,36]. In line with a clinician's perspective, symptoms are assumed to co-occur because of functional relations between them rather than due the common dependence on an underlying disorder entity [33,35,36]. With its inherently transdiagnostic outlook [34,37], the network approach is well suited for conceptualizing the psychopathology of help-seeking populations, where the patterns and strength of symptom expression is typically highly heterogeneous.

The integration of network analyses with ESM data enables rich insights beyond those obtained by established assessment instruments. Specifically, the intensive time-series data that result from ESM can be used to model symptom networks that offer a promising gateway into understanding the dynamics of psychopathology on the group and individual levels [38]. On the group level, dynamic symptom networks allow us to exploratively map out the potential average causal relations among individual symptoms in the same measurement window and across measurement windows. Personalized symptom networks are of special interest, as they allow the conceptualization of psychopathology as a set of person-specific dynamic processes [36,39]. By revealing the symptoms and processes most relevant to each individual, these approaches hold the potential to personalize interventions [36,40].

Due to these properties, many interesting studies have been published proving the potential of longitudinal symptom network models in advancing the psychopathological understanding of specific psychiatric conditions [41,42]. However, insights into the dynamic structure of psychopathology of a heterogeneous help-seeking population of a psychiatric early recognition center—the interactions of a broad, transdiagnostic set of symptoms, as well as the associations with risk and resilience factors and psychosocial functioning—are still lacking so far.

Thus, with this proposed study, we aim to provide the first explorative, transdiagnostic phenotyping through the combination of ESM with network analyses. This will be the one of the first studies aimed at phenotyping the transdiagnostic help-seeking population of an early recognition center for mental disorders by applying ESM.

Findings from this innovative approach integrated with those derived from established assessments represent a promising way to address a larger proportion of the help-seeking population as compared to current diagnosis-specific strategies aimed at preventing the burden of psychiatric disorders. Moreover, the results will have their core value in generating hypotheses regarding central dynamic psychopathological processes. These provide a basis for follow-up work dedicated to informing preventive interventions by testing experimentally whether the interventions on particular symptoms or processes lead to changes consistent with the estimated network model [43].

Aim

The PhenoNetz study aims to explore the transdiagnostic phenotyping of a help-seeking population of an early recognition center for mental disorders using innovative, intensive longitudinal data collection via a smartphone app. A better understanding of the relevant psychopathology in this population is of great relevance given the lack of adequate interventions [44]. Combining ESM with network analyses allows for unique insights into the as yet underresearched early transdiagnostic psychopathological processes in the help-seeking population of an early recognition center of mental disorders, as well as to explore their association with risk, resilience, and psychosocial functioning.

Methods

Setting and Participants

In total, 100 participants will be recruited from the help-seeking population presenting at the early recognition center of mental disorders at the University Hospital of Cologne (Früherkennungs- und Therapiezentrum; FETZ) [45], with an expected dropout rate of 25% leading to a total of 75 participants in the final sample. Dropouts include the participants that withdraw from the study, are no longer reachable, or terminate the study without a sufficient number of ESM measurements (for details, see the data analysis section). The FETZ offers specialist diagnostics for the early recognition of mental disorders, with a focus on severe mental illness, in particular psychotic disorders. However, the first contact is independent of this focus and accessible for all people aged 18-40 years that have noticed any changes in their experience and behavior. Most patients find out about the FETZ through internet research or are referred by health care practitioners.

For a naturalistic characterization of the help-seeking population presenting at the FETZ using ESM, we will not impose specific inclusion criteria for participation in the PhenoNetz study. Similarly, to ensure the validity of the obtained data, only a small part of the help-seeking participants will be excluded based on the following criteria:

- acute suicidal thoughts
- IQ ≤ 70
- aged >40 years
- known previous illness of the central nervous system, as well as untreated, unstable somatic illnesses with known effects on the central nervous system (eg, untreated hypothyroidism)
- insufficient knowledge of the German language

Procedure and Materials

All patients presenting at the FETZ not fulfilling any of the listed exclusion criteria will be addressed either directly at the FETZ or via telephone or email (given permission to contact was obtained by the clinical personnel at the FETZ) and informed about the background, goal, design, risks, benefits, and data security aspects of the study. Any open questions the participants might have will be answered directly by one of the primary investigators (MR and LTB). All willing participants will provide written informed consent prior to their participation in the study. All participants will be compensated with €40 (US $42.08) for their participation. Participants can withdraw from the study at any time without negative consequences.

Figure 1 illustrates the study design. During the baseline assessment, data on sociodemographics, medication, substance use, psychopathology including psychosocial functioning, as well as risk and resilience factors will be assessed through both observer- and self-ratings (Table 1). All data will be collected via the Research Electronic Data Capture (REDCap) software [46]. In the baseline assessment, the mobile app used for ESM data collection in the study, *insightsApp* [47] (Figure 2a), will be installed on the personal smartphones of the participants. As the *insightsApp* only runs on Android devices, participants with personal smartphones using other operating systems (eg, iOS) will be provided with a study smartphone for the study period. Participants will be encouraged to complete as many surveys as possible without substantial inconvenience or compromising their personal safety (eg, disrupting sleep or while driving). Compensation for participation will not depend on the number of completed assessments.

Figure 1. Study design of the PhenoNetz study. Participants included will undergo baseline assessment with self- and observer-ratings, followed by a 14-day ESM data collection period. In the subsequent follow-up assessment, selected self- and observer-ratings will be collected again. If desired, the participants will receive personalized feedback on their ESM data after the 2 weeks of ESM data collection, such that the feedback does not interfere with ESM data collection. ESM: Experience Sampling Method.

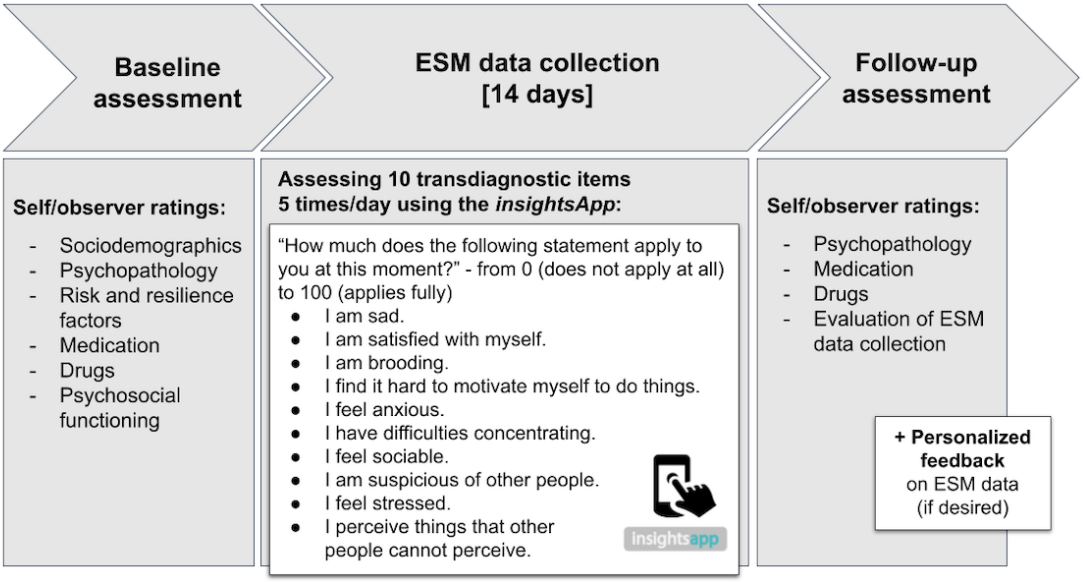

Figure 2. Layout of the *insightsApp*. (a) Main menu; (b) In-app reminder; (c) Visual analogue scale for answering transdiagnostic items.

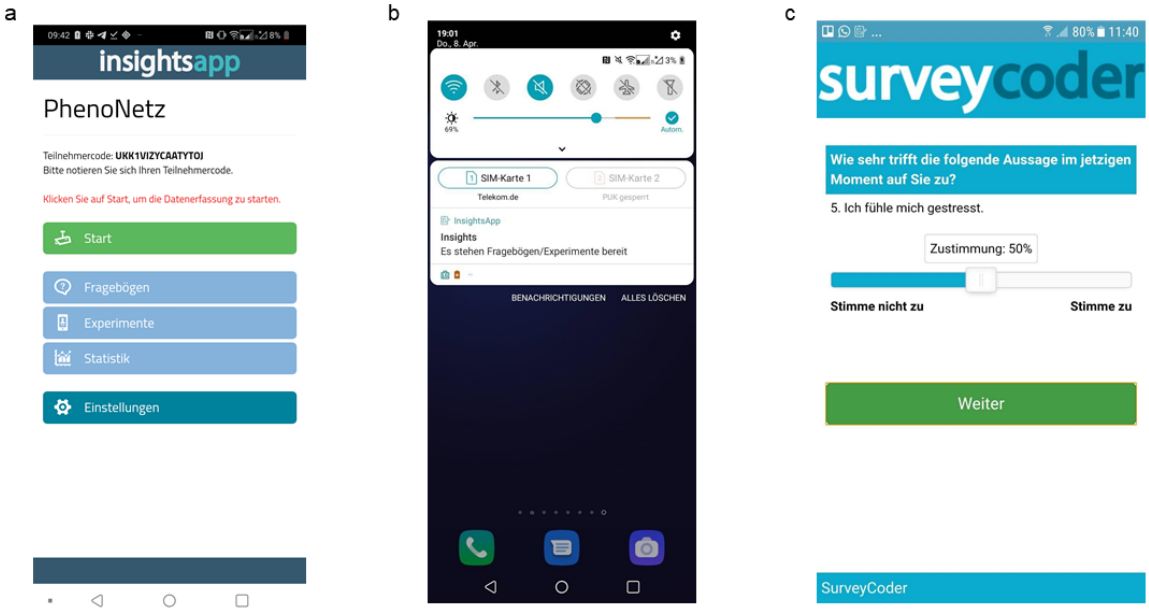

Table 1. Constructs with scales assessed at the baseline and follow-up assessments (before and after the Experience Sampling Method [ESM] period, respectively) of the PhenoNetz study.

Construct	Questionnaire	Self- vs observer -rating	Baseline assessment	Follow-up assessment
Sociodemographics	Self-designed questionnaire assessing gender, age, primary language, nationality, current living or housing conditions, highest level of education, highest vocational degree, current employment/professional activity, marital status/partnership, number of siblings, highest level of education of primary caregivers, highest vocational degree of primary caregivers	Observer-rating	✓	
Psychopathology				
Diagnostic classification	Structured Clinical Interview for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) [48]	Observer-rating	✓	
Current substance use	Analogous to the Personalized Prognostic Tools for Early Psychosis Management study [49]	Observer-rating	✓	✓
Current medication	Analogous to the Personalized Prognostic Tools for Early Psychosis Management study [49]	Observer-rating	✓	✓
Depression	Beck Depression Inventory [50]	Self-rating	✓	✓
Anxiety	State and Trait Anxiety Inventory [51]	Self-rating	✓	✓
Social phobia	Social Phobia Inventory [52]	Self-rating	✓	✓
Psychotic symptoms	Community Assessment of Psychic Experience [53]	Self-rating	✓	✓
Quality of life	World Health Organization Quality of Life Questionnaire [54]	Self-rating	✓	✓
Risk and resilience				
Childhood trauma	Childhood Trauma Questionnaire [55]	Self-rating	✓	
Bullying	Bullying Scale [56]	Self-rating	✓	
Resilience	Resilience Scale for Adults [57]	Self-rating	✓	
Coping	Coping Inventory for Stressful Situations [58]	Self-rating	✓	
Personality	NEO-Five Factor Inventory [59]	Self-rating	✓	
Attachment	Attachment Style Questionnaire [60]	Self-rating	✓	
Expressed emotion	Level of Expressed Emotion Scale [61]	Self-rating	✓	
Social support	Multidimensional Scale of Perceived Social Support [62]	Self-rating	✓	
Introspection	Self-Reflection and Insight Scale [63,64]	Self-rating	✓	✓
Self-efficacy	Self-Efficacy Scale [65]	Self-rating	✓	
Psychosocial functioning	Global Functioning Social and Role Scales [66]	Observer-rating	✓	
Experience with ESM period	Adapted from Frumkin et al [67]	Self-rating		✓

Using ESM, potentially relevant transdiagnostic (subthreshold) symptoms such as sadness, anxiety, psychotic experiences, and stress will be recorded (Textbox 1). The items are based on previous studies and questionnaires, given the lack of standardized ESM assessment in clinical populations [43,68]. In-app reminders will be sent out 5 times a day at fixed time points: 9:30 AM, 12:30 PM, 3:30 PM, 6:30 PM, and 9:30 PM, for a duration of 14 days (Figure 2b). Fixed sampling schemes are common in network applications to ESM data [43,67,69-71], given that they lead to equidistant measurements, an important assumption of 2-step multilevel vector autoregressive (mlVAR) modeling [38]. In psychiatric populations, fixed sampling schemes have also been associated with increased compliance [72]. In each survey, participants will be asked how much they endorse a certain feeling or behavior at the time of filling out the survey: “Wie sehr trifft die folgende Aussage im jetzigen Moment auf Sie zu?” (How much does the following statement apply to you at this moment?). Responses will be given on a visual analogue scale (as a percentage) from 0=“trifft überhaupt nicht zu” (does not apply at all) to 100=“trifft voll und ganz zu” (applies fully), with a slider that can be moved in 1-unit increments (Figure 2c). Participants will be asked to fill in the

items as soon as possible after receiving the in-app reminder, but no later than 60 minutes afterwards, following prior research (eg, [43,73,74]). Filling in the items takes about 1-1.5 minutes in total. Similar ESM protocols were deemed acceptable for clinical populations in prior studies [31,67,75]. The *insightsApp* will be used only for the regular, active collection of transdiagnostic symptoms by means of the described self-report questions. No personal information (such as name and phone number, etc.) or passive data are accessed, stored, or transferred by the *insightsApp*. To maximize the number of completed surveys for each participant, the participants will be contacted at least once during the assessment period to assess instruction adherence, identify any concerns associated with the method, and help the participants with any problems in completing the ESM questionnaire.

Textbox 1. Experience Sampling Method (ESM) items assessed in the PhenoNetz study (along with the English translation).

1. Ich bin traurig (I am sad).
2. Ich nehme Dinge wahr, die andere Menschen nicht wahrnehmen können (I perceive things that other people cannot perceive).
3. Ich habe Schwierigkeiten, mich zu konzentrieren (I have difficulties concentrating).
4. Ich bin kontaktfreudig (I feel sociable).
5. Ich fühle mich gestresst (I feel stressed).
6. Ich bin zufrieden mit mir (I am satisfied with myself).
7. Ich fühle mich ängstlich (I feel anxious).
8. Es fällt mir schwer, mich zu Dingen zu motivieren (I find it hard to motivate myself to do things).
9. Ich bin misstrauisch gegenüber anderen Menschen (I am suspicious of other people).
10. Ich grüble (I am brooding).

In the follow-up assessment conducted after the 14 days of ESM data collection, information on psychopathology, medication, and substance use will be assessed again, referring to the 14 days during which ESM data were collected (Table 1). In addition, experiences and strain associated with the ESM data collection will be assessed via a questionnaire translated and adjusted from a previous study conducted in clinical participants [67] (Table S1 in Multimedia Appendix 1). If desired, participants will be provided with a personalized feedback report on their ESM data.

Data Security

Using a smartphone app installed on the personal smartphone of the participants for data assessment requires particular attention to data security (a broader discussion on ethical concerns regarding digital phenotyping procedures in the psychological and psychiatric sciences have been previously described [76,77]). Therefore, subjects must provide additional consent to allow data to be collected within the app and grant the necessary permissions to the app on the smartphones (such as being notified by the app about available surveys). The ESM data collected by the *insightsApp* are pseudonymized (16-digit alphanumeric codes) and sent directly to a server hosted and maintained by a professional web hosting service after each survey. Answers to the surveys are only stored temporarily locally on the smartphones and deleted once they are transmitted to the server. To secure the data transfer from the smartphone to the server, the connection between the *insightsApp* and the backend software on the server is encrypted by the use of a Secure Sockets Layer certificate.

Safety

Given that this study is observational, there are no direct risks associated with participation. Previous studies have demonstrated good acceptance of ESM protocols similar to the one implemented in this study. Even if participants become more aware of their symptoms due to high-frequency data collection, this does not have a negative effect in terms of worsening symptoms [31,67,78]. Participants can terminate the ESM data collection at any time without giving reasons. Participants who are acutely suicidal or a danger to others will immediately be presented to the service physician for further assessment. Should this become apparent in a telephone call, participants will be reported to the responsible social psychiatric service.

Data Analytic Plan

All statistical analyses will be conducted in the R statistical software (R Foundation for Statistical Computing) [79]. Descriptive analysis of the sample will include mean, SD, median, and IQR as appropriate. The participants included in the analysis will be compared to those that dropped out of the study or were excluded due to too few available measurements (see sample size and the required number of ESM observations) via appropriate classes of permutation tests [80]. Changes in measures that were assessed twice, pre- and post-ESM (see Table 1), will be compared via linear mixed modeling. Prior to the analyses of ESM data, we will detrend the ESM data by fitting fixed-effects linear regression models to each ESM item, regressing out a linear trend on time (ie, general increases/decreases in items over time) and mean-center ESM items per person. We will then generate group-level and personalized networks via a 2-step mlVAR modeling approach as described in detail below. These analyses will allow us to examine symptom dynamics within multiple individuals (n>1; fixed effects) and for individual participants (n=1; random effects). Originally, we planned to estimate and analyze “truly” personalized networks solely based on data from individual participants (such as those that could be derived via a graphical

vector autoregressive model [28]). However, results from a simulation study [81], published as a preprint 1 month after our study commenced, suggest that our sampling scheme potentially lacks the power to detect a nonnegligible proportion of true edges in truly personalized networks, which is why we decided to refrain from this analytic approach.

2-Step mlVAR Model

We will use a mlVAR model, as implemented in the R package "mlVAR." In the mlVAR model, the average dynamical relationships on the group level are modeled as fixed effects, whereas regression coefficients are allowed to vary between patients as random effects.

First, we will estimate 3 group-level network structures including the 10 assessed symptoms, reflecting the average process of all participants (fixed effects): between-subject (an undirected partial correlation network between the means of participant's scores, capturing, in general, whether participants high on a given node are also high on other nodes during the 2-week course of the study), contemporaneous (an undirected partial correlation network showing how symptoms relate to each other in the same window of measurement, controlling for temporal relationships), and temporal (a directed network displaying symptoms predicting each other across an approximately 3-hour lag, while controlling for all other experiences in the model at the prior measurement). Centrality will be assessed using strength centrality (indicating the summed absolute edge strengths connected to a specific node) in the contemporaneous network, and in-strength (indicating the summed absolute strengths of all incoming edges) and out-strength (indicating the summed absolute strengths of all outgoing edges) in the temporal network will be assessed using the R package "qgraph" [82].

Second, we will generate 2 types of personalized networks for each participant based on estimated random effects of the mlVAR model: a contemporaneous network and a temporal network. These personalized networks are not truly idiographic, in the sense that they borrow information from other subjects [38,41]. However, in doing so, the mlVAR model can perform well in estimating personalized networks even if the number of ESM observations is comparatively low for a particular participant. Given that the mlVAR model does not perform participant-specific model selection, all estimated personalized networks will contain all edges [38].

We will use orthogonal estimation for contemporaneous and temporal effects. For the contemporaneous and temporal group-level networks, we will use the conservative "AND-rule" approach in retaining and plotting significant edges. A detailed description of methodological details has been described previously [38,41].

Specifically, we have planned the following analyses:

1. We will compute group longitudinal networks (between-person, contemporaneous, and temporal [28]) as described above.
2. We will identify symptom centrality and unique partial correlations among symptoms in the contemporaneous and temporal group-level networks. We hypothesize that on the group level, feeling stressed will be the most central symptom in the contemporaneous network and predict most other experiences in the temporal network, given that stress experience is frequently discussed as a transdiagnostic factor in psychopathological experiences [13-16]. For the temporal network, we have no a priori hypothesis with regard to the most central item.
3. We will evaluate the degree of association between risk factors (eg, childhood trauma) and network connectivity, assessed by the global strength of personalized networks (temporal and contemporaneous) in a linear modeling approach. Based on prior research and theoretical considerations [33,83,84], we hypothesize that risk factors will be associated with increased network connectivity. Similarly, we hypothesize that poorer psychosocial functioning will be associated with increased network connectivity.
4. We will explore how the strength of specific symptom-symptom connections in individual contemporaneous and temporal networks relates to the degree of presence of specific risk and resilience factors.

Sample Size and the Required Number of ESM Observations

Formal power analyses have not yet been worked out for group-level network models based on intensive longitudinal data. Power at the intraindividual level is a function of within-person variability; there should be sufficient variability such that the intraclass coefficient is not too close to 1, which should usually be the case when having a large number of assessments per person as in our study [85,86]. The performance of network estimation methods also depends on the unknown true network structure—the network equivalent of a true effect size in power analysis [41]. Supplementary materials from Epskamp et al [38] report simulation results for mlVAR models, showing that mlVAR models are excellent in recovering the fixed effect structures with a small amount of data, starting at 50 participants. With our targeted sample size of 75, which represents a realistic recruitment goal in the population of interest, we will surpass this threshold, leading to an adequately powered analysis for the estimation of a mlVAR model. Due to the methodological novelty of symptom networks based on intensive time-series data, there exist no guidelines on the number of ESM observations required [41]. More observations collected over a longer period of time improves the stability and validity of the results; however, this has to be balanced against the feasibility of the integration of the study into the daily lives of the participants. With 75 targeted observations collected over 14 days, our study is similar to the study designs of previous ESM projects conducted in psychiatric populations [67,70,73-75,87,88]. Following recommended guidelines [89] and prior studies [38,71], participants with fewer than one-third of the possible ESM observations (ie, 23) will be excluded from the network estimation.

Ethics Approval

Ethics approval was granted by the Ethics Committee of the University Hospital Cologne in October 2020 (reference number 20-1092).

Results

Study recruitment started on November 11, 2020, and was completed on November 10, 2021. Of the 258 participants who were screened, 93 (36%) fulfilled the inclusion criteria and were willing to participate in the study. Of these 93 participants, 86 (92%) completed the study. As of May 2022, data analysis is ongoing. The first results are expected to be published in 2022.

Discussion

Expected Findings

This study aims to extract an explorative phenotyping of the heterogenous help-seeking population of a psychiatric early recognition center. Applying ESM, we will attempt to depict transdiagnostic symptom networks and explore their association with protective and risk factors, as well as psychosocial functioning.

The diverse and transdiagnostic character of help-seeking populations [7] limits the potential of current, narrow concepts of prevention in psychiatry [17,19]. Our exploratory study might provide a first glimpse at the dynamics between transdiagnostic symptoms as well as the associations with outcome and preceding conditions independent of diagnostic categories. Such new insights might be more valuable for alternative preventive approaches targeting a broader patient group than currently established approaches [90]. The central transdiagnostic items and processes we will identify might represent anchor points for interventions [91], which might deviate from diagnosis-specific manuals only focusing on symptoms and processes covered by diagnostic criteria [92]. Furthermore, insights into potential etiological processes, identified by the association with risk and resilience factors as well as psychosocial functioning, might inform prevention strategies [44,92]. Dynamic models based on ESM data being more in line with the true nature of psychopathology instead of static models [25,27,92] might be more effective in the prediction of outcome. In particular, transdiagnostic symptomatology was not often depicted by ESM studies so far [72]. Hypotheses based on the findings of our explorative study might guide future research.

Strengths and Limitations

The atheoretical approach of our study facilitates truly innovative insights not biased or limited by established theories and structures. In addition, the choice for a naturalistic sample with only a limited set of inclusion and exclusion criteria is valuable for external validity.

However, there are several limitations in the design of our study that need to be considered. First, we acknowledge that the use of study smartphones may result in the underrepresentation of iPhone users in our study, as well as less valid data collection than if the participants can use their own smartphones.

The biggest challenge during the conceptualization of the study was the lack of officially validated ESM items. In general, as gold standards for the novel methodology of ESM are missing, researchers construct their own ESM items or refer to items used in previous studies [43,68,93]. Furthermore, most ESM studies focus on specific diagnoses (eg, major depressive disorder [72]). In a *transdiagnostic* ESM design, by contrast, it is difficult to cover the entire diversity of different disorders due to the further limited number of items per diagnosis-specific phenomenology. These difficulties underscore a recent call for valid and reliable scales suitable for investigating the short-term dynamics of emotions and state mental health problems [43].

Future Directions

ESM represents only one of the various powerful elements (eg, digital phenotyping [94,95]) used to gain insights into relevant variables collected in everyday life to improve prevention and targeted early intervention. Studying the digital footprints left by the human-smartphone interaction (eg, log-in frequency, the use of different apps, and calling behavior) can provide additional important insights into the psychopathological states in help-seeking individuals [96]. Exploring the potential of ESM as a self-monitoring intervention in help-seeking populations (similar to approaches in depressive disorder [26]) is another exciting avenue for future research.

Conclusion

In clinical science, intensive longitudinal assessments of symptoms in daily life are deservedly receiving more and more attention [36,40,41] that might result in enhanced patient benefit. By applying ESM and network analyses, our study intends to contribute a milestone toward innovation in understanding help-seeking populations in psychiatry, helping a greater proportion of this heterogeneous and crucial target group [40]. Subsequent impacts on early states and the progress of mental disorders might reduce the associated personal, familial, societal, clinical, and economic burden more effectively.

Acknowledgments

The study is funded by the Köln Fortune program, Faculty of Medicine, University of Cologne (grant 304/2020).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaire to assess experiences and strain associated with the ESM data collection translated and adjusted from a previous study conducted in clinical participants. ESM: Experience Sampling Method.
[PDF File (Adobe PDF File), 99 KB-Multimedia Appendix 1]

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Abbreviations

ESM: Experience Sampling Method
FETZ: Früherkennungs- und Therapiezentrum (the early recognition center of mental disorders at the University Hospital of Cologne)
mlVAR: multilevel vector autoregressive

Edited by T Leung; submitted 25.11.21; peer-reviewed by M Drukker, RP Rajkumar; comments to author 14.03.22; revised version received 11.05.22; accepted 12.05.22; published 01.08.22

Please cite as:
Rosen M, Betz LT, Montag C, Kannen C, Kambeitz J
Transdiagnostic Psychopathology in a Help-Seeking Population of an Early Recognition Center for Mental Disorders: Protocol for an Experience Sampling Study
JMIR Res Protoc 2022;11(8):e35206
URL: https://www.researchprotocols.org/2022/8/e35206
doi: 10.2196/35206
PMID:

3. General Discussion

There is an urgent need for improved prevention and treatment of psychotic disorders because of the significant personal burden and societal costs associated with them. A large set of potentially malleable environmental risk factors have been shown to contribute to the onset, progression, and maintenance of psychotic disorders. However, due to problematic assumptions in the prevalent common cause model (e.g., that environmental risk factors influence all symptoms in the same way through the disorder itself), the associations between specific risk factors and psychotic psychopathology have remained poorly understood. As an alternative conceptualization of psychopathology, the network approach has been proposed, which focuses on individual symptoms and their interactions with environmental risk factors. In doing so, it provides a means to help disentangle the complex pathways from environmental risk to psychosis. A better understanding these pathways has the potential to guide future research and improve the prevention and care of psychotic disorders.

Taking a transdiagnostic network perspective, this thesis presented a body of work that advances knowledge about how important environmental risk factors contribute to the risk of developing psychotic disorders. The papers included focused on (1) pathways from recent stressful life events to psychotic psychopathology, (2) pathways from childhood trauma to perceived stress, (3) pathways from cannabis use characteristic to psychotic experiences, (4) the heterogeneity in symptom networks of psychosis as a function of environmental and demographic risk factors, and (5) the study protocol for an ESM study in a help-seeking population, which will allow to link environmental risk factors to personalized networks. This discussion section summarizes the main findings of each paper, presents their overall theoretical and clinical implications, and identifies challenges and future research directions.

3.1 Summary of findings from individual papers

Chapter 2.1 (Betz et al., 2020) built upon previous work showing that stressful life events are implicated in the onset of psychosis (Beards et al., 2013). To model the psychological pathways through which recent stressful life events increase the risk for psychotic disorders, we used data from patients at-risk for psychosis and recent onset psychosis from the multicentric, European PRONIA study. The results of this network analysis show that the burden of recent life events is not directly related to positive and negative psychotic symptoms, but only indirectly through symptoms of general psychopathology, such as depression, guilt, and anxiety. Thus, this work extends previous evidence for an affective pathway to psychosis from early negative events to recent stressful life events and confirms the central role of affective disturbances in early stages of psychosis.

Against the backdrop of the proposed affective pathway from adverse life events to an increased liability for psychopathology at large, including psychotic disorders (McLaughlin et al., 2017, 2020; Myin-Germeys & van Os, 2007; Reininghaus, Gayer-Anderson, et al., 2016), chapter 2.2 (Betz, Penzel, Rosen, & Kambeitz, 2021) explored the pathways through which different domains of childhood trauma differentially impact stressful experiences in adulthood. In a network approach using data from two large, nationally representative samples from the United States, domains of child neglect were found to be exclusively associated with stressful experiences reflecting decreased perceived self-efficacy, whereas domains of child abuse were primarily associated with increased perceived helplessness. On the one hand, this work provides further evidence for the proposed differential functional role of different types of childhood trauma along two primary dimensions, i.e., neglect ('deprivation') and abuse ('threat') (McLaughlin et al., 2014). On the other hand, this work extends the previous literature by providing

a detailed characterization of the putative psychological stress processes underlying different types of childhood trauma, which provides an important foundation for developing interventions that directly address these relationships. This line of research is relevant not only to psychotic disorders, but to a wide range of mental health problems.

Chapter 2.3 (Betz et al., 2022) turned to another central, malleable environmental risk factor for psychotic disorders, cannabis use (Moore et al., 2007; Sideli et al., 2020). In light of the neurodevelopmental model of psychosis (Murray et al., 2017), we explored the specific effects of developmental cannabis use on psychopathology in data from a large general population sample from the United States, controlling for the effects of lifetime cumulative cannabis use, as well as early life risk factors. Findings from this cross-sectional, mixed network-analytic approach showed particularly pronounced unique positive associations between frequency of cannabis use and specific delusional experiences (persecutory delusions and thought broadcasting). Age of cannabis use initiation was negatively related to visual hallucinatory experiences and irritability, implying that these experiences become more likely the earlier use is initiated. Earlier initiation, but not lifetime frequency of cannabis use, was related to early risk factors. Thus, this work extends previous research by our group (Penzel et al., 2021) demonstrating the unique role of early cannabis use on brain development by providing a characterization of those facets of psychopathology associated with the effects of an earlier age of onset of cannabis use in the general population.

In Chapter 2.4 (Betz, Penzel, Rosen, Bhui, et al., 2021), a recursive partitioning approach was used to comprehensively examine potential etiological divergences in psychosis risk in a large English general population sample. Specifically, we investigated which environmental and demographic factors explained heterogeneity, and which edges in symptom networks of psychosis expression differed in strength depending on exposure to the identified moderating factors. Findings point to sex-specific etiological mechanisms contributing to psychosis risk: In women, an affective pathway to psychosis may be of particular importance. In men, an ethnic minority background was associated with strong interconnections between individual psychotic experiences, which has been linked to poor outcomes. This work provides crucial evidence for large heterogeneity in the structure of symptom networks as a function of environmental and demographic risk factors.

Finally, chapter 2.5 (Rosen et al., 2022) presented the protocol for an ESM study in the help-seeking population of the Early Recognition Center for Mental Disorders of the University Hospital Cologne. Specifically, the goal of the PhenoNetz study is to provide a transdiagnostic phenotyping of this heterogeneous population based on dynamic symptom networks estimated at group and individual level. The results of this study will contribute to the existing literature by analyzing key dynamic psychopathological processes in a help-seeking population. Building on the findings of the work presented in this thesis, it will be particularly interesting to examine how the derived personalized symptom networks vary as a function of environmental exposure.

3.2 Etiological complexity in the psychosis continuum

3.2.1 Theoretical integration of main findings

In summary, the results of the present work show that the pathways through which environmental risks contribute to psychotic psychopathology are diverse and multifaceted. In the estimated networks, there was some degree of specificity in the observed associations between certain environmental exposures, mediating components, and symptoms of psychosis. This pattern of results corroborates

the notion that explanations arising from a few simple laws (such as: environmental risk → disorder entity → symptoms) poorly fit the nature by which psychotic psychopathology arises and is maintained (Kendler, 2008).

In contrast to what would be expected from a simplistic common cause model, where all symptoms have the same or similar risk factors (Isvoranu et al., 2016, 2020), environmental risk factors have been found to contribute to the risk of psychotic psychopathology in specific ways (Betz et al., 2020; Betz et al., 2022). For example, while there were direct associations between cannabis use characteristics and hallucinatory and persecutory experiences, early and recent stressful life events were primarily indirectly associated with positive psychotic psychopathology (Betz et al., 2020; Betz et al., 2022). Complementing this, the present results also support the idea that individual symptoms differ to some degree in terms of the risk mechanisms involved (Cosgrave et al., 2021; Isvoranu et al., 2016, 2017, 2020). For example, visual hallucinatory experiences were found to become more likely as a function of earlier onset of cannabis use, while tactile hallucinatory experiences were more likely following childhood abuse, suggesting that past traumatic events may shape the nature of the hallucinatory experience (Betz et al., 2022). Such differences in processes at the level of individual symptoms provide important insights with relevance to clinical practice that are obscured when sum scores are used. Similarly, psychopathology beyond psychotic symptoms is often not modeled in etiological analyses, being considered a mere 'epiphenomenon' of psychosis (Upthegrove et al., 2017). However, the results of this thesis highlight the important role of individual affective symptoms in the etiology of psychotic psychopathology (for details, see chapter 3.3). Overall, the observations from this thesis therefore undergird a research strategy that aims to identify pathways linked to environmental exposure based on a comprehensive and multidimensional set of individual symptoms.

Similarly, environmental exposures should be modeled individually rather than combined into aggregate measures, as is often observed. For example, this thesis shows that different subtypes of childhood trauma (e.g., domains of childhood abuse vs. neglect) are associated with different stress-related pathways to psychosis (Betz, Penzel, Rosen, & Kambeitz, 2021; Isvoranu et al., 2017; McLaughlin et al., 2014). Likewise, environmental risk factors for psychosis were found to mutually influence each other (Betz et al., 2020; Betz et al., 2022), which is consistent with previous research (Guloksuz et al., 2018; Isvoranu et al., 2016). For instance, we showed that urban upbringing was associated with an earlier age of cannabis use initiation, which bears implications for public health interventions (Betz et al., 2022). Together, these results suggest distinct functional roles of different environmental exposures, even at the level of seemingly homogeneous constructs such as 'childhood trauma', as well as a complex interplay at the level of environmental risk. Thus, this thesis does not support the view that the effects of environmental factors simply add up and increase the risk of psychosis unspecifically (e.g., Stepniak et al., 2014). Rather, exposure to multiple risk factors may make the individual more susceptible to developing psychotic psychopathology by acting through multiple pathways that likely reinforce each other. These aspects must be addressed through both specific and comprehensive modeling of environmental exposures (for details, see chapter 3.6).

Adding an additional level of complexity, results of this work suggest that environmental risk factors play different roles in the development of psychosis in women and men (Betz, Penzel, Rosen, Bhui, et al., 2021). For example, various aspects of interpersonal trauma appear to play a greater role in women than in men. This finding extends suggestions that sex is an important determinant of differences in psychopathology, comorbidity, neurocognition, and brain abnormalities across the psychosis continuum to include the role of environmental exposure (Riecher-Rössler et al., 2018; Rosen et al., 2020; Seitz-

Holland et al., 2021). Thus, this thesis argues for considering sex as an important determinant of how environmental risk factors contribute to psychotic psychopathology rather than as a mere covariate.

3.2.2 Implications for clinical practice

Collectively, the results of this thesis confirm the notion that the etiology of psychotic psychopathology is very complex. Addressing this complexity requires specific and comprehensive measures for each component of the network: psychopathology, environmental risk, and moderating demographic factors such as gender. Such a nuanced approach has the potential to advance not only research, but also clinical care. In contrast to approaches based on latent disorder entities that force a "nomothetic system onto human suffering" (Hofmann & Hayes, 2019, p. 45), considering the distinct functional roles of different types of environmental exposure accounts for variation on the route to psychotic psychopathology (Betz et al., 2020; Betz, Penzel, Rosen, & Kambeitz, 2021; Betz, Penzel, Rosen, Bhui, et al., 2021): As the degree and pattern of environmental exposure differs across patients, so does their clinical presentation, distress level, and risk for poor outcomes. In other words, psychotic psychopathology should be understood within the specific context of a patient's life and past experiences. Focusing on an individual patient's clinical presentation, as well as his or her history of potentially modifiable risk factors, as opposed to abstract disorder categories, has been shown to reduce essentialist, dehumanizing thinking in clinicians, with positive impact on patient care (Kim et al., 2016; Lebowitz & Appelbaum, 2019). Hence, raising awareness of the heterogeneity of risk pathways to psychotic psychopathology, for example in medical training, could be beneficial.

Information about the individual patient could also be used to select and supplement empirically supported treatment approaches (Hofmann et al., 2016; Piccirillo & Rodebaugh, 2019). Presently, etiological information, for example, regarding exposure to psychosocial adversity, is often either not inquired at all in mental health services (Read et al., 2018a), and even when it is available, it is often not considered in clinical decision-making (Read et al., 2018b). As discussed throughout this thesis, information about exposure to risk factors can potentially inform the selection of appropriate treatment options tailored to the patient's needs and should therefore be more routinely collected and heeded in clinical care. At an even higher level of personalization, networks of person-specific dynamics between symptoms and risk factors could enrich the clinician's personal and theoretical heuristics to gain an understanding of the functional relationships between variables that contribute to or maintain a particular patient's mental health problems (Hofmann et al., 2016; Hofmann & Hayes, 2019; Scholten et al., 2021; von Klipstein et al., 2020). Based on data collected in the patient's daily life, insights captured by personalized networks have high ecological validity and are unaffected by retrospective bias (Epskamp, Waldorp, et al., 2018). In patients diagnosed with psychotic disorders, ESM has been shown to be feasible (e.g., Reininghaus, Kempton, et al., 2016). The insights gained in this population are potentially particularly valuable because the psychopathological presentation is often complex, making it difficult to capture using traditional case formulation methods (von Klipstein et al., 2020). Personalized networks can also empower patients by instilling a sense of participation in their own care (Epskamp, van Borkulo, et al., 2018). Although personalized networks are therefore potentially very useful, they present some methodological challenges (described in detail in chapter 3.6). In addition, personalized network models in their current form may be too complex for clinicians to interpret, and the presentation of results may need to be further adapted to facilitate implementation in practice (Scholten et al., 2021; von Klipstein et al., 2020). Ultimately, personalized network models, like any other model, are bound by their assumptions and the nature and quality of the underlying data. Mirroring this, overall survey completion rate emerged as an

important determinant of the informative value of personalized networks in preliminary analyses of data from our PhenoNetz study (Rosen et al., 2022). Therefore, personalized network models, when used responsibly, should not be understood as providing definitive answers, but rather as providing an additional perspective that feeds into a collaborative process in which the patient and physician work out the next steps of treatment (Bastiaansen et al., 2020; von Klipstein et al., 2020).

3.3 The distinct role of affective disturbances in the psychosis continuum

3.3.1 Theoretical integration of main findings

When we zoom into the specific etiological pathways identified in this thesis, a recurring finding becomes apparent: Pathways from environmental exposure, particularly early and recent stressful life events, to psychosis frequently involve affective psychopathology, corroborating its key role across the psychosis continuum (Betz et al., 2020; Betz, Penzel, Rosen, Bhui, et al., 2021; Betz et al., 2022). Thus, this thesis adds to the accumulating evidence for a so-called affective pathway to psychosis, in which stress-induced affective disturbance, such as depression, guilt feelings and anxiety, pave ways to persistent psychotic psychopathology (Alameda et al., 2020; Griffiths et al., 2021; Isvoranu et al., 2017; Kramer et al., 2014; Myin-Germeys & van Os, 2007; Reininghaus, Gayer-Anderson, et al., 2016; Upthegrove et al., 2017).

To sketch the contribution of early and recent stressful life events in the affective pathway to psychosis, the findings of this thesis can be integrated within cognitive models of psychosis, which assign a central role to beliefs and appraisal processes in formation and maintenance of psychotic psychopathology (Freeman, 2007, 2016; Freeman et al., 2002, 2013; Garety et al., 2001). In the context of adverse life experiences, such as childhood trauma, negative beliefs about the self (e.g., 'I cannot handle my problems') and others (e.g., 'Others will harm me') may develop (Betz, Penzel, Rosen, & Kambeitz, 2021; Hardy et al., 2021; LoPilato et al., 2021). Stressful life events, on the other hand, may act as a direct trigger of affective disturbance (Betz et al., 2020; Freeman et al., 2002). Stress-induced affective disturbance, shaped reciprocally by negative beliefs about the self and others, might then drive a preferentially negative or threatening appraisal of ongoing experiences and events, feeding into positive psychotic psychopathology, particularly in women (Betz et al., 2020; Betz, Penzel, Rosen, & Kambeitz, 2021; Betz, Penzel, Rosen, Bhui, et al., 2021; Freeman, 2007; Freeman et al., 2002; Hardy et al., 2021; Klippel et al., 2017; LoPilato et al., 2021; Myin-Germeys & van Os, 2007). Additionally, long term affective disturbances may blend in (Betz et al., 2020; Freeman et al., 2002). This explanatory model is compatible with the view that environmental risk factors, particularly early trauma, proportionally shape the extent to which initially simple, unspecific states of affective disturbance become 'complicated' by psychotic experiences, which are potentially mediated by dysregulated dopaminergic signaling (Guloksuz et al., 2016; Howes & Murray, 2014; Linscott & van Os, 2013; Radhakrishnan et al., 2019; van Nierop et al., 2015). Psychotic experiences (e.g., 'Others are monitoring me') may in turn confirm negative beliefs about the self and others and also feed back into affective disturbances, which may result in a vicious cycle that pushes some individuals toward more and more distressing, severe and persistent levels of psychotic psychopathology (Freeman et al., 2002; Klippel et al., 2017; Kramer et al., 2014; Upthegrove et al., 2014; Wilson et al., 2020). Stressful life events continue to contribute at this point by triggering states of affective disturbance in which psychotic psychopathology flourishes (Betz et al., 2020; Freeman et al., 2002; Hartley et al., 2013; Kramer et al., 2014; Wilson et al., 2020). Negative symptoms, such as social withdrawal, may arise as a result of the patient avoiding potentially threatening

or negative experiences due to negative affect, particularly anxiety and depression, respectively (Betz et al., 2020; Freeman et al., 2002).

Overall, the relationships among the various components are complex and reciprocal, so the above sketch is necessarily partial. The more events, beliefs and affective disturbance are present, the more likely it is that psychotic psychopathology will be formed and maintained (Freeman et al., 2002). For example, childhood trauma is associated with increased reports of stressful life events (Betz et al., 2020), so there are likely interactions in shaping psychotic psychopathology via negative beliefs and affective disturbance. Moreover, some processes, for instance trauma-induced negative beliefs, may differ in importance across the sexes (Betz, Penzel, Rosen, Bhui, et al., 2021). For the sake of conciseness, I have discussed only the most relevant potential cognitive-behavioral pathways that are directly related to early and recent stressful life events; naturally, other factors, including biological ones, are involved (Bloomfield et al., 2019; Garety et al., 2007). A proposal for integrating the presented psychologically-oriented findings with biological research is outlined in chapter 3.4.

3.3.2 Implications for clinical practice

In summary, the results of this work confirm the idea that affective disturbance is central to the development and maintenance of psychosis and should not be treated solely as a comorbidity. The entailed conceptual shift towards transdiagnostic psychopathology has important implications also for clinical practice (Garety et al., 2001; Hartley et al., 2013; Smith et al., 2006; Upthegrove et al., 2017, 2021; Wilson et al., 2020). Targeting the affective pathway to psychosis, in addition to traditional treatment of psychotic symptoms, may represent an important advance in the prevention and treatment of psychotic psychopathology (Alameda et al., 2020; Griffiths et al., 2021). The finding that 24% of psychotic patients relapse within 1 year despite antipsychotic treatment, the first-line intervention for psychotic disorder, underscores the need for complementary psychosocial and psychological treatment approaches (Bighelli et al., 2021; Ceraso et al., 2020). Several specific recommendations can be derived from the present work that are worthy of further investigation.

First, it may be worthwhile to preventively target specific negative self- and other beliefs that are more likely to be held after childhood trauma (Betz, Penzel, Rosen, & Kambeitz, 2021), for instance through trauma-focused cognitive behavioral therapy (Alameda et al., 2020; Bloomfield et al., 2021; Hardy, 2017; Hardy et al., 2021). The rationale is that re-evaluating these beliefs may attenuate distressing appraisals of stressful events as well as initial psychotic experiences, thus making progression to persistent psychotic symptomatology less likely (Alameda et al., 2020; Hardy, 2017; Peters et al., 2017; Reininghaus, Kempton, et al., 2016). Similarly, when clinically relevant psychotic symptomatology is present, it may be useful to help patients understand their problems as partly the result of trauma-related beliefs, especially if insight is still intact (Hardy, 2017; LoPilato et al., 2021; Peters et al., 2017; Smith et al., 2006). The findings of this work, as well as previous research, suggest that it may be beneficial to tailor trauma-focused approaches depending on whether experienced childhood trauma primarily reflects experiences of neglect or abuse (Betz, Penzel, Rosen, & Kambeitz, 2021; LoPilato et al., 2021; McLaughlin et al., 2014; Read et al., 2018b). Complementing this, personalized network approaches could help identify particularly central negative beliefs and appraisals for each individual (Hofmann & Hayes, 2019; Rosen et al., 2022; Scholten et al., 2021).

Second, a sizable proportion of help-seeking patients are currently left unprovided with care in the psychiatric realm, given that those seeking help often present with an unspecific mix of psychopathology and thus, do not meet specific diagnostic criteria signaling need for intervention (Fusar-Poli et al., 2014;

Michel et al., 2021; Rickwood et al., 2014; Rosen et al., 2022). Initial psychotic experiences often present themselves in association with affective disturbances, such as anxious and depressed mood, as well as sleep problems (Betz, Penzel, Rosen, Bhui, et al., 2021; Betz et al., 2022). These affective disturbances are often of greater concern than psychotic experiences even for those help-seeking patients who meet at-risk criteria for psychosis (Fusar-Poli et al., 2014; Rickwood et al., 2014). Likewise, many risk factors, including early and recent stressful life events, are transdiagnostic and act primarily via nonspecific pathways of disturbed affective states that can diverge into many different types of psychopathology (Guloksuz et al., 2015; Kessler, 1997; McLaughlin et al., 2020; Myin-Germeys & van Os, 2007; Nolen-Hoeksema & Watkins, 2011). Thus, one promising approach is to introduce early, explicitly transdiagnostic interventions that target affective disturbances and could be applied to a larger number of patients seeking help as part of a so-called stepped care approach (Cross & Hickie, 2017; McLaughlin et al., 2020; Rosen et al., 2022). While such an approach provides the important opportunity to reduce psychopathology broadly, the available evidence also specifically lends credence to the idea that targeting affective disturbances and sleep problems holds potential to prevent progression to more severe clinical syndromes characterized by persistent psychotic psychopathology that may be more difficult to treat (Betz, Penzel, Rosen, Bhui, et al., 2021; Deng et al., 2021; Freeman et al., 2017; Griffiths & Birchwood, 2020; Rosen et al., 2022).

Similarly, depressed and anxious mood may potentially serve as important symptom targets in early phases of psychotic disorders (Alameda et al., 2020; Betz et al., 2020; Deng et al., 2021; Griffiths et al., 2021; Upthegrove et al., 2017; Wilson et al., 2020). Around 23% and 29% of patients in early phases of psychotic disorders report depressive or affective symptoms, respectively (Wilson et al., 2020), highlighting the broad impact it would have to target these symptoms more routinely in clinical practice. Improvement in affective symptoms, such as through transdiagnostic metacognitive therapy, may lead to indirect improvement in psychotic psychopathology as well as better long-term treatment outcomes (Alameda et al., 2020; Bebbington, 2015; Gregory et al., 2017; Upthegrove et al., 2017; Wilson et al., 2020). The results presented in this thesis tentatively suggest that such an approach may be particularly warranted following stressful life events when affective disturbances are common (Betz et al., 2020). Here, a preventive approach could consist in reducing social stress in the patient's environment (Betz et al., 2020). Complementary to this, worsening of affective psychopathology after stressful life events may be averted by timely intervention, e.g., through so-called just-in-time adaptive interventions that provide immediate access to support, typically via a smartphone app, when the patient needs it most (Nahum-Shani et al., 2018; Reininghaus, Depp, et al., 2016).

In general, it is important to recognize that while this work represents an important first step toward a new perspective on etiological pathways in the psychosis continuum, it is exploratory and hypothesis-generating. Therefore, any hypotheses derived need to be tested in appropriate designs, such as large-scale randomized controlled trials, before they can be routinely implemented in clinical practice. Some of the ideas outlined in this chapter, such as trauma-focused cognitive behavioral therapy for psychosis, are currently already being tested (South London and Maudsley NHS Foundation Trust, 2020). In summary, formal recognition of the central role of affective psychopathology, particularly after early and recent stressful life events, has the potential to improve prevention and treatment outcomes in psychotic disorders.

3.4 Integrating different levels of analysis: a multilayered network perspective

So far, the results of this work have been discussed mainly from a psychologically-oriented (network) perspective. This is a high-level explanatory perspective based on psychological constructs, i.e., symptoms and risk factors, which can be profitably studied in isolation (Kendler, 2008). In some cases, this explanatory perspective may be the most intuitive and appropriate level of explanation sufficient to drive progress in non-pharmacological treatments, for example (Borsboom et al., 2019; Kendler, 2005, 2008; Lilienfeld, 2007; Miller, 2010). Examples include the impact of first-person experiences such as stressful life events (Betz et al., 2020) on psychopathology, where a lower, biological level of explanation may be less efficient (Borsboom et al., 2019; Kendler, 2005, 2008; Miller, 2010). For example, at the level of psychological constructs, the pattern of associations between stressful life events and affective disturbance is easily understood, whereas simply listing the biological processes involved would not provide the same understanding because "the pattern [...] is not visible at the lower level" (Borsboom et al., 2019, p. 9).

However, investigations should not stop at the level of psychologically-oriented symptom networks: Following explanatory pluralism, each level of explanation will only lead to partial answers (Kendler, 2005, 2008; Lilienfeld, 2007). A comprehensive account of the etiology of psychotic psychopathology requires an active, bitwise integration of information derived from mutually informative levels of analysis (Kendler, 2005, 2008; Lilienfeld, 2007). Thus, explanations at the level of psychology can be richly complemented by explanations at the level of biology, for instance (Borsboom, 2017; Kendler, 2005; Lilienfeld, 2007; Miller, 2010). As an example, consider childhood trauma, where research has identified several relevant components at the psychological and biological levels that contribute to its association with psychotic psychopathology. At the psychological level, alterations in cognitive and emotional processes are involved (Betz, Penzel, Rosen, & Kambeitz, 2021; Betz, Penzel, Rosen, Bhui, et al., 2021; Garety et al., 2001), while at the biological level, lasting dysregulations in autonomic, endocrine, and dopaminergic systems have been implicated (Aas et al., 2019; Bloomfield et al., 2019). The difficult task ahead is to integrate these findings (Kendler, 2008). From my view, a particular challenge lies in the fact that biological research into the role of environmental factors has thus far often focused on specific diagnostic categories, such as schizophrenia, or sum scores of positive symptoms. It remains to be seen how well these explanations translate to symptom-based psychological accounts of environmental risk-based pathways. Likely, greater phenotypic specificity, i.e., focusing on individual symptoms, is required also at the biological level of explanation for optimal integration (Garety et al., 2007).

A relatively straightforward first step to gain insight into the linkage of psychological and biological levels of explanations consists in integrating biological variables into symptom networks as nodes or moderators (Fried & Cramer, 2017; Isvoranu, Guloksuz, et al., 2020). With regard to childhood trauma, the network models reported in this thesis may, for example, be extended with objective measures of the long-term stress response, such as hair cortisol (Aas et al., 2019). Such an approach provides a first step toward a holistic view of the role of cognitive and physiological stress responses contributing to the affective pathway to psychosis (Bloomfield et al., 2019, 2021). In a more sophisticated attempt to link different levels of analysis, several authors have recently proposed multilayer network accounts, i.e., modeling a network of different networks in a layer each (e.g., symptom networks, environmental networks, brain networks) with connections between and within the layers (Blanken et al. 2021; de Boer et al., 2021; Guloksuz et al., 2017). Such an approach may complement and contextualize existing level-specific knowledge in terms of etiology of psychotic psychopathology. In the context of this thesis, it may be particularly promising

to integrate findings on the role of developmental cannabis use in the etiology of psychosis derived from symptom networks (Betz et al., 2022) and brain networks (Penzel et al., 2021). An iterative process – identifying potentially relevant pathways on the psychological and biological level, and subsequent integration – will deepen our understanding of both types of processes involved in the development and maintenance of psychosis (Kendler, 2008).

3.5 Methodological and conceptual considerations

Some methodological and conceptual aspects that recur throughout this work should be highlighted. First, reciprocally relevant risk factors were modeled concurrently whenever possible (Betz et al., 2020; Betz, Penzel, Rosen, Bhui, et al., 2021; Betz et al., 2022), given that risk factors, just like symptoms, exhibit complex patterns of dependencies (Guloksuz et al., 2018). Thus, our modeling strategy aimed to disentangle different etiological pathways to psychosis rather than selectively examining individual risk factors. However, inclusion of measures of environmental exposure was limited to those that were available in the used datasets. Likewise, measures of genetic risk could have enriched this thesis through possible interactions with environmental exposure (Guloksuz et al., 2019; Pries et al., 2018; Radhakrishnan et al., 2019), but were unfortunately not available. Thus, the presented findings provide only a partial picture and should be replicated and expanded in data sets with comprehensive information on environmental and genetic risk factors as they become available (Guloksuz et al., 2018).

Owing to the limitations inherent to large-scale epidemiological research, information on the amount, timing and duration of the exposure to the environmental risk factors was not always available, or only in a coarse, retrospective format. Even with appropriate network estimation methods, binary assessments of risk factors (present vs. absent) do not allow conclusions to be drawn about the effects of the amount of exposure to a particular risk factor. Similarly, exposures during the sensitive period from infancy to early adolescence, when neurodevelopment is still ongoing, may play a different role than more proximal experiences (Murray et al., 2017; Penzel et al., 2021; Radua et al., 2018). This pattern of results was also evident in one of the papers presented, in which earlier age at onset of cannabis use was associated with a higher proportion of specific psychotic and affective experiences (Betz et al., 2022). For other exposures, specifically childhood trauma, a differentiated weighting or specific assessment of temporal proximity would have been interesting, but unfortunately was not possible due to lack of relevant information. Likewise, the effects of repeated compared to single exposure may differ depending on the environmental risk factor (Guloksuz et al., 2018). Future research should therefore focus on refined, ideally longitudinal, assessments of environmental exposures to analyze the differential role of specific risk pathways depending on the proximity and duration of risk factors. Most relevant pathways identified by binary measures should be replicated and extended by continuous measures of environmental risk.

Moreover, the empirical work presented in this thesis focused exclusively on environmental risk factors. However, it is increasingly recognized that protective factors, such as the availability of social support, may be equally important in understanding the etiology of psychotic psychopathology (Radua et al., 2018). Insight into the role of protective factors and their interactions with environmental risk factors can be particularly useful for designing appropriate interventions. In our PhenoNetz study, we have therefore collected measures of both risk and protective factors of all participants (Rosen et al., 2022).

A final methodological note concerns the replicability of network structures, which are estimated primarily exploratory from empirical data. Network estimation typically involves measures to prevent overfitting, such as regularization (Epskamp, Waldorp, et al., 2018). Nonetheless, it is advisable to em-

pirically assess the degree to which findings from network models replicate across different datasets or reflect idiosyncrasies of a specific dataset; ideally either through pairwise statistical comparisons of results, or more advanced approaches, such as meta-analytic network aggregation (Borsboom et al., 2021; Epskamp et al., 2021). In Betz, Penzel, Rosen and colleagues (2020), we found good replicability of network structures in a replication sample collected approximately five years later using identical methods. In Betz, Penzel, Kambeitz-Ilankovic and colleagues (2020), we replicated findings from Isvoranu et al. (2017), showing largely comparable pathways from childhood trauma to psychotic psychopathology via affective psychopathology than originally reported. For the other two empirical studies (Betz, Penzel, Rosen, Bhui, et al., 2021; Betz et al., 2022), we unfortunately did not have a suitable replication sample available. This was largely due to the large sample size required for the statistical procedures used or the unavailability of important assessments in potential replication samples, which would have made quantitative comparison of results beyond mere visual inspection impossible. Thus, an estimate of replicability is needed for these studies. To facilitate replication, all empirical papers presented as part of this thesis were accompanied by published code. In a highly exploratory and data-driven field, comprehensive reporting, ideally accompanied by code and data sharing (Burger, Isvoranu, et al., 2020), is vital to counter "a lurking replicability crisis" (Fried & Cramer, 2017, p. 999).

3.6 Challenges and future directions for the network approach in the psychosis continuum

The findings presented in this thesis add to an accumulating body of literature that makes it clear that our explanations for how environmental influences increase the risk of psychotic psychopathology will ultimately be complex rather than simple. Addressing this etiological complexity from a network perspective presents several challenges that highlight directions for future research.

First, the number of environmental risk factors that have been associated with psychotic disorders is large (Radua et al., 2018). On top of that, this thesis suggests that for some exposures, such as childhood trauma, the study of more granular components may be needed to provide a comprehensive picture (Betz, Penzel, Rosen, & Kambeitz, 2021). Similarly, symptom domains considered relevant to the psychosis continuum have expanded to include a wide range, such as positive, negative, and affective symptoms, as well as autistic traits (Betz et al., 2020; Betz, Penzel, Rosen, Bhui, et al., 2021; Isvoranu et al., 2017, 2021). Omitting relevant variables could lead to false claims about putative causal relationships, while modeling many components without enough participants leads to analyses with too little power (Epskamp, Borsboom, et al., 2018; Fried & Cramer, 2017). Thus, an integrative, potentially multilayered network approach to the role of various environmental exposures in different domains of psychopathology requires very large samples with more comprehensive assessments than are currently available. Even with sufficiently large data sets, such as those obtained through data sharing, researchers may need to make a careful selection of the variables most relevant to their specific research question, and there is currently no obvious solution to the problem of 'where to draw the line' between relevant and irrelevant variables.

Second, due to the dominance of the essentialist framework in psychiatric research, datasets agnostic to traditional diagnostic categories are not yet widely available (Guloksuz et al., 2017). Thus, network-analytic studies aimed at elucidating etiological pathways often fall back on datasets with a structure biased by assumed latent disorder categories, e.g., in that they include only patients meeting traditional diagnostic criteria for psychotic disorders (e.g., Betz et al., 2020; Isvoranu et al., 2017). When based on a comprehensive assessment of psychopathology, these approaches can be regarded as an inter-

mediate solution (Guloksuz et al., 2017). However, some findings derived from such datasets may be the result of biases, such as Berkson's bias: Selecting participants by symptom severity can induce spurious negative edges in cross-sectional symptom networks (de Ron et al., 2021). To model etiological pathways truly independent of latent disorder categories, researchers should eventually move toward representative general population samples (Betz, Penzel, Rosen, & Kambeitz, 2021; Betz, Penzel, Rosen, Bhui, et al., 2021; Betz et al., 2022; Isvoranu et al., 2016) or transdiagnostic patient samples (Rosen et al., 2022).

Third, items commonly used for network modeling come from questionnaires that were constructed to measure underlying constructs, such as disorder severity. Thus, an edge may not only arise from putative causal relationships, but also from items measuring the same or very similar constructs (e.g., social withdrawal and social avoidance) (Betz et al., 2020; Fried & Cramer, 2017). Currently, there is no established approach to differentiate these two types of edges. Especially as more variables are entered into the network, it is crucial to make sure that all items indeed reflect topologically distinct constructs to avoid false putative causal claims. Items that can be understood to measure the same construct and show largely the same associations to the other variables of interest can be combined (Burger, Stroebe, et al., 2020; Fried & Cramer, 2017). In the future, data collected using questionnaires specifically designed for network analyses, with fine-grained items reflecting distinct constructs, could complement existing datasets.

Fourth, most network studies aimed at providing a better understanding of the role of environmental risk factors in the psychosis continuum are based on a cross-sectional snapshot of data. These studies are valuable to generate hypotheses about putative causal relations (von Klipstein et al., 2021); in particular for some time-invariant environmental exposures, such as childhood trauma (Betz, Penzel, Rosen, & Kambeitz, 2021). However, it is not clear a priori to what extent etiological pathways identified cross-sectionally can be extrapolated to the level of the individual. Moreover, cross-sectional networks cannot provide information on dynamic associations between time-variant risk factors, such as stressful life events, and symptoms. Therefore, leveraging longitudinal data constitutes an important way to compute temporal networks. These make it possible to assess dynamic associations between specific environmental risk factors and symptoms at the group and individual level.

With longitudinal data, however, comes a fifth challenge: designing the sampling scheme to get the time scale right for the etiological process of interest. It is not always easy to gauge if the occurrence of an environmental stressor, such as a stressful life event, is linked to changes in psychopathology minutes, days, or weeks later. Modeling etiological processes at the wrong time scale may lead to incorrect estimates of relationships (Fried & Cramer, 2017). Additionally, if the time scale of the process of interest is very small, highly intensive, burdensome sampling schemes are needed, which are of limited practical feasibility (Vachon et al., 2019). Similar feasibility concerns apply to the study of rare, time-varying environmental exposures and related attempts to assess how some individuals progress to increasingly severe levels of psychotic psychopathology. Both research questions require an extended period of 'real time' assessment over several months or even years. In this context, passive data collection on the participant's smartphone could be a valuable alternative, providing valid insights with minimal burden (Montag et al., 2020). To study individual progression across the psychosis continuum, participants could also be followed up prospectively, with short periods of ESM every few months.

A sixth and related challenge concerns statistical power in networks based on intensive longitudinal data: As the number of included individual symptoms and risk factors increases, so does the number of assessment points needed to reliably detect edges in these networks (Epskamp, Waldorp, et al., 2018; Mansueto et al., 2020). Thus, researchers must balance a holistic view against feasibility of data collection

and model estimation. One way to gain statistical power for the estimation of personalized networks is the inclusion of prior patient or clinician knowledge via Bayesian approaches (Burger et al., 2021). Still, for most research questions, researchers will need to make a theoretically and clinically informed selection of components to be assessed in ESM studies. Likewise, the creation of ESM items and the analysis of ESM data is currently highly conditional on subjective choices, which may be particularly problematic when moving towards clinical implementation of person-specific analyses based on ESM data (Bastiaansen et al., 2020). In perspective, the field should therefore work toward well-validated items and scales and establish best practices for data collection and analysis in ESM research.

A final challenge consists in integrating findings from network analyses focused on between-person and within-person processes. In short, the former can shed light onto why people differ from each other. Within-person network analyses, on the other hand, highlight why a specific person differs from their own average across time. Ultimately, both observed types of variation are the result of within-person causes (Hamaker, 2012), and parsing them may be challenging. In an effort to integrate all available levels of analysis, I suggest that an "idiothetic approach" (Fraenkel, 1995, p. 5) to investigating the role of environmental exposure in psychosis etiology may be a useful research framework: To investigate how patients respond in a formally similar fashion to similar environmental risk factors, for example, with heightened emotional distress to stressful life events (Betz et al., 2020; Betz, Penzel, Rosen, & Kambeitz, 2021), yet each with their own variations, ideally to be identified in a data-driven manner (Rosen et al., 2022).

Despite these challenges, the network approach represents a powerful framework for capturing the increasingly apparent etiological complexity that characterizes the psychosis continuum. With a research community dedicated to advancing the relatively young field by sharing methodological tools, data, and code, promising avenues for further research with high clinical relevance are within reach.

3.7 Conclusion

> "As we enter the third decade of the twenty-first century, the causes of the major forms of mental illness remain an enigma, the product, it seems increasingly obvious, of a complex of biological and social factors."
> —(Scull, 2021, p. 2765)

In recent years, it has become more and more clear that psychotic psychopathology is a very complex phenomenon that arises from a plethora of components, linked with intricate interactions across biological, psychological, and social levels of analysis (Fried & Robinaugh, 2020; Radua et al., 2018; Scull, 2021). To embrace this complexity, it is necessary to leave the problematic common cause framework behind and move to more appropriate strategies in psychosis research (Guloksuz et al., 2018; Isvoranu, Boyette, et al., 2020; Isvoranu et al., 2016).

In this spirit, this thesis used an innovative, data-driven network approach to contribute advances to the understanding of the etiology of psychosis. The findings presented may guide future research and pave the way for improved prevention and treatment of psychotic disorders. Specifically, environmental risk factors were shown to act through diverse, potentially sex-specific pathways that often involve affective psychopathology. This pattern of results corroborates the notion that psychosis etiology is best approached from a comprehensive, transdiagnostic perspective. In clinical practice, greater attention to potentially malleable risk factors may improve the selection of appropriate interventions and treatments. Specifically, this thesis shows that after trauma and stressful life events, affective disturbances and

negative beliefs are likely key factors in the affective pathway to psychosis and represent potential intervention targets. In perspective, the use of personalized network approaches may help clinicians to tailor therapeutic strategies based on the dynamics of a patient's symptoms and environmental risk factors as captured in the natural flow of daily life. Recently proposed multilayered network approaches have potential to further improve our understanding of the etiology of psychotic psychopathology by linking psychological and biological levels of analysis.

While there are still some important challenges to overcome, the field has seen significant progress and exciting developments in recent years that make me optimistic that the network approach will continue to provide an important agenda to understand the complex pathways to psychosis.

3.8 References

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4. Summary

Psychotic disorders impose high burden on both the affected individual and society. Despite extensive research efforts in recent decades, their etiology remains poorly understood, hindering progress in prevention and treatment. Two distinct developments in the field may represent ways forward: First, there is a growing recognition of the importance of several potentially malleable environmental risk factors, such as childhood trauma, stressful life events, or cannabis use, in the onset, progression, and maintenance of psychotic disorders. Second, the ubiquitous common cause model of psychotic disorders is increasingly challenged by alternative conceptualizations of mental disorders, such as the network approach to psychopathology. In the common cause model, symptoms are viewed as mere effects of a common cause (the disorder itself, e.g., 'schizophrenia'), i.e., symptoms covary because of their joint dependence on an assumed latent disorder entity. This traditional view also assumes that environmental factors influence symptoms *via* the disorder entity. In contrast, the network approach to psychopathology views mental disorders as networks of directly interacting symptoms and other components, such as environmental risk factors. Patterns of covariation between symptoms and other components are assumed to reflect meaningful relationships and become the focus of analysis.

Building upon these developments, this thesis proposes a network approach to disentangle potential pathways by which environmental risk factors increase the risk for psychotic disorders. Specifically, the five presented papers focus on individual symptoms and their associations with common environmental risk factors of psychotic disorders. Network structures were generated from empirical data by estimating unique pairwise relationships, i.e., the associations between any two variables that remain after controlling for all other variables under consideration; primarily in the form of undirected pairwise Markov random fields. The first paper built upon evidence for an affective pathway from childhood trauma to psychosis and demonstrated that a similar pathway applied to exposure to recent stressful life events in at-risk and recent onset psychosis patients. Specifically, results showed that burden of recent life events did not link to positive and negative psychotic symptoms directly, but only indirectly, via symptoms of general psychopathology, such as depression, guilt, and anxiety. The second paper zoomed into the proposed affective pathway via increased stress reactivity through which childhood trauma is thought to contribute to the liability for psychopathology at large, including psychotic disorders. The findings provide a detailed characterization of putative psychological stress processes underlying distinct types of childhood trauma in the general population: childhood trauma reflecting deprivation (i.e., neglect) was exclusively associated with stressful experiences representing low perceived self-efficacy, whereas childhood trauma reflecting threat (i.e., abuse) was specifically associated with stressful experiences reflecting perceived helplessness. The third paper then addressed another important risk factor for psychotic disorders, cannabis use. The results suggest that characteristics of cannabis use in the general population may contribute differentially to the risk for certain psychotic experiences and affective symptoms: Network associations were particularly pronounced between increased frequency of cannabis use and certain delusional experiences, i.e., persecutory delusions and thought broadcasting, on the one hand, and earlier onset of cannabis use and visual hallucinatory experiences and irritability, on the other. The fourth paper investigated which environmental and demographic factors explained heterogeneity in symptom networks of psychosis to highlight potential etiological divergence in risk for psychosis in the general population. Results point to distinct sex-specific etiological mechanisms contributing to psychosis risk: In women, an affective pathway to psychosis may have distinct importance, especially after interpersonal trauma. In men, an ethnic minority background was associated with strong interconnections between individual psychotic experiences, which has been

linked to poor outcomes in previous research. The fifth and final paper presented the protocol for an experience sampling study in the help-seeking population of the Early Recognition Center for Mental Disorders of the University Hospital Cologne. A central goal in this project will be to elucidate how personalized symptom networks derived from intensive longitudinal data differ as a function of environmental exposure.

In sum, findings from this thesis illustrate that environmental risk factors increase psychosis risk through diverse, potentially sex-specific pathways that often involve affective psychopathology. This confirms the notion that the etiology of psychosis is complex and best understood from a broad, transdiagnostic perspective. The results presented are also relevant for clinical practice as they pave the way for a better selection of appropriate interventions and treatments. In particular, this thesis highlights affective disturbances and negative beliefs as potential intervention targets in the affective pathway to psychosis, especially following trauma and stressful life events. In perspective, the use of personalized network approaches may improve the ability to tailor therapeutic strategies based on the dynamics of a patient's symptoms and environmental risk factors as captured in daily life. Recently proposed multilayered network approaches have potential to further advance our understanding of psychosis etiology by linking psychological and biological levels of analysis.

5. Zusammenfassung

Psychotische Störungen stellen sowohl für die Betroffenen als auch für die Gesellschaft eine große Belastung dar. Trotz umfangreicher Forschungsanstrengungen in den letzten Jahrzehnten ist ihre Ätiologie nach wie vor nur unzureichend verstanden, was Fortschritte bei der Prävention und Behandlung behindert. Zwei unterschiedliche Entwicklungen im Feld könnten einen Weg in die Zukunft weisen: Erstens wird die Bedeutung potenziell beeinflussbarer umweltbedingter Risikofaktoren wie Traumata in der Kindheit, belastende Lebensereignisse oder Cannabiskonsum, für das Entstehen, den Verlauf und die Aufrechterhaltung psychotischer Erkrankungen zunehmend anerkannt. Zweitens wird das allgegenwärtige Common Cause-Modell zunehmend durch alternative Konzeptualisierungen psychischer Störungen in Frage gestellt, z. B. durch den Netzwerkansatz der Psychopathologie. Im Common Cause-Modell werden Symptome als bloße Auswirkungen einer gemeinsamen Ursache (*common cause*; der Störung selbst, z. B. 'Schizophrenie') betrachtet, d. h. die Symptome kovariieren aufgrund ihrer gemeinsamen Abhängigkeit von einer angenommenen latenten Störungsentität. Diese traditionelle Sichtweise geht auch davon aus, dass Umweltfaktoren die Symptome *über* die latente Störungsentität beeinflussen. Im Gegensatz dazu betrachtet der Netzwerkansatz der Psychopathologie psychische Störungen als Netzwerke aus direkt interagierenden Symptomen und anderen Komponenten, wie z. B. Umweltrisikofaktoren. Es wird davon ausgegangen, dass die beobachteten Kovariationsmuster zwischen Symptomen und anderen Komponenten sinnvolle Beziehungen widerspiegeln. Diese Kovariationsmuster rücken daher in den Mittelpunkt der Analyse.

Aufbauend auf diesen Entwicklungen wird in dieser Arbeit ein Netzwerkansatz vorgeschlagen, um mögliche Wege zu entschlüsseln, über die Umweltrisikofaktoren das Risiko für psychotische Störungen erhöhen. Die fünf vorgestellten Artikel konzentrieren sich auf einzelne Symptome und ihre Assoziationen mit allgemein anerkannten umweltbedingten Risikofaktoren für psychotische Störungen. Die Netzwerkstrukturen wurden aus empirischen Daten generiert, indem eindeutige paarweise Beziehungen geschätzt wurden, d. h. die Assoziationen zwischen zwei beliebigen Variablen, die nach Kontrolle aller anderen betrachteten Variablen verbleiben; in erster Linie in Form von ungerichteten Markow-Netzwerken. Der erste Artikel baute auf Hinweisen für einen affektiven Pfad von Traumata in der Kindheit hin zur Psychose auf und wies bei Risikopatienten und Patienten mit kürzlich aufgetretener Psychose nach, dass ein ähnlicher Zusammenhang auch für belastende jüngere Lebensereignisse besteht. Insbesondere zeigten die Ergebnisse, dass die Belastung durch jüngere Lebensereignisse nicht direkt mit positiven und negativen psychotischen Symptomen zusammenhängt, sondern nur indirekt über Symptome der allgemeinen Psychopathologie wie Depression, Schuldgefühle und Angst. Der zweite Artikel befasste sich mit dem vorgeschlagenen affektiven Pfad über eine erhöhte Stressreaktivität, über den Kindheitstraumata zur Anfälligkeit für Psychopathologie im Allgemeinen, einschließlich psychotischer Störungen, beitragen sollen. Die Ergebnisse dieser Arbeit liefern eine detaillierte Charakterisierung der mutmaßlichen psychologischen Stressprozesse, die verschiedenen Arten von Kind-heitstraumata in der Allgemeinbevölkerung zugrunde liegen: Kindheitstraumata, die Deprivation (d. h. Vernachlässigung) widerspiegeln, waren ausschließlich mit Stresserfahrungen assoziiert, die eine geringe wahrgenommene Selbstwirksamkeit reflektieren, während Kindheitstraumata, die Bedrohung (d. h. Missbrauch) widerspiegeln, speziell mit Stresserfahrungen assoziiert waren, die wahrgenommene Hilflosigkeit reflektieren. Der dritte Artikel befasste sich mit einem weiteren wichtigen Risikofaktor für psychotische Störungen, dem Cannabiskonsum. Die Ergebnisse deuten darauf hin, dass Merkmale des Cannabiskonsums in der Allgemeinbevölkerung in unterschiedlicher Weise zum Risiko für bestimmte psychotische Erfahrungen und affektive Symptome beitragen können: Besonders

ausgeprägt waren die Zusammenhänge zwischen einer erhöhten Häufigkeit des Cannabiskonsums und bestimmten wahnhaften Erfahrungen, d. h. Verfolgungswahn und Gedankenübertragung, einerseits und einem früheren Beginn des Cannabiskonsums und visuellen halluzinatorischen Erfahrungen und Reizbarkeit andererseits. Im vierten Artikel wurde untersucht, welche umweltbedingten und demografischen Faktoren die Heterogenität in Symptomnetzwerken der Psychose erklären, um so mögliche ätiologische Divergenzen beim Psychoserisiko in der Allgemeinbevölkerung aufzuzeigen. Die Ergebnisse deuten auf unterschiedliche geschlechtsspezifische ätiologische Mechanismen hin, die zum Psychoserisiko beitragen: Bei Frauen könnte insbesondere nach einem interpersonellen Trauma ein affektiver Pfad zur Psychose eine besondere Bedeutung haben. Bei Männern wurde ein ethnischer Minderheitenhintergrund mit starken Zusammenhängen zwischen einzelnen psychotischen Erfahrungen in Verbindung gebracht, was in Vorarbeiten mit schlechten Outcomes in Verbindung gebracht wurde. Im fünften und letzten Artikel wurde das Studienprotokoll für eine Experience-Sampling Studie in der Hilfesuchpopulation des Früherkennungs- und Therapiezentrums für psychische Krisen der Uniklinik Köln vorgestellt. Ein zentrales Ziel dieses Projekts wird es sein, herauszufinden, wie personalisierte Symptomnetzwerke, die aus intensiven Längsschnittdaten abgeleitet wurden, in Abhängigkeit von der Exposition zu Umweltrisikofaktoren variieren.

Zusammengefasst zeigen die Ergebnisse dieser Arbeit, dass umweltbedingte Risikofaktoren das Psychoserisiko über verschiedene, möglicherweise geschlechtsspezifische Pfade erhöhen, die häufig affektive Psychopathologie beinhalten. Dies bekräftigt die Vorstellung, dass die Ätiologie der Psychose komplex ist und am besten aus einer umfassenden, transdiagnostischen Perspektive verstanden wird. Die vorgestellten Ergebnisse sind auch für die klinische Praxis relevant, da sie den Weg für eine bessere Auswahl geeigneter Interventionen und Behandlungen ebnen. Insbesondere wurden in dieser Arbeit affektive Psychopathologie und negative Überzeugungen als potenzielle Interventionsziele auf dem affektiven Pfad zur Psychose hervorgehoben, insbesondere nach Traumata und belastenden Lebensereignissen. Perspektivisch könnte der Einsatz personalisierter Netzwerk-Ansätze dabei helfen, therapeutische Strategien auf Grundlage der Dynamik zwischen Symptomen und Risikofaktoren, die im täglichen Leben erfasst werden, individuell anzupassen. Kürzlich vorgeschlagene mehrschichtige Netzwerkansätze haben das Potenzial, unser Verständnis der Psychose-Ätiologie durch die Verknüpfung psychologischer und biologischer Analyseebenen weiter zu verbessern.

6. Appendix

6.1 Supplementary material for "General psychopathology links burden of recent life events and psychotic symptoms in a network approach"

Supplementary Table 1. Diagnosis ascertained by the Structured Clinical Interview for DSM-IV (SCID) in the Clinical High-Risk (CHR) and Recent Onset Psychosis (ROP) sample.
Supplementary Table 2. Comparison of baseline demographic and clinical characteristics of women and men.
Supplementary Table 3. Comparison of baseline demographic and clinical characteristics of those participants included in longitudinal modeling and those participants excluded due to missing data.
Supplementary Results 1. Robustness analyses.
Supplementary Results 2. Comparison of networks estimated in CHR and ROP.
Supplementary Results 3. Comparison of networks estimated in women and men.
Supplementary Figure 1. Life events in the early psychosis spectrum reported at baseline (N = 547).
Supplementary Figure 2. Edge values with 95% confidence intervals obtained from bootstrapping in the original sample for the main network model.
Supplementary Figure 3. Case-dropping bootstrap for the main network model.
Supplementary Figure 4. Edge values with 95% confidence intervals obtained from bootstrapping in the original sample for the main network model after inclusion of different childhood trauma types as covariates.
Supplementary Figure 5. Case-dropping bootstrap for the main network model after inclusion of different childhood trauma types as covariates.
Supplementary Figure 6. Cross-sectional networks of relationships between burden of recent life events and symptomatology assessed with the Positive and Negative Syndrome Scale (PANSS) estimated separately in Clinical High-Risk (CHR) and Recent Onset Psychosis (ROP) participants.
Supplementary Figure 7. Cross-sectional networks of relationships between burden of recent life events and symptomatology assessed with the Positive and Negative Syndrome Scale (PANSS) estimated separately in women and men.
Supplementary Figure 8. The Cologne Chart of Life Events.

Supplementary Tables

Supplementary Table 1. Diagnosis ascertained by the Structured Clinical Interview for DSM-IV (SCID) in the Clinical High-Risk (CHR) and Recent Onset Psychosis (ROP) sample.

Diagnosis	Frequency (%)
CHR (n = 265)	
Major depressive disorder	51.3
No current axis I disorder	22.3
Obsessive compulsive disorder	3.8
Panic disorder	3.8
Generalized anxiety disorder	3.0
Adjustment disorder	1.9
Dysthymic disorder	1.9
Anxiety disorder NOS	1.5
Bipolar II disorder	1.5
Depressive disorder NOS	1.5
Cannabis dependence	1.1
Dissociative disorder	1.1
Social phobia	1.1
Bipolar I disorder	0.08
Other axis I disorder	0.08
Specific phobia	0.08
Anorexia	0.08
Bipolar disorder other	0.08
Body dysmorphic disorder	0.08
Somatization disorder	0.08
ROP (n = 282)	
Schizophrenia	36.9
Psychotic disorder NOS	14.5
Schizophreniform disorder	12.8
Brief psychotic disorder	8.2
Schizoaffective disorder	8.2
Major depressive disorder (with psychotic features)	7.4
Delusional disorder	6.7

Diagnosis	Frequency (%)
Bipolar I disorder (with psychotic features)	5.0
Bipolar II disorder (with psychotic features)	0.04

Abbreviations: CHR: Clinical High-Risk; NOS: Not Otherwise Specified; ROP: Recent Onset Psychosis.

Supplementary Table 2. Comparison of baseline demographic and clinical characteristics of women and men. Means (SD) unless stated otherwise.

Variable	Women (n = 260)	Men (n = 287)	Comparison
Studygroup (% ROP)	46.2	56.4	$\chi^2 = 5.79, p = .020$
Age	24.8 (5.9)	24.5 (5.4)	$Z = -0.50, p = .617$
PANSS (subscale scores)			
Positive	14.3 (5.9)	15.5 (6.4)	$Z = 2.16, p = .029$
Negative	14.3 (7.3)	15.4 (7.2)	$Z = 1.74, p = .081$
General	31.9 (9.9)	32.3 (10.0)	$Z = 0.39, p = .701$
Total	60.6 (19.7)	63.3 (19.6)	$Z = 1.56, p = .117$
Number of recent life events (median, range)	4 (0-10)	3 (0-10)	$Z = -3.90, p < .001$
Burden of recent life events (sum)	7.5 (7.0)	5.6 (5.6)	$Z = -3.40, p = .001$
CTQ-SF (subscale scores)			
Emotional Abuse	10.8 (4.8)	9.3 (4.1)	$Z = -3.45, p < .001$
Physical Abuse	6.6 (3.4)	6.4 (2.6)	$Z = -1.05, p = .302$
Sexual Abuse	6.5 (3.4)	5.7 (2.2)	$Z = -3.04, p = .002$
Emotional Neglect	11.7 (4.4)	11.6 (3.8)	$Z = -0.25, p = .804$
Physical Neglect	7.5 (3.0)	7.5 (2.6)	$Z = 0.01, p = 1$
GAF-Disability (past month)	49.6 (14.7)	47.6 (13.4)	$Z = -1.63, p = .104$
GAF-Symptoms (past month)	46.9 (13.9)	45.9 (14.2)	$Z = -0.83, p = .400$
BDI-II (total score)	25.9 (12.9)	22.1 (12.6)	$Z = -3.21, p = .002$

Abbreviations: BDI: Beck Depression Inventory; CTQ-SF: Childhood Trauma Scale-Short Form; GAF: Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; ROP = Recent-Onset Psychosis

Supplementary Table 3. Comparison of baseline demographic and clinical characteristics of those participants included in longitudinal modeling and those participants excluded due to missing data. Means (SD) unless stated otherwise.

Variable	Included (n = 337)	Excluded (n = 210)	Comparison
Studygroup (% ROP)	50.1	53.8	$\chi^2 = 0.69, p = .412$
Sex (% female)	46.0	50.0	$\chi^2 = 0.83, p = .386$
Age	24.6 (5.6)	24.8 (5.6)	$Z = 0.50, p = .620$
PANSS (subscale scores)			
Positive	15.2 (6.4)	14.6 (6.0)	$Z = -1.10, p = .271$
Negative	15.2 (7.0)	14.4 (7.7)	$Z = -1.24, p = .218$
General	32.8 (9.6)	31.0 (10.4)	$Z = -2.09, p = .038$
Total	63.2 (19.0)	60.0 (20.6)	$Z = -1.86, p = .059$
Number of recent life events (median, range)	3 (0-10)	3 (0-10)	$Z = -1.91, p = .060$
Burden of recent life events (sum)	6.8 (6.4)	5.9 (6.3)	$Z = -1.66, p = .101$
CTQ (subscale scores)			
Emotional Abuse	9.8 (4.3)	10.4 (4.8)	$Z = 1.28, p = .202$
Physical Abuse	6.3 (2.8)	6.8 (2.4)	$Z = 1.51, p = .135$
Sexual Abuse	6.1 (2.8)	6.0 (3.1)	$Z = -0.11, p = .920$
Emotional Neglect	11.4 (4.0)	12.1 (4.3)	$Z = 1.58, p = .115$
Physical Neglect	7.3 (2.7)	8.0 (3.0)	$Z = 2.50, p = .011$
GAF-Disability (past month)	48.7 (14.3)	48.4 (13.7)	$Z = -0.25, p = .804$
GAF-Symptoms (past month)	46.0 (14.0)	47.0 (14.1)	$Z = 0.76, p = .437$
BDI (total score)	23.8 (12.2)	24.3 (14.0)	$Z = 0.42, p = .682$

Abbreviations: BDI: Beck Depression Inventory; CTQ-SF: Childhood Trauma Scale-Short Form; GAF: Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; ROP = Recent-Onset Psychosis

Supplementary Results

Supplementary Results 1. Robustness analyses.

The CS-coefficient indicated high stability for the edge weights of the network in figure 1a (original network without controlling for covariates), as 75% of the sample could be dropped while maintaining a correlation of at least $r = .7$ with the edge weights of the original network model. The corresponding plot is available in supplementary figure 3. Regarding estimates of individual edges, the bootstrapping analysis suggested that all edges present in the original network were also included in the majority of network models built on bootstrapped samples, and that the edge weights were overall estimated with good accuracy (supplementary figure 2). Overall, we found a similar pattern for the network model when additionally including different types of childhood trauma as covariates (figure 1b). CS-coefficient suggested high stability (CS = 0.75, supplementary figure 5). Edges retained in the original covariate network model were present in the majority of bootstrapped networks, and edge weights were overall estimated with good accuracy (supplementary figure 4).

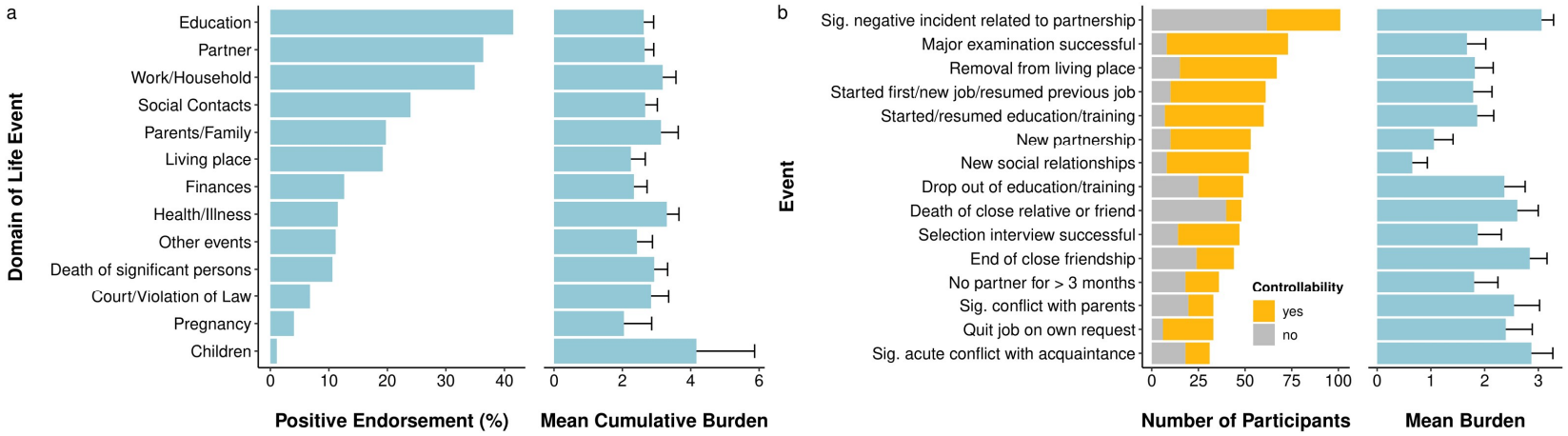
Supplementary Results 2. Comparison of networks estimated in CHR and ROP.

Statistical network comparison based on permutation tests indicated no significant differences in network structure (Test statistic $M = 0.25$, $p = .075$), global strength (Test statistic $S = 1.31$, $p = .157$) nor any individual edge weights (all p's > .210 after controlling the false discovery rate) between networks estimated in CHR and ROP (for a visualization of the networks, supplementary figure 6).

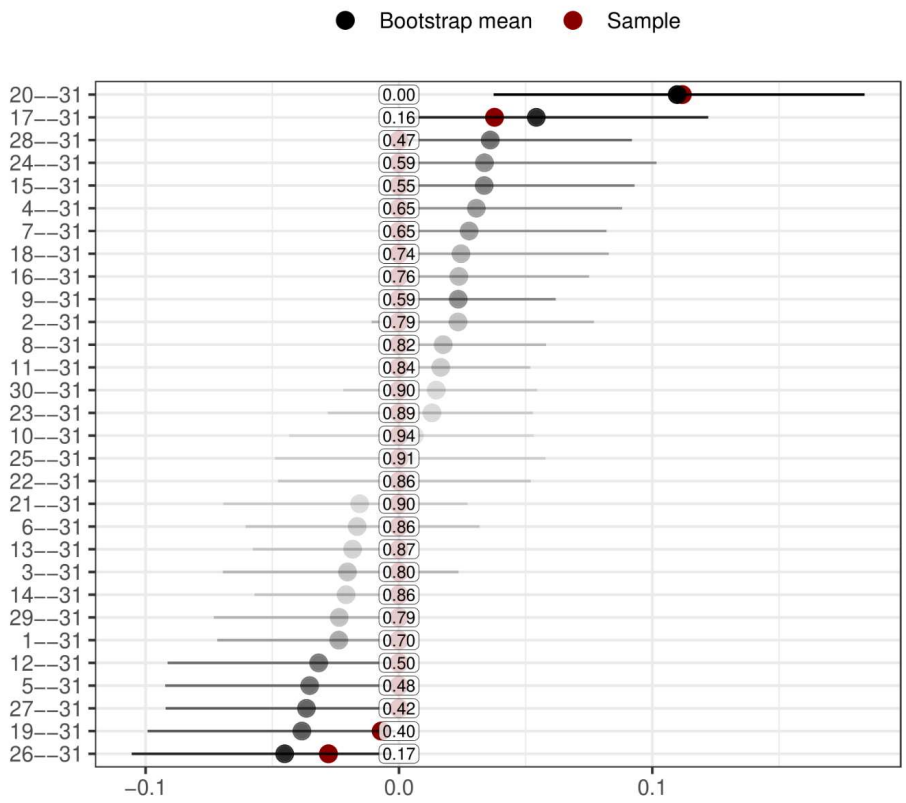
Supplementary Results 3. Comparison of networks estimated in women and men.

Statistical network comparison based on permutation tests indicated no significant differences in network structure (Test statistic $M = 0.20$, $p = .391$), global strength (Test statistic $S = 1.44$, $p = .110$) nor any individual edge weights (all p's > .240 after controlling the false discovery rate) between networks estimated in women and men (for a visualization of the networks, supplementary figure 7).

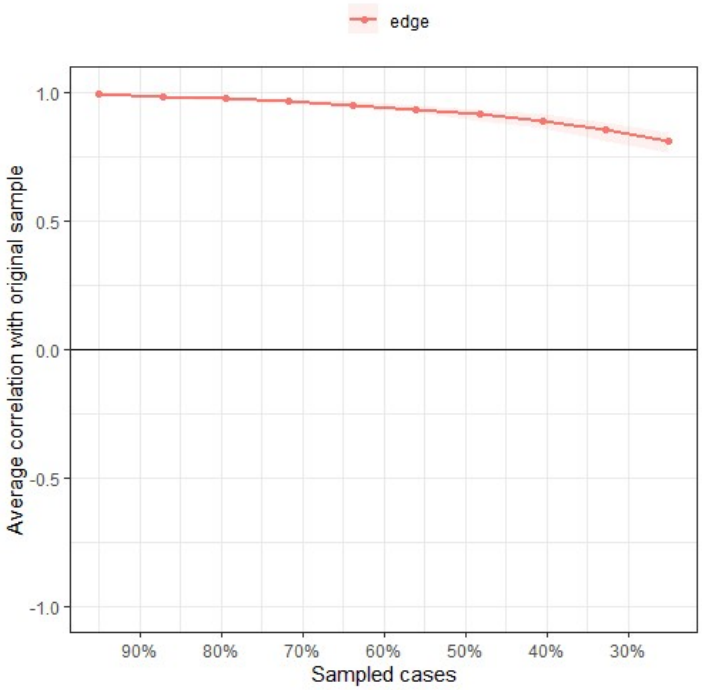
Supplementary Figures



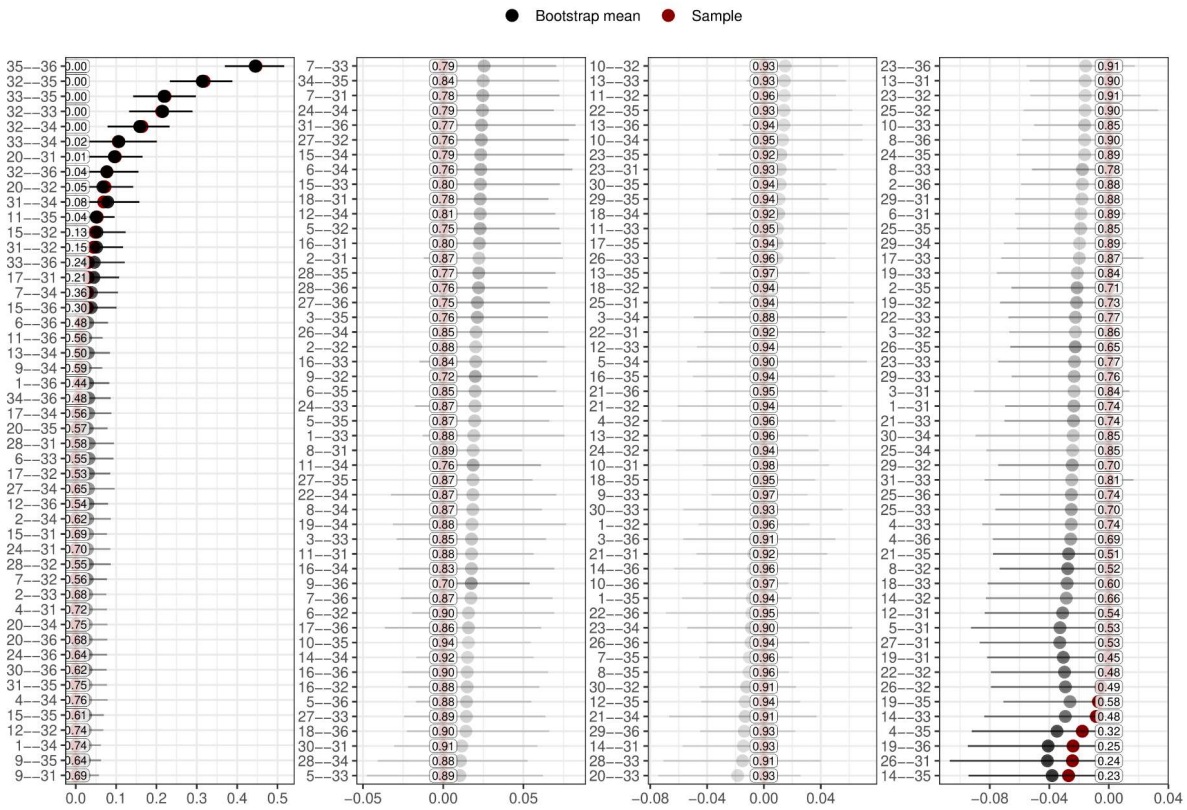
Supplementary Figure 1. Life events in the early psychosis spectrum reported at baseline ($N = 547$). a) Domains of the Cologne Chart of Life Events (CoLE; Ruhrmann, 2013) with rates of positive endorsement and mean cumulative burden. Positive endorsement indicates if a participant reported at least one life event of the respective domain. Mean burden is cumulative as participants could name multiple life events per domain. Life events directly linked to the mental health status of the participants (e.g. hospitalization, start of treatment) were excluded. b) The fifteen most reported individual life events, along with their reported mean burden. Controllability depicts the number of participants that experienced the life event as controllable. Error bars represent the 95% confidence interval.



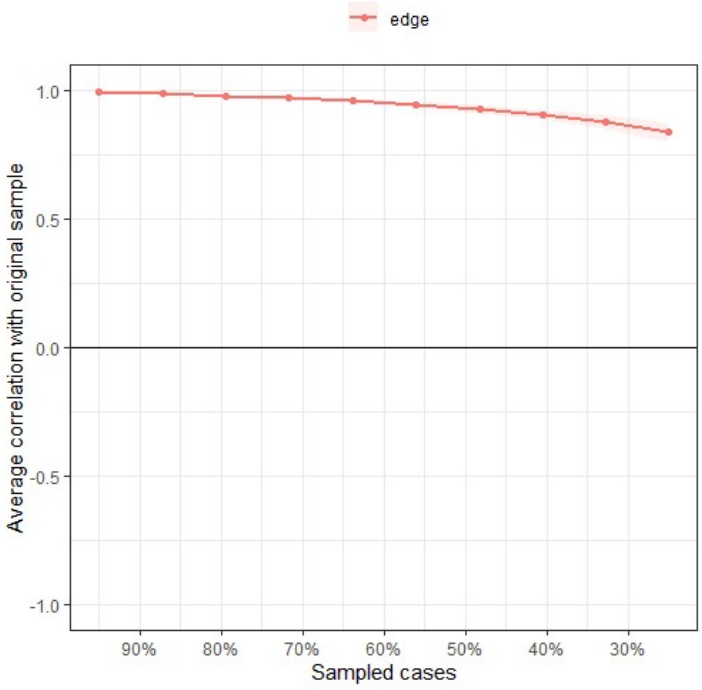
Supplementary Figure 2. Edge values with 95% confidence intervals obtained from bootstrapping in the original sample for the main network model. For readability, we only plot edges related to burden of life events. Confidence intervals are calculated based on those networks in which the edge was included (rather than set to zero). The transparency of the confidence interval reflects how often the edge was included in the networks generated in the bootstrapping procedure. The number in the box gives the proportion of sampled networks in which each edge was set to zero. For the node labels, see figure 1 in the main text.



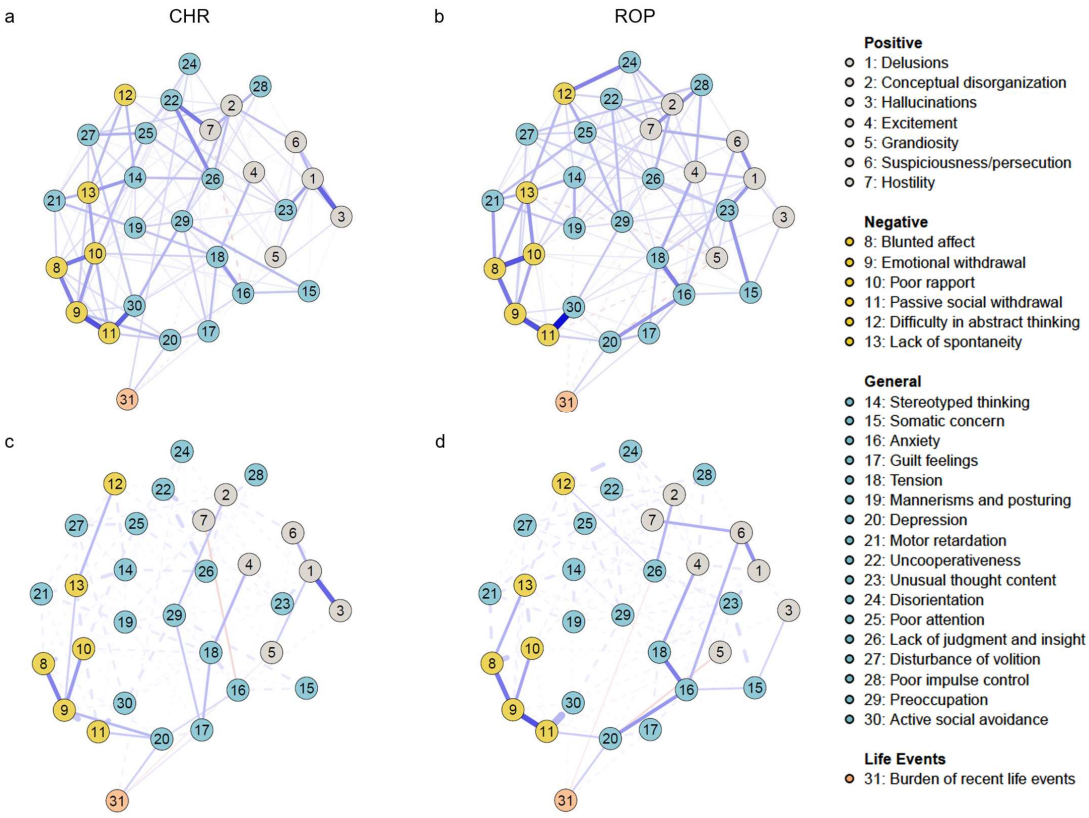
Supplementary Figure 3. Case-dropping bootstrap for the main network model. The x-axis depicts the percentage of cases of the sample used at each step. The y-axis depicts the average of correlations between the edge weights from the original network and the edge weights from networks that were re-estimated after dropping increasing percentages of cases. Lines indicate the means and areas indicate the range from the 2.5th quantile to the 97.5th quantile. The maximum proportion of observations that could be dropped while confidently (95%) retaining results that correlate highly ($r > .7$) with the centrality estimates in the original sample was 75%, indicating high stability (Epskamp et al., 2018).



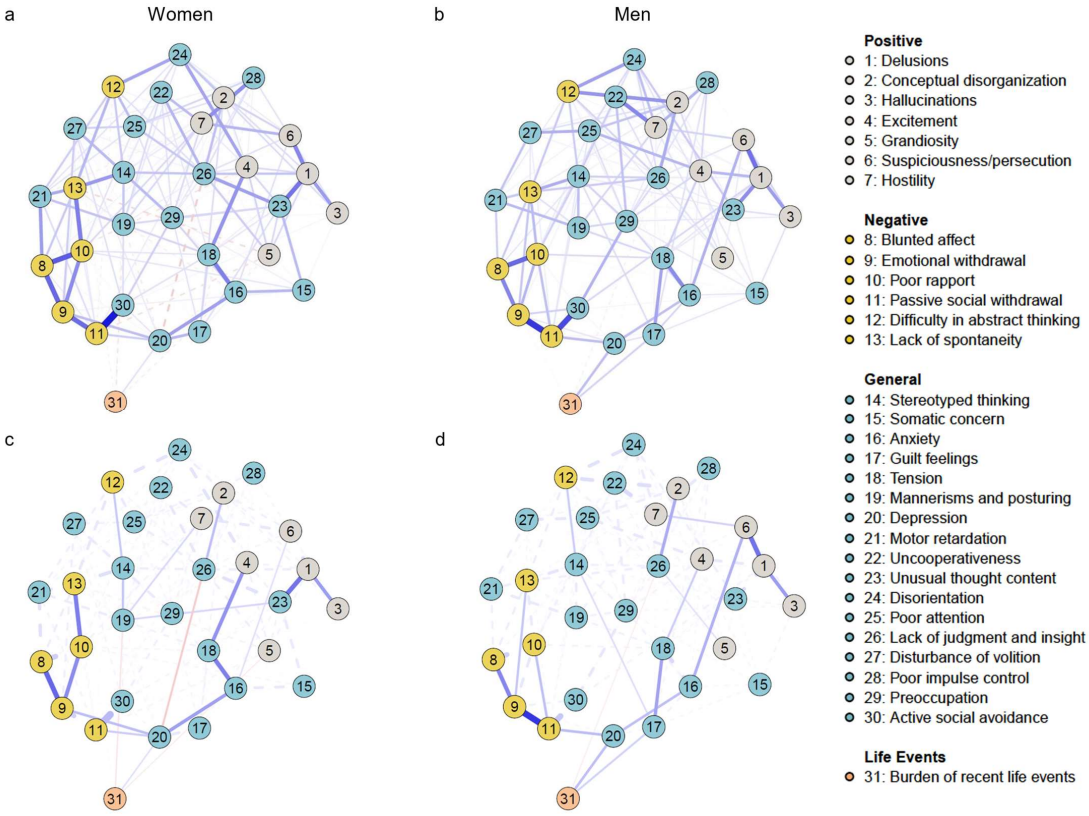
Supplementary Figure 4. Edge values with 95% confidence intervals obtained from bootstrapping for the main network model after inclusion of different childhood trauma types as covariates. For readability, we only plot edges related to life events and the types of childhood trauma. Confidence intervals are calculated based on those networks in which the edge was included (rather than set to zero). The transparency of the confidence interval reflects how often the edge was included in the networks generated in the bootstrapping procedure. The number in the box gives the proportion of sampled networks in which each edge was set to zero. For the node labels, see figure 1 in the main text.



Supplementary Figure 5. Case-dropping bootstrap for the main network model after inclusion of different childhood trauma types as covariates. The x-axis depicts the percentage of cases of the sample used at each step. The y-axis depicts the average of correlations between the edge weights from the original network and the edge weights from networks that were re-estimated after dropping increasing percentages of cases. Lines indicate the means and areas indicate the range from the 2.5th quantile to the 97.5th quantile. The maximum proportion of observations that could be dropped while confidently (95%) retaining results that correlate highly ($r > .7$) with the centrality estimates in the original sample was 75%, indicating high stability (Epskamp et al., 2018).



Supplementary Figure 6. Cross-sectional networks of relationships between burden of recent life events and symptomatology assessed with the Positive and Negative Syndrome Scale (PANSS) estimated separately in Clinical High-Risk (CHR) and Recent Onset Psychosis (ROP) participants. Upper panel: Network depicting unique associations between burden of recent life events and individual symptoms a) in CHR and b) in ROP participants. The wider the edge, the stronger the association. Blue (red) edges reflect positive (negative) connections. Lower panel: Networks highlighting shortest paths (Brandes, 2008) between burden of recent life events and the positive and negative symptom domain of the PANSS c) in CHR and d) in ROP participants. Solid lines represent shortest paths, dashed lines represent connections that do not lie on the shortest paths. The wider the edge, the stronger the association. Blue (red) edges reflect positive (negative) connections.



Supplementary Figure 7. Cross-sectional networks of relationships between burden of recent life events and symptomatology assessed with the Positive and Negative Syndrome Scale (PANSS) estimated separately in women and men. Upper panel: Network depicting unique associations between burden of recent life events and individual symptoms a) in women and b) in men. The wider the edge, the stronger the association. Blue (red) edges reflect positive (negative) connections. Lower panel: Networks highlighting shortest paths (Brandes, 2008) between burden of recent life events and the positive and negative symptom domain of the PANSS c) in women and d) in men. Solid lines represent shortest paths, dashed lines represent connections that do not lie on the shortest paths. The wider the edge, the stronger the association. Blue (red) edges reflect positive (negative) connections.

Supplementary Figure 8. The Cologne Chart of Life Events. The Cologne Chart of Life Events (CoLE; Ruhrman, 2013) was adapted from the Munich Life Event List (Wittchen et al., 1989) and comprises a list with 117 events from 12 domains.

FETZ Chart of Life Events

1. In the last ...[1], did you experience any special event concerning...				2. After collecting life events and their domains, ask following questions:					3. Final question!
A. Education B. Work / Household C. Partner D. Pregnancy E. Children F. Parents / Family G. Social Contacts H. Death I. Home J. Finances K. Court L. Health/Illness M. Other events	Y Y Y Y Y Y Y Y Y Y Y Y Y	N N N N N N N N N N N N N	**Event** (number according to list on next page)	**How many days ago did it start?**	**Course** 1,2,3,... = frequency 8 = continuously 9 = not known	**Experienced as controllable?** Yes / No	**Subjective evaluation** 1 = very positive 2 = positive 3 = neutral 4 = negative 5 = very negative	**Subjective burden** 0 = no burden 1 = slight 2 = moderate 3 = severe 4 = very severe	**Rank order** 1 = most important 2= second most important, 3, 4...

[1] Healthy Controls and Patients: At T0 ask for the last 12 months
Healthy Controls: At T1 and T2 ask for period since the last examination (If T1 examination was skipped ask for the whole period since T0)
Patients: At Follow-up (IV3,6,12,15 and T1/T2) ask for the last 3 months (If the patient did not appear regularly ask for the whole period since the last examination)

PRONIA LIFE EVENTS INSTRUMENT – Coding

A. Education

1. Selection interview successful
2. Selection interview unsuccessful
3. Started/ resumed an education or vocational training
4. Major[2] examination successful
5. Major examination unsuccessful
6. Drop out of education / training
7. Acute significant conflicts with other students
8. Long-standing conflicts with students/teachers (> 3 months)
9. Significant positive change of conditions at place of education / training [3]
10. Significant negative change of conditions at place of education / training (see footnote 2)
11. (1) to (6) happened to a close relative / close friend (if yes, please specify relationship)

B. Work / Household

12. Selection interview successful
13. Selection interview unsuccessful
14. Started first/new job / resumed previous job (after > 6 months)
15. Quit job on own request
16. Dismissed
17. Acute significant conflicts with colleagues/boss
18. Long-standing conflicts with colleagues/boss (> 3 months)
19. Significant positive change of conditions at work[4]
20. Significant negative change of conditions at work (see footnote 3)
21. Significant professional success
22. Significant professional failure
23. unable to work (> 3 months)
24. unemployed (> 3 months)
25. Long-standing overwhelming due to job/household related tasks (> 3 months)
26. Military / voluntary service started/resumed/finished
27. Early retirement
28. Any significant events according to the list above happening to a close relative / close friend (if yes, please specify relationship)

If not the principle earner:

29. Significant professional success of principal earner
30. Significant professional failure of principal earner
31. Unemployment / other reasons for diminished income[5] of principal earner

C. Partner

32. New partnership (> 3 months)
33. First sexual intercourse
34. Significant negative incident related to partnership[6], including failure to establish new partnership with a person known for > 3 months
35. Significant positive incident (including marriage, decision to cohabit)
36. Significant long-standing conflict with partner (> 3 months)
37. No partner for > 3 months
38. Any significant positive event happening to partner
39. Any significant negative event happening to partner

D. Pregnancy

40. Infertility
41. Pregnancy
42. Pre/postnatal complications
43. Miscarriage
44. Termination of pregnancy
45. Birth
46. Stillbirth
47. Sterilization
48. Any of the events above happened to partner
49. Any of the events above happened to close relative /close friend

E. Children

50. Moving out / in again
51. Any negative acute change in relationship to children
52. Any longstanding conflict with children with impact on relationship (> 3 months)
53. Any significant physical or mental health problems of children[7]
54. Conflict with law / becoming criminal
55. Acute adverse events (e.g. victim of significant violence)

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[2] major: examination has special meaning for training, i.e. required to proceed or final exams

[3] e.g. change of school or class

[4] e.g. significant impact change of usual working conditions, i.e. procedures or tasks

[5] e.g. unable to work due to illness

[6] Separation, divorce, adultery of partner/respondent, significant crisis due to other reasons

[7] [experienced as] life threatening, leading to disability, hospitalization, drug abuse etc.

56. Long-standing adverse events (e.g. bullying)
57. Marriage Separation/Divorce

F. Parents / Family

58. Moving out of parent's home
59. Moving back to parents (< 6 months after leaving)
60. Significant conflict with parents
61. Significant conflict with close relatives living in the same household
62. Significant conflict with close relatives living outside household
63. Significant long-standing conflict with parents
64. Significant long-standing conflict with close relatives living in the same household
65. Significant long-standing conflict with close relatives living outside household
66. Significant conflict of parents
67. Separation / divorce of parents

G. Social Contacts

68. New social relationships (> 3 months, not partnership)
69. End of close friendship
70. Significant acute conflict with acquaintance
71. Long-standing conflict with acquaintance
72. Loneliness (> 3 months)

H. Death of personally significant persons

73. Partner
74. Child
75. Parent
76. Close relative or close friend
77. Other personally significant person

I. Living place

78. Removal
79. Building house
80. Major refurbishment / conversion
81. Moving to a favorable neighborhood (save, good relationships)
82. Moving to an adverse neighborhood (dangerous, violent, criminality)
83. Significant acute conflict with neighbors
84. Significant long-standing conflict with neighbors (> 3 months)
85. Contract was terminated by owner
86. Becoming homeless
87. Any significant events according to the list above happening to a close relative / close friend (if yes, please specify relationship)

J. Finances

88. Significant financial problems
89. Significant improvement of financial conditions
90. Significant worsening of financial conditions
91. Any significant events according to the list above happening to a close relative / close friend (if yes, please specify relationship)

K. Court/Violation of Law

92. Criminal offense against person
93. Criminal offense against person's properties
94. Committed crime
95. Prosecuted
96. Contact to police (as a suspect)
97. Detention
98. Imprisoned / brought to corresponding institution (not hospital)
99. Fine or corresponding penalty (not prison or corresponding institution)
100. Any significant events according to the list above happening to a close relative / close friend (if yes, please specify relationship)

L. Health/Illness

101. Accident with personal damage
102. Hospitalization (incl. day time clinic)
103. Surgery
104. Significant somatic illness (requiring continuous treatment or disabling)
105. Significant mental Illness (requiring continuous treatment or disabling)
106. Suicide attempt
107. Discharge from hospital / day time clinic
108. Starting pharmacological treatment
109. Starting psychological consultation / treatment
110. Any significant events according to the list above happening to a close relative / close friend (if yes, please specify relationship)

M. Other events

111. Accident (no personal damage)
112. Disaster victim (fire, hurricane etc.)
113. Unwanted reduction / cessation of personally significant leisure time activities (sports, music, travelling etc.)
114. Getting reminded of traumatic events
115. Getting a pet
116. Losing a pet (if significant relationship)
117. Any significant events according to the list above happening to a close relative / close friend (if yes, please specify relationship)

Supplementary References

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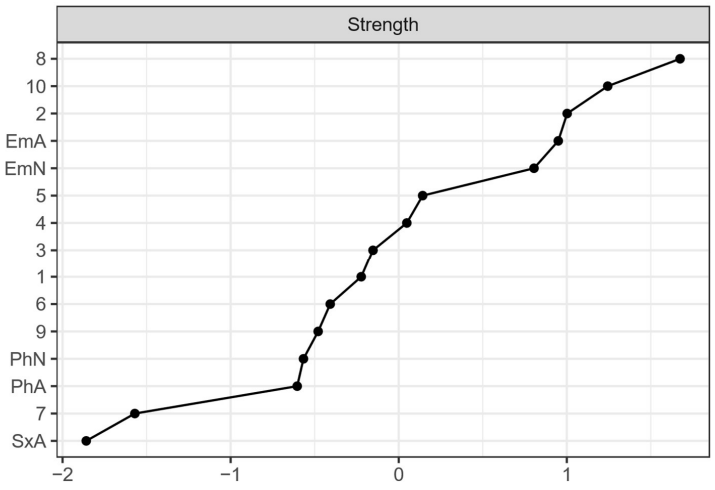
Wittchen, H. U., Essau, C. A., Hecht, H., Teder, W., & Pfister, H. (1989). Reliability of life event assessments: test-retest reliability and fall-off effects of the Munich Interview for the Assessment of Life Events and Conditions. *Journal of Affective Disorders, 16*(1), 77–91. https://doi.org/10.1016/0165-0327(89)90059-1

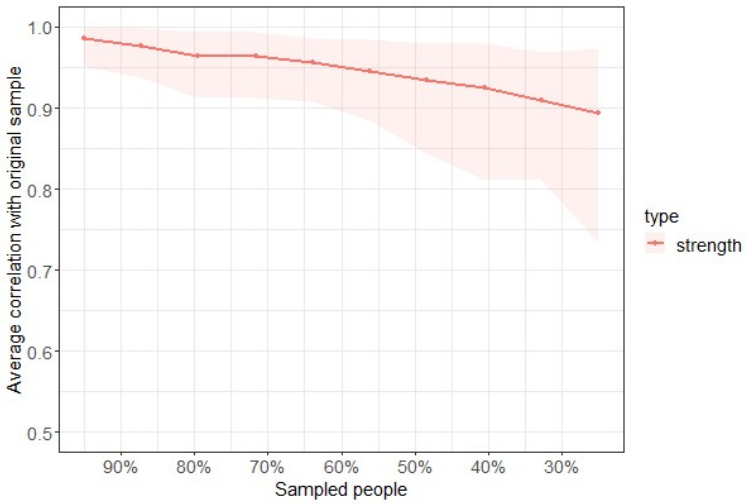
6.2 Supplementary material for "Relationships between childhood trauma and perceived stress in the general population: a network perspective"

Supplementary Figure 1. Centrality plot depicting z-standardized strength centrality indices of the network generated based on the original sample.
Supplementary Figure 2. Stability of centrality indices by case dropping subset bootstrap in the original sample.
Supplementary Figure 3. Stability of edge weights by case dropping subset bootstrap in the original sample.
Supplementary Figure 4. Edge values with confidence intervals obtained from bootstrapping in the original sample.
Supplementary Figure 5. Centrality plot depicting z-standardized strength centrality indices of the network generated based on the replication sample.
Supplementary Figure 6. Stability of centrality indices by case dropping subset bootstrap in the replication sample.
Supplementary Figure 7. Stability of edge weights by case dropping subset bootstrap in the replication sample.
Supplementary Figure 8. Edge values with confidence intervals obtained from bootstrapping in the replication sample.
Supplementary Figure 9. Comparison of networks generated in a) the original sample (MIDUS Biomarker Project, n = 1252), b) the replication sample (MIDUS Refresher Biomarker Project, n = 862) and c) the combined sample (n = 2114).
Supplementary Table 1. Weighted adjacency matrix for the network model generated based on the original data set.
Supplementary Table 2. Weighted adjacency matrix for the network model generated based on the replication data set.
Supplementary Table 3. Weighted adjacency matrix for the network model generated based on the combined data set.
Supplementary Table 4. Weighted adjacency matrix for the network model generated based on data of the male participants from the combined sample.
Supplementary Table 5. Weighted adjacency matrix for the network model generated based on data of the female participants from the combined sample.

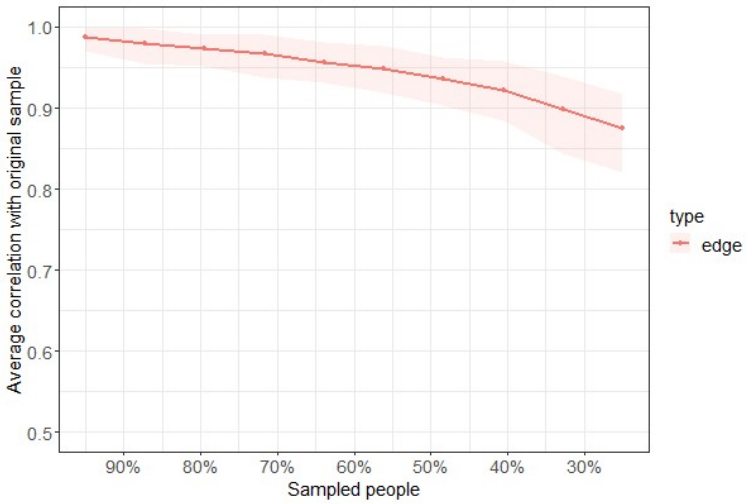
Supplementary Figures



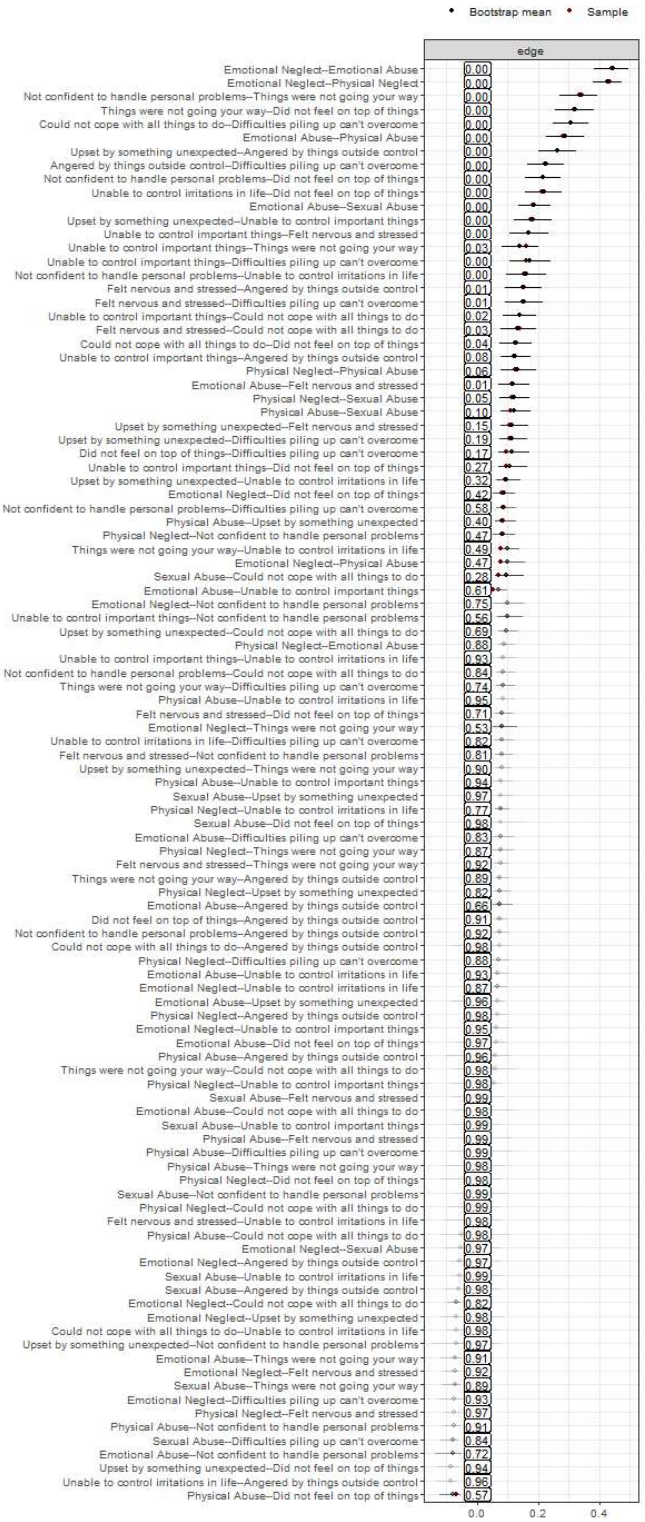
Supplementary Figure 1. Centrality plot depicting z-standardized strength centrality indices of the network generated based on the original sample. Labels: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.



Supplementary Figure 2. Stability of centrality indices obtained by case-dropping subset bootstrap in the original sample (Costenbader & Valente, 2003). The x-axis depicts the percentage of cases of the original sample used at each step. The y-axis depicts the average of correlations between the strength centrality values from the original network and the strength centrality values from networks that were re-estimated after dropping increasing percentages of cases. The maximum proportion of observations that could be dropped while confidently (95%) retaining results that correlate highly ($r > .7$) with the strength centrality estimates in the original sample was 75%, indicating high stability.

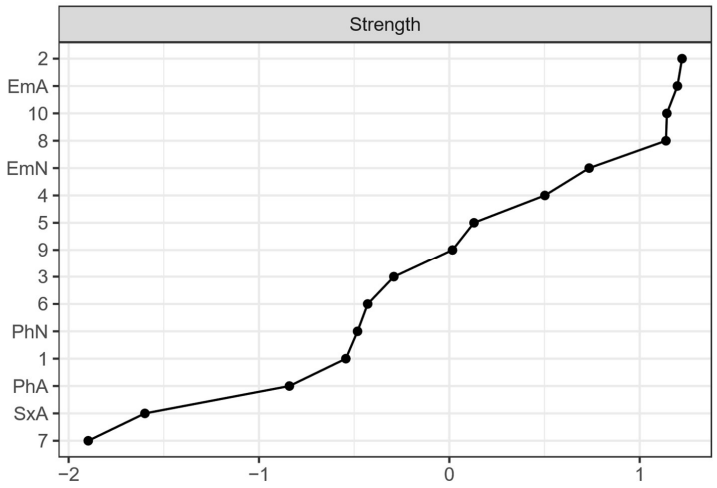


Supplementary Figure 3. Stability of edge weights obtained by case-dropping subset bootstrap in the original sample (Costenbader & Valente, 2003). The x-axis depicts the percentage of cases of the original sample used at each step. The y-axis depicts the average of correlations between the edge weights from the original network and the edge weights from networks that were re-estimated after dropping increasing percentages of cases. The maximum proportion of observations that could be dropped while confidently (95%) retaining results that correlate highly ($r > .7$) with the centrality estimates in the original sample was 75%, indicating high stability.

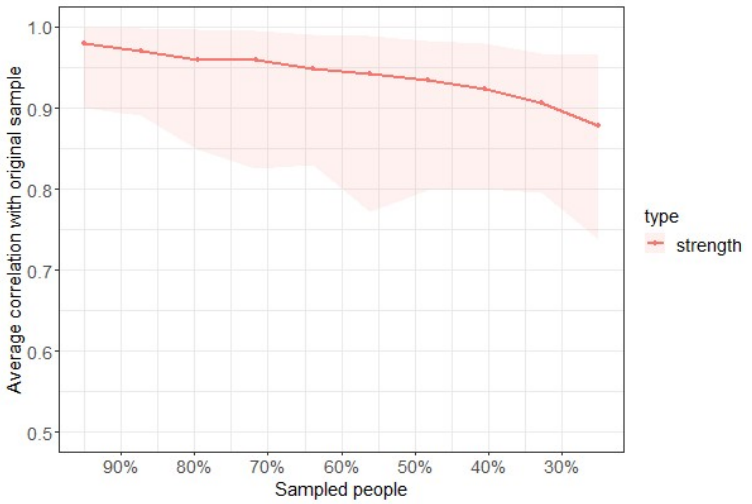


Supplementary Figure 4. Edge values with 95% confidence intervals obtained from bootstrapping in the original sample. Confidence intervals are calculated based on those networks in which the edge was included

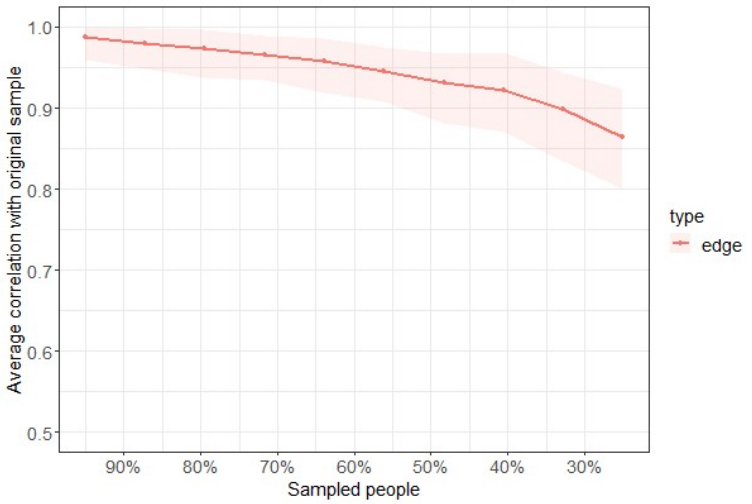
(rather than set to zero). The transparency of the confidence interval reflects how often the edge was included in the networks generated in the bootstrapping procedure. The number in the box gives the proportion of sampled networks in which each edge was not included (i.e., set to zero).



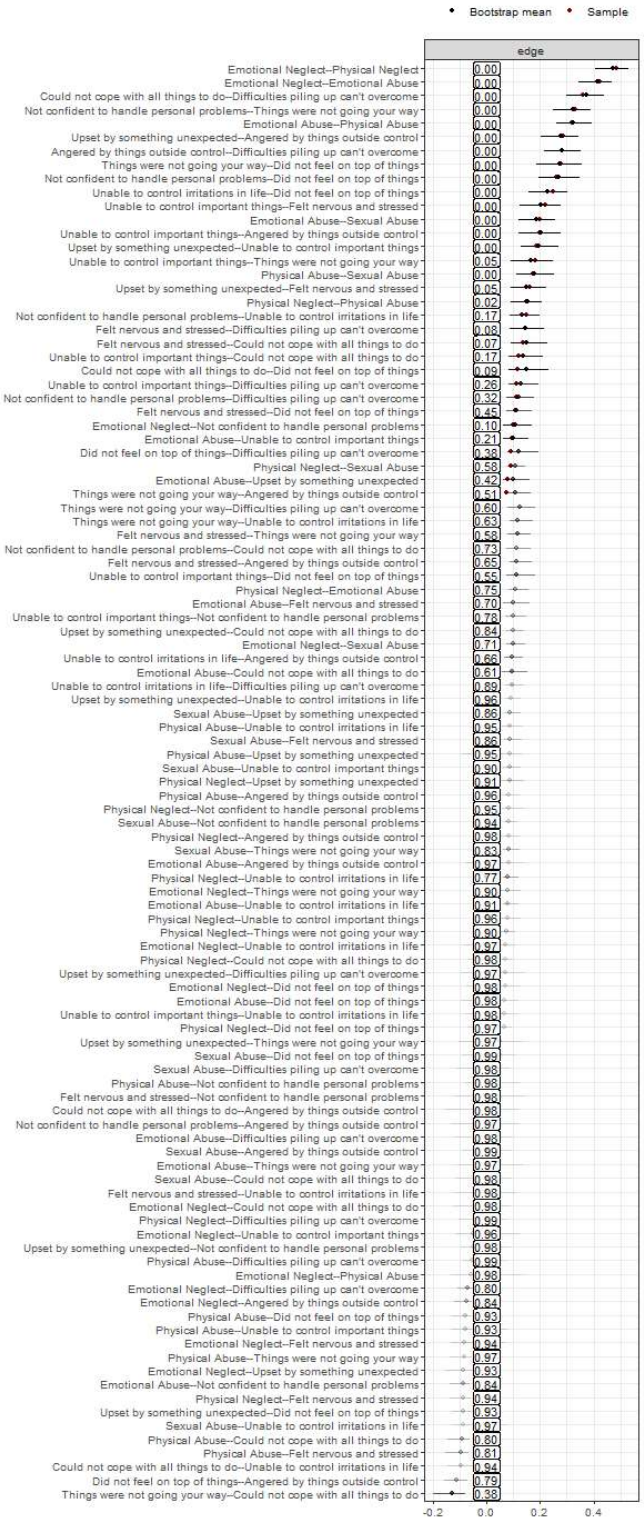
Supplementary Figure 5. Centrality plot depicting z-standardized strength centrality indices of the network generated based on the replication sample. *Labels*: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.



Supplementary Figure 6. Stability of centrality indices obtained by case-dropping subset bootstrap in the replication sample (Costenbader & Valente, 2003). The x-axis depicts the percentage of cases of the replication sample used at each step. The y-axis depicts the average of correlations between the strength centrality values from the original network and the strength centrality values from networks that were re-estimated after dropping increasing percentages of cases. The maximum proportion of observations that could be dropped while confidently (95%) retaining results that correlate highly ($r > .7$) with the strength centrality estimates in the original sample was 75%, indicating high stability.

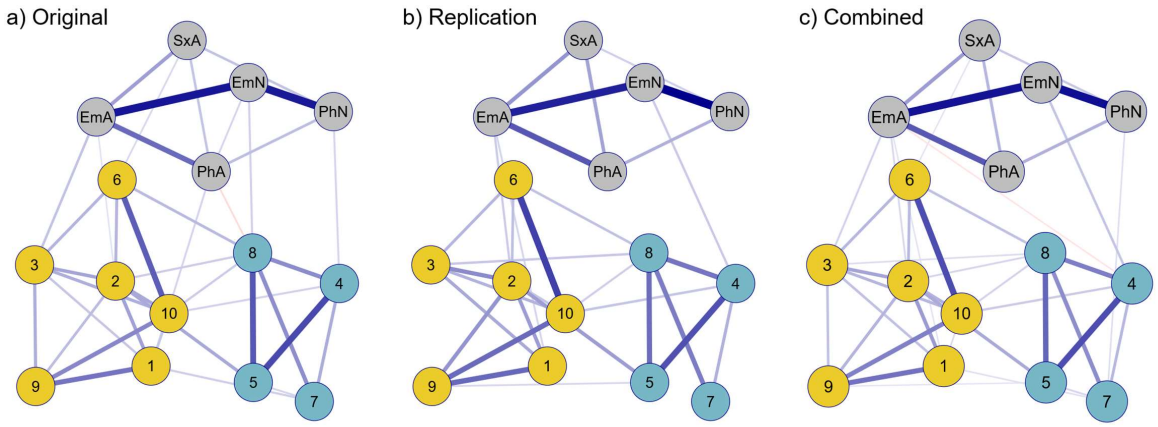


Supplementary Figure 7. Stability of edge weights obtained by case-dropping subset bootstrap in the replication sample (Costenbader & Valente, 2003). The x-axis depicts the percentage of cases of the replication sample used at each step. The y-axis depicts the average of correlations between the edge weights from the original network and the edge weights from networks that were re-estimated after dropping increasing percentages of cases. The maximum proportion of observations that could be dropped while confidently (95%) retaining results that correlate highly ($r > .7$) with the centrality estimates in the original sample was 75%, indicating high stability.



Supplementary Figure 8. Edge values with 95% confidence intervals obtained from bootstrapping in the replication sample. Confidence intervals are calculated based on those networks in which the edge was

included (rather than set to zero). The transparency of the confidence interval reflects how often the edge was included in the networks generated in the bootstrapping procedure. The number in the box gives the proportion of sampled networks in which each edge was not included (i.e., set to zero).



Supplementary Figure 9. Comparison of networks generated in a) the original sample (MIDUS Biomarker Project, n = 1252), b) the replication sample (MIDUS Refresher Biomarker Project, n = 862) and c) the combined sample (n = 2114). Blue coloring of edges indicates positive relationships, and red coloring indicates negative relationships. The thicker the edge, the stronger the association between two variables. Node coloring represents the three communities detected with the walktrap algorithm (Pons & Latapy, 2005). The blue-colored community represents "perceived self-efficacy" and the yellow-colored community represents "perceived helplessness" (Roberti, Harrington, & Storch, 2006). We plotted all three networks with the force-directed layout of the original network, generated by the Fruchterman-Reingold algorithm (Fruchterman & Reingold, 1991). To facilitate comparison, minimum and maximum of edge weights were scaled identically across networks. *Labels*: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.

Supplementary Tables

Supplementary Table 1. Weighted adjacency matrix for the network model generated based on the original data set.

	EmN	PhN	EmA	PhA	SxA	1	2	3	4	5	6	7	8	9	10
EmN	0	0.43	0.44	0.08	0	0	0	0	0	0	0	0	0.09	0	0
PhN	0.43	0	0	0.12	0.11	0	0	0	0.08	0	0	0	0	0	0
EmA	0.44	0	0	0.28	0.18	0	0.05	0.11	0	0	0	0	0	0	0
PhA	0.08	0.12	0.28	0	0.11	0.08	0	0	0	0	0	0	-0.07	0	0
SxA	0	0.11	0.18	0.11	0	0	0	0	0	0	0.07	0	0	0	0
1	0	0	0	0.08	0	0	0.18	0.11	0	0	0	0.09	0	0.26	0.10
2	0	0	0.05	0	0	0.18	0	0.17	0	0.16	0.14	0	0.09	0.12	0.16
3	0	0	0.11	0	0	0.11	0.17	0	0	0	0.14	0	0	0.15	0.15
4	0	0.08	0	0	0	0	0	0	0	0.34	0	0.16	0.22	0	0.09
5	0	0	0	0	0	0	0.16	0	0.34	0	0	0.08	0.32	0	0
6	0	0	0	0	0.07	0	0.14	0.14	0	0	0	0	0.13	0	0.30
7	0	0	0	0	0	0.09	0	0	0.16	0.08	0	0	0.21	0	0
8	0.09	0	0	-0.07	0	0	0.09	0	0.22	0.32	0.13	0.21	0	0	0.10
9	0	0	0	0	0	0.26	0.12	0.15	0	0	0	0	0	0	0.23
10	0	0	0	0	0	0.10	0.16	0.15	0.09	0	0.30	0	0.10	0.23	0

Abbreviations: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.

Supplementary Table 2. Weighted adjacency matrix for the network model generated based on the replication data set.

	EmN	PhN	EmA	PhA	SxA	1	2	3	4	5	6	7	8	9	10
EmN	0	0.48	0.42	0	0	0	0	0	0.10	0	0	0	0	0	0
PhN	0.48	0	0	0.15	0.09	0	0	0	0	0	0	0	0	0	0
EmA	0.42	0	0	0.32	0.20	0.08	0.10	0	0	0	0	0	0	0	0
PhA	0	0.15	0.32	0	0.17	0	0	0	0	0	0	0	0	0	0
SxA	0	0.09	0.20	0.17	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0.08	0	0	0	0.19	0.16	0	0	0	0	0	0.28	0
2	0	0	0.10	0	0	0.19	0	0.22	0	0.18	0.12	0	0	0.20	0.11
3	0	0	0	0	0	0.16	0.22	0	0	0	0.14	0	0.11	0	0.14
4	0.10	0	0	0	0	0	0	0	0	0.33	0	0.15	0.26	0	0.11
5	0	0	0	0	0	0	0.18	0	0.33	0	0	0	0.28	0.07	0
6	0	0	0	0	0	0	0.12	0.14	0	0	0	0	0.12	0	0.36
7	0	0	0	0	0	0	0	0	0.15	0	0	0	0.25	0	0
8	0	0	0	0	0	0	0	0.11	0.26	0.28	0.12	0.25	0	0	0.09
9	0	0	0	0	0	0.28	0.20	0	0	0.07	0	0	0	0	0.28
10	0	0	0	0	0	0	0.11	0.14	0.11	0	0.36	0	0.09	0.28	0

Abbreviations: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.

Supplementary Table 3. Weighted adjacency matrix for the network model generated based on the combined data set.

	EmN	PhN	EmA	PhA	SxA	1	2	3	4	5	6	7	8	9	10
EmN	0	0.46	0.45	0	0	0	0	0	0.11	0	0	0	0	0	0
PhN	0.46	0	0	0.15	0.10	0	0	0	0	0	0	0.06	0	0	0
EmA	0.45	0	0	0.31	0.19	0.05	0.07	0.08	-0.05	0	0	0	0	0	0
PhA	0	0.15	0.31	0	0.14	0	0	0	0	0	0	0	0	0	0
SxA	0	0.10	0.19	0.14	0	0	0	0	0	0	0.05	0	0	0	0
1	0	0	0.05	0	0	0	0.19	0.12	0	0	0	0.06	0	0.27	0.07
2	0	0	0.07	0	0	0.19	0	0.17	0	0.16	0.13	0	0.08	0.14	0.15
3	0	0	0.08	0	0	0.12	0.17	0	0	0	0.13	0	0.07	0.12	0.14
4	0.11	0	-0.05	0	0	0	0	0	0	0.33	0	0.13	0.24	0	0.10
5	0	0	0	0	0	0	0.16	0	0.33	0	0	0.08	0.29	0.05	0
6	0	0	0	0	0.05	0	0.13	0.13	0	0	0	0	0.12	0	0.33
7	0	0.06	0	0	0	0.06	0	0	0.13	0.08	0	0	0.21	0	0
8	0	0	0	0	0	0	0.08	0.07	0.24	0.29	0.12	0.21	0	0	0.08
9	0	0	0	0	0	0.27	0.14	0.12	0	0.05	0	0	0	0	0.24
10	0	0	0	0	0	0.07	0.15	0.14	0.10	0	0.33	0	0.08	0.24	0

Abbreviations: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.

Supplementary Table 4. Weighted adjacency matrix for the network model generated based on data of the male participants from the combined sample.

	EmN	PhN	EmA	PhA	SxA	1	2	3	4	5	6	7	8	9	10
EmN	0	0.45	0.40	0	0	0	0	0	0	0	0	0.06	0.07	0	0
PhN	0.45	0	0	0.12	0.10	0	0	0	0	0.07	0	0	0	0	0
EmA	0.40	0	0	0.35	0.11	0	0.09	0.07	0	0	0	0	0	0	0
PhA	0	0.12	0.35	0	0.1	0	0	0	0	0	0	0	0	0	0
SxA	0	0.10	0.11	0.10	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0.15	0.12	0	0	0	0	0	0.31	0.08
2	0	0	0.09	0	0	0.15	0	0.17	0	0.15	0.14	0	0.10	0.15	0.16
3	0	0	0.07	0	0	0.12	0.17	0	0	0	0.09	0	0	0.16	0.15
4	0	0	0	0	0	0	0	0	0	0.31	0	0.16	0.30	0	0.08
5	0	0.07	0	0	0	0	0.15	0	0.31	0	0	0	0.30	0	0
6	0	0	0	0	0	0	0.14	0.09	0	0	0	0	0.11	0	0.34
7	0.06	0	0	0	0	0	0	0	0.16	0	0	0	0.21	0	0
8	0.07	0	0	0	0	0	0.10	0	0.30	0.30	0.11	0.21	0	0	0.13
9	0	0	0	0	0	0.31	0.15	0.16	0	0	0	0	0	0	0.21
10	0	0	0	0	0	0.08	0.16	0.15	0.08	0	0.34	0	0.13	0.21	0

Abbreviations: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.

Supplementary Table 5. Weighted adjacency matrix for the network model generated based on data of the female participants from the combined sample.

	EmN	PhN	EmA	PhA	SxA	1	2	3	4	5	6	7	8	9	10
EmN	0	0.45	0.48	0	0	0	0	0	0.08	0	0	0	0	0	0
PhN	0.45	0	0	0.15	0.12	0	0	0	0	0	0	0	0	0	0
EmA	0.48	0	0	0.30	0.19	0.07	0.05	0.08	0	0	0	0	0	0	0
PhA	0	0.15	0.30	0	0.20	0	0	0	0	0	0	0	0	0	0
SxA	0	0.12	0.19	0.20	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0.07	0	0	0	0.24	0.11	0	0	0.08	0	0	0.25	0
2	0	0	0.05	0	0	0.24	0	0.17	0	0.21	0.11	0	0	0.16	0.14
3	0	0	0.08	0	0	0.11	0.17	0	0	0	0.12	0	0.14	0.09	0.14
4	0.08	0	0	0	0	0	0	0	0	0.36	0	0.13	0.2	0	0.12
5	0	0	0	0	0	0	0.21	0	0.36	0	0	0.08	0.31	0	0
6	0	0	0	0	0	0.08	0.11	0.12	0	0	0	0	0.15	0	0.32
7	0	0	0	0	0	0	0	0	0.13	0.08	0	0	0.24	0	0.08
8	0	0	0	0	0	0	0	0.14	0.20	0.31	0.15	0.24	0	0	0
9	0	0	0	0	0	0.25	0.16	0.09	0	0	0	0	0	0	0.29
10	0	0	0	0	0	0	0.14	0.14	0.12	0	0.32	0.08	0	0.29	0

Abbreviations: EmN = Emotional Neglect; PhN = Physical Neglect; EmA = Emotional Abuse; PhA = Physical Abuse; SxA = Sexual Abuse; 1 = Upset by something unexpected; 2 = Unable to control important things; 3 = Felt nervous and stressed; 4 = Not confident to handle personal problems; 5 = Things were not going your way; 6 = Could not cope with all things to do; 7 = Unable to control irritations in life, 8 = Did not feel on top of things; 9 = Angered by things outside control; 10 = Difficulties piling up can't overcome.

Supplementary References

Costenbader, E., & Valente, T. W. (2003). The stability of centrality measures when networks are sampled. *Social Networks*, *25*(4), 283–307. https://doi.org/10.1016/S0378-8733(03)00012-1

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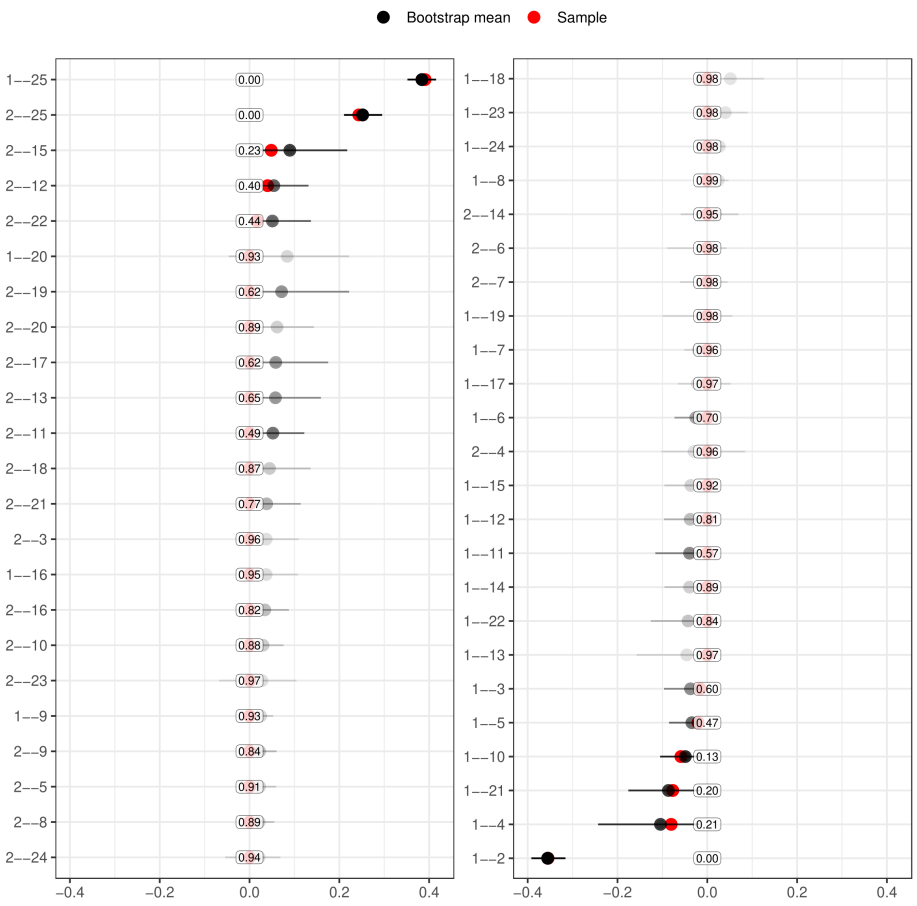
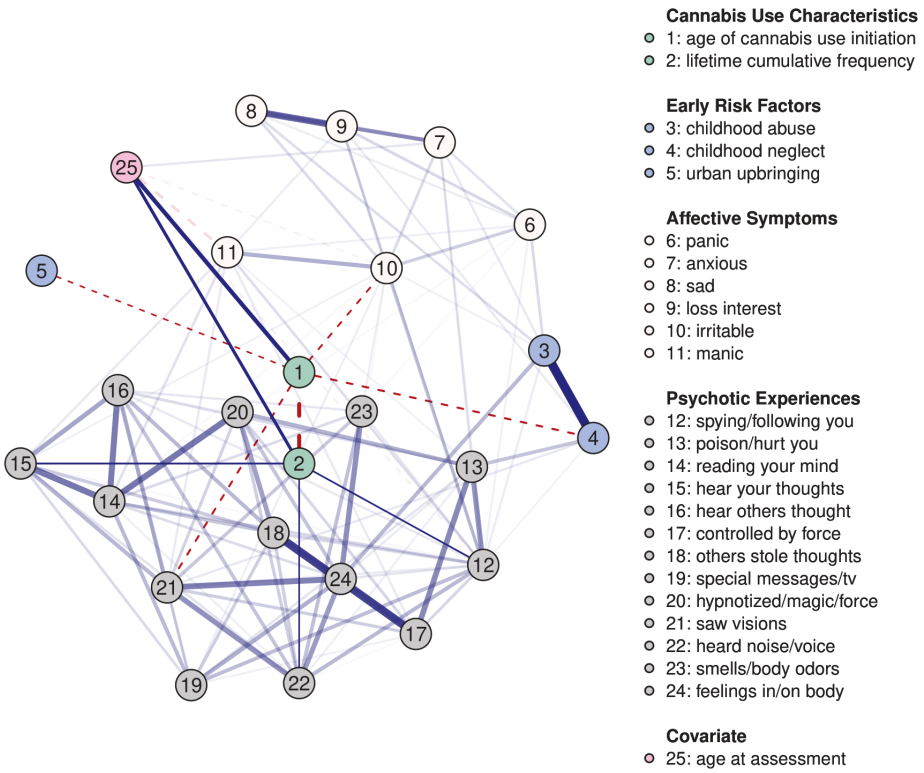
6.3 Supplementary material for "A network approach to relationships between cannabis use characteristics and psychopathology in the general population"

Supplementary Figure 1. Values of edges related to cannabis use characteristics (age of cannabis use initiation, lifetime cumulative frequency of cannabis use) with 95% confidence intervals obtained from bootstrapping.
Supplementary Figure 2. Network of cannabis use characteristics (age of cannabis use initiation, lifetime cumulative frequency of cannabis use), early risk factors, psychotic experiences, and affective symptoms (N = 2,544), including only edges which were present in at least 50% of the models generated based on non-parametric bootstrapped samples.
Supplementary Figure 3. Stability of edge weights obtained by case-dropping subset bootstrap.
Supplementary Figure 4. Network of cannabis use characteristics (age of cannabis use initiation, lifetime cumulative frequency of cannabis use), early risk factors, psychotic experiences, and affective symptoms (N = 2,544) across a range of reasonable values for gamma (0, 0.05, ... 0.25).
Supplementary Table 1. Summary statistics for network variables along with relevant identifiers and corresponding node numbers plotted in the network.

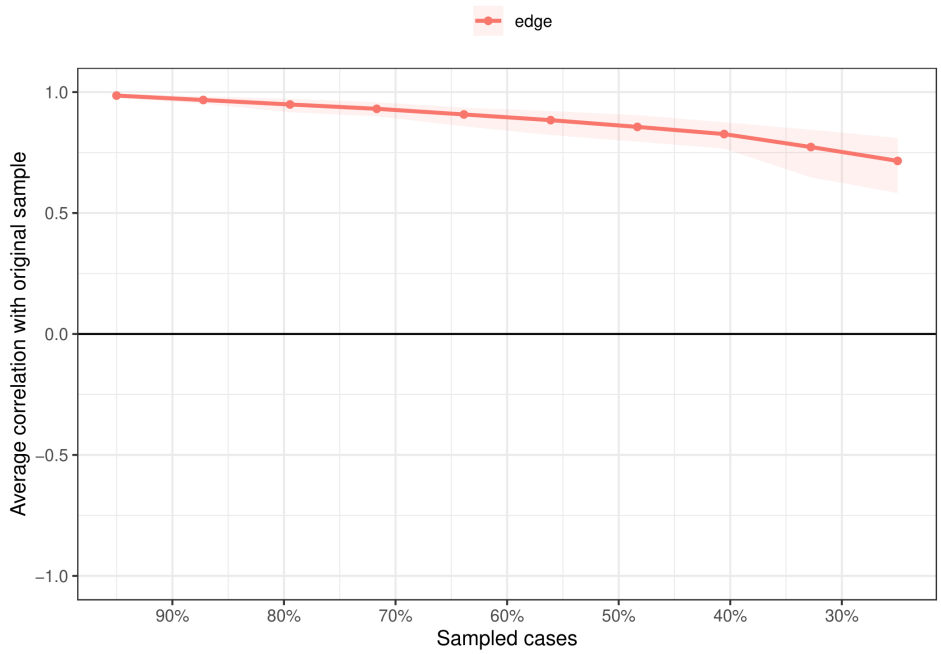
Supplementary Figures



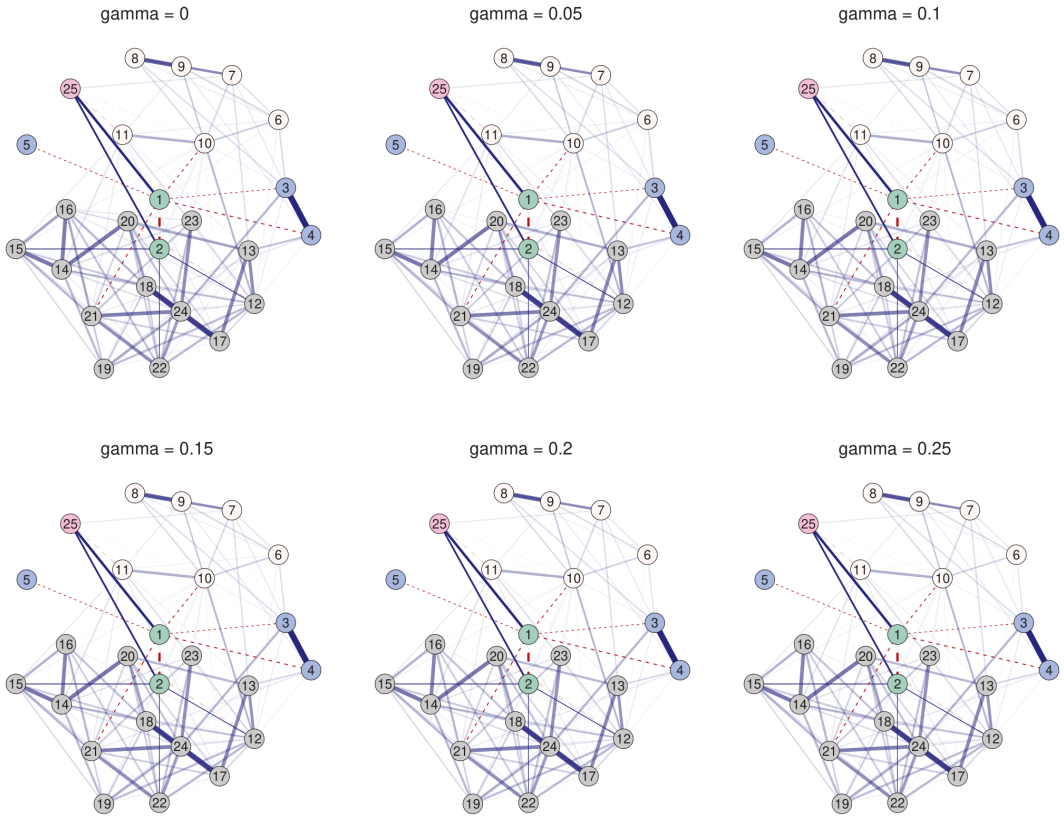
Supplementary Figure 1. Values of edges related to cannabis use characteristics (age of cannabis use initiation, lifetime cumulative frequency of cannabis use) with 95% confidence intervals obtained from bootstrapping. Confidence intervals are calculated based on those networks in which the edge was included (rather than set to zero). The transparency of the confidence interval reflects how often the edge was included in the networks generated in the bootstrapping procedure. The number in the box gives the proportion of sampled networks in which each edge was not included (i.e., set to zero). *Node labels*: 1 = age of cannabis use initiation, 2 = lifetime cumulative frequency of cannabis use, 3 = childhood abuse, 4 = childhood neglect, 5 = urban upbringing, 6 = panic, 7 = anxious, 8 = sad, 9 = loss interest, 10 = irritable, 11 = manic, 12 = spying/following you, 13 = poison/hurt you, 14 = reading your mind, 15 = hear your thoughts, 16 = hear others thought, 17 = controlled by force, 18 = others stole thoughts, 19 = special messages/tv, 20 = hypnotized/magic/force, 21 = saw visions, 22 = heard noise/voice, 23 = smells/body odors, 24 = feelings in/on body, 25 = age at assessment.



Supplementary Figure 2. Network of cannabis use characteristics (age of cannabis use initiation, lifetime cumulative frequency of cannabis use), early risk factors, psychotic experiences, and affective symptoms (N = 2,544), including only edges which were present in at least 50% of the models generated based on non-parametric bootstrapped samples. Solid blue (dashed red) lines represent positive (negative) associations between variables and wider, more saturated edges indicate stronger associations. Given that the focus of the paper is to investigate the relations between the cannabis use characteristics and aspects of psychopathology, the edges connecting to the two relevant variables (age of cannabis use initiation, lifetime cumulative frequency of cannabis use) have been manually un-faded, i.e., we set these edges deliberately opaque, while the edges between the other nodes in the network retain transparency. Variable groups are differentiated by color.



Supplementary Figure 3. Stability of edge weights obtained by case-dropping subset bootstrap (Costenbader & Valente, 2003). The x-axis depicts the percentage of cases of the sample used at each step. The y-axis depicts the average of correlations between the edge weights from the original network and the edge weights from networks that were re-estimated after dropping increasing percentages of cases. The maximum proportion of observations that could be dropped while confidently (95%) retaining results that correlate highly ($r > .7$) with the edge weight estimates in the original sample was 59.5%, indicating high stability (Epskamp et al., 2018).



Supplementary Figure 4. Network of cannabis use characteristics (age of cannabis use initiation, lifetime cumulative frequency of cannabis use), early risk factors, psychotic experiences, and affective symptoms (N = 2,544) across a range of reasonable values for gamma (0, 0.05, ... 0.25). The higher gamma, the higher the amount of regularization imposed on the network (Epskamp et al., 2018). *Node labels*: 1 = age of cannabis use initiation, 2 = lifetime cumulative frequency of cannabis use, 3 = childhood abuse, 4 = childhood neglect, 5 = urban upbringing, 6 = panic, 7 = anxious, 8 = sad, 9 = loss interest, 10 = irritable, 11 = manic, 12 = spying/following you, 13 = poison/hurt you, 14 = reading your mind, 15 = hear your thoughts, 16 = hear others thought, 17 = controlled by force, 18 = others stole thoughts, 19 = special messages/tv, 20 = hypnotized/magic/force, 21 = saw visions, 22 = heard noise/voice, 23 = smells/body odors, 24 = feelings in/on body, 25 = age at assessment.

Supplementary Table. Summary statistics for network variables along with relevant identifiers and corresponding node numbers plotted in the network.

Network Variable	Question	Node	
Cannabis Use Characteristics			
Age of cannabis use initiation (mean, SD)	How old were you the first time you used marijuana or hashish?	1	16.7 (3.2)
Lifetime cumulative frequency (median)	About how many times in your life have you used marijuana or hashish?	2	11 to 49 times
Early Risk Factors			**% yes**
Childhood abuse	*See details in the method section.*	3	16.6
Childhood neglect	You were seriously neglected as a child (yes/no).	4	4.6
Urban upbringing	Was the area where you were raised during most of your childhood rural, a small town, a medium-sized town, a suburb, or a city? *(details in method)*	5	46.4
Affective Symptoms			**% yes**
Panic	Have you ever in your life had a spell or attack when all of a sudden you felt frightened, anxious or very uneasy in situations when most people would not be afraid or anxious?	6	35.4
Anxious	Have you ever had a period of one month or more when most of the time you felt worried or anxious?	7	52.6
Sad	In your lifetime, have you ever had two weeks or more when nearly every day you felt sad, blue, or depressed?	8	54.3
Loss interest	Has there ever been two weeks or more when you lost interest in most	9	50.2

Network Variable	Question	Node	
	things like work, hobbies, or things you usually liked to do for fun?		
Irritable	Has there ever been a period of several days when you were so irritable that you threw or broke things, started arguments, shouted at people, or hit someone?	10	36.0
Manic	Has there ever been a period of at least two days when you were so happy or excited that you got into trouble, or your family or friends worried about it, or a doctor said you were manic?	11	11.7
Psychotic Experiences			**% yes**
Spying/following you	Have you ever believed that people were spying on you or following you?	12	14.3
Poison/hurt you	Have you ever believed that you were being secretly tested or experimented on, that someone was plotting against you, or that someone was trying to poison you or hurt you?	13	3.9
Reading your mind	Have you ever believed that someone was reading your mind?	14	7.8
Hear your thoughts	Have you ever believed that others could hear your thoughts?	15	4.5
Hear others thought	Have you ever believed you could actually hear what another person was thinking, even though that person was not speaking?	16	7.5
Controlled by force	Have you ever been convinced that you were under the control of some power or force, so that your actions and thoughts were not your own?	17	3.8

Network Variable	Question	Node	
Others stole thoughts	Have you ever been convinced that strange thoughts, or thoughts that were not your own, were being put directly into your mind, or that someone or something could steal your thoughts out of your mind?	18	2.7
Special messages/tv	Have you ever believed that you were being sent special messages through television or the radio, or that a program had been arranged just for you alone?	19	2.7
Hypnotized/magic/force	Have you ever felt strange forces working on you, as if you were being hypnotized or magic was being performed on you, or you were being hit by laser beams or X-rays?	20	1.3
Saw visions	Have you ever had the experience of seeing something or someone that others present could not see -- that is, had a vision when you were wide awake?	21	9.0
Heard noise/voice	Have you ever had the experience of hearing things that other people could not hear, such as noises or a voice?	22	8.6
Smells/body odors	Have you ever been bothered by strange smells around you that nobody else was able to smell, perhaps even odors coming from your own body?	23	5.0
Feelings in/on body	Have you ever had unusual feelings inside or on your body, like being touched when nothing was there or feeling something moving inside your body?	24	8.5

Supplementary References

Costenbader, E., & Valente, T. W. (2003). The stability of centrality measures when networks are sampled. *Social Networks*, *25*(4), 283–307. https://doi.org/10.1016/S0378-8733(03)00012-1

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6.4 Supplementary material for "Disentangling heterogeneity of psychosis expression in the general population: sex-specific moderation effects of environmental risk factors on symptom networks"

Supplementary Method 1. Assessment of psychopathology.
Supplementary Method 2. Assessment of demographic and environmental risk factors.
Supplementary Method 3. Identification of network subgroups via recursive partitioning.
Supplementary Table 1. Comparison of participants included in and excluded from the analysis due to missing values.
Supplementary Table 2. Results from case-drop subset bootstrapping.
Supplementary Figure 1. Results from recursive partitioning disaggregated by sex, depicted as decision trees of partial correlation networks.
Supplementary Figure 2. Accuracy of the edge-weights in the network estimated in the full sample.
Supplementary Figure 3. Accuracy of the edge-weights in the network estimated in women.
Supplementary Figure 4. Accuracy of the edge-weights in the network estimated in men.
Supplementary Figure 5. Accuracy of the edge-weights in the network estimated in women who reported sexual abuse in childhood.
Supplementary Figure 6. Accuracy of the edge-weights in the network estimated in women who did not report sexual abuse in childhood.
Supplementary Figure 7. Accuracy of the edge-weights in the network estimated in women who did not report sexual abuse in childhood, but physical abuse.
Supplementary Figure 8. Accuracy of the edge-weights in the network estimated in women who reported neither sexual abuse nor physical abuse in childhood.
Supplementary Figure 9. Accuracy of the edge-weights in the network estimated in women who reported neither sexual abuse nor physical abuse in childhood, but domestic violence.
Supplementary Figure 10. Accuracy of the edge-weights in the network estimated in women who reported neither sexual abuse in childhood, physical abuse in childhood, nor domestic violence.
Supplementary Figure 11. Accuracy of the edge-weights in the network estimated in men who reported domestic violence.
Supplementary Figure 12. Accuracy of the edge-weights in the network estimated in men who did not report domestic violence.
Supplementary Figure 13. Accuracy of the edge-weights in the network estimated in men who did not report domestic violence, but cannabis use in the past year.
Supplementary Figure 14. Accuracy of the edge-weights in the network estimated in men who reported neither domestic violence nor cannabis use in the past year.
Supplementary Figure 15. Accuracy of the edge-weights in the network estimated in men who reported neither domestic violence nor cannabis use and reported having a White or 'Other' ethnic background.
Supplementary Figure 16. Accuracy of the edge-weights in the network estimated in men who reported neither domestic violence nor cannabis use and reported having a Black or South Asian ethnic background.

Supplementary Methods

Supplementary Method 1. Assessment of psychopathology.

We obtained affective symptoms of worry, sleep disturbance, generalized anxiety and depression from the Revised Version of the Clinical Interview Schedule (CIS-R; Lewis, Pelosi, Araya, & Dunn, 1992). We coded these symptoms as present if they had been reported in the past month and persisted for at least two weeks (Moffa et al., 2017). Persecutory ideation and hallucinatory experiences were obtained from the Psychosis Screening Questionnaire (Bebbington & Nayani, 1995). Persecutory ideation was defined as present given a positive response to the question: 'Over the past year, have you felt that people were deliberately acting to harm you/your interests?'. Similarly, hallucinatory experiences were defined as a positive response to the question: 'In the past year, have you ever heard voices saying quite a few words or sentences when there was no-one around that might explain it?'

Supplementary Method 2. Assessment of demographic and environmental risk factors.

Early-life adversities. Early-life adversities comprised physical abuse and sexual abuse before the age of 16, as well as separation experiences from parents (institutional care and local authority care until the age of 16).

Specifically, physical abuse was defined as a positive response to the question: 'Before the age of 16, were you ever severely beaten by a parent, step-parent or carer?'. Sexual abuse was defined via a positive endorsement of any of the following questions: 'Before the age of 16, did anyone talk to you in a sexual way that made you feel uncomfortable?', 'Before the age of 16, did anyone touch you, or get you to touch them, in a sexual way without your consent?', and 'Before the age of 16, did anyone have sexual intercourse with you without your consent?'.

Two items taken from the 'parenting' section of the APMS (National Centre for Social Research, University of Leicester, 2017) were selected to define separation from parents, requiring "yes" responses to at least one of the following questions: Institutional care: 'Up to the age of 16 did you spend any time in any kind of institution such as a children's home, borstal, or young offenders unit?'; Local Authority care: 'Were you ever taken into Local Authority care (i.e., into a children's home or foster care) as a child up until the age of 16?'

Later-life adversities. Later-life adversities comprised bullying, domestic violence, cannabis use in the past year, alcohol use, ethnic background, and deprivation.

Specifically, respondents had to select 'bullying' and/or 'violence in the home' from a list of options on a card following the question, 'Now looking at this card, could you tell me if you have ever experienced any of these problems or events, at any time in your life?'. We coded responses as "yes" if the respective risk factor was reported and "no" if not.

Cannabis use in the past year was defined via a positive response to the question 'Have you used cannabis in the last year?'.

Alcohol use was assessed with the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de La Fuente, & Grant, 1993). The range of possible scores is from 0 to 40 where 0 indicates an abstainer who has never had any problems from alcohol. A score of 1 to 7 suggests low-risk consumption according to World Health Organization (WHO) guidelines. Scores from 8 to 14 suggest hazardous or harmful alcohol consumption and a score of 15 or more indicates the likelihood of alcohol dependence (moderate-severe alcohol use disorder).

Respondents were also asked to indicate their ethnicity, and our analyses included four categories: White, Black, South Asian and Mixed/Other.

Deprivation in the APMS 2007 was assessed via index of multiple deprivation (IMD) 2004 data. This is a derived measure of social and economic deprivation based on seven domains or neighborhood variables: income; employment; health and disability; education, skills and training; barriers to housing and services; living environment; and crime. Data for the IMD 2004 was collected between 1997 and 2003 and the APMS 2007 (National Centre for Social Research, University of Leicester, 2017) reported 5 quintiles of deprivation, where 1 represents the least deprived and 5 represents most deprived.

Supplementary Method 3. Identification of network subgroups via recursive partitioning.

We used a model-based recursive partitioning approach to identify meaningful subgroups given the included environmental and demographic factors, as implemented in the R package 'networktree', version 1.0.1 (Jones, Mair, Simon, & Zeileis, 2020). The 'networktree' approach determines sample splits based on significant invariance in the correlation matrix of the network variables under consideration, yielding non-overlapping partitions of the sample with maximally heterogeneous symptom networks (Jones et al., 2020). Specifically, a log-likelihood-based score function is used to assess how much each participant deviates from parameters (i.e., pairwise correlation-coefficients in the correlation matrix that are the basis for network models) estimated in the full sample. In a well-fitting symptom network model not subject to significant heterogeneity, individual deviations should be close to 0 and randomly fluctuate around it. Based on structural change tests, p-values are generated for each moderating variable, assessing the extent to which a given moderating variable can capture deviations in parameters, i.e., heterogeneity in symptom networks. The moderating variable with the lowest p-value serves as a so-called splitting variable, given that this p-value is below α, which is Bonferroni-corrected for the number of moderating variables tested (Jones et al., 2020). Thus, the algorithm prioritizes the "biggest" splits first. The procedure of testing for invariance in network structures is repeated recursively within the newly identified subgroups until no significant invariance in network structures can be detected. To ensure stability and interpretability of the results, we set the minimum number of observations within any final group of the decision tree to 1% of the total sample size, i.e., 73.

Supplementary Tables

Supplementary Table 1. Comparison of participants included in and excluded from the analysis due to missing values. We used permutation-tests as implemented in the *R* package 'coin' (Hothorn, Hornik, van de Wiel, & Zeileis, 2008), specifically the Pearson χ^{2} test for count data, and the Wilcoxon-test for interval data.

Variable Yes (%)/Median (IQR)	Included (n = 7,242)	Excluded (n = 161)	Test statistic, *p*-value
Network Variables			
worry	36.0	33.8	$\chi^2 = 0.32, p = .609$
sleep problems	34.6	41.6	$\chi^2 = 3.37, p = .082$
anxiety	17.3	18.6	$\chi^2 = 0.21, p = .676$
depression	22.9	35.0	$\chi^2 = 12.8, p < .001$
persecutory ideation	7.7	7.7	$\chi^2 = 0.001, p = 1$
hallucinatory experiences	0.80	0.50	$\chi^2 = 22.5, p < .001$
Potential Moderators			
sex (% female)	56.8	56.5	$\chi^2 = 0.006, p = 1$
age (years)	50 (30)	58 (40)	$Z = 4.53, p < .001$
ethnic background	White: 92.7, Black: 2.6, South Asian: 2.6, Mixed/Other: 2.1	White: 85.6, Black: 1.8, South Asian: 7.2, Mixed/Other: 5.4	$\chi^2 = 14.8, p = .006$
deprivation	3 (2)	3 (3)	$Z = 2.76, p = .005$
bullying	18.9	19.1	$\chi^2 = 0.003, p = 1$
separation from parents	3.4	4.2	$\chi^2 = 0.21, p = .803$
domestic violence	9.5	8.7	$\chi^2 = 0.08, p = .877$
physical abuse	4.8	8.5	$\chi^2 = 2.09, p = .151$
sexual abuse	13.5	10.8	$\chi^2 = 0.41, p = .595$
cannabis use in past year	5.7	2.6	$\chi^2 = 2.00, p = .212$
alcohol consumption (AUDIT score)	4 (5)	2 (5)	$Z = -4.60, p < .001$

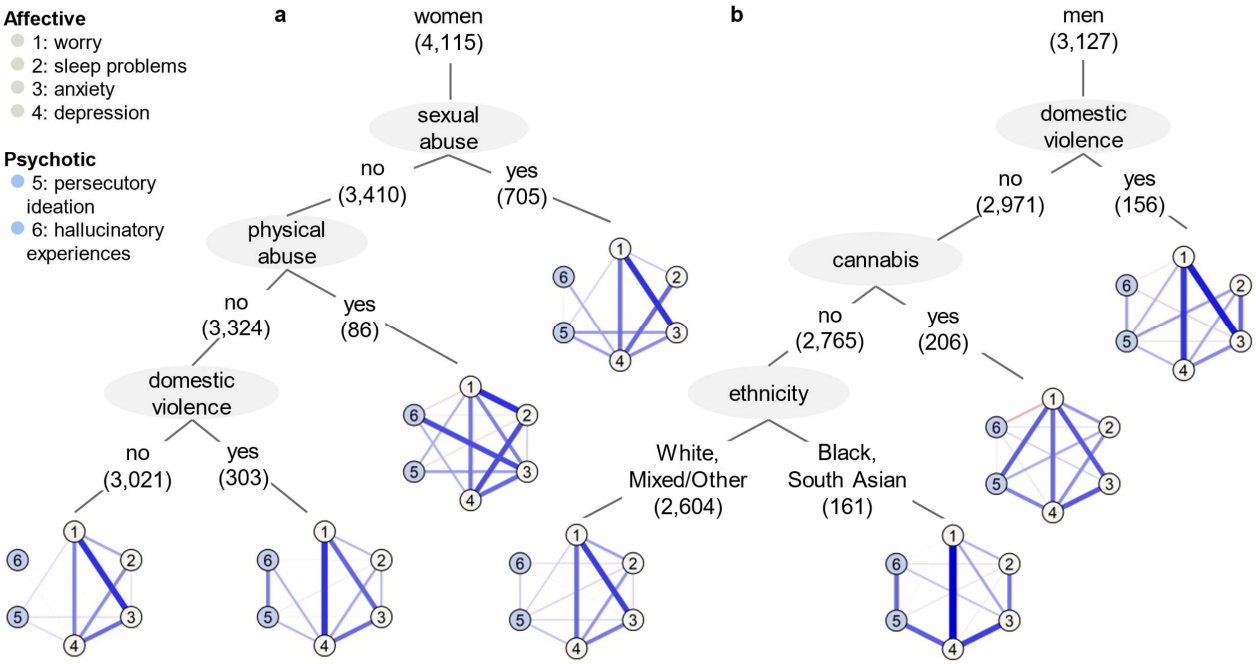
Supplementary Table 2. Results from case-drop subset bootstrapping (Costenbader & Valente, 2003; Epskamp, Borsboom, & Fried, 2018). For subgroup networks, see figure 2 in main manuscript.

Subgroup	CS coefficient
Full sample	0.75
First split (figure 2a)	
women	0.75
men	0.75
Second split (figure 2b)	
sexual abuse: yes	0.75
sexual abuse: no	0.75
Third split (figure 2c)	
physical abuse: yes	0.28
physical abuse: no	0.75
Fourth split (figure 2d)	
domestic violence: yes	0.52
domestic violence: no	0.75
Fifth split (figure 2e)	
domestic violence: yes	0.44
domestic violence: no	0.75
Fifth split (figure 2f)	
cannabis: yes	0.44
cannabis: no	0.75
Sixth split (figure 2g)	
ethnicity: Black or South Asian	0.52
ethnicity: White or Mixed/Other	0.75

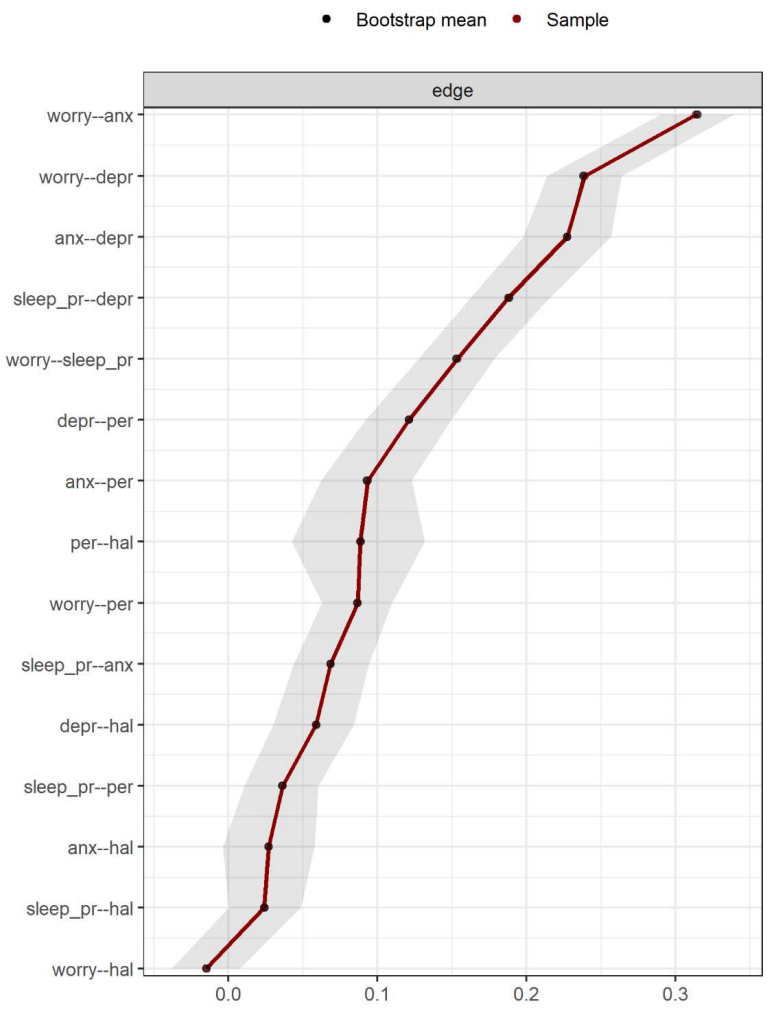
Abbreviations: CS coefficient = correlation stability coefficient.

Note: Figure 2 can be found in the main manuscript.

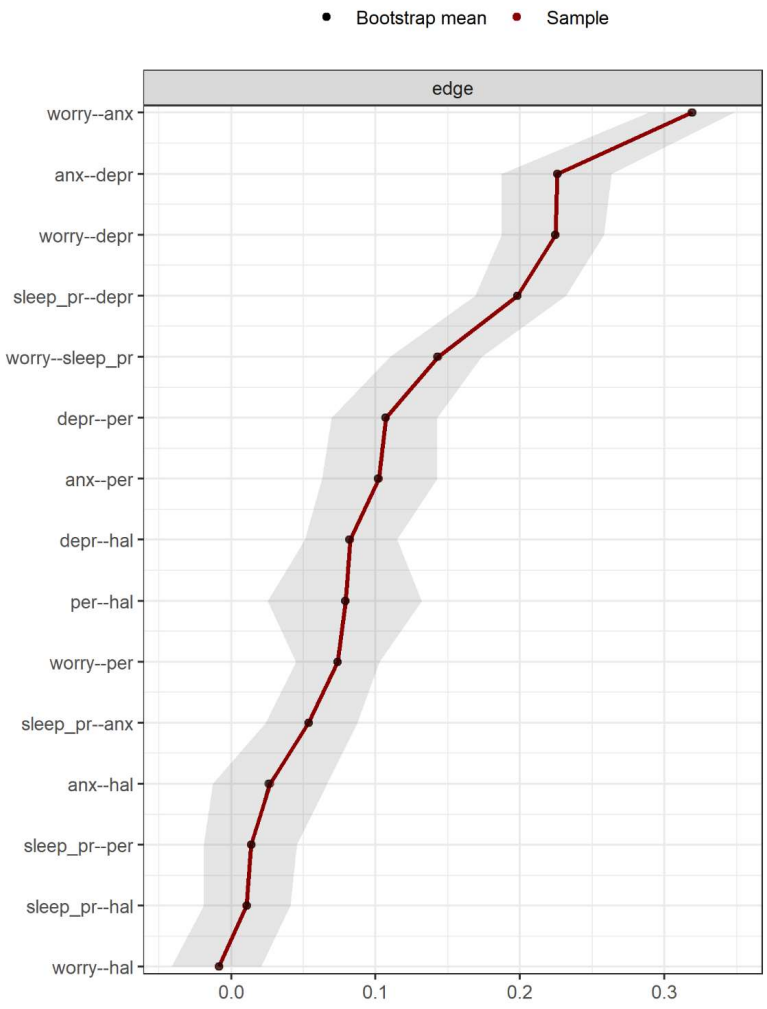
Supplementary Figures



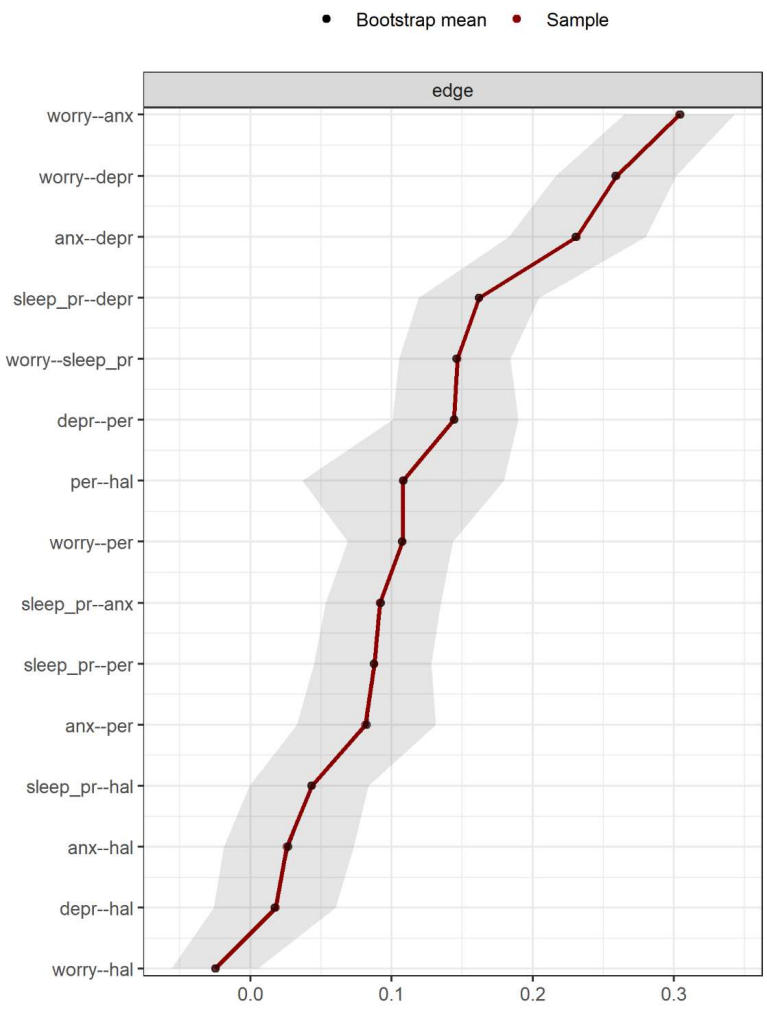
Supplementary Figure 1. Results from recursive partitioning disaggregated by sex, depicted as decision trees of partial correlation networks. Numbers behind splitting factors give the sample size retained after the corresponding sample split. Symptom groups are differentiated by color. The thicker and less transparent the edge, the stronger the partial correlation between two symptoms. Blue (red) edges indicate positive (negative) relationships. To ensure visual comparability, edge weights were scaled identically across all networks. Only edge weights larger than 0.01 are depicted.



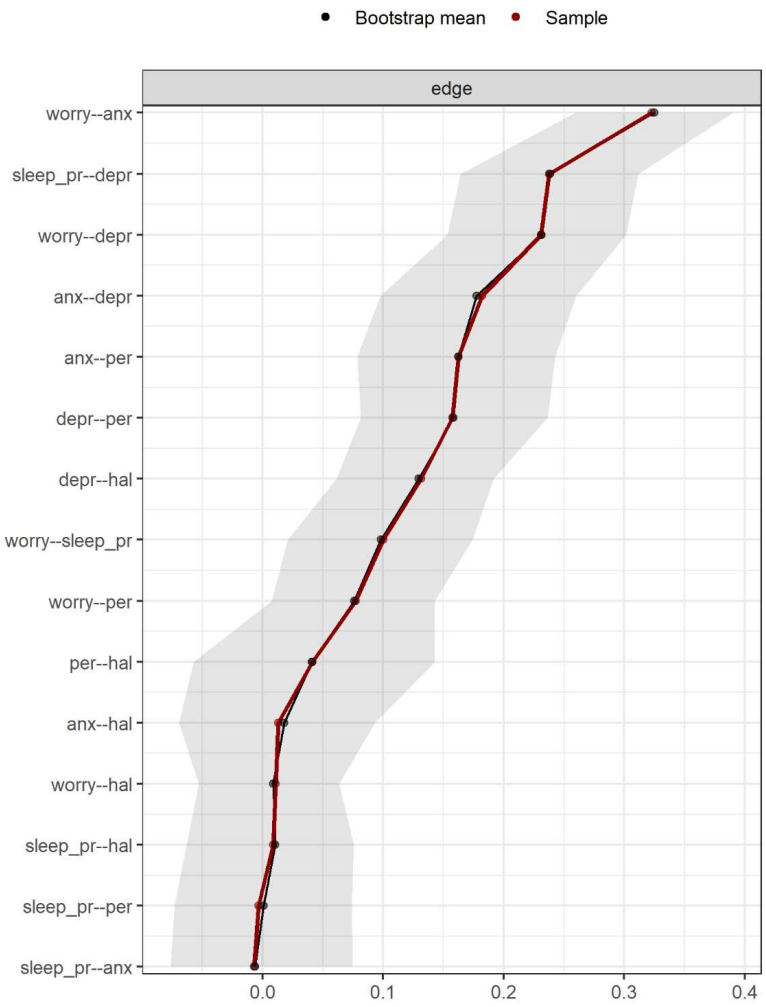
Supplementary Figure 2. Accuracy of the edge-weights in the network estimated in the full sample. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



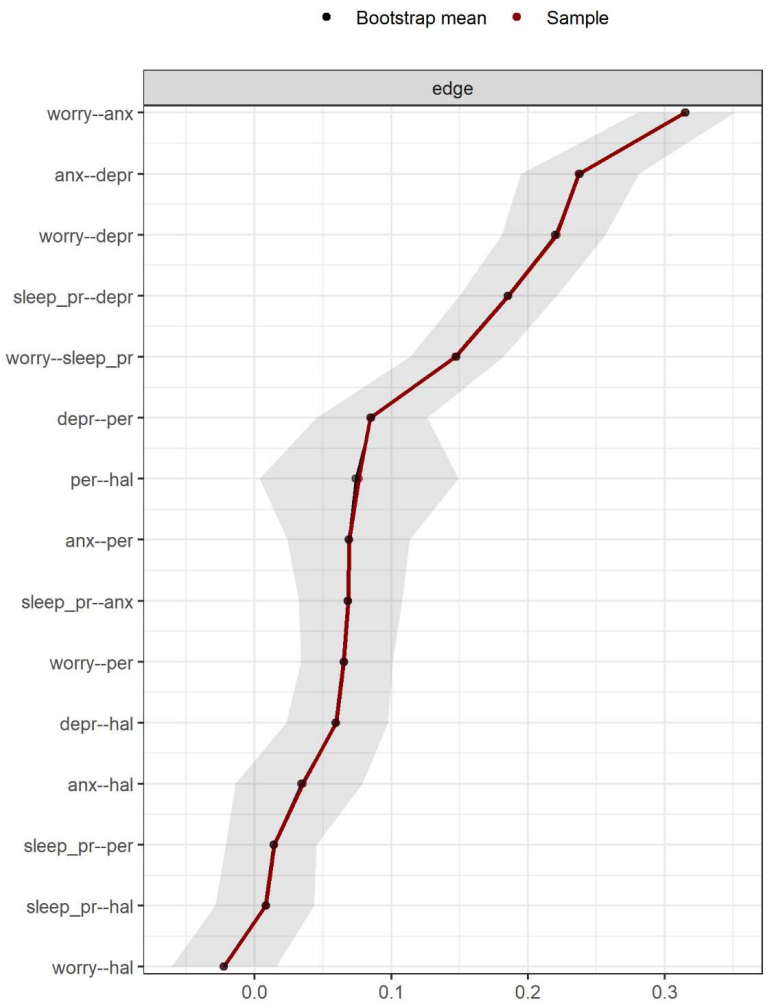
Supplementary Figure 3. Accuracy of the edge-weights in the network estimated in women. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



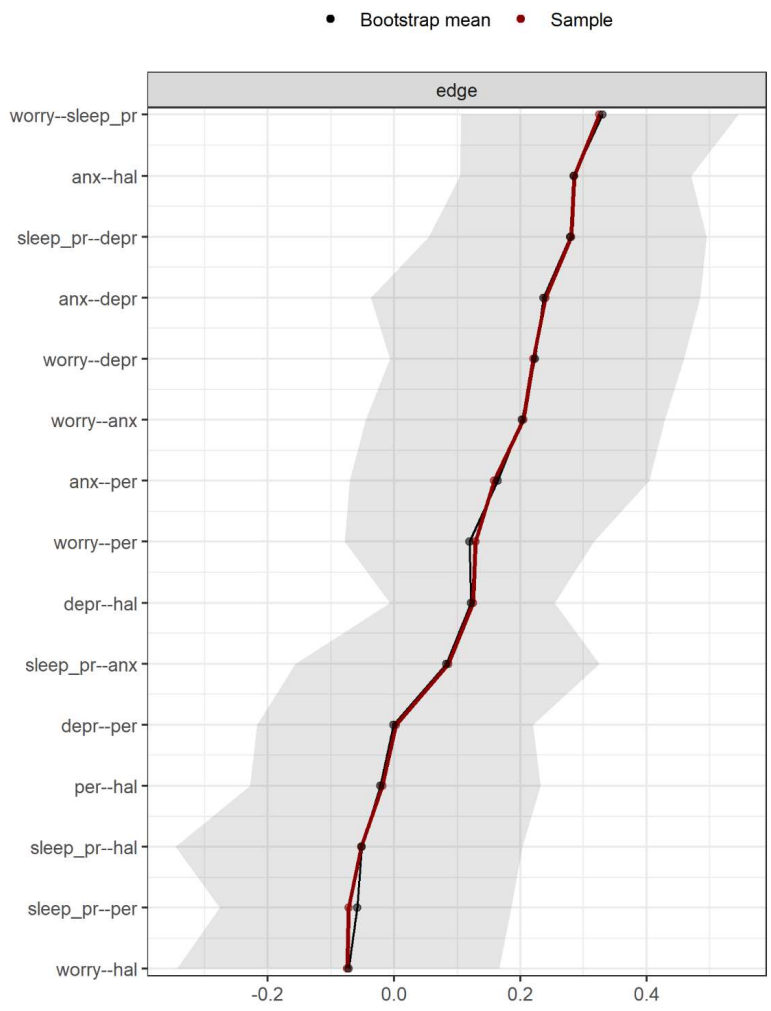
Supplementary Figure 4. Accuracy of the edge-weights in the network estimated in men. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



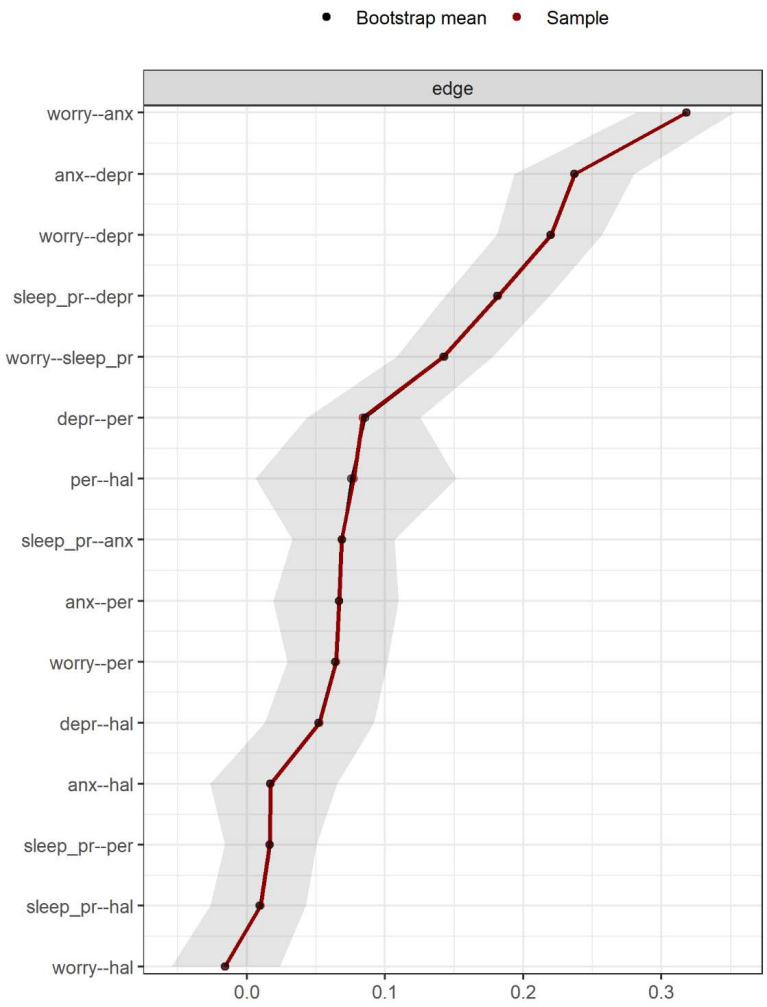
Supplementary Figure 5. Accuracy of the edge-weights in the network estimated in women who reported sexual abuse in childhood. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



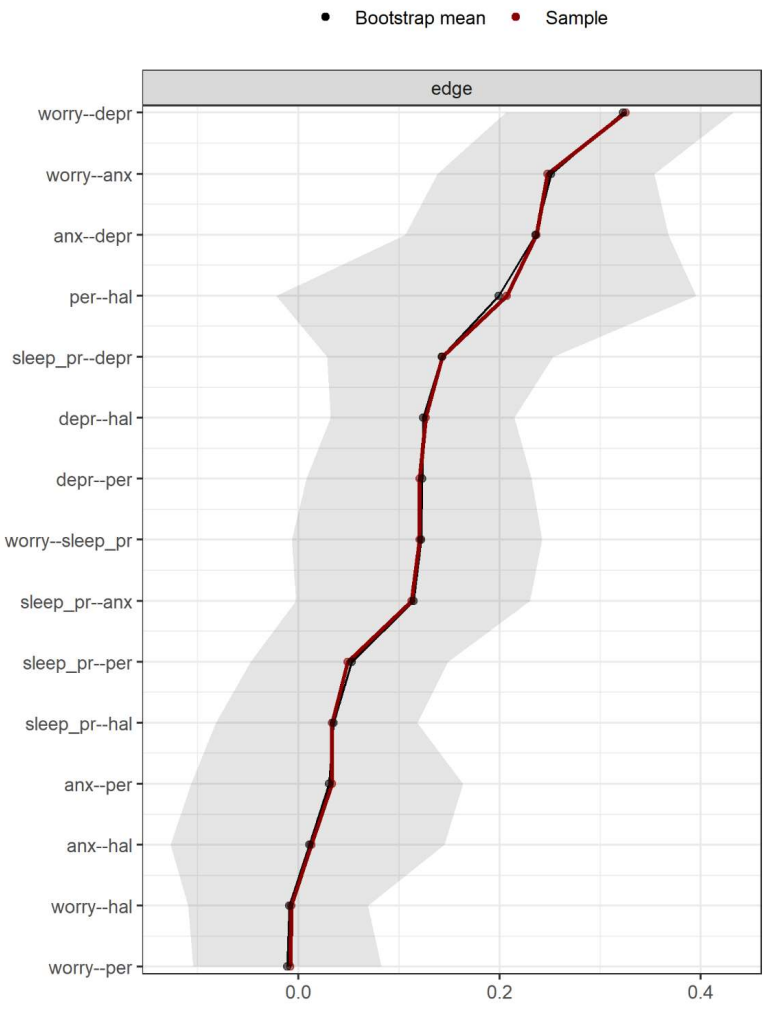
Supplementary Figure 6. Accuracy of the edge-weights in the network estimated in women who did not report sexual abuse in childhood. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



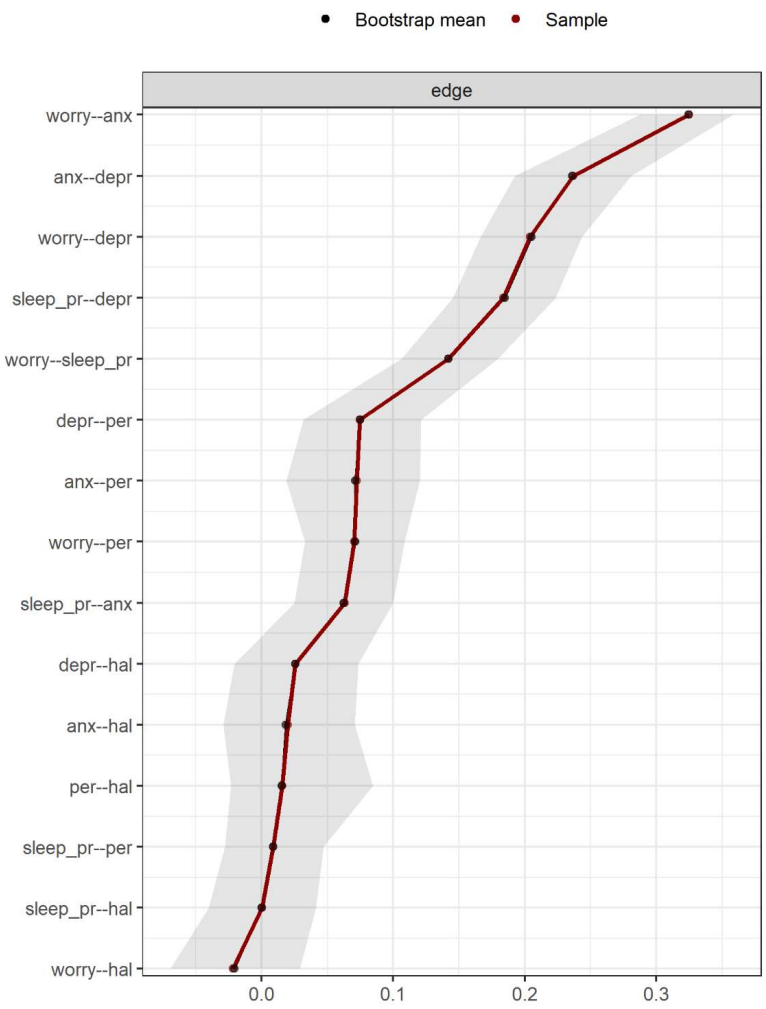
Supplementary Figure 7. Accuracy of the edge-weights in the network estimated in women who did not report sexual abuse in childhood, but physical abuse. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are generally well-aligned with the sample values, thus indicating accurate estimations. Of note, the bootstrapped confidence intervals are relatively wide, thus some caution is recommended especially when interpreting the strength of weaker edges.



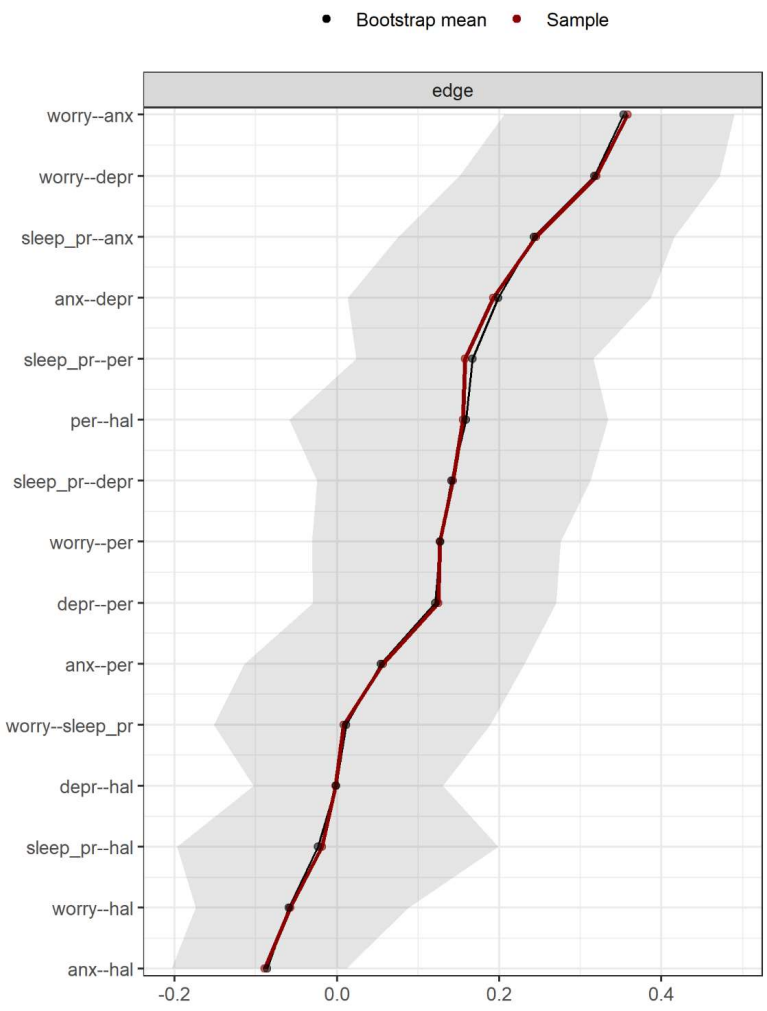
Supplementary Figure 8. Accuracy of the edge-weights in the network estimated in women who reported neither sexual abuse nor physical abuse in childhood. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



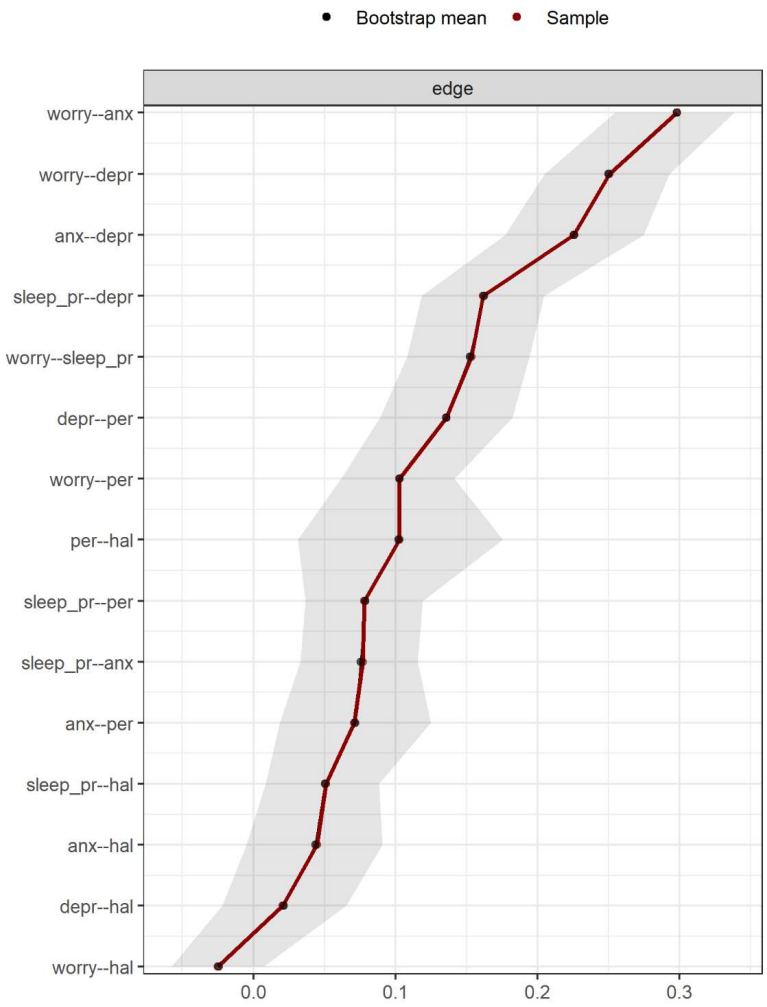
Supplementary Figure 9. Accuracy of the edge-weights in the network estimated in women who reported neither sexual abuse nor physical abuse in childhood, but domestic violence. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are generally well-aligned with the sample values, thus indicating accurate estimations. Of note, the bootstrapped confidence intervals are relatively wide, thus some caution is recommended especially when interpreting the strength of weaker edges.



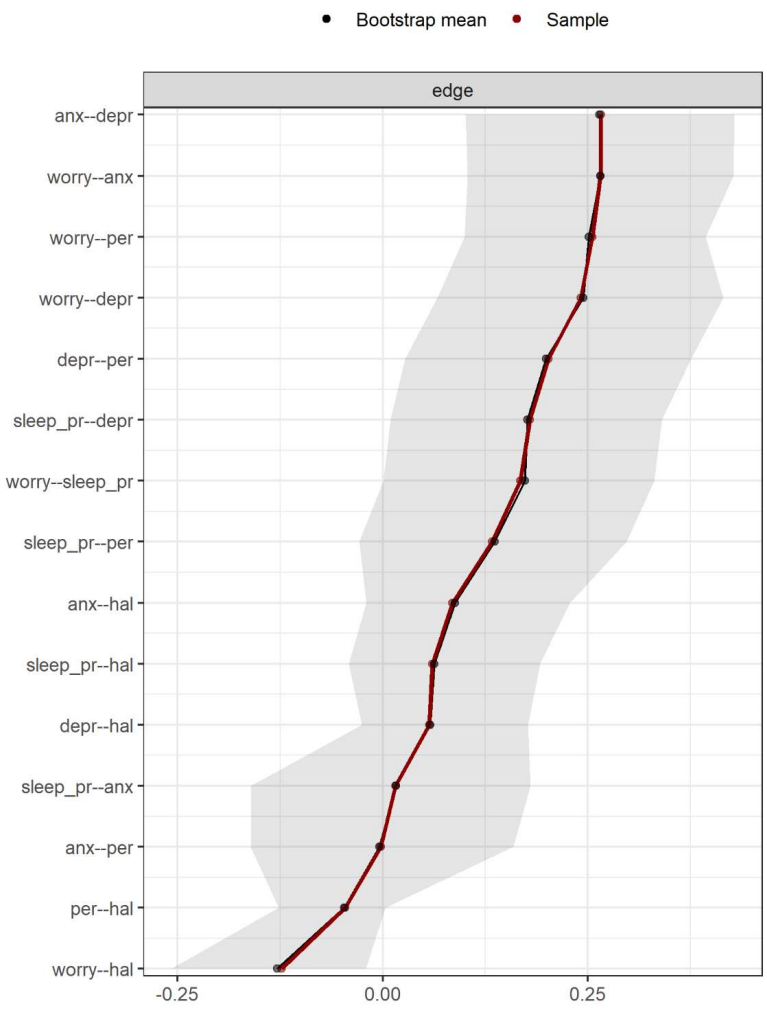
Supplementary Figure 10. Accuracy of the edge-weights in the network estimated in women who reported neither sexual abuse in childhood, physical abuse in childhood, nor domestic violence. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



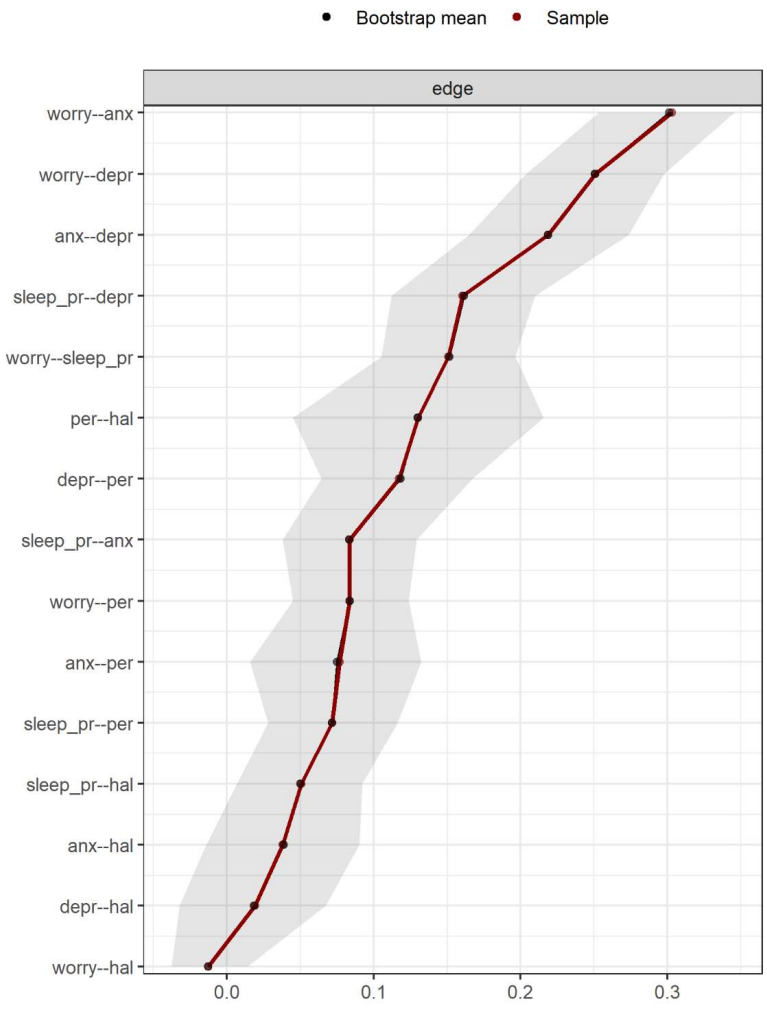
Supplementary Figure 11. Accuracy of the edge-weights in the network estimated in men who reported domestic violence. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are generally well-aligned with the sample values, thus indicating accurate estimations. Of note, the bootstrapped confidence intervals are relatively wide, thus some caution is recommended especially when interpreting the strength of weaker edges.



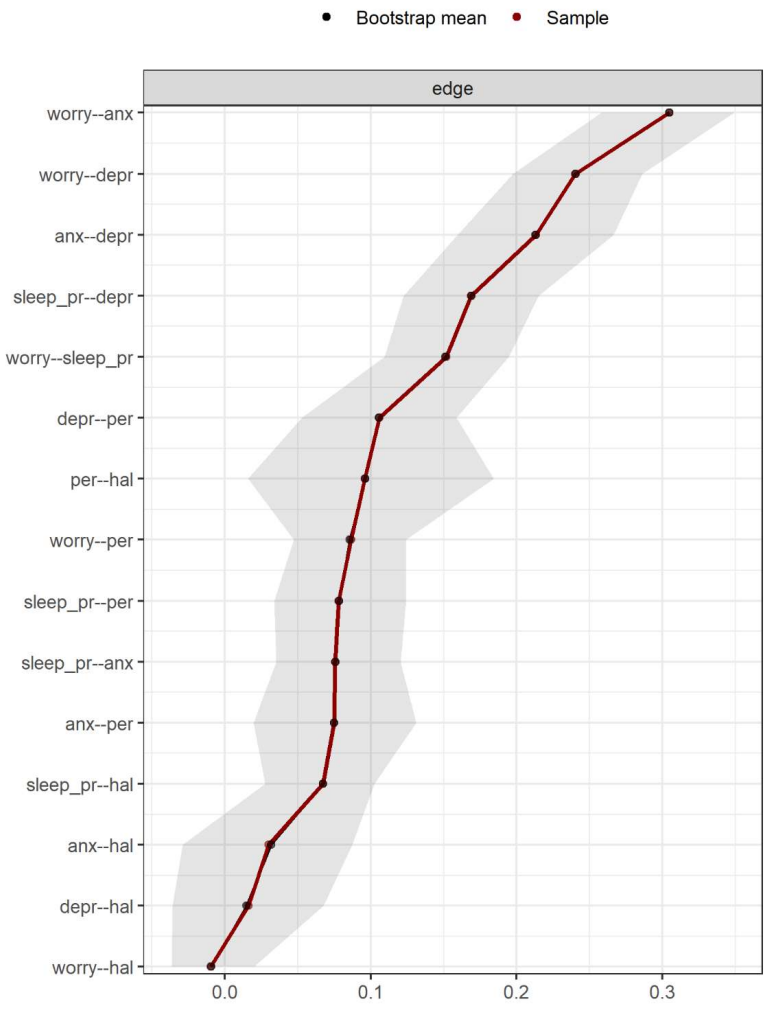
Supplementary Figure 12. Accuracy of the edge-weights in the network estimated in men who did not report domestic violence. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



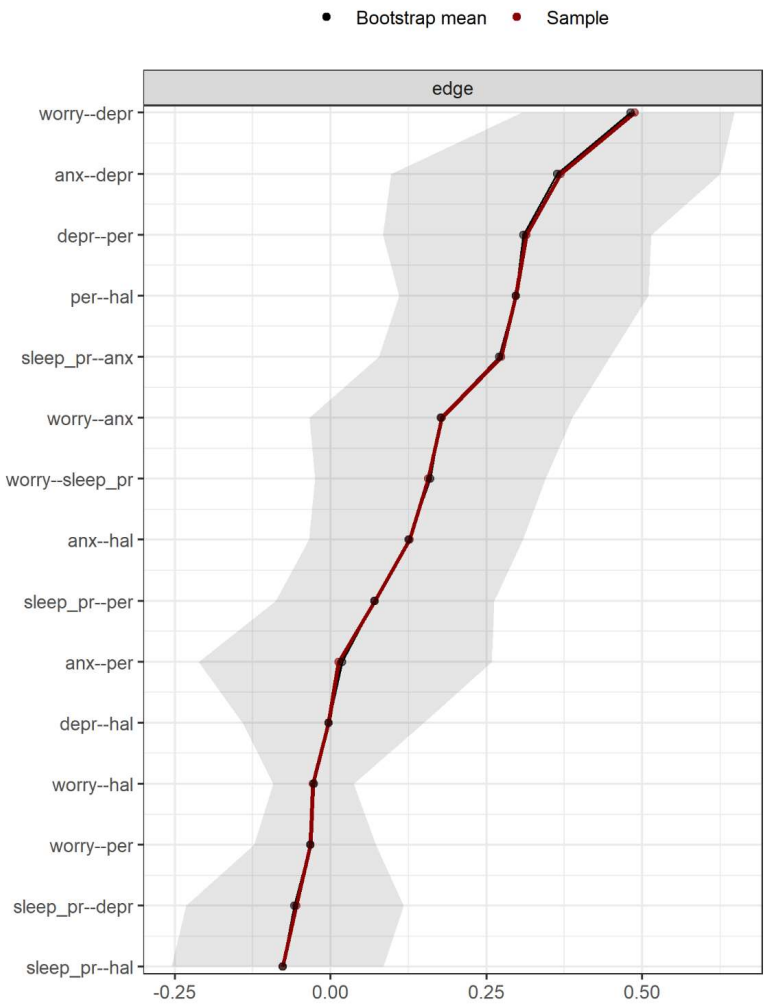
Supplementary Figure 13. Accuracy of the edge-weights in the network estimated in men who did not report domestic violence, but cannabis use in the past year. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are well-aligned with the sample values, thus indicating accurate estimations. Of note, the bootstrapped confidence intervals are relatively wide, thus some caution is recommended especially when interpreting the strength of weaker edges.



Supplementary Figure 14. Accuracy of the edge-weights in the network estimated in men who reported neither domestic violence nor cannabis use in the past year. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



Supplementary Figure 15. Accuracy of the edge-weights in the network estimated in men who reported neither domestic violence nor cannabis use and reported having a White or 'Other' ethnic background. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are very well-aligned with the sample values, thus indicating accurate estimations.



Supplementary Figure 16. Accuracy of the edge-weights in the network estimated in men who reported neither domestic violence nor cannabis use and reported having a Black or South Asian ethnic background. The grey horizonal area within the plot represents the 95% quantile range of the parameter values across 5000 bootstraps. The red dots indicate the sample values for the analyzed data, while the black dots indicate the bootstrap mean values. The sample values lie within the bootstrapped confidence intervals and the bootstrap mean values are well-aligned with the sample values, thus indicating accurate estimations. Of note, the bootstrapped confidence intervals are relatively wide, thus some caution is recommended especially when interpreting the strength of weaker edges.

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6.5 Supplementary material for "Transdiagnostic psychopathology in a help-seeking population of an early recognition center for mental disorders: protocol for an experience sampling study"

Supplementary Table. Questionnaire to assess experiences and strain associated with the ESM data collection translated and adjusted from a previous study conducted in clinical participants (Frumkin et al., 2020).

Supplementary Table. Questionnaire to assess experiences and strain associated with the ESM data collection translated and adjusted from a previous study conducted in clinical participants (Frumkin et al., 2020).

	Stimme überhaupt nicht zu	Stimme nicht zu	Weder noch	Stimme zu	Stimme stark zu
Es war mir lästig, jeden Tag fünf mal zehn Fragen zu beantworten.					
Ich war mir meiner Stimmung/ meiner Symptome bewusst.					
Das Beantworten der Fragen in der App hat mir meine Stimmung/ meine Symptome bewusster gemacht.					
Ich habe mich schlechter gefühlt, wenn ich mir meiner Stimmung/ meiner Symptome bewusst war.					
Ich habe mich besser gefühlt, wenn ich mir meiner Stimmung/ meiner Symptome bewusst war.					

Supplementary Reference

Frumkin, M., Piccirillo, M., Beck, E. D., Grossman, J., & Rodebaugh, T. (2020). Feasibility and utility of idiographic models in the clinic: A pilot study. *Psychotherapy Research, 31*(4), 520-534. https://doi.org/10.1080/10503307.2020.1805133

6.6 Author contributions to publications

1. **Betz, L. T.***, Penzel, N.*, Kambeitz-Ilankovic, L., Rosen, M., Chisholm, K., Stainton, A., Haidl, T. K., Wenzel, J., Betrolino, A., Borgwardt, S., Brambilla, P., Lencer, R., Meisenzahl, E., Ruhrmann, S., Salokangas, R. K. R., Schultze-Lutter, F., Wood, S. J., Upthegrove, R., Koutsouleris, N., Kambeitz, J., & PRONIA Consortium (2020). General psychopathology links burden of recent life events and psychotic symptoms in a network approach. *npj Schizophrenia, 6*(1), 1-8. https://doi.org/10.1038/s41537-020-00129-w.
* denotes shared first authorship

L.T.B., N.P. and J.K. conceived the conceptual idea for the project.
L.T.B. wrote the analysis code, with conceptual contributions from N.P.
L.T.B. and N.P. interpreted the results.
L.T.B. prepared the figures, tables, and supplementary materials.
L.T.B. and N.P. drafted the manuscript, with contributions from J.K. and L.K.-I.
L.T.B., N.P., J.K., L.K.-I., M.R., K.C., A.S., T.H., J.U., A.B., S.B., P.B., R.L., E.M., S.R., R.K.R.S., F.S.-L., S.J.W., R.U. and N.K. were involved in acquisition of data.
N.K., L.K.-I., S.R., R.K.R.S., P.B., S.B., and S.J.W. were involved in obtaining funding.
J.K., L.K.-I., S.R., F.S.-L., S.J.W., P.B., A.B., R.L., R.U., S.B. and N.K. were involved in supervision.
All authors contributed to the critical revision of the manuscript for important intellectual content.

Collaboration:
Data used in the publication come from the PRONIA study, a Collaboration Project funded by the European Union under the 7th Framework Programme under grant agreement n° 602152 (for more information, visit www.pronia.eu). The University Hospital of Cologne was one of the study centers in the PRONIA study.

2. **Betz, L. T.**, Penzel, N., Rosen, M., & Kambeitz, J. (2021). Relationships between childhood trauma and perceived stress in the general population: a network perspective. *Psychological Medicine, 51*(15), 2696–2706. https://doi.org/10.1017/S003329172000135X.

L.T.B. and J.K. conceived the conceptual idea for the project.
L.T.B. performed all analyses, interpreted the results, prepared the figures, tables, and supplementary materials and drafted the manuscript.
N.P., M.R. and J.K. contributed to the interpretation of results and revised the manuscript for important intellectual content.

3. **Betz, L. T.**, Penzel, N., & Kambeitz, J. (2022). A network approach to relationships between cannabis use characteristics and psychopathology in the general population. *Scientific Reports, 12*(1), 1–10. https://doi.org/10.1038/s41598-022-11092-0.

L.T.B. and J.K. conceived the conceptual idea for the project.
L.T.B. performed all analyses, interpreted the results, prepared the figures, tables, and supplementary materials and drafted the manuscript.

N.P. and J.K. contributed to the interpretation of results and revised the manuscript for important intellectual content.

4. **Betz, L. T.**, Penzel, N., Rosen, M., Bhui, K., Upthegrove, R., & Kambeitz, J. (2021). Disentangling heterogeneity of psychosis expression in the general population: sex-specific moderation effects of environmental risk factors on symptom networks. *Psychological Medicine*, 1–10. https://doi.org/10.1017/S0033291721003470.

L.T.B. and J.K. conceived the conceptual idea for the project.
L.T.B. performed all analyses, interpreted the results, prepared the figures, tables, and supplementary materials and drafted the manuscript.
N.P., M.R., K.B., R.U. and J.K. contributed to the interpretation of results and revised the manuscript for important intellectual content.

5. Rosen, M.*, **Betz, L. T.***, Montag, C., Kannen, C., & Kambeitz, J. (2022). Transdiagnostic psychopathology in a help-seeking population of an early recognition center for mental disorders: protocol for an experience sampling study. *JMIR Research Protocols 11*(8), e35206. https://doi.org/10.2196/35206.

* denotes shared first authorship

L.T.B., M.R. and J.K. conceived the idea for the PhenoNetz-study.
L.T.B. and M.R. developed the study design, prepared the figures, tables, and supplementary material, and drafted the manuscript.
L.T.B. conceived the statistical approach and developed all relevant analysis code for the project.
C.M., C.K. and J.K. revised the manuscript for important intellectual content.

Collaboration:
C.M. and C.K. from Ulm University provided the Android software ("app") used for intensive longitudinal data collection via smartphone ("experience sampling") in the PhenoNetz-study, and provided technical support throughout the study.

6.7 Danksagung

Meine Promotion war eine Zeit voller spannender Erlebnisse und neuer Erkenntnisse, in der mich viele verschiedene Menschen begleitet haben. Dafür möchte ich an dieser Stelle Danke sagen.

Zunächst gilt mein Dank Prof. Dr. Joseph Kambeitz, der mir als mein Betreuer die Promotion in seiner Arbeitsgruppe ermöglicht hat. Joseph, deine Offenheit für neue Ideen, wie den Netzwerk-Ansatz, hat mich seit der Master-Arbeit geprägt, und war auch für weite Teile dieser Dissertation maßgeblich. Du hast mir von Anfang an großes Vertrauen beim Entwickeln neuer Forschungsideen entgegengebracht und mir spannende Kooperationen ermöglicht. Egal wie beschäftigt du warst, du hast dir Zeit für Rat und Feedback genommen, was ich sehr zu schätzen weiß.

Herzlicher Dank geht auch an Prof. Dr. Anja Görtz-Dorten und Prof. Dr. Silvia Daun für ihr Engagement als meine Tutorinnen. Aus jedem unserer Treffen konnte ich neue Ideen aufgreifen, und unser wertschätzender Austausch hat mich stets bestärkt und mir Selbstvertrauen für neue Herausforderungen gegeben.

Nicht zu vergessen sind außerdem meine zahlreichen Kollaborator:innen, die mit ihren konstruktiven Kommentaren jedes meiner Paper bereichert und mir spannende Perspektiven für meine Projekte aufgezeigt haben.

Als empirische Arbeit stützt sich diese Dissertation auf Daten aus verschiedenen Studien. Erst durch die Offenheit der Teilnehmer:innen für Forschung werden Vorhaben wie diese Promotion überhaupt möglich – vielen Dank dafür.

Für die freundschaftliche Atmosphäre in der Arbeitsgruppe geht ein großer Dank an alle aktuellen und ehemaligen Mitglieder des Kambeitz-Labs, und insbesondere an Nora und Marlene. Nora, mit dir als Büropartnerin gemeinsam Ideen zu entwickeln und zu diskutieren war einer der schönsten Aspekte meiner Promotion. Natürlich bleiben auch unsere kulinarischen Erkundungstouren in Köln unvergessen. Marlene, ohne dich wäre mein Ankommen in Köln nicht halb so schön verlaufen. Mit deiner klinisch orientierten Perspektive hast du maßgeblich zu den Papern in dieser Arbeit beigetragen. Von unseren zahlreichen gemeinsamen Forschungsabenteuern bleibt die „PhenoNetz“-Studie mein Herzensprojekt, auch wenn wir beide als iPhone-Nutzerinnen manchmal an den technischen Finessen unserer Android-Studiensmartphones verzweifelt sind ;)

Resi, Peter und Philipp, danke für eure familiäre Unterstützung in allen erdenklichen Lebenslagen, die mir sehr viel bedeutet.

Stephan, in allen Höhen und Tiefen bist du einfach der beste Partner an meiner Seite, den ich mir vorstellen kann - danke für alles.

6.8 Curriculum Vitae

Der Lebenslauf ist in dieser Version aus Gründen des Datenschutzes nicht enthalten.

6.9 Erklärung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertationsschrift selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Stellen - einschließlich Tabellen, Karten und Abbildungen -, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, sind in jedem Einzelfall als Entlehnung kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertationsschrift noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss der Promotion nicht ohne Genehmigung der / des Vorsitzenden des IPHS-Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Prof. Dr. Joseph Kambeitz betreut worden.
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Übersicht der Publikationen:

Betz, L. T.*, Penzel, N.*, Kambeitz-Ilankovic, L., Rosen, M., Chisholm, K., Stainton, A., Haidl, T. K., Wenzel, J., Bertolino, A., Borgwardt, S., Brambilla, P., Lencer, R., Meisenzahl, E., Ruhrmann, S., Salokangas, R. K. R., Schultze-Lutter, F., Wood, S. J., Upthegrove, R., Koutsouleris, N., Kambeitz, J., & PRONIA Consortium. (2020). General psychopathology links burden of recent life events and psychotic symptoms in a network approach. *npj Schizophrenia, 6*(1), 40. https://doi.org/10.1038/s41537-020-00129-w.

Betz, L. T., Penzel, N., Rosen, M., & Kambeitz, J. (2021). Relationships between childhood trauma and perceived stress in the general population: a network perspective. *Psychological Medicine, 51*(15), 2696–2706. https://doi.org/10.1017/S003329172000135X.

Betz, L. T., Penzel, N., & Kambeitz, J. (2022). A network approach to relationships between cannabis use characteristics and psychopathology in the general population. *Scientific Reports, 12*(1), 1–10. https://doi.org/10.1038/s41598-022-11092-0.

Betz, L. T., Penzel, N., Rosen, M., Bhui, K., Upthegrove, R., & Kambeitz, J. (2021). Disentangling heterogeneity of psychosis expression in the general population: sex-specific moderation effects of environmental risk factors on symptom networks. *Psychological Medicine*, 1–10. https://doi.org/10.1017/S0033291721003470.

Rosen, M.*, **Betz, L. T.***, Montag, C., Kannen, C., & Kambeitz, J. (2022). Transdiagnostic psychopathology in a help-seeking population of an early recognition center for mental disorders: protocol for an experience sampling study. *JMIR Research Protocols 11*(8), e35206. https://doi.org/10.2196/35206.

* geteilte Erstautorschaft

Ich versichere, dass ich alle Angaben wahrheitsgemäß nach bestem Wissen und Gewissen gemacht habe und verpflichte mich, jedmögliche, die obigen Angaben betreffenden Veränderungen, dem IPHS-Promotionsausschuss unverzüglich mitzuteilen.

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