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A comprehensive approach to heightened stress-sensitivity as a psychosis-proneness mechanism

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A comprehensive approach to heightened stress-sensitivity as a psychosis-proneness mechanism

By

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CONTENTS

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1. INTRODUCTION

Schizophrenia and related psychotic disorders are chronic and severe mental illnesses characterized by persistent disturbances in an individual's thoughts, perceptions, and behaviors as defined by American Psychological Association (APA, 2022). They are considered among the most severe mental conditions, affecting ~24 million individuals globally, with symptoms usually emerging in late adolescence or early adulthood, disrupting every aspect of individuals' lives, and yielding a large proportion of young people with co-occurring medical conditions and chronic disorders (Institute of Health Metrics and Evaluation—IHME, 2019; Tsai & Rosenheck, 2013). Compared to other mental disorders, schizophrenia and psychosis spectrum have a disproportionately high disability burden and financial cost for patients and their families (Desai et al., 2013; GBD, 2019). Despite decades of research and therapeutic improvements, treatment methods remain non-curative.

Current etiological models suggest that schizophrenia and the rest of disorders comprised in the psychosis spectrum can be viewed as an extended phenotype expressed across a continuum of individual differences in symptom expression and level of impairment (Kwapil & Barrantes-Vidal, 2015; Kaymaz & van Os, 2010; van Os et al., 2009). The concept of the extended phenotype can be best understood through the *schizotypy* model, as proposed by Claridge (1997) and Kwapil et al. (2008). Schizotypy provides valuable insights towards understanding the transition from predisposition to disorder, encompassing a wide spectrum of subclinical expression to the prodrome to schizophrenia-spectrum personality disorders to full-blown psychosis (Kwapil and Barrantes-Vidal, 2015; Lenzenweger, 2010; Docherty et al., 2018). It represents the phenotypic manifestation of the underlying vulnerability for schizophrenia-spectrum psychopathology, that is *psychosis-proneness*, a term used to describe a continuum of traits, characteristics, or risk factors that increase the likelihood of experiencing psychotic-like symptoms or transitioning to a full-blown psychotic episode (van Os et al., 2009)

There has been a historical emphasis on genetics as a significant contributor to psychosis risk, with studies utilizing the candidate gene approach to identify specific genes (e.g., COMT) responsible for the development of the disorder (Niculescu et al., 2000; Modinos et al., 2013; Zwicker et al., 2018). Mounting research has increasingly shown that environmental factors, particularly the interaction between genes and the environment, play a critical role in the risk for clinical and subclinical manifestations of this extended phenotype (van Os et al., 2014; Taylor et al., 2022; Misiak et al., 2018). Childhood adversity has been identified as a crucial environmental risk factor for the onset of psychosis and has become the focus of considerable research interest, alongside genetic factors (Barrantes-Vidal, 2014; Morgan & Gayer-Anderson, 2016; van Winkel et al., 2013). Despite advances in research on childhood adversity and genetic susceptibility, the limitations in measurement and research design hinder identifying underlying mechanisms on the pathway to specific maladaptive outcomes (McLaughlin et al., 2014; Border & Keller, 2017).

One major field of etiological investigation revolves around the concept of *stress-sensitivity* (Post, 1992), which is influenced by both environmental factors such as childhood adversity and genetic factors (Meaney et al., 2001). Through the process of psychobiological sensitization to stress (Post, 1985; Monroe & Harkness, 2005; Gunnar, & Quevedo, 2007;

Stroud, 2020), stress-sensitivity is considered as a risk factor and a mechanism mediating the association between exposure to early-life adversity and psychosis (Vaessen et al., 2017; Vaessen, 2018). It has been defined as a trait of individual differences characterized by heightened reactivity at lower levels of stress exposures resulting from individual's vulnerability mechanism that are acquired or inborn (Hammen, 2015). However, the crucial premise that heightened stress-sensitivity is highly a *stable* psychobiological trait has received in fact limited research attention. It has often been conflated with other personality traits like neuroticism (Eysenck, 1947) or symptom expressions (e.g., depression; Liu & Alloy, 2010). As a result, there is still a need to understand how stress-sensitivity develops and how it represents individual differences in response to stress. This necessitates the exploration of potential underlying mechanisms, including genetic susceptibility and exposure to childhood adversity,

Therefore, to better understand the behavior of the stress-sensitivity trait, particularly in nonclinical individuals with a predisposition to psychosis (Barrantes-Vidal et al., 2015), it is crucial to conduct a comprehensive investigation and advance methodological approaches. Nonclinical samples can play a significant role in establishing normative ranges and patterns of stress-sensitivity prior to the onset of psychosis. Such research provides valuable insights into the factors that contribute to risk and resilience, facilitates the development of interventions, and holds broader implications for promoting mental well-being at a public health level. Importantly, the primary focus is on early detection, prevention, or reduction of symptom expression, with particular attention to individuals at risk of schizophrenia and the psychosis spectrum. Nevertheless, it is equally important to consider protective factors, as addressing them, we can identify strengths and resources that can be harnessed to promote resilience and prevent the development of psychopathology. Thus, to truly understand stress-sensitivity and its link to psychopathology, a comprehensive approach that considers underlying mechanisms of risk, but also protective factors, is essential.

2. BACKGROUND

2.1. Psychosis and Schizophrenia Spectrum

2.1.1. Dimensional Conceptualization of the Psychosis Phenotype

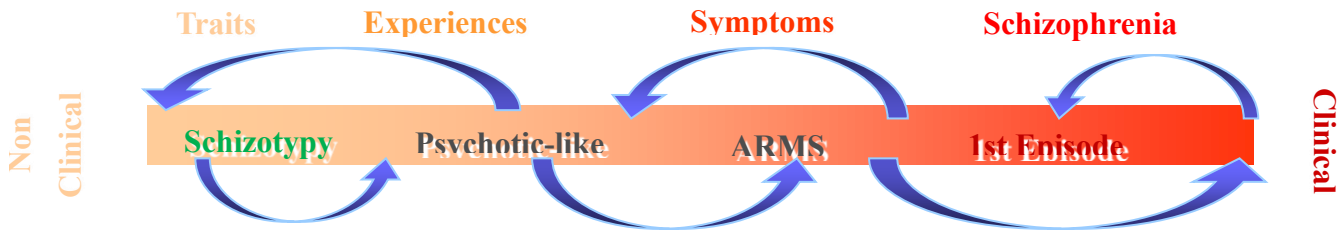
The dimensional conceptualization of psychosis and schizophrenia spectrum disorders refers to an approach that takes a wider perspective by recognizing that psychotic experiences and symptoms exist on a continuum across a broad range of personality, subclinical, and clinical manifestations rather than discrete categorical entities (Altinbas et al., 2020; Claridge, 1997; Debbané & Barrantes-Vidal, 2015; Kwapil & Barrantes-Vidal, 2015). This framework acknowledges that individuals may experience psychotic-like symptoms to differing extents, even in the absence of a clinical diagnosis. Within the dimensional model, psychosis is viewed as a construct with different dimensions including positive of psychotic-like symptom dimensions (e.g., false realities such as hallucinations and delusions), negative of deficit symptom dimensions (e.g., volitional impairments, alogia, and affective flattening), and cognitive-behavioral disorganized symptom dimensions (e.g., disturbances in the ability to organize and express thoughts and behavior such as disorganized speech or catatonic behavior) (American Psychiatric Association, 2013, 2022; Kwapil & Barrantes-Vidal, 2015; Kwapil et

al., 2015. The term *Schizotypy*, a concept that reflects genetic and non-genetic etiological continuity, (Barrantes-Vidal et al., 2015; Claridge, 1997; Ettinger et al., 2015; Kaymaz & van Os, 2010) was first introduced by Rado, 1953 and Meehl, 1962, to describe the continuum of psychosis-spectrum psychopathology ranging from nonclinical (schizotypy traits, psychotic-like experiences), subclinical ("prodrome" or at-risk-mental-states), and clinical states (personality and psychotic disorders) (Debbané & Barrantes-Vidal, 2015; Kwapil & Barrantes-Vidal, 2015) (Figure 1). This fully dimensional model of schizotypy, proposes schizotypy as a part of a normal personality, being a source of both healthy variation and predisposition to psychosis (Barrantes-Vidal et al., 2015) and it serves as a unifying construct that provides unique benefits for understanding the transition from predisposition to disorder (Kwapil & Barrantes-Vidal, 2015; Grant et al., 2018). Thus, schizotypy traits are considered a proxy indicator of psychosis-proneness (Barrantes-Vidal, Racioppi, & Kwapil, Mason & Claridge, 2015).

Schizotypy traits, which encompass schizophrenic-like traits and symptoms as described by Kraepelin (1919) and Bleuler (1950) can be associated to positive aspects such as creativity and unconventional thinking, perspectives, and insights (Acar et al., 2018), however, when these traits have a maladaptive, chronic, and dysfunctional nature they can result in the clinical diagnosis of Schizotypy Personality Disorder (SPD; Kendler,1985). Schizotypal traits frequently correspond with key symptoms of schizophrenia; as a result, SPD has been classified in both the Schizophrenia and Other Psychotic Disorders and Personality Disorders categories, with diagnostic criteria including ideas of references, unusual perceptions, odd belief, and magical thinking, paranoid thoughts, odd thinking and speech, suspiciousness, constricted affect, lack of close friends, and excessive social anxiety (Diagnostic and Statistical Manual of Mental Disorders—DSM-V; American Psychiatric Association, 2013).

Although the large majority of individuals with schizotypy traits will not develop psychosis, studying those with these traits at risk can be useful for elucidating the etiological factors of schizophrenia spectrum disorders and for avoiding the confounds typically associated with schizophrenia diagnosis (Barrantes-Vidal et al., 2015; Schultze-Lutter et al., 2019). By focusing on those individuals at risk, researchers can explore the etiological factors that contribute to the development of psychosis and gain insights into the underlying mechanisms of protective factors and resilience before the onset of full-blown psychosis. This approach enhances our understanding of the early stages of psychosis and may provide valuable information for preventive interventions and the promotion of mental well-being (Barrantes-Vidal et al., 2015; Gottesman & Gould, 2003).

Figure 1.



Kwapil & Barrantes-Vidal, 2015

2.2. Childhood Adversity and Psychosis-Proneness

2.2.1. Operationalization and Prevalence

Childhood adversity affects the global population (Zhang et al., 2020) and has lifelong physical and mental health consequences (Bellis et al., 2019; Nelson et al., 2020). Albott et al. (2018) found that two-thirds of people have experienced at least one type of childhood adversity, and a quarter have experienced several types of maltreatment. Childhood adversity encompasses a range of stressful and traumatic experiences, including abuse (emotional, physical, and sexual), neglect (emotional and physical), bullying, family dysfunction (such as parental divorce or separation, household substance abuse, role reversal, family violence and illness, and lack of adequate nutrition), as well as general trauma such as war and natural disasters (Felitti & Anda, 2010; Butchart et al., 2006; Bifulco & Thomas, 2012). Childhood is a sensitive period in which stable, responsive, nurturing relationships are essential for a child's cognitive and emotional growth, while adversity, on the other hand, impairs normal brain functioning and development (Woodard & Pollak, 2020; Wade et al., 2022). Consequences of early adversity may begin in childhood (Merrick et al., 2017; Negriff et al., 2020) and persist through adulthood (Kolovos et al., 2017). Children exposed to early adversity are more likely to experience social-emotional problems in middle childhood (Choi et al., 2019), subclinical symptoms in adolescence (Luby et al., 2017), and develop common forms of psychopathology throughout adulthood (McLaughlin et al., 2019; Juwariah et al., 2022).

2.2.2. Approaches to Childhood Adversity

Despite the progress made in the complex field of childhood adversity, a significant research challenge continues to be the conceptualization, operationalization, and variability of adversities across studies (McLaughlin et al., 2021; Smith & Pollak, 2021; Brumley et al., 2019). Recent reviews on early adversity (Spies et al., 2019) have identified three main approaches in the study of childhood adversity: the examination of *specific types* of adversity, *cumulative* risk, and *dimensional* approaches. Researchers have examined the impact of cumulative exposure to adversity, while mechanistic studies have focused on how specific exposures contribute to adult outcomes. In fact, different research designs may provide complementary information since distinct qualitative types of adversity can cause specific psychological and biological dysregulations and, at the same time, contribute to a general vulnerability background (Hoppen & Chalder, 2018).

Specificity models, which focus on the effects of one type of adversity (e.g., abuse), have received a lot of research attention (Brown et al., 2015, Smith & Pollak, 2020). This model assumes that specific types of maltreatment predict specific maladaptive outcomes (Brown et al., 2015). However, research separating out a particular type of maltreatment can be problematic as there is often a high degree of co-occurrence between types of maltreatment (Cecil et al., 2017; McLaughlin et al., 2021). The cumulative approach has been the most common measure of the impact of adversity on the development of psychopathology (Lacey & Minnis, 2020). The cumulative index assumes adversities are additive (Metzler et al., 2017). It can easily detect the number of adversity risk factors needed for maladaptive outcomes (Ettekal et al., 2019), which makes it useful, particularly in studies with smaller sample sizes (Evans et al., 2013). However, the cumulative index does not differentiate between experiences

that may affect neurobiological and psychological development in different ways (McLaughlin et al., 2014).

In recent years, Dimensional Models of Adversity and Psychopathology (DMAP; McLaughlin et al., 2014; McLaughlin & Sheridan, 2016) have gained attention as a means of understanding developmental mechanisms associated with various types of adversity. These models propose that multiple exposures to adversity can be conceptualized along two dimensions of environmental experience: Threat (involves harmful experiences or the threat of harm) and Deprivation (includes the absence of expected inputs from the environment) (McLaughlin et al., 2021). While the dimensional approach offers a valuable framework for examining distinct environmental experiences, some relevant adverse exposures, such as intrafamilial adversity and role reversal, are not included in these dimensions, despite posing a risk for psychopathology (Berman et al., 2022; Smith et al., 2021).

As such, researchers stress the importance of using multiple techniques and assessments to better understand the underlying mechanisms between childhood adversity and psychopathology (McLaughlin et al., 2021; Brumley et al., 2019). Complementary assessment methods, such as empirically-driven specificity and cumulative approaches, allow for data reduction, can cover a range of adverse experiences and allow for examination of adversity co-occurrences (Kristjansson et al., 2016; Alvarez et al., 2015). Meanwhile, the dimensional approach facilitates multilevel research, examining interactions with other levels of explanation, such as genetic and person factors. Through this approach, tailored treatment options can be developed to prevent the transition to maladaptive outcomes in adulthood (Miller et al., 2011).

2.2.3. Childhood Adversity and Psychopathology

Childhood adversity has been found to increase the risk of various psychopathological outcomes (Hales et al., 2022; McKay et al., 2022). In psychiatric disorders, childhood adversity is strongly associated with depression (Liu et al., 2017), anxiety (Huh et al., 2017), bipolar disorder (Aas et al., 2016), post-traumatic stress disorder (Lewis et al., 2019), and is considered one of the strongest risk factors for psychosis (Mayo et al., 2017). The likelihood of developing a psychotic disorder is two- to fourfold higher in individuals who have experienced childhood adversity (Morgan et al., 2020; Rosenfield et al., 2022). The expression of symptoms is also linked to childhood adversity, with positive symptom dimensions (Velikonja et al., 2015), psychotic-like experiences, suspiciousness (Cristóbal-Narváez et al., 2016a; Sheinbaum et al., 2015), negative symptoms (Van Dam et al., 2015), paranoia (Sheinbaum et al., 2020), and depressive and anxiety symptoms (Alameda et al., 2020).

Research has shown that specific types of adversity are associated with specific mental health outcomes. Physical abuse and neglect, for instance, have been strongly linked to anxiety (Guo et al., 2021), and sexual abuse and physical neglect have been found to be related to psychosis and schizophrenia (Vaskinn et al., 2020). In addition, family dysfunction and peer victimization have been linked to depression (Guerrero-Muñoz et al., 2021; Sayyah et al., 2022), anxiety, and psychotic symptoms (Juwariah et al., 2022). Studies have also noted that abuse can result in positive and disorganized psychotic symptom dimensions, whereas neglect seems to be more strongly associated with negative and depressive symptom dimensions (Alameda et al., 2021). Specifically, sexual, and emotional abuse have been found to have the

strongest links to schizotypal characteristics, particularly paranoid ideation (Velikonja et al., 2019; Quidé et al., 2018). Similarly, Bentall et al. (2012) found that rape and molestation were associated with hallucinations, while family adversity, such as parental antipathy and role reversal, led to paranoid and schizotypal personality features (Sheinbaum et al., 2015).

Different types of adversity are often interrelated, and their co-occurrence can increase the likelihood of psychopathology outcomes (Spies et al., 2019; Stein et al., 2022). A cumulative index suggests that the outcomes worsen after repeated exposures to adversity (Priebe et al., 2018). Children who experience multiple adversities, such as emotional abuse and neglect (Kumari, 2020) and/or sexual and emotional abuse (Velikonja et al., 2019) may be at an increased risk of developing depression and anxiety (Ip et al., 2016; Wiens et al., 2020), as well as psychosis (Morgan et al., 2020). The cumulative effects of abuse show an association with psychotic-like experiences, where physical and sexual abuse lead to both auditory and visual hallucinations (Shevlin et al., 2011), and physical neglect, abuse, family adversity (e.g., parental separation) lead to paranoia and psychoticism (Wang et al., 2019).

Theoretical predictions of a dimensional model of childhood adversity have been examined to determine if the dimensions of Threat and Deprivation have unique associations with increased risk for psychopathology, primarily focusing on brain structure and function (LoPilato et al., 2019) and different aspects of maladaptive cognition and emotional processing (Schäfer et al., 2023). However, there has been less attention to subclinical and clinical psychopathology, specifically psychosis (LoPilato et al., 2021). Research has shown that the "intention of harm," a component of the Threat dimension, plays a pivotal role as a form of abusive and threatening experience in childhood (Arseneault et al., 2011; Morgan et al., 2020; van Nierop et al., 2014) and is highly related to positive symptom dimensions of psychosis (Gibson et al., 2016; Velikonja et al., 2015; Dizinger et al., 2022), as well as to depressive and anxiety symptoms (McGinnis et al., 2022). The Deprivation dimension, which includes neglect and lack of anticipated stimuli in childhood, has been linked to the negative dimension of psychosis, although there are conflicting findings and less research focus on this topic (Alameda et al., 2021; Bailey et al., 2018; Cristóbal-Narváez et al., 2016a).

2.3. Longitudinal trajectories of Stress-Sensitivity and Psychosis-Proneness

2.3.1. The Operationalization of Stress-Sensitivity

Numerous studies have demonstrated that individuals vary in their susceptibility to environmental and genetic influences, with some being more sensitive than others (Belksy & Pluess, 2009; Belsky, 2013; Slagt et al., 2016; Pluess, 2015). The concept of *sensitivity*, particularly heightened sensitivity to stress, has been linked to the development of a range of psychopathologies such as anxiety, depression, and schizophrenia spectrum disorders, which have shown that early adversity and genetic expression interact to predict individual differences in overly reactive response to stress (Hammen, 2015; Meaney, 2001). It has been hypothesized that a way in which stress impacts the risk of psychopathology is through *stress sensitization*, a process in which repeated exposure to stressors leads to increased sensitivity to stress over time (Post, 1985; Post, 1992; Collip et al., 2008). This means that individuals become more susceptible to environmental stressors and experience exacerbated responses to subsequent exposures, even if the exposures are less severe (Van Winkel et al., 2008). As such, a concept

of heightened *stress-sensitivity* refers to an individual's rapid overstimulation and high reactivity to minor stress and daily hassles (Harkness et al., 2015; Hammen, 2015), and evidence suggests that it may be related to abnormal changes in brain structure and function (Vyas et al., 2016) as well as changes in stress-related hormone activity (Henckens et al., 2016). Stress-sensitivity is considered a major risk factor for developing various psychopathological disorders, particularly anxiety, depression, and psychosis (Rauschenberg et al., 2017; DeVylder et al., 2016; Godoy et al., 2018; Turner et al., 2020).

Various methods can be used to measure stress-sensitivity, including the most common self-report measure, the Perceived Stress Scale (PSS), which assesses psychological and behavioral stress-responses (Crosswell & Lockwood, 2020), laboratory assessments such as the Trier Social Stress Test (TSST), which measures physiological responses (e.g., changes in heart rates, blood, and cortisol levels) (Narvaez et al., 2020), and momentary assessments such as the Experience Sampling Methodology (ESM), which is a structured diary technique assessing participants' feelings and thoughts on multiple occasions as they occur in daily life (Larson & Csikszentmihalyi, 1983).

2.3.2. Assumption of Trait and Stability

Pioneering researchers of human behavior and developers of personality-temperament theories, *trait* has been defined as a "continuous dimension of personality" (Jung, 1993), an "unique characteristic" (Allport, 1931) that describes individual differences in behavioral, cognitive, and emotional patterns (Roberts et al., 2009). Temperamental traits are considered to be stable, fixed in early childhood and resistant to developmental and environmental changes throughout the lifespan (Vyse et al., 2004), often contrasted to a more temporary response to the environment, that is, a *state* experience (Revelle, 1995).

Stress-sensitivity is assumed to be a stable trait that manifests through individual differences in the propensity to experience heightened stress compared to that of an average person (Harkness et al., 2015). People who are stress-sensitive are easily annoyed by issues such as noise, traffic congestion, even a constructive form of criticism (Ellis & Boyce, 2008). So far, stress-sensitivity has been captured in variety of temperamental traits such as neuroticism (Eysenck, 1947), harm avoidance (Cloninger et al., 1993), rumination (Nolen-Hoeksema & Morrow, 1991), trait anxiety (Spielberger, 1975; Meijer, 2001), trait arousability (Mehrabian, 1995), and negative affectivity (Watson et al., 1988). It has been associated with depression (Liu & Alloy, 2010; Farb et al., 2015; Davison et al., 2021), bipolar disorder (Weiss et al., 2015), anxiety disorders (Farmer et al., 2015; Moore et al., 2020), and psychosis (Hernaus et al., 2015; Vaessen et al., 2017). There has been limited investigation into the longitudinal examination of stress-sensitivity, particularly during the transition from adolescence to young adulthood. Instead, related constructs of temperament that tap stress-sensitivity, such as neuroticism (Engert et al., 2021), have been studied more frequently form of high reactivity (e.g., ESM; Myin-Germeys & van Os, 2007, Myin-Germeys et al., 2009; Paetzold et al., 2021; Rauschenberg et al., 2017).

2.3.3. Predictors of Stress-Sensitivity

The traumagenic neurodevelopmental model (Read et al., 2014) and sensitivity hypotheses (Post, 1992) propose that severe stress experienced during critical developmental periods of childhood (combined with genetic factors) can disrupt psychobiological stress

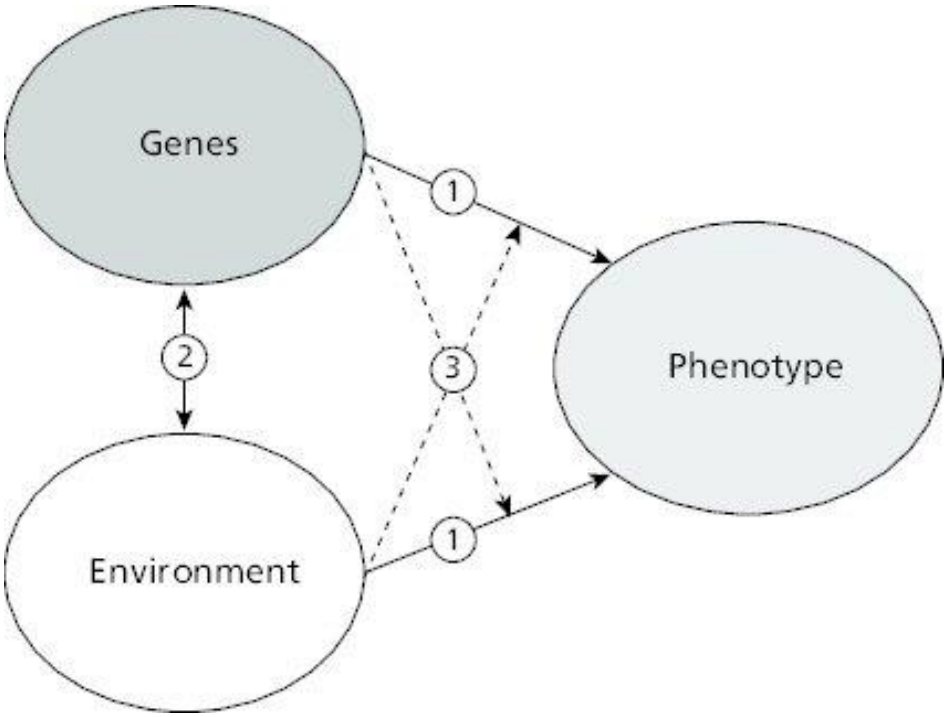
regulatory mechanisms [e.g., gene expression (Leighton et al., 2017), Hypothalamic Pituitary Adrenal -HPA- axis (Starr et al., 2021), amygdala functioning (Weissman et al., 2020), and attachment (Lahousen et al., 2019)], resulting in abnormal stress responses.

Environmental adversity, especially in childhood, can exacerbate stress-sensitivity, making individuals more prone to negative affect and reduced positive affect in adulthood (Paetzold et al., 2021), increased subjective stress appraisals (LoPilato et al., 2020), and higher perceived intensity of daily-life stress (Mosley-Johnson et al., 2021). Some specific genetic variants, such as FKBP5, COMT, BDNF have been associated to heightened stress-sensitivity (Caspi et al., 2010; van Winkel et al., 2008; Hernaus et al., 2013; Cristóbal-Narváez et al., 2016b). For example, individual variation in the FKBP5 gene is linked to the dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis, which has been identified as a critical neurobiological mechanism underlying the emergence of psychotic symptoms (van Winkel et al., 2008). However, the interaction between genetic susceptibility and environmental adversity (GxE) (Figure 2 and Figure 3) greatly affects stress-sensitivity, where this interplay of individual's genetic makeup influences their response to the environment and the environment may trigger genetic expression, leading to significant stress-related problems (Davidson et al., 2021).

The majority of the GxE research examining genetic predictors of stress-sensitivity has been conducted using a candidate gene approach (Hernaus et al., 2013), but polygenic approaches have been proposed as a complementary strategy that could better represent the genetic profile and explain variations within the stress-sensitivity mechanism (Rutter et al., 2006; Halldorsdottir & Binder, 2017; Bulik-Sullivan & Neale, 2015; Maier et al., 2015). Polygenic Risk Score (PRS) takes into account the contributions of many common genetic variants across the entire genome, weighting each SNP by the effect size obtained from a Genome Wide Association Study (GWAS)– a research approach that identifies genomic variants statistically associated with a given disease or trait. Two genetic scores based on genome-wide association studies (GWAS) have been reported in relation to stress-sensitivity. The first score, developed by Arnau-Soler et al. (2018), is known as the Polygenic Risk Score for stress-sensitivity (PRS-SS). It was derived from the association between genetic variants and levels of neuroticism, which serves as a proxy phenotype for stress-sensitivity, in individuals diagnosed with Major Depressive Disorder (MDD). The second score, identified by Crawford et al. (2021), is relevant to the function of the HPA-axis and is referred to as the Genetic Risk Score for HPA-axis function (GRS-HPA). This score was derived from a GWAS conducted on morning plasma cortisol levels (which is the end-product glucocorticoid of the HPA axis; Stephens & Wand, 2012) in a sample from the general population.

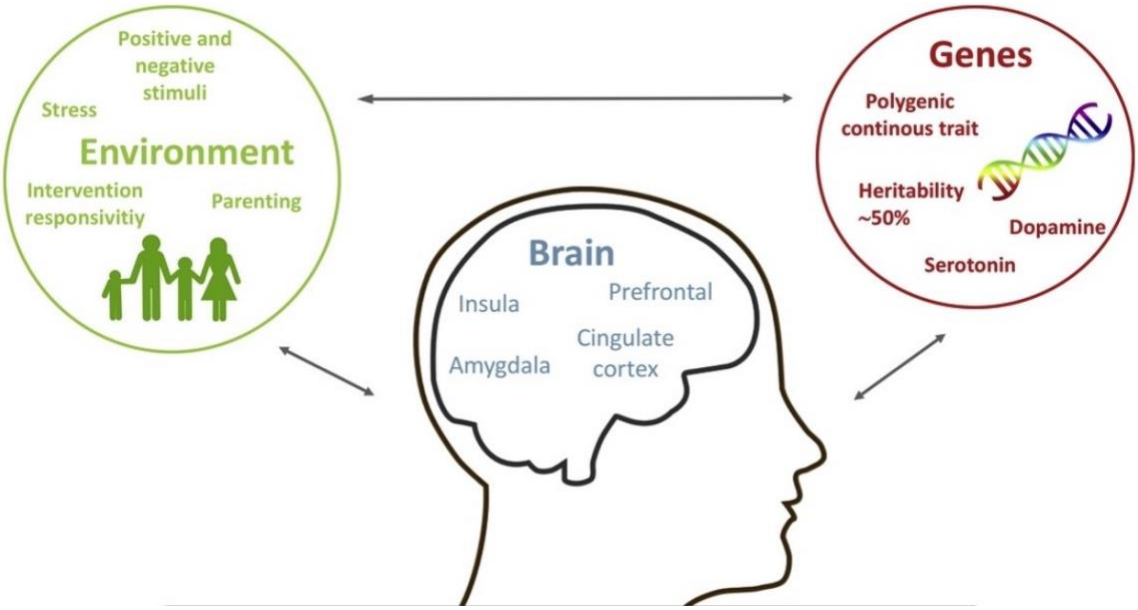
Previous research has demonstrated that genetic variants associated with stress-regulation systems, such as FKBP, interact with childhood adversity to influence reactivity to stress. This includes both momentary (Cristóbal-Narváez et al., 2017; van Winkel et al., 2014) and retrospective (McKenna et al., 2021) assessments of stress, as well as exposure to stressful life events (Feurer et al., 2017; Starr & Huang, 2019). However, little research has focused on genetic markers of stress-sensitivity as predictors of this trait (Arnau-Soler et al., 2018), thus, it is yet to be determined how these genetic risk scores can predict changes in sensitivity to stress, particularly in the interaction with the early environment.

Figure 2.



Pluess & Meaney, 2015

Figure 3.



Greven et al., 2019

2.3.4. Stress-Sensitivity and its Predictors as a Psychosis-Proneness Mechanism

There is compelling evidence that associates high stress-sensitivity to all stages of the psychosis spectrum (DeVylder et al., 2016; Collip et al., 2013; Aiello et al., 2012; Walker et al., 2008). Abnormal stress responses, such as sensitization of the HPA axis and dysregulation of the dopamine system, have been linked to increased psychotic symptoms prior to the onset of psychosis (van der Steen et al., 2017). These abnormal stress response mechanisms may explain how individuals attribute abnormal emotional salience to their internal representations and external stimuli, leading to subclinical psychotic experiences and affective responses. (Kapur, 2003) suggesting a contribution of heightened stress-sensitivity to the manifestation of psychosis-related symptoms.

Studies using moment-to-moment assessments, such as the Experience Sampling Method (ESM), have further supported the association between sensitivity to stress and psychotic experiences. (Schneider et al., 2020). These studies have shown that individuals, particularly those predisposed by genetic and environmental influences who exhibit high reactivity to stress (triggered by minor stressors, daily activities and social situations), tend to experience increased intensity of subclinical psychotic experiences and affective responses in their daily lives (Collip et al., 2008; Myin-Germeys & van Os, 2007; Reininghaus et al., 2016). Similarly, elevated retrospective stress appraisals were found to contribute to increase attenuated psychotic symptoms in those previously exposed to early adversity (Gibson et al., 2016). More so, individuals with both genetic vulnerability and a history of childhood adversity tend to be more stress-sensitive and have a greater risk of developing psychosis (Holtzman et al., 2013; Myin-Germeys & van Os, 2007).

2.4. The Associations of Psychosocial Stressors and Protective Factors with Psychosis-Proneness in the context of the COVID-19 Pandemic

2.4.1. Psychosocial Risk Factor of Psychosis during COVID-19: Loneliness

The COVID-19 pandemic has had a profound impact on people's daily lives, causing stressors that have negatively affected the mental health of the entire population (World Health Organization—WHO, 2020; NIH, 2022). Researchers have noted an increase in predicted psychosis spectrum cases, as well as a rise in depression, anxiety, stress, and psychosis symptoms (Brown et al., 2020; Fierini et al., 2020). The restrictions imposed by governments worldwide, such as lockdowns, social distancing, and isolation, have led to loneliness being a significant factor in the increased prevalence of mental health problems (Gizdic et al., 2022; Allé & Berntsen, 2021).

While social withdrawal is often seen as a symptom of psychosis, research has shown that loneliness itself can be a risk factor for the onset of the disorder (Lim et al., 2018; da Rocha et al., 2018). Individuals with a large social network can experience loneliness, as it is a subjective emotion that arises from a perceived social relationship deficit (Macdonald et al., 1998; Hawkley, 2015). It is an unpleasant and distressing experience, leading to poor physical and mental health outcomes, particular in individuals at risk of psychosis (Stefanidou et al., 2021). Loneliness can cause psychotic symptoms through direct or several other mechanisms, such as in combination with depression, anxiety, and stress that exacerbate psychotic-like symptoms (Heinrich & Gullon, 2006). It can also increase negative self- and other beliefs

leading to paranoia experiences (Lamster et al., 2017). Therefore, addressing loneliness within a multi-faceted psychosocial intervention is crucial for those at risk of developing psychosis and schizophrenia.

It is worth noting that loneliness is often chronic, meaning that long-term interventions may be necessary. Addressing loneliness can be a challenging process, requiring an understanding of the factors that contribute to it. However, interventions that target the underlying causes of loneliness, such as social isolation or a lack of social support, can help individuals who are experiencing loneliness to improve their mental health and well-being. Overall, the COVID-19 pandemic has highlighted the need to prioritize mental health and develop effective interventions to address the negative effects of loneliness and other psychosocial stressors on the psychosis risk.

2.4.1. Psychosocial Protective Factors of Psychosis during and post COVID-19: Resilience and Social Connectedness

Resilience is a critical factor that can help individuals cope with adversity and illness and promote a faster recovery, particularly in those with psychosis (Babić et al., 2020; Rutten et al., 2013). It acts as a defense mechanism that helps buffer against traumatic and stressful situations while maintaining functional levels (Deluca et al., 2022). Resilience provides a substantial protective effect with favorable outcomes across the entire psychosis spectrum (Wambua et al., 2020; Yeo et al., 2022; DeLuca et al., 2022), reducing negative and mood symptoms and improving functioning (Luther et al., 2020; Mizuno et al., 2016). It also protects against the development of psychopathology symptoms during large collective traumas, such as natural disasters and pandemics (Rossi et al., 2020). Therefore, interventions aimed at reducing the risk of developing psychopathology, specifically psychosis symptoms, should consider resilience as a significant factor.

In promoting resilience, social connectedness plays a crucial role, especially during difficult times (Nitschke et al., 2020). However, in psychosis, social connectedness is often inadequate, resulting in smaller network sizes and more severe positive and negative symptoms (Gayer-Anderson & Morgan, 2013; Koenders et al., 2017; Degnan et al., 2018; Vogel et al., 2021). Conversely, satisfactory social connectedness and support act as protective factors, reducing loneliness, psychosis symptoms, and potential relapse and readmissions (da Rocha et al., 2018; Vázquez Morejón et al., 2018; Degnan et al., 2018).

Through providing a sense of belonging, strengthening social ties, and encouraging altruism, social connectedness and support promote resilience, especially among those exposed to trauma and difficult circumstances, such as the COVID-19 pandemic (Agashe et al., 2021; Nitschke et al., 2021). Recent studies support the idea that collective impulse protects individuals during times of stress and uncertainty (Duan et al., 2019; Vukojevic et al., 2020; Bastian et al., 2014; Garcia & Rime, 2019), exemplifying the phrase "we're all in this together". Understanding the relationship between social connectedness and resilience is essential to develop evidence-based mental health interventions, especially for vulnerable individuals and those with psychosis. Therefore, identifying the aspects that hinder recovery and addressing social determinants of mental health is crucial.

3. AIMS AND OUTLINE OF THIS THESIS

As a putative risk mechanism for psychosis, the current thesis investigates the complex phenotype of stress-sensitivity across a broad spectrum of contexts and timeframes. It offers an in-depth investigation of childhood adversity with a particular focus on schizophrenia-related phenotypes as well as of genetic variations in predicting longitudinal trajectories of stress-sensitivity. More so, this thesis explores other related psychosocial factors that are both significant risk and protective factors in psychosis in the face of the highly stressful and uncertain life situation of the COVID-19 pandemic.

Thus, this thesis comprises several research sections and objectives. The **first** and **second sections** are part of the Barcelona Longitudinal Investigation of Schizotypy (BLISS), which is a longitudinal follow-up project that explores risk and resilience factors for schizophrenia-spectrum psychopathology in Spanish young adults, across almost eight years. The doctoral candidate used data from various of these datawaves to address a number of research issues. The **third section** of the thesis involves data collection on the general population in Croatia. Croatia has experienced multiple generations of war trauma resulting from World War I, World War II, and the Croatian Independence War (Lampe et al., 2022). As a result, the population has adapted to increasing levels of adversity over time, making it a unique opportunity to examine risk and resilience to psychosis and support the stress-sensitivity mechanism within this population.

To begin, the **first section** of this thesis aimed to improve the understanding of childhood adversity and its relationship to psychopathology. The study in *Chapter 1* presented an in-depth conceptualization of childhood adversity, combining factor analytic and cumulative risk approaches. To achieve this, the study first identified the underlying dimensions of gold-standard measures of childhood adversity by combining self-report and interview measures. The resulting specific adversity factors and cumulative risk index were based on the DMAP conceptual model. And secondly, the cross-sectional associations between childhood adversity dimensions and cumulative risk with the measures of depression, anxiety, and psychosis-spectrum symptom dimensions were investigated. The study did not set an a priori hypothesis regarding the number or nature of derived adversity dimensions, but distinction between the dimensions of *Threat* and *Deprivation,* and some degree of specificity in their associations with psychopathology symptoms was expected. The childhood adversity dimensions were examined simultaneously to test current recommendations (Cecil et al., 2017; Sheridan & McLaughlin, 2020). Lastly, cumulative adversity was expected to increase the levels of symptoms. The *Chapter 2* aimed to build upon the findings from Chapter 1 and in longitudinal manner explored how such adversity dimensions prospectively predict psychopathology symptoms, social, as well as psychological factors across the three most recent assessments of the BLISS sample—the last one spanning almost eight years from baseline. In this study, we included social-psychological outcomes related to constructs relevant to adversity exposures such as attachment styles, and social adaptations (e.g., subjective perception of social support and loneliness, quantitative social network). It was hypothesized that previously assessed dimensions of adversity would provide additional information on their association to psychopathology symptoms, social, and psychological outcomes. Specifically, based on literature (e.g., McLaughlin et al., 2020) and our previous findings, exposure to childhood adversity would predict greater levels of psychopathology as

well as insecure attachment styles, loneliness, and decreased social adjustments and support. *Threat* would yield the strongest associations with psychopathology, specifically positive symptom dimensions, and *Deprivation* with negative symptom dimensions. Again, no a priori hypothesis was given to *Intrafamilial Adversity*, but it was expected to find associations with insecure attachment based on prior research on adverse experiences with caregiving figures (Bifulco & Thomas, 2012). Despite significant advancements in the field of childhood adversity in recent decades, researchers still lack comprehensive operationalization of adversity while grappling with difficult conceptual and measurement issues (Lacey & Minnis, 2020). Thus, the findings of the first section of this thesis provided detailed conceptualization and understanding of the impact of childhood adversity on the development of psychopathology and highlighted the need for complementary approaches and comprehensive assessment of distinct yet related childhood adversity experiences (Cecil et al., 2017; McLaughlin et al., 2021).

The **second section** of this thesis then investigated stress-sensitivity as a trait of individual differences and its underlying mechanisms in the context of gene, environment, and their interactions. First, the study in *Chapter 3* investigated the longitudinal stability of stress-sensitivity as a *trait* of individual differences using retrospective appraisals of perceived stress (PSS) and novel momentary ESM measures of daily-life stress appraisal across nonclinical levels of psychosis risk in adolescents and young adults. This phenotype is assumed to be a biologically related stable trait, but there is scant evidence supporting this major assumption in psychosis research. Thus, considering the *trait* assumption, the study hypothesized that stress-sensitivity would be relatively stable across time following both assessment measures, and that distinct longitudinal trajectories of stress-sensitivity would be found across individuals. Secondly, *Chapter 4* investigated the predictors of stable stress-sensitivity phenotype across measurements used in Chapter 3. Previously assessed childhood adversity dimensions, novel psychological polygenic risk score and biological genetic risk score, and their interaction were examined. The study hypothesized that individuals with a high genetic susceptibility to stress-sensitivity (i.e., high PRS-SS and GRS-HPA) and high levels of childhood adversity would exhibit persistent stress-sensitivity compared to those with low genetic susceptibility and low adversity. Additionally, following the DMAP model, it was expected that the dimension of *Threat*, as the strong key factor for the development of subclinical and clinical symptomatology, would yield the most significant interactions with genetic markers of stress-sensitivity.

Finally, the **third section** of this thesis included investigation of related significant risk and protective factors in the development of psychosis during and post COVID-19 pandemic in. In *Chapter 5,* the role of psychosocial predictors of both physical and mental health, particularly loneliness was explored among the Croatian population during the pandemic. This investigation focused on psychosis risk, depression, anxiety, and stress. Additionally, the study examined the effects of the current pandemic, loneliness, and psychosis risk in individuals with a history of trauma exposures. The study hypothesized that loneliness would have a negative impact on overall mental health and would act as a significant risk factor in predicting psychotic symptoms. Specifically, it was anticipated that individuals with a history of trauma would be more vulnerable to the effects of the current pandemic, loneliness, and psychosis risk. Building on findings from Chapter 5, the study in *Chapter 6* sought to examine the role of psychosocial

predictors in determining general and mental health in the Croatian population two years after the beginning of pandemic. Specifically, the study focused on the role of social connectedness and resilience as protective factors of psychosis-risk, depression, anxiety, and stress. It was hypothesized that the rates of mental and general health problems would increase. Specifically, we anticipated that symptomatology and social connectedness would play a crucial role in determining resilience, particularly among individuals who had experienced trauma in the past. Given Croatia's recent history of transgenerational war trauma and the relative lack of prodromal data, these studies presented a unique opportunity to examine the impact of loneliness and other psychosocial factors of risk and resilience on psychosis-proneness.

Taking an integrative approach, this thesis examined the stress-sensitivity as a psychosis-proneness mechanism considering the interplay of genes, environment, and gene-environment interactions (GxE) as risk factors for heightened stress-sensitivity. The research studies of this thesis included an in-depth investigation of childhood adversity, polygenic and genetic risk scores, and related psychosocial factors associated with psychosis. Also, the manifestations of psychopathology in the context of the COVID-19 pandemic proposing protective factors that could alleviate their impact on the development of psychosis were explored.

4. EMPIRICAL WORK

SECTION 1

CHILDHOOD ADVERSITY AND PSYCHOSIS-PRONENESS

Chapter 1

Empirically-derived dimensions of childhood adversity and cumulative risk: Associations with measures of depression, anxiety, and psychosis-spectrum psychopathology

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Abstract

Background: Investigating different approaches to operationalizing childhood adversity and how they relate to transdiagnostic psychopathology is relevant to advance research on mechanistic processes and to inform intervention efforts. To our knowledge, previous studies have not used questionnaire and interview measures of childhood adversity to examine factor-analytic and cumulative-risk approaches in a complementary manner.

Objective: The first aim of this study was to identify the dimensions underlying multiple subscales from three well-established childhood adversity measures (the Childhood Trauma Questionnaire, the Childhood Experience of Care and Abuse Interview, and the Interview for Traumatic Events in Childhood) and to create a cumulative risk index based on the resulting dimensions. The second aim of the study was to examine the childhood adversity dimensions and the cumulative risk index as predictors of measures of depression, anxiety, and psychosis-spectrum psychopathology.

Method: Participants were 214 nonclinically ascertained young adults who were administered questionnaire and interview measures of depression, anxiety, psychosis-spectrum phenomena, and childhood adversity.

Results: Four childhood adversity dimensions were identified that captured experiences in the domains of *Intrafamilial Adversity*, *Deprivation*, *Threat*, and *Sexual Abuse*. As hypothesized, the adversity dimensions demonstrated some specificity in their associations with psychopathology symptoms. *Deprivation* was uniquely associated with the negative symptom dimension of psychosis (negative schizotypy and schizoid symptoms), *Intrafamilial Adversity* with schizotypal symptoms, and *Threat* with depression, anxiety, and psychosis-spectrum symptoms. No associations were found with the *Sexual Abuse* dimension. Finally, the cumulative risk index was associated with all the outcome measures.

Conclusions: The findings support the use of both the empirically-derived adversity dimensions and the cumulative risk index and suggest that these approaches may facilitate different research objectives. This study contributes to our understanding of the complexity of childhood adversity and its links to different expressions of psychopathology.

Keywords: childhood adversity, childhood trauma, psychopathology, dimensional models, cumulative risk, schizotypy, psychosis, depression, anxiety.

Highlights

*We investigated how different approaches to operationalizing childhood adversity relate to transdiagnostic psychopathology.
*Four childhood adversity dimensions were found to underlie multiple subscales from three well-established childhood adversity measures.
*The childhood adversity dimensions demonstrated some specificity in their associations with the psychopathology symptom domains and the cumulative risk index was associated with all the outcomes.

1. Introduction

The term childhood adversity refers to a range of negative early-life experiences that constitute deviations from the expectable environment and are likely to require considerable adaptation by a child (McLaughlin, 2016). These experiences include childhood abuse and neglect, bullying, witnessing domestic violence, losses, and non-interpersonal experiences, such as accidents and natural disasters (Bifulco & Thomas, 2012; Butchart et al., 2006). Childhood adversity has been increasingly recognized as a leading risk factor for the development of multiple psychopathological conditions and subclinical manifestations, including depression, anxiety, and psychosis spectrum phenotypes (Copeland et al., 2018; Humphreys et al., 2020; Varese et al., 2012).

Despite the notable progress in the field of childhood adversity over the last decades, researchers continue to grapple with challenging conceptual and measurement issues (Lacey & Minnis, 2020). One such issue concerns how best to study the effects of childhood adversity on the risk for psychopathology (McLaughlin et al., 2021; Smith & Pollak, 2021), which has implications for advancing research on mechanistic processes and the design of intervention efforts (Danese & Lewis, 2022; Lacey & Minnis, 2020). For example, specificity models (i.e., focusing on the effects of individual adversity subtypes, such as sexual abuse) have received considerable theoretical attention and have been widely investigated. However, the evidence of the substantial co-occurrence of different adversity subtypes (and the resulting potential overestimation of the effects of individual subtypes in such models) has highlighted the need for complementary approaches (Cecil et al., 2017; McLaughlin et al., 2021).

Currently, the most common approach to measuring the effects of childhood adversity is the cumulative risk approach (Lacey & Minnis, 2020), which involves calculating a cumulative score by summing the number of adversities an individual experienced. Thus, cumulative risk is an additive model that focuses on the amount (not the kind) of adversities (Evans et al., 2013; Sheridan & McLaughlin, 2020). This approach offers several advantages, such as ease of interpretation and benefits in terms of statistical power (Ettekal et al., 2019; Evans et al., 2013). Furthermore, a robust body of research demonstrates that experiencing an increased number of childhood adversities is associated with an increased risk for a range of psychopathological outcomes (Chapman et al., 2004; Evans et al., 2013; Stein et al., 2022). Nevertheless, the cumulative risk approach has been considered insufficient to fully characterize the effects of childhood adverse experiences because, among other things, it does not consider the patterning of adversities and assumes that all adversities impact development via similar mechanisms (Lacey & Minnis, 2020; McLaughlin & Sheridan, 2016).

Other approaches to operationalizing childhood adversity have focused on deriving dimensions of adversity. Theory-driven dimensional models suggest that different adversity subtypes share common features that are likely to influence developmental processes in similar ways (McLaughlin et al., 2021). In this regard, the Dimensional Model of Adversity and Psychopathology (McLaughlin & Sheridan, 2016) is an influential framework that proposes that childhood adversities can be conceptualized along two dimensions that have distinct pathways to psychopathology. These dimensions are threat (involving harm or threat of harm, e.g., abuse) and deprivation (involving lack of expected environmental inputs, e.g., neglect). Although empirical support for this approach has begun to accumulate (e.g., Miller et al., 2018;

Schäfer et al., 2023), one limitation is that some adversity subtypes do not clearly map onto these dimensions or may include aspects of both (Smith & Pollak, 2021).

On the other hand, researchers have also obtained dimensions using empirically-driven methods, such as factor-analytic approaches, which group childhood adversities based on the extent to which they are correlated with each other. Factor scores have gained attention in the assessment of several constructs, such as externalizing and internalizing disorders (Caspi et al., 2014) and, to a lesser extent, childhood adversity (Brumley et al., 2019). Factor-analytic approaches allow for examining the impact of the specific patterning of childhood adversity subtypes (Lacey & Minnis, 2020) and have benefits for improving measurement parsimony (Mersky et al., 2017). Overall, the empirical literature in this domain is somewhat inconsistent, likely related to differences in the childhood adversity subtypes included across studies (Lian et al., 2022; Mersky et al., 2017). Other empirically-driven methods include person-centered approaches, such as latent class analysis, which identifies subgroups of individuals with similar patterns of adversities. Although studies vary in the number and composition of classes, several have identified low adversity and poly-victimization classes (Debowska et al., 2017; McLafferty et al., 2021) and differential associations between some adversity classes and mental health outcomes (Hagan et al., 2016; O'Donnell et al., 2017). Of note, studies using empirically-driven methods to operationalize adversity have tended to focus on experiences of abuse and neglect (Lacey & Minnis, 2020). Therefore, more work is needed that incorporates additional relevant experiences within the family (e.g., role reversal) and other relational environments (e.g., peer bullying).

Research has robustly linked childhood adversity with dimensional and categorical measures of depression, anxiety, and psychosis-spectrum phenomena using various approaches, including cumulative risk (Copeland et al., 2018; Kim et al., 2021; Longden et al., 2016; Morgan et al., 2020). Although variability in the operationalization of adversity complicates comparing results using other approaches, some notable findings have emerged. For example, depression has been prominently linked with experiences in the domain of emotional maltreatment (Humphreys et al., 2020; Mandelli et al., 2015). Meanwhile, in the field of psychosis, the adversity-psychosis link is especially robust for the positive symptom dimension (Gibson et al., 2016; Velikonja et al., 2015), and experiences characterized by an 'intention to harm' appear to be of particular relevance (Arseneault et al., 2011; Morgan et al., 2020; van Nierop et al., 2014). Even though the negative dimension of psychosis has received less attention (Gibson et al., 2016), evidence indicates stronger or more consistent associations with neglect than with other adverse experiences (Alameda et al., 2021; Bailey et al., 2018; Cristóbal-Narváez et al., 2016).

Several previous studies in the field have been limited by covering a narrow range of experiences and using checklist measures of adversity. Hence, using comprehensive questionnaire and interview measures should allow for greater precision of models linking childhood adversity and psychopathology (Bifulco & Schimmenti, 2019). Furthermore, research using different approaches in a complementary manner may offer useful insights regarding the operationalization of childhood adversity. For example, in a recent study, McGinnis et al. (2022) found that different theory-driven dimensions of adversity and a cumulative measure (constructed from these dimensions plus an additional adversity scale) were associated with long-term psychiatric and functional outcomes. They concluded that their

results supported using the cumulative measure for estimating relative risk for these outcomes and the adversity dimensions for obtaining mechanistic insights. Thus, using theoretically - or empirically-derived dimensions of adversity to build a cumulative risk index may provide a valuable integration and contribute to the refinement of cumulative models.

The present study

Leveraging interview and self-report assessments of a range of childhood adversities, the present study used factor-analytic and cumulative risk approaches in a complementary manner to investigate associations of childhood adversity with transdiagnostic psychopathology assessed in a non-clinically ascertained sample of young adults. Specifically, the first aim of the study was to use principal components analysis (PCA) to identify the dimensions underlying multiple subscales from three well-established childhood adversity measures and to create a cumulative risk index based on the resulting dimensions. As part of this aim, we sought to examine whether the PCA-derived childhood adversity dimensions were consistent with those proposed by the Dimensional Model of Adversity and Psychopathology, in which experiences of threat and deprivation are distinguished. The second aim of the study was to examine the PCA-derived childhood adversity dimensions and the cumulative risk index as predictors of depression, anxiety, and psychosis-spectrum symptom dimensions, assessed via questionnaire and interview measures.

PCA is an exploratory approach, and we did not make specific hypotheses regarding the number and nature of the PCA-derived dimensions. However, we expected that the resulting dimensions would show at least some degree of specificity in their associations with psychopathology symptoms. To provide a robust test of this hypothesis and consistent with current recommendations (Cecil et al., 2017; Sheridan & McLaughlin, 2020), the childhood adversity dimensions were examined simultaneously to determine their unique effects. Finally, we expected that higher cumulative adversity would be associated with higher levels of symptoms.

2. Methods

2.1. Participants and procedure

The present study is part of the Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; Barrantes-Vidal et al., 2013a, 2013b). Participants were students from the Universitat Autonòma de Barcelona who completed a battery of self-report and interview measures. Specifically, at time 1 (T1), 589 undergraduates completed self-report questionnaires as part of mass-screening sessions. Usable screening data was obtained from 547 participants (42 were excluded due to the invalid protocols). The mean age was 20.6 years (SD=4.1) and 83% were women. A subset of 339 participants was invited to take part in an interview study with the goal of assessing 200 individuals. Those invited included all 189 who had standard scores based upon sample norms of at least 1.0 on one or more measures of schizotypy and psychotic like experiences, and 150 randomly selected participants who had standard scores < 1.0 on these measures. This enrichment procedure was done to increase the variance associated with mental health outcomes in the sample. At time 2 (T2), 214 participants (mean age= 21.4; SD=2.4; 78% female) completed the interview study. Of the participants, 123 had elevated scores in one or more of the measures of schizotypy and psychotic-like

experiences, and 91 had standard scores < 1.0. The mean time interval between T1 and T2 was 1.7 years (SD=0.2; range=1.4–2.2 years). The university ethics committee approved the study and participants provided informed consent at both assessments.

2.2.Measures

Clinical psychologists and trained advanced graduate students in clinical psychology administered the measures described below, along with other measures not used in the present study.

2.2.1. Childhood adversity measures

At T1, participants completed the Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein and Fink, 1998), a self-report measure that assesses sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. CTQ items are answered on a 5-point Likert-type scale ranging from 'never true' to 'very often true' and are summed to obtain a score for each subtype of maltreatment.

At T2, participants were administered two interview measures, the Childhood Experience of Care and Abuse (CECA; Bifulco et al., 1994) and the Interview for Traumatic Events in Childhood (ITEC; Lobbestael et al., 2009; Lobbestael & Arntz, 2010). The CECA is a semi-structured, investigator-based interview that focuses on objective aspects of childhood experiences. The following CECA scales were used: Parental antipathy, role reversal, parental discord, violence between parents, and bullying. The scales are rated on a 4-point scale ranging from 'marked' to 'little/none,' based on specific rating rules and benchmark thresholds. When applicable, overall scale ratings were obtained (i.e., peak rating taking into account behaviour from both mother and father figure; see Sheinbaum et al., 2015). CECA scores were reversed such that higher scores indicate greater severity. The ITEC is a semi-structured interview that assesses sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. Every endorsed ITEC item is followed by questions covering different parameters of the experience, including the age of onset, perpetrator(s), duration, and frequency. These parameters are rated according to predefined answer categories and are used to calculate composite severity scores for each maltreatment subtype.

2.2.2 Psychopathology measures

At T1, participants completed the depression and anxiety subscales of the Symptom Checklist- 90-Revised (SCL-90-R; Derogatis, 1977), the suspiciousness subscale of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991), and the Wisconsin Schizotypy Scales (WSS). The WSS are composed of the Perceptual Aberration Scale (Chapman et al., 1978), the Magical Ideation Scale (Eckblad & Chapman, 1983), the Revised Social Anhedonia Scale (Eckblad et al., 1982), and the Physical Anhedonia Scale (Chapman et al., 1976). The WSS reliably yield two factors, positive and negative schizotypy, that account for 80% of their variance. Participants were assigned positive and negative schizotypy dimensional scores based upon norms from 6,137 American young adults (Kwapil et al., 2008). Note that the factor structure underlying the WSS was found to be invariant across Spanish and American samples (Kwapil et al., 2012).

At T2, we used the Structured Clinical Interview for DSM–IV Axis II Disorders (SCID–II; First et al., 1997) to assess schizophrenia-spectrum personality disorders. Dimensional scores were computed by summing individual item ratings for each personality disorder. Depression was assessed via interview with the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1992) and via questionnaire with the Beck Depression Inventory-II (BDI; Beck et al., 1996). All of the measures are widely used and demonstrate good psychometric properties in young adult samples.

3. Statistical Analysis

We first calculated descriptive statistics for the study variables and Pearson correlations among the childhood adversity subscales. To obtain the childhood adversity dimensions, we performed a PCA with an oblique (Promax) rotation, given that dimensions of childhood adversity are not expected to be independent. A parallel analysis was conducted to determine the optimal number of factors to retain in the PCA (Lim & Jahng, 2019). Factors were retained if their associated eigenvalue was larger than the 95th percentile of the corresponding eigenvalues derived from the random dataset (Ledesma & Valero-Mora, 2007). In addition, following guidelines by Hair et al. (2014), the cut-off used for interpreting factor loadings from the PCA was .40. When the childhood adversity subscales loaded above .40 on more than one factor, they were interpreted as belonging to the factor on which they had the highest loading.

Linear regression analyses were computed to compare the PCA-derived childhood adversity factor scores and the cumulative risk index as predictors of ten questionnaire and interview measures of depression, anxiety, and psychosis-spectrum psychopathology. Note that the factor scores and cumulative index were examined in separate regression models. In the regression analyses examining the dimensions as predictors, the childhood adversity factor scores were entered simultaneously to examine their unique contribution. In the regression analyses examining the cumulative risk approach, the cumulative risk index was entered as the sole predictor. The cumulative index was calculated by summing the dichotomized factor scores (dichotomized as 'present=1' or 'absent=0' at the 75^{th} percentile; see Evans et al., 2013). Bootstrap procedures with 2,000 samples were used for the regression models.

4. Results

Descriptive statistics for all study variables are displayed in Table 1. The intercorrelations of the childhood adversity subscales are reported in the Supplemental Material.

4.1. PCA of childhood adversity subscales

The parallel analysis indicated that a four-factor solution best accounted for the data. The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the PCA (KMO=.77) and Bartlett´s test of sphericity was significant ($\chi 2$ (105) = 1270.22, $p<0.001$). The PCA yielded five components with Eigen values greater than 1. However, following the parallel analysis, we retained the first four factors.

Table 2 presents the factor loadings of the rotated four-factor solution. The four factors explained 63% of the total variance and their intercorrelations ranged from -.04 to .49. Factor 1 accounted for 32.3% of the variance and was related to subscales indexing *Intrafamilial*

Adversity, including CECA parental discord, CECA role reversal, CECA violence between parents, CECA antipathy, and ITEC emotional neglect. Factor 2 explained 12.4% of the variance and was mostly related to subscales indexing *Deprivation*, including ITEC physical neglect and CTQ physical and emotional neglect. Factor 3 accounted for 10.1% of the variance and was related to adversities indexing *Threat*, including CECA bullying by peers, ITEC emotional and physical abuse, and CTQ emotional and physical abuse. Finally, Factor 4 accounted for 8.1% of the variance and was mostly related to experiences of *Sexual Abuse*, including ITEC and CTQ sexual abuse. Although the highest factor loading per subscale was used to interpret the factors, the following subscales had secondary loadings on an additional factor: ITEC emotional abuse on Factor 1, CECA violence between parents on Factor 4, and CTQ emotional abuse, CTQ physical abuse, and ITEC emotional neglect on Factor 2.

4.2. Associations of the childhood adversity dimensions and the cumulative risk index with psychopathology

Table 3 shows the results of the linear regression analyses examining the PCA-derived childhood adversity dimensions and the cumulative risk index as predictors of the questionnaire and interview measures of depression, anxiety, and psychosis-spectrum psychopathology (the bivariate correlations between the adversity dimensions and outcomes are presented in Supplemental Table 2). The results of the regression analyses using the childhood adversity factor scores as predictors showed that *Intrafamilial Adversity* was significantly associated with schizotypal symptoms, *Deprivation* with negative schizotypy and schizoid symptoms, and *Threat* with all the outcome measures except for schizoid symptoms and CDSS depression. *Sexual Abuse* was not associated with these outcomes. The results of the regression analyses using the cumulative risk index as a predictor showed that cumulative risk was significantly associated with all the outcome measures. The models using the adversity dimensions explained between 8.5% and 25.3% of the variance in the psychopathology symptoms, whereas those using the cumulative risk index explained between 5% and 17.3% of the variance.

As seen in Table 3, the total effects tended to be larger for the adversity dimensions model (average effect size across the ten analyses of .18 [medium effect]) compared to the cumulative approach (average effect size of .12 [small effect]). All of the individual betas for the *Intrafamilial Adversity*, *Deprivation*, and *Sexual Abuse* dimensions were small effects. However, the effects sizes tended to be larger for the *Threat* dimension, especially for outcomes such as schizotypal and paranoid personality disorder symptoms. The beta values in the regression analyses represent the results for the residualized predictors after partialling out variance from the other three adversity dimensions. Examination of the correlations in Supplemental Table 2 indicates that bivariate associations of the individual adversity dimensions tended to be on the order of small-medium effects for *Intrafamilial Adversity* and *Deprivation*, and medium effects for the *Threat* dimension. There were no significant correlations with the *Sexual Abuse* dimension (all the values were below .1).

5. Discussion

This study aimed to 1) identify the dimensions underlying multiple subscales from three well-established childhood adversity measures and 2) use these dimensions and a cumulative risk index based on them as predictors of depression, anxiety, and psychosis-spectrum

psychopathology. To our knowledge, this is the first investigation to use questionnaire and interview measures of adversity to examine factor-analytic and cumulative-risk approaches in a complementary manner. Our results identified four meaningful childhood adversity dimensions and showed that both approaches to operationalizing adversity (i.e., empirically-derived dimensions and cumulative risk) yielded significant associations with the measures of psychopathology. As hypothesized, the adversity dimensions demonstrated some specificity in their associations with the psychopathology symptom domains. Furthermore, the cumulative risk index was associated with all the outcomes. Overall, the study contributes to current efforts to elucidate how different operationalization approaches can inform our understanding of the complexity of childhood adversity and its links to different expressions of psychopathology.

5.1. Childhood adversity dimensions

Regarding the first aim of the study, the results identified four childhood adversity dimensions that captured experiences in the domains of *Intrafamilial Adversity*, *Deprivation*, *Threat*, and *Sexual Abuse*. The finding that the dimensions distinguished between experiences of threat and deprivation provides empirical support to the conceptual distinction proposed by the Dimensional Model of Adversity and Psychopathology. At the same time, however, the results did not fully align with the model, as not all of the proposed threat-related adversities clustered together in our data. Most notably, the CTQ and ITEC sexual abuse subscales formed a coherent separate dimension. This resonates with the results of large factor-analytic studies of adversity items in which sexual abuse loaded separately from other forms of abuse (Brown et al., 2013; Ford et al., 2014). Together, this evidence appears to bolster the view that sexual abuse may be considered a distinct form of adversity (Cohen-Cline et al., 2019) - even distinct from those that also share an element of threat. Alternatively, the findings could be related to issues previously reported to attenuate the association between sexual and non-sexual maltreatment (i.e., the overall low base rate of sexual abuse and that most cases are accompanied by other maltreatment subtypes; see Vachon et al., 2015). Additional research across diverse sample types may help clarify the nature of this finding.

Another consideration concerning the threat-deprivation distinction is that CTQ physical and emotional abuse cross-loaded onto the *Deprivation* dimension. This finding seems to be consistent with the common co-occurrence of experiences of abuse and neglect, which has been proposed to complicate distinguishing among these experiences in research using data-driven approaches (Sheridan et al., 2020). In this regard, the fact that CTQ, but not ITEC, subscales cross-loaded onto *Deprivation* may suggest that interview measures that assess multiple features of maltreatment are better able than self-reports to differentiate between the domains of abuse and neglect. This possibility is in line with several researchers' contention that in-depth interview measures that allow for probing and clarification offer greater precision in their assessment of environmental experience (Bifulco & Schimmenti, 2019; Fisher et al., 2015; Lobbestael et al., 2009).

We also found that *Intrafamilial Adversity* explained the most variance in our data, indicating that the threat-deprivation model is insufficient to account for the variability in childhood adversity. Four CECA subscales and one ITEC subscale loaded primarily onto this dimension. While shared method variance may have contributed to the clustering of CECA subscales, the finding that CECA bullying loaded exclusively onto *Threat* appears to

strengthen the interpretation that these negative environmental experiences within the family environment represent a distinct construct. That ITEC emotional neglect loaded primarily onto this dimension may reflect that this subscale's assessment of the failure to meet a child's emotional needs also taps into elements associated with other poor parenting behaviors (e.g., those related to role reversal). Although previous research has not assessed the same adversity subtypes included in our study, the emergence of this dimension is broadly consistent with earlier findings that adversities related to household dysfunction tend to form a separate factor (Ford et al., 2014; Mersky et al., 2017).

5.2. Associations of childhood adversity with the psychopathology measures

Regarding the second aim of the study, we found that when the adversity dimensions were modeled together, they tended to explain more variance in the outcomes than the cumulative risk index. This dovetails with epidemiological research comparing latent maltreatment factors with a cumulative maltreatment score (Brumley et al., 2019) and supports the utility of this empirical approach. Additionally, the analyses with the adversity dimensions showed that *Threat* was a significant predictor of depression, anxiety, and psychosis-spectrum psychopathology. Notably, within the psychosis symptom domains, *Threat* was more consistently associated with phenotypes involving positive psychotic features, which is in keeping with research pointing to the relevance of adversities characterized by an 'intention to harm' in conferring risk for reality distortion (Arseneault et al., 2011; van Nierop et al., 2014). Our results pertaining to *Threat* are also in agreement with a recent study that found that a dimension of threat-related adversities was associated with anxiety and depressive disorders (McGinnis et al., 2022). It is of note that we found *Threat* to be associated with self-reported depressive symptoms across two time points using different instruments, but not with interview-rated symptoms. Although the reason for this discrepancy is unclear, it may be partly due to a relatively low representation of CDSS ratings in our sample, which had lower mean scores than those reported in a study that established reference values in a healthy sample (Müller et al., 2005). On the whole, the results with the *Threat* dimension are consistent with theoretical and empirical accounts of the patterns of multifinality associated with threat-related adversities (McLaughlin, 2016; McLaughlin et al., 2020).

In line with our expectations, the results with the adversity dimensions demonstrated the presence of specific effects. In particular, *Deprivation* showed a unique association with the negative dimension of psychosis across self-report and interview-based assessments. This parallels meta-analytic findings demonstrating associations between neglect and negative symptoms (Alameda et al., 2021; Bailey et al., 2018) and extends such findings by showing an association over-and-above the variance accounted for by other adversity dimensions. Moreover, these results support prior theorizing that the absence of expected environmental inputs may shape the risk for deficit-like features, such as diminished emotional experience and social disinterest (Gallagher & Jones, 2013).

In addition, *Intrafamilial Adversity* was uniquely associated with schizotypal PD symptoms. This is important considering that identifying environmental precursors to schizotypal PD can contribute to our etiological understanding of the schizophrenia spectrum (Kwapil & Barrantes-Vidal, 2015). However, the symptom heterogeneity that characterizes schizotypal PD complicates the interpretation of this finding - particularly because positive,

negative, and disorganized symptoms are thought to involve different developmental pathways (Barrantes-Vidal et al., 2015). Thus, future work considering the multidimensional nature of this construct may better elucidate its associations with childhood adversity. Finally, it is worth noting that the *Sexual Abuse* dimension was not associated with our other adversity dimensions or our outcome measures both in the regression and bivariate analyses. While there is ample research demonstrating links between sexual trauma and psychopathology (Noll, 2021), the evidence in nonclinical populations is less consistent (Vachon et al., 2015). However, some caution should be taken in interpreting the results for the *Sexual Abuse* dimension. This is likely driven by the fact that a very small proportion of participants reported any sexually abusive experiences (only about 10% did so on the CTQ, with the majority reporting the lowest rating for such experiences). This may in part reflect less willingness of participants to report sexual abuse relative to other forms of abuse. Therefore, additional work is needed to examine these associations in vulnerable populations with greater sexual abuse prevalence and severity.

The current study also found that the cumulative risk index was associated with all the symptoms – indicating that an undifferentiated measure of adversity provides broad (and undifferentiated) associations with psychopathology outcomes. This converges with the literature showing that the accumulation of adverse experiences is pivotal in conferring risk for various psychopathological outcomes, including depression, anxiety, and psychosis-spectrum phenomena (Copeland et al., 2018; Evans et al., 2013; Kim et al., 2021; Morgan et al., 2020). Furthermore, the findings support the predictive value of focusing on the cumulative effect of empirically-derived adversity dimensions, which to our knowledge had not been previously examined. Thus, we believe that a risk score constructed from individual adversity dimensions offers a refinement of cumulative indices that merits further investigation.

The results of this study suggest that both operationalization approaches may offer complementary information to the field. From a theoretical perspective, drawing on previous literature (e.g., Bentall et al., 2014; Evans et al., 2013), it seems plausible that the experiences comprising the childhood adversity dimensions could shape certain developmental processes in partially specific ways while also contributing to a general vulnerability that cumulatively impacts the expression of psychopathology. From a research standpoint, we believe the results highlight a point that other scholars have made (Henry et al., 2021; McGinnis et al., 2022) - namely, that the optimal operationalization approach may be goal-dependent. For instance, while the empirically-derived dimensions may facilitate identifying potential specificity and underlying mechanisms, the cumulative approach may help maximize adversity-outcome associations and facilitate investigating complex interactions with other levels of explanation (e.g., genetic factors).

5.3. Strengths and limitations

A strength of the current study is the comprehensive assessment of childhood adversity and psychopathology conducted with both questionnaire and interview measures. In particular, employing in-depth interview measures of childhood adversity serves to minimize biases associated with subjective responding (Bifulco & Schimmenti, 2019; Lobbestael et al., 2009). In addition, the focus on subclinical phenotypes is considered to facilitate etiological research as participants do not present with the critical confounding factors associated with clinical

status, such as high comorbidity, biographical disruption, stigma, medication side effects, etc. (e.g., Barrantes-Vidal et al., 2015).

The limitations of the study include its cross-sectional nature, which limits inferences about the causal effects of childhood adversities. In addition, our use of a predominantly female university student sample may restrict the generalizability of the findings. In this regard, we note that a recent review found that college student samples tend to produce similar findings than non-student samples in the field of trauma research (Boals et al., 2020). Nevertheless, research in community samples with a more representative distribution of sociodemographic characteristics would enhance generalizability. Finally, additional studies are necessary to examine the extent to which the findings apply to the clinical expression of these phenotypes.

5.4. Conclusions and future directions

In sum, this study investigated different approaches to operationalizing childhood adversity and their links to transdiagnostic psychopathology. The use of comprehensive adversity measures allowed us to obtain a fine-grained characterization of the environment that is not typically afforded by epidemiological research and thus complements existing literature in the field. Using longitudinal designs and investigating the moderators of the links identified in the present study represents an important avenue for future research. For example, some research has found sex differences in the exposure and effects of childhood adversities (e.g., Haahr-Pedersen et al., 2020). Therefore, future work with sex-balanced samples may consider investigating sex as a moderating variable. Furthermore, dimensional models have suggested some specificity in the mechanisms linking different childhood adversity dimensions with psychopathology (McLaughlin et al., 2021). In this regard, elucidating mediating mechanisms and their specificity is a relevant next step that may help identify potential targets for intervention. Continued work in this area is crucial to advance our understanding of risk and resilience in the service of informing preventive intervention and clinical practice for individuals who have experienced childhood adversity.

Authors contribution. Alena Gizdic: conceptualization and methodology, formal analyses, writing-original draft, review and editing, visualization**;** Tamara Sheinbaum: conceptualization and methodology, writing-original draft, review and editing, visualization, data curation**;** Thomas R. Kwapil: conceptualization and methodology, statistical consultation, review and editing; Neus Barrantes-Vidal: conceptualization and methodology, supervision, funding acquisition, resources, data curation, investigation, project administration, writing original draft, review and editing.

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Data availability statement. The data that support the findings of this study are available on request from the corresponding author N.B.V. The data are not publicly available due to privacy or ethical restrictions.

Tables and Figures

Table 1. Descriptive statistics for the childhood adversity subscales and the psychopathology measures.

Measure	Mean	SD	Observed Range	Possible Range
Adversity subscales				
CTQ Emotional abuse	7.07	3.19	5–22	5–25
CTQ Physical abuse	5.42	1.35	5–17	5–25
CTQ Sexual abuse	5.39	1.87	5–25	5–25
CTQ Emotional neglect	9.27	3.43	5–21	5–25
CTQ Physical neglect	5.91	1.52	5–14	5–25
ITEC Emotional abuse*	3.96	4.50	0–22.58	NA
ITEC Physical abuse*	0.93	2.59	0–25.46	NA
ITEC Sexual abuse*	0.17	0.94	0–9.52	NA
ITEC Emotional neglect*	1.51	2.97	0–15.20	NA
ITEC Physical neglect*	1.59	3.22	0–21.40	NA
CECA Bullying	1.61	0.92	1–4	1–4
CECA Parental discord	1.70	1.00	1–4	1–4
CECA Violence between parents	1.13	0.48	1–4	1–4
CECA Antipathy	1.57	0.91	1–4	1–4
CECA Role reversal	1.59	0.87	1–4	1–4
Psychopathology measures				
Positive schizotypy*	0.31	1.18	–1.28–5.13	NA
Negative schizotypy*	0.21	1.22	–1.63–5.18	NA
Suspiciousness	2.97	2.05	0–8	0–8
Paranoid symptoms	1.53	2.08	0–12	0–14
Schizoid symptoms	0.90	1.54	0–8	0–14
Schizotypal symptoms	1.00	1.93	0–13	0–18
SCL-90-R Anxiety	6.99	5.64	0–29	0–40
SCL-90-R Depression	12.33	8.23	0–43	0–52
CDSS Depression	1.21	2.07	0–13	0–27
BDI Depression	5.33	5.33	0–29	0–63

Note1: CTQ= Childhood Trauma Questionnaire; ITEC= Interview for Traumatic Events in Childhood; CECA= Childhood Experience of Care and Abuse; SCL-90-R=Symptom Checklist-90-Revised; CDSS= Calgary Depression Scale for Schizophrenia; BDI=Beck Depression Inventory-II. SD=Standard Deviation; NA: Not applicable.
Note2: *Total range of ITEC severity scores are calculated for each individual based on a formula that includes parameters such as the age of onset, proximity to the perpetrator, and duration; The WSS dimensional scores are standardized scores with a mean of zero and SD of 1.

Table 2. Results of the Principal Components Analysis with Promax rotation.

Adversity subscales	**Factor scores**			
	1 Intrafamilial Adversity	**2 Deprivation**	**3 Threat**	**4 Sexual Abuse**
CECA Parental discord	**.875**	-.119	-.011	.073
CECA Role reversal	**.771**	.082	-.048	-.029
CECA Violence between parents [a]	**.524**	-.087	-.218	.458
ITEC Emotional neglect [a]	**.513**	.455	-.070	-.044
CECA Antipathy	**.506**	.047	.345	-.179
CTQ Physical neglect	-.077	**.860**	-.218	-.016
ITEC Physical neglect	.221	**.727**	-.131	.045
CTQ Emotional neglect	-.051	**.709**	.158	.004
CECA Bullying	-.194	-.202	**.859**	.114
ITEC Emotional abuse [a]	.461	-.125	**.706**	.002
ITEC Physical abuse	.190	-.020	**.578**	-.086
CTQ Emotional abuse [a]	-.048	.479	**.517**	.071
CTQ Physical abuse [a]	-.142	.421	**.482**	.064
ITEC Sexual abuse	.015	-.012	.051	**.904**
CTQ Sexual abuse	-.066	.081	.119	**.875**
Percentage of Variance	32.25%	12.40%	10.05%	8.07%
Eigenvalue	4.84	1.86	1.51	1.21

Note1: Highest factor loadings for a given factor are bolded.
Note2: [a] This subscale has a loading of .40 or above on more than one factor.

Table 3. Linear regressions examining prediction of psychopathology measures by the childhood adversity dimensions and the cumulative risk index.

	Regression Models												
	Adversity Dimensions										**Cumulative Risk**		
	Intrafamilial Adversity		Deprivation		Threat		Sexual Abuse		Total Effect		Risk Index	Total Effect	
Criteria	**β**	f^2	**β**	f^2	**β**	f^2	**β**	f^2	$\underline{R^2}$	f^2	**β**	$\underline{R^2}$	f^2
Questionnaire													
Positive Schizotypy	.094	.01	.150	.02	.169*	.02	.095	.01	.116***	.13	.356***	.092***	.10
Negative Schizotypy	-.113	.01	.215**	.04	.216**	.04	-.008	.00	.114***	.13	.316***	.067***	.07
Suspiciousness	-.009	.00	.138	.02	.317***	.09	.031	.00	.160***	**.19**	.415***	.173***	**.21**
SCL-90 Anxiety	.091	.01	.133	.01	.256***	.06	.045	.00	.153***	**.18**	.336***	.113***	.13
SCL-90 Depression	.132	.02	.040	.00	.358***	.12	.093	.01	.205***	**.26**	.391***	.153***	.13
BDI Depression	.130	.02	.009	.00	.263**	.06	.018	.00	.115***	.13	.288***	.083***	.10
Interview													
Paranoid Symptoms	.080	.01	.012	.00	.434***	**.18**	.010	.00	.226***	**.29**	.401***	.161***	**.19**
Schizoid Symptoms	.028	.00	.152*	.02	.180	.03	-.005	.00	.091***	.10	.225**	.050***	.05
Schizotypal Symptoms	.168*	.03	.085	.01	.362**	.13	.037	.00	.253***	**.34**	.373***	.139***	**.16**
CDSS Depression	.151	.02	.028	.00	.181	.03	.006	.00	.085***	.09	.249**	.062***	.07

p<0.05, ** p<0.01, *** p<0.001.

Note 1: Bootstrap procedures (with 2,000 samples) were employed.

Note 2: SCL-90=Symptom Checklist-90-Revised; CDSS= Calgary Depression Scale for Schizophrenia; BDI=Beck Depression Inventory-II

Note 3: According to Cohen (1992), f^2 values above .15 are medium effect sizes (in bold).

Supplemental Material

Supplemental Table 1. Pearson correlations among childhood adversity subscales.

	CTQ EA	CTQ PA	CTQ SA	CTQ EN	CTQ PN	CECA Bullying	CECA Discord	CECA Violence	CECA Antipathy	CECA Role Rev.	ITEC SA	ITEC PA	ITEC EA	ITEC EN
CTQ PA	***.62***													
CTQ SA	.16*	.13												
CTQ EA	***.61***	**.35**	.06											
CTQ PN	**.34**	.23**	.03	**.46**										
CECA Bullying	**.33**	.21**	.12	.20**	.16*									
CECA Discord	.25**	.14*	-.01	.21**	.16*	.06								
CECA Violence	.02	.05	.17*	.04	.11	-.01	**.35**							
CECA Antipathy	**.46**	**.31**	-.06	**.34**	.10	.13	**.38**	-.01						
CECA Role Rev.	.28**	.15*	.06	.26**	.20**	.10	**.51**	.18*	**.42**					
ITEC SA	.05	.02	***.72***	.05	-.03	.04	.06	.26**	-.07	-.06				
ITEC PA	**.34**	**.33**	-.04	**.31**	.21**	.25**	.27**	.05	**.36**	.24**	-.03			
ITEC EA	***.54***	**.46**	.03	**.40**	.18**	**.43**	***.59***	.11	***.59***	**.47**	.03	***.54***		
ITEC EN	**.41**	.26**	.11	**.38**	**.31**	.09	**.37**	.02	***.58***	***.55***	.00	.22**	**.46**	
ITEC PN	**.40**	**.45**	.08	**.41**	**.39**	.07	.29**	.11	**.3**4**	**.37**	.09	**.33**	**.32**	***.53***

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

*Note*1: PA=Physical abuse, SA=Sexual abuse, EN=Emotional neglect, PN=Physical neglect, Discord= Parental discord, Violence= Violence between parents, Role Rev.=Role reversal

Note2: Correlations of .10 indicate small effect sizes, .30 indicate medium effect sizes (in bold), and .50 indicate large effect sizes (bold and italics)

Supplemental Table 2. Pearson correlations of the childhood adversity dimensions with the psychopathology measures.

	Intrafamilial Adversity	Deprivation	Threat	Sexual Abuse
Positive schizotypy	.26**	.27**	.27**	.09
Negative schizotypy	.06	.26**	.27**	-.01
Suspiciousness	.16*	**.30****	**.38****	.02
SCL-90 Anxiety	.24*	.29**	**.35****	.03
SCL-90 Depression	.28**	.28**	**.43****	.07
BDI Depression	.23**	.19**	**.31****	.00
Paranoid symptoms	.24**	.26**	**.47****	-.01
Schizoid symptoms	.16*	.24**	.26**	-.01
Schizotypal symptoms	**.33****	**.34****	**.46****	.02
CDSS Depression	.23**	.19**	.25**	-.01

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

*Note*1: SCL-90=Symptom Checklist-90-Revised, CDSS= Calgary Depression Scale for Schizophrenia, BDI=Beck Depression Inventory-II.

*Note*2: Correlations of .10 indicate small effect sizes and .30 indicate medium effect sizes (in bold).

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Longitudinal association of childhood adversity dimensions with social and psychological factors and symptoms of psychopathology

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Abstract

Objective: Multi-wave longitudinal research is needed to increase our understanding of the impact of childhood adversity dimensions on psychological and social development and symptoms of transdiagnostic psychopathology. The present study examined three empirically-derived childhood adversity dimensions as predictors of psychological, social, and symptom outcomes across three prospective assessments.

Method: Spanish young adults were assessed five times over eight years. The dimensions underlying multiple subscales from well-established childhood adversity measures administered at the first two assessment waves (described in a previous report) were used in the present study. Outcome data pertain to the last three assessment waves, with sample sizes ranging from 89 to 169. Participants were administered interviews and questionnaires assessing depression, anxiety, psychosis-spectrum phenomena, attachment, social network, social support, and loneliness.

Results: As expected, the childhood adversity dimensions demonstrated overlapping and differential prospective associations with psychopathology and social-psychological factors. *Deprivation* predicted the negative (deficit-like) dimension of psychosis, while *Threat* and *Intrafamilial Adversity* predicted the positive (psychotic-like) dimension. Depression and anxiety were predicted by different adversity dimensions across time. Furthermore, *Threat* predicted a smaller and less diverse social network, *Intrafamilial Adversity* predicted anxious attachment, and *Deprivation* predicted a smaller social network, anxious and avoidant attachment, perceived social support, and loneliness.

Conclusions: These longitudinal findings extend prior work by identifying associations of three meaningful childhood adversity dimensions with different risk profiles across psychological, social, and psychopathological domains. The findings enhance our understanding of the specific impact of different childhood adversity dimensions across the lifespan.

1. Introduction

Several environmental experiences have been the focus of investigation for their etiological relevance to schizophrenia-spectrum phenotypes (Brown, 2011; Wahbeh & Avramopoulos, 2021). Studies of clinical populations have provided valuable insights into the associations of environmental factors with psychotic disorders and their clinical features (Aas et al., 2016; Stanton et al., 2020). Given the continuity between the clinical and subclinical expressions of the schizophrenia spectrum (Barrantes-Vidal et al., 2015), focusing on the course of subclinical expressions may shed light on the role of early experiences in the development of these phenotypes (Kwapil & Barrantes-Vidal, 2012; Barrantes-Vidal et al., 2015).

Childhood adversity is a robust risk factor for schizophrenia-spectrum symptoms and disorders (Varese et al., 2012) and is also linked to the persistence of psychotic symptoms over time (Pionke-Ubych et al., 2022; Trotta et al., 2015). Distinct childhood adversities appear to pose elevated risk for different psychosis symptom domains (Bentall et al., 2014; Toutountzidis et al., 2022). Large-scale longitudinal studies have found links between experiences of maltreatment and psychotic symptoms (Abajobir et al., 2017; Beasley et al., 2020). Among the different symptom domains, positive symptoms are more consistently related to childhood abuse, whereas negative symptoms are more consistently linked to childhood neglect (Dizinger et al., 2022; Bailey et al., 2018). Furthermore, family adversity and bullying victimization are specifically associated with the presence and persistence of positive symptoms of psychosis (Fisher et al., 2013; Catone et al., 2015; Sheinbaum et al., 2015). Overall, it appears that experiences involving an "intention to harm" are more strongly related to positive symptoms than those without intent (Arseneault et al., 2011; Morgan et al., 2020; van Nierop et al., 2014). Considering the significant overlap between psychosis-spectrum symptoms and other common forms of psychopathology, most types of adversity are linked to anxiety and depressive symptoms (Alameda et al., 2021; Copeland et al., 2018; Humphreys et al., 2020), and childhood neglect, abuse, and peer bullying are associated with depressive symptom trajectories over time (Cohen et al., 2019; Paterniti et al., 2017; Li et al., 2022).

Childhood adversity negatively impacts adult social adaptations (McGinnis et al., 2022). For example, those who experienced adversity during their formative years are more likely to struggle to establish and maintain relationships, have difficulties at work or school, and have lower overall quality of life (Beilharz et al., 2022; Doyle & Cicchetti, 2017; McCrory et al., 2022). Furthermore, consistent with the notion that experiences within the caregiving environment are developmental antecedents of adult attachment styles, ample research links childhood maltreatment and different forms of attachment insecurity (Bifulco & Thomas, 2012; Raby et al., 2017; Widom et al., 2018).

A significant impediment to advancing childhood adversity research has been the variability in conceptualization and measurement approaches across studies (McLaughlin et al., 2021; Smith & Pollak, 2021; Brumley et al., 2019). Existing studies that rely exclusively on specificity (focusing on the effects of individual adversity subtypes) or cumulative (focusing on the number of adversities experienced) approaches are unlikely to fully reveal the underlying mechanism of childhood adversity. Recent theory-driven models of childhood adversity suggest focusing on core dimensions of environmental experience shared across different adversity subtypes—as these are likely to impact developmental processes similarly

(McLaughlin et al., 2021). In particular, the Dimensional Model of Adversity and Psychopathology (DMAP) proposes distinguishing between the dimensions of threat (i.e., experiences involving harm or threat of harm) and deprivation (i.e., absence of expected inputs from the environment) (McLaughlin & Sheridan, 2016). Several studies have supported the DMAP approach (e.g., Miller et al., 2018; Schäfer et al., 2023); nonetheless, it has also been noted that not all adversity subtypes map onto this framework (Smith & Pollak, 2021), highlighting the need to consider additional dimensions. At the same time, scholars have increasingly used data-driven approaches to identify meaningful dimensions of childhood adversity (Lacey & Minnis, 2020). In this regard, recent research has demonstrated the utility and explanatory power of empirically-derived childhood adversity dimensions for investigating associations with behavioral and psychopathological outcomes (Brieant et al., 2023; Brumley et al., 2019).

Despite a growing literature focused on dimensions of adversity, the longitudinal links of adversity dimensions with specific transdiagnostic symptoms, as well as social and psychological outcomes, are still understudied and poorly understood (McGinnis et al., 2022). Furthermore, the associations to specific outcomes may vary across different adversity dimensions and timeframes (McLaughlin & Sheridan, 2016; Sheridan et al., 2017; Lambert et al., 2017). For example, within the DMAP approach, Schäfer et al. (2023) found that threat predicted psychopathology both cross-sectional and longitudinally, whereas deprivation predicted psychopathology longitudinally. Thus, further research modeling adversity dimensions as simultaneous predictors of individual symptom manifestations and social and psychological outcomes is needed to elucidate the specificity and time course of dimension-outcome associations.

1.1. Present Study

In a previous report (Gizdic et al., 2023), we used the Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; Barrantes-Vidal et al., 2013a, 2013b) baseline sample to identify the dimensions underlying interview and self-report assessments of a range of childhood adversities and examine their cross-sectional association with measures of transdiagnostic psychopathology. Our findings indicated that the *Deprivation* dimension was uniquely associated with schizoid symptoms and negative schizotypy, the *Intrafamilial Adversity* dimension with schizotypal symptoms, and the *Threat* dimension with depression, anxiety, and psychosis-spectrum symptoms. In the present study, we examined the associations of the adversity dimensions with a broad spectrum of social, psychological, and symptom outcomes across the three most recent assessments of the BLISS sample—the last one spanning almost eight years from baseline. Specifically, we sought to extend our previous findings by 1) examining how baseline adversity dimensions predicted psychopathology symptom domains across three prospective assessments, and 2) including new social and psychological outcomes related to constructs relevant to adversity exposures such as attachment styles and social adaptations (e.g., subjective perception of social support and loneliness).

It was hypothesized that exposure to childhood adversity would predict greater levels of psychopathology, insecure attachment, loneliness, and diminished social adjustments and support. Based on previous work (e.g., McLaughlin et al., 2020) and our cross-sectional findings, we expected that the *Threat* dimension would show broad associations with

symptoms of psychopathology across time. Furthermore, within the psychosis symptom domains, we expected *Threat* to show more consistent associations with measures of the positive symptom dimension and *Deprivation* with the negative symptom dimension. Regarding the *Intrafamilial Adversity* dimension, we did not offer specific hypotheses related to psychopathology, but we expected to find associations with insecure attachment based on prior research on adverse experiences with caregiving figures (Bifulco & Thomas, 2012). Despite the advantages of a longitudinal design, we note that our sample sizes and measures vary across time points and explicitly acknowledge this as a limitation of this study.

2. Methods

2.1. Participants and Procedure

The data are drawn from the BLISS (Barrantes-Vidal et al., 2013a, 2013b), a multi-wave investigation examining risk and resilience for psychopathology. Students from the Universitat Autonoma de Barcelona were assessed at five time points across a mean interval of 7.8 years (SD=0.5 years). At T1, 547 participants (mean age=20.6 years; SD=4.1; 83% women) were screened, and a subset of this sample was invited to participate in an interview study, oversampling participants with standard scores based upon sample norms of at least 1.0 on measures of schizotypy and psychotic-like experiences, resulting in 214 participants at T2 (mean age=21.4 years; SD=2.4; 78% women). Due to funding constraints, 103 participants were assessed at T3 (mean age=23.6; SD=2.6; 62% women) that retained the original distribution of schizotypy scores, and 89 of this subset were re-assessed at T4 (mean age=24.8; SD=2.7; 62% women). Finally, at T5, we contacted all T2 participants and re-assessed 169 (79% of 214 candidate participants; mean age=28.0; SD=2.4; 81% women). The university ethics committee approved the study and participants provided informed consent at each assessment wave.

2.2. Measures

2.2.1. Childhood Adversity

At T1, childhood adversity was measured using the Childhood Trauma Questionnaire (CTQ; Bernstein and Fink, 1998), and at T2 with two interview measures—the Childhood Experience of Care and Abuse (CECA; Bifulco et al., 1994) and the Interview for Traumatic Events in Childhood (ITEC; Lobbestael et al., 2009; Lobbestael & Arntz, 2010).

As described in detail in Gizdic et al. (2023), we conducted a Principal Component Analysis (PCA) to identify the dimensions underlying multiple subscales from these measures. We identified four dimensions that explained 63% of the total variance: *Intrafamilial Adversity* (experiences within the caregiving environment, such as parental discord and role reversal), *Threat* (experiences including bullying and abuse), *Deprivation* (experiences of neglect), and *Sexual Abuse* (experiences of sexual abuse). Given that a very small proportion of participants in the sample endorsed experiences of sexual abuse, we did not use this dimension in the statistical analyses in the present study.

2.2.2. Psychopathology

At T3-T5, we used the suspiciousness subscale of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) and the short forms of Wisconsin Schizotypy Scales (WSS-

SF; Kwapil et al., 2012), which assess positive and negative schizotypy domains. Positive and negative schizotypy scores were computed following the method described in Gross et al. (2015). At T3-T4, we administered the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005), a structured interview to assess the psychosis prodrome and psychotic experiences in nonclinical populations. The severity of CAARMS-positive symptoms was used for analyses. We also used the Structured Clinical Interview for DSM–IV Axis II Disorders (SCID–II; First et al., 1997) to assess schizophrenia-spectrum (paranoid, schizotypal, and schizoid) personality disorders (PD). Dimensional scores were computed by adding individual item ratings for each PD. At T4, we administered the Negative Symptom Manual (NSM; Kwapil & Dickerson, 2001), an interview-based rating system of a range of negative symptoms. The global summary score was used for analyses.

Depressive symptoms were assessed via interview with the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1992) at T3 and via questionnaire with the Beck Depression Inventory-II (BDI; Beck et al., 1996) at T3-T5. To assess anxiety symptoms, we used the Beck Anxiety Inventory (BAI; Beck et al., 1988) at T3-T4 and the anxiety subscale of the Symptom Checklist- 90-Revised (SCL-90-R; Derogatis, 1977) at T5.

2.2.3 Social and Psychological Outcomes

At T3-T5, we administrated the Psychosis Attachment Measure (PAM; Berry et al., 2006) to assess anxious and avoidant attachment styles. At T4-T5, the Multidimensional Scale of Perceived Social Support (MSPSS; Zimet et al., 1988) was used to obtain subjective reports of social support. At T5, subjective feelings of loneliness were assessed with the 3-item UCLA Loneliness Scale (Hughes et al., 2004). Finally, participants' social adjustment was assessed using items from the Social Network Index (SNI; Cohen, 1997) at T5. Specifically, the following variables were used: people in social network (number of people with whom the participant has regular contact), network diversity (number of social roles the participant regularly interacts with), and embedded network (number of network domains in which the participant is active).

2.3. Data analysis

We calculated descriptive statistics for the study variables and computed Pearson correlations to examine the bivariate associations of the childhood adversity dimensions with each psychopathology, social, and psychological outcome measure. Next, linear regression analyses were computed to examine the adversity dimensions as predictors of the outcome measures assessed at each time point. The adversity dimensions were entered simultaneously in the regression models to examine each dimension's unique prediction over-and-above the other adversity dimensions. Effect sizes are noted in the tables following Cohen (1992). Bootstrap procedures with 2,000 samples were used for the regression models.

3. Results

Descriptive statistics for the study variables are displayed in Table 1. Supplementary Table 1 presents the correlations of the adversity dimensions assessed with measures at T1 and T2 at the time of derivation and for the samples at T3, T4, and T5. The correlations were largely consistent for the overlapping samples at the three follow-up assessments (generally on the

order of medium effect sizes), with the exception of large effects for *Deprivation* and *Threat* at T3 and T4. Table 2 presents the bivariate correlations of the three childhood adversity dimensions with the psychopathological, social, and psychological variables. Regarding the psychopathology phenotypes, at T3, *Intrafamilial Adversity* and *Threat* were associated with all the phenotypes except for negative schizotypy and schizoid symptoms, and *Deprivation* was associated with all the phenotypes. At T4, *Intrafamilial Adversity* was associated with suspiciousness, paranoid symptoms, BDI depression, and BAI anxiety; *Deprivation* with all the phenotypes except negative schizotypy*;* and *Threat* with all the phenotypes except the schizotypy dimensions and schizoid symptoms. Finally, at T5, *Intrafamilial Adversity* was not associated with the psychopathology measures, and both *Deprivation* and *Threat* were associated with suspiciousness, BDI depression, and SCL-90 anxiety.

Regarding the social and psychological outcomes, at T3, *Intrafamilial Adversity* was associated with anxious attachment, and *Deprivation* and *Threat* with avoidant attachment. At T4, the three dimensions were associated with anxious attachment and decreased perceived social support, and *Deprivation* was also associated with avoidant attachment. At T5, *Intrafamilial Adversity* was not associated with these outcomes; *Deprivation* was associated with a smaller network of people and all the psychological variables; and *Threat* with a smaller network of people, smaller network diversity, and all the psychological outcomes.

Table 3 shows the results of the linear regression analyses examining the childhood adversity dimensions as simultaneous predictors of the psychopathology, social, and psychological outcomes at the three assessment time points. These results should be considered in light of the incremental information they provide about unique associations of the adversity dimensions with outcome measures over-and-above the information for the bivariate correlations presented in Table 2. Regarding the psychopathology phenotypes, at T3, *Intrafamilial Adversity* predicted schizotypal symptoms, CAARMS positive symptoms, and BAI anxiety; *Deprivation* predicted schizoid symptoms and BAI anxiety; and *Threat* predicted CAARMS positive symptoms, paranoid and schizotypal symptoms, and CDSS depression. At T4, *Intrafamilial Adversity* predicted suspiciousness; *Deprivation* predicted schizotypal and NSM negative symptoms; and *Threat* predicted paranoid symptoms. At T5, *Deprivation* predicted BDI depression, and *Threat* predicted suspiciousness and SCL-90 anxiety.

Regarding the social and psychological outcomes, at T3, *Intrafamilial Adversity* predicted anxious attachment. At T4, *Intrafamilial Adversity* predicted anxious attachment, and *Deprivation* predicted a diminished perception of social support. At T5, *Deprivation* predicted a smaller social network of people, anxious and avoidant attachment, and increased loneliness. *Threat* predicted a smaller network size and diversity but did not predict the psychological outcomes.

4. Discussion

In a previous study (Gizdic et al., 2023), we identified the dimensions underlying self-report and interview measures of childhood adversity and their associations with transdiagnostic psychopathology. The current study investigated the associations between the adversity dimensions and various social, psychological, and psychopathology outcomes across three prospective assessments. To our knowledge, several of these outcomes have not been previously examined within a longitudinal framework considering different dimensions of

childhood adversity. Our results demonstrated that the adversity dimensions had overlapping and differential prospective associations with psychopathology symptom domains and social-psychological factors, with notable specificity identified for some outcomes. Overall, the findings confirm and extend prior research indicating that empirically-derived dimensions of childhood adversity are associated with maladaptive outcomes (Brieant et al., 2023; Brumley et al., 2019) and support using a multidimensional approach to facilitate a nuanced understanding of the impact of childhood adversity on different domains of functioning across the lifespan.

The present study found a wider range of associations between the adversity dimensions and the outcome measures in the bivariate analyses compared with the regressions examining their unique contributions. This pattern of results aligns with our cross-sectional study and ample research focused on childhood maltreatment (de Oliveira et al., 2018; Lobbestael et al., 2010; Sullivan et al., 2006). Furthermore, it seems consistent with the notion that some links between adverse environmental experiences and developmental outcomes might be driven by what is common (shared variance) across such experiences (Cecil et al., 2017; Schuurmans et al., 2022), highlighting the relevance of research efforts to characterize both the common and specific effects of different adversity dimensions.

Note that the analysis and interpretation of both the bivariate and regression results provide unique information for understanding the impact of the adversity dimensions and their results should be integrated for a full understanding of the dimensions – especially given the moderate to large correlations of the adversity dimensions. The bivariate correlations provide a baseline method for assessing the association of the adversity dimensions with psychopathology and impairment, although they do not allow for separation of their unique contribution. In contrast, the regression analyses allow for examination of the association of each adversity dimension with the outcome measures over-and-above the other adversity dimensions (although caution should be exercised in interpreting these partialed effects in light of concerns raised by Hoyle et al., 2023). Finally, the total *R*-square value from the regression analyses provides a useful indication of the full contribution of the three dimensions.

Childhood Adversity Dimensions and Psychopathology

Based on our cross-sectional findings and other theoretical and empirical work (McLaughlin et al., 2020), we expected that *Threat* would show broad associations with symptoms of psychopathology across time. This was largely supported in the bivariate analyses and at T3 in the regression analyses, but fewer unique associations emerged at later time points. While this finding may reflect methodological factors, it may also suggest that the impact of *Threat* on psychopathology is broader during the first years of navigating the transition from late adolescence to early adulthood, which tend to be years marked by instability. This pattern merits further exploration considering that the effects of adversity on psychopathological outcomes have been found to vary across the lifespan, perhaps due to a combination of variables, such as salient developmental challenges and the unfolding of other risk and protective factors (Cohen et al., 2017; La Rocque et al., 2014).

The findings supported the hypothesis that *Threat* would show more consistent associations with the positive symptom dimension of psychosis and *Deprivation* with the negative symptom dimension. In particular, we found that *Threat* uniquely predicted measures

of positive psychotic features across time, especially those tapping paranoid beliefs. This supports the interpretation that early environments characterized by threat contribute to the unfolding of risk for reality distortion (Arseneault et al., 2011). Likewise, *Deprivation* uniquely predicted schizoid symptoms at T3 and negative symptoms at T4, which substantiates theories that an absence of expected inputs from the environment forecasts risk for deficit features (Gallagher & Jones, 2013). To our knowledge, this is the first study to demonstrate these links in a longitudinal framework examining unique contributions of different adversity dimensions. We found that *Intrafamilial Adversity* predicted measures of the positive symptom dimension at T3 and T4. This finding is in line with research investigating some of the components of this dimension, such as parental role reversal (Sheinbaum et al., 2015) and parental discord/violence (Kelleher et al., 2008), and demonstrates the significance of experiences within the caregiving environment over-and-above those captured in the *Threat* dimension—which encompasses experiences across different relational domains. Relatedly, it is worth noting that although our cross-sectional study found a unique association between *Intrafamilial Adversity* and schizotypal symptoms, the present study found that the three adversity dimensions uniquely predicted schizotypal symptoms across time—*Threat* and *Intrafamilial Adversity* at T3 and *Deprivation* at T4. This finding is unsurprising given the heterogeneous nature of this phenotype and reinforces the notion that specifying its positive, negative, and disorganized features should enhance etiological research (Barrantes-Vidal et al., 2015; Kwapil & Barrantes-Vidal, 2012).

In line with previous studies (e.g., Henry et al., 2021; McGinnis et al., 2022), the childhood adversity dimensions were prospectively associated with symptoms of anxiety and depression. The finding that different dimensions emerged as unique predictors across time might suggest relatively little specificity for these outcomes, although our use of different measures in some assessment waves may have contributed to this result. Another possibility suggested by recent research is that, for these outcomes, distinguishing between emotional versus other forms of adversity might be more relevant than the threat-deprivation distinction (*see* Humphreys et al., 2020; Schlensog-Schuster et al., 2022). In this regard, the three childhood adversity dimensions investigated in this study comprise some adverse experiences within the emotional/psychological domain. Future work should continue to examine different approaches to grouping childhood adversities to inform models of vulnerability to depression and anxiety phenotypes.

Childhood Adversity Dimensions and Social-psychological Outcomes

The findings pertaining to social-psychological outcomes support the notion that adverse environmental experiences have a lasting impact on different domains of psychological and social functioning (Alink et al., 2012; Bifulco & Thomas, 2012; Pfaltz et al., 2022). In line with our hypotheses, *Intrafamilial Adversity* was prospectively associated with insecure attachment and specifically predicted anxious attachment at T3 and T4. This suggests that the internalization of the experiences comprised in this dimension may contribute to the formation of internal working models organized around a need for approval and preoccupation with relationships (Schimmenti & Bifulco, 2015) and the reliance on hyperactivating emotion regulatory strategies (Mikuincer & Shaver, 2007). In addition, we found that *Deprivation* uniquely predicted anxious and avoidant attachment at T5. This result parallels research

showing that experiences of neglect are associated with attachment insecurity (Borelli et al., 2015) and both anxious and avoidant attachment (Kim et al., 2021). Taken together, these findings might be interpreted to suggest that neglect of the child's physical and emotional needs may foster internal working models of the self as unworthy and others as unavailable or unreliable, contributing to the risk for different forms of attachment insecurity.

Regarding the more "objective" characteristics of social relationships, we found that *Threat* and *Deprivation* uniquely predicted having a smaller social network, consistent with research documenting such associations in the broader maltreatment literature (McCrory et al., 2022). Furthermore, *Threat* uniquely predicted network diversity, indicating that threat-related experiences possibly contribute to developmental adaptations that restrict the range of social roles in which individuals are likely to engage. Finally, we found that different adversity dimensions were associated at the bivariate level with the perception of social support and loneliness. However, the regressions suggested that these associations were best accounted for by the *Deprivation* dimension. Therefore, experiencing childhood neglect may be particularly detrimental to the perception of social connection and support, which could potentially be related to or further compounded by a tendency to construe interactions with the social world in terms of previous experiences of neglect (*see* Luyten & Fonagy, 2019).

Finally, examination of the total *R*-square values in Table 3 indicates that the three adversity dimensions combined accounted for moderate to large proportions of variance in many of the outcome measures (especially at T3 and T4). This is especially notable given the range of factors that contribute to psychopathology and impairment in young adults. The effects were especially striking for positive schizophrenia-spectrum characteristics including psychotic-like paranoid, and schizotypal features (despite the fact that this was a non-clinically ascertained sample). Thus, the multidimensional approach for characterizing adverse experiences demonstrates powerful unique effects for the adversity dimensions, as well as sizable total effects.

Strengths and Limitations

Strengths of this study include the multi-wave, longitudinal research design, the comprehensive assessment of psychopathology and social-psychological outcomes, and the use of empirically-derived adversity dimensions obtained from in-depth interviews and self-report measures covering a wide range of adversity experiences. However, there are some limitations to consider. One limitation is that using a predominantly female sample initially drawn from a college population may limit the generalizability of the findings. Although studies involving student and non-student populations have produced similar results in the field of trauma research (Boals et al., 2020), it will be important to examine whether these findings are replicated in samples with more varied sociodemographic characteristics and in clinical populations. Furthermore, the variations in sample size and measures used across time points, while common in longitudinal studies (Curran et al., 2008; Heinzel et al., 2016), raise the possibility that some of the findings are related to this methodological limitation. Along the same lines, another shortcoming is that we did not use clinical interviews at T5. At this assessment wave, we had the restriction of using only self-report measures to maximize the sample size, but this yielded greater differences in the pool of comparable measures of psychopathology.

Conclusion and Future Directions

In closing, our findings extend prior work by demonstrating prospective associations of empirically-derived childhood adversity dimensions with different risk profiles across psychological, social, and symptom domains. In addition, these results add novel longitudinal evidence to the growing literature highlighting the utility of theoretically- and empirically-derived dimensions of environmental experience to investigate the developmental consequences of childhood adversity (Brieant et al., 2023; Guyon-Harris et al., 2021; McGinnis et al., 2022; McLaughlin et al., 2021). In this context, it is worth noting that theoretical and empirical work has implicated the social-psychological outcomes examined in this study in pathways to psychopathology following the experience of childhood adversity (e.g., Jaya et al., 2017; McCrory et al., 2022; Schimmenti & Bifulco, 2015; Sheinbaum et al., 2020; Williams et al., 2018). Therefore, a relevant next step is investigating their potential mediating or moderating effects. Furthermore, future studies could focus more on examining protective factors to enhance our understanding of resilience and the processes that mitigate maladaptive outcomes. Overall, increasing our understanding of the impact and underlying mechanisms of childhood adversity dimensions across the lifespan is crucial to refining conceptual models of adversity and identifying intervention targets.

Authors contribution. Tamara Sheinbaum: conceptualization and methodology, writing-original draft, review and editing, visualization, data curation Alena Gizdic: conceptualization and methodology, formal analyses, writing-original draft, review and editing, visualization**;** Thomas R. Kwapil: conceptualization and methodology, statistical consultation, review and editing; Neus Barrantes-Vidal: conceptualization and methodology, supervision, funding acquisition, resources, data curation, investigation, project administration, writing original draft, review and editing.

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Tables and Figures

Table 1. Descriptive Statistics for the psychopathology symptom domains and the social and psychological factors.

	Time 3 (N=102/103)				Time 4 (N=89)				Time 5 (N=169)			
Measure	N	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range
Psychopathology												
Positive schizotypy	102	-.70	.63	-1.27–3.79	89	-.77	.39	-1.27–2.02	169	-.70	.42	-1.17–2.44
Suspiciousness	102	1.33	1.78	0–8	89	1.25	1.53	0–7	169	1.44	1.57	0–8
CAARMS positive	103	1.21	2.16	0–12	89	1.17	1.96	0–9	-	-	-	-
Paranoid PD	103	1.65	2.11	0–10	89	1.65	2.30	0–12	-	-	-	-
Schizotypal PD	103	1.33	1.98	0–10	89	1.08	1.78	0–8	-	-	-	-
Negative schizotypy	102	-.14	1.05	-1.06–4.21	89	-.17	.93	-1.06–4.70	169	-.08	.96	-1.06–5.02
Negative symptoms	-	-	-	-	89	2.13	3.05	0–13	-	-	-	-
Schizoid PD	103	1.01	1.80	0–8	89	1.02	1.95	0–11	-	-	-	-
CDSS depression	103	1.55	2.41	0–11	-	-	-	-	-	-	-	-
BDI depression	102	6.17	6.80	0–28	89	5.64	6.59	0–33	168	5.47	6.16	0–35
SCL-90 anxiety	-	-	-	-	-	-	-	-	168	5.40	4.75	0–28
BAI anxiety	102	5.00	5.77	0–42	89	5.54	5.78	0–39	-	-	-	-
Social-Psychological												
SNI Network diversity	-	-	-	-	-	-	-	-	169	4.12	1.27	0–7
SNI People in network	-	-	-	-	-	-	-	-	169	9.36	3.98	0–21
SNI Embedded network	-	-	-	-	-	-	-	-	169	2.02	.85	0–4
Anxious attachment	102	1.11	.54	.25–2.50	89	1.00	.54	.13–2.50	169	1.04	.52	.13–2.63
Avoidant attachment	102	1.08	.47	.25–2.38	89	1.09	.51	.25–2.63	169	1.16	.55	.13–2.75
Loneliness	-	-	-	-	-	-	-	-	168	3.93	1.22	3–8
Perceived social support	-	-	-	-	89	72.34	10.74	35–84	168	73.26	11.24	13–84

Note: N=sample size; M=Mean; SD=Standard deviation; CAARMS= Comprehensive Assessment of At-Risk Mental States; PD=Personality Disorders (SCID-II); CDSS= Calgary Depression Scale for Schizophrenia; BDI=Beck Depression Inventory-II; SCL-90=Symptom Checklist-90-Revised; BAI= Beck Anxiety Inventory; SNI=Social Network Index.

Table 2. Bivariate correlations of the childhood adversity dimensions with the psychopathology symptom domains and the social and psychological factors.

		Time 3			Time 4			Time 5		
		Intrafamilial Adveristy	Deprivation	Threat	Intrafamilial Adveristy	Deprivation	Threat	Intrafamilial Adveristy	Deprivation	Threat
	Criteria									
Psychopathology	Positive schizotypy	**.31****	**.44****	**.41****	.14	**.32****	.17	-.01	.14	.12
	Suspiciousness	**.34****	**.41****	**.46****	**.39****	**.37****	**.42****	.14	**.30****	**.33****
	CAARMS positive	**.43****	**.42****	**.47****	.20	**.34****	**.33****	-	-	-
	Paranoid PD	**.34****	**.46****	***.56****	**.35****	**.44****	***.52****	-	-	-
	Schizotypal PD	**.39****	**.47****	***.50****	.11	**.46****	**.35****	-	-	-
	Negative schizotypy	-.05	.20*	.12	-.10	.09	.02	-.07	.11	.06
	Negative symptoms	-	-	-	.16	**.42****	**.32****	-	-	-
	Schizoid PD	.12	**.31****	.18	-.02	**.33****	.18	-	-	-
	CDSS depression	**.35****	**.35****	**.47****	-	-	-			
	BDI depression	**.33****	**.37****	**.40****	.29**	**.39****	**.41****	.04	.28**	.21**
	SCL-90 anxiety	-	-	-	-	-	-	.12	.16*	**.30****
	BAI anxiety	**.45****	***.50****	**.45****	.25*	.26*	.24*	-	-	-
Social-	SNI Network diversity	-	-	-				-.03	-.11	-.20**
Psychological	SNI People in network	-	-	-	-	-	-	-.05	-.23**	-.26**
	SNI Embedded network	-	-	-	-	-	-	.00	-.08	-.12
	Anxious attachment	.29**	.11	.19	**.38****	.23*	.26*	.02	.22**	.19*
	Avoidant attachment	.09	.26**	.25*	.09	.23*	.19	.11	**.32****	.20**
	Loneliness	-	-	-	-	-	-	.03	.28**	.23**
	Perceived social support	-	-	-	**-.48****	**-.38****	**-.48****	-.12	-.21**	-.20**

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Note1: According to Cohen, effect size of .10 is small, .30 is medium (in bold), and .50 is a large (bold and italics)

Note2: CAARMS= Comprehensive Assessment of At-Risk Mental States; PD=Personality Disorders (SCID-II); CDSS= Calgary Depression Scale for Schizophrenia; BDI=Beck Depression Inventory-II; SCL-90=Symptom Checklist-90-Revised; BAI= Beck Anxiety Inventory; SNI=Social Network Index.

Table 3. Linear regressions examining childhood adversity dimensions predicting subclinical symptoms and social adaptation, and psychological measures across three time points.

		Time 3					Time 4					Time 5				
		Intrafamilial Adversity	Deprivation	Threat			Intrafamilial Adversity	Deprivation	Threat			Intrafamilial Adversity	Deprivation	Threat		
	Criteria	**β**	**β**	**β**	**Total R^2**	***f*²**	**β**	**β**	**β**	**Total R^2**	***f*²**	**β**	**β**	**β**	**Total R^2**	***f*²**
Psychopathology	Positive schizotypy	.14	.26	.19	.24	**.31**	.04	.35	-.07	.10	.11	-.10	.14	.09	.03	.03
	Suspiciousness	.18	.15	.30	.26	***.35***	.26*	.12	.25	.25	**.33**	-.04	.20	.25*	.14	**.16**
	CAARMS positive	.27*	.14	.29*	.31	***.45***	.07	.20	.17	.14	**.16**	-	-	-	-	-
	Paranoid PD	.14	.14	.42**	.35	***.54***	.17	.13	.37*	.31	***.45***	-	-	-	-	-
	Schizotypal PD	.21*	.21	.29*	.33	***.48***	-.07	.43**	.09	.22	**.28**	-	-	-	-	-
	Negative schizotypy	-.14	.23	.03	.05	.06	-.14	.17	-.04	.03	.03	-.15	.15	.05	.03	.03
	Negative symptoms	-	-	-	-	-	.00	.37*	.07	.18	**.22**	-	-	-	-	-
	Schizoid PD	.02	.32*	-.04	.09	.10	-.15	.41	-.04	.13	**.15**	-	-	-	-	-
	CDSS depression	.20	.03	.38*	.26	***.35***	-	-	-	-		-	-	-	-	-
	BDI depression	.19	.16	.22	.21	**.27**	.15	.19	.23	.21	**.27**	-.12	.27*	.13	.10	.11
	SCL-90 anxiety	-	-	-	-		-	-	-	-		.01	.02	.30**	.09	.10
	BAI anxiety	.29*	.30*	.15	.35	***.54***	.17	.15	.08	.10	.11	-	-	-	-	-
Social-Psychological	SNI Network diversity	-	-	-	-	-	-	-	-	-	-	.06	-.04	-.21*	.04	.05
	SNI People in network	-	-	-	-	-	-	-	-	-	-	.10	-.16*	-.22**	.09	.10
	SNI Embedded network	-	-	-	-	-	-	-	-	-	-	.07	-.06	-.16	.02	.02
	Anxious attachment	.26*	-.08	.14	.10	.10	.32*	.05	.11	.16	**.19**	-.12	.21*	.14	.07	.08
	Avoidant attachment	-.02	.19	.13	.08	.09	-.01	.18	.07	.06	.06	-.04	.30***	.08	.12	.11
	Loneliness	-	-	-	-	-	-	-	-	-	-	-.13	.27**	.14	.11	**.12**
	Perceived social support	-	-	-	-	-	.03	-.41**	-.13	.24	**.31**	-.01	-.15	-.13	.06	.06

*p<0.05, ** p<0.01, *** p<0.001

Note1: Bootstrap procedures (with 2,000 samples) were employed.

Note2: According to Cohen, f-square of .02 is small, .15 is medium (in bold), and .35 is a large effect size (in bold and italics)

Note3: CAARMS= Comprehensive Assessment of At-Risk Mental States; PD=Personality Disorders (SCID-II); CDSS= Calgary Depression Scale for Schizophrenia; BDI=Beck Depression Inventory-II; SCL-90=Symptom Checklist-90-Revised; BAI= Beck Anxiety Inventory; SNI=Social Network Index.

Supplementary Table 1. Correlations of the Adversity Dimension Scores Across Assessments

Correlation	Derivation (n = 214)	Time 3 (n = 102)	Time 4 (n = 89)	Time 5 (n = 169)
Intrafamilial Adversity & Deprivation	**.41**	**.36**	**.35**	**.42**
Intrafamilial Adversity & Threat	**.37**	**.37**	**.35**	**.35**
Deprivation & Threat	**.49**	**.65**	**.66**	**.47**

All correlations $p < .001$
Medium effect sizes in bold, large effect sizes in bold and italics

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SECTION 2

LONGITUDINAL TRAJECTORIES OF STRESS-SENSITIVITY AND PSYCHOSIS-PRONENESS

Chapter 3

A longitudinal study of the stability and trajectories of stress-sensitivity in young adults: retrospective and momentary daily-life assessments of stress appraisals

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Abstract

Stress-sensitivity is a major contributor to many psychopathological phenotypes. The critical assumption that heightened stress-sensitivity is a highly stable psychobiological trait over-time has been scarcely investigated. This study examines the stability and developmental trajectories of stress-sensitivity across challenging moments of personal development. Nonclinical young adults comprising normative and elevated scores on schizotypy completed stress-sensitivity measures at three waves with retrospective Perceived Stress Scale (PSS) and momentary Experience Sampling Methodology (ESM). Three longitudinal modeling techniques were used to examine individuals' trajectories of stress over time. There was an overall pattern of stress-sensitivity stability over time for both retrospective and momentary stress measures. All measurements revealed two distinct classes of longitudinal trajectories, consistent with individuals with high and low stress-sensitivity. Except for momentary situational stress, the pattern of stability was maintained across all high stress-sensitivity classes for all measures. Findings support the assumption that stress-sensitivity is a stable trait. Stability was higher for those with longitudinal trajectories of high stress-sensitivity and was slightly better captured by retrospective measures of perceived stress than momentary assessments−consistent with the contextually-driven nature of momentary responses. The characterization of stress-sensitivity may provide a better understanding of underlying mechanisms, risk, and protective factors in the development of psychopathology.

Keywords: Stress-sensitivity, trait development, experience-sampling-methodology, stress, longitudinal

Introduction

Stress-sensitivity has been defined as a trait characterized by increased reactivity to stress (including lower levels of stress exposure) that results from an acquired and/or inborn vulnerability (Hammen, 2015). Stress-sensitivity has been captured with different measurements such as biological and psychophysiological reactivity (Boyce & Ellis, 2005), as well as a variety of temperamental traits such as neuroticism (Eysenck, 1947), harm avoidance (Cloninger et al., 1993), rumination (Nolen-Hoeksema & Morrow, 1991), trait anxiety (Spielberger, 1975; Meijer, 2001), trait arousability (Mehrabian, 1995), and negative affectivity (Watson et al., 1988). Temperamental traits are defined as enduring characteristics that are fixed in early childhood and relatively resistant to developmental and environmental changes throughout the lifespan (Rettew & McKee, 2005), and thus are considered stable over time. It has been suggested that stress-sensitivity might act as a unit of analysis itself, whereas these temperamental traits would constitute broader constructs overlapping with stress-sensitivity (Vaessen, 2018). While stability has been prevalent in longitudinal studies using temperamental constructs that tap stress-sensitivity, such as neuroticism (Engert et al., 2021) or trait rumination (Katz et al., 2019), scarce studies have examined the stability of the specific stress-sensitivity construct (Snippe et al., 2017). These include a few prospective studies examining individuals' perceived stress over time but obtained mixed findings, particularly among adolescents and young adults. For example, two studies reported stability for perceived stress across time in adolescence (Prado-Gascó et al., 2019; Humer et al., 2022), whereas one study found an increase (Spivey et al., 2020) and another reported a decrease in perceived stress in young men and stability in young women over time (Batabyal et al., 2021). Note that all of these studies included relatively limited sample sizes.

Stress-sensitivity has typically been assessed psychometrically (e.g., the Perceived Stress Scale (PSS); Cohen et al., 1983) or in the laboratory (e.g., the Trier Social Stress Test (TSST); Kirschbaum et al., 1993). However, recent studies have employed methods with greater ecological validity, such as Experience Sampling Methodology (ESM), a structured diary technique assessing participants' experiences on multiple occasions as they occur in daily-life (Myin-Germeys et al., 2018). ESM complements and offers additional advantages compared to traditional psychometric assessment procedures by assessing momentary experiences in participants' daily-life. This reduces retrospective bias and provides contextualized assessments of momentary psychological experiences and person-environment interactions (e.g., Mehl & Conner, 2012; Myin-Germeys et al., 2011). So far, these studies have focused on measuring momentary *stress-reactivity*, a concept that has been more related to the "state" (Myin-Germeys et al., 2018; Vaessen et al., 2015) than the "trait" aspect of heightened stress-sensitivity, measuring, for instance, the affective or psychotic response when participants appraise situations or social interactions as stressful (Myin-Germeys et al., 2005; Schneider et al., 2020; Paetzold et al., 2021; Barrantes-Vidal et al., 2013a). The extent to which ESM relates to conventional psychometric measures of heightened stress-sensitivity is largely unknown.

Recent etiological investigations have examined the role of stress-sensitivity in the causal pathway to a large variety of psychopathology phenotypes (e.g., Vaessen et al., 2017; DeVylder et al., 2016; Udachina et al., 2017). However, the critical assumption that elevated stress-sensitivity is a highly *stable trait* has been scarcely tested. The limited extant

longitudinal studies tend to have time intervals that may be too brief to truly capture the developmental course of the stress-sensitivity trait (Katz et al., 2019; Koffer et al., 2016) and have yielded mixed findings. Therefore, the goal of this study was to examine the stability of stress-sensitivity and individuals' trajectories of stress over time, both retrospectively (PSS) and momentary (ESM) in a sample of non-clinically ascertained young adults. Considering the "trait" assumption, it was hypothesized that stress-sensitivity would be relatively stable across time following both assessment measures and that different longitudinal classes of stress-sensitivity trajectories would be identified across individuals. Three longitudinal modeling techniques will be used to assess the data; Latent Growth Curve Modeling (LGCM) and Linear Mixed Model (LMM) will be used to evaluate the stability of PSS and ESM, while Latent Class Analysis (LCA) will group individuals` trajectories of stress-sensitivity over time.

Methods

Participants and Procedure

The data collected is part of the Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; Barrantes-Vidal et al., 2013a, b) investigating schizotypy characteristics and psychosis risk and expression. Students from the Universitat Autonòma de Barcelona (UAB) completed a comprehensive battery of self-report, interview, and ESM measures across five data collection time points (the mean interval between T1 and T5 was 7.8 years; SD=0.5).

At the initial assessment, T1 (detailed in Barrantes-Vidal et al., 2013a, b; Racioppi et al., 2018; Sheinbaum, Racioppi, Kwapil, & Barrantes-Vidal, 2020), valid data were obtained from 547 unselected students (mean age=20.6 years; SD=4.1; 83% women). A subset of this sample was selected for longitudinal follow-up with in-depth interview assessment protocols, oversampling participants with standard scores > 1.0 on measures of schizotypy and psychotic-like experiences. Thus, the sample included a mix of participants with low schizotypy scores as well as scores across the schizotypy spectrum. We believe this provides an appropriate sample for examining the stability of stress-sensitivity, as it should include participants who experience a relatively wide degree of stress-sensitivity. At T2, a sub-selected sample of 214 participants was assessed (mean age=21.4; SD=2.4; 78% women). At T3, due to severe funding limitations, 103 participants were assessed (mean age=23.6; SD=2.6; 62% women) who retained a distribution of schizotypy scores, and 89 of this subset were re-assessed at T4 (mean age=24.8; SD=2.7; 62% women). At T5, we contacted all participants assessed at T2 and were able to validly reassess 169 participants (79% of 214 participants; mean age=28.0; SD=2.4; 81% women). This study was approved by Ethics Committee of the Universitat Autònoma de Barcelona (Comissió d'Ètica en l'Experimentació Animal i Humana ;CEEAH). The participants provided their written informed consent to participate in this study.

Measurement of Stress-sensitivity

Stress-sensitivity measures were jointly administered at three time points (T3, T4, and T5) that constitute the focus of this study.

Retrospective Assessment

The 14-item *PSS* is a well-validated conventional psychometric self-report measure capturing individual differences in stress appraisal during the past month (Cohen et al., 1983).

The response format consists of a 5-point Likert-type scale (0=Never to 4=Very often) with item example ‘‘*In the last month, how often have you…’’*and *‘‘felt nervous and stressed?’’*, and a total score is provided. Questions are formed in a general manner rather than asking about specific experiences and events that may occur in an individual’s life (Cohen et al., 1983). Items refer to the past month, capturing the impact of events that may still affect individuals’ levels of stress and thus may be considered a good proxy for trait stress-sensitivity. Cronbach's alpha indicated good reliability for PSS measure at each time point (T3=0.84; T4=0.89; T5=0.86).

Momentary Assessment

ESM was used to measure subjective and contextualized appraisals of stress in the flow of daily-life. Participants were randomly signaled eight times a day during a 7-day period on personal digital assistants or smartphones to complete brief questionnaires assessing their current experience (e.g., affect, thoughts) in their daily-life environment. A detailed description of the ESM assessment and validation data can be found in Barrantes-Vidal et al. (2013a). Items were answered on a 7-point scale ranging from “not at all” to “very much”, except for the social contact item (“*Right now, are you alone?*”) which was answered dichotomously. Four individual items tapped stress-related appraisals. One item assessed ‘situational stress’ (*“Right now, my current situation is stressful”)*. Regarding social stress appraisals, two items were prompted when participants reported that they were not alone: “*Right now, I feel close to this person (these people) (reversed)”* and *“Right now, I prefer to be alone”;* and another item was prompted to participants when they reported that they were alone, “*Right now, I am alone because people do not want to be with me”*. Participants completed an average of 39.3 (SD=9.7) usable questionnaires at T3, 39.7 (SD=8.2) at T4 and 39.8 (SD=7.4) at T5.

Data Analysis

LGCM

The trajectory of PSS over time (T3, T4, and T5) was analyzed with LGCM. LGCM captures individual differences in longitudinal assessment by estimating two latent variables representing a) the intercept or average score across all individuals, and b) the slope, that is average change of the score over time (Wigman et al., 2011). This method was used to examine individuals’ trajectories in sensitivity to stress over time. Analyses were conducted in R Version 3.6.3 (R Core Team, 2013) using Laavan package for structural equation modeling (Rosseel et al., 2012), as well as Amelia package (Honaker et al., 2011) and the MICE package (van Buuren & Groothuis-Oudshoorn, 2011) that allows for multiple imputations. Multiple imputation is considered a better imputation alternative to handle missing data (Lee & Shi, 2021), even if these data is not missing at random (van Ginkel et al., 2020) and the proportion of missing data is up to 40% (Jakobsen et al., 2017). Thus, we used multiple imputation to handle missing data and pooled estimated results using Rubin's rule (Rubin & Schenker, 1986). Following van Buuren (2018) recommendation to impute 20 to 100 data sets and in order to find a balance between imputed data uncertainty and computational time, we imputed 50 data sets and estimated the growth model from each of them using replaced missing values. The Tucker Lewis Index (TLI), the Comparative Fit Index (CFI), the Root Mean Square Error of

Approximation (RMSEA), and the Standardized Root Mean Square Residual were used to evaluate the model fit using chi-square test statistics (SRMR).
Details on the model estimation using LGCM and R script can be found in supplementary materials (Appendix S1).

LMM

The longitudinal analysis of ESM scores was assessed by the linear mixed-effects model (LMM; Laird & Ware, 1982). It is an extension of simple linear models that allows for both fixed and random effects and is used to estimate the linear relationship between two variables, specifically with repeated measures data (Liu et al., 2012). The LMM procedure is recommended for the analysis of linear trend related to time with multilevel longitudinal data (see Bauer, 2003; Pusponegoro et al., 2017). A two-level linear mixed-effects model was used where repeated measurement occasions are nested in persons. Thus, all time points within individuals were used for the analysis. Analyses were conducted in R Version 3.6.3 (R Core Team, 2013) using the *lme4* package (Bates et al., 2015), *lmerTest* package (Kuznetsova et al., 2017) to obtain p values, and *optimx* package (Nash & Varadhan, 2011) to optimize the model. We estimated the model considering linear mixed effects where momentary stress is predicted by *Time* (T3, T4, and T5) to test if there are differences in the *mean* of momentary stress across different time points. Note that all ESM items were analyzed separately. The model included correlated random intercept and slope.
Details on R script example using LMM (Appendix S1)

LCA

We conducted LCA to categorize individuals into classes (or clusters) with similar stress-sensitivity trajectories as measured by PSS and ESM. The analyses were conducted using the function *Lcmm* from the R package (Proust-Lima et al., 2017). We estimated a latent class model assuming a linear trajectory for the latent process with correlated random intercept and slope. Variable *Time* was indicated as a predictor and *Stress* as an outcome. By estimating the model fit indices, we further identified the number of classes with each latent class representing the individuals' stress trajectory. The number of classes was selected according to the goodness-of-fit provided by the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample-size Adjusted BIC (SABIC). The model with the lowest fit indices was considered.
Details on R script example using LCA (Appendix S1)

Results

A total of 102 participants completed PSS at T3 (mean age=23.5; SD=2.6; 63% female), 89 at T4 (mean age=24.9; SD=2.7; 62% female), and 168 at T5 (mean age=28.0; SD=2.4; 81% female), while a total of 89 participants completed ESM situational and social stress items at T3 (mean age=23.4; SD=2.5; 67% female), 84 at T4 (mean age=24.7; SD=2.6; 63% female), and 159 at T5 (mean age=27.9; SD=2.3; 79% female). Table 1 provides descriptive data for the measures used in the study.
Examining Stress-sensitivity Trajectories with PSS

The chosen unconstrained growth model fitted the data well (χ=3.12; p=0.077; robust TLI=1.000; CFI=0.968; RMSEA=0.107; and SRMR=0.042). Although RMSEA was not as favorable as expected, most of the fit indices showed a good model fit.

LGCM indicated a positive and significantly different from zero mean latent intercept (Table 2), however, neither the mean latent slope nor its variance was significant, which indicated an absence of significant overall change in perceived stress over time. LCA provided the lowest AIC, BIC and SABIC for the model with two classes (Table S1). The posterior means of high average class probabilities (0.88 for class 1 and 0.85 for class 2) indicated that participants were satisfactorily assigned to their respective classes. As shown in Table 3, the first class with the highest percentage of participants (67%; M=15.78; SD=0.93) resulted in the lower overall mean compared to the second class (33%; M=26.67; SD=0.60), thus class 1 was labeled *low stress-sensitivity class* (low ss class) and class 2, *high stress-sensitivity class* (high ss class). Across all three time points, the high ss class indicated higher mean compared to the low ss class. The effect of time (slope) for the high ss class indicated no significant change, while for the low ss class the effect of time was positive indicated a slight but significant increase in stress over time (Table 3; Figure 1a).

Examining Stress-sensitivity Trajectories with ESM

ESM Situational Stress

LMM indicated that there were no significant differences in the mean of situational stress across the three-time points (Table 2). The fixed slope was not significant, thus again indicated an absence of significant change in situational stress over time. LCA provided the lowest AIC, BIC and SABIC for the model with two classes (Table S1). The posterior means of high average class probabilities (0.98 for class 1 and 0.94 for class 2) indicated that participants were satisfactorily assigned to their respective classes. Class 1 with the highest percentage of participants (93%; M=2.04; SD=0.16) indicated the lower overall mean compared to class 2 (7%; M=3.62; SD=0.67); thus, we again labeled the classes as *low ss* class 1 and *high ss* class 2. At T3 and T4, the high ss class had lower means than the low ss class, while at T5 the mean for the high ss class was higher (Table S1). The effect of time (slope) for both classes was significant. However, for the high ss class the effect was positive, meaning that for this group sensitivity to stress increased over time, while for the low ss class, the effect was negative, thus indicating the decrease in stress-sensitivity over time (Table 3; Figure 1b).

ESM Social Stress

LMM showed that there were no significant differences in the mean of social stress items across the three-time points (Table 2). For all items, the estimated fixed intercept was positive and significantly different from zero, while the slope showed no significance. The results again indicated an absence of significant change in social stress across time. In LCA, for the items "*I am alone because people do not want to be with me"* and *"I prefer to be alone"*, the goodness-of-fit statistics indicated a model with one class, while for the item *"I feel close to this person (these people) (reversed)"*, the model indicated two classes (Table S1). The posterior means of high average class probabilities (0.96 for class 1 and 0.85 for class 2); thus, participants were satisfactorily assigned to their respective classes. As LCA did not identify

individuals with different trajectories for the first two items, only a description of classes for the item *"I feel close to this person (these people) (reversed)"* is provided (Table 3).

In the selected model, the first class with the highest percentage of participants (89%; M=2.29; SD=0.02) indicated the lower overall mean compared to the second class (11%; M=3.75; SD=0.15); therefore, we again labeled *low ss* class 1 and *high ss* class 2. Across all three time points, the high ss class indicated higher mean compared to the low ss class (Table 3). The effect of time (slope) for both classes was not significant, indicating the absence of change over time and, thus, stability of the social stress for both groups (Table 3; Figure 1c).

Discussion

To the best of our knowledge, this is the first study examining the stability of stress-sensitivity as a trait of individual differences in a longitudinal design combining retrospective and ESM-momentary measures of subjective stress appraisals. The main findings of this study suggested an overall pattern of stress-sensitivity stability over time which held true for both retrospective appraisals of perceived stress as well as momentary and contextualized situational and social stress appraisals. Further examination revealed two different classes (high and low) of longitudinal trajectories for all measures. High ss individuals showed stability for retrospective perceived stress and momentary social stress, but an increase for momentary situational stress. In contrast, those in the low ss class showed stability in momentary social stress, but an increase in retrospective perceived stress and a decrease in momentary situational stress over time.

It is noteworthy that this sample was composed of young adults facing a challenging developmental stage characterized by important life milestones (such as building the start of a professional career in a job market with very high unemployment rates and becoming independent from family with very low salaries) and personal instability (changing household arrangements and jobs, financial difficulties, etc.). Despite the fact that this likely entails facing elevated and changing levels of stressful life events across time in this sample, stress-sensitivity appraisals remained stable. Thus, as hypothesized, an overall pattern of stability across measures lends credence to the "trait" assumption of stress-sensitivity. Although we identified different trajectories of stress-sensitivity—consistent with the existence of individual differences for this particular trait, the exploratory nature of the employed LCA did not allow us to set a priori hypotheses on the stability of those specific trajectories. As expected in a nonclinical functional sample, the majority of participants belonged to the low ss class; the high ss class included only 7% and 11% of individuals when using the momentary ESM situational and social stress (respectively) and 33% of individuals when using retrospective PSS measure. Regarding stability in high versus low classes of stress-sensitivity across measures, stability was overall consistent for individuals highly responsive to stress, whereas individuals with both low ESM situational stress and PSS classes did not show stability over time. Although no a priori hypotheses were offered given the exploratory nature of these analyses, these findings support the stability of stress-sensitivity, specifically for individuals with high levels of this trait. Only for individuals with high ss on momentary situational stress, stability over time was not found. This may relate to the low number of participants classified in the high ss group with this measure (7%) and the fact that the item 'My current situation is stressful' has a strong context-related nature since it explicitly asks for a specific situation in a

particular moment. Thus, it may capture momentary stress-reactivity, as well as trait-sensitivity; that is capturing the *state* as well as the *trait* phenomena and thus making it challenging for this item to yield stable trajectories of high stress-sensitivity over time. Nonetheless, the differences found between the retrospective and momentary measures support the notion that stress is a complex construct manifested at various levels. Considering that the measures were taken at different periods and time frames, slight variations in stress response are expected. Present results suggest the need for further examining the trait of stress-sensitivity as captured by different measurements, which has been, so far, scarcely investigated in the literature. The use of different methodologies when assessing the same construct may provide distinct, yet complementary, information (Carstensen et al., 2011; Myin-Germeys et al., 2009). Thus, using traditional retrospective as well as real-life assessments might be capturing different, though correlated, aspects of the subjective stress experience. Whereas momentary assessments are more directly related to the immediate experience or appraisal of stress in specific contexts, retrospective measures prompt a reflective process that more likely evokes the trait behavior.

One of the main strengths of the present work is the repeated measurement of stress-sensitivity across multiple time points combining conventional psychometric measurement of subjective appraisals of recent stressors with an ecological valid measurement of prospective daily-life stress appraisals captured in a real-life context. Moreover, stress-sensitivity has been mainly studied in clinical populations and within the context of symptom exacerbation and recurrence (Liu & Alloy, 2010; Farb et al., 2015; Hernaus et al., 2015), which poses the challenge of distinguishing the specific nature and trajectory of stress-sensitivity from that of other disease-related etiological factors, the impact of symptom expression, psychological changes related to patient status, treatment effects, etc. Nonetheless, the study is not without limitations. First, we used a sample with predominantly female participants. Future studies would benefit from assessing stress-sensitivity in community samples with balanced gender distributions. Secondly, the sample size (specifically for ESM) may have limited the ability to obtain a wider distribution of scores for some of the social stress items and, consequently, the inability to detect distinct developmental trajectories with these items. For example, the fact that different trajectories were found for the ESM social stress item, 'I feel close to this person (these people)*'* but not for items 'I am alone because people do not want to be with me' and 'I prefer to be alone', might be explained by the very low mean scores and variance shown by participants on these items. Nevertheless, lower mean levels of stress exposure are usually expected in nonclinical high-functioning samples compared to studies assessing stress-related phenotypes in highly exposed samples (e.g., combat; Andrews et al., 2009; Davis et al., 2022) or clinical samples (Technow et al., 2015).

In conclusion, our findings support the assumption that stress-sensitivity is a relatively stable trait as measured with retrospective and momentary daily-life prospective approaches. A traits stability was found in a sample of young adults facing critical life-changing challenges and personal instability. The stability was more consistent in high stress-sensitivity individuals compared to low and better captured when using a retrospective measure of perceived stress than momentary daily-life appraisals of stressful situations. The ability to identify differences in susceptibility to stress and stress-related disorders makes it crucial to study stress-sensitivity as a trait of individual differences (Weyn et al., 2022; Farmer & Kashdan, 2015). This allows

for the development of active and focused coping strategies to manage stress. The further characterization of stress-sensitivity should improve our understanding of risk factors for the development of psychopathology, with an emphasis on individual differences and stress-targeting interventions.

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Data availability statement. The data that support the findings of this study are available on request from the corresponding author N.B.V. The data are not publicly available due to privacy or ethical restrictions.

Tables and Figures

Table 1. Descriptive data of the stress-sensitivity proxy measures at each time point.

	Time 3					Time 4					Time 5				
	N	M	SD	Range	ESM beeps[a]	N	M	SD	Range	ESM beeps[a]	N	M	SD	Range	ESM beeps[a]
PSS	102					89					168				
		19.97	7.43	6-40	-		19.35	8.80	5-40	-		20.23	7.57	5-43	-
ESM	89					84					159				
Situational stress															
My current situation is stressful		2.25	1.69	1-7	3493		2.32	1.78	1-7	3334		2.03	1.5	1-7	6098
ESM	89					84					159				
Social stress															
I am alone because people do not want to be with me		1.13	0.55	1-6	1577		1.14	0.58	1-7	1427		1.07	0.49	1-7	2520
I feel close to this person (these people) $_r$		2.30	1.74	1-7	1916		2.44	1.76	1-7	1906		2.38	1.77	1-7	3578
I prefer to be alone		1.81	1.51	1-7	1916		1.89	1.52	1-7	1905		1.81	1.56	1-7	3578

Note1. PSS=Perceived Stress Scale, ESM=Experience Sampling Methodology, M=Mean, SD=Standard Deviation,$_r$=reversed
[a]ESM beeps is the number of responses obtained by ESM

Table 2. Analysis of the longitudinal stress-sensitivity trajectories for each stress measure.

	Mean intercept	Mean slope
PSS (LGCM)	19.75***	0.16
ESM situational stress (LMM)		
My current situation is stressful	2.53***	-0.09
ESM social stress (LMM)		
I am alone because people do not want to be with me	1.21***	-0.03
I feel close to this person (these people) $_r$	2.40***	0.005
I prefer to be alone	1.87***	-0.003

**p<0.05; **p<0.01; *** p<0.001*

Note1. Absence of an overall change in stress-sensitivity trajectories over time is indicated by non-significant slopes; PSS=Perceived Stress Scale, ESM=Experience Sampling Methodology, $_r$=reversed; LGCM=Latent Growth Curve Modelling; LMM=Linear Mixed Model.

Table 3. Descriptive data of the classes for each stress-sensitivity measure.

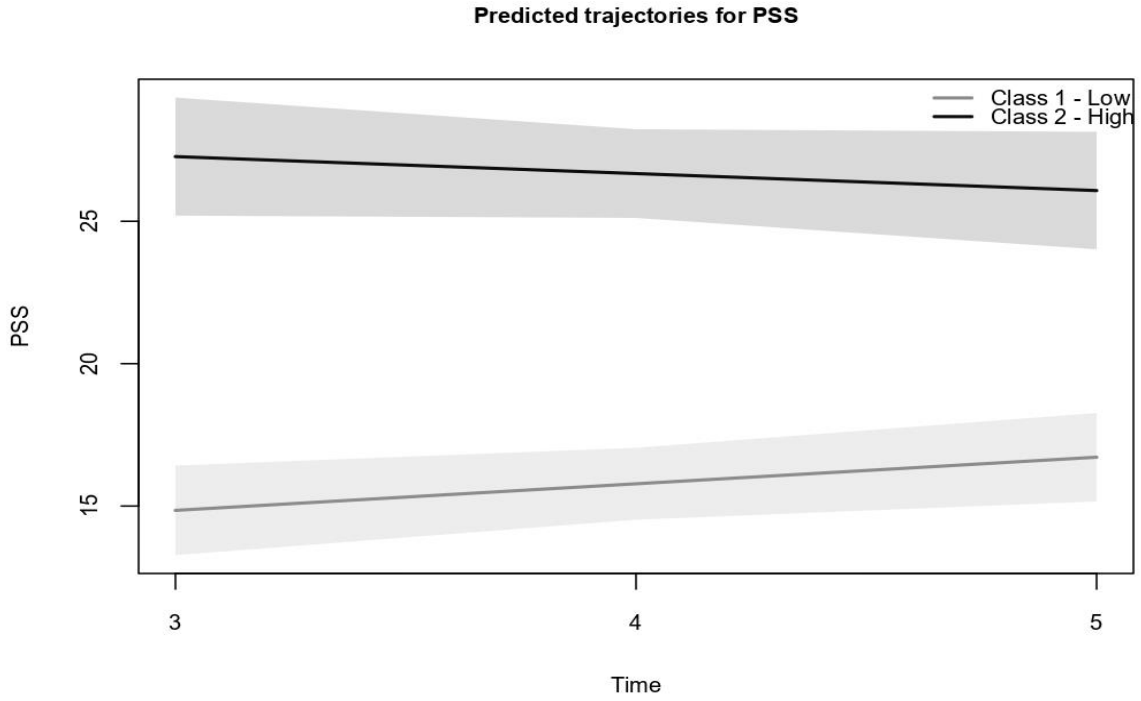
	N (%)	Intercept	Slope	Overall mean scores	Mean (CI) across three time points		
					Time 3	Time 4	Time 5
PSS perceived stress							
Class 1 (low ss)	126 (67%)	13.91***	0.93*	15.78 (SD=0.93)	14.85 (13.28,16.42)	15.78 (14.52,17.04)	16.72 (15.16,18.27)
Class 2 (high ss)	61 (33%)	27.87***	-0.60	26.67 (SD =0.60)	27.27 (25.20, 29.34)	26.67 (25.12, 28.23)	26.08 (24.02,28.14)
ESM situational stress							
Class 1 (low ss)	162 (93%)	2.66***	-0.15**	2.04 (SD =0.155)	2.95 (3.07, 4.17)	3.62 (3.07, 4.17)	1.89 (1.78, 2.00)
Class 2 (high ss)	12 (7%)	0.96	0.66***	3.62 (SD =0.665)	2.12 (1.96, 2.44)	2.04 (1.89, 2.20)	4.28 (3.73, 4.84)
ESM social stress							
Class 1 (low ss)	154 (89%)	2.29***	-0.02	2.22 (SD =0.017)	2.24 (2.05, 2.43)	2.22 (2.08,2.35)	2.20 (2.04, 2.37)
Class 2 (high ss)	20 (11%)	3.20***	0.14	3.75 (SD =0.137)	3.62 (2.74, 4.49)	3.75 (3.17, 4.33)	3.90 (3.44, 4.34)

**p<0.05; **p<0.01; *** p<0.001*

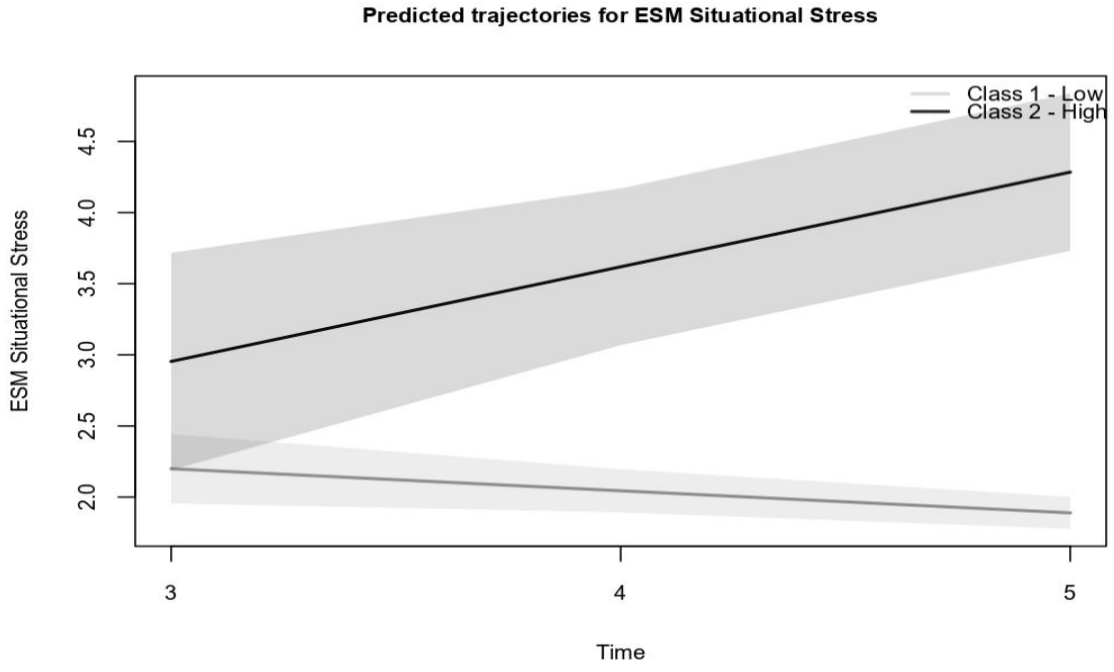
Note1. ESM Social Stress item (I feel close to this person/these people; reversed)

Figure 1. Developmental trajectories for low (class1) and high (class2) stress-sensitivity. a) PSS perceived stress; b) ESM situational stress; c) ESM social stress

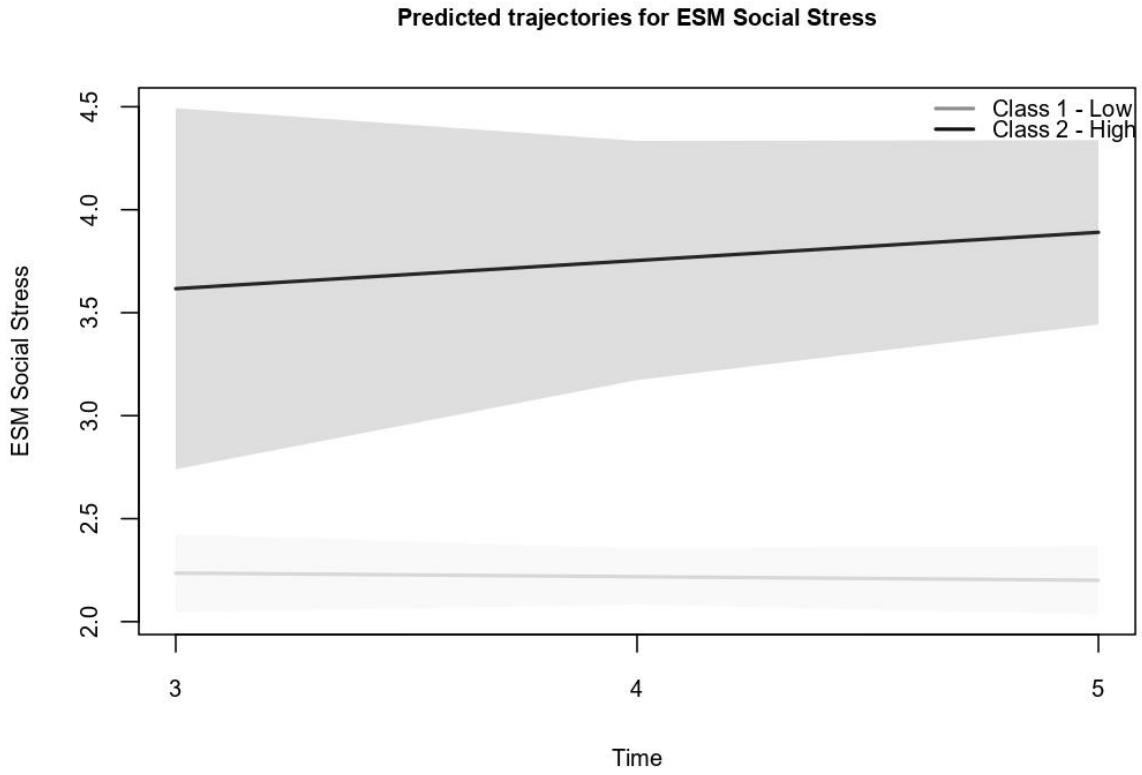
a) PSS perceived stress



b) ESM situational stress



c) ESM social stress



Note1. Trajectories show mean scores of a) PSS, b) ESM situational stress, c) ESM social stress across the three time points.

Supplemental Material Appendix 1
(Appendix S1)

Model Specification and Procedures

Model estimation using Latent Growth Curve Modeling (LGCM)

Indicators of the growth model were set to load 1 on the intercept and to load 0 on the slope at T3, to load 1 on the slope at T4, and to load 2 on the slope at T5, and residual variances were unconstrained. To estimate the model, we used the R package s*emTools* (Jorgensen et al., 2019), and the function *growth.mi*, which considers data with missing observations. Furthermore, the function simultaneously performs multiple imputation and estimate a SEM using the Lavaan and Amelia packages and combines the results using Rubin's rules (Rubin et

al., 1986). As parameter estimation, we used robust maximum likelihood parameter estimates (MLR). Means and variances of intercept and slope were estimated. In order to handle missing data, we used multiple imputation procedure (Rubin et al., 1986).

LGCM

R script

```
## Preliminaries
### Prelim - Installing libraries used in this script

library(haven)
Stress_Sensitivity <- read_sav("Stress Sensitivity_PSS.sav")
View(Stress_Sensitivity)
library(foreign)
summary(Stress_Sensitivity)

# Compute covariance matrix and mean
time <- c("PSS_T3", "PSS_T4", "PSS_T5")
stress.time =  Stress_Sensitivity[time]
stress.time[sample(1:nrow(stress.time),10),1] = NA
stress.cov <- cov(Stress_Sensitivity[time])
stress.mean <- colMeans(Stress_Sensitivity[time])
names(stress.mean) <- colnames(stress.cov) <- rownames(stress.cov) <-
c("Time1", "Time2", "Time3")
stress.cov
stress.mean

## Plot longitudinal data
# Data is in wide format, ready to estimate SEM
# Data set must be in long format to plot the data
library(tidyr)

# The arguments to gather():
# - data: Data object
# - key: Name of new key column (made from names of data columns)
# - value: Name of new value column
# - ...: Names of source columns that contain values
# - factor_key: Treat the new key column as a factor (instead of character vector)
stress.sensitivity.long <- gather(Stress_Sensitivity, time, stress, PSS_T3,
PSS_T4, PSS_T5, factor_key=TRUE)
head(Stress_Sensitivity)

# Plot the longitudinal data
library(ggplot2)
ggplot(stress.sensitivity.long, aes(x = time, y = stress, color =
as.factor(number), group = number)) +
  geom_point() +
  geom_line() +
  theme_classic(base_size = 18) +
  theme(legend.position = "none") +
  labs(title = "Individual Stress Sensitivity Trajectories", y = "Stress",
x = "Time")
```

#LGCM
#Data preparation 2: in the previous step (plot longitudinal data) we needed the column with the code of each participant (i.e. number), however for LGCM we need to eliminate that column with the following function:

```
library(dplyr)

# Drop 1st column of the dataframe
Stress_Sensitivity<- select(Stress_Sensitivity,-c(1))

names(Stress_Sensitivity) = c("Time1","Time2","Time3")
Stress_Sensitivity = data.frame(Stress_Sensitivity)

# Exploring missing values
# missing data patterns
library(mice)
md.pattern(stress.time)

#Basic latent curve model specification: handling missing values
library(lavaan)

# multiple imputation using mice
library(semTools)
library(Amelia)


##Model 5

# unconstrained model, the correlation between the errors are note constraint to be zero
stress.model5 <- '

# intercept
i =~ 1*Time1 + 1*Time2 + 1*Time3
# slope
s =~ 0*Time1 + 1*Time2 + 2*Time3
'

# Multiple Imputation
# 50 imputed dataset
stress.time.sim <- amelia(Stress_Sensitivity, m=50)
stress.time.sim$imputations
stress.fit <- growth.mi(stress.model5, Stress_Sensitivity, m=50, miPackage
= "Amelia", seed = 12345, estimator = "MLR")
summary(stress.fit, fit.measures=TRUE)

----------
```

Model estimation using Linear Mixed Model (LMM)
R script—example of the ESM Situational stress item "My current situation is stressful"

```
## Preliminaries
### Prelim - Installing libraries used in this script
```{r, echo=TRUE, warning=TRUE, results="hide", message=FALSE}

# This code chunk simply makes sure that all the
# libraries used here are installed.
# Check if R packages are installed
```
```

```
list.of.packages =
c("foreign","lme4","lmerTest","optimx","lcmm","lattice","car")
new.packages = list.of.packages[!(list.of.packages %in%
installed.packages()[,"Package"])]
if(length(new.packages)) install.packages(new.packages)
```

Load data set
Import DB

```
library(foreign)
esm.sit.stress.db <- read.spss("SITUATIONAL STRESS PN3 PN4 PN5.sav",
to.data.frame=TRUE)
```

List of the subject's ID's

```
subjno.i = unique(esm.sit.stress.db$number)
subjno.i
```

#To estimate the realtion between two variable using linear mixed effect models, we usually mean centered the predictors using the individual's mean
Compute the individual's mean of Stress in each wave

```
Person_mean_ESMStress_l2 = aggregate(esm.sit.stress.db$EsmSTRESS,
list(esm.sit.stress.db$number,esm.sit.stress.db$wave), FUN = mean,
data=data, na.rm=TRUE)

library(lattice)
Person_mean_ESMStress_l2$time.wave =
as.numeric(Person_mean_ESMStress_l2$Group.2)
color <- Person_mean_ESMStress_l2$Group.1
xyplot(x ~ time.wave, Person_mean_ESMStress_l2, groups = Group.1,
col=color, lwd=2, type="l")
```

Estimate model Stress is predicted by time (wave)
This analysis considered time as a linear effect

```
library(lme4)
library(lmerTest)
library(optimx)
ctrl = lmerControl(optimizer = "optimx", calc.derivs = FALSE,
optCtrl = list(method = "nlminb", starttests = FALSE, kkt = FALSE))
```

The analysis considered time as a factor (studying if there are mean differences in stress over time)

```
lmm.2 = lmer(EsmSTRESS ~ wave + (1 + wave| number), data =
esm.sit.stress.db,control=ctrl,REML=TRUE)
summary(lmm.2)
```

**We repeated the same procedure for all ESM items*

Model estimation using Latent Class Analysis (LCA)
R script—example of the perceived stress, PSS

Data preparation

```
library(foreign)
Stress_Sensitivity <- read.spss("Stress Sensitivity_PSS.sav",
to.data.frame=TRUE)
```

```
library(tidyr)
# The arguments to gather ():
# - data: Data object
# - key: Name of new key column (made from names of data columns)
# - value: Name of new value column
# - ...: Names of source columns that contain values
# - factor_key: Treat the new key column as a factor (instead of character vector)
stress.long <- gather(Stress_Sensitivity, time, stress, PSS_T3, PSS_T4,
PSS_T5, factor_key=TRUE)
stress.long$time <- as.numeric(stress.long$time)

## Plot longitudinal data
library(lattice)
color <- stress.long$number
xyplot(stress ~ time, stress.long, groups = number, col=color, lwd=2,
type="l")

## Estimate the model with only one class (G=1)
install.packages('lcmm')
library(lcmm)

# In this model we are estimating linear trajectories
m1 <- hlme(stress ~ time,random =~ time, subject = 'number', data =
stress.long) # ng=1
summary(m1)

## Estimate the model with more than one class (G>1)

#Estimation considering 2 classes:
m2 <- hlme(stress ~ time,random =~ time, subject = 'number', data =
stress.long, ng = 2, mixture=~time, B=m1)
summary(m2)

#Estimation considering 3 classes:
m3 <- hlme(stress ~ time,random =~ time, subject = 'number', data =
stress.long, ng = 3, mixture=~time, B=m1)
summary(m3)

#Estimation considering 4 classes:
m4 <- hlme(stress ~ time,random =~ time, subject = 'number', data =
stress.long, ng = 4, mixture=~time, B=m1)
summary(m4)

## Choose the best model
summarytable(m1,m2,m3,m4, which = c("G", "loglik", "conv", "npm", "AIC",
"BIC", "SABIC", "entropy", "%class"))

# Model selection: the number of classes will be selected by comparing BIC, SABIC and AIC.
summary(m2)
#or
summary(m3)
#or
summary(m4)
-----
```

```
# Predictions of the model
# We select the model with 2 classes
# We compute the number of participants in each class
# classification
postprob(m2)

# We select the model with 2 classes
# Create dataset for prediction
# data_pred <- data.frame(time=seq(1,3,length.out=3))
data_pred <- data.frame(time=seq(1,3,length.out=3))

# Predictions are computed for each class at the point estimate:
pred <- predictY(m2, data_pred, var.time = "time", draws=TRUE)

# Compute a matrix that includes the time (wave) and the estimated means for each class
mean_PSS_matrix = cbind(pred$times,pred$pred)

# Compute the mean for each class across the waves and the confidence intervals
mean_PSS_waves =
aggregate(mean_PSS_matrix,by=list(mean_PSS_matrix$time),mean)
mean_PSS_waves

# Compute the mean of means and the standard deviation
## Class 1
mean(mean_PSS_waves$Ypred_class1)
sd(mean_PSS_waves$Ypred_class1)
## Class 2
mean(mean_PSS_waves$Ypred_class2)
sd(mean_PSS_waves$Ypred_class2)

# Graph of the predictions versus observations
plot(m2, which="fit", var.time="time", marg=FALSE, shades = TRUE)

plot(pred, lty=1,lwd=5,ylab="PSS",main="Predicted trajectories for PSS")

# Add confidence intervals
predIC <- predictY(m2, data_pred, var.time = "time",draws=TRUE)
windowsFonts(A = windowsFont("Arial"))  # Specify font
plot(predIC, xaxt = "n", lty=1, lwd=2, xlab="Time", ylab="PSS",
main="Predicted trajectories for PSS", shades=TRUE,
     legend = NULL, col=c("grey55","grey5"), family = "A",
     cex.lab = .8, # Font size 8
     cex.axis = .8,
     cex.main = .8,
     cex.sub = .8)
legend("topright",legend=c("Class 1 - Low","Class 2 - High"),
       col=c("grey55","grey5"), lty=1, lwd=2, bty='n', cex = 0.8)
axis(1, at=1:3, labels=c(3,4,5), cex.axis = .8,)
#create a new variable in the database class each participant belongs to (i.e. 1 or 2):
Participant.class.2 = m2$pprob[,1:2]
Participant.class
```

** We repeated the same procedure for PSS and ESM items*

Supplementary Material 2

The number of stress-sensitivity classes according to the goodness-of-fit provided by the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample-size Adjusted BIC (SABIC). The model with the lowest fit indices was considered.

Table S1. Criteria for deciding the number of classes (LCA) within latent variables of stress-sensitivity.

Stress-sensitivity measure		# of classes	AIC	BIC	SABIC
PSS perceived stress		1	2432.522	2451.909	2432.904
		2	**2425.154**	**2454.234**	**2425.728**
		3	2431.154	2469.928	2431.919
		4	2430.838	2479.305	2431.794
ESM situational stress		1	44576.70	44595.65	44576.65
		2	**44537.47**	**44565.90**	**44537.40**
		3	44543.47	44581.38	44543.38
		4	44549.47	44596.86	44549.36
ESM social stress	I am alone because people do not want to be with me	**1**	**7315.755**	**7334.709**	**7315.709**
		2	7321.755	7350.186	7321.686
		3	7139.402	7177.311	7139.312
		4	7145.402	7192.788	7145.289
	I feel close to this person (these people) $_r$	1	28280.65	28299.61	28280.61
		2	**28267.23**	**28295.66**	**28267.16**
		3	28273.23	28311.14	28273.14
		4	28279.23	28326.61	28279.12
	I prefer to be alone	**1**	**25737.48**	**25756.44**	**25737.44**
		2	25743.48	25771.91	25743.41
		3	25679.83	25717.74	25679.74
		4	25685.83	25733.22	25685.72

Note1: Best model fit indicated by lowest AIC, BIC and SABIC in bold. AIC=Akaike Information Criterion, BIC=Bayesian Information Criterion, SABIC=Sample-size Adjusted BIC. Lowest values indicate the best discrimination of classes; $_r$=reversed.

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The interaction of polygenic susceptibility to stress and childhood adversity dimensions predicts longitudinal trajectories of stress-sensitivity

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Abstract

Background. Stress-sensitivity (SS) is considered a psychobiological trait possibly resulting from the interaction of genetic and environmental factors (GxE). This study examined whether the interaction of SS-related Polygenic and Genetic Risk Scores (PRS and GRS) with interview-based dimensions of childhood adversity predicted longitudinal trajectories of low versus high SS.

Methods. Participants were nonclinically-ascertained young adults comprising normative and elevated scores on schizotypy. SS trajectories were defined in a previous report based on three prospective assessments (23.5, 25, 28 years-old) of both retrospective (Perceived Stress Scale; PSS) and momentary (Experience Sampling Methodology; ESM) stress ratings. GxE effects of a (PRS-SS and GRS-HPA) with childhood adversity dimensions (Intrafamilial Adversity, Threat and Deprivation) on SS trajectories were examined.

Results. Threat was the most consistent predictor of persistently high SS. PRS-SS moderated the association of Threat with high-PSS. GRS-HPA moderated the effects of all adversity dimensions on high-PSS. The interaction of PRS-SS with Deprivation and GRS-HPA with Intrafamilial Adversity predicted trajectories of momentary social stress, but the effects were driven by those with lower genetic susceptibility.

Conclusions. Genetic-HPA-axis moderates the effects of all adversity dimensions on persistent SS trajectories, as well as PRS-SS and Threat, particularly for retrospective stress measure. The findings highlight the complex interplay between GxE factors and suggest that PSS may better capture SS trait since stressful experience may be difficult to perceive and articulate in the moment. Including biologically-meaningful GRS indexing SS and adversity dimensions in future studies using comprehensive stress measures would enhance our knowledge on high SS susceptibility and its relationship with diverse psychopathological outcomes.

Keywords: Stress-sensitivity, trait development, gene-environment interactions, Polygenic-risk-scores, adversity-dimensions, stress, longitudinal.

1. Introduction

Stress-sensitivity is a trait involving heightened reactivity to stress that may arise from a combination of acquired and inborn vulnerability factors (Harkness et al., 2015; Hammen, 2015). Relatedly, *stress-reactivity* refers to an individual's physiological and psychological response to stressors. The significance of stress-sensitivity and stress sensitization in the development and maintenance of psychopathology is widely acknowledged, as evidenced by their inclusion in the Research Domain Criteria (RDoC) Matrix by the National Institute of Mental Health (NIMH) (Clinton et al., 2021). Research indicates that stress can impact psychopathology through a process known as *stress sensitization*, wherein repeated exposure to stressors leads to increased physiological and psychological reactivity and sensitivity to stress over time (Post, 1992; Collip et al., 2008; Stround, 2020). Several models, including the sensitization model (*kindling hypothesis*; Post, 1992) and the neurodevelopmental traumagenic (Read et al., 2014) , propose that early life adversity in interaction with genetic factors disrupts several multilevel systems involved in stress regulation [e.g., gene expression (Leighton et al., 2017), Hypothalamic Pituitary Adrenal -HPA- axis (Starr et al., 2021), amygdala functioning (Weissman et al., 2020), and attachment (Lahousen et al., 2019)], leading to abnormal reactivity to stress (Stroud, 2020; Russell et al., 2018). Individuals exposed to adversity and sensitized to stress often reflect strong and persistent autonomic, adrenocortical, and/or other exaggerated biological and psychological responses to stressors, placing them at a high risk of developing a variety of disorders (Stroud, 2020; Wade et al., 2019). Moreover, exposure to early adversity has also been associated with increased reactivity to minor stressors in daily-life in the context of momentary stress appraisals (Reininghaus et al., 2016a; Cristóbal-Narváez et al., 2016a, b). This heightened reactivity further supports the process of stress sensitization, as it reinforces the brain's response to stress (Collip et al., 2008).

A challenge in the investigation of how adversity impacts stress-sensitivity is the operationalization and measurement of environmental exposures. Research has focused on studying a theory-driven Dimensional Model of Adversity and Psychopathology (DMAP; McLaughlin & Sheridan, 2016) that proposes two different dimensions, *Threat* (involving harm or the threat of harm) and *Deprivation* (absence of expected environmental inputs) (McLaughlin & Sheridan, 2016). These dimensions are emphasized as the core features of childhood adversity, comprising of a range of different exposures. Some studies show similar associations of adversity dimensions with the stress-response system (Smith & Pollak, 2021), whereas others highlight pathways that are unique to a particular dimension of adversity (McLaughlin et al., 2021; McLaughlin et al., 2019). Both dimensions, for example, are known to contribute to disruptions in stress-response and increased stress-sensitivity (Vogel et al., 2021; McLaughlin et al., 2021; Sisk & Gee, 2022), yet individuals exposed to *Threat* may exhibit higher perceptual sensitivity to anger and levels of stress, and develop greater attention biases to more threatening cues reflecting increased sensitivity to stress (Chen et al., 2010; McLaughlin & Lambert, 2017)—findings that may not be applicable to deprivation alone (Stevens et al., 2021; Busso et al., 2017; McLaughlin et al., 2021).

Several studies have identified genetic variants (e.g., FKBP5, COMT, BDNF) that shape different stress-regulating mechanisms directly associated with stress-sensitivity (van Winkel et al., 2008; Hernaus et al., 2013; Cristóbal-Narváez et al., 2016b). However, traditional candidate-gene approaches are being considered a simplistic view explaining just a small portion of genetic variation for complex traits such as environmental responsiveness (Rutter et al., 2006; Halldorsdottir & Binder, 2017). In contrast, novel approaches based on Genome Wide Association Studies (GWAS) consider the contributions of many common genetic variants of small magnitude across the whole genome showing larger cumulative effect sizes and greater predictive power (Bulik-Sullivan & Neale, 2015; Maier et al., 2015). So far, two GWAS-based genetic scores in the context of stress-sensitivity have been described. Arnau-Soler et al's (2018) developed a Polygenic Risk Score related to stress-sensitivity (PRS-SS) derived from the association between genetic variants and neuroticism levels (as a proxy phenotype of stress-sensitivity) in individuals with Major Depression Disorder (MDD). Second Crawford et al.'s (2021) GWAS for morning plasma cortisol identified a genetic risk score relevant to the HPA-axis function (GRS-HPA) in a population-based sample. Cortisol, as the end-product glucocorticoid of the HPA axis, plays a crucial role in adaptation to environmental stress by facilitating physiological and behavioral responses to threats (Stephens & Wand, 2012)

Research on gene-environment interaction (GxE) examines the synergistic effects between genetic risk factors and environmental exposures on stress-sensitivity mechanisms (Leighton et al., 2017; Davidson et al., 2021). Previous research has shown that genetic variants associated with stress-regulation systems (e.g., FKBP) in interaction with childhood adversity (Cristobal-Narvaez et al., 2016b, 2017; Starr & Huang, 2019) account for variance in reactivity to stress, including both momentary (Cristóbal-Narváez et al., 2017; van Winkel et al., 2014) and retrospective (McKenna et al., 2021) appraisals of stress as well as exposure to stressful life events (Feurer et al., 2017; Starr & Huang, 2019). In comparison, limited GxE studies have tested the *predictive ability* of PRS (e.g., PRS for schizophrenia), particularly when combined with environmental exposures such as childhood adversity—with caution due to small sample and effect sizes across, the evidence of positive findings regarding the predictability of the PRS are noted (Woolway et al., 2022). However, the predictive ability of PRS proxies of *stress-sensitivity* and their interplay with environmental adversity to understand individual differences in stress-sensitivity trait is yet to be elucidated.

Thus, it is still unclear how the interaction of genetic variation relevant to stress-sensitivity with childhood adversity dimensions may account for individuals' trajectories of trait stress-sensitivity. The present study examined whether the interaction of two genetic risk scores for stress-sensitivity and childhood adversity dimensions predict prospectively defined trajectories of both retrospective and momentary appraisals of stress-sensitivity.

The present study

In a previous report (Gizdic et al., 2023b, submitted), we examined the stability of stress-sensitivity trait in a sample of nonclinical young adults using data of three prospective assessments spanning a total of 4.5 years. An overall pattern of stress-sensitivity stability over time for both retrospective appraisals of stress as well as momentary and contextualized situational and social stress appraisals was found. Furthermore, we explored differential developmental trajectories of stress-sensitivity and identified two classes: participants with persistently high and low stress-sensitivity scores (Gizdic et al., 2023b, submitted). The current study examines the contribution of i) two genetic risk scores related to stress-sensitivity, (PRS-SS and GRS-HPA, ii) self-report and interview-based childhood adversity dimensions, and iii) their interaction in predicting the previously identified high and low stress-sensitivity trajectories.

It was hypothesized that the interaction of high genetic susceptibility to stress-sensitivity (i.e., high PRS-SS and GRS-HPA) with high levels of childhood adversity would predict persistent trajectories of elevated stress-sensitivity. Specifically, and drawing from dimensional models of adversity, we expected that *Threat*, as the dimension that is considered a strong key factor for the development of a variety of subclinical and clinical symptomatology (Morgan et al., 2020; Beards et al., 2020; Moriyama et al., 2018), would yield the most significant interactions with stress-sensitivity related PRS and GRS.

2. Methods

2.1 Participants and Procedure

The data was collected as a part of the Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; Barrantes-Vidal et al., 2013a,b), in which students from Universitat Autonòma de Barcelona (UAB) repeatedly completed a comprehensive battery of self-report, interview, and ESM measures for a total of five data collection time points (mean interval between T1 and T5 was 7.8 years; SD=0.5). , At T1 a large pool of 547 unselected students (mean age=20.6 years; SD=4.1; 83% women) were validly screened with a psychometric battery (see details in Barrantes-Vidal et al., 2013a,b; Racioppi et al., 2018; Sheinbaum et al., 2020). A subset of this sample (oversampled with standard scores > 1.0 on measures of schizotypy and psychotic-like experiences to ensure enough variance in these skewed variables), was selected for in-depth assessments at T2, yielding 214 participants (mean age=21.4; SD=2.4; 78% women). Due to funding restrictions, half of T2 sample was invited at T3 (N=103; mean age=23.6; SD=2.6; 62% women) and re-assessed at T4 (N=89; mean age=24.8; SD=2.7; 62% women). At T5, we contacted participants assessed at T2 and were able to validly reassess 169 participants (79% of the potential T2 214 participants; mean age=28.0; SD=2.4; 81% women). At T2, participant's genotype was obtained.

In a previous study (Gizdic et al., 2023b, submitted), longitudinal stress-sensitivity trajectories were defined with data collected at T3, T4, and T5 (mean interval between T3 and T5 was 4.6; SD=0.5). We used two complementary approaches to index SS and create longitudinal SS trajectories. One the one hand, we used the Perceived Stress Scale (PSS; Cohen

et al., 1983), a retrospective self-reported measure of perceived stress including items asking about stress appraisals during past month available for N=187 in which the data was imputed by multiple imputation procedure (Lee & Shi, 2021). Multiple imputation is commonly used to generate multiple datasets with filled missing data. Subsequent analyses are then performed on a "mean/pooled" database created from these generated datasets, rather than obtaining a new database with replaced missing data (Rubin's rule; Rubin & Schenker, 1986); on the other hand, we used momentary assessments of social and situational appraisals of stress in participants' daily life using Experience Sampling Methodology (ESM; Myin-Germeys et al., 2007) (available for N=174). The present study included those participants with 1) valid genetic data, and 2) retrospective (PSS) and momentary (ESM) stress-sensitivity trajectories across T3, T4, and T5, yielding a total of N=177 (PSS) and N=165 (ESM) participants.

2.2 Measures

Calculation of Polygenic Risk Scores (PRS)

DNA was extracted from saliva or cotton swabs and genotyped using the Illumina Infinium Global Screening Array-24 v2.0 (GSA) BeadChip at the "Centro Nacional de Genotipado" (CEGEN-PRB3-ISCIII; CNIO-Madrid). Please see details on the genotyping, quality control and imputation procedures in supplementary materials.

Two genetic risk scores for stress-sensitivity were employed. We created a PRS-SS based on Arnau-Soler et al. (2018) who conducted a Genome Wide Interaction Study (GWIS) to identify the genetic variants that contributed to the higher neuroticism levels seen in individuals with a lifetime diagnosis of MDD. As increases in neuroticism have been linked to negative life events (Riese et al., 2014; Jeronimus et al., 2013), and negative life events have been linked to MDD (Tennant, 2002; Kendler et al., 2004), they suggested that a genetic score derived from the difference in neuroticism levels seen in individuals with MDD versus controls would allow to identify genetic variants important for stress-sensitivity. Secondly, a GRS related to the HPA axis function (GRS-HPA) was calculated based on Crawford et al.'s (2021) GWAS. In this GWAS. genetic variation in the *SERPINA1* and *SERPINA6* genes was associated with variations in morning plasma cortisol to identify proxy variants for variation in HPA axis function, one of the major neural systems implicated in regulating the physiological and behavioral responses to stress. PRS and GRS were calculated by adding the number of risk alleles carried by each individual multiplied by their effect sizes reported in the references GWIS/GWAS.

We applied the classical Clumping + Thresholding (C+T) method with PLINK v1.9. Independent variants were selected by clumping ($r2 < 0.1$ within a 1000 kb window for PRS-SS and $r2<.02$ within a 1000 kb window for GRS-HPA) using the 1000 Genomes Project phase 3 (www.internationalgenome.org; The 1000 Genomes Project Consortium, 2015) as a linkage disequilibrium (LD) reference panel. 95300 SNPs for PRS-SS and 105631 SNPs for GRS-HPA, survived clumping. For analyses with PRS-SS, we employed the nominal p-value threshold ($p<0.05$) given the exploratory nature of the study hypotheses, the lack of previous

GxE studies employing PRS-SS, and with fact no SNPs reached genome-wide significance ($p<5\times10–8$) in the original GWIS (Arnau-Soler et al., 2018). Using a conservative p-value (e.g., $p<0.05$) attempts to reduce the probability of including false positive genetic variants that may be present when increasing *p value* thresholds (Wray et al., 2014). As functional variants in genes SERPINA1 and SERPINA6 associated with variation in morning plasma cortisol were identified, we used a genome-wide significance threshold ($p<5\times10–8$) for GRS-HPA.

Childhood Adversity

To assess childhood adversity, three complementary measures were used. At T1, we administered the Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein and Fink, 1998), a self-report measure that assesses sexual abuse, physical and emotional abuse, and physical and emotional neglect. At T2, The Interview for Traumatic Events in Childhood (ITEC; Lobbestael et al., 2009; Lobbestael & Arntz, 2010), a semi-structured interview also assessing sexual abuse, physical and emotional abuse, and physical and emotional neglect, with follow-up questions assessing different parameters of abuse (such as age of onset, perpetrator(s), duration, and frequency) in order to calculate composite severity scores for each maltreatment subtype. Lastly, at T2, we also administered the semi-structured Childhood Experience of Care and Abuse (CECA; Bifulco et al., 1993), an investigator-based interview focusing on objective aspects of childhood experiences. Specifically, 5 subscales, including parental antipathy, role reversal, parental discord, violence between parents, and bullying, were used.

We computed principal components analysis (PCA) with Promax rotation to identify the dimensions underlying multiple subscales from the three childhood adversity measures (Gizdic et al., 2023a). Four factors labeled *Intrafamilial Adversity*, *Deprivation*, *Threat* and *Sexual Abuse* explained 63% of the total variance. Given the highly skewed nature of the sexual abuse factor, we did not to use this factor in further analyses.

2.3 Statistical Analyses

As indicated, in the previous study individuals were assigned to a high *versus* a low class of stress-sensitivity according to the longitudinal trajectories of two measures, the PSS and ESM (see Gizdic et al. 2023b, submitted). For ESM, one item indexed situational stress (*"My current situation is stressful")* and one was used to tap social stress (*"I feel close to this person (these people) (reversed)".* This last item was only asked if participants had responded to a previous question that they were with people at that moment. Thus, three categorical outcome measures were defined with two values each (high vs. low scores): PSS (n=61, 33% of N=187 in high class), ESM situational stress (n=12, 7% of N=174 in high class), and ESM social stress (n=20, 11% of N=174 in high class)—details of these analyses and the distribution of the classes of longitudinal trajectories can be found in Gizdic et al. (2023b, submitted).

In order to avoid GxE bias due to possible gene-environment correlations, Pearson's correlations between the study variables were examined. Two sets of Hierarchical binomial

logistic regressions were computed in two steps, one using the PRS-SS and the other using the GRS-HPA. At the first step, the genetic (PRS-SS or GRS-HPA) and adversity scores were entered to examine the direct effects on longitudinal stress-sensitivity trajectories. At the second step, the interaction between each genetic and each adversity factor was entered to examine multiplicative effects. When a significant interaction was found, the effect of the interaction was examined using simple slope analyses (PROCESS; Hayes, 2013). To consider possible population stratification, all analyses were corrected for two ancestry-informative principal components. Effects were considered significant when p-values were <0.05. All analyses were performed using the SPSS Version 22.0 software (IBM Corp. Released, 2013).

3. Results

Descriptive statistics and Pearson's correlations are presented in Table 1. No significant correlations were found between PRS-SS, GRS-HPA and childhood adversity variables. The PRS-SS and GRS-HPA were not associated. As to be expected, childhood adversity dimensions showed significant associations. The bivariate regressions of the main effects of PRS-SS, GRS-HPA and childhood adversity dimensions are reported in the Supplementary Material (Table S1).

3.1. *Predictors of Longitudinal Trajectories of Stress-Sensitivity: GxE Interactions*

As shown in Table 2, there were no direct effects of PRS-SS on any stress-sensitivity trajectories (except for a trend association of PRS-SS with ESM social stress trajectories; p<0.10). The *Threat* dimension had a direct association with the PSS trajectory, such that higher levels of threat were associated with an increased likelihood of belonging to the high-PSS class. Both *Threat* and *Deprivation* dimensions were associated with an increased likelihood of belonging to the high-ESM social stress class, whereas no associations emerged with ESM situational stress. Finally, *Intrafamilial Adversity* did not yield significant direct associations.

There was a significant interaction between PRS-SS and *Threat* in predicting PSS stress-sensitivity trajectories, whereas PRS-SS showed a significant interaction with *Deprivation* in the prediction of ESM momentary appraisals of social stress. Following simple slope analyses, in the interaction with *Threat*, those with high and moderate PRS-SS levels were associated with the high-PSS class, but not those with low PRS-SS levels (high reflects +1 SD, moderate is the mean, and low is -1 SD) (Figure 1a). In contrast, *Deprivation* was associated to high-ESM social stress class at low and moderate but not high PRS-SS levels (Figure 1b). Only a trend between PRS-SS and *Threat* was found in predicting stress-sensitivity trajectories of ESM momentary situational stress appraisals, in which only those with high PRS-SS levels were closely associated with the high-ESM situational stress class.

Regarding the GxE models using GRS-HPA, no direct effects of GRS-HPA on stress-sensitivity trajectories were observed (Table 2). Higher levels of *Threat* were associated with an increased likelihood of belonging to the high-PSS class. *Deprivation* was associated with an increased likelihood of belonging to the high-ESM social stress class—with *Threat* showing

a trend association. GRS-HPA showed significant interactions with all three adversity dimensions in predicting PSS stress-sensitivity trajectories.

Simple slope analyses indicated that the association between *Deprivation* (Figure 2b) and *Threat* (Figure 2c) with membership to the high-PSS class was significant only for those with high GRS-HPA. The association between *Intrafamilial Adversity* and high-PSS class had no significant slope (Figure 2a). Only GRS-HPA and *Intrafamilial Adversity* had a significant interaction for ESM social stress, with the effects being only significant for those with lower GRS-HPA (Figure 2d). Finally, no interaction effects of GRS-HPA and adversity dimensions emerged for ESM situational stress.

4. Discussion

To our knowledge, this is the first study examining the moderating effect of two genetic risk scores related to stress-sensitivity (PRS-SS and GRS-HPA) on interview-based dimensions of childhood adversity in predicting longitudinal trajectories of low versus high stress-sensitivity. Both retrospective (i.e., PSS) and momentary (i.e., ESM) measures of subjective stress were used. Genetic variability associated to stress-sensitivity, mostly the GRS-HPA, moderated the impact of childhood adversity for membership in the persistently high-PSS class, whereas results were more mixed for momentary stress trajectories.

Threat was directly associated with pertaining to the high-PSS class, and the interaction of PRS-SS with *Threat*, as well as GRS-HPA with all adversity dimensions, predicted an increased likelihood of high-PSS stress-sensitivity membership. These results indicate that individuals with high genetic susceptibility to stress were more likely to experience persistently high stress levels across almost five years when exposed to early adversity. The fact that GRS-HPA yielded more interaction effects than PRS-SS may be indicating a greater moderating role for a genetic score indexing biological variation in one of the main neural systems directly involved in regulating the effects of stress (i.e., the HPA axis) as compared to the PRS-SS, which relied on self-reported items. Particularly, the GRS-HPA included a single genetic locus associated to morning plasma cortisol at a genome-wide significance level. This locus comprised SERPINA1 and SERPINA6 genes, both involved in the transportation and availability of plasma cortisol, as reported by Crawford et al. (2021). The present findings are consistent with previous studies showing an association between the GRS-HPA and increased physiological (i.e., stress-induced salivary cortisol levels; Utge et al., 2018) and behavioral (increased negative affect following negatively appraised events; Torrecilla et al., *to be submitted*) stress-reactivity. Also, large GWAS samples sometimes limit the accurate assessment of the phenotypes, particularly when these rely on a few self-reported items. Instead, incorporating additional knowledge such as biologically-meaningful genetic risk scores into the further selection of relevant SNPs, as suggested by bioinformatics techniques such as Gene Set Enrichment Analysis (Holden et al., 2008) might enhance the formation of polygenic scores. In the case of the HPA-axis activity, glucocorticoid and mineralocorticoid receptor genes (e.g., FKBP5, NR3C1, NR3C2) might be particularly relevant for the study of

genetic susceptibility to stress-sensitivity, as shown by previous research (Feurer et al., 2017; Di Iorio et al., 2017; Starr et al., 2019a,b; Huang & Starr, 2019; McKenna et al., 2020; Chen et al., 2021). More so, further GWAS may benefit from long-term and more stable measures of cortisol such as hair cortisol, as compared to morning plasma cortisol (Neumann et al., 2017), to study genetic variability linked to the HPA-axis function and thus, to stress-sensitivity.

In terms of the childhood adversity dimensions, *Threat* was the most consistent predictor of membership to a high stress-sensitivity trajectory (PSS and ESM social stress), followed by *Deprivation* (ESM social stress). These results seem to be consistent with strong evidence linking threat-related adversity with altered patterns of detecting threatening cues and heightened social-emotional processing (Mc Laughlin et al., 2019); *Threat* showed main and interaction effects with both genetic markers of stress-sensitivity on PSS trajectories, as well as a main effect on momentary social stress and a trend interaction effect with PRS-SS on momentary situational stress. Thus, *Thread* had overall a large impact on the persistence of high stress-sensitivity. Drawing from the dimensional models of adversity, these findings support previous literature considering *Threat* to show strong associations with psychopathology outcomes (Morgan et al., 2020; Beards et al., 2020; Moriyama et al., 2018), and seem consistent with the hypothesis that persistently high stress-sensitivity may be an underlying mechanism underpinning this relationship.

No main or interaction effects were found for situational stress trajectories except for a trend association between PRS-SS and *Threat*, with high PRS-SS scores being more likely to show a trajectory of high momentary situational stress when exposed to greater levels of *Threat*. Of note, the stress-sensitivity trajectories defined by momentary stress ratings with ESM had a lower proportion of individuals in the high-classes (11% for high-ESM social stress and 7% for high-ESM situational stress) as compared to individuals classified in the high stress trajectory as defined by the retrospective PSS (33%). This may have influenced the ability to detect any GxE effect on trajectories of momentary situational stress. Furthermore, it is likely that momentary ratings of situational stress are more impacted by real-life external circumstances as compared to momentary appraisals of the social interactions and to retrospective measures of perceived stress of the preceding month. Possibly, the assessment of interpersonal stressors and evaluative measures such as the PSS are more influenced by trait-like variables such as stress-sensitivity than ratings of contextual stress.

Finally, the interaction effects predicting momentary social stress were intriguing. PRS-SS interacted with *Deprivation* and GRS-HPA with *Intrafamilial Adversity* to predict trajectories of ESM social stress. However, the direction of the interaction effects did not align with expectations as, in both cases, the effects were driven by those with lower genetic scores. This might be related in part to the unbalanced distribution of the stress-sensitivity groups.

Strengths & Limitations

The current study had several strengths, including a comprehensive assessment of stress measures, both retrospectively and in the moment, across multiple time points. The study also

introduced two genetic proxies of stress-sensitivity derived from different genome-wide approaches: a genetic score obtained from a psychological phenotype related to stress-sensitivity (PRS-SS) and a genetic score potentially indexing biological underlying factors of stress-sensitivity (GRS-HPA). This allowed for the exploration of the different genetic components that might be influencing individual differences in stress-sensitivity. Additionally, the study employed a comprehensive assessment of childhood adversity that combined fine-grained interview and self-report measures of a wide range of childhood adversities (Gizdic et al., 2023a), which greatly improved the reliability of this measurement. The majority of studies examine stress-sensitivity in clinical populations and address its association with symptom exacerbation and recurrence (e.g., Liu et al., 2012; Farb et al., 2015; Hernaus et al., 2015), whereas the nonclinical nature of our sample allowed for examining the construct of stress-sensitivity and its determinants without confounding factors related to clinical status such as symptom intensity, comorbidity, the effects of treatments, etc. Furthermore, the sample consisted of non-clinical young adults that are currently facing a period of critical developmental life-stage involving many challenging life milestones such as searching for a professional career, independence from parents, separation from the household and setting new living arrangements, etc. Thus, it is expected that this sample would provide a wider range of variability in response to stress. However, limitations of this study include a limited sample size, the predominance of women participants, and the small number of individuals with high stress-sensitivity trajectories as captured by momentary ESM (discussed in Gizdic et al., 2023b, submitted).

Conclusions

This study suggests that genetic susceptibility to stress-sensitivity plays a moderating role in the association between different types of early adversity and high persistent stress-sensitivity longitudinal trajectories, particularly when measured with a retrospective measure of subjective stress. The most relevant adversity dimension was *Threat*, followed by *Deprivation*, and variation in GRS-HPA yielded more effects than PRS-SS, possibly because it indexes variability in biologically-relevant stress-sensitivity functions.

Future research should examine the interplay between genetic susceptibility with both early and recent stressful exposures to better understand the mechanisms underlying stress-sensitivity and its relationship with psychopathological outcomes. This could inform prevention and intervention programs to target resilience-building factors and reduce risk factors for psychopathology in individuals with heightened stress-sensitivity.

Authors contribution:
Neus Barrantes-Vidal: conceptualization and methodology, supervision, funding acquisition, resources, data acquisition, data curation, investigation, project administration, writing original draft, review and editing
Alena Gizdic: formal analyses, writing-original draft, review and editing, visualization
Pilar Torrecilla: formal analyses, writing-original draft, review and editing
Tamara Sheinbaum: data acquisition, data curation, investigation, review and editing
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Rosa Araceli: genetic data analysis, review and editing
Ginette Lafit: software supervision, approved final draft, statistical consultation
Inez Myin-Germeys: approved final draft
Thomas R. Kwapil: conceptualization and methodology, statistical consultation, review and editing

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Conflict of Interest. None

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.

Tables and Figures

Table 1. Descriptives and Pearson correlations of study variables

	Descriptives	*Pearson correlations*						
	M (SD) or %	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1.PRS-SS	2.23 (5.83)	0.10	0.04	0.004	-0.15	0.08	-0.002	0.12
2.GRS-HPA	0.04 (0.03)		-0.02	-0.06	-0.05	-0.08	-0.07	-0.08
3.Intrafamilial Adversity	-0.03 (0.94)			0.39***	0.29***	0.02	-0.04	-0.10
4.Deprivation	-0.04 (0.97)				0.42**	0.12	0.02	0.18*
5.Threat	-0.06 (0.91)					0.16*	0.03	0.16
6.SS PSS (N=177)	30% high						0.19*	0.05
7.SS ESM Situational stress (N=165)	6% high							-0.03
8.SS ESM Social stress (N=165)	11% high							

*p < 0.05, ** p < 0.01, *** p < 0.001

Note 1: Descriptives and Pearson correlations are presented for the total sample of N=177.

Note 2:PRS=Polygenic Risk Score, GRS=Genetic Risk Score, SS= Stress-sensitivity, HPA= Hypothalamic Pituitary Adrenal, PSS=Perceived Stress Scale, ESM= Experience Sampling Methodology, M=Mean, SD=Standard Deviation

Table 2. Interaction between polygenic risk score (PRS), genetic risk score (GRS) and childhood adversity in predicting prospective stress-sensitivity trajectories.

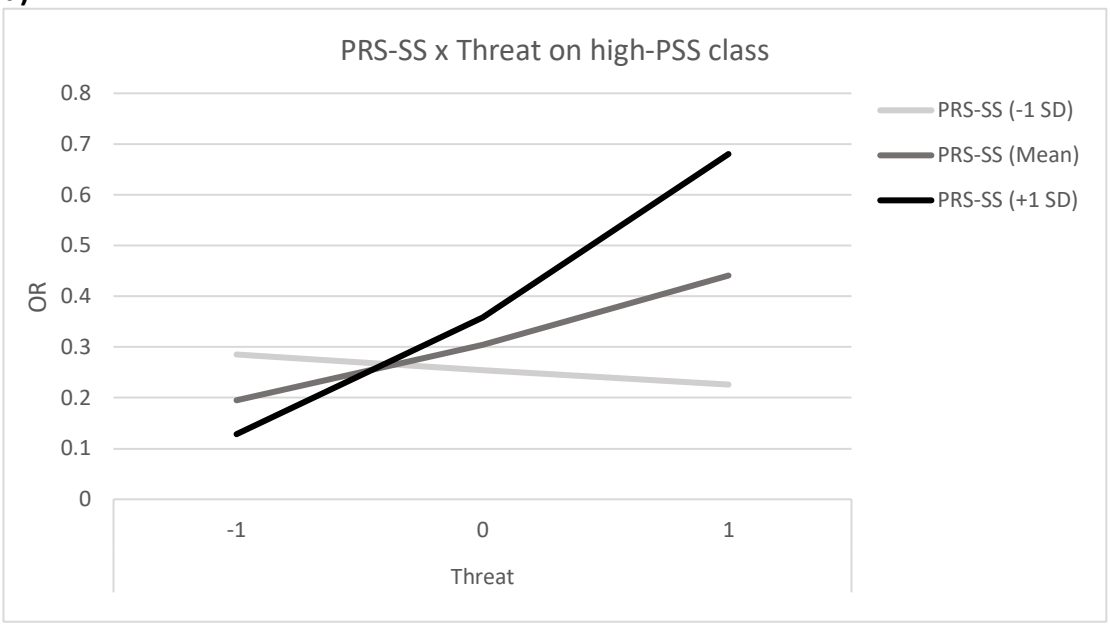
		Step 1				*Step 2*	
		PRS/GRS		**Childhood adversity**		**PRS/GRS x Childhood adversity**	
		OR	95% CI	OR	95% CI	OR	95% CI
SS trajectory by PSS							
PRS-SS	Intrafamilial adversity	1.19	0.86, 1.66	1.01	0.71, 1.43	1.16	0.80, 1.67
	Deprivation	1.19	0.86, 1.66	1.26	0.91, 1.74	0.95	0.61, 1.48
	Threat	1.28	0.91, 1.79	1.52*	1.05, 2.20	**2.28****	**1.29, 4.03**
GRS-HPA	Intrafamilial adversity	0.83	0.60, 1.16	1.01	0.71, 1.44	**1.48***	**1.01, 2.17**
	Deprivation	0.84	0.60, 1.18	1.25	0.91, 1.73	**1.77***	**1.12, 2.80**
	Threat	0.84	0.60, 1.18	1.44*	1.01, 2.04	**1.50***	**1.02, 2.21**
SS trajectory by ESM Situational Stress							
PRS-SS	Intrafamilial adversity	0.10	0.53, 1.89	0.83	0.39, 1.76	0.99	0.47, 2.09
	Deprivation	0.10	0.53, 1.90	1.09	0.61, 1.96	1.54	0.68, 3.50
	Threat	1.02	0.53, 1.95	1.15	0.61, 2.17	2.50^{+}	0.92, 6.79
GRS-HPA	Intrafamilial adversity	0.72	0.36, 1.46	0.82	0.39, 1.76	1.46	0.67, 3.16
	Deprivation	0.73	0.36, 1.47	1.07	0.58, 1.95	1.22	0.56, 2.68
	Threat	0.73	0.36, 1.47	1.119	0.58, 2.15	1.41	0.71, 2.83
SS trajectory by ESM Social Stress							
PRS-SS	Intrafamilial adversity	1.49	0.91, 2.43	0.69	0.37, 1.30	1.48	0.84, 2.59
	Deprivation	1.51	0.92, 2.49	1.59*	1.06, 2.40	**0.44***	**0.23, 0.83**
	Threat	1.66^{+}	0.97, 2.76	1.74*	1.09, 2.79	0.76	0.47, 1.21
GRS-HPA	Intrafamilial adversity	0.72	0.43, 1.22	0.69	0.37, 1.29	**1.92***	**1.03, 3.58**
	Deprivation	0.75	0.44, 1.29	1.55*	1.04, 2.31	1.15	0.68, 1.94
	Threat	0.75	0.45, 1.27	1.55^{+}	1.00, 2.39	1.04	0.65, 1.64

$^{+}$ $p < 0.10$, $^{*}p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note 1:PRS=Polygenic Risk Score, GRS=Genetic Risk Score, SS= Stress-sensitivity, HPA= Hypothalamic Pituitary Adrenal, PSS=Perceived Stress Scale, ESM= Experience Sampling Methodology, OR=Odds Ratio, Cl= Confidence Intervals

Figure 1. Graphic representations of GxE interactions between PRS-SS and adversity on SS trajectories.

a)



b)

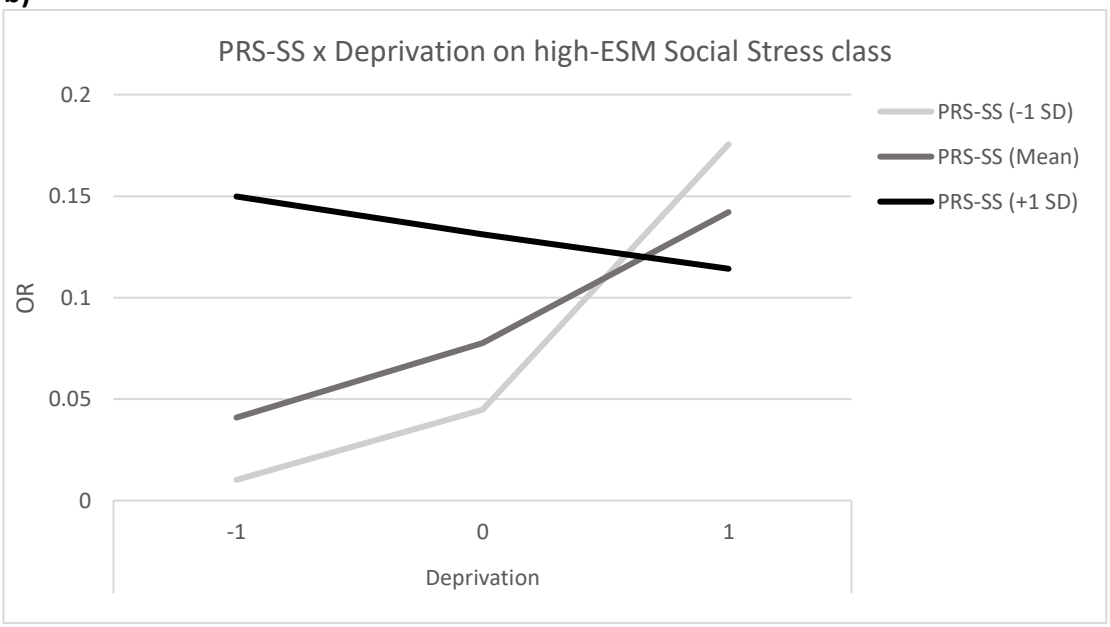
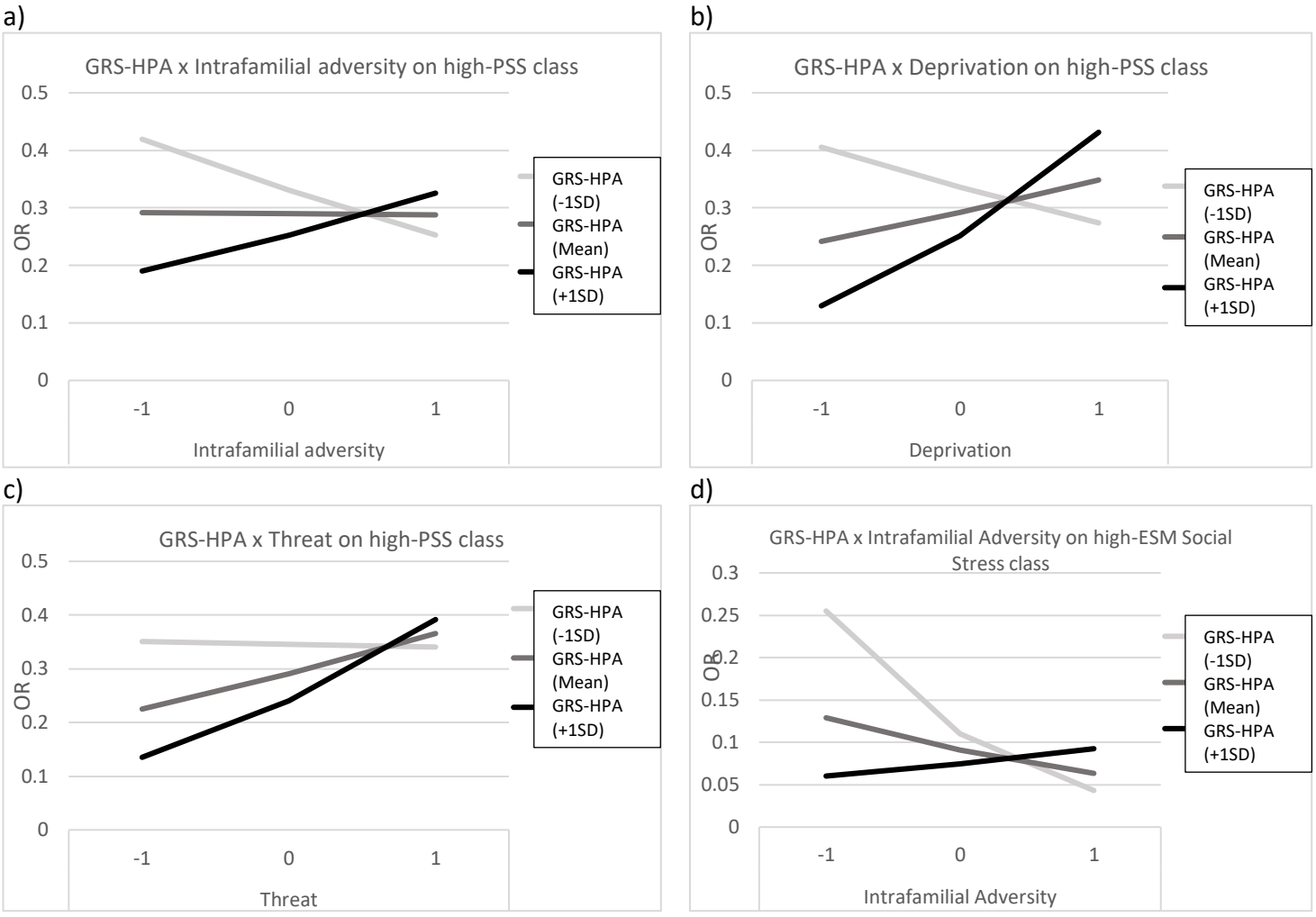


Figure 2. Graphic representations of significant GxE interactions between GRS-HPA and adversity on SS trajectories.



SUPPLEMENTARY MATERIAL

Supplementary Material 1.

Genotyping, Quality Control, and Imputation

DNA was extracted from saliva or cotton swabs using the prepIT-L2P kit (DNA Genotek Inc., Ottawa, Ontario, Canada) and the RealPure Genomic DNA Extraction Kit (Durviz S.L.U., Valencia, Spain) for saliva samples and cotton swab samples, respectively. DNA samples were genotyped using the Illumina Infinium Global Screening Array-24 v2.0 (GSA) BeadChip at the "Centro Nacional de Genotipado" (CEGEN-PRB3-ISCIII; CNIO-Madrid). Genotype calls were generated with GenomeStudio v2.0.4 (Illumina Inc., San Diego, CA, USA). A quality control (QC) was carried out with PLINK v1.9 (www.cog-genomics.org/plink/1.9/; Chang et al., 2015) in order to exclude SNPs that: had a missing call rate >2%; had a Minor Allele Frequency (MAF) <0.1%; or deviated from Hardy-Weinberg equilibrium with a P-value <0.001. Subjects were excluded when: had a missing call rate >2%; were related with other participants or duplicated samples according to the pairwise identity by descent method (PI_HAT >0.25); or had non-European ancestry according to a Multidimensional Scaling (MDS) analysis. The MDS analysis was carried out with PLINK v1.9 to represent population admixture and the first 10 ancestry components were extracted. From the total sample of 214 individuals that were assessed at T2 of the BLISS, 17 subjects were excluded during QC leaving a sample of 197 subjects. MDS components were recalculated in this final sample and the first two components were used in all models including PRS as independent variable. Imputation was performed in the Michigan Imputation Server (Das et al., 2016) considering the Haplotype Reference Consortium panel (www.haplotype-reference-consortium.org; McCarthy et al., 2016). A post-imputation QC was performed to exclude SNPs that: had an imputation quality score of R2 <0.3; or had a MAF <1%. A total of 7,755,414 SNPs passed post-imputation QC.

Supplementary Material 2.

Table S1. Bivariate regression of the main effects (PRS and childhood adversity).

	PRS				Childhood adversity					
	PRS SS		GRS HPA		Intrafamilial adversity		Deprivation		Threat	
	OR	95%CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SS trajectory by PSS	1.19	0.86, 1.66	0.83	0.60, 1.16	1.01	0.72, 1.44	1.26	0.92, 1.74	1.45*	1.01, 2.06
SS trajectory by ESM Situational Stress	1.00	0.52, 1.89	0.72	0.36, 1.46	0.83	0.39, 1.76	1.09	0.61, 1.96	1.14	0.61, 2.14
SS trajectory by ESM Social Stress	1.48	0.91, 2.41	0.73	0.43, 1.23	0.70	0.38, 1.30	1.57	1.05, 2.35	1.56	1.01, 2.42

*$p < 0.05$

Note 1:PRS=Polygenic Risk Score, GRS=Genetic Risk Score, SS= Stress-sensitivity, HPA= Hypothalamic Pituitary Adrenal, PSS=Perceived Stress Scale, ESM= Experience Sampling Methodology, OR=Odds Ratio, Cl= Confidence Intervals

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SECTION 3

THE ASSOCIATION OF PSYCHOSOCIAL STRESSORS AND PROTECTIVE FACTORS WITH PSYCHOSIS-PRONENESS IN THE CONTEXT OF THE COVID-19 PANDEMIC

Chapter 5

Loneliness and psychosocial predictors of psychosis-proneness during COVID-19: Preliminary findings from Croatia

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Abstract

The present study investigated psychosocial predictors of psychosis-risk, depression, anxiety, and stress in Croatia during the COVID-19 pandemic. Given Croatia's recent transgenerational war trauma and the relative lack of available prodromal data, this study presents a unique opportunity to examine the impact of loneliness and other psychosocial factors on psychosis-risk and mental health in this population. 404 Croatian participants completed an anonymous online survey of physical and mental health questions. 48 participants met the criteria for elevated psychosis-risk on prodromal questionnaire (PQ-16). Loneliness had a significant impact on psychosis-risk. Exposure to trauma was associated with psychosis-risk and loneliness, while domestic abuse/violence was associated only with the distress surrounding psychotic-like symptoms. COVID concern was also associated with psychosis-risk. Lastly, the associations between psychosis-risk and depression, anxiety, and stress were robust. These findings highlight the important role of loneliness in psychosis-proneness in Croatia. Depression, anxiety, and stress were also closely related to elevated psychosis-risk. Loneliness is a highly salient issue for individuals with psychosis and it is important to target loneliness within a multi-faceted psychosocial intervention for those at risk for schizophrenia.

1. Introduction:

The survival and flourishing of social species such as humans depends largely on close-knit social networks and cooperation. Existing evidence indicates that social connectedness supports good health outcomes (Holt-Lunstad, 2018; Ehsan et al., 2019) including mental health (Degnan et al., 2018; Nitschke et al., 2021). However, in the last two years there have been significant social changes brought about by the global COVID-19 pandemic and consequential public health measures. Increased unemployment, financial insecurity, and poverty are likely to have long-lasting impacts on mental health outcomes (Holmes et al., 2020) but disrupted social connectedness due to the pandemic may have an even broader impact on mental health across all age groups, socioeconomic strata, and cultures (e.g., Dean et al., 2021). The pandemic necessitated social distancing measures to control the spread of the virus. These public health strategies may have had detrimental effects on mental health including increased feelings of loneliness, isolation, and anxiety (Carvalho et al., 2020).

Deterioration of mental health among the general public may be as severe as effects found among the survivors of SARS-CoV-2. About 34% of patients infected with SARS-CoV-2 were diagnosed with psychiatric disorders in the 6 months following their illness (Taquet et al., 2021), most commonly, mood and/or anxiety disorders (Butler et al., 2020). Although there is relatively low incidence of psychotic disorder after COVID-19 infection (1.4%), there have been reports of sudden onset of psychosis in individuals with no psychiatric history (Kozato, Mishra & Firdosi, 2021). Among the general population, the prevalence of mental health conditions during the COVID-19 may be just as alarming. Dean et al. (2021) reported overall increase in psychosocial distress across four countries. Importantly, Lee et al. (2021) found depression in 36.8%, anxiety in 29.5%, stress in 24.5% and prodromal psychosis signs in 12.8% of the general Korean population despite the very low COVID infection rate in the country.

Despite the shift towards studying the consequences of the pandemic on mental health, there is still a lack of data from the general population. Social distancing and enforced social isolation may exacerbate psychosocial stress related to the pandemic, potentially contributing to psychosis onset (Javed & Shad, 2021). Moreover, while social stress and social withdrawal are often regarded as prodromal symptoms of psychosis (van Winkel et al., 2008; Mäki et al., 2014), growing evidence identifies loneliness itself as a reliable risk factor for psychosis onset (da Rocha et al., 2018; Mäki et al., 2014), especially during the COVID-19 pandemic (Tso & Park, 2020). Research increasingly highlights the impact of loneliness on psychosis symptom expression, especially in non-clinical population (da Rocha et al., 2018).

Loneliness is defined as a discrepancy between an individual's preferred and actual social relations (Peplau & Perlman, 1982; Cacioppo, et al., 2015). Increased loneliness is associated with lower education level, lower income, unemployment, single-status and history of psychiatric diagnosis (Cacioppo et al., 2015). There are significant mental health consequences of loneliness. For example, higher levels of loneliness are associated with sensitivity to stress and threats (Nowland et al., 2018) and the severity of post-traumatic stress disorder (PTSD) (Solomon et al., 2015). Compared to the pre-pandemic period, there has been

a three-fold increase in severe loneliness brought about by COVID-19 (O'Sullivan et al., 2021). This exacerbation of loneliness might be partially attributed to various public health interventions that were implemented to impede the spread of coronavirus including lockdowns, curtailing of social gatherings, and restricted travel. Consequently, social isolation has been associated with depression, anxiety, and increased rates of suicide attempts among the general population (Elovainio et al., 2017). With respect to the COVID-19 pandemic, the risk for psychiatric disorders appears to be significantly increased by loneliness (Tso & Park, 2020; Park et al., 2020). Moreover, the impact of existing PTSD symptomatology on perceived stress was mediated by loneliness (Jeftić et al., 2021): individuals might experience post-traumatic stress reactions (e.g., trauma-related fear and heightened physiological arousal) when triggered by traumatic reminders like lockdown and severe restrictions (Tsur et al., 2018).

Although trauma triggers lose their intensity over time (Howell et al., 2015), it is important to examine how they may be associated with risk for psychiatric disorders following recent war experiences in Croatia. The impact of war-related trauma in Croatia has had detrimental effects on mental health and quality of life in this population (Babić-Banaszak et al., 2002; Vukojević et al., 2020). Similarly, the survivors of the war in Bosnia and Herzegovina were found to suffer from severe trauma even after 25 years. This study concluded that war experiences and reminders have devastating mental health consequences (Jeftić et al., 2021).

In the first study on mental health in Croatia conducted during the first national lockdown (May 2020), between 17.8 % - 19.1% of participants reported severe depression, anxiety, and stress (Jokić Begić et al., 2020). A second study in Croatia (Ajduković et al., 2020) conducted during July 2020, when the restrictions had been partially relaxed, reported that between 7.7% - 7.8% of participants were at risk for either depression or anxiety disorder, with high levels of stress in 7.2% of participants; these findings may show high levels of adaptability and resilience during the pandemic. Interestingly, in comparison to mental health data emerging from other European countries and some parts of Asia, Croatia seems to have relatively lower incidences of stress, anxiety, and depression disorders (Newby et al., 2020; Park et al., 2020; Rossi et al., 2020). Studies have also shown that the prevalence of PTSD among individuals in Croatia who had experienced at least one traumatic event during the COVID-19 pandemic was 14% (Ajduković et al. 2020), which is similar to prevalence in Ireland, where COVID-19-related PTSD rate is 17.7 % (Karatzias et al., **2020**). Despite the background of existing war-related trauma, mental health risk in the Croatian population during the pandemic appears to be broadly similar to that of other countries. However, it is possible that within the Croatian population, shared pain or adversity affected by war promotes solidarity, resulting in social cohesion (see Bastian et al., 2014). Upon large scale disasters such as a massive earthquake or a terrorist attack, people who work together to survive and help each other emotionally are more socially resilient and have better mental health outcomes (see Garcia and Rime, 2019). Thus, it may be that individual differences in vulnerability to psychological disorders might be uniquely affected by trauma and social disconnection.

The present study investigated the role of psychosocial predictors of both physical and mental health (and, in particular, of loneliness) among the Croatian population during COVID-19, with specific focus on psychosis risk, depression, anxiety and stress. We hypothesized that loneliness would have a negative impact on mental health overall and will act as significant risk factor in predicting psychotic symptoms. Further, we expect that individuals with a history of trauma will be more vulnerable to the effects of the current pandemic, loneliness, and psychosis risk. Because of Croatia's recent history of transgenerational war trauma and the relative lack of prodromal data, this study presented a unique opportunity to examine the impact of loneliness and other psychosocial factors on psychosis-proneness.

2. Methods

2.1. Participants and procedure

The sample consisted of 404 adults (aged 18 and above) residing in Croatia. The participants completed an online, anonymous survey in Croatian, created via SurveyMonkey. The survey link was distributed via online channels and platforms including university emailing lists, social media platforms, and in person. Before starting the survey, participants acknowledged their participation was voluntary, and consented to participate and have their anonymous data used for analysis. The survey was open to everyone and described by introducing type of questions that will be asked, including the possibility to stop at any time. The average time of survey completion was about 24 minutes. Data collection occurred between July and September 2020, during the first peak wave of COVID-19 pandemic. This study received exempt status from the Vanderbilt University Institutional Review Board (Vanderbilt IRB exempt #200337).

2.2. Measures

The survey consisted of 183 questions that asked about participant demographics, questions regarding COVID-19 concern, past trauma exposure, and general and mental health, including validated measures to assess loneliness (the UCLA (University of California, Los Angeles) Loneliness Scale; Russell, 1996); depression, anxiety, and stress (Depression, Anxiety and Stress Scale (DASS-21); Lovibond & Lovibond, 1995) and psychosis risk (Prodromal Questionnaire-16 (PQ-16); Ising et al., 2012). Also, questions about social network were asked (Social Network Index (SNI); Cohen, 1997).

To assess the effects of the COVID-19 pandemic on individuals' daily lives, we asked participants to self-report changes in their financial situation, current/past quarantine periods, number of days spent at home, and level of concern about the pandemic. Likert scale ratings were given with appropriate responses to each item (i.e., for level of COVID concern, options ranged from *not at all concerned* to *extremely concerned*). To assess past and cumulative trauma, participants were asked to report experiences of traumatic events from an established list (e.g., natural disasters, war, sudden loss of family, abuse, and neglect, forced displacement

etc.) with the option to write-in events that were not included in the list. Also, questions about instances of domestic violence/abuse in the past month were asked.

DASS-21 yielded three subscale scores quantifying depression, stress, and anxiety, which were then stratified into 5 severity levels ranging from *none* to *extremely severe.* The PQ-16 assessed the number of psychotic-like experiences endorsed by each participant (i.e., their *total score*) and accompanying distress (i.e., their *distress score*). A *total score* of 6 or more qualifies high risk status for psychosis (Ising et al., 2012). Subjective feelings of loneliness and social isolation were assessed with the UCLA Loneliness Scale. Quality, size, and diversity of social networks (e.g., number of social roles, embedded social networks, and regular contacts) were assessed with SNI.

2.3. Statistical analysis

Descriptive statistics were performed to measure demographic information, general and mental health statuses, COVID-19 concern, and incidence of trauma and domestic violence. *T*-tests were conducted to assess general health between age groups, genders, trauma groups, and concern levels regarding COVID-19. Hierarchical linear regressions were also performed to assess the roles of psychosocial predictors, loneliness, and social network size in determining physical and mental health variables. In the first step, independent variables for age, gender, domestic violence, trauma experience, and concern for COVID- 19 were used to form the basic model. In the second step, loneliness, social network diversity, and social network size were included in the full model. For each dependent variable (e.g., self-reported health, days physically ill, days when physical and mental health limited engagement in usual activities, days when pain limited functioning, days mentally ill, days feeling anxious, DASS, and PQ-scores), change in R^2 between the basic model and full model was used to examine whether the addition of loneliness and/or the social network variables explained more of the variance in these variables, after controlling for age, gender, domestic violence, trauma, and COVID concern. Bonferroni correction of $p < 0.0045$ was applied to minimize Type I Errors.

3. Results

The total of 404 (78.5% females) participants participated in the study. See Table 1 for the detailed descriptive data of the demographic information. From those, 85.4% completed the general health items (Table 2) of which 71-73% went on to complete the mental health item. DASS was completed by 81% of participants (Table 3, Figure 1), PQ was completed by 71% of which 17% were a high risk for psychosis (Table 3), SNI was completed by 76% and 73.5% completed UCLA Loneliness (Table 3). Participants indicated an overall good physical and mental health over the past 30 days (Table 2).

In the first step, the analysis of psychosocial measures of general and mental health showed a significant negative association of age on general health, DASS subscales, and both PQ total and distress scores (Table 4). Domestic abuse/violence was negatively associated to general health in which there was an increase of days when mental health was poor and when

activities were affected by poor health as well as increased DASS depression. COVID-19 concern led to a decrease in general health items; to an increase in the number of days when mental health was poor, when usual activities were affected by health and by pain, and to an increased feelings of worry, anxiety, or tension. Past incidence of traumatic experience increased the number of days mental health was poor, the days spent worried, anxious, or tense as well as stress, anxiety, and depression. In the second step, there was a significant negative association between loneliness and indices of general health in this sample. The increased loneliness was positively associated with the number of days physical health and mental health was poor; days when usual activities were affected by health and by pain, and days when the participant felt worried, anxious, or tense. Also, increased loneliness was associated with greater stress, anxiety, and depression. Lastly, participants reported the number of days in the past month when they experienced poor physical health. These "sick days" were negatively associated with the SNI (social network index) such that those with diminished social network were more likely to report increased number of sick days.

The analysis of PQ items indicated that 16.7% participants met the criteria as high-risk for psychosis. Loneliness was positively associated to prodromal total and distress scores (Figure 2). Gender influenced both PQ total and distress scores in which women endorsed fewer items and reported less distress compared to man. However, there were no significant sex differences in experience of loneliness. Domestic abuse/violence was positively associated only to PQ distress as well as was the concern with COVID. Furthermore, exposure to trauma was positively associated to loneliness, but not to prodromal symptoms of psychosis. Importantly, both PQ total and distress scores were associated with DASS subscales in which higher PQ led to higher experience of stress, anxiety, and depression (Figure 3).

4. Discussion

The preliminary findings highlight the important role of psychosocial factors, specifically loneliness, in determining mental wellbeing in Croatia during the COVID-19 pandemic. Although most participants indicated overall good general health, our findings show that a substantial number of psychosocial predictors including high levels of COVID concern led to a decrease in both general health and wellbeing. There was an overall increase in the number of days when mental health was not good, when usual activities were affected by poor health or pain, and when participants felt worried, anxious, or tense. Our findings are in line with overall research on the impact of COVID-19 pandemic on mental health, suggesting that social isolation and distancing might increase signs of anxiety, depression, stress, and loneliness (Carvalho et al., 2020).

In our study, loneliness was found to be a considerable problem in the general population during the pandemic. It was associated with poor general health as well as poor mental health, feelings of worry, anxiety, or tension. Loneliness had a statistically significant impact on psychosis-proneness; with psychosis-proneness being strongly associated with depression, anxiety, and stress. This finding is in line with growing evidence for loneliness as

a transdiagnostic risk factor across many different mental disorders, but especially as a major risk factor for psychosis (da Rocha et al., 2018). The COVID-19 pandemic has disrupted social connectedness and networking, which can provide protection against the distress, but also against the feelings of loneliness. Given the relationship between loneliness and psychosis (Badcock et al., 2020) it is not surprising that psychosis-risk and loneliness are highly interrelated during the pandemic.

With respect to trauma, domestic abuse/violence was also associated with elevated risk for psychosis. The impact of previous trauma strongly affected the mental health and increased stress, anxiety, depression, and the number of days feeling worried, anxious, and tense during the pandemic. Surprisingly, previous exposure to trauma was relatively weakly associated with psychosis-risk, despite the history of wars and recent natural disasters in Croatia. One of the potential reasons for the weak association could be the lower prevalence of psychosis in the general population compared with the much greater rates of depression, anxiety, and stress. This is supported by the previous research findings showing that within Croatian population, prevalence of depression, anxiety and stress is very high (Loncar et al., 2006; Mollica et al., 2001). Furthermore, one must consider the population-wide adaptation to increasing levels of adversity over time across multiple generations in Croatia, which has survived one-hundred years of war trauma resulting from the World War I, World War II, Independence War between 1991 and 1995 (Lampe et al., 2022). Thus, COVID-19 pandemic situation, even though dire, maybe not have been experienced as stressful or traumatic as previous nation-wide catastrophes. Another possible explanation could be ascribed to mirroring behaviors (Dilthey and Rickman, 1976), which suggests that individuals tend to feel and behave similarly to the overall crowd; strengthening the notion that all are bound together in this pandemic situation, resulting in resilience and protection from adverse effects (Vukojevic et al., 2020; Bastian et al., 2014; Gracia et al., 2019). Lastly, post-trauma recovery treatments are commonly available in Croatia; for example, past war victims and survivors have undergone excessive PTSD treatments and/or are still under medical supervision and therapy. Therefore, this existing mental health infrastructure might have provided much needed additional support. Perhaps this is an important lesson to prepare for future pandemics.

There are several caveats. First, although the sample size was relatively good, many participants did not complete the questionnaire resulting in the overall smaller sample size for some of the measures (e.g., PQ-16). Second, the sample consisted of predominantly females, thus limiting its generalizability. Likewise, high educational level of the participants (master's degree), may be another factor limiting the generalizability of the study. However, we note that despite the potential protection associated with higher education, we still observed mental health challenges during COVID. Thirdly, the cross-sectional nature of the study lacks the longitudinal data to track changes in mental health over time. Regardless, the study allowed for a robust investigation of multiple psychosocial predictors of psychosis-risk, providing preliminary evidence for an adverse effect of COVID-19 pandemic on loneliness and

prodromal symptoms of psychosis that are a major gap in the literature within the Croatian population.

5. Conclusions

We investigated the mental health consequences of COVID-19 pandemic in the general Croatian population to identify factors that may increase the risk for psychosis. We found that loneliness is a significant factor that can exacerbate mental health problems especially psychosis-risk. Loneliness has already been identified as a highly salient issue for individuals with psychosis and underscores the importance of assessing and targeting loneliness within a multi-faceted psychosocial intervention for those at risk for psychosis (Badcock et al., 2020). Our findings are consistent with previous studies that suggest loneliness is a reliable risk factor for an onset of psychosis (da Rocha et al., 2018; Mäki et al., 2014). Therefore, to mitigate the potential epidemic of mental illness in the near future that may result from COVID-19, there is an urgent need to prepare clinicians, caregivers, and stakeholders to focus on the impact of loneliness on mental health (Badcock et al., 2020). Lastly, the results reported in the present study could help inform future public health strategies during global catastrophes similar to the current pandemic (Valiente et al., 2021)

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Tables and Figures

Table 1. Demographic information

	N (Total)	M (SD)	Range			
Age	404	39.6 (13.7)	17–73			
				N	**%**	**p***
Gender						
Male				84	20.8	
Female				317	78.5	<0.001
Prefer not to answer				3	0.7	
Education						
Elementary school				3	0.7	
High school				75	18.6	
Technical school				27	6.7	
Bachelor's degree				56	13.9	<0.001
Master's degree				189	46.8	
Doctoral degree				47	11.6	
Other				5	1.2	
Prefer not to answer				2	0.5	
Employment status						
Full time (including full time students)				309	76.5	
Part time ((including part time students)				16	4.0	
Unemployed				40	9.9	<0.001
Retired				11	2.7	
Other				28	6.9	
Healthcare Worker						
Yes				91	22.5	
No				269	66.6	<0.001
n/a				44	10.9	
Current Living situation						
Living alone				59	14.6	
Living with friends/roommates				8	2.0	
Living with partner				49	12.1	
Living with family				282	69.8	<0.001
Homeless				1	0.2	
Other				4	1.0	
Prefer not to answer				1	0.2	
General Health						
Poor				5	1.2	
Fair				25	6.2	
Good				71	17.6	<0.001
Very good				161	39.9	
Excellent				83	20.5	

n/a	59	14.6	
COVID-19 concern			
Not concerned	60	14.8	
Somewhat concerned	228	56.3	
Moderately concerned	51	12.6	
Extremely concerned	6	1.5	<0.001
Traumatic experience			
Yes	185	45.8	
No	152	37.6	
n/a	67	16.6	

Note: M=mean; SD=standard deviation; n/a=not answered.

Table 2. General health items (n=345)

	Mean	**SD**	**Range**
Physical health was not good [n]	3.09	4.83	0–30
Mental health was not good [n]	5.97	8.05	0–30
Feeling happy (positive)[p]	17.02	9.10	0–30
Feeling hopeful [p]	14.00	10.58	0–30
Feeling love [p]	18.62	19.06	0–30
Usual activities were affected due to health problems [n]	5.59	8.30	0–30
Usual activities were affected due to pain [n]	3.67	7.03	0–30
Feeling worried. anxious. or [n]	7.52	8.92	0–30

p=positive direction, n=negative direction

Note1: Number of days (over the past 30 days) in which health problems occurred; SD=standard deviation.

Table 3: Descriptive data for the main psychosocial predictors.

	Mean	SD	Range
DASS (N=331)			
Depression	6.72	7.21	0–39
Anxiety	4.44	5.52	0–32
Stress	8.46	6.98	0–35
PQ			
Items endorsed	2.90	3.17	0–16
Distress endorsed	3.12	5.48	0–36
SNI			
High-Contact Roles	4.32	2.98	0–11
People in Social Network	3.80	2.65	0–10
Embedded Networks	2.23	1.92	0–8
Loneliness	39.74	8.83	22–66

Note: DASS=Depression, Anxiety and Stress; PQ= prodromal questionnaire; SNI=Social Network Index; Loneliness= the UCLA Loneliness scale.

Table 4. Psychosocial predictors of general and mental health status

		Model statistics				Variable statistics		
		df	ΔR^2	ΔF	p	β	T	p
General health								
Step 1		5	0.124	7.873	<0.001			
Step 2		3	0.030	3.232	0.023			
	Age					-0.132	2.219	0.027*
	Gender					-0.001	0.015	0.988
	Domestic abuse/violence					-0.192	3.376	0.001*
	COVID-19 concern					-0.117	2.034	0.043*
	Traumatic experience					-0.089	1.510	0.132
	SNI Social Network					-0.071	0.932	0.352
	SNI Embedded Network					0.026	0.361	0.718
	Loneliness					-0.179	3.047	0.003*
Days physical health not good								
Step 1		5	0.076	4.591	<0.001			
Step 2		3	0.074	8.039	<0.001			
	Age					-0.094	1.579	0.116

	Gender					0.045	0.795	0.427
	Domestic abuse/violence					0.08	1.398	0.163
	COVID-19 concern					0.108	1.885	0.061
	Traumatic experience					0.107	1.805	0.072
	SNI Social Network					0.162	2.134	0.034*
	SNI Embedded Network					-0.109	1.495	0.136
	Loneliness					0.266	4.521	<0.001*
Days mental health not good								
Step 1		5	0.148	9.659	<0.001			
Step 2		3	0.129	16.352	<0.001			
	Age					-0.100	1.815	0.071
	Gender					0.042	0.800	0.424
	Domestic abuse/violence					0.116	2.201	0.029*
	COVID-19 concern					0.137	2.590	0.010*
	Traumatic experience					0.166	3.038	0.003*
	SNI Social Network					-0.035	0.501	0.617
	SNI Embedded Network					-0.115	1.707	0.089
	Loneliness					0.318	5.846	<0.001*
Days usual activities affected by health								
Step 1		5	0.077	4.623	<0.001			
Step 2		3	0.062	6.675	<0.001			
	Age					-0.112	1.875	0.062
	Gender					0.048	0.830	0.407
	Domestic abuse/violence					0.168	2.919	0.004*
	COVID-19 concern					0.136	2.357	0.019*
	Traumatic experience					-0.045	0.757	0.450
	SNI Social Network					0.021	0.275	0.783
	SNI Embedded Network					0.028	0.377	0.706
	Loneliness					0.265	4.467	<0.001
Days usual activities affected by pain								
Step 1		5	0.058	3.453	0.005			
Step 2		3	0.029	2.94	0.034			
	Age					-0.139	2.248	0.025*
	Gender					0.052	0.880	0.380
	Domestic abuse/violence					0.064	1.090	0.277
	COVID-19 concern					0.129	2.162	0.031*
	Traumatic experience					0.07	1.150	0.251
	SNI Social Network					0.053	0.674	0.501
	SNI Embedded Network					0.037	0.488	0.626
	Loneliness					0.176	2.879	0.004*
Days feeling worried. anxious or tense								
Step 1		5	0.137	8.892	<0.001			

Step 2		3	0.095	11.364	<0.001			
	Age					-0.195	3.445	0.001*
	Gender					0.044	0.820	0.413
	Domestic abuse/violence					0.087	1.603	0.110
	COVID-19 concern					0.153	2.796	0.006*
	Traumatic experience					0.132	2.348	0.020*
	SNI Social Network					0.028	0.393	0.695
	SNI Embedded Network					-0.074	1.073	0.284
	Loneliness					0.306	5.457	<0.001*
DASS stress								
Step 1		5	0.152	9.824	<0.001			
Step 2		3	0.179	24.203	<0.001			
	Age					-0.165	3.102	0.002*
	Gender					0.032	0.621	0.535
	Domestic abuse/violence					0.046	0.912	0.363
	COVID-19 concern					0.032	0.623	0.534
	Traumatic experience					0.229	4.335	<0.001*
	SNI Social Network					0.052	0.767	0.444
	SNI Embedded Network					0.004	0.062	0.951
	Loneliness					0.448	8.457	<0.001*
DASS anxiety								
Step 1		5	0.129	8.133	<0.001			
Step 2		3	0.127	15.491	<0.001			
	Age					-0.216	3.851	<0.001*
	Gender					-0.016	0.297	0.767
	Domestic abuse/violence					0.096	1.791	0.074
	COVID-19 concern					0.049	0.897	0.371
	Traumatic experience					0.158	2.835	0.005*
	SNI Social Network					-0.023	0.324	0.747
	SNI Embedded Network					0.084	1.231	0.219
	Loneliness					0.375	6.719	<0.001*
DASS depression								
Step 1		5	0.158	10.342	<0.001			
Step 2		3	0.219	31.834	<0.001			
	Age					-0.171	3.328	0.001*
	Gender					0.044	0.899	0.370
	Domestic abuse/violence					0.121	2.451	0.015*
	COVID-19 concern					0.050	1.018	0.309
	Traumatic experience					0.161	3.157	0.002*
	SNI Social Network					-0.014	0.211	0.833
	SNI Embedded Network					-0.023	0.372	0.711
	Loneliness					0.477	9.341	<0.001

PQ total								
Step 1		5	0.135	8.371	<0.001			
Step 2		3	0.168	21.264	<0.001			
	Age					-0.219	3.980	<0.001*
	Gender					-0.202	3.833	<0.001*
	Domestic abuse/violence					0.094	1.779	0.076
	COVID-19 concern					0.074	1.395	0.164
	Traumatic experience					0.002	0.042	0.966
	SNI Social Network					-0.068	0.974	0.331
	SNI Embedded Network					0.050	0.736	0.462
	Loneliness					0.418	7.647	<0.001*
PQ distress								
Step 1		5	0.155	9.809	<0.001			
Step 2		3	0.173	22.671	<0.001			
	Age					-0.217	4.017	<0.001*
	Gender					-0.118	2.279	0.023*
	Domestic abuse/violence					0.208	4.009	<0.001
	COVID-19 concern					0.059	1.140	0.255
	Traumatic experience					0.033	0.611	0.542
	SNI Social Network					-0.035	0.511	0.610
	SNI Embedded Network					0.073	1.096	0.274
	Loneliness					0.434	8.091	<0.001

Note1. Predictive variables kept in the second step: age, gender, domestic abuse/violence, level of concern about COVID-19, and traumatic experience.
Note2. DASS=Depression, Anxiety and Stress; PQ= prodromal questionnaire.
SNI=Social Network Index; Loneliness= the UCLA Loneliness scale.

Figure 1. Levels of depression, anxiety, and stress among 331 respondents.

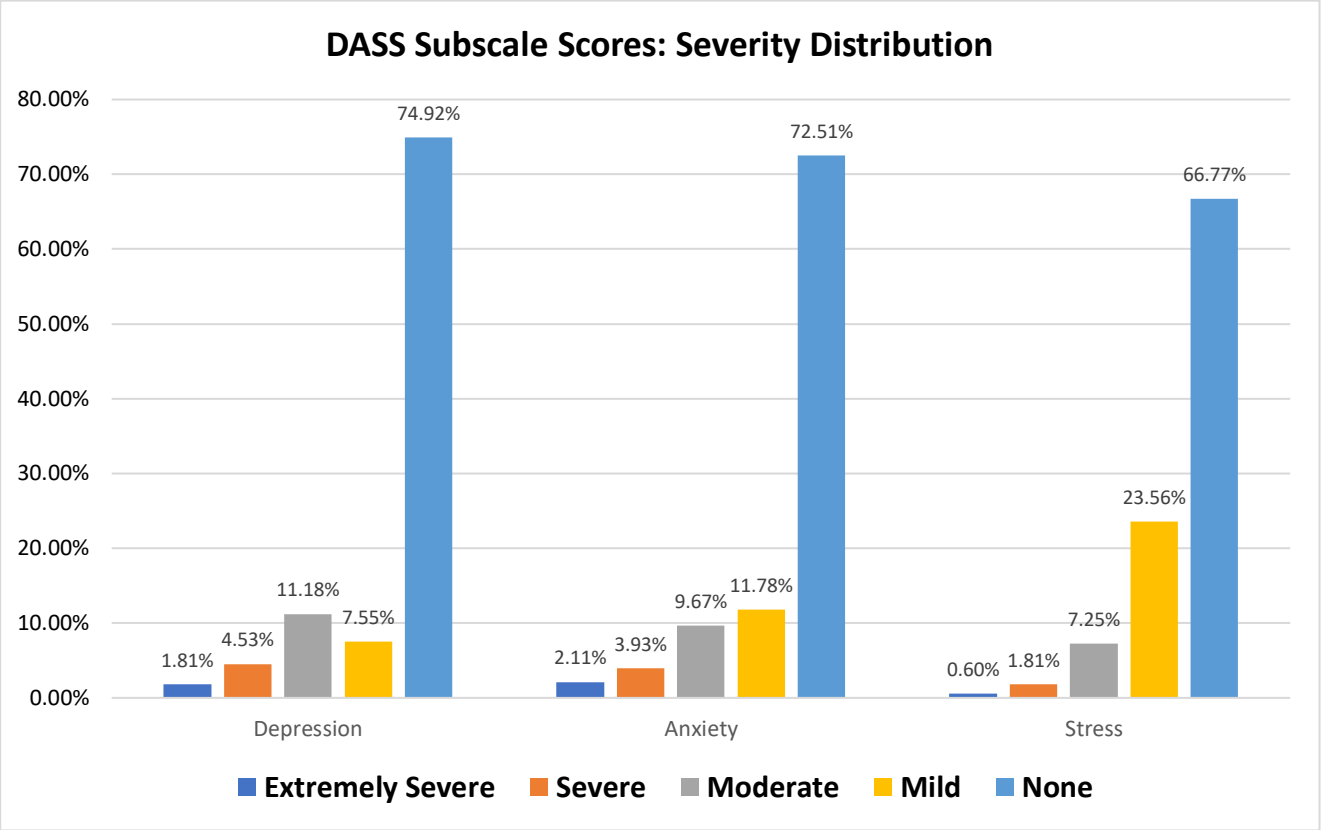


Figure 2: Impact of loneliness on prodromal (PQ-16) scores during COVID-19

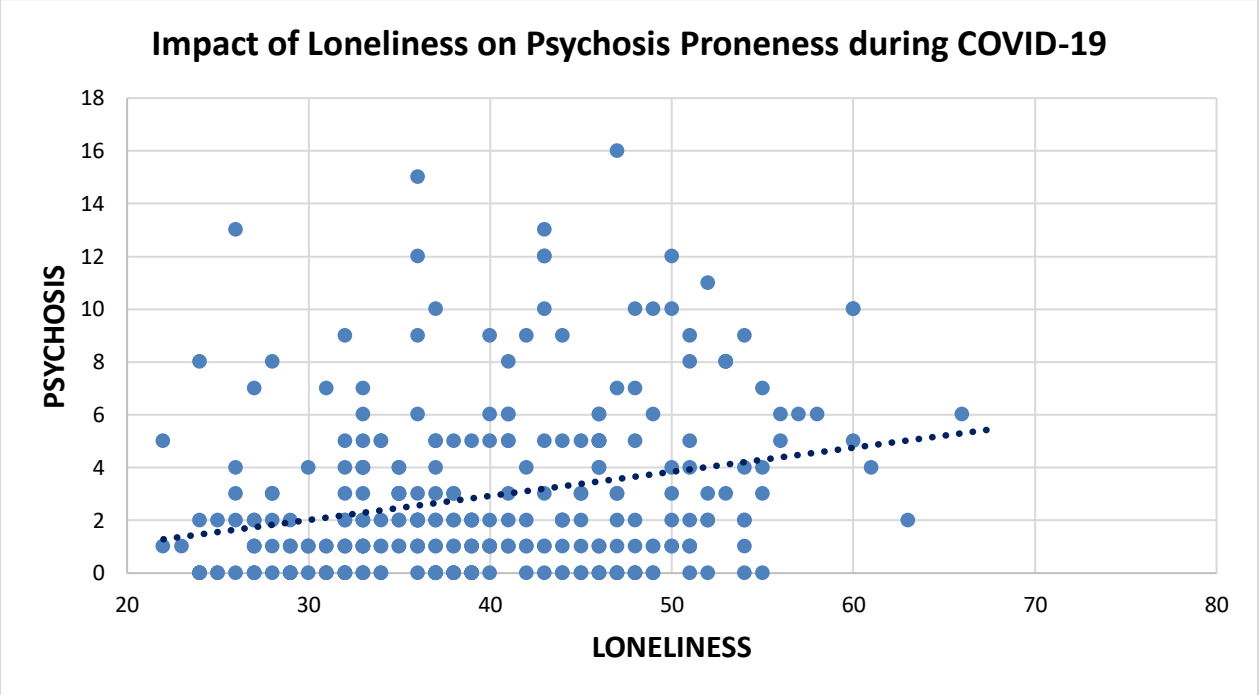
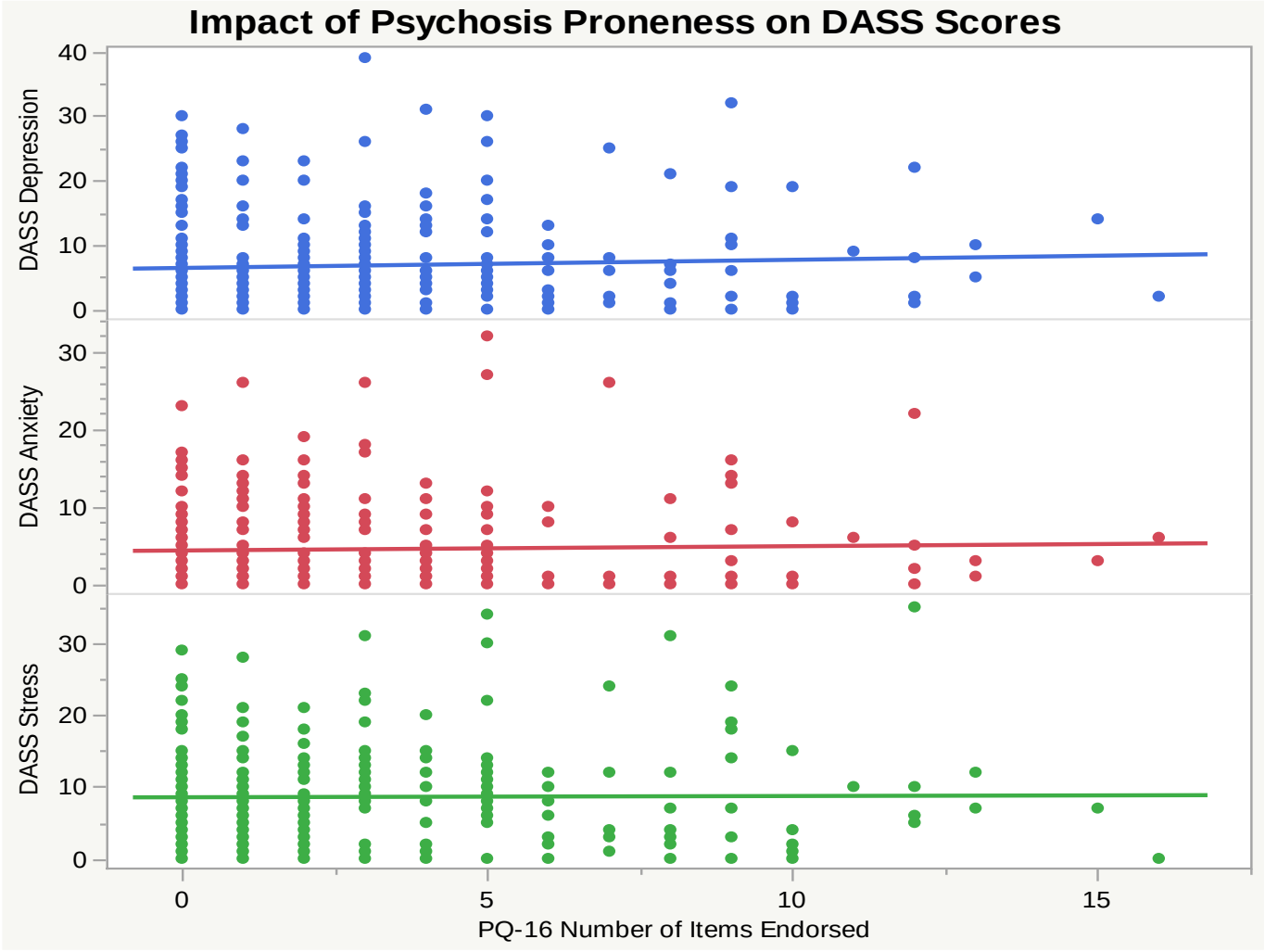


Figure 3: Impact of prodromal symptoms on depression, anxiety, and stress during COVID-19.



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Chapter 6

Social connectedness and resilience post COVID-19 pandemic: Buffering against trauma, stress, and psychosis

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Abstract

Background: Evidence suggests the COVID-19 pandemic will have lasting effects on individuals' mental health, which has been severely disrupted by the spread of the virus. The present study investigated psychosocial predictors of psychosis-risk, depression, anxiety, and stress in Croatia two years after the onset of the COVID-19 pandemic. Given the existing transgenerational war trauma and associated psychiatric consequences in Croatian population, a significant pandemic-related deterioration of mental health was expected.

Aims: Recent studies suggest that after an initial increase in psychiatric disorders during the pandemic in Croatia, depression, stress, and anxiety rapidly declined. These findings present a unique opportunity to examine the role of social connectedness and resilience in the face of the global pandemic psychosis-risk and mental health in this population

Methods: We examined resilience, social connectedness, and psychiatric disorder risk two years after the COVID-19 pandemic in 377 Croatian adults using an anonymous online mental health survey.

Results: There was an exacerbation of all mental ill health variables, including depression, anxiety, stress, and a doubled risk for psychosis outcome post-COVID pandemic. Stress decreased levels of resilience, however, those exposed to previous traumatic experience and greater social connectedness had higher resilience levels.

Conclusion: These findings suggest that individual differences in underlying stress sensitization of Croatian population due to past trauma may continue to influence mental health consequences two years after the COVID-19 pandemic. It is essential to promote the importance of social connectedness and resilience in preventing the development of a variety of mental health disorders.

1. Introduction

The COVID-19 pandemic has severely disrupted every aspect of daily life, resulting in countless economic, social, and behavioral changes. Two years after the outbreak of the COVID-19 pandemic, research has primarily focused on elucidating the effects of the first pandemic wave on general and mental health (Orfei et al., 2022; Taylor et al., 2021; Penninx et al., 2022). Numerous studies have reported substantial increases in psychiatric morbidity, including anxiety, depression, insomnia, and post-traumatic stress disorder (PTSD) (Wang et al., 2020; Goldberg et al., 2022; Raina et al., 2021), as well as a dramatic increase in loneliness and psychosis prevalence (Carvalho et al., 2020), which has further elucidated the role of loneliness as a significant and important risk factor for psychosis-risk (Gizdic et al., 2022; Tso & Park, 2020). The development of psychotic symptoms, depression, stress, and anxiety symptoms in individuals with no history of psychiatric disorders is supported by evidence indicating an increased incidence of first-case psychopathology in COVID-19 patients (Taquet et al., 2021; Desai et al., 2021; Cao et al., 2022). One year post-pandemic, an increased prevalence of fatigue, sleep problems, memory loss, and concentration difficulties was reported globally (Boscolo-Rizzo et al., 2021, Liu et al., 2022; Han et al., 2022), as well as a persistent increase in anxiety, stress, and depression (Lakhan et al., 2020; Brooks et al., 2020; Shah et al., 2021; Joshi et al., 2021; Pierce et al., 2020; Meaklim et al., 2023), and psychotic-like symptoms (Lim et al., 2020; Taquet et al., 2021; Brown et al., 2020; Wu et al., 2021). Even after the lockdown restrictions were eased, general physical and mental health has deteriorated since the beginning of COVID-19 (Patel et al., 2022; Vadivel et al., 2021).

Furthermore, a number of studies across the globe have also identified a variety of risk factors for psychosis during the COVID-19 pandemic, including younger age, female gender identity, unemployment, loneliness, and a history of trauma (Tso & Park, 2020; Dean et al., 2021; Bauer et al., 2021; Lee et al., 2021; Proto & Quintana-Domeque, 2021). Previous exposure to trauma, in particular, is predicted to increase the prevalence of psychopathology and mental disorders during COVID-19 (Gizdic et al., 2022), given that trauma is widely predictive of nearly all subclinical and clinical psychopathology and negative outcomes (Lu et al., 2013; Auxéméry, 2012). Although the intensity of trauma triggers may diminish over time (Howell et al., 2015), it is important to consider their continued association with poor wellbeing, particularly among Croatians who have experienced war and natural disasters (e.g., earthquakes). War-related trauma and post-traumatic reminders have had a devastating and lasting effect on the mental health and quality of life of this population (Babić-Banaszak et al., 2002; Vukojević et al., 2020; Jeftić et al., 202). Specifically, the first wave of the COVID-19 pandemic increased the prevalence of nearly all psychopathology symptoms in Croatia (Jokić Begić et al., 2020; Gizdic et al., 2022). Surprisingly, these rates decreased after a few months (from May to July 2020), when restrictions were partially relaxed (Ajduković et al., 2020). In comparison to other European countries (and parts of Asia), Croatia seemed to have a relatively lower incidence of depression, stress, and anxiety (Newby et al., 2020; Park et al., 2020; Rossi et al., 2020). Although continuous increases in symptoms were anticipated through 2020, these

results are suggestive of high levels of resilience and adaptability among this population throughout the pandemic.

As a result, researchers have examined the concept of resilience and discovered that it may serve as a protective factor not only against trauma exposures but also against the development of psychopathology symptoms (Pietrzak et al., 2011), despite the fact that patterns of vulnerability levels vary among individuals (Sominsky et al., 2020). Psychological resilience is an active, process-oriented defense mechanism that appears to be derived in part from having meaningful, supportive, and functional social networks. For instance, individuals with a higher degree of social connectedness and a lower level of loneliness tend to have a higher level of general wellbeing and are better protected against mental health issues during the COVID-19 pandemic (Lee et al., 2021; Killgore et al., 2020; Groarke et al., 2020). However, social connectedness appears to be an especially important protective factor among trauma survivors. In some cases, individuals within a traumatized group become more resilient to adversity to the extent that their functioning is sometimes enhanced following exposure to adversity (Ayed et al., 2019; Finstad et al., 2021). During stressful and uncertain events, for instance, people tend to imitate the behavior and emotions of those around them (Duan et al., 2019), indicating that there is a collective social impulse that protects us. The 2020 study by Vukojević et al. suggested that, when people are together in a catastrophic situation, the catchphrase "we are in this together" has a deeper meaning due to the protective effect of crowd influence on our psyche. A possible explanation can be found in the Croatian experience of war (as well as the recent earthquake). Shared pain during a shared experience of disaster can unite people and inspire them to help each other, which promotes solidarity and increases social resilience, ultimately resulting in better mental health outcomes (Bastian et al., 2014; Garcia & Rime, 2019). According to Bastian et al. (2014) study, shared pain can increase cooperation and social bonding by acting as "social glue."

In this study, we investigated a) psychosocial predictors of general and mental health in the Croatian population two years after the COVID-19 pandemic, and b) the role of mental health status and social connectedness in influencing resilience among Croatian individuals. We hypothesized based on our previous research (Gizdic et al., 2022), mental health symptomatology and social connectedness would play a significant role in resilience levels, particularly among those who had experienced trauma in the past.

2. Methods

2.1. Participants and procedures

All participants were Croatian adults (aged 18 and above) who completed an online survey created via Survey Monkey in Croatian that was distributed via online platforms and channels (such as the university emailing lists, social media platforms etc.) and in person. Before starting the survey, participants were informed of the study goals and aims, introduced to the type of questions and amount of time for completion of the study, as well as their ability to stop at any time. Participation was anonymous, voluntary, and open to everyone aged 18 and up (detailed in Gizdic et al., 2022). The survey took an average of 17 minutes to complete

(74%). Data collection occurred between February and May 2022, following two peak waves of the COVID-19 pandemic (1.7 years after data collection during the first wave; survey 1 ran from July to September 2020; Gizdic et al., 2022). This study received exempt status from the Vanderbilt University Institutional Review Board (Vanderbilt IRB exempt #200337).

2.2. Measures

Following the previous survey (Gizdic et al., 2022), we repeated the same patterns of questions with slight modifications and addition of new scales. The present survey consisted of 159 questions regarding participant demographics, COVID-19 concern, general and mental health, including well-validated mental health measures of depression, anxiety, stress, psychosis, social connectedness, and social isolation. We also inquired about COVID-19 vaccination hesitancy, resilience, and exposure to trauma.

General information regarding COVID-19 diagnosis, concern, vaccination, and dosage, was requested to examine the overall effects of the pandemic on participants' daily lives. Ratings were given with appropriate responses to each item (i.e., for level of COVID concern, questions were scored on a 4-point Likert scale, ranging from *0=not at all concerned* to *4=extremely concerned*). Participants self-reported the changes in their current living situation, employment, number of days feeling positive emotions (love, happiness, and hope), as well as changes in their general health. To better understand previous trauma exposures, we included questions asking about adversity in childhood–emotional, physical, and sexual abuse; emotional and physical neglect; and included the Brief Trauma Questionnaire (BTQ; Schnurr et al., 2002)–a 10-item, self-report questionnaire that asks general trauma questions (e.g., *Have you ever been in an active war zone or served in a job that exposed you to war-related casualties?*) with follow up questions rating the severity of each traumatic event endorsed (e.g., *If so, did you think your life was in danger or were you possibly seriously injured?*).

The Short Scale for Measuring Loneliness (the UCLA Loneliness-short; Hughes et al., 2004) was used to assess subjective feelings of loneliness and social isolation; the Social Network Index (SNI; Cohen, 1997) was used to assess social connectedness including social network quality, size, and diversity (e.g., number of social high contact roles, embedded social networks, and regular people contacts); depression, anxiety, and stress subscales was assessed with Depression, Anxiety and Stress Scale – 21-item version (DASS-21; Lovibond & Lovibond, 1995), and psychosis risk and distress was assessed with the Prodromal Questionnaire-16 (PQ-16; Ising et al., 2012).

We also included a measure of vaccination hesitancy (adult Vaccine Hesitancy Scale, aVHS; Akel et al., 2022) asking participants about their own hesitancy and perceptions of effectiveness, reliability, and potential risks of vaccinations (e.g., *Vaccines are important to my health*). The responses were rated on a 5-point Likert scale ranging from *strongly disagree* to *strongly agree.* We added the 4-item Brief Resilient Coping Scale (BRCS; Sinclair & Wallston, 2004), which assesses participants' levels of resilience (i.e., successful recovery from stressful situations).

2.3. Statistical analysis

Descriptive statistics were used to assess participants' health, traumatic experiences, COVID-19 concern, and vaccination hesitancy. To achieve the first study goal, hierarchical linear regressions were performed that examined the role of psychosocial predictors, loneliness, vaccination hesitancy, resilience, and social networks, in determining general and mental health. In the first step, independent variables for age, gender, social distancing adherence, childhood abuse and neglect, general traumas, and COVID-19 concern were used to form the basic model. In the second step, the full model included social network diversity, size, embedded social networks, loneliness, vaccination hesitancy, and resilience. For each dependent variable (e.g., self-reported general health, days feeling happy, feeling hopefully, and loving, DASS depression, stress, and anxiety, and PQ-scores), the change in R^2 between the basic model and full model was used to examine whether adding social network variables, loneliness, and/or vaccination hesitancy and resilience explained more variance after controlling for age, gender, trauma, social distancing, and COVID concern.

To achieve the second goal of the study, we again tested the relationships between resilience, trauma, social networks, loneliness, vaccination, and mental health variables. However, to gain further clarity on the role and directionality of resilience as a factor in wellbeing, we repeated the regression analysis but used resilience as a dependent variable to examine whether psychosocial variables predict the levels of resilience. In the first step, the same independent variables as in the previous model were entered (e.g., age, gender, etc.) as a basic model. In the second step, social network diversity, social network size, and embedded social networks, as well as loneliness, vaccination hesitancy, DASS scales, and PQ total and distress, were included in the full model. After controlling for age, gender, traumas, social distancing, and COVID concern, the change in R2 between models was used to determine if adding social network variables, loneliness, vaccination hesitancy, DASS scales, and PQ total and distress explained more variance in resilience. A Bonferroni correction of $p < 0.0045$ was applied to both analyses to minimize Type I Errors.

3. Results

A total of 377 Croatian adults (78% females; mean age=29.2, SD=12.31) participated in the study. Table 1 displays descriptive statistics for all study variables. Two years after the pandemic, participants reported overall good general health (42%), but they were still concerned with the pandemic (54%). 57% of participants received a COVID-19 vaccination, with a slight decrease in average general health before (mean=2.31; SD=1.02) and after vaccination (mean=2.29; SD=1.24). Overall, participants reported a relatively high number of days when they felt love, happiness, or hope (Table 2). Questions assessing social connectedness, levels of loneliness and social isolation, and resilience were completed by approximately 83-86% of participants, whereas the DASS was completed by 79% of participants and the PQ-16 was completed by 77% of participants, of whom 28% were at high risk for psychosis (see Table 3).

In the first goal of the study, we examined the psychosocial predictors of health two years after the first wave of the pandemic. Concern with COVID, childhood abuse and neglect, general trauma, loneliness, and vaccination hesitancy were negatively associated with general health status. On the other hand, SNI embedded social network and resilience were positively associated with overall general health. COVID concern, age, and loneliness decreased the number of days when participants felt happy. Loneliness decreased the number of days when the participants felt hopeful and loving. SNI embedded social network and resilience both increased the number of days feeling happy and hopeful. Social distancing, SNI high contact role, and resilience all increased the number of days when participants felt love. Furthermore, age and resilience were found to be negatively associated with DASS depression, DASS stress, and DASS anxiety. Childhood abuse and neglect, loneliness, and COVID concern were found to be positively associated with DASS stress. Only childhood abuse and neglect and loneliness were linked to depression and anxiety symptoms from DASS. With respect to psychosis-risk, there was a negative relationship between age and psychosis symptoms and related distress. In contrast, there was a positive association between psychosis symptoms (PQ-16 score) and the following: childhood abuse and neglect, loneliness, and vaccination hesitancy. Similarly, there was a positive association between childhood abuse and neglect, loneliness with levels of distress surrounding psychosis symptoms (PQ-16 distress). These findings suggest that greater vaccination hesitancy, childhood abuse and neglect, and increased loneliness all contribute to an increased risk of psychosis (Table 4).

A second set of analyses revealed that stress was negatively associated with levels of resilience, whereas general trauma and SNI high contact role were positively associated with resilience (Table 5). As such, although stress decreased levels of resilience, those with previous exposure to general trauma and greater social connectedness (i.e., a high number of people in their social network) had increased resilience levels.

4. Discussion

The present study sought to investigate the long-term mental health consequences of the COVID-19 pandemic in the Croatian population, emphasizing the importance of psychosocial factors in determining mental wellbeing. We specifically highlighted the effects of previous traumatic experience and the important role of social connectedness in resilience– a particularly relevant topic for the Croatian population given the country's previous transgenerational war trauma and natural disasters. Although most participants reported good general health and an increase in the number of days, they felt positive emotions compared to our previous study (Gizdic et al., 2022), the current findings show that people are still concerned about the COVID-19 pandemic, even two years after the first wave. There was a higher level of vaccination hesitancy within this population. Nonetheless, according to Think Global Health (2021), the average vaccination rate in the European Union (EU) is 65%, and in comparison, to Croatia, Bulgaria, for example, had only 22% of its population vaccinated and

a very high death rate. Thus, this may appear to be a matter applicable to the global population rather than Croatia in particular.

Concern about COVID, vaccination hesitancy, but also past trauma and increased loneliness post-pandemic may have contributed to a decline in overall general health. In turn, the number of embedded social networks (i.e., the number of different network domains in which a participant is active) and resilience levels led to better general health and more days when participants felt happy and hopeful. The number of days participants felt love increased with social network diversity (i.e., the number of people with whom the participant has regular contact), resilience, and, unexpectedly, with social distancing adherence. Social distancing measures have been put in place throughout the pandemic to curb the spread of the COVID-19 virus. In many places, social distancing is seen as a pro-social behavior–one that protects the community from COVID-19 (Wider et al., 2022). Evidence suggests that widespread experience of hardship or pain increases cooperation, collaboration, and social bonding (Bastian et al., 2014). Given the history of shared trauma experienced by the Croatian population (e.g., war, earthquake), it is possible that increased social distancing adherence is viewed as extremely pro-social, collaborative, and benevolent behavior, thereby increasing feelings of love in participants' daily lives. Furthermore, Croatian social contacts are relatively reserved; for example, culturally normative public interpersonal greetings do not typically involve physical contact (such as hugging or kissing). As a result, it is possible that adherence to social distancing conforms to Croatian social norms and expectations and may involve less significant change in daily life routines than other aspects of the pandemic.

Overall, our findings are consistent with previous research on the detrimental and enduring effects of the COVID-19 pandemic on mental health, indicating that the pandemic and related social isolation, as well as past trauma, continue to have a large and pervasive impact on individual wellbeing (Patel et al., 2022; Vadivel et al., 2021). However, our results also highlight social connectedness (i.e., social network domains) and resilience as promising protective factors in preventing the further development of unfavorable mental and general health outcomes.

In addressing the first aim of the study, we noted a drastic increase in the prevalence of stress, depression, and anxiety symptoms. Surprisingly, the rate of psychosis risk post-pandemic nearly doubled when compared to the prevalence of high-risk psychosis rates at the beginning of the pandemic (Gizdic et al., 2022). These findings reflect the impact of ongoing and continued stress caused by the COVID-19 pandemic and suggest the pandemic will continue to have long-lasting consequences on individuals' functioning and wellbeing (Goldberg et al., 2022). These results are also supported by previous findings from the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003, which showed that almost 82% of SARS survivors continued to experience poor mental health and related outcomes, including stress disorders such as PTSD (Mak et al., 2010). While the effects of viral pandemics on stress around the world are clear, it is also important to consider the nuances of populations with high exposure to adversity, such as the Croatian population.

Early adversity has been shown to leave neurobiological vulnerabilities that make individuals more sensitive to future stress (Read et al., 2014; Cristóbal-Narváez et al., 2016; Russell et al., 2018; Smith & Pollak, 2020), thereby increasing the risk of developing anxiety disorders, depression, and other broad dimensions of psychopathology (Vaessen et al., 2017; Stroud, 2020; Wade et al., 2019). The *stress sensitization* model sheds light on the link between stress and the prevalence of affective disorders (Post, 1992; Stroud, 2020). According to this model and considering previous war- and natural disaster-related trauma, the Croatian population would be expected to be more sensitive to the changes caused by the pandemic relative to other populations. As a result, it appears that childhood adversity and subsequent stress exposure, such as the COVID pandemic, exacerbated depression, anxiety, and stress, particularly psychosis symptoms. These findings may add to the evidence of an underlying mechanism of increased stress-sensitivity. Contrary to our expectations, resilience had no effect on levels of psychosis, but it did lead to a decrease in stress levels. Thus, it may be plausible to think that building on resilience levels would lead to decreased stress levels and an amelioration of sensitivity to further stress.

Loneliness is another important factor to consider in this interplay. Following our previous findings (Gizdic et al., 2022), this psychosocial factor remains a highly important risk factor in predicting a variety of symptom developments, particularly psychosis, even after two years of the pandemic, while social connectedness appears to serve as both a preventive and protective factor. As a result, strengthening social networks may have plausible effects on alleviating psychopathology symptoms, reducing levels of loneliness, and protecting against future stress.

There are several limitations to our study. First, despite the relatively large sample size, many participants did not complete the entire questionnaire, resulting in a smaller sample size for some of the measures (e.g., PQ-16 and DASS). Second, the majority of the sample consisted primarily of female participants, which may have limited its generalizability. Regardless, the study enabled a comprehensive investigation of multiple psychosocial predictors of psychopathology and psychosis-risk following two years after the COVID-19 pandemic, with evidence of long-term adverse effects of the pandemic and highlighting the significance of resilience and social connectedness.

To conclude, investigating the long-term mental health consequences of the COVID-19 pandemic and emphasizing the importance of psychosocial factors on mental wellbeing may help further detect the potential underlying mechanism of stress-sensitivity. We specifically highlighted the effects of previous traumatic experiences as well as the critical role of social connectedness in association to levels of resilience. Therefore, to mitigate the mental health consequences of large-scale traumatic events such as the pandemic in the future, it would be crucial to implement public health strategies that enhance and support social connectedness and resilience, especially for psychosis–a particularly relevant topic for the Croatian population given the lack of prodromal data and the country's history of exposure to transgenerational war trauma (including early exposures) and natural disasters.

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Tables and Figures

Table 1. Demographic information.

	N (Total)	M (SD)	Range		
Age	377	29.40 (12.31)	18–78		
				N	**%**
Gender					
Male				85	22.5
Female				292	77.5
Education					
Elementary school				1	0.3
High school				134	35.5
Technical school				15	4.0
Bachelor's degree				101	26.8
Master's degree				89	23.6
Doctoral degree				31	8.2
Other				3	0.8
Prefer not to answer				3	0.8
Employment status					
Full time (including full time students)				214	56.8
Part time ((including part time students)				40	10.6
Unemployed				56	14.9
Retired				8	2.1
Other				59	15.6
Healthcare Worker					
Yes				31	8.2
No				237	62.9
n/a				109	28.9
Current Living situation					

Living alone	43	11.4
Living with friends/roommates	38	10.1
Living with partner	40	10.6
Living with family	237	62.9
Homeless	1	0.3
Other	5	1.3
General Health		
Poor	11	2.9
Fair	37	9.8
Good	69	18.3
Very good	156	41.4
Excellent	71	18.8
n/a	33	8.8
Medical Condition		
Yes	23	6.1
No	321	85.1
n/a	33	91.2
Mental Health Diagnosis		
Yes	112	29.7
No	264	70.0
n/a	1	0.3
COVID Diagnosis		
Yes	192	50.9
No	137	36.3
I do not know	15	4.0
n/a	33	8.8
COVID-19 concern		
Not concerned	76	20.2
Somewhat concerned	203	53.8
Moderately concerned	54	14.3
Extremely concerned	11	2.9
n/a	33	8.8
COVID-19 Vaccination		
Yes	214	56.8
No	130	34.5
n/a	33	8.8
General Health Post-vaccination		
Not vaccinated	130	34.5
Poor	3	0.8
Fair	10	2.7
Good	52	13.8
Very good	84	22.3
Excellent	65	17.2

n/a	33	8.8
COVID-19 Vaccination		
Yes	214	56.8
No	130	34.5
n/a	33	8.8
Trauma Experience		
Childhood abuse and neglect		
0 (no trauma)	133	40.1
1 (single)	62	18.7
2	59	17.8
3	58	17.5
4	20	6.0
General Trauma		
0 (no trauma)	79	23.8
1 (single)	95	28.6
2	94	28.3
3	48	14.5
4	16	5.0

Note: M=Mean; SD=Standard deviation; n/a=not answered.

Table 2. General health items (n=344).

	Mean	SD	Range
Feeling happy	16.37	9.16	0–30
Feeling hopeful	12.54	9.86	0–30
Feeling love	15.39	10.84	0–30

Note: Number of days (over the past 30 days) participant felt positive emotions; SD=standard deviation.

Table 3: Descriptive data for the main psychosocial predictors.

	N (%)	Mean	SD	Range
DASS	298 (79%)			
Depression		6.82	5.22	0–21
Anxiety		5.38	4.50	0–21
Stress		8.11	5.06	0–21
PQ	289 (76.7%)			
Items endorsed		4.24	3.38	0–16
Distress endorsed		5.42	6.72	0–37
SNI	311 (82.5%)			

High-Contact Roles		3.95	1.71	0–12
People in Social Network		15.61	8.10	1-46
Embedded Networks		3.12	1.42	0–8
Loneliness	309 (82%)	5.31	1.83	3-9
Resilience	325 (86.2%)	14.01	2.89	4-10
Vaccination hesitancy	340 (90.2%)	27.70	6.62	14-46

Note: DASS=Depression, Anxiety and Stress; PQ= Prodromal questionnaire; SNI=Social Network Index; Loneliness= the UCLA Loneliness scale; Resilience= BRCS Resilience scale; Vaccination hesitancy= VHS Vaccination hesitancy scale; SD=Standard deviation

Table 4. Psychosocial predictors of general and mental health status.

		Model statistics				Variable statistics		
		df	ΔR^2	ΔF	p	β	T	p
General health								
Step 1		6	0.096	5.350	<0.001			
Step 2		4	0.114	2.583	0.025			
	Age					-0.087	-1.489	0.138
	Gender					0.030	0.559	0.577
	Social distancing					0.090	1.377	0.170
	COVID concern					-0.123	-2.092	0.037*
	Childhood abuse/neglect					-0.142	-2.460	0.014*
	Trauma general					-0.158	-2.867	0.004*
	SNI High contact role					-0.227	-1.942	0.053
	SNI People sum					0.031	0.373	0.709
	SNI Embedded network					0.172	2.883	0.004*
	Loneliness					-0.134	-2.258	0.025*
	Vaccination hesitancy					-0.153	-2.374	0.018*
	Resilience					0.174	3.145	0.002*
Days feeling happy								
Step 1		6	0.077	4.223	<0.001			
Step 2		3	0.257	12.399	<0.001			
	Age					-0.148	-2.799	0.005*
	Gender					0.051	1.033	0.302
	Social distancing					-0.024	-0.464	0.643
	COVID concern					-0.113	-2.131	0.034*
	Childhood abuse/neglect					-0.091	-1.712	0.088
	Trauma general					-0.047	-0.942	0.347

	SNI High contact role					0.078	0.728	0.467
	SNI People sum					0.066	0.863	0.389
	SNI Embedded network					0.237	4.328	<0.001*
	Loneliness					-0.377	-6.926	<0.001*
	Vaccination hesitancy					-0.106	-1.807	0.072
	Resilience					0.155	3.048	0.003*
Days feeling hopeful								
Step 1		6	0.083	4.529	<0.001			
Step 2		3	0.229	10.557	<0.001			
	Age					-0.052	-0.962	0.337
	Gender					0.076	1.519	0.130
	Social distancing					0.065	1.222	0.223
	COVID concern					-0.021	-0.396	0.693
	Childhood abuse/neglect					-0.087	-1.617	0.107
	Trauma general					0.012	0.231	0.818
	SNI High contact role					0.106	0.972	0.332
	SNI People sum					0.007	0.096	0.923
	SNI Embedded network					0.195	3.497	0.001*
	Loneliness					-0.320	-5.787	<0.001*
	Vaccination hesitancy					-0.066	-1.104	0.270
	Resilience					0.219	4.239	<0.001*
Days feeling love								
Step 1		6	0.090	5.004	<0.001			
Step 2		3	0.181	7.538	<0.001			
	Age					-0.056	-0.965	0.335
	Gender					-0.036	-0.692	0.490
	Social distancing					0.115	2.076	0.039*
	COVID concern					0.054	0.959	0.338
	Childhood abuse/neglect					-0.098	-1.771	0.078
	Trauma general					0.045	0.853	0.394
	SNI High contact role					0.190	3.152	0.002*
	SNI People sum					0.015	0.202	0.840
	SNI Embedded network					-0.109	-1.021	0.308
	Loneliness					-0.309	-5.452	<0.001*
	Vaccination hesitancy					-0.062	-1.010	0.313
	Resilience					0.165	3.110	0.002*
DASS stress								
Step 1		6	0.234	14.824	<0.001			
Step 2		2	0.203	13.173	<0.001			
	Age					-0.194	-4.158	<0.001*
	Gender					-0.072	-1.564	0.119
	Social distancing					-0.048	-1.002	0.317
	COVID concern					0.110	2.264	0.024*
	Childhood abuse/neglect					0.114	2.294	0.022*

	Trauma general					0.076	1.614	0.108
	SNI High contact role					0.049	0.914	0.361
	SNI People sum					-0.010	-0.205	0.838
	SNI Embedded network					-0.007	-0.142	0.887
	Loneliness					0.360	7.163	<0.001*
	Vaccination hesitancy					0.050	0.908	0.364
	Resilience					-0.234	-4.933	<0.001*
DASS anxiety								
Step 1		6	0.217	13.421	<0.001			
Step 2		2	0.193	11.710	<0.001			
	Age					-0.175	-3.668	<0.001*
	Gender					-0.045	-0.962	0.337
	Social distancing					-0.062	-1.253	0.211
	COVID concern					0.091	1.825	0.069
	Childhood abuse/neglect					0.117	2.296	0.022*
	Trauma general					0.075	1.553	0.122
	SNI High contact role					0.034	0.615	0.539
	SNI People sum					-0.015	-0.291	0.771
	SNI Embedded network					<0.001	0.009	0.993
	Loneliness					0.380	7.386	<0.001*
	Vaccination hesitancy					0.094	1.673	0.095
	Resilience					-0.194	-4.003	<0.001*
DASS depression								
Step 1		6	0.236	15.021	<0.001			
Step 2		2	0.198	12.735	<0.001			
	Age					-0.155	-3.315	0.001*
	Gender					-0.079	-1.720	0.087
	Social distancing					-0.087	-1.807	0.072
	COVID concern					0.092	1.878	0.061
	Childhood abuse/neglect					0.149	2.998	0.003*
	Trauma general					0.069	1.457	0.146
	SNI High contact role					0.009	0.165	0.869
	SNI People sum					-0.064	-1.300	0.195
	SNI Embedded network					-0.029	-0.568	0.570
	Loneliness					0.363	7.217	<0.001*
	Vaccination hesitancy					0.065	1.183	0.238
	Resilience					-0.222	-4.684	<0.001*
PQ total								
Step 1		6	0.218	13.090	<0.001			
Step 2		2	0.087	2.266	<0.001			
	Age					-0.218	-4.132	<0.001*
	Gender					-0.017	-0.319	0.750
	Social distancing					-0.013	-0.210	0.834

	COVID concern					0.015	0.266	0.790
	Childhood abuse/neglect					0.250	4.433	<0.001*
	Trauma general					0.023	0.432	0.666
	SNI High contact role					-0.027	-0.452	0.651
	SNI People sum					-0.023	-0.408	0.683
	SNI Embedded network					-0.040	-0.701	0.484
	Loneliness					0.287	5.252	<0.001*
	Vaccination hesitancy					0.153	2.479	0.014*
	Resilience					-0.052	-0.981	0.328
PQ distress								
Step 1		6	0.233	14.276	<0.001			
Step 2		1	0.087	35.953	<0.001			
	Age					-0.192	-3.748	<0.001*
	Gender					-0.037	-0.717	0.474
	Social distancing					0.028	0.528	0.598
	COVID concern					0.068	1.263	0.208
	Childhood abuse/neglect					0.244	4.382	<0.001*
	Trauma general					0.014	0.264	0.792
	SNI High contact role					-0.069	-1.174	0.241
	SNI People sum					-0.047	-0.852	0.395
	SNI Embedded network					-0.069	-1.220	0.223
	Loneliness					0.323	5.996	<0.001*
	Vaccination hesitancy					0.084	1.379	0.169
	Resilience					-0.045	-0.843	0.400

**p<0.05*

Note1. Predictive variables kept in the second step: age, gender, social distancing, level of concern about COVID-19, and traumatic experience (childhood abuse and neglect, and trauma general).

Note2. DASS=Depression, Anxiety and Stress; PQ= prodromal questionnaire; SNI=Social Network Index

Table 5. Resilience and psychosocial predictors of mental health status.

		Model statistics				Variable statistics		
		df	ΔR^2	ΔF	p	β	T	p
Resilience								
Step 1		6	0.063	3.172	0.005			
Step 2		2	0.152	6.439	<0.001			
	Age					-0.027	-0.419	0.675
	Gender					-0.090	-1.624	0.106
	Social distancing					-0.008	-0.144	0.886
	COVID concern					0.040	0.665	0.507
	Childhood abuse/neglect					-0.009	-0.148	0.882
	Trauma general					0.119	2.103	0.036*
	SNI High contact role					0.215	3.423	0.001*
	SNI People sum					-0.074	-0.916	0.361

SNI Embedded network	-0.024	0.202	0.840
Loneliness	-0.108	-1.643	0.101
Vaccination hesitancy	0.039	0.202	0.840
DASS Depression	-0.136	-1.064	0.288
DASS Stress	-0.382	-6.278	<0001*
DASS Anxiety	-0.098	-0.952	0.342
PQ symptoms	0.011	0.178	0.859
PQ distress	0.059	0.862	0.390

**p<0.05*

Note1. Predictive variables kept in the second step: age, gender, social distancing, level of concern about COVID-19, and traumatic experience (childhood abuse and neglect, and trauma general).

Note2. DASS=Depression, Anxiety and Stress; PQ= Prodromal questionnaire.

SNI=Social Network Index; Vaccination hesitancy= VHS Vaccination hesitancy scale

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5. GENERAL DISCUSSION

The main objective of this thesis was to explore the stability and underlying mechanisms of stress-sensitivity as a trait among nonclinical young adults, given its close association with psychosis-proneness. A comprehensive methodology was employed to examine the longitudinal stability of stress-sensitivity and its determinants, including genes, environment, and gene x environment interactions, over time. The study commenced by testing the assumption that stress-sensitivity is a highly stable trait. This involved examining the longitudinal trajectories of individual differences in stress appraisals, both retrospectively and momentary in daily-life situations. Subsequently, the study investigated factors contributing to account for an individual's susceptibility to stress, such as childhood adversity, polygenic and genetic risk scores, and potential interactions between these variables. To address the complexities associated with evaluating childhood adversity (Lacey & Minnis, 2020), we first provided an advanced conceptualization of childhood adversity based on the theoretical foundation of the DMAP model (McLaughlin et al., 2016). The dimensional adversity factor scores were validated in a cross-sectional manner, examining a range of psychosis-related symptom dimensions, and later in a longitudinal manner, considering various social, psychological, and symptom outcomes across three most recent assessments of the BLISS sample— the last one spanning almost eight years. Next, the dimensional adversity factor scores previously obtained from three established interview and self-report measures were integrated into the stress-sensitivity model. This allowed for the examination of the longitudinal direct and interaction effects of these adversity dimensions, as well as two genetic markers of stress-sensitivity, on individual stress appraisals. Furthermore, the importance of considering loneliness as a prominent risk factor for psychosis, along with social connectedness and resilience as protective factors during high uncertainty situations like the COVID-19 pandemic, was highlighted. The main findings from each section of this thesis are summarized below, followed by a discussion of their implications for preventive measures. Finally, the strengths and limitations of the thesis are discussed, along with recommendations for future research topics.

5.1. Integration of Findings

This thesis comprehensively investigates the complex trait of stress-sensitivity and its underlying mechanisms. Through a longitudinal, multidimensional assessment of young adults in a nonclinical sample, it is demonstrated that stress-sensitivity is a highly stable trait, resistant to developmental and environmental changes throughout the lifespan. The thesis explores both environmental and genetic predictors of stress-sensitivity, including dimensions of childhood adversity and the polygenic and genetic risk of stress-sensitivity. Additionally, the study highlights the multidimensional model of schizotypy as a valuable tool for understanding the etiological mechanisms and pathways associated with schizophrenia-spectrum psychopathology, particularly in individuals with high schizotypy scores. Loneliness is identified as a potential predictor of psychosis, acting as a mechanism underlying stress-

sensitivity. Protective factors such as social connectedness and resilience are proposed to mitigate the effects of adversity, stress-sensitivity, and psychosis during challenging life situations. This thesis provides important insights into the development of stress-sensitivity and its potential link to psychopathology, offering implications for preventive measures and future research directions.

The thesis work presented in *Section 1* examined different approaches to operationalizing childhood adversity and their cross-sectional and longitudinal links to a wide range of transdiagnostic psychopathology, social and psychological outcomes. In *Chapter 1*, the study identified dimensions underlying multiple subscales from three well-established childhood adversity measures and used these dimensions in conjunction with a cumulative risk index to demonstrate its association to depression, anxiety, and psychosis-spectrum psychopathology. To the best of our knowledge, this was the first study to examine the complementarity of factor-analytic and cumulative-risk approaches using interview and self-report measures. The study identified four meaningful dimensions of childhood adversity, including two dimensions suggested by the Dimensional Model of Adversity and Psychopathology (DMAP) model—*Threat* and *Deprivation*—and two dimensions, *Intrafamilial Adversity* and *Sexual Abuse*. The finding that *Threat* and *Deprivation* are distinguished by distinct dimensions lends empirical support to the conceptual distinction proposed by the DMAP model, while *Intrafamilial Adversity* and *Sexual Abuse* suggest that the threat-deprivation model on its own may be insufficient to account for all the variation in childhood adversity, thus should be considered for future evaluations of adversity exposures. As hypothesized, the adversity dimensions and cumulative risk demonstrated specificity in their associations with the psychopathology symptom domains. *Threat* demonstrated the strongest associations with psychopathology outcomes, including depression, anxiety, and particularly positive schizotypy dimensions, whereas *Deprivation* demonstrated associations with negative psychosis dimensions. *Intrafamilial Adversity* was uniquely associated with schizotypal personality disorder (SPD) symptoms, whereas there was no association with *Sexual Abuse*. All psychopathology outcomes were predicted by a cumulative risk index. Overall, the findings regarding *Threat* are consistent with research indicating the importance of "intention to harm" adversities in conferring risk for reality distortion (Arseneault et al., 2011; van Nierop et al., 2014), as well as anxiety and depressive disorders (McGinnis et al., 2022), whereas in the absence of expected environmental inputs, that is, *Deprivation*, deficit-like features (i.e., diminished emotional experience and social disinterest) corresponding to negative psychosis dimensions may increase (Gallagher & Jones, 2013). Additionally, SPD symptoms were exclusive to *Intrafamilial Adversity* which draws attention to the multidimensional nature of this construct (including positive, negative, and disorganized psychosis features; Barrantes-Vidal et al., 2015), and importance of identifying specific environmental precursors to schizotypal PD in order to comprehend the etiology of schizophrenia spectrum disorders (Kwapil & Barrantes-Vidal, 2015). Regarding the dimension of *Sexual Abuse*, the relationship between sexual abuse and psychopathology is well

established in the literature (Noll, 2021), but the evidence of exposure in nonclinical populations is less consistent (Vachon et al., 2015). This might explain the lack of significance between psychopathology and *Sexual Abuse* in our study, especially since the endorsement of sexual abuse in our sample was low, which may have been insufficient to capture any associations with psychopathology outcomes. Lastly, our findings showed that a standardized measure of adversity, in the form of the cumulative risk index, had broad and distinct associations with psychopathology outcomes. This supports previous research demonstrating that cumulative adversity increases the risk of psychopathological outcomes (Copeland et al., 2018; Evans et al., 2013; Morgan et al., 2020; Kim et al., 2021), particularly the cumulative effect of empirically derived adversity dimensions, which has not previously been investigated.

Chapter 2 built upon the findings of chapter 1 by examining the predictive validity of childhood adversity dimensions in relation to a broad range of psychopathology symptoms and social-psychological outcomes across three prospective assessments of the BLISS study (Barrantes-Vidal et al. 2013). The chapter excluded the cumulative index (as the complementarity of childhood adversity approaches was discussed in previous chapter) and the dimension of *Sexual Abuse* due to the low variance in the data sample, respectively. The study examined the longitudinal associations of the adversity dimensions with a broad spectrum of psychopathology symptoms. The study added social-psychological constructs, including attachment styles, subjective perception of social support, objective quantitative social network, and loneliness. To the best of our knowledge, this study is the first to examine several outcomes in a longitudinal framework, considering various dimensions of childhood adversity. Our results revealed that these adversity dimensions were associated with both overlapping and distinct prospective effects on psychopathology symptom domains and social-psychological factors. The findings supported the hypothesis that *Threat* is consistently associated with positive symptoms of psychosis, while *Deprivation* is linked to negative symptoms. Specifically, *Threat* uniquely predicted positive psychotic features over time, particularly paranoid beliefs, suggesting that early environments characterized by threat contribute to the risk of reality distortion (Arseneault et al., 2011). Similarly, *Deprivation* uniquely predicted schizoid and negative symptoms, supporting theories that a lack of expected inputs from the environment predicts deficit features (Gallagher & Jones, 2013). *Intrafamilial Adversity* predicted positive symptom measures, highlighting the significance of experiences within the caregiving environment (such as parental role reversal and parental discord/violence) beyond what the *Threat* dimension captures (as this dimension encompasses experiences across different relational domains). Additionally, childhood adversity dimensions were prospectively associated with symptoms of anxiety and depression, although different dimensions emerged as unique predictors over time, suggesting there may be limited specificity for these outcomes. The findings regarding social-psychological outcomes support the notion that adverse environmental experiences have enduring effects on psychological and social functioning (Alink et al., 2012; Bifulco & Thomas, 2012; Pfaltz et al., 2022). As such, *Intrafamilial Adversity* was prospectively associated with insecure attachment, specifically predicting

anxious attachment, which may indicate that internalizing experiences from this dimension contributes to the formation of internal working models centered around a need for approval and preoccupation with relationships (Schimmenti & Bifulco, 2015) as well as and the reliance on hyperactivating emotion regulatory strategies (Mikuincer & Shaver, 2007). *Deprivation* uniquely predicted anxious and avoidant attachment, aligning with research on neglect and attachment insecurity (Borelli et al., 2015; Kim et al., 2021). Moreover, *Threat* and *Deprivation* uniquely predicted having a smaller social network, with *Threat* specifically predicting network diversity. This suggests that threat-related experiences may lead to developmental adaptations that limit engagement in diverse social roles, although these associations were best accounted for by the *Deprivation* dimension. Experiencing childhood neglect may be particularly detrimental to the perception of social connection and support, potentially influenced by interpreting social interactions based on previous neglect experiences (Luyten & Fonagy, 2019). Overall, the three adversity dimensions combined accounted for a substantial proportion of variance in many outcome measures, which is noteworthy given the various factors contributing to psychopathology and impairment in young adults. The effects were particularly pronounced for positive schizophrenia-spectrum characteristics, including psychotic-like, paranoid, and schizotypal features, despite the non-clinical sample. This highlights the powerful unique effects of the multidimensional approach in characterizing adverse experiences, as well as the overall significant effects.

Section 2 of the thesis aimed to examine the stability of the stress-sensitivity phenotype as a trait of individual differences in young individuals and its predictors, considering the strong association between the environment and genes and the stress-sensitivity trait. *Chapter 3* provided evidence supporting the stability of stress-sensitivity as an individual difference trait using two different measures: retrospective stress appraisal with the Perceived Stress Scale (PSS) and momentary situational and social subjective stress appraisals with the Experience Sampling Method (ESM) questionnaire. The ESM questionnaire included two items: one tapping situational stress ("My current situation is stressful") and one tapping social stress ("I feel close to this person/people" reversed). Advanced statistical methods reveled two classes (high and low stress-sensitivity) that classified individuals based on their developmental trajectories of sensitivity to stress. The majority of participants belonged to the low stress-sensitivity class. However, when using the ESM momentary measure instead of the PSS retrospective measure, a smaller proportion of participants belonged to the high ss class, which was expected considering the nonclinical functional sample. Individuals highly responsive to stress generally exhibited stability in stress-sensitivity across measures, while those with low momentary situational stress and low PSS scores experienced changes in stress-sensitivity. Although no a priori hypotheses were offered due to the exploratory nature of the analyses, these findings supported the stability of stress-sensitivity, especially for individuals with high levels of this trait. More so, the findings may indicate that stress-sensitivity shares similarities with other personality traits particularly in relation to highly sensitive individuals who generally exhibit a heightened sensitivity to internal and external cues, resulting in a more

intense and profound emotional and physiological response with tendency to perceive and process information deeply, leading to a greater awareness and sensitivity to subtle changes in the environment (Lionetti et al., 2019; Pluess et al., 2023). More so, the developmental nature of the stress-sensitivity trait was particularly prominent when assessed using retrospective stress appraisals. However, the stability of the stress-sensitivity trait over time was not observed in individuals belonging to the high class of momentary situational stress, possibly due to the item's context-specific nature ("My current situation is stressful"), which specifically asks about a particular situation at a given moment. This could explain why only 7% of participants were categorized as high stress-sensitivity using this measure. Momentary stress appraisals capture individuals' real-time experiences and appraisals of stress in specific situations, thus high stress-sensitive individuals may exhibit variability in their momentary stress appraisals due to the situational context and immediate emotional state. They may be more influenced by immediate factors and mood fluctuations, resulting in less stability in their momentary stress appraisals compared to their overall perceived stress levels assessed retrospectively. Therefore, it is likely that momentary stress-reactivity and trait-sensitivity, or the *state* and *trait* phenomena, were captured by this item, making it difficult to yield stable trajectories of high stress-sensitivity over time. Nevertheless, the distinctions between the retrospective and momentary measures supported the idea that stress is a multifaceted construct manifested at different levels in different situations. Given that the measurements were taken at various times and intervals, small variations in the stress response were expected.

Chapter 4 investigated the moderating effect of stress-sensitivity Polygenic Risk Score s(PRS-SS) and Genetic Risk Score (GRS-HPA) on interview-based dimensions of childhood adversity in predicting longitudinal trajectories of low versus high stress-sensitivity. Both retrospective (i.e., PSS) and momentary (i.e., ESM) measures of subjective stress appraisals were used. Genetic variability, mostly GRS-HPA, moderated the impact of childhood adversity for membership in the persistently high-PSS class, whereas results were less clear for momentary stress trajectories. *Threat* was directly associated with pertaining to the high-PSS class, and the interaction of PRS-SS with *Threat*, as well as GRS-HPA and all adversity dimensions, predicted an increased likelihood of high-PSS stress-sensitivity membership. The results indicated that individuals with high genetic susceptibility were more likely to experience persistently high stress levels when exposed to adversity. The fact that GRS-HPA yielded more interaction effects than PRS-SS may be indicating a greater moderating role for a GRS indexing biological variation in one of the main neural systems directly involved in regulating the effects of stress (i.e., the HPA axis), as compared to the PRS-SS. Large GWAS samples sometimes limit the accurate assessment of the phenotypes, particularly when these rely on a few self-reported items. Instead, incorporating additional knowledge such as biologically-meaningful data into the selection of relevant SNPs might enhance the formation of polygenic and genetic risk scores (Holden et al., 2008).

As for the momentary stress trajectories, *Deprivation* and *Threat* showed direct effects on high trajectories of social stress, consistent with strong evidence linking threat-related

adversity with altered patterns of detecting threatening cues and heightened social-emotional processing (Mc Laughlin et al., 2019). As such, PRS-SS interacted with *Deprivation* and GRS-HPA with *Intrafamilial Adversity* to predict trajectories of ESM social stress. However, the direction of the interaction effects did not align with expectations as in both cases, the effects were driven by those with lower genetic susceptibility. No main or interaction effects were found for situational stress trajectories except for a trend association between PRS-SS and *Threat*, with high PRS-SS more likely to show a high situational stress trajectory when exposed to greater levels of *Threat*. Of note, stress-sensitivity trajectories obtained momentarily with ESM showed a smaller percentage of individuals in high-class (11% for high-ESM social stress and 7% for high-ESM situational stress) compared to individuals classified in a high trajectory as measured retrospectively with PSS (33%). This disparity in percentages may have contributed to the unexpected findings in the trajectories of momentary social stress and could have impacted the ability to detect any gene-environment interaction (GxE) effects on the trajectories of momentary situational stress.

It is relevant to highlight that the dimension of *Threat* indicated both main and interaction effects with both genetic markers of stress-sensitivity on PSS trajectories, as well as a main effect on momentary social stress and a trend interaction effect with PRS-SS on momentary situational stress. Compared to other adversity dimensions, *Threat* greatly predicted persistence of high stress-sensitivity. *Threat* as assumed to be a strong factor in the manifestation of psychopathology outcomes (Morgan et al., 2020; Beards et al., 2020; Moriyama et al., 2018), seems consistent with the hypothesis that persistently high stress-sensitivity may be an underlying mechanism underpinning this relationship.

The work in *Section 3* of the thesis offered a unique opportunity to investigate significant psychosocial predictors of risk and resilience in psychosis during and after situations of high uncertainty and stress, such as the COVID-19 pandemic. In *Chapter 5*, the study provided preliminary evidence of psychosocial predictors of psychosis, depression, anxiety, and stress during the COVID-19 pandemic. Specifically, loneliness was identified as a highly significant psychosocial predictor of a broad spectrum of psychopathology, particularly psychosis, despite participants reporting generally good general health. Many psychosocial predictors, such as high levels of COVID concern, were associated with a decline in general health and well-being. The findings revealed a significantly elevated incidence of psychopathology symptoms, as well as an increase in the number of days when mental health was poor, when normal activities were impaired by poor health or pain, and when participants felt anxious, tense, or worried. These findings were consistent with previous studies that have examined the impact of stressful life circumstances, where factors such as social isolation and distancing exacerbate feelings of anxiety, depression, stress, and loneliness (da Rocha et al., 2018; Mäki et al., 2014). Furthermore, the study also examined the impact of previous trauma exposures in this population with a transgenerational history of wars and recent natural disasters, and surprisingly found that trauma was only weakly associated with psychosis risk. It may be that the low prevalence of psychosis in this general population, relative to the much

higher rates of depression, anxiety, and stress, is one of the potential causes of the weak association. Nevertheless, loneliness emerged as an important factor to consider, as it was highly associated with poor mental health, feelings of worry, anxiety, or tension, and psychosis risk. Psychosis-proneness was also found to be strongly associated with depression, anxiety, and stress, supporting the evidence linking loneliness to a variety of mental disorders, including psychosis.

The findings presented in *Chapter 6* highlighted the role of psychosocial predictors in determining general and mental health two years after the COVID-19 pandemic. The study specifically examined the effects of previous traumatic experiences, both in childhood and general trauma, and emphasized the crucial role of protective factors such as social connectedness in determining resilience levels. The results indicated devastating long-term mental health effects of the COVID-19 pandemic, including a significant increase in depression, anxiety, and stress. Notably, the rate of psychosis risk post-pandemic nearly doubled compared to the prevalence of high-risk psychosis rates at the beginning of the pandemic, particularly in those with previous traumatic experiences. Post-pandemic concerns, along with past trauma and increased loneliness, contributed to a significant decline in general health. On the other hand, the number of embedded social networks, which refers to the number of different network domains in which a participant is active, and resilience levels were associated with better general health and increased happiness and hopefulness. Additionally, the number of days participants experienced love increased with social network diversity, resilience, and surprisingly, social distancing adherence. Interestingly, despite expectations, resilience had no effect on psychosis levels but did reduce stress levels. The findings suggested that enhancing resilience may result in decreased stress levels and, consequently, lower sensitivity to future stress. However, loneliness remained a highly significant risk factor in predicting various symptom developments, particularly psychosis, even after two years of the pandemic. On the other hand, social connectedness served as both a preventative and protective factor. Therefore, strengthening social networks may have plausible effects on alleviating psychopathology symptoms, decreasing levels of loneliness, and preventing future stress. Furthermore, the study revealed that individuals exposed to childhood adversity, following stressful life exposure, experienced exacerbated depression, anxiety, and stress, particularly in relation to psychosis symptoms. These results may strengthen the evidence for the underlying mechanisms of heightened stress-sensitivity. Overall, the findings suggested that social connectedness plays a critical role in mental health outcomes and enhancing resilience and social networks may have positive effects on reducing psychopathology symptoms, alleviating loneliness, and preventing future stress.

Taken together, this thesis presented novel insights into stress-sensitivity, childhood adversity, loneliness, social connectedness, and resilience as risk and protective factors in the psychosis-proneness. The findings shed light on the complex interplay of these factors and contribute to a deeper understanding of the underlying mechanisms that maintain stress-

sensitivity over time, and ultimately, provide valuable insights into the risk factors and potential protective factors for schizophrenia-spectrum psychopathology.

5.2. Implications for Clinical Interventions

Literature suggests that each trait traditionally corresponding to the Big Five personality model (e.g., neuroticism, agreeableness, etc.) displays certain relations to stress exposures, but that the trajectory and manifestation depend on the individual's characteristics and behaviors (Luo et al., 2022). The evidence that stress-sensitivity is a highly stable trait, and as such resembles the behavior of other personality traits, helps us understand individual differences and experiences in response to stressful situations (Weyn et al., 2022). Investigating stress-sensitivity as a psychosis-proneness relevant mechanism and its differences can aid in the identification of vulnerable individuals at high risk of encountering stressful situations and/or enduring intense psychological reactions to the experiences, thereby improving the accuracy of interventions (Luo et al., 2022; Weyn et al., 2022). This can help develop proactive and coping strategies to reduce stress, emotional overload, rigidity in reactions, and the daily occurrence of distressing events (Golonka & Gullla, 2021; Farmer & Kashdan, 2015) and ultimately contribute to improved outcomes in psychopathology, especially psychosis.

Individuals` genetic susceptibility to stress and environmental factors, such as childhood adversity, account for a large part of variance in their heightened stress-sensitivity (Boyce et al., 2016; Hall et al., 2022). These indications are provided by the in-depth examination, including the conceptualization and adequate evaluation of childhood adversity and genetic variation. The clarification of specific adversity exposures associated to the range of maladaptive outcomes was enhanced with the conceptualization of factor analytic dimensional approach of childhood adversity, while the ability to identify genetic susceptibility to stress-sensitivity was improved by two genetic markers of stress-sensitivity both from genome-wide studies revealing phenotypic association (PRS-SS; Arnau-Soler et al., 2018) and genetic variants biologically associated with the function of the main stress-regulation system (GRS-HPA; Crawford et al., 2021).

The study of various methods to operationalize childhood adversity and their links to transdiagnostic psychopathology resulted in the conceptual distinction of distinct yet related childhood adversity dimensions and provided complementary information to the field. The four dimensions of childhood adversity appear to shape specific developmental processes while also adding to a general vulnerability that affects the manifestation of psychopathology in a cumulative way (Bentall et al., 2014; Evans et al., 2013). As such, empirically derived dimensions may aid in the identification of potential specificity and underlying mechanisms, but the cumulative approach may maximize adversity-outcome associations and allow for the exploration of complex interactions with other levels of explanation (e.g., genetic factors) (Henry et al., 2021; McGinnis et al., 2022). These techniques aid in the comprehension of childhood adversity, its direct linkages to psychopathology, and its pathway to heightened stress-sensitivity.

Particularly, the findings related to the dimension of *Threat* and its constant cross-sectional, but also longitudinal associations with psychopathology phenotypes involving positive psychotic features (as well as depression and anxiety) contributes significantly to preventive intervention and clinical practice implications within the psychosis symptom domain. More so, *Threat* was strongly associated with elevated stress-sensitivity trajectories both directly and in the interaction with genetic psychological and biological markers. As a risk for reality distortion (Gizdic et al., 2023; Arseneault et al., 2011; van Nierop et al., 2014), as well as abnormal stress response, it appears that individuals exposed to *Threat* exhibit higher perceptual sensitivity to anger and levels of stress and develop greater attention biases to more threatening cues reflecting an increased sensitivity to stress (Chen et al., 2010; Stevens et al., 2021; Busso et al., 2017; McLaughlin et al., 2021). Findings including *Intrafamilial Adversity* lend support to the evidence of proactive types of maltreatment, that is, the exposure to threat in childhood seems to be the strongest predictor of maladaptive outcome in adulthood. Lastly, *Deprivation* paralleled meta-analytic findings demonstrating associations between neglect and negative symptoms (Alameda et al., 2021; Bailey et al., 2018), but also extending such findings when accounted for by other adversity dimensions. Thus, these findings emphasized the clear distinguishment between different types of adversity exposures and suggested that targeting specific adversity types and aiming on early intervention may be particularly important in mitigating the negative effects of adversity on individuals' wellbeing.

The clinical implications of the DMAP model and fine-grained characterization of the environment with comprehensive adversity measures provided a better understanding of first, how different types of adversity led to different psychopathology expressions and psychosis symptom dimensions, as well as social and psychological outcomes, and second, how they related to stress-sensitivity differences, whereas genetic variants associated with stress-sensitivity helped identify stress genes that manifest abnormal psychological and biological responses to stress. With the investigation of nonclinical psychosis (schizotypy) populations, these factors provided insight into the complex GxE interactions between environmental stressors and genetic variants early on and made progress in understanding the development of stress-sensitivity as a psychosis-proneness mechanism.

The research on psychosocial predictors of psychopathology and psychosis-proneness, particularly loneliness, is noteworthy because not only it is directly linked to psychosis, but it may also contribute as an underlying mechanism of an increased stress-sensitivity on the pathways to other forms of psychopathology. Loneliness as a highly silent issue may underpin heightened stress and social threat sensitivity, which can aggravate psychotic symptoms (Nowland et al., 2018; da Rocha et al., 2018). Investigation of psychosocial predictors during the COVID-19 pandemic revealed how individuals cope with and respond to extremely stressful life situations. This can be used to develop effective strategies for managing stress and intervene with stress-related issues at an early stage. In addition, the complementary research offered the chance to investigate the role of protective factors. As such, social connectedness appears to act as a protective factor improving resilience, and buffering against trauma,

loneliness, and stress-sensitivity to a wide range of psychopathology. Fostering social connectedness can help to reduce sensitivity to stress and psychopathology symptoms and ultimately prevent transition to psychosis (Ozbay et al., 2007).

From a methodological standpoint, the results of this thesis highlight the importance of adapting a proper research design and measurements with clearly defined conceptualizations and high reliability. In this respect, complementary assessment of retrospective and momentary stress appraisals provided a more comprehensive view of individual stress responses (Epel et al., 2018). In addition to the commonly used PSS scale, the ESM proves a valid method for examining the stress appraisals of individuals, particularly in the context of momentary social stress. It captures daily interactions with the environment and can clarify the context in which dynamic changes occur, which possess a challenge when assessed in laboratory settings using questionnaires and interviews (Myin-Germeys et al., 2009; Oorschot et al., 2009). As a clinical implication, ESM can be used to tailor solutions to each individual by providing a timely response to their demands in the context of their everyday lives (Myin-Germeys et al., 2016). More so, it appears that preventing clinical outcomes can be accomplished by reducing the stressors that individual at increased risk encounter in their everyday lives. The area of preventative treatments appears to benefit the most from this evidence. In fact, ESM is presently being used in cutting-edge therapeutic approaches to create ecological momentary interventions (EMIs) aimed at lowering susceptibility through mitigating the effect of symptoms and reinforcing positive behaviors in everyday life (Hartmann et al., 2015; Kramer et al., 2014).

5.3. Strengths and Limitations

The strengths of the studies presented in this thesis include a comprehensive longitudinal evaluation of both retrospective and momentary measures of stress appraisals with repeated measurements across multiple time points. Using both retrospective perceived and momentary daily-life stress measures provided a more complete understanding of individual experience with stress. Longitudinal design enabled an understanding of the impact of time and the direction of change over time (Caruana et al., 2015). Furthermore, this thesis provided a thorough evaluation of childhood adversity approaches and psychopathology using both questionnaire and interview measures. Interview measures allow probing and clarification of relevant details and help to reduce biases associated with subjective responding (Bifulco & Schimmenti, 2019; Lobbestael et al., 2009), while self-reports are adaptable, and can capture inner thoughts, emotions, beliefs, and attitudes, which may not be directly observable by others. (Fisher et al., 2015; Bifulco et al., 2019). Next, both cross-sectional and longitudinal examination of adversity in relation to psychopathology phenotypes and social, and psychological outcomes, facilitates etiological research without the critical confounding factors associated with clinical status, such as high comorbidity, biographical disruption, stigma, medication adverse effects, etc (e.g., Barrantes-Vidal et al., 2015). Moreover, a novel formation of two stress-sensitivity proxies from genome-wide studies finding phenotypic association

(PRS-SS; Arnau-Soler et al., 2018) and genetic variants biologically associated with the function of the main stress-regulation system (GRS-HPA; Crawford et al., 2021) greatly contributes to the scientific genome-wide literature.

While studies on stress-sensitivity in clinical populations are common (e.g., in the association with symptom exacerbation and recurrence) (Liu & Alloy, 2010; Farb et al., 2015; Hernaus et al., 2015), this thesis investigation included nonclinical young adults who may be going through critical developmental and challenging life milestones such as searching for a professional career, independence, and personal instability (e.g., separation from the household and living arrangements). Investigating stress-sensitivity and underlying mechanisms in nonclinical at-risk young adults is a significant gap in the literature, and it can provide a valuable insight into the developmental trajectories associated with metal health issues, allowing for the development of early prevention treatments and methods.

Finally, a robust investigation of multiple psychosocial predictors of psychosis-risk, providing preliminary evidence for an adverse effect of the COVID-19 pandemic on loneliness and prodromal symptoms of psychosis during the pandemic as well as two years after the pandemic fills the major gap in the literature considering the Croatian population. The two investigations identified risk as well as protective factors during and post an extremely stressful life situation, which may point to potential underlying stress-sensitivity mechanism in the pathways to psychosis and contribute to the understanding of psychosis and psychopathology manifestations on the cultural level, but also given the transgenerational war trauma (including early exposures), recent natural disaster, and significant lack of Croatian prodromal data.

The studies outlined in this thesis have significant strengths but also limitations. First, as part of the BLISS schizotypy investigation, the studies presented in the first and second sections of this thesis were conducted with a sample of Spanish university students, with a predominance of female participants. Future study in community samples with more representative sociodemographic distributions would improve generalizability. However, the large distribution of scores and measures of characteristics and symptoms in this population indicates that the constructs of interest have adequate and valid variance. Second, the limited sample size (particularly for ESM) may have conditioned the ability to obtain a more diverse distribution of scores for some of the social stress items, resulting in an inability to identify distinct developmental trajectories for these items. As a result, the fact that different trajectories were discovered for some of the ESM social stress items (e.g., 'I feel close to this person/these people') could be explained by participants' relatively low mean scores and variance on this item. Nonetheless, nonclinical high-functioning samples are likely to have lower mean levels of stress exposure than studies assessing stress-related phenotypes in highly exposed or clinical samples (e.g., combat; Andrews et al., 2009; Davis et al., 2022).

There are few limitations in the third section of the research works. First, despite the relatively large sample size, many participants did not complete the questionnaire, resulting in a smaller total sample size for some of the measures (e.g., PQ-16). Second, the participants were primarily females, with a majority holding graduate degrees, which may have limited the

study's generalizability. Third, while the same investigation principles were applied in both studies (except for minor questionnaire changes between two studies survey), they were not longitudinal in nature following the same person during and after the pandemic. As a result, cross-sectional studies lack continuous data to monitor mental health changes. Regardless, the studies allowed for a thorough examination of numerous psychosocial predictors of psychopathology and psychosis-risk, as well as proof of long-term negative effects of the pandemic and the importance of resilience and social connectedness in psychosis-proneness.

5.4. Future Directions

Schizophrenia and psychosis spectrum are one of the most disabling and potentially chronic conditions (van Os & Kapur, 2009). As a first treatment for psychosis, antipsychotic medications are frequently advised, but their efficacy is variable (Meltzer, 1992) with a high risk of serious side effects (Ray et al. 2001; Zipursky et al., 2013). Cognitive behavioral therapy (CBT), psychoeducation, and social skills training have been shown to reduce overall psychotic symptoms, improve functioning, and enhance quality of life (Health Quality Ontario, 2018; Chien et al., 2013). Nevertheless, these interventions require patient participation, can be time-consuming, and may not be suitable for all patients with psychotic symptoms (Thomas, 2015). Given the psychosis continuum and the comorbidity of early-stage clinical diseases, it would be extremely beneficial to develop and test preventive intervention strategies not only in the clinical population, but also in young people at transdiagnostic risk (Nelson et al., 2018). In light of these findings, schizotypy research is crucial for studying schizophrenia vulnerability and identifying at-risk nonclinical populations prior to the onset of clinical stages. Thus, in order to better tailor new preventive intervention strategies, future research should first target pathways and underlying mechanisms manifested in vulnerable nonclinical populations before proceeding to clinical stages. This includes further investigation of physical, genetic, psychological, and environmental factors that make an individual more likely to develop the disorder (Davis et al., 2016). Given the close relationship to psychosis, research should consider the advanced characterization of stress-sensitivity, but also its underlying mechanism of environmental and genetic factors that would aid in targeting more positive and resilience-building factors in prevention and intervention programs to buffer against stressful situations and reduce risk factors for the development of psychopathology.

Incorporating socioeconomic factors, gene-gene interactions, and gene-environment interactions could pave the way for a novel way of utilizing PRS in clinical practice and risk reduction for psychosis, as it has yet to be used in clinical settings (Calafato et al., 2018). The study also indicated that PRS may modify environmental effects for better prediction performance and individual exposure profile (Iyegbe et al., 2014). This could possibly enable early intervention treatments in the field of psychosis, focusing on prevention programs and environmental adversity reduction, which can further educate about novel resilience and protective treatment methods. Increasing the efficiency and accuracy of PRS will provide more clinical consequences and eliminate constraints on risk prediction. Furthermore, including

family history can provide information not only about genetic heritability from a positive family history, but also those with a negative family history (Iyegbe et al., 2014). Thus, both positive family history can be helpful and representative of genetic status and vulnerability in most instances, while focusing on negative family history can provide additional evidence of the important environmental role. The incorporation of polygenic risk scores (PRS) to account for environmental influences may have a substantial impact on schizophrenia research and its application in clinical and therapeutic contexts.

The use of comprehensive adversity measures allowed to obtain a fine-grained characterization of the environment that is not typically afforded by epidemiological research and thus complements existing literature in the field. Empirically-derived adversity dimensions and the cumulative risk index may facilitate different research objectives overcoming the complexity of childhood adversity and its links to different expressions of psychopathology and outcomes. Using longitudinal designs and elucidating the mechanisms and moderators of the links identified in the present studies represent an important avenue for future research. Continued work in this area is crucial to advance our understanding of risk and resilience in the service of informing preventive intervention and clinical practice for individuals who have experienced childhood adversity.

Consequently, as a result of the novel thinking based on evolutionary theory, individuals may differ in their sensitivity (referred to as susceptibility) to environment across a range of exposures (not just negative ones), and thus beneficial moderation effects by genetic variation should be expected from positive environment. According to the *differential susceptibility (DS)* model (Belsky & Pluess, 2009; Belsky & van Ijzendoorn, 2017; Boyce, 2016; Ellis & Boyce, 2011), individuals traditionally thought to be more vulnerable may be better conceptualized as having a greater susceptibility to environmental influences (i.e., being more plastic, sensitive, or malleable) for "better" and "worst". As a result, future study should investigate the interactions of PRS and positive environmental factors such as social connectedness, social support, and resilience.

5.5. Conclusions

In conclusion, this thesis presented a comprehensive approach to the complex phenotype of stress-sensitivity and its predictors as a putative risk mechanism for psychosis across a broad spectrum of contexts and timeframes. The findings of this thesis collectively indicate that:

1) Investigating how different approaches to defining childhood adversity in relation to transdiagnostic psychopathology can significantly contribute to advancing research on mechanistic processes and provide insights for intervention efforts. Four childhood adversity dimensions underlying multiple subscales from three well-established childhood were identified capturing experiences in the domains of *Intrafamilial Adversity*, *Deprivation*, *Threat*, and *Sexual Abuse*. As expected, the adversity dimensions demonstrated some specificity in

their associations with psychopathology symptoms. *Deprivation* showed unique association with the negative symptom dimension of psychosis (negative schizotypy and schizoid symptoms), *Intrafamilial Adversity* with schizotypal symptoms, and *Threat* with depression, anxiety, and psychosis-spectrum symptoms. No associations were found with the *Sexual Abuse* dimension, most likely due to the very skewed distribution of this dimension in this sample. Finally, when considering the cumulative risk index, it was found to be associated with all the outcome measures. (Section 1; Chapter 1)

2) Across the three most recent assessments of the BLISS sample, conducted over a span of almost eight years from baseline, the childhood adversity dimensions exhibited both overlapping and distinct prospective associations with psychopathology and social-psychological factors as expected. *Deprivation* predicted the negative (deficit-like) dimension of psychosis, while *Threat* and *Intrafamilial Adversity* predicted the positive (psychotic-like) dimension. Depression and anxiety were predicted by different adversity dimensions across time. Furthermore, *Threat* predicted a smaller and less diverse social network; *Intrafamilial Adversity* predicted anxious attachment; and *Deprivation* predicted a smaller social network, anxious and avoidant attachment, perceived social support, and loneliness. These longitudinal findings build upon previous research by highlighting the associations of three meaningful dimensions of childhood adversity with diverse risk profiles across psychological, social, and psychopathological domains which enhance our understanding of the specific impact of different childhood adversity dimensions across the lifespan. (Section 1; Chapter 2)

3) Stress-sensitivity is a highly stable psychobiological trait resulting from the interaction of genetic and environmental factors (GxE). Stability was higher for those with longitudinal trajectories of high stress-sensitivity and was slightly better captured by retrospective measures of perceived stress than momentary assessments−consistent with the contextually-driven nature of momentary responses. The dimension of *Threat* assessed at baseline was the most consistent predictor of persistently high stress-sensitivity across a period of almost 5 years. In terms of GxE interactions, genetic variability related to the HPA-axis (GRS-HPA) moderated the effects of all adversity dimensions on the persistence of stress-sensitivity trajectories, as well as PRS-SS and *Threat*, particularly for a retrospective stress measure. The interaction of PRS-SS with *Deprivation* and GRS-HPA with *Intrafamilial Adversity* predicted trajectories of momentary social stress, but the effects were driven by those with lower genetic susceptibility (Section 2; Chapter 3 and 4)

4) Loneliness poses a notable risk for mental health issues, particularly psychosis. The Croatian population experienced a significant association between psychosis risk and loneliness during the pandemic. The COVID-19 pandemic has disrupted social connectedness, which typically protects against distress and the feelings of loneliness. The presence of psychosis-proneness and social isolation exhibited a strong correlation with depression, anxiety, and stress levels (Section 3; Chapter 5).

5) After two years since the onset of the COVID-19 pandemic, there has been a notable deterioration in mental health, including increased levels of depression, anxiety, and stress, as well as a doubling of the risk of psychosis outcome. However, it is worth noting that there is evidence of divergent outcomes, indicating the presence of resilience among certain individuals. Factors such as prior trauma exposure and social connectedness exhibit a strong association with higher levels of resilience. This suggests that individual differences, particularly the influence of past trauma and stress sensitization, continue to shape the mental health consequences experienced by the Croatian population even two years after the COVID-19 pandemic (Section 3; Chapter 6)

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Zwicker, A., Denovan-Wright, E. M., Uher, R. (2018). Gene-environment interplay in the etiology of psychosis. *Psychological Medicine*, 48(12), 1925–1936. https://doi.org/10.1017/S003329171700383X

Curriculum Vitae .....

Alena Gizdic

Curriculum Vitae

1. Personal Information

Official name: Alena Gizdić *("Gizdic, Alena" in publications*)
Date and place of birth: December 4, 1992, Split, Croatia, 21000
Nationality: Croatian
Address: Carrer de Tavern, 38, 2-2 Barcelona, Spain, 08021
Address2: Ulica Ruđera Boškovića, 5, Split, Croatia, 21000
Phone: +34656750201 (ESP) / +385917248212 (CRO)
Email (Primary):gizdic.alena@gmail.com
Email (Institutional): alena.gizdic@uab.cat

2. Education

Graduate University:
Universitat Autònoma de Barcelona
University of Health and Science
Doctoral Degree in Clinical and Health Psychology Barcelona, Spain 08021
+34935811111
(September 2018- expected graduation: May 2023)

Graduate University:
Lipscomb University
University of Liberal Arts and Science
Master of Science in Psychology (*Summa Cum Laude*) Nashville, Tennessee 37204
+1 615 966 1000
(August 2016- December 2017)

Undergraduate University:
Cumberland University
University of Arts and Science
Bachelor of Science in Psychology, Pre-Medical (*Cum Laude*) Lebanon, Tennessee 37087
+1 615 444 2562
(January 2012 – May 2015)

Secondary Education:
5th Gymnasium "Vladimir Nazor" Split, Croatia 21000
+1 385 21348381
(August 2007- August 2011)

3. Professional Exams

- Marco Común Europeo de Referencia (MCER): Spanish (B2); 2018
- Medical College Admission Test (MCAT); 2014, 2015
- American Chemical Society Exam (ASC Exam); 2013, 2014, 2015
- Graduate Record Examination (GRE); 2015, 2017
- Suite of Assessments (SAT): 2012
- Test of English as a Foreign Language (TOEFL): 2012

4. Technical (IT) skills

- **Data Management and Research:** Data quality assessment, Data analysis, Database design and management**,** Visualization of data insights**,** Data science research methods, survey creation and data mining**.**
- **Computer Science and Statistics:** System administration, Microsoft office, Advanced statistical software functions including SPSS, STATA, RStudio, Mplus, Excel and statistical techniques (Multilevel methodological and statistical analysis, Structural equation modeling, multiple regression analysis, imputation methods, factorial analysis)

5. Honors and Awards

Complementary Research Grant: Mobility grant for beneficiaries of the University Teacher Training program (FPU). Reference: FPU18 / 04901. Dates: 01/06/2022 – 02/12/2022. Funding entity: Ministry of Education, Culture and Sport (MEDC). Project: National R + D + i Plan 2012 (Ref. PSI2017-87512-C2-1-R) granted to PI: Prof. N. Barrantes-Vidal. Amount funded: 6000 €.

Research Grant: FPU 2019 - Call for scholarships and grants for doctoral training of the national university teacher training program 2018 (FPU). Reference: FPU18 / 04901. Dates: 23/09/2019 - 30/04/2023. Funding entity: Ministry of Education, Culture and Sport (MEDC). Project: National R + D + i Plan 2012 (Ref. PSI2017-87512-C2-1-R) granted to PI: Prof. N. Barrantes-Vidal.

Research Grant: FI 2019- Grants for the recruitment of novice research staff. Reference: RESOLUTION EMC / 2176/2018- DOGC 25/09/2018 (BDNS 417789). Dates: 01/04/2019 - 22/09/2019. Funding entity: Agency for the Management of University and Research Grants (AGAUR). Project: National R + D + i Plan 2012 (Ref. PSI2017-87512-C2-1-R) granted to PI: Prof. N. Barrantes-Vidal.

Research Grant: PAS 2018 - Temporary Hiring of Administration and Specific Funding Services Staff. Reference: 21202. Dates: 1/09/2018 - 31/03/2019. Funding entity: Research Support Assistant - for the Dpt. Clinical and Health Psychology. Project: Icrea 2012-02 ICREA ACADEMY AWARD 2012 granted to Prof. Barrantes-Vidal.

- The research study and treatment intervention (1st place); Tennessee Psychology Association (TPA) Conference. November 2017
- Graduate Assistant Scholarship; Lipscomb University, Nashville TN. 2016, 2017
- KappaAlpha Order Educational Foundation Scholarship (KAOEF); Lexington, Virginia. 2016
- Academic Scholarship Award; Cumberland University, Nashville, TN. 2012, 2013, 2014, 2015
- Women's Tennis Scholarship; Cumberland University, Lebanon, TN. 2012, 2013, 2014, 2015. (Captain of a women tennis team 2012-2015)
- Dean's List Award; Cumberland University, Lebanon, TN. 2012, 2013, 2014, 2015
- TranSouth Scholar Athlete Award; Cumberland University, Lebanon, TN. 2012, 2013, 2014, 2015
- COSIDA Academic All-District Award, Cumberland University, Lebanon, TN. 2014

6. Research and Clinical Employment

1. **Universitat Autònoma de Barcelona; Laboratory of Person-Gene-Environment Interaction in Psychopathology.**
   Department of Clinical and Health Psychology
   Title: Doctoral Student
   Date: September 2018- expected graduation: September 2023
   Address: Facultat de Psicologia, Carrer de la Fortuna, 08193 Barcelona, Spain
   Phone#: +34.935.811.855
   Contact: Neus Vidal Barrantes, PhD

2. **Vanderbilt University; Body, Mind and Brain Lab**
   Department of Clinical Psychology and Neuroscience
   Title: Research Analyst
   Date: May 2017 – December 2017
   Address: 111 21st Ave. S, Wilson Hall, Suite 213 Nashville, Tennessee 37204
   Phone#:615.322.3435
   Contact: Sohee Park, PhD

3. **Lipscomb University**
   Department of Psychology
   Title: Research and Graduate Assistant
   Date: January 2017- December 2017
   Address: 1 University Park Drive, Nashville, Tennessee 37211
   Phone #:615.966.1000
   Contact: Dale Alden, PhD

4. **Lipscomb University**
   Department of Psychology
   Title: Office and Research Assistant
   Date: August 2016- December 2016
   Address: 1 University Park Drive, Nashville, Tennessee 37211

Phone #: 615.966.1000
Contact: Shanna Ray, PhD

5. **Vanderbilt Psychiatric Hospital**
   Thought and Mood Disorders Unit
   Title: Mental Health Specialist II
   Date: July 2015- May 2017
   Address:1601 23rd Avenue South, Nashville, Tennessee, 37204
   Phone #: 615.579.4020
   Contact: Jennifer Barut, PhD

6. **Oasis Emergency Teen Center**
   Title: Relief Coordinator/ Intern
   Date: August 2014 – December 2014
   Address: 1704 Charlotte Avenue #200, Nashville, Tennessee 37203
   Phone #:615.327.4455
   Contact: Devin Terry, LMSW

7. Research and Training Abroad

Centre: Department of Psychology, University of Split.
Place: Split, Croatia *Dates:* 01/06/2022- 02/12/2022
Length: 6 months
Advisor: Dr. Drako Hren, PhD
Research grant: Mobility grant for beneficiaries of the University Teacher Training program (FPU)

8. International Collaborations in Research Projects:

1. **International Consortium of Paranoia Research (ICPR)**
   Principal Investigators: Sohee Park; PhD, Michael Hajduk, PhD; Amy Pinkham
   Dates: 2022- Ongoing

2. **Vanderbilt University; Body, Mind and Brain Lab**
   Department of Clinical Psychology and Neuroscience; Nashville, TN USA
   Principal Investigator: Sohee Park, PhD
   Website: http://parklab.vanderbilt.edu
   Dates: 2019- Ongoing

3. **University of Split, Croatia**
   Department of Psychology and Department of Health Studies
   Associates: Dr. Darko Hren, Phd and Dr. Vesna Antičević, PhD
   Webistes: https://www.ffst.unist.hr/en/departments/psychology ; http://ozs.unist.hr/en/
   Dates: 2021- Ongoing

4. **University of Lausanne (UNIL); Cognitive and Affective Regulation laboratory (CARLA)**
   Principal Investigator: Christine Mohr, PhD
   Website:https://applicationspub.unil.ch/interpub/noauth/php/Un/UnPers.php?PerNum=1116121&LanCode=8
   Dates: 2018- Ongoing

9. Member of Funded Research Projects

a) Excellence Research Networks

Person-Environment Interaction in Risk and Resilience for Mental Health - (SGR 2021)
Principal Investigator: Neus Barrantes-Vidal
Project Reference: **2021SGR01010**
Funding Agency: Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) - Generalitat de Catalunya
Amount Funded: 40.000€
Duration: 01/01/2022-31/12/2024
Investigators Universitat Autònoma de Barcelona: Ballespí, S., Chanes, L., **Gizdic, A.,** Torrecilla, P., Galiano, J., Icancovsky, T., Robles, M., Clusa, D. (Fundació Sanitària Sant Pere Claver), Pérez, A (Fundació Sanitària Sant Pere Claver), Villarreal, B. (Fundació Sanitària Sant Pere Claver), Barcelona), Ramos, I. (Fundació Mútua de Terrassa per a la Docència i Recerca Biomèdica i Social), Escarmís, D. (Fundació Sanitària Sant Pere Claver), Vallmajó, M. (Fundació Sanitària Sant Pere Claver), Massanet, M. (Fundació Sanitària Sant Pere Claver).
External Collaborators: Kwapil, T.R. (University of Illinois at Urbana-Champaign, USA), Myin-Germeys, I. (KU Leuven, Belgium), Lafit, G (KU Leuven, Belgium), van Ijzendoorn, M.H. (Erasmus University Rotterdam), Bakermans-Kranenburg, M. (ISPA Lisbon), Sheinbaum, T. (Instituto Nacional de Psiquiatría, Méjico), Domínguez, T. (Instituto Nacional de Psiquiatría, Méjico), European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI), International Consortium for Schizotypy Research, Sharp, C. (University of Houston, USA), Rockwood, N. (Loma Linda University), Malberg, N. (Yale School of Medicine), Feldman-Barret, L. (Northeastern University), Camprodon, J. (Massachusetts General Hospital), Güell, M. (Universitat Pompeu Fabra), Doruk, D. (Acacia Counseling and Wellness), Wormwood, J. (University of New Hampshire).

Person-Environment Interaction in Risk and Resilience for Mental Health - (SGR 2017)
Principal Investigator: Neus Barrantes-Vidal
Project Reference: 2017SGR1612
Funding Agency: Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) - Generalitat de Cataluña

Amount Funded: 18.250€
Duration: 2018 to 2021 (3,5 years)
Investigators Universitat Autònoma de Barcelona: Ballespí, S., Chanes, L., Cristóbal, P., Hinojosa, L., Monsonet, M., Racioppi, A., **Gizdic, A.,** Torecilla, P.
External Collaborators: Debbané, M. (University of Geneva, Switzerland), Domínguez, T. (Instituto de Psiquiatría, Méjico), García, B. (UAB)., Feldman, L. (Northeastern Univeristy, USA), Kwapil, T.R. (University of Illinois at Urbana-Champaign, USA), Myin-Germeys, I. (KU Leuven, Belgium), Pérez, A. (Fundació Sanitària Sant Pere Claver); Rosa, A., (UB), Sharp, C. (University of Houston, USA); Sheinbaum, T. (University of Southern California, USA), Vilagrà, R. (Centre de Salut Mental de Sarrià-Sant Gervasi, Barcelona).

b) Research Projects

<u>Universitat Autònoma de Barcelona, Barcelona, Spain</u>

1. **<u>Project</u>: Testing the shift from a 'Disease Risk' to a 'Differential Susceptibility' conceptualization of person-environment and gene-environment interactions in the psychosis**
   Principal Investigator: Neus Vidal Barrantes
   Project Reference: PID2020-119211RB-I00
   Funding Agency: Spanish Ministry of Science, Innovation and Universities, Plan Nacional de I+D+i (National Plan of R+D+i).
   Amount Funded: 145.200€ (120.000 direct costs) plus a 4-year predoctoral contract
   Duration: 1/9/2021 - 31/8/2024 (3 years)
   A*ssociate scientists:* Bakermans-Kranenburg, M. (Vrije University, NL); Kwapil, T.R. (University of Illinois at Urbana-Champaign, USA); Rosa, A. (University of Barcelona); van IJzendoorn (Leiden University, NL). *Clinical scientists*: D. Clusa, M. Vallmajó, M.A., Massanet (Fundació Sanitària Sant Pere Claver, Barcelona). Doctoral students: **Gizdic, A. (UAB),** Torecilla- González, P. (UAB), Valeria Lavín (UAB), Jackie Nonweiler (UAB)

2. **<u>Project</u>*:* A new approach to the concept and study of risk in psychosis**
   Principal Investigator: Neus Vidal Barrantes, PhD
   Project Reference: PSI2017-91814-EXP.
   Funding Agency: Spanish Ministry of Science, Innovation and Universities, Plan Nacional de I+D+i (National Plan of R+D+i), "Science Explora" Call
   Amount Funded: 36.300€
   Duration: 1/11/2018 – 30/06/2021 (2 years plus a 6-month extension)
   Investigators: Ballespí, S., Rosa, A. *Workteam*: Kwapil, T.R. (University of Illinois at Urbana-Champaign, USA); Sheinbaum, T. (University of Southern California, USA), Papiol, S. (Ludwig Maximilian University, Germany).
   Teamwork: Cristóbal, P. (UAB)., Domínguez, T. (Instituto de Psiquiatría de Méjico), Herrera, S. (Fundació Sanitària Sant Pere Claver), Hinojosa, L. (UAB), Kwapil, T.R. (University of Illinois at Urbana-Champaign, USA), Monsonet, M. (UAB), Montoro,

M. (Fundació Sanitària Sant Pere Claver), Myin-Germeys, I. (KU Leuven, Belgium), Racioppi, A. (UAB), Sheinbaum, T. (University of Southern California, USA), Torices, I. (Fundació Sanitària Sant Pere Claver), **Gizdic, A.** (UAB), Torecilla- González, P.(UAB).

Coordinated Project: Developmental trajectories of risk and resilience to psychosis: Integrative study of Gene-Person-Environment Interactions across the Extended Psychosis Phenotype
Principal Investigator: Neus Barrantes-Vidal (Universitat Autònoma de Barcelona, UAB)
Funding Agency: Spanish Ministry of Economy and Competitiveness (MINECO), Plan Nacional de I+D+I (National Plan of R+D)
Project Reference: PSI2017-87512-C2-00
Duration: January 2018 to December 2021 (including a 12-month extension)
Total funding: 128.260€ plus a 4-year predoctoral contract (*Formación de Personal Investigador*) associated to the project

Subproject 1: Developmental trajectories of risk and resilience to psychosis: Longitudinal examination of the psychological and biological stress sensitization hypothesis
Principal investigator: Neus Barrantes-Vidal (Faculty of Psychology, UAB)
Project Reference: PSI2017-87512-C2-1-R
Amount Requested: 154.807€
Amount Funded: 99.220,00 € + A 4-year predoctoral contract (FPI)
Investigators: Ballespí, S. (UAB).

Vanderbilt University, Nashville, TN, USA

3. **Project: COVID 19 and Mental health: Cross-Cultural comparison of psychosocial distress: USA, South Korea, France, Hong Kong, Mexico, Spain, and Croatia**
   Principal Investigator: Sohee Park, PhD
   Funding Agency: Vanderbilt University (IRB exempt status #201000)
   Duration: 2019- Ongoing
   Contributors: Park, S. (VU), Baxter, T (VU), Griffith, T. (VU), Dean, D. (VU), Lee, H.H, (VU), Tso, I. F. (VU), Giersch, A. (VU), Felsenheimer, A. (VU), **Gizdic, A** (UAB).
   Current supplemental materials: Cross-Cultural comparisons of psychosocial distress in the USA, South Korea, France, and Hong Kong during the initial phase of COVID-19 on PsyArXiv
   Current supplemental materials: Deterioration of mental health despite successful control of the COVID-19 pandemic in South Korea on PsyArXiv

4. **Project: Physiology-based virtual reality training for social skills in schizophrenia (Vanderbilt University, Nashville TN, United States)**
   Principal Investigator: Sohee Park
   Funding Agency: National Institute of Health (NIH)

Duration: 2016-2018
Contributors: Park, S. (VU), Nilanjan, S. (VU), Adery, L. (VU), Ichinose, M. (VU), Torregrossa, L. (VU), Wade, J. (VU), Nichols, H. (VU), Bekele, E. (VU) Bian. D. (VU), Granholm, E. (VU), Sarkar, N. **Gizdic, A** (VU).
Current supplemental materials: https://grantome.com/grant/NIH/R21-MH106748-01A1

University of Lausanne, Lausanne, Swizerland

5. **Project: Evolution and Maintenance of Genetic Colour Polymorphism in Barn owls.**
   (Faculty of Biology and Medicine, Department of Ecology and Evolution- Roulin Group, Lausanne, Switzerland)
   Principal Investigator: Alexandre Rouling, PhD (UNIL) and Christine Mohr, PhD (UNIL)
   Funding Agency: University of Lausanne, Switzerland
   Duration: 2019- Ongoing

6. **Project: International Colour-Emotion Association: Which emotions do you associate with colors? Cross-Cultural investigation.**
   (Faculty of Social and Political Sciences, Institute of Psychology, Cognition and Affective Regulation Laboratory-CARLA, Lausanne, Switzerland)
   Principal Investigator: Christine Mohr, PhD and Jonauskaite Domicele, PhD
   Funding Agency: University of Lausanne, Switzerland
   Duration: 2018- Ongoing
   Contributors: Jonauskaite, D.**,** Abdel-Khalek, A. M., Abu-Akel, A., Al-Rasheed, A. S., Antonietti, J.-P., Ásgeirsson, Á. G., Atitsogbe, K. A., Barma, M., Barratt, D., Bogushevskaya, V., Bouayed Meziane, M. K., Chamseddine, A., Charernboom, T., Chkonia, E., Ciobanu,T., Corona Cabrera, V., Creed, A., Dael, N., Daouk, H., Dimitrova, N., Doorenbos, C. B., Fomins, S., Fonseca-Pedrero, E., Gaspar, A., **Gizdic, A.,** Griber, Y. A., Grimshaw, G. M., Hasan, A. A., Havelka, J., Hirnstein, M., Karlsson, B. S., Jejoong, K., Konstantinou, N., Laurent, E., Lindeman, M., Manav, B., Marquardt, L., Mefoh, P., Mroczko-Wąsowicz, A., Mutandwa, P., Muthusi, S., Ngabolo, G., Oberfeld, D., Papadatou-Pastou, M., Perchtold, C. M., Pérez-Albéniz, A., Pouyan, N., Rashid Soron, T., Roinishvili, M., Romanyuk, L., Salgado Montejo, A., Sultanova, A., Tau, R., Uusküla, M., Vainio, S., Vargas, V., Volkan, E., Wąsowicz, G., Zdravković, S., Zhang, M., & Mohr, C
   Current supplemental materials: The sun is no fun without rain: Physical environments affect how we feel about yellow across 55 countries. on ScienceDirect

Other projects and thesis

- **Universitat Autónoma de Barcelona; Doctoral Thesis Research.** Title: *A comprehensive approach to heightened stress-sensitivity as a psychosis-proneness mechanism*. Date: September 2018- Present. Supervisor: Neus Vidal- Barrantes, PhD ("Barrantes- Vidal, Neus" in publications).

- **Vanderbilt University; Interdisciplinary Research.** Title: *Physiology-Based Emotion Sensing Robotic Technology for Social Cognitive Intervention in Schizophrenia***.** Date: January 2017- December 2017**.** Supervisor: Sohee Park, PhD.

- **Lipscomb University; Graduate Thesis Research.** Title: *Sleep Deprivation, Attention, and Quality of Life in Veterans***.** Date: August 2016- December 2017**.** Research investigating the effects of sleep deprivation on attention and quality of life in combat and non-combat veterans. Dale Alden, PhD.

- **Lipscomb University; Graduate Research.** *Hemispatial Neglect- Line Bisection Test***.** September 2016- December 2017**.** Research study seeks to design an electronic administration of the line bisection test and use that technology to determine what is normal and abnormal performance on the line bisection test. Dale Alden, PhD

- **Vanderbilt University Medical Center; Evidence-Based and Nursing Research.** Title: *The Effects of Physical Activity on Inpatients in a Psychiatric Hospital Setting*. October 2015- September 2017. Supervisor: Susan Cortez, PhD; Nancy Wells, DNSc, RN, FAAN; James Barnett, PhD.

- **Cumberland University; Undergraduate Research.** Title: *Post-Traumatic Stress Disorder and Major Depressive Disorder***.** Date: August 2014 – May 2015**.** Supervisor: Jenny L. Mason, PhD.

10. Publications

International Publications (Peer-reviewed)

Submitted for Publication

1. **Gizdic, A.,** Torrecilla, P., Lafit, G., Myin-Germeys, I., Kwapil, T.R., Barrantes-Vidal, N. (*Submitted for Publication*). A longitudinal study of the stability and trajectories of stress-sensitivity in young adults: retrospective and momentary daily-life assessments of stress appraisals.

2. **Gizdic, A.,** Torrecilla, P., Sheinbaum, T., Mas-Bermejo, P., Papiol, S., Rosa, A., Lafit, G., Myin-Germeys, I., Kwapil, T.R., Barrantes-Vidal, N. (*Submitted for Publication*). The interaction of polygenic susceptibility to stress and childhood adversity dimensions predicts longitudinal trajectories of stress-sensitivity

3. Sheinbaum, T., **Gizdic, A.,** Kwapil, T.R., Barrantes-Vidal, N. (*Submitted for Publication*). Childhood adversity dimensions in the longitudinal association to subclinical psychopathology symptoms, social and psychological outcomes.

2023

4. **Gizdic, A.,** Sheinbaum, T., Kwapil, T.R., Barrantes-Vidal, N. (2023). Empirically-derived dimensions of childhood adversity and cumulative risk: Associations with subclinical depression, anxiety, and psychosis-spectrum psychopathology. *European Journal of Psychotraumatology.* IF JCRSSCI2021: 5.783. Quartile 1. Category: Psychology, Clinical (rank: 22/130). In press.

5. **Gizdic, A.,** Baxter, T., Barrantes-Vidal, N., & Park, S. (2023). Social connectedness and resilience post COVID-19 pandemic: Buffering against trauma, stress, and psychosis. *Psychiatry Research Communications*, *3*(2), 100126. doi: 1016/j.psycom.2023.100126. IF JCRSSCI2021: 11,225. Quartile 1. Category: Psychiatry (ranking: 9/142).

2022

6. **Gizdic, A.,** Baxter, T., Barrantes-Vidal, N., Park, S. (2022). Loneliness and psychosocial predictors of psychosis-proneness during COVID-19: Preliminary findings from Croatia. *Psychiatry Research,* 317, 114900. doi: 10.1016/j.psychres.2022.114900. IF JCRSSCI2021: 11,225. Quartile 1. Category: Psychiatry (ranking: 9/142).

2019

7. Jonauskaite, D., Abdel-Khalek, A., Abu-Akel, A., Al-Rasheed, A. S., Antonietti, J.P., Ásgeirsson, Á. G., Atitsogbe, K. A., Barma, M., Barratt, D., Bogushevskaya, V., Meziane, M. K. B., Chamseddine, A., Charernboom, T., Chkonia, E., Ciobanu, T., Corona, V., Creed, A., Dael, N., Daouk, H., Dimitrova, N., Doorenbos, C. B., Fomins, S., Fonseca-Pedrero, E., Gaspar, A., **Gizdic, A.,** Griber, Y. A., Grimshaw, G. M., Hasan, A. A., Havelka, J., Hirnstein, M., Karlsson, B. S. A., Katembu, S., Kim, J., Konstantinou, N., Laurent, E., Lindeman, M., Manav, B., Marquardt, L., Mefoh, P., Mroczko-Wąsowicz, A., Mutandwa, P., Ngabolo, G., Oberfeld, D., Papadatou-Pastou, M., Perchtold, C. M. ; Pérez-Albéniz, A., Pouyan, N., Soron, T. R. Roinishvili, M., Romanyuk, L., Montejo, A. S., Sultanova, A., Tau, R., Uuskülabe, M., Vainio, S., Vargas-Soto, V., Volkan, E., Wąsowicz, G., Zdravković, S., Zhang, M., Mohr, C. (2019). The sun is no fun without rain: Physical environments affect how we feel about yellow across 55 countries. *Journal of Environmental Psychology*. doi: 10.1016/j.jenvp.2019.101350 66,101350. IF JCRSCI2019: 3,301. Quartile 1. Category: Psychology, Multidisciplinary (ranking: 22/138).

2018

8. Adery, L. H., Ichinose, M., Torregrossa, L. J., Wade, J., Nichols, H., Bekele, E., Bian. D., **Gizdic, A.,** Granholm, E., Sarkar, N., Park, S. (2018). The acceptability and feasibility of a novel virtual reality based social skills training game for schizophrenia: Preliminary findings. *Psychiatry research*, *270*, 496–502. doi: 10.1016/j.psychres.2018.10.014. IF JCRSSCI2018: 2,208. Quartile 3. Category: Psychiatry (ranking: 85/146).

11. Presentations

Talks and Oral Communications

1. **Gizdic, A.,** Sheinbaum, T., Kwapil, T.R., Barrantes-Vidal, N. (2022). Empirically-derived dimensions of childhood adversity and cumulative risk: Associations with subclinical depression, anxiety, and psychosis-spectrum psychopathology. Presented as an oral presentation at the 22nd International Society for Psychological and Social Approaches to Psychosis (ISPS), Perugia. Italia. Aug 31st- Sept 4th.
2. **Gizdic, A.,** Sheinbaum, T., Kwapil, T.R., Barrantes-Vidal, N. (2022). The association between early-life adversity and subclinical psychotic phenotypes: A prospective study. Presented as an oral presentation at the International Consortium for Schizotypy Research (ICSR), Marburg, Germany. June 2nd- 4th.
3. **Gizdic, A.,** Torrecilla, P., Lafit, G., Myin-Germeys, I., Kwapil, T.R., Barrantes-Vidal, N. (2021). The association of a longitudinally defined stress-sensitivity phenotype with psychosis-proneness**.** Presented as an oral presentation in the virtual 8th European Conference on Schizophrenia Research (ECSR). September 23rd- 25th, Virtual Conference.
4. **Gizdic, A.,** Torrecilla, P., Lafit, G., Myin-Germeys, I., Kwapil, T.R., Barrantes-Vidal, N. (2021). The association of a longitudinally defined stress-sensitivity phenotype with psychosis-proneness**.** Presenting as an oral presentation in the virtual Congress of the Schizophrenia International Research Society (SIRS). April 17th- 21st, Virtual Conference.

Posters

1. **Gizdic, A.,** Baxter, T., Barrantes-Vidal, N., Park, S. (2021). The role of loneliness in psychosis-proneness during COVID-19: Preliminary findings from Croatia. Presenting as a poster in the virtual 8th European Conference on Schizophrenia Research (ECSR). September 23rd- 25th, Virtual Conference.
2. **Gizdic, A.,** Baxter, T., Barrantes-Vidal, N., Park, S. (2021). The role of loneliness in psychosis-proneness during COVID-19: Preliminary findings from Croatia. Presenting as a poster presentation in the virtual Congress of the Schizophrenia International Research Society (SIRS). April 17th- 21st, Virtual Conference.
3. Torrecilla, P., **Gizdic**, A., Barrantes-Vidal, N. (2021). Examining the association of hair cortisol levels with a comprehensive and longitudinally defined phenotype of persistent stress-exposure and stress-related symptoms in schizotypy. Presented virtually at the 2021 Congress of the Schizophrenia International Research Society. April 17th - 21st, 2021, Virtual Conference.
4. Torrecilla, P., **Gizdic, A**., Racioppi, A., Monsonet, M., Kwapil, T.R., & Barrantes-Vidal, N. (2020). Stress sensitization as the underlying mechanism linking childhood trauma and psychotic-like symptoms in nonclinical young adults. Presented as a poster in the virtual 2020 Congress of the Schizophrenia International Research Society (SIRS). April 4th-8th, Virtual Conference. Abstract published in *Schizophrenia Bulletin*, 46 (S1), S232.

5. **Gizdic, A.,** Hinojosa-Marqués, L., Kwapil, T. R., & Barrantes Vidal, N. (2020). The relationship between attachment styles and clinical presentation in early psychosis patients. Presented as an abstract in the virtual Congress of the Schizophrenia International Research Society (SIRS). April 4th-8th, Virtual Conference. Abstract published in *Schizophrenia Bulletin*, 46 (S1), S177–S178. doi:10.1093/schbul/sbaa030.425
6. Torregrossa, L., Adery, L. H., Ichinose, M., Nichols, H., **Gizdic, A.,** Wade, J., Blan, D., Gramholm, E., Sarkar, N., Park, S. (2018). Novel virtual reality social skill training for individuals with schizophrenia. Presented as a poster in the virtual 2018 Congress of the Schizophrenia International Research Society (SIRS). April 4th-8th, Florence, Italy. Abstract published in *Schizophrenia Bulletin*, 44 (S1), S195–S196. doi:10.1093/schbul/sby016.480.
7. Ichinose, M., Wade, J., Adery, L. H., Torregrossa, L., Nichols, H., BIan, D., **Gizdic, A.,** Sarkar, N., & Park, S. (2018). T205. Changes in social attention and emotion recogniti9on folowwing a pilot social simulation computer game intervention for individuals with schizophrenia. Presented as a poster in the virtual 2018 Congress of the Schizophrenia International Research Society (SIRS). April 4th-8th, Florence, Italy. Abstract published in *Schizophrenia Bulletin*, 44 (Suppl 1), S196. doi.org/10.1093/schbul/sby016.481.
8. **Gizdic, A.,** Cortez, S., Barrett, J., & Wells, N., (2017). Effects of physical activity on inpatients in psychiatric hospital setting. Presented as a poster in the Tennessee Counseling Association (TCA) Conference. Nov 17th, Nashville, TN.
9. **Gizdic, A.,** Cortez, S., Barrett, J., & Wells, N., (2017). Effects of physical activity on inpatients in psychiatric hospital setting. Presented as a poster at the Cumberland University Colloquium. Oct 2017, Nashville, TN.
10. **Gizdic, A.,** & Alden, D. (2017). Sleep deprivation, attention, and quality of life in veterans. Presented as a poster at the 6th Annual Lipscomb University Student Scholars Symposium. April 2017, Nashville, TN.
11. **Gizdic, A.,** & Alden, D. (2017). Sleep deprivation, attention, and quality of life in veterans. Presented as a poster in the Middle TN Counseling Association (MTCA) Conference. February 2017, Kentucky, TN.
12. **Gizdic, A.,** & Mason, J., (2015). Post-Traumatic Stress Disorder and Major Depressive Disorder. Presented as a poster at the Cumberland Univeristy Colloquium. Dec 2015, Nashville, TN.

12. Teaching Experience

Graduate and undergraduate psychology classes

- **Univerisitat Autònoma de Barcelona**
  Personality Disorders (Trastornos de la Personalidad) (10 hrs)
  Date: Spring 2023

- **Univerisitat Autònoma de Barcelona**
  Personality Disorders (Trastornos de la Personalidad) (60 hrs)
  Date: Spring 2022

- **Univerisitat Autònoma de Barcelona**
  Psychopathology (Psicopatología de Ciclo Vital) (25hrs)
  Date: Fall 2020

- **Cumberland University; Cognitive Psychology** (10hrs)
  Date: April 2016

- **Cumberland University; Research Methods** (10hrs)
  Date: August 2015, August 2017

13. Professional Training

Introduction to Metacognitive Therapy (MCT)
Description: Introduction and practice of Metacognitive therapy, and data supporting evidence for MCT paradigm.
Date: October 2017

Hypnosis Workshop: Medical Application and Ethical Issues
Description: Performance of hypnotic inductions, demonstration and practice under the supervision of trained psychologists.
Date: August 2017

Physiology-Based Virtual Reality Training (VR)
Description: Computer based program allowing children and adults to learn basic social interactions in consistent and accepting way.
Date: May 2017

Analysis of Functional NeuroImages (AFNI)
Description: Set of C programs for processing, analyzing, and displaying functional MRI (FMRI) data.
Date: April 2017