Transdiagnostic approaches to mental health

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Linking adversity, cognition, candidate mechanisms, and novel digital interventions

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DISSERTATION

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PARANIMFEN

Dr. Clara Snijders

Lex Westbroek

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APPENDIX

CHAPTER 1

General introduction

The complex and multifaceted nature of mental health

Mental disorders are among the strongest contributors to the global burden of disease - next to cardiovascular and infectious diseases, cancer, and neonatal disorders [1, 2] - and have been found to be the second leading cause of death in young age groups [3]. Mental health's central role in public health has gained global recognition in recent years, as evidenced by its formal inclusion in the United Nation's Sustainable Development Goals [4] and the World Health Organization's goal of universal health coverage [5]. Nevertheless, many people with mental health problems do not receive adequate treatment and the perceived stigma associated with mental health problems remains high [6, 7], preventing many individuals from seeking help or to openly talk about their mental health. Thus, understanding key determinants and underlying mechanisms in order to improve prediction of their onset, course, and outcome, as well as developing and implementing novel intervention strategies remain some of society's greatest challenges.

Psychopathologies have a complex aetiology, differ greatly in their phenomenology, and typically first appear during childhood, adolescence, and early adulthood (e.g., around half of all mental disorders emerge before the age of 15 and around three fourth by the age of 18) [8, 9]. They are often characterized by transitional staging processes from subclinical to clinical severity [10], as highlighted by clinical staging models [11, 12], and have an estimated lifetime prevalence of around 18-36% [8, 13, 14]. It is therefore crucial to disrupt illness trajectories at a developmentally early stage [15-17] and to further expand the reach of, and developing innovative strategies for, mental health services, including the provision of easily accessible, person-centred, non-stigmatizing mental health care as well as mental health promotion and prevention programs in diverse communities and settings [18-20].

Despite decades of extensive biopsychosocial research on mental health and significant individual suffering and societal costs, contemporary aetiological models for most psychopathologies continue to fall short of accurately predicting disease onset or determining individual pathways to poor mental health, including whether signs and symptoms will improve or worsen over time [21-25]. Moreover, many individuals continue to have residual symptoms after treatment completion and relapse rates are staggering high, especially for severe mental disorders [26]. In fact, in contrast to many other medical disciplines (e.g., oncology, cardiology), there are no reliable biomarkers that can be used to accurately index the risk for, or the presence of, mental disorders [27, 28]. The sheer complexity of studied constructs, which continues to grow as methodological sophistication increases, appears to significantly complicate, rather than facilitate, significant advancements in the development of more effective non-pharmacological and pharmacological treatments [29-33]. Thus, even with intensive global research efforts, the likelihood that a person in need of care will feel better following treatment - perhaps the most valid of all success criteria - has remained relatively stable in recent years for most mental disorders [34, 35].

Some of the challenges mental health research is currently facing may be explained in part by fundamental problems with the way the dominant traditional medical model conceptualizes mental disorders [21, 29, 36]. This involves the persistent belief that mental disorders (1) are classifiable disease entities that differ markedly from one another and are unambiguous in their phenotypic representation and biological correlates, (2) are associated with disease-specific mechanisms and risk factors, (3) are qualitatively distinct from subclinical expressions of poor mental health, and that (4) findings on mechanisms and outcomes originated from experimental studies are ecologically valid and generalizable to mental health problems in real-life contexts and everyday situations. In contrast to these views, however, accumulating evidence lends evidence that mental disorders share a high degree of overlap at the (poly-)genetic [37-39], biological systems [40-42], and symptom level [24, 43-46], that most socio-environmental risk factors are non-specifically impacting mental health outcomes [47-50], and findings from research labs do not always translate to real-world settings [51-54].

To help address some of these challenges, efforts have been made to (i) understand psychopathologies more dimensionally, cutting across traditional diagnostic boundaries described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) [55-57], (ii) advocate and systematically study concepts of mental ill-health continua and spectra and the clinical utility of staging models [12, 58-60], (iii) investigate the effects of exposure to socio-environmental risk and resilience factors on transdiagnostic extended phenotypes [61-63], (iv) identify transdiagnostic candidate mechanisms which have been found to be non-specifically associated with a range of mental health outcomes [23, 24, 46, 64], (v) examine how mental health problems unfold in, and are associated with, specific contexts in the flow of daily life to increase ecological validity and generalisability, enabling ecological translation of findings to real-life contexts [51, 52, 65-67], and (vi) develop, evaluate, and implement novel transdiagnostic intervention strategies encompassing the full spectrum of public mental health provision (i.e., mental health promotion, prevention, and treatment of mental disorders) [65, 68, 69].

This thesis builds on these recent developments in order to extend the body of existing knowledge. The theoretical foundation described in this chapter lays the groundwork for the remainder of thesis.

The extended transdiagnostic psychosis phenotype

In line with developments towards a more dimensional understanding of mental disorders, the extended and transdiagnostic psychosis phenotype has been proposed [46, 57]. This has been based on findings that psychotic experiences - the subclinical expression of psychotic symptoms, which includes subtle manifestations of delusional ideations, hallucinations or thought problems - are common in the general population [46, 70-72] and frequently co-occur with, or are preceded by, forms of affective dysregulation (e.g., depression, anxiety) [73-76]. This also corroborates findings on frequent comorbidity between affective disorders and psychosis spectrum disorders in diverse clinical settings [73] as well as findings on overlapping genetic liability [38]. Psychotic experiences have also been found to be bidirectionally associated with other mental disorders [77], suggesting that they may not only represent an indicator of early psychosis in some cases, but also an important risk marker for a wide range of non-psychotic mental disorders [23, 76-78].

Contemporary models of psychosis emphasize the role of cognitive factors, including biases, schemas, and cognitive deficits, in illness trajectories by implying their contribution to the transformation of experiences of aberrant salience (i.e., characterized by placing inappropriate significance on neutral events, external objects, or internal representations) into psychotic symptoms [79-81]. More specifically, individuals' perception of, and responses to, these excessively vivid experiences are thought to be influenced by cognitive factors and may therefore be critical for the transition from subclinical to clinical severity [81-84]. Cognitive factors have also been found to influence the perception of events as threatening and externally caused [83, 85], further strengthening their potential role in the exacerbation of psychotic symptoms over time [86, 87]. Thus, seeing and interpreting the world around us is heavily influenced by cognitive factors, which are influenced by a multitude of biopsychosocial risk and resilience factors.

One of the most comprehensively studied cognitive factor in psychosis is the jumping to conclusions (JTC) bias [88-90]. The JTC bias is characterised by making hasty decisions based on insufficient information and has consistently been found to occur more often in individuals with subclinical or clinical psychosis when compared to comparison subjects and individuals with other mental health conditions, including affective disorders [90]. This suggests that the JTC bias may be specifically association with psychosis and not with frequently co-occurring affective dysregulations. Further, it has been proposed that the JTC bias may contribute to the formation and persistence of delusional ideations, but recent meta-analytic evidence has been inconsistent [91]. Similarly, cognitive deficits, such as a decreased working memory performance, have been shown to be more likely to occur in individuals with psychosis as compared to controls [92, 93], while there is, in contrast to the JTC bias, no evidence supporting the notion of specificity as cognitive deficits have been shown to be associated with various psychopathological domains [94, 95].

However, it is currently unknown whether these well-established cognitive factors for psychosis are also associated with a transdiagnostic psychosis phenotype of co-occurring affective dysregulation and psychotic experiences and whether the JTC bias contributes to the progression and persistence of psychosis over time, as proposed by contemporary aetiological models [81, 83].

Adverse childhood experiences and mental health

In addition to cognitive factors, exposure to adversity has been found to be associated with poor mental health outcomes. Most prominently, the effects of adverse childhood experiences (ACEs) on mental health have extensively been studied over the recent years. ACEs, a specific type of socio-environmental risk, are defined as highly stressful events or situations that occur early in life and are potentially traumatic. They may occur as a single traumatic event (e.g., negative life events like a severe car accident) or as ongoing threats (e.g., bullying victimization in school settings or sexually abusive family members) that jeopardize a young person's safety, trust, and bodily integrity and, thus, require significant social, emotional, neurobiological, and behavioural adaptation [96]. There has been large body of research robustly showing that exposure to ACEs, including childhood trauma and bullying victimization, is associated with a 2 to 3 times increased risk for developing a range of mental disorders, including depression [97, 98] and psychosis [99-102]. Although earlier work proposed specific adversity-psychopathology (e.g., more intrusive forms of childhood trauma may be more strongly linked to an increased risk for experiencing delusional ideations as compared to other outcomes) as well as time-of-exposure-outcome (e.g., effects on mental health are more severe if exposure occurs in early childhood) associations, more recent studies suggest that effects of ACEs appear to be non-specific, such that any form of ACEs, and at any time during childhood, is associated with a range immediate and prolonged poor mental health [101, 103-106]. There are some studies, however, which provide some evidence for time sensitivity of exposure on outcome [107-110]. There has also been strong evidence of dose-response relationships and cumulative effects, implicating that higher levels as well as greater numbers of exposure to ACEs progressively increase the likelihood of developing mental health problems [101, 111-114]. Studies have also demonstrated that exposure to ACEs mostly clusters in a relatively small number of individuals, leading to high rates of poly-victimization in those exposed to any form of ACEs [115-118]. The experience of ACEs is also prevalent in the society, ranging from an estimated lifetime prevalence of around 30% for bullying victimization [119] to around 12% for sexual abuse [120], although prevalence estimates strongly differ by type, sex, and country.

Stress sensitive as a candidate mechanism linking adversity and mental health

While there is compelling evidence that cognitive factors and ACEs are associated with mental disorders, little is known about underlying mechanisms, especially in the realm of youth mental health. It is quite unlikely, however, that the various types of ACEs are linked to as many different mechanisms. It is more likely that there are shared common pathways, or candidate mechanisms, which can be studied across various levels of investigation (e.g., biological, behavioural, cognitive). The most widely studied mechanism is behavioural sensitization [121], which posits that repeated exposure to ACEs leads to a gradual increase of individuals' stress response to subsequent adversities as well as minor stressors in daily life. Hence, stress sensitivity, sometimes also referred to as stress reactivity, may be a putative mechanism linking exposure to ACEs and mental health outcomes and may be contributing to a vicious cycle of poor mental health outcomes over time [121].

There are several ways to investigate whether individuals who were exposed to ACEs are more sensitive towards stress. On the behavioural level, the Experience Sampling Method (ESM) [122] or Ecological Momentary Assessment (EMA) [123] can be used. ESM is a powerful self-report diary technique [52] which allows for assessing appraisals of subjective experiences, symptoms, and minor stressful events in daily life with high ecological validity. This method is particularly well suited to test the proposition that those exposed to ACEs have a higher stress sensitivity by investigating whether exposure to ACEs is associated with increased sensitivity to stress. More specifically, in a frequently used ESM study design, individuals are prompted 10 times a day over 6 consecutive days to fill in short questionnaires on their smartphone or personal digital assistant. This fine-grained ESM-data (i.e., up to 60 assessment points per person when using described sampling scheme) can be used to approximate individuals' stress sensitivity by looking at individual's affective response (e.g., increase in negative affect) to minor daily stressors (e.g., event-related or social stress) in daily life [124].

There have been several studies that have investigated whether individuals' response to stress is modified by prior exposure to ACEs. Overall, these findings consistently suggest that individuals with depression, an at-risk mental state for psychosis, and psychotic disorders who were exposed to childhood trauma (e.g., physical abuse) or negative life events (e.g., parental separation) showed an elevated stress sensitivity in daily life [125-127]. This supports the notion that stress sensitivity may be an important transdiagnostic mechanism linking adversity and mental health outcomes in diverse clinical samples. However, there have been no studies that specifically investigated the effects of bullying victimization on stress sensitivity in help-seeking individuals and evidence of the effects of negative life events on stress sensitivity is scarce. Moreover, all studies examining the effects of various types of ACEs on stress sensitivity have exclusively included samples of help-seeking adults. As a result, it is currently unknown whether reported findings also generalize to young help-seeking individuals at developmentally early stages of psychopathology.

From candidate mechanism to novel treatment targets

As exemplified by reported findings, ESM is a powerful tool to investigate how adversity and other forms of socio-environmental risk may impact mental health outcomes in daily life through transdiagnostic candidate mechanisms. There have been recent efforts to translate these findings to inform novel intervention strategies, most notably Ecological Momentary Interventions (EMIs) [128]. EMIs are a promising approach for targeting transdiagnostic candidate mechanisms, including stress sensitivity [68], and mental health outcomes in daily life using mobile devices. More specifically, while principles of ESM emphasize that psychological experiences, behaviours, and outcomes are highly dynamic and best understood and studied in everyday contexts, EMIs purposefully build on these theoretical foundations by inferring that mechanisms and outcomes may also be best modifiable in everyday contexts and situations, outside clinicians' office [65] (See Figure 1).

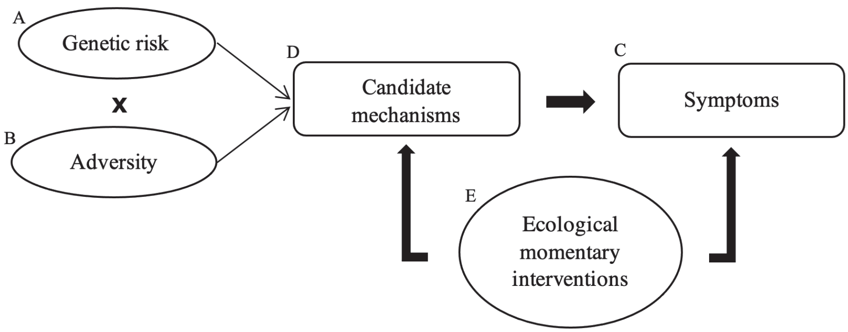

Figure 1. Simplified schema of how adversity impacts mental health through biopsychosocial candidate mechanisms. Genetic risk (A) and adversity (B), and their interaction (X), impact on symptoms (C) through candidate mechanisms (D). This may be directly targeted on the behavioural level using ecological momentary interventions (E) in real-life contexts by using cutting-edge digital technologies.

Most EMIs that have been developed and evaluated to date have been delivered using dedicates applications on the smartphone [129-132]. Thus, as rates of smartphone ownership are high and in close proximity to users, EMIs allow various possibilities to reach individuals in their natural environments in which mental health problems occur [65] and to directly test ecological interventionist causal models [66]. They also enable adaptive, real-time, and real-world delivery of intervention components in daily life at the right time and context by real-time processing of ESM data [65]. However, there is currently only very limited evidence that have demonstrated the feasibility and safety of EMIs and initial therapeutic effects on candidate mechanisms and mental health outcomes in young help-seeking individuals.

The recent surge of digital intervention

The rapid technological advances have not only contributed to the development and evaluation of EMIs, a specific type of digital interventions [68], but also a plethora other forms of technology enabled mental health services [133], which offer ample of possibilities for the digitalisation and personalisation of mental health care [134]. In this context, telemedical and internet-based (eHealth) interventions and smartphone-based mobile health (mHealth) interventions play a particularly important role as they enable low-threshold and real-time delivery of evidence-based psychological interventions that can be tailored to individual needs and preferences [65, 67, 135]. Moreover, over the recent years, other technologies have gained traction, including wearables and virtual reality (VR) devices, that are increasingly being used for the delivery of digital interventions for the prevention and treatment of various mental disorders as well as mental health promotion [136-138]. These numerous types of digital interventions could contribute to further personalise existing mental health services, thereby improving clinical and social outcomes and lowering direct and indirect costs. However, the number of studies that have synthesized the available evidence across the whole spectrum of public mental health provision is very limited.

COVID-19 pandemic and public mental health

In the first quarter of 2020, the majority of European countries implemented a variety of public health measures to combat the spread of the SARS-CoV-2 coronavirus. Physical distancing and quarantine have been among the most effective measures used to reduce infection rates. However, these preventive measures may have negative consequences on public mental health [139]. Digital inventions may be particularly helpful for providing mental health promotion and prevention programs at the population level and to ensure continued mental health care [67]. However, the evidence whether public health measures have negative psychosocial consequences on public mental health remains inconclusive, particularly among youth, and evidence-based recommendations on the use of existing eHealth and mHealth interventions developed and evaluated in recent years are currently lacking, potentially impeding the development and implementation of digital strategies for public mental health. This strongly hinders the evidence-based development and implementation of digital strategies for improving public mental health during this unparalleled public health crisis [67].

Aims and outline of this thesis

The overall aim of this thesis is twofold. First, the thesis aims to investigate how adverse childhood experiences, cognitive factors, and candidate mechanisms confer risk for developing transdiagnostic phenotypes of depression, anxiety, and psychosis (**Part 1**). Second, the thesis aims to explore to what extend digital interventions hold promise for, and are currently being used to, alleviating mental health burden in public mental health provision (i.e., mental health promotion, prevention of, and treatment for mental disorder) (**Part 2**).

More specifically, the studies presented in this thesis investigated the following aims:

Part 1

Chapter 2 investigates associations of the jumping to conclusions bias and decreased working memory performance with co-occurring affective disturbances and psychotic experiences in the general population.

Chapter 3 extends the knowledge base of **chapter 2** and further investigates whether the JTC bias contributes to psychosis progression and persistence in the general population.

Chapters 4, 5, and 6 examine whether the exposure to various types of ACEs, that is, (i) childhood trauma, (ii) bullying victimisation, and (iii) negative life events, amplifies individuals' sensitivity to stress in a sample, of help-seeking adolescents and young adults with high levels of depressive, anxiety and psychotic symptoms, their biological siblings, and comparison subjects.

Part 2

Chapter 7 builds on findings of preceding chapters on the role of stress sensitivity in the realm of youth mental health and investigates, in an uncontrolled phase I pilot study, the feasibility, safety, and initial therapeutic effects of a novel, accessible, transdiagnostic, ecological momentary, compassion-focused intervention for improving emotional resilience to stress ('EMIcompass') in help-seeking youth with psychotic, depressive, and/or anxiety symptoms.

Chapter 8 explores the clinical potential of emerging digital technologies, such as smartphones, smartwatches, fitness trackers and head-mounted displays, for helping individuals with subclinical expressions of psychosis as well as psychosis spectrum disorder.

Chapters 9 and 10 examine the COVID-19 pandemic and its consequences on youth mental health as well as the use of digital technologies. More specifically, **Chapter 9** investigates the associations between social isolation, COVID-19-related cognitive preoccupation, worries, and anxiety, objective social risk indicators, and psychological distress, as well as use of, and attitude toward, mobile health (mHealth) interventions in youth. **Chapter 10** systematically synthesises the theoretical and empirical base, user perspective, safety, effectiveness, and cost-effectiveness of digital interventions related to public mental health provision (i.e., mental health promotion, prevention, and treatment of mental disorders) that may help to reduce the consequences of the COVID-19 pandemic.

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PART 1

Cognition and mechanisms in transdiagnostic phenotypes

CHAPTER 2

Reasoning bias, working memory performance, and a transdiagnostic phenotype of affective disturbances and psychotic experiences in the general population

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Abstract

Background: The jumping to conclusions (JTC) reasoning bias and decreased working memory performance (WMP) are associated with psychosis, but associations with affective disturbances (i.e. depression, anxiety, mania) remain inconclusive. Recent findings also suggest a transdiagnostic phenotype of co-occurring affective disturbances and psychotic experiences (PEs). This study investigated whether JTC bias and decreased WMP are associated with co-occurring affective disturbances and PEs.

Methods: Data were derived from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2). Trained interviewers administered the Composite International Diagnostic Interview (CIDI) at three time points in a general population sample (N = 4618). The beads and digit-span task were completed to assess JTC bias and WMP, respectively. CIDI was used to measure affective disturbances and an add-on instrument to measure PEs.

Results: Compared to individuals with neither affective disturbances nor PEs, the JTC bias was more likely to occur in individuals with co-occurring affective disturbances and PEs [moderate psychosis (1–2 PEs): adjusted relative risk ratio (RRR) 1.17, 95% CI 0.98–1.41; and high psychosis (3 or more PEs or psychosis-related help-seeking behaviour): adjusted RRR 1.57, 95% CI 1.19–2.08], but not with affective disturbances and PEs alone, whereas decreased WMP was more likely in all groups. There was some evidence of a dose–response relationship, as JTC bias and decreased WMP were more likely in individuals with affective disturbances as the level of PEs increased or help-seeking behaviour was reported.

Conclusion: The findings suggest that JTC bias and decreased WMP may contribute to a transdiagnostic phenotype of co-occurring affective disturbances and PEs.

Keywords: Anxiety; depression; cognitive bias; cognitive deficits; jumping to conclusions; mania; psychosis; reasoning bias; transdiagnostic phenotype; working memory

Introduction

Psychotic experiences (PEs) are common [1, 2], with an estimated lifetime prevalence of 7%, but transitory for most individuals [3]. However, PEs persist in around 20% and evolve into a psychotic disorder in about 7% [3-6]. Recent findings also suggest that PEs frequently co-occur with symptoms of common mental disorders (i.e. depression, anxiety) [7-12] and that the degree of co-occurrence may be influenced by exposure to socio-environmental risk [13-15]. In line with these findings, the polygenic risk score for schizophrenia has been shown to be associated with PEs and affective disturbances in relatives of individuals with psychotic disorder and comparison subjects [16] and developmental psychopathology in children and adolescents [17-19]. This was further supported by a considerable overlap of genetic liability and molecular neuropathology between psychotic disorders and affective disorders [20-26]. Thus, evidence suggest an extended and transdiagnostic psychosis phenotype with temporal and phenomenological continuity across developmental stages of psychotic and affective disorders and shared socio-environmental and genetic risk [1, 2, 27-29].

Contemporary models of psychosis [30-33] propose various risk factors and mechanisms involved in illness onset, including cognitive biases and deficits, but whether these factors are also associated with transdiagnostic phenotypes remains largely under-researched. The jumping to conclusions (JTC) reasoning bias describes the tendency to make hasty decisions based on insufficient information [34] and has been consistently found to occur more often in individuals with subclinical and clinical psychosis [34-37]. Based on cognitive models [38, 39], it has been suggested that the JTC bias is particularly involved in the formation and maintenance of delusional ideations [35, 40], with some recent evidence supporting this assumption [34]. Similarly, cognitive deficits have been demonstrated across severity levels of psychosis, which is considered a core finding supporting the neurodevelopmental hypothesis [41, 42], with several studies focussing on decreased working memory performance (WMP) as a proxy for cognitive deficits [43-52].

In contrast, there have been inconsistent findings for the presence of both the JTC bias and decreased WMP in non-psychotic disorders. A recent meta-analysis found some evidence that the JTC bias was more likely in individuals with non-psychotic disorders [37]. However, effect sizes varied considerably across studies and those of low quality reported the strongest effects. After outliers were excluded from analyses, no effects for depression, anxiety disorders, and obsessive-compulsive disorders were found. Similarly, studies investigating decreased WMP in those with non-psychotic disorders are mixed and the evidence differs largely across domains of psychopathology. There is evidence for decreased WMP in individuals with subclinical and clinical anxiety [53], while findings for depression and mania appear to be more heterogeneous with some studies reporting a lowered [54, 55], and others a similar WMP [56-58] compared to controls.

Taken together, there is robust evidence that JTC bias and decreased WMP are associated with psychosis, but attempts to show similar associations in individuals with affective disturbances have led to mixed results. As there is evidence that affective disturbances and PEs frequently co-occur in general population and clinical samples, an important next step is to investigate whether the JTC bias and decreased WMP contribute to a transdiagnostic phenotype. It is reasonable to assume that risk factors and mechanisms proposed in contemporary models of psychosis [30-33] extend to individuals with affective disturbances if they are accompanied by PEs, which may give rise to generalisability and specificity of recent findings.

Aims and hypotheses

The aim of the current study was to investigate associations of the JTC bias and decreased WMP with co-occurring affective disturbances and PEs in the general population. More specifically, we tested the following hypotheses: First, compared to individuals with neither affective disturbances nor PEs (group 1), the JTC bias is more likely to occur in those with sole presence of PEs (group 3) and in those with co-occurring affective disturbances and PEs (further stratified into moderate psychosis=1-2 PEs (group 4); and high psychosis=3 or more PEs or psychosis-related help-seeking behaviour (group 5)), but not in those with sole presence of affective disturbances (group 2). Second, decreased WMP is associated with an increased likelihood of reporting sole presence of affective disturbances (group 2), sole presence of PEs (group 3) and co-occurring affective disturbances and PEs (group 4 and group 5). Third, there is evidence for a dose-response relationship, in which the JTC bias and decreased WMP is more likely to occur in those with affective disturbances as the level of PEs increases or individuals report psychosis-related help-seeking behaviour (comparing group 5 and group 4).

Materials and methods

Sample

Data were derived from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), a three-wave psychiatric epidemiological cohort study conducted to estimate the prevalence, incidence, and course of psychiatric disorders in the Dutch general population. Based on a multistage, stratified random sampling of households, all respondents were interviewed at home with the Composite International Diagnostic Interview (CIDI) version 3.0 [59-61] and additional questionnaires. Inclusion criteria were: aged 18-65 years. Exclusion criteria were: insufficient command of the Dutch language. The first wave (T0) was performed from November 2007 to July 2009, with a total of 6646 persons interviewed (response rate 65.1%). This sample was representative for the Dutch general population although younger subjects were slightly underrepresented [62]. For the second wave (T1), performed from November 2010 to June 2012, all T0 respondents were approached. Of these, 5303 individuals were interviewed again (response rate of 80.4% with those deceased excluded). The attrition rate was not associated with 12-month prevalence of psychopathology at baseline [63]. From November 2013 to June 2015, the third wave (T2) was completed with 4618 persons who were interviewed a third time (response rate of 87.8% from T1 with those deceased excluded). Again, attrition rate was not associated with the 12-month prevalence of mental disorders at T1, except for alcohol and drug dependence and bipolar disorder [64]. The time between baseline and second follow-up was, on average, 6 years and 6 days. The study was approved by the Medical Ethics Review Committee for Institutions of Mental Health Care. After having been informed about the study aims, respondents provided written informed consent at each wave. The face-to-face interviews were carried out by trained interviewers, who were not clinicians, using a laptop computer. A more detailed description of the methodology is presented elsewhere [62, 65].

Data collection

Sociodemographic characteristics and socio-environmental factors

Data on age, sex, level of education, urbanicity, ethnic minority status, cannabis use, and childhood trauma were collected using a sociodemographic schedule, trauma questionnaire, and the CIDI.

Working memory performance

At the second wave (T1), participants were asked to complete the digit-span task to assess working memory performance. The procedure and items were based on the Wechsler Adult Intelligence Scale (WAIS-III) [66, 67]. The digit-span task was divided into two parts, consisting of a forward (6 items) and backward (6 items) task condition. Both parts were separated by three unrelated interview sections. For each item, participants were asked to repeat two different sequences of digits, spanning from 4 to 9 digits for the forward and 3 to 8 digits for the backward condition. If at least one out of two sequences was repeated correctly, the interviewer moved to the next item. For each completed item, one digit was added to increase difficulty. Scores were based on the number of correct answers and up to 4 (forward condition) and 2 (backward condition) extra points. For study purposes, the sum score was computed and transposed to T0 and T2 as performance at T1 was considered to represent individuals' trait cognitive ability.

JTC bias

As part of the third wave (T2), the beads task was completed to assess the presence or absence of the JTC bias. The beads task [68] is an experimental task designed to measure individuals' reasoning style under ambiguous conditions. Participants were shown two jars containing red and blue coloured beads in opposite ratios. In this study, the more difficult version of the beads task with a colour ratio of 60:40 beads was used to increase sensitivity to detect JTC bias in a general population sample. The jars as well as all instructions were presented on a computer screen. After both jars were shown and a training session was completed, participants were instructed that all beads are drawn consecutively from one jar and, once presented, are returned to the same jar. After each draw, participants were asked whether they want to make a decision from which jar the beads were drawn or if they would like to see another bead, with the possibility to see up to 10 beads before a decision had to be made. The order of presented beads was predetermined and the dominant colour presented in the training session selected at random. Again, the number of beads drawn at T2 was considered to represent individuals' reasoning style and the values were transposed to T0 and T1. Consistent with previous studies [34], JTC bias was defined as making a decision based on two or fewer beads [37].

Affective disturbances

Depression, anxiety, and mania were measured at three time points using core items of the CIDI version 3.0. This measure uses a true-false response format asking for the prevalence of symptoms for various mental disorders, including depressive episode, social phobia, generalised anxiety disorder, and manic episode (e.g. feeling fearful, depressed, experiences of a panic attack). All items are presented in Supplementary Table 1.

Psychotic experiences (PEs)

Studies concluded that earlier versions of the CIDI are not reliable and valid measures for psychotic disorders [69]. Thus, a psychosis measure was constructed based on the section of psychotic symptoms in CIDI 1.1. The instrument consisted of 20 items asking for the lifetime prevalence of PEs (i.e. 15 delusional and 5 hallucinatory experiences). In case PEs were endorsed, participants were asked to state, on a 4-point Likert scale, the frequency, distress, and the impact of PEs on their daily life, including whether they had sought help for these experiences. Sum scores were calculated by adding reported PEs. More details are described elsewhere [13] and used items are reported in Supplementary Table 1.

Grouping absence, presence and co-occurrence of affective disturbances and psychotic experiences

Individuals were grouped based on answers given on measures assessing depression, anxiety, mania, and PEs. Five groups were generated representing the absence, sole presence, or co-occurrence of affective disturbances and PEs: neither affective disturbances nor PEs (group 1); sole presence of affective disturbances (group 2); sole presence of PEs (group 3); co-occurring affective disturbances and PEs (further stratified into moderate psychosis=1-2 PEs (group 4); and high psychosis= 3 or more PEs or psychosis-related help-seeking behaviour (group 5)).

Statistical analysis

All analyses were carried out using STATA version 13.1 [70]. As the digit-span task and beads task were completed at T1 and T2, respectively, analyses were performed on samples with differing numbers of observations. First, socio-demographic characteristics (i.e. age, sex, education level) and socio-environmental factors (i.e. urbanicity, ethnic minority status, cannabis use, and childhood trauma) were compared across groups using linear regression and chi-square tests as appropriate. Second, to investigate associations of JTC bias (binary variable) and working memory performance (continuous variable) with co-occurring affective disturbances and PEs, the MLOGIT command was used to fit multinomial logistic regression models. The CLUSTER option was used to compute cluster-robust standard errors to correct for clustering of data (i.e. three observations for each individual). Sum scores of the digit-span task were recoded that higher scores represent lower WMP and standardized (mean=0, SD=1). Lastly, relative risk ratios (RRRs) for group status by JTC bias and decreased WMP were compared using the Wald test. All models were adjusted for various a priori defined potential confounders. First, we adjusted for socio-demographic characteristics and socio-environmental factors and, in models with JTC bias as the independent variable, we also adjusted for WMP.

Results

Basic sample characteristics

In total, thqe sample consisted of 4618 participants at the third wave. Of these, 4596 completed the beads task (99.5%) with 13788 observations for all three timepoints. There were no differences between individuals who completed the beads task and those who did not with regard to socio-demographic characteristics and other variables. The sample characteristics are presented in Table 1. Overall, individuals who reported affective disturbances and/or PEs were more likely to be younger, female, less educated, more often from an ethnic minority group, to have used cannabis regularly at least once during lifetime, and to have experienced childhood trauma before the age of 16. There were considerable differences between those with sole presence of affective disturbances and co-occurring affective disturbances and PEs in terms of most sample characteristics and socio-environmental risk factors. Basic characteristics of the sample of individuals who completed the digit-span task at T1 are presented in Supplementary Table 2.

Table 1. Basic characteristics of groups derived from 4596 participants

Overall number of observations (*N*= 13788)	**Group 1: No symptoms (*N*= 6439)**	**Group 2: Affective disturbance (*N*= 5965)**	**Group 3: Psychotic experience (*N*= 240)**	**Group 4: Affective disturbance + moderate psychosis [f] (*N*= 798)**	**Group 5: Affective disturbance + high psychosis [f] (*N*= 346)**	**test statistics**	**p**
Age (years), mean (S.D.)	49.5 (12.7)	46.6 (12.2)	47.8 (12.5)	45.8 (12.5)	43.9 (12.5)	F= 35.92, df= 4	<0.001
Gender, n (%)							
male	3204 (49.8)	2435 (40.8)	97 (40.4)	275 (34.5)	133 (38.4)	χ^2 = 144.06, df= 4	<0.001
female	3235 (50.2)	3530 (59.2)	143 (59.6)	523 (65.5)	213 (61.6)		
Level of education, n (%)							
primary	240 (3.7)	240 (4.02)	10 (4.2)	49 (6.1)	16 (4.62)	χ^2 = 88.36, df= 12	<0.001
lower secondary	1632 (25.4)	1493 (25.0)	72 (30.0)	238 (29.8)	117 (33.8)		
higher secondary	1999 (31.1)	1909 (32.0)	87 (36.3)	291 (36.5)	127 (36.7)		
higher professional	2568 (39.9)	2323 (38.9)	71 (29.6)	220 (27.6)	86 (24.9)		
Urbanicity [a, g]							
countryside	657 (10.2)	498 (8.4)	26 (10.8)	62 (7.8)	23 (6.7)	χ^2 = 43.44, df= 16	<0.001
village	2594 (40.3)	2308 (38.7)	102 (42.5)	306 (38.4)	123 (35.6)		
small city	827 (12.9)	768 (12.9)	36 (15.0)	103 (12.9)	60 (17.3)		
medium city	966 (15.0)	1017 (17.1)	33 (13.8)	131 (16.4)	64 (18.5)		
big city	1389 (21.6)	1369 (23.0)	43 (17.9)	195 (24.5)	76 (22.0)		
Minority status [b]							
yes	356 (5.5)	14 (5.8)	391 (6.6)	70 (8.8)	42 (12.1)	χ^2 = 35.29, df= 4	<0.001
no	6083 (94.5)	226 (94.2)	5574 (93.5)	728 (91.2)	304 (87.9)		
Regular cannabis use [c, g]							
yes	36 (0.6)	160 (2.8)	4 (1.7)	38 (5.0)	28 (8.6)	χ^2 = 193.37, df= 4	<0.001
no	6299 (99.4)	5593 (97.2)	234 (98.3)	725 (95.0)	296 (91.4)		
Childhood trauma (80th perc.) [d]							
yes	689 (10.7)	1.318 (22.1)	47 (19.6)	265 (33.2)	162 (46.8)	χ^2 = 620.57, df= 4	<0.001
no	5750 (89.3)	4647 (77.9)	193 (80.4)	533 (66.8)	184 (53.2)		

Table 1. (continued) Basic characteristics of groups derived from 4596 participants

Overall number of observations (*N*= 13788)	**Group 1: No symptoms (*N*= 6439)**	**Group 2: Affective disturbance (*N*= 5965)**	**Group 3: Psychotic experience (*N*= 240)**	**Group 4: Affective disturbance + moderate psychosis [f] (*N*= 798)**	**Group 5: Affective disturbance + high psychosis [f] (*N*= 346)**	**test statistics**	**p**
Draws to decision							
mean (SD)	2.1 (2.6)	2.1 (2.6)	1.9 (2.4)	1.9 (2.4)	1.7 (2.3)	F= 4.10, df= 4	0.003
Working memory performance [e, g]							
mean (SD)	20.0 (3.9)	20.2 (3.8)	21.1 (3.6)	20.9 (3.9)	21.1 (4.0)	F= 11.86, df= 4	<0.001
Distribution of affective disturbances (n, %)							
Depression	-	4180 (70.1)	-	616 (77.2)	297 (85.8)	-	-
Anxiety	-	4414 (74.0)	-	657 (82.3)	314 (90.8)		
Mania	-	2209 (37.0)	-	374 (46.9)	210 (60.7)		

Note: Data with an overall number of 13788 observations from surveys of 4596 participants who completed all assessments at all three time-points (T0, T1, T2), including the beads task

[a] defined as exposure to urban environment until the age of 16 years, classified based on Dutch classification data of population density: countryside (large distance to amenities), village (<25.000 inhabitants), small city (25000 – 50000 inhabitants), medium city (50000 – 100000 inhabitants), and larger cities (>100000 inhabitants)

[b] born in any other country than The Netherlands

[c] regular cannabis use was based on the section of Illegal Substance Use from CIDI 3.0. A pattern of use of once per week or more during lifetime (T0) or previous 3 years (T1, T2) were used as the cut-off score

[d] based on sum scores of items asking for five types of childhood trauma before the age of 16: two incidents or more of emotional neglect (i.e. not listened to, ignored or unsupported), physical abuse (i.e. kicked, hit, bitten or hurt with object or hot water), psychological abuse (i.e. yelled at, insulted, unjustly punished, treated, threatened, belittled or blackmailed) or one incidence or more of sexual abuse (i.e. any unwanted sexual experience) and peer victimization (i.e. bullying). The childhood trauma sum score was dichotomized at the 80th percentile

[e] sum scores of the digit-span task (range 6-30) were recoded, such as high numbers indicate lower working memory performance and vice versa

[f] defined as: moderate psychosis, 1-2 psychotic experiences; high psychosis, 3 or more psychotic experiences or psychosis-related help-seeking behaviour

[g] number of missing values: urbanicity: 12 observations; cannabis use: 375 observations; working memory performance (digit-span task): 207 observations

Table 2. Results (relative risk ratios and 95% CI) on the association of JTC reasoning bias with all groups *Note:* df, degrees of freedom; CI, confidence interval; RRR, relative risk ratio

		Unadjusted Model 1		Model 2[a]		Model 3[b d]		Model 4[c, e]	
		RRR (95% CI)	p	adj. RRR (95% CI)	p	adj. RRR (95% CI)	p	adj. RRR (95% CI)	p
Lifetime psychiatric symptoms									
Group 1 (reference): no symptoms (*N*= 6.439)									
Reasoning bias									
absent (n, %)	*3.159 (49.1)*	1		1		1		1	
present (n, %)	*3.280 (50.9)*								
Group 2: affective disturbance alone (*N*= 5.965)									
Reasoning bias									
absent (n, %)	*2.923 (49.0.)*	1.00	0.957	1.06	0.202	1.05	0.317	1.03	0.492
present (n, %)	*3.042 (51.0)*	(0.92 – 1.09)		(0.97 – 1.15)		(0.96 – 1.14)		(0.94 – 1.13)	
Group 3: psychotic experiences alone (*N*= 240)									
Reasoning bias									
absent (n, %)	*105 (43.8)*	1.24	0.136	1.25	0.125	1.24	0.142	1.18	0.262
present (n, %)	*135 (56.2)*	(0.93 – 1.64)		(0.94 – 1.65)		(0.93 – 1.64)		(0.89 – 1.56)	
Group 4: Affective disturbance and moderate psychosis (*N*= 798)									
Reasoning bias									
absent (n, %)	*353 (44.2)*	1.21	0.027	1.25	0.012	1.23	0.023	1.17	0.088
present (n, %)	*445 (55.8)*	(1.02 – 1.44)		(1.05 – 1.49)		(1.03 – 1-48)		(0.98 – 1.41)	
Group 5: Affective disturbance and high psychosis (*N*= 346)									
Reasoning bias									
absent (n, %)	*135 (39.0)*	1.51	0.003	1.62	<0.001	1.66	<0.001	1.57	0.002
present (n, %)	*211 (61.0)*	(1.15 – 1.97)		(1.24 – 2.11)		(1.26 – 2.19)		(1.19 – 2.08)	

[a] Adjusted for socio-demographics (i.e. age, gender, level of education)
[b] Adjusted for socio-demographics and socio-environmental risk factors (i.e. urbanicity, minority status, cannabis use, and childhood trauma)
[c] Adjusted for socio-demographics, socio-environmental risk factors, and working memory performance

[d] test for differences in relative risk ratios across groups for Model 3:

	χ^2 **(df)**	*p*
affective disturbance only vs. *affective disturbance + moderate psychosis*	3.46 (1)	0.063
affective disturbance only vs. *affective disturbance + high psychosis*	11.23 (1)	<0.001
affective disturbance + moderate psychosis *affective disturbance + high psychosis*	4.10 (1)	0.043

[e] test for differences in relative risk ratios across groups for Model 4:

	χ^2 **(df)**	*p*
affective disturbance only vs. *affective disturbance + moderate psychosis*	2.05 (1)	0.153
affective disturbance only vs. *affective disturbance + high psychosis*	9.06 (1)	0.003
affective disturbance + moderate psychosis *affective disturbance + high psychosis*	3.78 (1)	0.052

Table 3. Results (relative risk ratios and 95% CI) on the association of working memory performance with all groups

	Unadjusted Model 1		Model 2[a]		Model 3[b, c]	
	RRR (95% CI)	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**
Lifetime psychiatric symptoms[g]						
Group 1 (reference): no symptoms (N= 6.901)						
Working memory performance	1		1		1	
Group 2: affective disturbance alone (N= 6.534)						
Working memory performance	1.03 (0.99 – 1.07)	0.169	1.06 (1.02 – 1.11)	0.004	1.06 (1.02 – 1.11)	0.006
Group 3: psychotic experiences alone (N= 261)						
Working memory performance	1.29 (1.22 – 1.48)	<0.001	1.28 (1.12 – 1.47)	<0.001	1.26 (1.09 – 1.45)	0.001
Group 4: Affective disturbance and moderate psychosis (N= 879)						
Working memory performance	1.23 (1.12 – 1.34)	<0.001	1.24 (1.13 – 1.37)	<0.001	1.21 (1.09 – 1.34)	<0.001
Group 5: Affective disturbances and high psychosis (N= 398)						
Working memory performance	1.33 (1.16 – 1.54)	<0.001	1.37 (1.17 – 1.60)	<0.001	1.31 (1.11 – 1.54)	0.001

Note: df, degrees of freedom; CI, confidence interval; RRR, relative risk ratio
[a] Adjusted for socio-demographics (i.e. age, gender, level of education)
[b] Adjusted for socio-demographics and socio-environmental risk factors (i.e. urbanicity, minority status, cannabis use, and childhood trauma)

[c] test for differences in relative risk ratios across groups for Model 3:

	χ^2 **(df)**	*p*
affective disturbance only vs. *affective disturbance + moderate psychosis*	7.01 (1)	0.008
affective disturbance only vs. *affective disturbance + high psychosis*	6.90 (1)	0.009
affective disturbance + moderate psychosis *affective disturbance + high psychosis*	0.88 (1)	0.349

JTC bias and co-occurring affective disturbances and PEs

As shown in Table 2 and Figure 1, there was evidence that, compared to individuals with neither affective disturbances nor PEs, JTC bias was more likely to be present in those with co-occurring affective disturbances and PEs (moderate psychosis: RRR=1.23, 95% CI 1.03 – 1.48, *p*=0.023; high psychosis: RRR=1.66, 95% CI 1.26 – 2.19, *p*<0.001), but not in those with sole presence of affective disturbances (RRR=1.05, 95% CI 0.96 – 1.14, *p*=0.317) and sole presence of PEs (RRR=1.24, 95% CI 0.93 – 1.64, *p*=0.142) after adjustment for age, sex, education level, urbanicity, ethnic minority status, cannabis use, and childhood trauma. When we additionally adjusted for working memory performance, the associations were attenuated (moderate psychosis: RRR=1.17, 95% CI 0.98 – 1.41, *p*=0.088; high psychosis: RRR=1.57, 95% CI 1.19 – 2.08, *p*=0.002). When we compared associations across groups, we found no significant differences in group 2 vs. group 4 (*p*=0.153), whereas significant differences were apparent in the comparison of group 2 vs. group 5 (*p*=0.003) and group 4 vs. 5 (*p*=0.052). Model fit statistics are provided in Supplementary Table 3.

Working memory performance and co-occurring affective disturbances and PEs

As shown in Table 3 and Figure 1, we found evidence that decreased WMP was more likely in individuals with sole presence of, or co-occurring, affective disturbances and PEs (affective disturbances: RRR=1.06, 95% CI 1.02 – 1.11, *p*=0.006; PEs: RRR=1.26, 95% CI 1.09 – 1.45, *p*=0.001; co-occurring affective disturbances and moderate psychosis: RRR=1.21, 95% CI 1.09 – 1.34, *p*<0.001; co-occurring affective disturbances and high psychosis: RRR=1.31, 95% CI 1.11 – 1.54, *p*<0.001) compared to those with neither affective disturbances nor PEs, after adjusting for socio-demographic characteristics and socio-environmental factors.

When we compared associations across groups, we found significant differences in group 2 vs. group 4 (*p*=0.008) and group 2 vs. group 5 (*p*=0.009), but not group 4 vs. group 5 (*p*=0.349). Model fit statistics are provided in Supplementary Table 3.

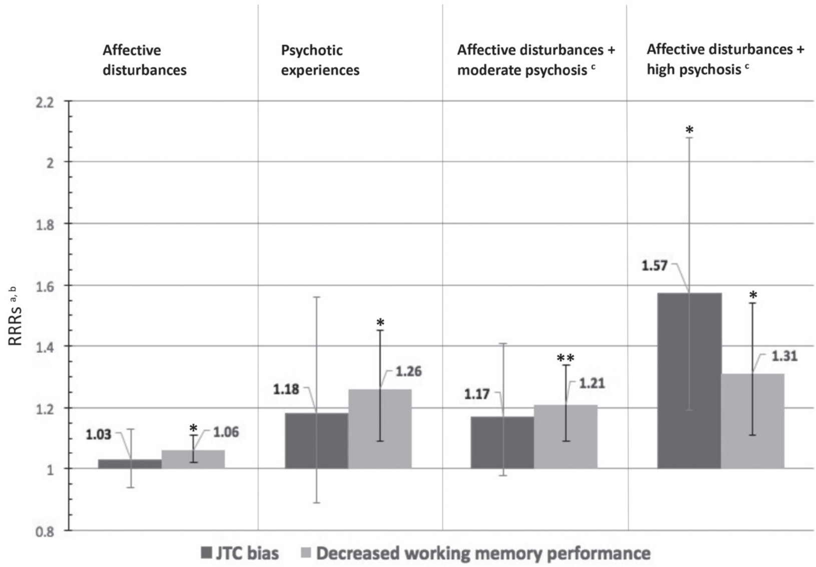

Figure 1. Results on the association of JTC reasoning bias and decreased WMP with all groups
Note: RRRs and 95% CI are shown; RRRs, relative risk ratios; CI, confidence interval; JTC bias, jumping to conclusions reasoning bias, WMP, working memory performance
* p<0.05, ** p<0.001
[a] adjusted for age, gender, level of education, urbanicity, minority status, cannabis use, and childhood trauma, and in models with JTC as independent variable also working memory performance
[b]compared to individuals with neither affective disturbances nor psychotic experiences (reference group RRR = 1)
cdefined as: moderate psychosis, 1-2 psychotic experiences; high psychosis, 3 or more psychotic experiences or psychosis-related help-seeking behaviour

Discussion

Main findings

This study investigated whether the JTC bias and decreased WMP are associated with a transdiagnostic phenotype of co-occurring affective disturbances and PEs in the general population. First, we found that the JTC bias was more likely to be present in individuals with co-occurring affective disturbances and PEs, but not in those with sole presence of affective disturbances or PEs. There was some attenuation of this association when we additionally adjusted for WMP. Second, decreased WMP was associated with an increased likelihood of reporting sole presence of and co-occurring affective disturbances and PEs. Third, there was some evidence of a dose-response relationship, as JTC bias and decreased WMP was progressively more likely to be present in individuals with affective disturbances as the level of PEs increased or psychosis-related help-seeking behaviour was reported, though some inconsistencies were observed for comparisons across groups.

Methodological considerations

The strength of the current study was that analyses were based on a large population-based cohort study. However, several methodological considerations should be taken into account before interpreting our findings. First, the number of individuals with JTC bias was greater than that reported in other studies [34]. We assume that assessment length may have resulted in fatigue effects and decreased motivation, leading to hastier decisions independent from individuals' reasoning style. However, this does not prevent us from inferring valuable insights given robust RRRs found in the current study. Second, the digit-span and beads task were assessed once during the study period and scores were considered to reflect trait cognitive ability and reasoning style. Ideally, tasks would have been completed at all three time points to calculate more robust estimates. However, assessment burden associated with the inclusion of both tasks at all three assessments was considered to be high and potential benefits comparably low, given reports of low variability for both the JTC bias [71, 72] and WMP [73] over time. Third, cross-sectional modelling of data derived from three waves did not allow for investigating temporality of JTC bias and decreased WMP with psychopathological outcomes. Future studies may employ longitudinal pathway analyses to further investigate the temporality of reported findings. Fourth, the transdiagnostic phenotypes of co-occurring affective disturbances and PEs were computed based on an observational and not a data-driven approach.

Comparison with previous research

We found that JTC bias is more prevalent in individuals who reported affective disturbances and PEs at least once during their lifetime compared to those who experienced neither affective disturbances nor PEs. This adds to recent findings of robust associations between JTC bias and psychosis [34-37] and suggests, for the first time, that JTC bias contributes to a transdiagnostic phenotype in the general population. This association, however, was found to be attenuated when we additionally adjusted for WMP, indicating that cognitive deficits may mediate, to a degree, the manifestation of reasoning style and its impact on mental health. This finding is in line with studies which have demonstrated altered neuropsychological functioning to be associated with JTC bias [74-76]. It has been suggested [43, 77] that JTC bias may partly be explained by difficulties in keeping information in mind but more studies are warranted to further investigate the role of cognitive deficits as an alternative explanation of the association between JTC bias, affective disturbances, and PEs. Echoing recent findings [37], there was no evidence that the JTC bias was more likely to be present in individuals who reported lifetime affective disturbances but not PEs.

When looking at differences across groups, we found some evidence for a dose-response relationship as the JTC bias was more likely to occur in individuals with affective disturbances as the number of PEs increased or psychosis-related help-seeking behaviour was reported. While these results suggest some degree of specificity of JTC bias for psychosis [37], some inconsistencies were observed. Critically, there was only weak evidence (at trend level) that JTC bias was more likely to be present in individuals with sole presence of PEs. This may be explained by potentially imprecise estimates as a result of the small number of observations in this group - the smallest of all (*N*= 240), which is a notable finding per se given psychosis has long been studied in isolation [27].

Similarly, there was some, albeit less strong, evidence for a dose-response relationship for the association between decreased WMP and affective disturbances and PEs. Interestingly, individuals who reported both affective disturbances and PEs showed a greater decrease in WMP compared to those with affective disturbances but not PEs. However, there were, again, some inconsistencies in group comparisons for this dose-response relationship. The finding of decreased WMP in those with sole presence of and co-occurring affective disturbances and PEs suggest that, as has recently been noted [78-81], cognitive deficits may constitute a more broadly distributed vulnerability factor across various (transdiagnostic) psychopathological domains.

Overall, reported findings point to the need to further investigate whether psychological processes and mechanisms involved in the development and maintenance of psychosis extend to transdiagnostic phenotypes in both general population and clinical samples to overcome shortcomings of focussing only on psychosis and to further corroborate contemporary aetiological models [27, 28]. Studies that do not exclude but purposefully allow for comorbidities are now warranted to facilitate progress in research, treatment, and aetiological models as well as dimensional and transdiagnostic approaches to psychopathology [28, 29, 82, 83] to achieve the goals set by the Research Domain Criteria [84].

Conclusion

Our findings suggest that JTC bias and decreased WMP may contribute to a transdiagnostic phenotype of co-occurring affective disturbances and PEs, with some evidence supporting specificity of JTC bias with psychosis. Future studies should further investigate specificity and generalisability of psychological processes and mechanisms to transdiagnostic phenotypes. Further, investigating putative mechanisms involved in the formation and maintenance of transdiagnostic phenotypes may be an important next step for the development of process-based treatment protocols [27, 28, 85-89] to, ultimately, alleviate individual's mental health burden.

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Supplementary material

Table S1. Items used to measure anxiety, depression, mania, and psychotic experiences

Psychopathological domain	
Anxiety (CIDI 3.0)	
Item 1	SC20[a] "Have you ever in your life had an attack of fear or panic when all of a sudden you felt very frightened, anxious, or uneasy?"
Item 2	SC20a [a] "Have you ever had an attack when all of a sudden you became very uncomfortable, either became short of breath, dizzy, nauseous, or your heart pounded, or you thought that you might lose control, die, or go crazy?"
Item 3	SC26[a] "Did you ever have a time in your life when you were a "worrier" – that is, when you worried a lot more about things than other people with the same problems as you?"
Item 4	SC26a[a] "Did you ever have a time in your life when you were much more nervous or anxious than most other people with the same problems as you?" SC26b[a] "Did you ever have a period lasting one month or longer when you were anxious and worried most days?"
Item 5	SC29[a] "Was there ever a time in your life when you felt very afraid or really, really shy with people, like meeting new people, going to parties, going on a date, or using a public bathroom?"
Depression (CIDI 3.0)	
Item 1	SC21[a] "Have you ever in your life had a period lasting several days or longer when most of the day you felt sad, empty or depressed?"
Item 2	SC22[a] "Have you ever had a period lasting several days or longer when most of the day you were very discouraged about how things were going in your life?"
Item 3	SC23[a] "Have you ever had a period lasting several days or longer when you lost interest in most things you usually enjoy like work, hobbies, and personal relationships?"
Mania (CIDI 3.0)	
Item 1	SC24[a] "Have you ever had a period lasting four days or longer when you became so happy or excited that you either got into trouble, people worried about you, or a doctor said you were manic?"
Item 2	SC25[a] "Have you ever had a period lasting four days or longer when most of the time you were very irritable, grumpy, or in a bad mood?"
Psychotic experiences	

Table S1. (continued) Items used to measure anxiety, depression, mania, and psychotic experiences

Item 1	"people were spying on you"
Item 2	„people were following you"
Item 3	"you were secretly being tested on"
Item 4	"someone was conspiring against you"
Item 5	"a 'double' had taken the place of a loved one"
Item 6	"someone was reading your mind"
Item 7	"you could hear the thoughts of others"
Item 8	"others could hear your thoughts"
Item 9	"alien thoughts were placed in your head"
Item 10	"someone took thoughts from your head"
Item 11	"special messages were sent to you through media"
Item 12	"you were influenced by strange energies"
Item 13	"you were being controlled by an outer force"
Item 14	"your thoughts were being influenced by machines"
Item 15	"any other delusion reported by subject"
Item 16	"you saw things that no one else could see"
Item 17	"you could hear things that no one else could hear"
Item 18	"your own thoughts were broadcasted"
Item 19	"you smelled strange things, that others could not smell"
Item 20	"you had strange sensations, like being touched when no one was around"

Note: CIDI, Composite International Diagnostic Interview
[a] denotations are based on screening items of the CIDI Version 3.0

Table S2. Basic characteristics of groups derived from 5212 participants

Overall number of observations (N=14973)	**Group 1: No symptoms (*N*= 6901)**	**Group 2: Affective disturbance (*N*= 6534)**	**Group 3: Psychotic experience (*N*= 261)**	**Group 4: Affective disturbance + moderate psychosis [e] (*N*= 879)**	**Group 5: Affective disturbance + high psychosis [e] (*N*= 398)**	**test statistics**	**p**
Age (years), mean (S.D.)	48.9 (12.9)	46.0 (12.3)	46.7 (13.2)	44.8 (12.6)	43.3 (12.8)	F= 41.56, df= 4	<0.001
Gender, n (%)							
male	3448 (50.0)	2693 (41.2)	111 (42.5)	315 (35.8)	152 (38.2)	χ^2 = 144.42, df= 4	<0.001
female	3453 (50.0)	3841 (58.8)	150 (57.4)	564 (64.2)	246 (61.8)		
Level of education, n (%)							
primary	267 (3.9)	273 (4.2)	13 (5.0)	54 (6.1)	22 (5.5)	χ^2 = 91.94, df= 12	<0.001
lower secondary	1773 (25.7)	1658 (25.4)	77 (29.5)	265 (30.2)	131 (32.9)		
higher secondary	2154 (31.2)	2115 (32.4)	98 (37.6)	319 (36.3)	146 (36.7)		
higher professional	2707 (39.2)	2488 (38.1)	73 (28.0)	241 (27.4)	99 (24.9)		
Urbanicity [a, f]							
countryside	705 (10.2)	550 (8.4)	26 (10.0)	66 (7.5)	29 (7.3)	χ^2 = 44.09, df= 16	<0.001
village	2777 (40.3)	2508 (38.4)	111 (42.5)	337 (38.3)	145 (36.5)		
small city	885 (12.8)	846 (13.0)	37 (14.2)	109 (12.4)	68 (17.1)		
medium city	1030 (14.9)	1110 (17.0)	36 (13.8)	147 (16.7)	66 (16.6)		
big city	1498 (21.7)	1516 (23.2)	51 (19.5)	220 (25.0)	89 (22.4)		
Minority status [b]							
yes	408 (5.9)	443 (6.8)	15 (5.75)	77 (8.8)	51 (12.8)	χ^2 = 37.29, df= 4	<0.001
no	6493 (94.1)	6091 (93.2)	246 (94.3)	802 (91.2)	347 (87.2)		
Regular cannabis use [c, f]							
yes	45 (0.7)	181 (2.9)	6 (2.3)	47 (5.6)	37 (9.9)	χ^2 = 239.76, df= 4	
no	6737 (99.3)	6120 (97.1)	252 (97.7)	786 (94.4)	336 (90.1)		<0.001

Table S2 (continued) Basic characteristics of groups derived from 5212 participants

Overall number of observations (N=14973)	Group 1: No symptoms (*N*= 6901)	Group 2: Affective disturbance (*N*= 6534)	Group 3: Psychotic experience (*N*= 261)	Group 4: Affective disturbance + moderate psychosis [e] (*N*= 879)	Group 5: Affective disturbance + high psychosis [e] (*N*= 398)	test statistics	p
Childhood trauma (80^{th} perc.) [d]							
yes	754 (10.9)	1483 (22.7)	56 (21.5)	312 (35.5)	194 (48.7)	χ^2 = 743.86, df= 4	<0.001
no	6147 (89.1)	5051 (77.3)	205 (78.5)	567 (64.5)	204 (51.3)		
Depression	-	4615 (70.6)	-	685 (77.9)	342 (85.9)	-	-
Anxiety	-	4838 (74.0)	-	722 (82.1)	363 (91.2)		
Mania	-	2455 (37.6)	-	424 (48.2)	241 (60.6)		

Note: Data with an overall number of 14973 observations from surveys of 5212 participants who completed all assessment at T1, including the digit-span task and with potentially missing data at T2

[a] defined as exposure to urban environment until the age of 16 years, classified based on Dutch classification data of population density: countryside (large distance to amenities), village (<25000 inhabitants), small city (25000 – 50000 inhabitants), medium city (50000 – 100000 inhabitants), and larger cities (>100000 inhabitants).

[b] born in any other country than Netherlands

[c] regular cannabis use was based on the section of Illegal Substance Use from CIDI 3.0. A pattern of use during the lifetime period of heaviest use of once per week or more were used as the cut-off.

[d] based on sum scores of items asking for five types of childhood trauma before the age of 16: two incidents or more of emotional neglect (not listened to, ignored or unsupported), physical abuse (kicked, hit, bitten or hurt with object or hot water), psychological abuse (yelled at, insulted, unjustly punished, treated, threatened, belittled or blackmailed) or one incidence or more of sexual abuse (any unwanted sexual experience) and peer victimization (bullying). The childhood trauma sum score was dichotomized at the 80^{th} percentile.

[e] defined as: moderate psychosis, 1-2 psychotic experiences; high psychosis, 3 or more psychotic experiences or psychosis-related help-seeking behaviour

[f] number of missing values: urbanicity: 11 observations; cannabis use: 426 observations

Table S3. Model fit statistics for multinomial logistic regression models

	df	LL	AIC	BIC
Models regarding JTC bias				
Model 1	**8**	**-13734.56**	**27485.12**	**27545.03**
Model 2	**20**	**-13515.73**	**27071.46**	**27221.23**
Model 3	**36**	**-13177.58**	**26427.17**	**26696.75**
Model 4	**40**	**-13152.55**	**26385.11**	**26684.65**
Models regarding WMP				
Model 1	**8**	**-15196.59**	**30409.18**	**30469.86**
Model 2	**20**	**-14961.39**	**29962.78**	**30114.46**
Model 3	**36**	**-14567.11**	**29206.21**	**29479.25**

Note: df, degrees of freedom; LL= Log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

CHAPTER 3

The jumping to conclusions reasoning bias as a cognitive factor contributing to psychosis progression and persistence: findings from NEMESIS-2

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Abstract

Background: Contemporary models of psychosis implicate the importance of affective dysregulation and cognitive factors (e.g. biases and schemas) in the development and maintenance of psychotic symptoms, but studies testing proposed mechanisms remain limited. This study, uniquely using a prospective design, investigated whether the jumping to conclusions (JTC) reasoning bias contributes to psychosis progression and persistence.

Methods: Data were derived from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2). The Composite International Diagnostic Interview and an add-on instrument were used to assess affective dysregulation (i.e. depression, anxiety and mania) and psychotic experiences (PEs), respectively. The beads task was used to assess JTC bias. Time series analyses were conducted using data from T1 and T2 (N = 8666), excluding individuals who reported high psychosis levels at T0.

Results: Although the prospective design resulted in low statistical power, the findings suggest that, compared to those without symptoms, individuals with lifetime affective dysregulation were more likely to progress from low/moderate psychosis levels (state of 'aberrant salience', one or two PEs) at T1 to high psychosis levels ('frank psychosis', three or more PEs or psychosis-related help-seeking behaviour) at T2 if the JTC bias was present [adj. relative risk ratio (RRR): 3.8, 95% confidence interval (CI) 0.8–18.6, p = 0.101]. Similarly, the JTC bias contributed to the persistence of high psychosis levels (adj. RRR: 12.7, 95% CI 0.7–239.6, p = 0.091).

Conclusions: We found some evidence that the JTC bias may contribute to psychosis progression and persistence in individuals with affective dysregulation. However, well-powered prospective studies are needed to replicate these findings.

Keywords: Cognitive models; jumping to conclusions; persistence; progression; psychosis; psychotic experiences; reasoning bias; transdiagnostic phenotype

Introduction

Psychosis spectrum disorders have a complex aetiology and multifaceted phenomenology. Psychotic experiences (PEs), the attenuated subclinical expression of positive psychotic symptoms, are common, with an estimated lifetime prevalence ranging from 5% to 8% [1]. PEs are often preceded by, or co-occur with, affective dysregulation (e.g. depression, anxiety) [2], which is in accordance with clinical observations of frequent comorbidity of affective disorders with psychotic disorders as well as substantially overlapping genetic liability [3]. These findings have been taken to suggest a transdiagnostic and extended psychosis phenotype with temporal and phenomenological continuity across developmental stages of psychotic and affective disorders [1]. Importantly, however, PEs are often transitory and neither inherently distressing nor inevitably impairing [4, 5], but persist in around 20% [6]. Of these, approximately 7% develop a psychotic disorder [6]. Consequently, there has been an increasing interest in identifying clinically relevant predictors for illness onset [7-9].

Contemporary models of psychosis implicate the importance of cognitive factors (e.g. schemas, biases) in illness trajectories by contributing to transforming experiences of aberrant salience into frank psychosis as well as symptom persistence [10, 11]. Specifically, individuals' appraisal of, and response to [12-14], these excessively vivid and intense experiences, which may be mediated by dysregulated dopaminergic signalling [10, 15], are thought to be integral for the development of psychosis-related distress and impairment [11]. The interpretation of experiences as threatening and of external causation [10, 11, 16, 17], combined with altered behaviour and cognitive responses, has been shown to be associated with psychosis spectrum disorders [14, 18].

The jumping to conclusions (JTC) reasoning bias is among the most widely studied cognitive biases in psychosis and describes individuals' tendency to make hasty decisions based on insufficient information [19]. It has been consistently found to be associated with subclinical and clinical psychosis [19-22] as well as a transdiagnostic phenotype of co-occurring affective dysregulation and PEs [23], but not with non-psychotic disorders [22]. Thus, the JTC bias may be an important cognitive factor involved in the formation and maintenance of psychosis, especially delusional ideations [18, 24], with some recent meta-analytical evidence supporting this assumption [19]. Critically, most studies have investigated associations of JTC bias with psychosis using cross-sectional designs [22] and evidence on proposed specificity of JTC bias with psychosis in individuals with a transdiagnostic phenotype of mental health problems remains very limited [23].

Longitudinal studies investigating the role of JTC bias in psychosis are rare. These studies suggest that JTC bias may be i) predictive for less improvement of psychotic symptoms over time [25], ii) stable despite symptom remission [26, 27], iii) associated with poorer outcomes in people with psychosis [28] as well as antipsychotic treatment response [29], and iv) associated with worse vocational functioning [30]. To our knowledge, no study has directly and prospectively tested the contribution and specificity of JTC bias to psychosis progression and persistence in individuals with co-occurring affective dysregulation, as proposed in recent integrative sociodevelopmental-cognitive models [10].

Aims and hypotheses

For the present study, we aimed to extend previous research by investigating whether the JTC bias contributes to psychosis progression and persistence in the general population. Specifically, the following hypotheses were tested: First, compared to individuals with neither affective dysregulation nor PEs, the JTC bias is associated with an increased risk to progress from low/moderate psychosis levels (i.e. one or two PEs; hereafter ‘state of aberrant salience’) at T1 to high psychosis levels (i.e. three or more PEs or psychosis-related help-seeking behaviour; hereafter ‘frank psychosis’) at T2 in individuals with co-occurring lifetime affective dysregulation. Second, the JTC bias does not contribute to first-occurrence of frank psychosis at T2 when individuals report sole presence of affective dysregulation at T1. Third, the JTC bias is associated with an increased risk to report persistence of frank psychosis between T1 and T2 in individuals with lifetime affective dysregulation.

Materials and methods

Sample

Data were obtained from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), a nationally representative cohort study designed to investigate the incidence, prevalence, course, and outcome of mental disorders.

For current analyses, we used data of the first three waves (T0-T2), while, in the meantime, the fourth wave (T3) has been completed. A multistage, stratified random sampling of households was applied to ensure representativeness of the sample in terms of age, region, and population density. First, a random sample of 184 of 443 municipalities was drawn, which were stratified by four regions (north, east, south, west) and five levels of population density. The four largest cities (i.e., Amsterdam, Rotterdam, The Hague, Utrecht) were also included. Thus, twenty-four strata were used to stratify the sample. The number of addresses selected per municipality was based on the distribution of the number of inhabitants aged 18-64 years. Secondly, a random sample of households was drawn from these addresses with the same probability to be selected. Finally, an individual aged 18-64 years was included based on the most recent birthday at first contact. The face-to-face interviews were performed at home by trained interviewers, who were not clinicians, using a laptop computer. The Composite International Diagnostic Interview (CIDI) version 3·0 [31] and additional questionnaires were used. The inclusion criterion was: aged 18-65 years. Exclusion criterion was insufficient command of the Dutch language. The first wave (T0) was conducted from November 2007 to July 2009 and enrolled 6646 participants (response rate 65·1%). Although younger subjects were slightly underrepresented, this sample was representative for the Dutch general population [32]. In the second wave (T1), carried out from November 2010 to June 2012, all respondents were approached, and, of these, 5303 individuals were interviewed again (response rate 80·4% from T0 with those deceased excluded). From November 2013 to June 2015, the third wave (T2) was completed with 4618 persons who were interviewed a third time (response rate 87·8% from T1 with those deceased excluded). Psychopathology reported at T0 (baseline) reflects lifetime prevalence, while symptoms reported at T1 and T2 reflect 3-year interval occurrence (i.e. between T0 and T1 and T1-T2, respectively). Data from T1 and T2 were used for the current study. The Medical Ethics Review Committee for Institutions of Mental Health Care approved the study. More details on the study are provided elsewhere [32].

Data collection

Sociodemographic characteristics and cognitive alterations

Data on age, sex, and level of education were assessed in the additional questionnaire. The digit-span task, based on the Wechsler Adult Intelligence Scale

(WAIS-III) [33], was used to assess working memory performance as a proxy for cognitive alterations.

JTC bias

The beads task, a probabilistic reasoning task, was completed at the third wave (T2) to assess the presence or absence of JTC bias. The beads task is designed to measure individuals' reasoning style under ambiguous conditions [34]. During the task, individuals were shown two jars with red and blue coloured beads in opposite ratios (i.e. 60 to 40 beads). The jars as well as all instructions were presented on a laptop screen. After a training session, participants were informed that the beads will be drawn consecutively from one jar and, once shown, returned to the same jar. After each draw, participants were asked whether they want to decide from which of the two jars the beads were drawn or if they prefer to see another bead. Although not communicated, participants were allowed to see up to 20 beads before they had to decide. The order of beads was fixed and the colour shown in the training session selected at random. The number of beads drawn at T2 was considered to represent individuals' trait reasoning style. Based on previous studies [19], the presence of JTC bias was defined as making a decision based on two or fewer beads [22].

Affective dysregulation

Affective dysregulation was assessed at all three timepoints using core items of the CIDI version 3·0. The CIDI measure for core symptoms uses a true-false response format to screen for the prevalence of various mental disorders, including depressive episode, social phobia, generalised anxiety disorder, and manic episode (e.g. feeling fearful, depressed, experiences of a panic attack). For current analyses, a variable was constructed that combines reported affective symptoms (i.e., depression, anxiety, and mania) from all assessment points (T0-T2). Thus, the variable affective dysregulation represents both lifetime prevalence (T0) as well as interval occurrence (T0-T1, T1-T2) (binary variable). All items are presented in Supplementary Table 1.

Psychotic experiences (PEs)

As earlier studies concluded that the CIDI is not a reliable and valid measures for psychotic disorders, a psychosis measure was constructed based on the psychosis section of the CIDI 1·1. The measure consisted of 20 items asking for PEs (i.e. 15 delusional and five hallucinatory experiences). At T0, the lifetime prevalence was assessed, while at T1 and T2, individuals were asked whether PEs have occurred between assessment points (i.e. interval occurrence). In case PEs were endorsed, participants were asked to state, on a 4-point Likert scale, the frequency, distress, and the impact of PEs on their daily life, including whether they had sought help for these experiences. For current analyses, we used the number of PEs endorsed, irrespective of reported frequency, distress, and impact. Sum scores were calculated by adding reported PEs. The used items are reported in Supplementary Table 1. To determine psychosis-related help-seeking behaviour, the service assessments of the CIDI 3.0 were used.

Grouping absence, presence and co-occurrence of affective dysregulation and psychotic experiences

In line with previous work [23, 35], individuals were grouped based on answers given on measures assessing depression, anxiety, and mania (summarized as affective dysregulation) and PEs. Five groups were generated representing the absence, sole presence, or co-occurrence of lifetime affective dysregulation and PEs: neither affective dysregulation nor PEs (group 1); sole presence of affective dysregulation (group 2); sole presence of PEs (group 3); affective dysregulation and aberrant salience (group 4; one or two PEs); affective dysregulation and frank psychosis (group 5; three or more PEs or psychosis-related help-seeking behaviour).

Statistical analysis

All analyses were performed using STATA version 13·1 [36]. First, individuals with frank psychosis and any affective dysregulation at T0 (lifetime prevalence) were excluded from analyses (*N*=198), making sure incident states of frank psychosis at T1 and T2 were identifiable. Second, socio-demographic characteristics (i.e. age, sex, education level) and cognitive alterations (working-memory performance) were compared across groups using linear regression and chi-square tests as appropriate. Third, the MLOGIT command was used to fit multinomial logistic regression models with time-lagged variables, while correcting for clustering of data (i.e. two observations for each individual) using the CLUSTER option. In order to test whether the JTC bias contributes to psychosis progression and/or persistence over time, reported symptoms at T1 (categorical variable with 5 levels), JTC bias (binary variable), and its interaction (psychopathological domains x JTC bias) were added to the model of T2 psychopathological domains as the dependent variable. Relative risk ratios (RRRs) for symptoms progression and persistence were compared using the Wald test. All models were adjusted for various *a priori* defined potential confounders. First, we adjusted for socio-demographic characteristics (i.e. age, sex, level of education) and, subsequently, for cognitive alterations (i.e. working memory performance). Missing values for exposure, outcome, or covariates were assumed to be missing at random and, thus, individuals were excluded from statistical modelling, but retained for crude RRRs estimates.

Results

Basic sample characteristics

In total, the sample consisted of 4618 participants at the third wave. Of these, 4333 completed the beads task, all measures, and did not report lifetime prevalence of co-occurring affective dysregulation and frank psychosis at T0, resulting in 8666 observations combining T1 and T2 (93·8%). There were no differences between individuals who completed the beads task and other measures and those who did not with regard to socio-demographic characteristics and cognitive alterations. The sample characteristics are presented in Table 1. As shown, individuals who reported affective dysregulation and/or PEs were slightly younger, female, less educated, and had more cognitive alterations. Group differences on variables, including exposure to various socio-environmental risk factors (e.g. childhood trauma, cannabis use, minority status, urbanicity), are reported elsewhere [23, 35] and provided in Table 1. Overall, there were considerable differences when individuals with sole presence of affective dysregulation and co-occurring affective dysregulation and PEs were compared in terms of most sample characteristics, socio-environmental risk factors, and cognitive alterations. A frequency table of reported PEs at T1 is provided in Supplementary Table 2.

JTC bias and psychosis progression and occurrence

As shown in Table 2, compared to individuals with neither affective dysregulation nor PEs at both timepoints, those who reported affective dysregulation and a state of aberrant salience at T1 were more likely, albeit below conventional alpha, to report frank psychosis at T2 if the JTC bias was present (adj. RRR: 3·8, 95% CI 0·8 – 18·6, *p*=0·101). In contrast, co-occurrence of affective dysregulation and frank psychosis at T2 was not influenced by JTC bias in individuals who reported sole presence of affective dysregulation at T1 (adj. RRR: 1·3, 95% CI 0·4 – 5·0, *p*=0·659).

Table 1. Basic characteristics of groups derived from 4333 participants over two time points

Overall number of observations (*N*= 8666)	**Group 1: No symptoms (*N*= 5036)**	**Group 2: Affective dysregulation (*N*= 3138)**	**Group 3: Psychotic experience (*N*= 137)**	**Group 4: Affective dysregulation + aberrant salience [f] (*N*= 272)**	**Group 5: Affective dysregulation + frank psychosis [f] (*N*= 83)**	**test statistics**	**p**
Age (years), mean (S.D.)	50·7 (12·4)	47·9 (12·1)	49·1 (11·7)	47·2 (12·6)	43·6 (11·4)	F= 21·70, df= 4	<0·001
Sex, n (%)							
male	2472 (49·1)	1236 (39·4)	56 (40·9)	97 (35·7)	31 (37·3)	$\chi2$ = 86·44, df= 4	<0·001
female	2564 (50·9)	1902 (60·6)	81 (59·1)	175 (64·3)	52 (62·7)		
Level of education, n (%)							
primary	192 (3·8)	127 (4·1)	7 (5·1)	18 (6·6)	8 (9·6)		
lower secondary	1275 (25·3)	780 (24·9)	37 (27·0)	87 (32·0)	27 (32·5)	$\chi2$ = 56·72, df= 12	<0·001
higher secondary	1542 (30·6)	1017 (32·4)	53 (38·7)	104 (38·2)	30 (36·1)		
higher professional	2027 (40·3)	1214 (38·7)	40 (29·2)	63 (23·2)	18 (21·7)		
Urbanicity, n (%) [a]							
countryside	652 (10·3)	490 (8·5)	23 (10·3)	57 (7·8)	5 (5·7)		
village (<25k)	2557 (40·3)	2241 (38·7)	92 (41·3)	280 (38·5)	32 (36·4)		
small city (25k – 50k)	820 (12·9)	739 (12·8)	36 (16·1)	91 (12·5)	18 (20·5)	$\chi2$ = 40·81, df= 16	0·001
medium city (50k -100k)	952 (15·0)	991 (17·1)	30 (13·5)	118 (16·2)	9 (10·2)		
big city (>100k)	1371 (21·6)	1337 (23·1)	42 (18·8)	181 (24·9)	24 (27·3)		
Minority status, n (%) [b]							
yes	270 (5·4)	207 (6·6)	5 (3·7)	26 (9·6)	8 (9·6)	$\chi2$ = 15·10, df= 4	0·005
no	4766 (94·6)	2931 (93·4)	132 (96·4)	246 (90·4)	75 (90·4)		
Regular cannabis use, n (%) [c]							
yes	8 (0·2)	17 (0·6)	1 (0·7)	2 (0·8)	2 (2·6)	$\chi2$ = 21·86, df= 4	<0·001
no	4940 (99·8)	2992 (99·4)	134 (99·3)	260 (99·2)	74 (97·4)		
Childhood trauma (80^{th} perc.), n (%) [d]							
yes	574 (11·4)	726 (23·1)	28 (20·4)	82 (30·1)	32 (38·6)	$\chi2$ = 261·16, df= 4	<0·001
no	4462 (88·6)	2412 (76·9)	109 (79·6)	190 (69·9)	51 (61·5)		

Table 1. (continued) Basic characteristics of groups derived from 4333 participants over two time points

Overall number of observations (*N*= 8666)	**Group 1: No symptoms (*N*= 5036)**	**Group 2: Affective dysregulation (*N*= 3138)**	**Group 3: Psychotic experience (*N*= 137)**	**Group 4: Affective dysregulation + aberrant salience [f] (*N*= 272)**	**Group 5: Affective dysregulation + frank psychosis [f] (*N*= 83)**	**test statistics**	**p**
Reasoning bias							
absent (n, %)	2468 (49·0)	1535 (48·9)	63 (46·0)	124 (45·6)	28 (33·7)	$\chi2$ = 9·15, df= 4	0·058
present (n, %)	2568 (51·0)	1603 (51·1)	74 (54·0)	148 (54·4)	55 (66·3)		
Working memory performance [e]							
mean (SD)	20·0 (3·9)	20·2 (3·8)	21·4 (3·6)	21·1 (4·1)	21·7 (3·6)	F= 10·27, df= 4	<0·001
Distribution of affective dysregulation across groups (n, %)							
Depression	-	2086 (66·5)	-	194 (71·3)	66 (79·5)		
Anxiety	-	2161 (69·0)	-	210 (77·2)	74 (89·2)	-	-
Mania	-	1211 (38·6)	-	126 (46·3)	44 (53·0)		

Notes: Data with an overall number of 8666 observations from surveys of 4333 participants who completed all assessments, including the beads task, at two time-points (T1 and T2),
excluding those with affective disturbances + frank psychosis at T0 (*N*=198)
[a] defined as exposure to urban environment until the age of 16 years, classified based on Dutch classification data of population density: countryside (large distance to amenities), village (<25000 inhabitants), small city (25000 – 50000 inhabitants), medium city (50000 – 100000 inhabitants), and larger cities (>100000 inhabitants)
[b] born in any other country than The Netherlands
[c] regular cannabis use was based on the section of Illegal Substance Use from CIDI 3·0. A pattern of use of once per week or more during lifetime (T0) or previous three years (T1, T2) were used as the cut-off
[d] based on sum scores of items asking for five types of childhood trauma before the age of 16: two incidents or more of emotional neglect (i.e. not listened to, ignored or unsupported), physical abuse (i.e. kicked, hit, bitten or hurt with object or hot water), psychological abuse (i.e. yelled at, insulted, unjustly punished, treated, threatened, belittled or blackmailed) or one incidence or more of sexual abuse (i.e. any unwanted sexual experience) and peer victimization (i.e. bullying). The childhood trauma sum score was dichotomized at the 80^{th} percentile
[e] sum scores of the digit-span task (range 6-30) were recoded: high numbers indicate lower working memory performance and vice versa
[f] defined as: aberrant salience: low to moderate psychosis levels, one or two psychotic experiences; frank psychosis: high psychosis levels, three or more psychotic experiences or psychosis-related help-seeking behaviour

Table 2. Results (RRR and 95% CI) on the association of symptoms at T1 with symptoms at T2 by group and JTC bias

	Model 1 [a]		**Model 2** [b]		**Model 3** [c]		**Model 4** [d]	
	RRR (95% CI)	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**
Reference: no symptoms at T1 and T2								
Outcome: Affective dysregulation + frank psychosis at T2								
Symptoms at T1								
Affective dysregulation	3·3 (1.2 – 8·7)	0·016	3·3 (1·2 – 8·7)	0·017	3·1 (1·2 – 8·2)	0·024	3·1 (1·2 – 8·1)	0·025
Psychotic experiences	25·7 (7·0 – 94·8)	<0·001	25·3 (6·8 – 93·4)	<0·001	23·8 (6·2 – 91·7)	<0·001	21·7 (5·7 – 83·2)	<0·001
Affective dysregulation + aberrant salience	9·6 (2·7 – 34·7)	0·001	9·6 (2·7 – 34·9)	0·001	8·1 (2·2 – 29·5)	0·002	7·4 (2·0 – 27·4)	0·003
Affective dysregulation + frank psychosis	79·2 (6·6 – 953·8)	0·001	78·0 (6·5 – 939·8)	0.001	54·1 (5·0 – 587·5)	0·001	50·5 (5·0 – 506·4)	0·001
Presence of reasoning bias								
JTC bias	1·1 (0·4 – 3·3)	0·843	1·1 (0·4 – 3·3)	0·852	1·2 (0·4 – 3·7)	0·715	1·2 (0·4 – 3·5)	0·779
Interaction of symptoms at T1 and reasoning bias								
Affective dysregulation x JTC bias	1·5 (0·4 – 5·5)	0·535	1·4 (0·4 – 5·1)	0·632	1·3 (0·4 – 5·0)	0·658	1·3 (0·4 – 5·0)	0·659
Psychotic experiences x JTC bias	0·5 (0·1 – 3·3)	0·509	0·6 (0·1 – 3·4)	0·525	0·5 (0·1 – 3·1)	0·453	0·5 (0·1 – 3·2)	0·474
Affective dysregulation + aberrant salience x JTC bias	4·2 (0·9 – 20·1)	0·071	3·7 (0·8 – 17·8)	0·105	3·6 (0·7 – 17·8)	0·111	3·8 (0·8 – 18·6)	0·101
Affective dysregulation + frank psychosis x JTC bias	10·7 (0·5 – 221·3)	0·124	10·8 (0·5 – 222·6)	0·123	13·0 (0·7 – 258·9)	0·093	12·7 (0·7 – 239·6)	0·091

Note: df, degrees of freedom; CI, confidence interval; RRR, relative risk ratio
[a] Unadjusted model, unrestricted sample (*N*=4596 individuals who completed the beads task at the third wave)
[b] Unadjusted model, restricted sample (*N*=4333 individuals who completed the beads task as well as other measures)
[c] Model adjusted for socio-demographics (i.e. age, gender, level of education), restricted sample
[d] Model adjusted for socio-demographics and cognitive alterations (i.e. working memory performance), restricted sample

Table 3. Symptom progression and persistence from T1 to T2 by JTC bias

Symptoms at T1 by JTC bias	**Symptoms at T2**				
	No symptoms	**Affective dysregulation**	**Psychotic experience**	**Affective disturbance + aberrant salience [a]**	**Affective dysregulation + frank psychosis[a]**
No symptoms					
JTC bias					
Present (n, %)	1476 (51·3)	402 (49·5)	23 (53·5)	19 (57·6)	7 (53·8)
Absent (n, %)	1404 (48·7)	410 (50·5)	20 (46·5)	14 (42·4)	6 (46·2)
Affective dysregulation					
JTC bias					
Present (n, %)	935 (50·2)	1032 (51·1)	25 (48·1)	67 (53·2)	20 (60·6)
Absent (n, %)	927 (49·8)	988 (48·9)	27 (51·9)	59 (46·8)	13 (39·4)
Psychotic experience					
JTC bias					
Present (n, %)	60 (61·8)	12 (40·0)	10 (66·7)	3 (30·0)	4 (50·0)
Absent (n, %)	37 (38·2)	18 (60·0)	5 (33·3)	7 (70·0)	4 (50·0)
Affective dysregulation + aberrant salience					
JTC bias					
Present (n, %)	95 (49·5)	151 (57·2)	15 (62·5)	55 (57·9)	16 (80·0)
Absent (n, %)	97 (51·5)	113 (42·8)	9 (37·5)	40 (42·1)	4 (20·0)
Affective dysregulation + frank psychosis					
JTC bias					
Present (n, %)	2 (40·0)	6 (50·0)	1 (33·3)	4 (50·0)	8 (88·9)
Absent (n, %)	3 (60·0)	6 (50·0)	2 (66·7)	4 (50·0)	1 (11·1)

Notes: Data with an overall number of 8666 observations from surveys of 4333 participants who completed all assessments, including the beads task and other measures, excluding those with high psychosis levels at T0 (*N*=198)
[a] defined as: aberrant salience: low- to moderate psychosis levels, one to two psychotic experiences; frank psychosis: high psychosis levels, three or more psychotic experiences or psychosis-related help-seeking behaviour

3

JTC bias and psychosis persistence

Presence of the JTC bias was associated, albeit below conventional alpha, with an increased risk to maintain frank psychosis at both timepoints in individuals with lifetime affective dysregulation (Table 2: adj. RRR: 12·7, 95% CI 0·7 – 239·6, *p*=0·091). The associations of all other symptoms at T1 with symptoms at T2 by JTC bias are provided in Supplementary Table 3 and model fit statistics for multinomial logistic regression models in Supplementary Table 4.

Discussion

Main findings

This study investigated whether the JTC bias contributes to psychosis progression and persistence in a community sample. Power was low and although associations were not significant at conventional alpha, we interpret findings at the level of clinical evidence rather than arbitrary statistical cut-off, as recommended recently [37] (i.e. most people would still buy a lottery ticket if the probability of winning was 90% instead of 95%). Thus, there was a suggestion that, compared to those who did not report any symptoms, individuals with lifetime affective dysregulation and a state of aberrant salience at T1 were more likely to report frank psychosis at T2 if the JTC bias was present. Similarly, there was a suggestion that the JTC bias contributed to the persistence of frank psychosis over time in individuals with lifetime affective dysregulation. These associations remained largely unchanged after adjusting for demographics (age, sex, education) as well as for cognitive alterations (working memory performance). However, large prospective cohort studies are needed to replicate these findings.

Methodological considerations

The unique strength of the current study is that the largest data set on JTC-bias to date was used, for the first time, to prospectively investigate the contribution of the JTC bias on psychosis progression and persistence in a longitudinal representative cohort study. However, the following limitations should be considered before interpreting our findings. First, as presented in Table 3, the number of individuals with lifetime affective dysregulation who progressed from a state of aberrant salience at T1 to frank psychosis at T2 or who reported persistence of frank psychosis at both timepoints were low (*N*=20 and *N*=9, respectively), resulting in imprecise estimates. The null hypothesis significance testing paradigm – and the p-value threshold intrinsic to it - is currently strongly debated with widely differing views [38-40]. Thus, reported findings should be considered as suggestive but not conclusive evidence. Well-powered longitudinal cohort studies are needed to replicate reported findings. However, this does not preclude, as argued above, inferring valuable insights given marked differences in the presence of JTC bias comparing respective groups (e.g. in 80% of individuals who progressed from aberrant salience at T1 to frank psychosis at T2 the JTC bias was present compared to 54% in those without symptoms at both timepoints). Second, the JTC bias was assessed only once during the study period (T2) and, thus, the presence or absence of JTC bias was conceptualized as individuals' trait reasoning style. Ideally, the beads task would have been completed at more timepoints for more robust estimates and to take potential fluctuation of reasoning style into account. However, assessment burden was considered to be too high and associated benefits too low, especially considering findings of low variability of JTC bias over time [27]. Importantly, however, an uncontrolled study including thirty-one help-seeking individuals with psychosis suggests that JTC bias may vary over time and that these changes may be associated with symptom severity [28]. Thus, more research is needed that specifically investigates stability of JTC bias and potential moderators and mediators of change. Third, although we excluded individuals with lifetime affective dysregulation and frank psychosis at T0, we did not exclude all individuals with psychosis (e.g. low psychosis levels) as resulting stratified groups were considered to be too small to test hypotheses. However, excluding those who have already progressed to high psychosis levels before the study period allowed us to investigate more accurately the role of JTC bias in psychosis progression as psychosis at T1 and T2 reflect first-time interval occurrence. Fourth, we conceptualized low to moderate levels of psychosis (i.e. individuals who endorsed one or two PEs) to represent a state of aberrant salience and high psychosis levels (i.e. individuals who endorsed three or more PEs or reported psychosis-related behaviour) to reflect frank psychosis. As individuals' level of distress and impairment were not directly considered in constructing scores, it is possible that some individuals with high psychosis levels, especially those who did not seek help from mental health services, did not experience any psychosis-related distress while, conversely, some with low to moderate levels of psychosis may experience distress. This would be at variance with established definitions of anomalous experiences of aberrant salience. Thus, our operationalization of distinguishing between individuals with aberrant salience and frank psychosis should be interpreted with caution. However, again, the low number of individuals who reported the emergence of help-seeking behaviour between T0 and T1 or T1 and T2 have prevented us from using this more valid indicator for frank psychosis. Fifth, recent evidence suggests that JTC bias may be a manifestation or consequence of general cognitive impairment and may not represent a specific cognitive factor involved in psychosis progression over time [41]. Thus, adjusting for various domains of individuals' cognitive ability would have been preferable. Critically, only working memory performance has been assessed at the second wave (T1) in NEMESIS-2 and used as a proxy for cognitive deficits to minimize assessment burden. In the current study, however, controlling for working memory performance did not attenuate reported associations (see Model 3 and 4 in Table 2). Sixth, PEs investigated in the current study differed in terms of quality and type (e.g. delusional ideations and hallucinations). As there is some evidence that JTC bias may be specific to the development of delusional ideations, investigating this further in sensitivity analyses would have been important. However, after stratification by type of PEs, group sizes were too small to investigate on specificity of JTC bias in relation to delusional ideations.

Comparison with previous research

The JTC bias is among the most widely studied cognitive biases in psychosis. However, to our knowledge, no study has prospectively investigated the role of JTC bias in psychosis progression and persistence, testing dominant models of psychosis ontogenesis. The findings of the current study support the suggestion that individuals with JTC bias are more likely to progress from states of aberrant salience to frank psychosis. Thus, JTC bias may not only cross-sectionally be associated with psychosis liability, as consistently shown [19-22], but may also influence the development of more severe psychosis levels or psychosis-related help-seeking behaviour over time. Similarly, the findings support the notion that the JTC bias may contribute to the persistence of frank psychosis. These findings are in accordance with recently proposed, but rarely tested, models of psychosis which have posited the importance of cognitive factors in the development and maintenance of psychosis [10, 15].

Whilst recognizing low power and statistically formally inconclusive findings, we hypothesize that if JTC bias indeed contributes to psychosis progression or persistence then, given high rates of JTC bias in individuals without any symptoms, it is likely that JTC bias adds to or combines with other genetic and socio-environmental risk factors. For example, an individual who has been exposed to childhood trauma or developmental hazards early in life may experience otherwise irrelevant stimuli as excessively salient, whilst, concurrently, risk exposure may have provoked the development of threat beliefs about the world and others [11]. Consequently, in search for an explanation, the initially non-distressing experiences of aberrant salience may be interpreted, as a secondary process, as threatening and externally caused [11] and, subsequently, lead to more severe psychosis levels and/or the development of help-seeking behaviour. As noted previously [11], the JTC bias may be particularly important during this stage: Individuals' tendency to gather less information to draw conclusions in a standardized cognitive task may translate to real-life situations in the form of hastier decisions about the negative intentions of others and, thus, lowering the probability of processing alternative explanations which may result in stronger delusional convictions. Thus, threat beliefs of salient experiences and associated appraisal processes may be influenced by the presence of JTC bias, especially when combined with low belief flexibility [42], another well-established cognitive factor. These processes may give rise to a vicious circle of increasing psychosis severity and distress. However, this has not been directly demonstrated and should be further investigated in future studies. Also, how JTC bias is associated with the behavioural response to psychosis as well as other cognitive factors like safety-seeking, avoidance, worrying, and unhelpful emotional regulation strategies [10, 11, 16] should be further investigated.

Conclusion

There was some evidence that the JTC bias may contribute to psychosis progression and persistence in individuals with lifetime affective dysregulation from the general population. However, large prospective studies are needed to replicate reported findings. An important next step is to further investigate the causal status of JTC bias in the development and maintenance of psychosis in order to inform promising treatment targets [18] and develop process-based treatment protocols that aim to directly manipulate reasoning bias and other cognitive factors [43].

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Supplementary material

Table S1. Items used to measure anxiety, depression, mania, and psychotic experiences

Psychopathological domains	
Anxiety (CIDI 3·0)	
Item 1	SC20[a] "Have you ever in your life had an attack of fear or panic when all of a sudden you felt very frightened, anxious, or uneasy?"
Item 2	SC20a [a] "Have you ever had an attack when all of a sudden you became very uncomfortable, either became short of breath, dizzy, nauseous, or your heart pounded, or you thought that you might lose control, die, or go crazy?"
Item 3	SC26[a] "Did you ever have a time in your life when you were a "worrier" – that is, when you worried a lot more about things than other people with the same problems as you?"
Item 4	SC26a[a] "Did you ever have a time in your life when you were much more nervous or anxious than most other people with the same problems as you?" SC26b[a] "Did you ever have a period lasting one month or longer when you were anxious and worried most days?"
Item 5	SC29[a] "Was there ever a time in your life when you felt very afraid or really, really shy with people, like meeting new people, going to parties, going on a date, or using a public bathroom?"
Depression (CIDI 3·0)	
Item 1	SC21[a] "Have you ever in your life had a period lasting several days or longer when most of the day you felt sad, empty or depressed?"
Item 2	SC22[a] "Have you ever had a period lasting several days or longer when most of the day you were very discouraged about how things were going in your life?"
Item 3	SC23[a] "Have you ever had a period lasting several days or longer when you lost interest in most things you usually enjoy like work, hobbies, and personal relationships?"
Mania (CIDI 3·0)	
Item 1	SC24[a] "Have you ever had a period lasting four days or longer when you became so happy or excited that you either got into trouble, people worried about you, or a doctor said you were manic?"
Item 2	SC25[a] "Have you ever had a period lasting four days or longer when most of the time you were very irritable, grumpy, or in a bad mood?"

Table S1. (continued) Items used to measure anxiety, depression, mania, and psychotic experiences

Psychotic experiences (CIDI 1·1)	
Item 1	“people were spying on you”
Item 2	„people were following you“
Item 3	“you were secretly being tested on”
Item 4	“someone was conspiring against you”
Item 5	“a 'double' had taken the place of a loved one”
Item 6	“someone was reading your mind”
Item 7	“you could hear the thoughts of others”
Item 8	“others could hear your thoughts”
Item 9	“alien thoughts were placed in your head”
Item 10	“someone took thoughts from your head”
Item 11	“special messages were sent to you through media”
Item 12	“you were influenced by strange energies”
Item 13	“you were being controlled by an outer force”
Item 14	“your thoughts were being influenced by machines”
Item 15	“any other delusion reported by subject”
Item 16	“you saw things that no one else could see”
Item 17	“you could hear things that no one else could hear”
Item 18	“your own thoughts were broadcasted”
Item 19	“you smelled strange things, that others could not smell”
Item 20	“you had strange sensations, like being touched when no one was around”

Note: Composite International Diagnostic Interview Version, CIDI
[a] denotations are based on screening items of the CIDI Version 3·0

Table S2. Frequencies of reported PEs at T1

Psychotic experiences		**Frequencies at T1[a] (n, %)**
(CIDI 1·1)		
	"Since our previous interview,...	
Item 1	...people were spying on you"	76 (1.8)
Item 2	...people were following you"	21 (0.5)
Item 3	...you were secretly being tested on"	16 (0.4)
Item 4	...someone was conspiring against you"	13 (0.3)
Item 5	...a 'double' had taken the place of a loved one"	1 (0.02)
Item 6	...someone was reading your mind"	18 (0.4)
Item 7	...you could hear the thoughts of others"	31 (0.7)
Item 8	...others could hear your thoughts"	17 (0.4)
Item 9	...alien thoughts were placed in your head"	10 (0.2)
Item 10	...someone took thoughts from your head"	4 (0.1)
Item 11	...special messages were sent to you through media"	5 (0.1)
Item 12	...you were influenced by strange energies"	1 (0.02)
Item 13	...you were being controlled by an outer force"	5 (0.1)
Item 14	...your thoughts were being influenced by machines"	8 (0.2)
Item 15	...any other delusion reported by subject"	21 (0.5)
Item 16	...you saw things that no one else could see"	51 (1.2)
Item 17	...you could hear things that no one else could hear"	27 (0.6)
Item 18	...your own thoughts were broadcasted"	10 (0.2)
Item 19	...you smelled strange things, that others could not smell"	35 (0.8)
Item 20	...you had strange sensations, like being touched when no one was around"	51 (1.2)

Note: Composite International Diagnostic Interview Version, CIDI
[a] Individuals who reported lifetime prevalence of affective dysregulation and frank psychosis (i.e., more than 3 psychotic experiences or psychosis-related help-seeking behavior) at T0 were excluded from analyses (*N*=198). Thus, reported frequencies represent interval occurrence of psychotic experiences.

Table S3. Results (RRR and 95% CI) on the association of all symptoms at T1 with all symptoms at T2 by group and JTC bias

	Model 1 [a]		Model 2 [b]		Model 3 [c]		Model 4 [d]	
	RRR (95% CI)	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**
Reference: no symptoms at T1 andT2								
Outcome: Affective dysregulation only at T2								
Symptoms at T1								
Affective dysregulation	3·7 (3·2 – 4·3)	<0·001	3·6 (3·1 – 4·3)	<0·001	3·5 (3·0 – 4·1)	<0·001	3·5 (3·0 – 4·1)	<0·001
Psychotic experiences	1·7 (0·9 – 3·0)	<0·001	1·7 (0·9 – 3·0)	0·082	1·6 (0·9 – 2·9)	0·103	1·6 (0·9 – 2·8)	0·117
Affective dysregulation + aberrant salience	4·0 (3·0 – 5·4)	<0·001	4·0 (3·0 – 5·4)	<0·001	3·8 (2·8 – 5·1)	<0·001	3·7 (2·8 – 5·0)	<0·001
Affective dysregulation + frank psychosis	6·9 (1·7 – 27·6)	0·007	6·8 (1·7 – 27·5)	0·007	6·0 (1·5 – 24·6)	0·012	6·0 (1·5 – 24·4)	0·013
Presence of reasoning bias								
JTC bias	0·9 (0·8 – 1·1)	0·430	0·9 (0·8 – 1·1)	0·388	1·0 (0·8 – 1·1)	0·796	1·0 (0·8 – 1·1)	0·725
Interaction of symptoms at T1 and reasoning bias								
Affective dysregulation x JTC bias	1·1 (0·9 – 1·4)	0·324	1·1 (0·9 – 1·4)	0·341	1·1 (0·9 – 1·4)	0·428	1·1 (0·9 – 1·4)	0·427
Psychotic experiences x JTC bias	0·47 (0·2 – 1·1)	0·075	0·4 (0·2 – 1·0)	0·060	0·4 (0·2 – 1·0)	0·055	0·4 (0·2 – 1·0)	0·057
Affective dysregulation + aberrant salience x JTC bias	1·4 (0·9 – 2·1)	0·098	1·5 (1·0 – 2·2)	0·070	1·4 (1·0 – 2·2)	0·082	1·5 (1·0 – 2·2)	0·080
Affective dysregulation + frank psychosis x JTC bias	2·7 (0·3 – 20·9)	0·352	1·6 (0·2 – 13·4)	0·661	1·7 (0·2 – 14·4)	0·630	1·7 (0·2 – 14·5)	0·631

Table S3. (continued) Results (RRR and 95% CI) on the association of all symptoms at T1 with all symptoms at T2 by group and JTC bias

	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	RRR (95% CI)	p	adj. RRR (95% CI)	p	adj. RRR (95% CI)	p	adj. RRR (95% CI)	p
Outcome: Psychotic experiences only at T2								
Affective dysregulation	2·1 (1·1 – 3·7)	0·016	2·0 (1·1 – 3·7)	0·016	2·0 (1·1 – 3·6)	0·020	2·0 (1·1 – 3·5)	0·022
Psychotic experiences	9·6 (3·6 – 25·6)	<0·001	9·5 (3·6 – 25·2)	<0·001	9·2 (3·5 – 24·2)	<0·001	8·4 (3·2 – 22·3)	<0·001
Affective dysregulation + aberrant salience	6·5 (2·9 – 14·7)	<0·001	6·5 (2·9 – 14·8)	<0·001	6·1 (2·7 – 13·9)	<0·001	5·8 (2·5 – 13·3)	<0·001
Affective dysregulation + frank psychosis	47·5 (7·5 – 300·1)	<0·001	46·8 (7·4 – 295·6)	<0·001	42·2 (6·6 – 268·2)	<0·001	39·6 (6·1 – 255·9)	<0·001
Presence of reasoning bias								
JTC bias	1·1 (0·6 – 2·0)	0·756	1·1 (0·6 – 2·0)	0·771	1·1 (0·6 – 2·0)	0·752	1·1 (0·6 – 1·9)	0·856
Interaction of symptoms at T1 and reasoning bias								
Affective dysregulation x JTC bias	0·9 (0·4 – 1·9)	0·738	0·8 (0·4 -1·9)	0·674	0·8 (0·4 – 1·9)	0·654	0·8 (0·4 – 1·9)	0·657
Psychotic experiences x JTC bias	1·1 (0·3 – 4·0)	0·883	1·1 (0·3 – 4·1)	0·856	1·1 (0·3 – 4·0)	0·886	1·1 (0·3 – 4·1)	0·855
Affective dysregulation + aberrant salience x JTC bias	1·5 (0·5 – 4·4)	0·458	1·6 (0·5 – 4·5)	0·419	1·5 (0·5 – 4·5)	0·425	1·6 (0·5 – 4·6)	0·412
Affective dysregulation + frank psychosis x JTC bias	0·7 (0·0 – 14·5)	0·806	0·7 (0·0 – 14·5)	0·809	0·7 (0·0 – 15·2)	0·828	0·7 (0·0 – 14·9)	0·816

Table S3. (continued) Results (RRR and 95% CI) on the association of all symptoms at T1 with all symptoms at T2 by group and JTC bias

	Model 1 [a]		Model 2 [b]		Model 3 [c]		Model 4 [d]	
	RRR (95% CI)	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**
Outcome: Affective disturbance + aberrant salience at T2								
Symptoms at T1								
Affective dysregulation	6·7 (3·7 – 12·1)	<0·001	6·4 (3·5 – 11·5)	<0·001	6·1 (3·4 – 11·0)	<0·001	6·1 (3·4 – 11·0)	<0·001
Psychotic experiences	19·3 (7·3 – 50·9)	<0·001	19·0 (7·2 – 50·1)	<0·001	17·9 (6·6 – 48·5)	<0·001	16·9 (6·2 – 45·7)	<0·001
Affective dysregulation + aberrant salience	41·1 (21·2 – 79·8)	<0·001	41·4 (21·3 – 80·3)	<0·001	36·5 (18·6 – 71·5)	<0·001	35·2 (17·9 – 69·0)	<0·001
Affective dysregulation + frank psychosis	135·7 (27·8 – 663·7)	<0·001	133·7 (27·3 – 653·9)	<0·001	107·2 (23·2 – 495·2)	<0·001	103·0 (21·5 – 492·9)	<0·001
Presence of reasoning bias								
JTC bias	1·4 (0·7 – 2·7)	0·373	1·3 (0·6 – 2·6)	0·472	1·3 (0·7 – 2·6)	0·443	1·3 (0·6 – 2·6)	0·487
Interaction of symptoms at T1 and reasoning bias								
Affective dysregulation x JTC bias	0·9 (0·4 – 1·9)	0·720	0·9 (0·4 – 1·9)	0·732	0·9 (0·4 – 1·9)	0·702	0·9 (0·4 – 1·9)	0·703
Psychotic experiences x JTC bias	0·2 (0·0 – 0·9)	0·039	0·2 (0·0 – 1·0)	0·049	0·2 (0·0 – 1·0)	0·045	0·2 (0·0 – 1·0)	0·047
Affective dysregulation + aberrant salience x JTC bias	1·0 (0·4 – 2·4)	0·992	1·1 (0·4 – 2·6)	0·853	1·1 (0·4 – 2·6)	0·869	1·1 (0·4 – 2·7)	0·847
Affective dysregulation + frank psychosis x JTC bias	1·4 (0·1 – 14·0)	0·790	1·2 (0·1 – 12·4)	0·901	1·3 (0·1 – 13·6)	0·835	1·3 (0·1 – 13·7)	0·847

Table S3. (continued) Results (RRR and 95% CI) on the association of all symptoms at T1 with all symptoms at T2 by group and JTC bias

	Model 1 [a]		**Model 2** [b]		**Model 3** [c]		**Model 4** [d]	
	RRR (95% CI)	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**	**adj. RRR (95% CI)**	**p**
Outcome: Affective disturbance + psychosis at T2								
Symptoms at T1								
Affective dysregulation	3·3 (1·2 – 8·7)	0·016	3·3 (1·2 – 8·7)	0·017	3·1 (1·2 – 8·2)	0·024	3·1 (1·2 – 8·1)	0·025
Psychotic experiences	25·7 (7·0 – 94·8)	<0·001	25·3 (6·8 – 93·4)	<0·001	23·8 (6·2 – 91·7)	<0·001	21·7 (5·7 – 83·2)	<0·001
Affective dysregulation + aberrant salience	9·6 (2·7 – 34·7)	0·001	9·6 (2·7 – 34·9)	0·001	8·1 (2·2 – 29·5)	0·002	7·4 (2·0 – 27·4)	0·003
Affective dysregulation + frank psychosis	79·2 (6·6 – 953·8)	0·001	78·0 (6·5 – 939·8)	0·001	54·1 (5·0 – 587·5)	0·001	50·5 (5·0 – 506·4)	0·001
Presence of reasoning bias								
JTC bias	1·1 (0·4 – 3·3)	0·843	1·1 (0·4 – 3·3)	0·852	1·2 (0·4 – 3·7)	0715	1·2 (0·4 – 3·5)	0·779
Interaction of symptoms at T1 and reasoning bias								
Affective dysregulation x JTC bias	1·5 (0·4 – 5·5)	0·535	1·4 (0·4 – 5·1)	0·632	1·3 (0·4 – 5·0)	0·658	1·3 (0·4 – 5·0)	0·659
Psychotic experiences x JTC bias	0·5 (0·1 – 3·3)	0·509	0·6 (0·1 – 3·4)	0·525	0·5 (0·1 – 3·1)	0·453	0·5 (0·1 – 3·2)	0·474
Affective dysregulation + aberrant salience x JTC bias	4·2 (0·9 – 20·1)	0·071	3·7 (0·8 – 17·8)	0·105	3·6 (0·7 – 17·8)	0·111	3·8 (0·8 – 18·6)	0·101
Affective dysregulation + frank psychosis x JTC bias	10·7 (0·5 – 221·3)	0·124	10·8 (0·5 – 222·6)	0·123	13·0 (0·7 – 258·9)	0·093	12·7 (0·7 – 239·6)	0·091

Note: df, degrees of freedom; CI, confidence interval; RRR, relative risk ratio
[a] Unadjusted model, unrestricted sample (*N*=4596 individuals who completed the beads task at the third wave)
[b] Unadjusted model, restricted sample (*N*=4333 individuals who completed the beads task as well as other measures)
[c] Model adjusted for socio-demographics (i.e. age, gender, level of education), restricted sample
[d] Model adjusted for socio-demographics and cognitive alterations (i.e. working memory performance), restricted sample

Table S4. Model fit statistics for multinomial logistic regression models

	Observations	df	LL (null)	LL (model)	AIC	BIC
Model 1	**8666**	**40**	**-7816.63**	**-7152.92**	**14385.85**	**14668.53**
Model 2	**8666**	**52**	**-7816.63**	**-7077.14**	**14258.28**	**14625.77**
Model 3	**8666**	**56**	**-7816.63**	**-7062.12**	**14236.24**	**14632.00**

Note: df, degrees of freedom; LL= Log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

CHAPTER 4

Stress sensitivity as a putative mechanism linking childhood trauma and psychopathology in youth's daily life

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Abstract

Objective: Childhood trauma (CT) is associated with a range of psychopathologies, including psychosis. However, evidence on underlying mechanisms remains limited. The study aimed to investigate whether CT impacts on youth mental health by modifying sensitivity to stress in daily life.

Method: The experience sampling method (ESM) was used to measure momentary stress, negative affect and psychotic experiences in 99 adolescents and young adults (43 help-seeking service users, 16 siblings and 40 controls). Before ESM assessments, CT and depressive, anxiety and psychotic symptoms were assessed.

Results: Stress sensitivity, that is, the association between momentary stress and (i) negative affect and (ii) psychotic experiences, was modified by physical and emotional abuse and, partially, emotional and physical neglect, but not sexual abuse in service users and controls. While there was strong evidence for increased stress sensitivity in service users when high vs. low levels of CT were compared, a pattern of resilience was evident in controls, with attenuated, or no differences in, stress sensitivity in those with high vs. low CT levels. Less consistent findings were observed in siblings.

Conclusions: Stress sensitivity may be an important risk and resilience mechanism through which CT impacts on mental health in youth.

Keywords: trauma; stress; psychopathology; child and adolescent psychiatry; early intervention

Introduction

More than 50% of all life-time cases of mental disorders (based on the *Diagnostic and Statistical Manual of Mental Disorders*; DSM-IV) appear before the age of 14 (early adolescence) and 75% before the age of 24 (young adulthood), often characterized by transitional staging processes from subclinical to clinical severity [1]. Thus, disruption of illness trajectories at a developmentally early stage is important [2, 3], as reflected in recent calls for a reform of youth mental health services [4]. A crucial step in developing early intervention strategies is to improve our understanding of underlying mechanisms involved [5].

In recent years, evidence has accumulated that subclinical expressions of positive psychotic symptoms are common among the adolescent [6, 7] and adult general population [7, 8] associated with a family history of psychotic disorder [7] and linked to an increased risk of developing psychotic [7] and non-psychotic disorders [9]. Recent findings further suggest that subclinical psychotic experiences co-occur with symptoms of common mental disorders (i.e. depression, anxiety) [10, 11] supporting observations that, in particular during the early stages of psychopathology, mixed states of symptoms frequently occur that lack diagnostic specificity [2, 5]. In line with an increased focus on dimensional models of psychopathology [12-18], recent findings have been taken to suggest an extended and transdiagnostic psychosis phenotype with temporal and phenomenological continuity and shared socio-environmental risk factors such as childhood trauma (CT) across developmental stages of psychotic and non-psychotic disorders [11, 17, 19].

Childhood trauma (CT) refers to potentially harmful experiences including sexual, physical, and emotional abuse and physical and emotional neglect [20]. It has been linked to the prevalence and persistence of subclinical psychotic experiences and the onset of psychotic disorders [21-24]. Studies have consistently shown an association between CT and an increased risk of experiencing psychotic symptoms in adolescence and adulthood, with most evidence supporting a link with sexual [20, 21, 23, 25-27], physical [28-33], and emotional [23, 27] abuse. In addition, CT was found to affect a range of other psychopathologies, including anxiety disorders, major depression, eating disorders, drug disorders, suicidality, and behavioural problems [34-39] and may be associated with an admixture of affective, anxiety and psychotic symptoms [40].

Although there is robust evidence linking CT and mental disorders, little is known about underlying mechanisms involved. In current models, CT is thought to make individuals more sensitive to subsequent adversity through enhanced stress sensitivity [28, 41-47]. The experience sampling method (ESM) provides a context-sensitive technique to investigate whether prior experiences of CT amplify stress sensitivity in daily life [44, 48-51]. Studies using ESM have found that individuals with prior experiences of childhood physical and sexual abuse showed elevated sensitivity towards minor daily stressors in frequent general practitioner attenders [48] and individuals suffering from depression, an at-risk mental state for psychosis, and psychotic disorders [47, 49, 50].

Taken together, high rates of CT [52, 53] and robust links with a range of psychopathologies point to the need to further investigate how CT impacts on mental health at a developmentally early stage of psychopathology. In the current study, we investigated whether CT impacts on youth mental health through an elevated stress sensitivity, characterized by strong emotional reactivity (i.e. increased negative affect) and more intense psychotic experiences in response to minor daily stressors. For this, we recruited a sample of help-seeking adolescents and young adults (service users), their biological siblings, and controls. Siblings of service users have an increased liability to psychopathology and, therefore, constitute an intermediate risk group, in which shared genetic and socio-environmental risk factors for mental health have been reported [54-56]

Aims and hypotheses of the study

This study aimed to test the following hypotheses: (1) within groups (service users, siblings, and controls), there is an association between momentary stress (event-related, activity-related, and social stress) and (i) negative affect and (ii) psychotic experiences [H1], (2) within groups, the association between momentary stress and (i) negative affect and (ii) psychotic experiences is modified by CT, with greater associations in individuals exposed to high *v.* low levels of various types of abuse and neglect [H2] and, lastly, (3) the difference in magnitude of associations of momentary stress with (i) negative affect and (ii) psychotic experiences between those exposed to high *v.* low levels of CT varies across groups, with greater differences in service users *v.* controls, service users *v.* siblings, and siblings *v.* controls [H3].

Materials and methods

Sample

We recruited a sample of help-seeking adolescents and young adults (service users), their siblings, and controls. The group of service users were recruited from the Mutsaers foundation (MF) in Limburg, the Netherlands. The MF provides secondary mental health services with a focus on child and adolescent psychiatry. Inclusion criteria were: aged 12-20 years; currently receiving treatment from MF mental health services. Exclusion criteria were: intellectual disability (IQ score below 70); insufficient knowledge of the Dutch language; being diagnosed according to DSM-IV with an Autistic Spectrum Disorder with the exception of Pervasive Developmental Disorder Not Otherwise Specified. In addition, siblings of service users were enrolled. Inclusion criteria were: aged 12-20 years; participation of a biological sibling. Exclusion criteria were the same as in the group of service users with the addition that siblings were excluded if they had a lifetime history of receiving treatment at a mental health service. Lastly, controls were recruited from schools of the same catchment area as MF mental health services. Inclusion criteria were: aged 12-20 years. Exclusion criteria were the same as in the sibling group. Our study was approved by the Medical Ethics Review Committee of Maastricht University Medical Centre in Maastricht, the Netherlands.

Data collection

Socio-demographic characteristics

Data on age, gender, ethnicity, level of education were collected using a detailed socio-demographic schedule.

Childhood trauma

CT was measured using the Dutch version of the short form of the Childhood Trauma Questionnaire (CTQ-SF) [57], adopted for use in adolescents and young adults. The CTQ-SF is an established 28-item self-report questionnaire with five sub-scales (i.e. sexual, physical and emotional abuse as well as physical and emotional neglect). It assesses CT before the age of 16 using a 5-point Likert scale (1= never true, 5= very often true). This allows the calculation of mean and categorical severity scores. Sufficient psychometric properties have been demonstrated [58-60].

Depressive, anxiety, and psychotic symptoms

The Beck Depression Inventory (BDI-II) was used to assess depressive symptoms occurring over the past 2 weeks asking 21-items rated on a 4-point scale (0–3) of increasing severity. It consists of 2 factors: negative cognition (9-items) and affective-somatic feelings (12-items). The Community Assessment of Psychic Experiences (CAPE), a self-report instrument with 42-items, was completed to capture the frequency and distress (both rated on a 4-point scale from 0–3) of positive (20-items) and negative (14-items) non-clinical psychotic and depressive (8 items) symptoms. The State-Trait Anxiety Inventory (STAI) [61] was used to measure state and trait anxiety. A Dutch version consisting of 60-items rated on a 4-point Likert scale (1-4) was used [62]. The first part (STAI-DY1) measures trait (20-items) and the second part (STAI-DY2) assesses state (40-items) anxiety. For all measures, good psychometric properties have been reported [62-66].

ESM measures

Momentary stress (event-related, activity-related and social stress), negative affect, and psychotic experiences were collected using the experience sampling method (ESM), a random time-sampling self-assessment technique. The ESM captures moment-to-moment daily variation in variables in real life outside the research laboratory with high ecological validity [51, 67, 68]. For data acquisition, participants received a personal digital assistant (PsyMate) [69] which beeped 10 times each day on 6 consecutive days at unpredictable moments between 7:30 am and 10:30 pm (scheduled at random within set blocks of time). Event-related, activity-related, and social stress were conceptualized as minor disturbances and distinctive unpleasant events, activities, and social situations occurring in the flow of daily life. Good concurrent validity with other stress measures has been reported [44, 70].

Event-related stress was assessed asking participants to report where they were (e.g. home, private room, family/friends, work/school, public place) and the most important event that had happened since the last beep by rating the pleasantness and importance ranging from “very unpleasant” (rating of -3) to “very pleasant” (rating of 3) and “very unimportant” (rating of -3) to “very important” (rating of 3). The coding was reversed that higher ratings indicate higher levels of stress (with ratings of −3 coded as 7 and ratings of 3 coded as 1). Activity-related stress was measured by asking “What am I doing (just before the beep)” (e.g. resting, smoking, watching TV) and 3 follow-up questions (“I would prefer doing something else”, “This activity is difficult for me”, “I can do this well” [reversed]) ranging from “not at all” (rating of 1) to “very much” (rating of 7). Social stress was measured by asking participants to specify categorically with whom they were spending time (e.g. nobody, partner, family) and to rate the current social context using the items “I would prefer to be alone”, “I find the people I am with pleasant” [reversed], “I feel safe (with these people)” [reversed], and “I feel threatened” (if with someone) or “I like to be alone” [reversed] and “I would prefer to have company” (if alone) ranging from “not at all” (rating of 1) to “very much” (rating of 7).

Negative affect was measured asking participants 5-items to rate the degree of feeling anxious, lonely, insecure, irritated, and down. Psychotic experiences were measured using 8-items asking for mental states associated with psychotic experiences: hallucinations, delusions, and thought problems (“I see things that aren’t really there”, “I hear things that aren’t really there”, “I feel suspicious/ paranoid”, “I feel harried”, “I feel unreal”, “My thoughts are influenced by other”, “I can’t get these thoughts out of my head“, “I feel like I am losing control“), both rated on a 7-point Likert scale ranging from “not at all” (rating of 1) to “very much” (rating of 7). High levels of internal consistency and good concurrent validity with interviewer-rated measures of psychotic experiences has been previously reported [50, 71].

Statistical analysis

Basic sample characteristics and ESM aggregate mean scores (i.e. over a period of 6 days for each participant) and standardized BDI-II, CAPE, and STAI-DY1/DY2 scores in service users, their siblings and controls were compared using linear regression and χ^2-tests as appropriate. Second, as ESM data has a multilevel structure with multiple observations (level-1) nested within participants (level-2), the ‘xtmixed’ command in Stata v. 13 [72] was used to fit linear mixed models. Separate models for each momentary stressor (event-related, activity-related, and social stress) as the independent variable and (i) negative affect and (ii) psychotic experiences as the outcome variable were computed, while controlling for potential confounders (i.e. age, gender, ethnicity, level of education). Third, CT was included into the model by adding two-way (stress x trauma, stress x group, trauma x group) and three-way (e.g. stress x trauma x group) interaction terms to investigate whether the associations between momentary stress and (i) negative affect and (ii) psychotic experiences were modified by prior exposure to childhood trauma (mean scores of sexual, physical and emotional abuse, and physical and emotional neglect) and group (service users, siblings, and controls). Likelihood ratio tests were calculated to assess improvements in model fit after interaction terms were added. Fourth, the 'lincom' command was used to compute linear combinations of coefficients for testing the hypotheses that, within each group, the association of momentary stress with (i) negative affect and (ii) psychotic experiences was greater in individuals exposed to high *v.* low levels of various forms of CT (+/- 1 S.D. of standardized CTQ scores, mean = 0, S.D. = 1) [73, 74]. Lastly, we investigated whether differences in the magnitude of associations of momentary stress with (i) negative affect and (ii) psychotic experiences between those exposed to high *v*. low levels of various forms of CT are greater in service users *v.* controls, service users *v.* siblings, and siblings *v.* controls.

Results

Basic sample and clinical characteristics

In total, the sample consisted of 109 adolescents and young adults eligible to participate in the study. Of these, 99 individuals (43 service users, 16 siblings, 40 controls) completed the ESM with ≥20 valid responses over the 6-day assessment period as well as the CTQ, BDI-II, CAPE, STAI-DY1/DY2. As shown in Table 1, service users, their siblings and controls did not differ in age, gender, or ethnicity. However, service users were less often educated to further or higher educational levels than siblings and controls. In addition to primary diagnosis of specific and non-specific mental disorders with a high proportion of comorbidity (55.8%) in the group of service users, there was evidence for differences in symptomatology in service users *v*. controls and service users *v*. siblings respectively, with higher levels of depression (BDI-II: B=0.68, p=0.001; B=1.02 p<0.001), state (B=0.46, p=0.035; only some evidence in service users *v.* siblings B=0.54, p=0.065) and trait (B=0.64, p=0.003; B=0.93, p=0.001) anxiety, and negative (B=0.40, p=0.066; B=0.72, p=0.014) and positive (B=0.73, p=0.001; B=0.81, p=0.004) psychotic-like experiences. Moreover, comparing CT in service users and controls, higher levels of sexual (B=0.45, p=0.041) and emotional (B=0.60, p=0.006) abuse as well as higher emotional (*B*=0.61, *p*=0.005) and physical (*B*=0.59, *p*=0.006) neglect were found, with some evidence of a difference in physical (*B*=0.42, *p*=0.059) abuse. Further, emotional (*B*=0.73, *p*=0.011) and physical (*B*=0.74, *p*=0.010) neglect were markedly higher in service users than siblings, but not significantly, however, in sexual (*B*=0.40, *p*=0.170), physical (*B*=0.31, *p*=0.283), and emotional (*B*=0.48, *p*=0.092) abuse. In addition, we found that physical (*intraclass correlation coefficient (ICC)*=0.80, 95% CI 0.47 – 0.95) and emotional (*ICC*=0.17, 95% CI 0.00 – 0.95) abuse as well as physical (*ICC*=0.48, 95% CI 0.11 – 0.87) and emotional (*ICC*=0.27, 95% CI 0.02 – 0.88) neglect scores, but not sexual (*ICC*=0.00, 95% CI 0.00 – 0.00) abuse scores, of service users and their siblings were correlated. There were no differences in various symptom domains and CT between siblings and controls.

Table 1. Basic sample characteristics

	Service users (n=43)	Siblings (n=16)	Controls (n= 40)	Test statistic	p
Age (years), mean (S.D.)	15.4 (1.4)	15.4 (2.4)	15.6 (2.0)	F=0.22, df=2	0.802
Gender, n (%)					
Male	17 (39.5)	7 (43.8)	17 (42.5)	χ^2=0.12, df=2	0.943
Female	26 (60.5)	9 (56.2)	23 (57.5)		
Ethnicity, n (%)					
White Dutch	27 (62.8)	10 (62.5)	25 (64.1)	χ^2=0.02, df=2	0.990
Other	16 (37.2)	6 (37.5)	14 (35.9)		
Level of education, n (%)[a]					
School	30 (69.8)	7 (43.8)	17 (42.5)		
Further	13 (30.2)	7 (43.8)	20 (50.0)	χ^2=9.69, df=4	0.046
Higher	-	2 (12.5)	3 (7.5)		
Number of valid beeps					
mean (range, min-max)	44.21 (25-59)	42.81 (23-57)	44.58 (24-58)	F=0.25, df=2	0.777
Attempted suicide, n (%)[b]					
During last year	6 (14.0)	-	-	-	-
Before age 17	8 (18.6)	-	-		
DSM-IV diagnosis, n (%)					
Pervasive developmental disorders NOS	10 (23.3)	-	5 (12.5)		
Attention-deficit and disruptive behaviour	6 (14.0)	3 (18.8)	-		
Adjustment disorders	4 (9.3)	-	-		
Anxiety disorders	2 (4.7)	-	-		
Depressive disorders	2 (4.7)	-	-		
Gender identity disorders	2 (4.7)	-	-		
Learning disorders	-	-	2 (5.0)		
Other disorders of infancy, childhood, or adolescence	5 (11.6)	-	-		
Parent-child relational problem	5 (11.6)	1 (6.3)	1 (2.5)		
Comorbid condition[c]	24 (55.8)	2 (4.7)	-		
None	7 (16.3)	12 (75.0)	32 (80.0)		
BDI-II sum scores, mean (S.D.)[d]	12.57 (9.31)	4.06 (3.32)	6.93 (7.00)	F=9.25, df=2	<0.001
BDI-II severity scores n (%)					
Minimal	20 (47.6)	15 (93.8)	32 (80.0)	χ^2=16.20, df=6	0.013
Mild	12 (28.6)	1 (6.3)	5 (12.5)		
Moderate	8 (19.1)	-	2 (5.0)		
Severe	2 (4.8)	-	1 (2.5)		

Table 1. (continued) Basic sample characteristics

	Service users (n=43)	Siblings (n=16)	Controls (n= 40)	Test statistic	p
CAPE sum scores, mean (S.D.)[d]					
Positive	9.84 (9.38)	4.00 (3.27)	4.60 (3.90)	F=7.67, df=2	<0.001
Negative	9.78 (6.93)	5.56 (3.90)	7.42 (4.83)	F=3.64, df=2	0.030
Depressive	7.57 (4.00)	4.31 (1.78)	4.67 (3.39)	F=8.91, df=2	<0.001
STAI-DY1 mean scores, mean (S.D.)[d]	1.76 (0.53)	1.52 (0.35)	1.56 (0.37)	F=2.95, df=2	0.057
STAI-DY2 mean scores, mean (S.D.)[d]	2.15 (0.52)	1.71 (0.25)	1.85 (0.42)	F=7.75, df=2	<0.001
CTQ mean scores, mean (S.D.)[d]					
Sexual abuse	1.29 (0.87)	1.05 (0.20)	1.02 (0.13)	F=2.37, df=2	0.099
Physical abuse	1.31 (0.77)	1.14 (0.32)	1.08 (0.23)	F=1.91, df=2	0.153
Emotional abuse	1.98 (1.05)	1.56 (0.45)	1.46 (0.65)	F=4.26, df=2	0.017
Emotional neglect	2.28 (0.95)	1.73 (0.36)	1.81 (0.51)	F=5.58, df=2	0.005
Physical neglect	1.45 (0.61)	1.10 (0.15)	1.17 (0.31)	F=5.39, df=2	0.006
CTQ severity scores n (%)					
Sexual abuse					
None/Minimal	35 (83.4)	15 (93.8)	39 (97.5)	χ^2=7.61, df=6	0.268
Low	2 (4.8)	-	-		
Moderate	2 (4.8)	1 (6.3)	1 (2.5)		
Severe	3 (7.1)	-	-		
Physical abuse					
None/Minimal	36 (85.7)	14 (87.5)	38 (95.0)	χ^2=5.32, df=6	0.503
Low	1 (2.4)	1 (6.3)	1 (2.5)		
Moderate	2 (4.8)	1 (6.3)	1 (2.5)		
Severe	3 (7.1)	-	-		
Emotional abuse					
None/Minimal	22 (52.4)	11 (68.8)	34 (85.0)	χ^2=11.93, df=6	0.064
Low	11 (26.2)	4 (25.0)	3 (7.5)		
Moderate	4 (9.5)	1 (6.3)	1 (2.5)		
Severe	5 (11.9)	-	2 (5.0)		
Physical neglect					
Minimal	28 (66.7)	16 (100.0)	37 (92.5)	χ^2=14.34, df=6	0.026
Low	7 (16.7)	-	2 (5.0)		
Moderate	4 (9.5)	-	-		
Severe	3 (7.1)	-	1 (2.5)		
Emotional neglect					
None/Minimal	18 (42.9)	11 (68.8)	23 (57.5)	χ^2=13.20, df=6	0.040
Low	13 (31.0)	5 (31.3)	15 (37.5)		
Moderate	4 (9.5)	-	2 (5.0)		
Severe	7 (16.7)	-	-		

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Table 1. (continued) Basic sample characteristics

Note: S.D., standard deviation; df, degrees of freedom; β, standardized regression coefficients; CI, confidence interval;
[a] categories defined as: school (primary education, LBO, MAVO, VMBO), further (MBO, HAVO, VWO), and higher (HBO, WO) of the Dutch educational system
[b] based on self-reports
[c] consisting of the following diagnostic categories in the group of service users: Additional codes (Parent-child relational problem, 33.3%; Borderline intellectual functioning, 13.3%; Neglect of child, 6.7%), Attention-deficit and disruptive behaviour disorders (10%), Learning disorders (10%), Personality Disorders (6.7%), Mild mental retardation (6.7%), Anxiety Disorders (3.3%), Dissociative Disorders (3.3%), Tic disorders (3.3%), Amphetamine related disorders (3.3%)
[d] difference in standardized coefficients across groups:

	Service users v. controls		***Siblings v. controls***		***Service users v. siblings***	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
BDI- II	0.68 (0.27 – 1.08)	0.001	-0.34 (-0.89 – 0.20)	0.221	1.02 (0.48 – 1.56)	<0.001
CAPE						
Positive	0.73 (0.31 – 1.14)	0.001	-0.08 (-0.63 – 0.47)	0.764	0.81 (0.26 – 1.36)	0.004
Negative	0.40 (-0.03 – 0.83)	0.066	-0.32 (-0.89 – 0.25)	0.273	0.72 (0.15 – 1.29)	0.014
Depressive	0.77 (0.37 – 1.18)	<0.001	-0.09 (-0.64 – 0.45)	0.731	0.87 (0.33 – 0.14)	0.002
STAI-DY1	0.46 (0.03 – 0.89)	0.035	-0.08 (-0.65 – 0.50)	0.796	0.54 (-0.03 – 1.11)	0.065
STAI-DY2	0.64 (0.23- 1.05)	0.003	-0.29 (-0.84 – 0.26)	0.294	0.93 (0.39 – 1.48)	0.001
CTQ						
Sexual abuse	0.45 (0.02 – 0.88)	0.041	0.05 (-0.53 – 0.63)	0.862	0.40 (-0.17 – 0.98)	0.170
Physical abuse	0.42 (-0.02 – 0.85)	0.059	0.10 (-0.48 – 0.69)	0.721	0.31 (-0.26 – 0.89)	0.283
Emotional abuse	0.60 (0.18 – 1.03)	0.006	0.12 (-0.45 – 0.69)	0.676	0.48 (-0.08 – 1.05)	0.092
Physical neglect	0.59 (0.17 – 1.01)	0.006	-0.15 (-0.71 – 0.41)	0.600	0.74 (0.18 – 1.30)	0.010
Emotional neglect	0.61 (0.19 – 1.03)	0.005	-0.12 (-0.68 – 0.44)	0.673	0.73 (0.17 – 1.29)	0.011

Aggregate scores

Overall, no differences in aggregated scores of various types of momentary stress (event-related, activity-related, and social stress) were found comparing service users and controls as well as siblings and controls (see Table 2). There was some evidence that service users experienced more (i) negative affect (p=0.077) and (ii) psychotic experiences (p=0.087) in their daily life compared to controls; no differences were found between siblings and controls.

Association between stress, negative affect, and psychotic experiences by group [H1]

Table 3 shows that, within service users and controls, each type of stress was associated with a small to moderate increase in (i) negative affect and (ii) psychotic experiences [H1], but not in siblings (except for association between event-related stress and negative affect). Further, there was evidence for two-way interaction effects of stress × group on (i) negative affect and (ii) psychotic experiences (all $p < 0.05$) excluding the association between social stress and negative affect (p=0.188).

Table 2. Aggregate ESM scores for momentary stress, negative affect and psychotic experiences in service users, siblings, and controls

	Service users	**Siblings**	**Controls**	**Service users *v*. Controls**		**Siblings *v*. Controls**	
	Mean (S.D.)	**Mean (S.D.)**	**Mean (S.D.)**	**B (95% CI)**	**p**	**B (95% CI)**	**p**
Stress							
Event-related	3.00 (0.77)	3.24 (0.71)	3.18 (0.75)	-0.10 (-0.41 – 0.22)	0.558	0.11 (-0.32 – 0.54)	0.628
Activity-related	2.78 (0.67)	2.62 (0.69)	2.71 (0.68)	0.08 (-0.21 – 0.37)	0.582	-0.07 (-0.46 – 0.32)	0.720
Social	2.75 (0.75)	2.53 (0.58)	2.63 (0.72)	0.09 (-0.21 – 0.39)	0.552	-0.11 (-0.52 – 0.29)	0.582
Negative affect	1.80 (0.67)	1.41 (0.47)	1.56 (0.60)	0.23 (-0.03 – 0.49)	0.077	-0.13 (-0.48 – 0.22)	0.469
Psychotic experiences	1.49 (0.64)	1.25 (0.52)	1.28 (0.46)	0.21 (-0.03 – 0.44)	0.087	-0.01 (-0.32 – 0.31)	0.963

Note: ESM, Experience Sampling Method; S.D., standard deviation; CI, confidence interval

Table 3. Association between momentary stress, negative affect and psychotic experiences, by group[a]

	Service users		Siblings		Controls		LR test for interaction[b]	
	adj. B (95% CI)	**p**	**adj. B (95% CI)**	**p**	**adj. B (95% CI)**	**p**	**χ^2 (df)**	**p**
				Outcome: Negative affect				
Stress								
Event-related	0.10 (0.08 – 0.12)	<0.001	0.05 (0.02 – 0.08)	0.002	0.08 (0.05 – 0.10)	<0.001	6.51 (2)	0.039
Activity-related	0.14 (0.11 – 0.16)	<0.001	0.03 (-0.02 - 0.08)	0.217	0.10 (0.07 - 0.13)	<0.001	13.84 (2)	0.001
Social	0.06 (0.04 – 0.08)	<0.001	0.02 (-0.01 – 0.06)	0.178	0.05 (0.03 – 0.07)	<0.001	3.34 (2)	0.188
				Outcome: Psychotic experiences				
Stress								
Event-related	0.04 (0.03 – 0.05)	<0.001	0.01 (-0.01 – 0.02)	0.556	0.01 (0.001 – 0.02)	0.029	20.58 (2)	<0.001
Activity-related	0.07 (0.06 – 0.08)	<0.001	0.02 (-0.01 – 0.05)	0.131	0.04 (0.02 – 0.05)	<0.001	15.77 (2)	<0.001
Social	0.03 (0.02 – 0.04)	<0.001	0.01 (-0.004 – 0.03)	0.119	0.01 (-0.00 – 0.02)	0.131	7.09 (2)	0.029

Note: df, degrees of freedom; CI, confidence interval; LR, likelihood ratio; v., versus
[a] Adjusted for age, gender, ethnicity, and level of education
[b] Likelihood ratio test for stress × group interaction; difference in coefficients across groups:

	Service users v. controls		***Siblings v. controls***		***Service users v. siblings***	
	adj. B (95% CI)	**p**	**adj. B (95% CI)**	**p**	**adj. B (95% CI)**	**p**
			Outcome: Negative affect			
Event	0.02 (-0.01 – 0.05)	0.141	-0.03 (-0.06 – 0.01)	0.192	0.05 (0.01 – 0.09)	0.013
Activity	0.03 (-0.01 – 0.07)	0.091	-0.07 (-0.13 - -0.01)	0.016	0.10 (0.05 – 0.16)	<0.001
Social	0.01 (-0.02 – 0.04)	0.487	-0.03 (-0.07 – 0.01)	0.216	0.04 (-0.002 – 0.07)	0.068
			Outcome: Psychotic experiences			
Event	0.03 (0.01 – 0.05)	<0.001	-0.01 (-0.03 – 0.01)	0.472	0.04 (0.02 – 0.06)	<0.001
Activity	0.03 (0.01 – 0.06)	0.001	-0.02 (-0.05 – 0.02)	0.324	0.05 (0.02 – 0.08)	0.001
Social	0.02 (0.005 – 0.04)	0.010	0.01 (-0.02 – 0.03)	0.640	0.02 (-0.01 – 0.04)	0.147

Association between stress, negative affect, and psychotic experiences by sexual, physical and emotional abuse and group [H2 & H3]

As presented in Table 4 and 5, there was no evidence that childhood sexual abuse amplified the association of event-related, activity-related and social stress with (i) negative affect and (ii) psychotic experiences in service users, their siblings and controls.

However, there was strong evidence that the association of various types of momentary stress with (i) negative affect and (ii) psychotic experiences was modified by physical and emotional abuse within [H2] and across [H3] groups as indicated by significant 3-way interaction effects described below and illustrated in Supplementary Figures (Figures S1).

Within groups (H2)

In service users exposed to high *v.* low levels of physical and emotional abuse, event-related (B=0.13, p<0.001; B=0.19, p<0.001) and activity-related (B=0.10, p<0.001; B=0.15, p<0.001) stress were associated with more intense (i) negative affect, and event-related stress (B=0.06, p<0.001; B=0.10, p<0.001) was associated with more intense (ii) psychotic experiences. In contrast to service users, activity-related (B=-0.16, p=0.033) and social (B=-0.26, p=0.014) stress were associated with less intense negative affect in daily life in controls exposed to high *v.* low levels of physical abuse. There was no evidence of effect modification by levels of emotional abuse in controls, except for a greater association between event-related (B=0.07, p=0.014) stress and psychotic experiences in those exposed to high *v*. low levels of emotional abuse. In siblings, there was no evidence that childhood abuse modified associations between momentary stress with (i) negative affect and (ii) psychotic experiences.

Table 4. Association between momentary stress and negative affect, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ² (df)	p
			Outcome: negative affect					
Event-related stress × sexual abuse × group[b]							3.86 (2)	0.145
Activity-related stress x sexual abuse x group[b]							2.95 (2)	0.229
Social stress x sexual abuse x group[b]							1.33 (2)	0.515
Event-related stress × physical abuse × group[b]							12.09 (5)	0.033
Level of physical abuse								
High (mean+1 SD)	0.21 (0.17 – 0.25)	<0.001	0.07 (-0.06 – 0.20)	0.288	0.07 (-0.08 – 0.23)	0.359		
Average (mean)	0.15 (0.11 – 0.18)	<0.001	0.09 (0.03 – 0.15)	0.003	0.13 (0.08 – 0.17)	<0.001		
Low (mean-1 SD)	0.08 (0.04 – 0.13)	0.001	0.11 (-0.004 – 0.22)	0.059	0.18 (0.07 – 0.29)	0.001		
High v. low[c]	0.13 (0.08 – 0.17)	<0.001	-0.04 (-0.25 – 0.17)	0.705	-0.11 (-0.36 – 0.15)	0.405		
Activity-related stress x physical abuse x group[b]							12.32 (2)	0.002
Level of physical abuse								
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	0.02 (-0.08 – 0.12)	0.705	0.04 (-0.05 – 0.14)	0.351		
Average (mean)	0.18 (0.15 – 0.22)	<0.001	0.04 (-0.02 – 0.11)	0.186	0.13 (0.09 – 0.17)	<0.001		
Low (mean-1 SD)	0.13 (0.09 – 0.18)	<0.001	0.07 (-0.05 – 0.18)	0.238	0.21 (0.13 – 0.29)	<0.001		
High v. low[c]	0.10 (0.05 – 0.15)	<0.001	-0.05 (-0.22 – 0.12)	0.577	-0.16 (-0.32 – -0.01)	0.033		
Social stress x physical abuse x group[b]							5.99 (2)	0.050
Level of physical abuse								
High (mean+1 SD)	0.10 (0.07 – 0.14)	<0.001	0.08 (-0.06 – 0.23)	0.257	-0.07 (-0.20 – 0.06)	0.305		
Average (mean)	0.11 (0.07 – 0.14)	<0.001	0.05 (-0.02 – 0.11)	0.151	0.06 (0.02 – 0.11)	0.007		
Low (mean-1 SD)	0.11 (0.07 – 0.16)	<0.001	0.01 (-0.11 – 0.13)	0.882	0.19 (0.10 – 0.29)	<0.001		
High v. low[c]	-0.01 (-0.05 – 0.04)	0.708	0.07 (-0.16 – 0.30)	0.529	-0.26 (-0.47 – -0.05)	0.014		

Table 4 (continued) . Association between momentary stress and negative affect by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ^2 (df)**	**p**
			Outcome: negative affect					
Event-related stress × emotional abuse × group[b]							16.15 (5)	0.006
Level of emotional abuse								
High (mean+1 SD)	0.22 (0.19 – 0.26)	<0.001	0.15 (0.01 – 0.29)	0.042	0.16 (0.08 – 0.24)	<0.001		
Average (mean)	0.13 (0.09 – 0.17)	<0.001	0.09 (0.04 – 0.15)	0.001	0.14 (0.10 – 0.18)	<0.001		
Low (mean-1 SD)	0.04 (-0.01 – 0.09)	0.142	0.04 (-0.09 – 0.17)	0.514	0.13 (0.07 – 0.18)	<0.001		
High v. low[c]	0.19 (0.14 – 0.24)	<0.001	0.10 (-0.14 – 0.35)	0.402	0.03 (-0.07 – 0.14)	0.537		
Activity-related stress x emotional abuse x group[b]							12.00 (2)	0.003
Level of emotional abuse								
High (mean+1 SD)	0.25 (0.21 – 0.29)	<0.001	0.01 (-0.11 – 0.13)	0.899	0.14 (0.07 – 0.20)	<0.001		
Average (mean)	0.17 (0.13 – 0.21)	<0.001	0.04 (-0.02 – 0.11)	0.183	0.14 (0.09 – 0.18)	<0,001		
Low (mean-1 SD)	0.09 (0.04 – 0.15)	<0.001	0.08 (-0.05 – 0.21)	0.222	0.13 (0.08 – 0.19)	<0.001		
High v. low[c]	0.15 (0.10 – 0.21)	<0.001	-0.07 (-0.29 – 0.14)	0.501	0.001 (-0.08 – 0.08)	0.980		
Social stress x emotional abuse x group[b]							4.38 (2)	0.111
Event-related stress × emotional neglect × group[b]							0.05 (2)	0.827
Activity-related stress x emotional neglect x group[b]							9.16 (2)	0.010
Level of emotional neglect								
High (mean+1 SD)	0.22 (0.18 – 0.26)	<0.001	-0.15 (-0.33 – 0.03)	0.097	0.13 (0.06 – 0.20)	<0.001		
Average (mean)	0.18 (0.14 – 0.22)	<0.001	-0.004 (-0.08 – 0.07)	0.905	0.14 (0.10 – 0.18)	<0.001		
Low (mean-1 SD)	0.14 (0.09 – 0.20)	<0.001	0.14 (0.03 – 0.25)	0.010	0.14 (0.08 – 0.20)	<0.001		
High v. low[c]	0.07 (0.02 – 0.13)	0.010	-0.29 (-0.54 – -0.04)	0.022	-0.01 (-0.11 – 0.09)	0.830		

Table 4 (continued) . Association between momentary stress and negative affect by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p
			Outcome: negative affect					
Social stress x emotional neglect x group[b]							3.19 (2)	0.203
Event-related stress × physical neglect × group[b]							0.63 (2)	0.426
Activity-related stress x physical neglect x group[b]							26.90 (2)	<0.001
Level of physical neglect								
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	-0.11 (-0.42 – 0.21)	0.512	0.05 (-0.02 – 0.12)	0.163		
Average (mean)	0.17 (0.13 – 0.21)	<0.001	-0.003 (-0.12 – 0.11)	0.962	0.13 (0.09 – 0.17)	<0.001		
Low (mean-1 SD)	0.11 (0.06 – 0.16)	<0.001	0.10 (-0.04 – 0.24)	0.164	0.20 (0.15 – 0.26)	<0.001		
High v. low[c]	0.12 (0.07 – 0.17)	<0.001	-0.21 (-0.64 – 0.23)	0.353	-0.16 (-0.25 – -0.06)	0.001		
Social stress x physical neglect x group[b]							6.70 (2)	0.035
Level of physical neglect								
High (mean+1 SD)	0.10 (0.06 – 0.14)	<0.001	0.38 (0.04 – 0.73)	0.028	0.01 (-0.08 – 0.10)	0.783		
Average (mean)	0.11 (0.07 – 0.15)	<0.001	0.15 (0.03 – 0.27)	0.016	0.08 (0.03 – 0.12)	0.001		
Low (mean-1 SD)	0.12 (0.07 – 0.17)	<0.001	-0.09 (-0.23 – 0.05)	0.223	0.14 (0.07 – 0.20)	<0.001		
High v. low[c]	-0.02 (-0.07 – 0.03)	0.373	0.47 (0.01 – 0.94)	0.046	-0.13 (-0.26 – 0.004)	0.058		

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of abuse (sexual, physical, and emotional) and neglect (physical and emotional) within and across groups (service users, siblings, controls))

[a] Adjusted for age, gender, ethnicity, and level of education

[b] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(TRAUMA_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times TRAUMA_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(TRAUMA_j \times GROUP_j) + \beta_7(STRESS_{ij} \times TRAUMA_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

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Table 4 (continued) . Association between momentary stress and negative affect by trauma in service users, siblings, and controls[a]

[c] Difference in the magnitude of associations of momentary stress with negative affect between those exposed to high v. low levels of various forms of abuse and neglect across groups (Δ high v. low):

	Service users v. controls		Siblings v. controls		Service users v. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: negative affect			
Δ high vs. low physical abuse across groups						
Event-related stress	0.23 (-0.02 – 0.49)	0.075	0.07 (-0.26 – 0.40)	0.692	0.17 (-0.05 – 0.38)	0.129
Activity-related stress	0.26 (0.10 – 0.42)	0.001	0.12 (-0.11 – 0.35)	0.325	0.15 (-0.03 – 0.33)	0.108
Social stress	0.26 (0.04 – 0.47)	0.020	0.34 (0.02 – 0.65)	0.034	-0.08 (-0.32 – 0.15)	0.491
Δ high vs. low emotional abuse across groups						
Event-related stress	0.15 (0.03- 0.27)	0.011	0.07 (-0.19 – 0.34)	0.602	0.08 (-0.17 – 0.33)	0.520
Activity-related stress	0.15 (0.06 – 0.25)	0.002	-0.07 (-0.30 – 0.15)	0.523	0.23 (0.01 – 0.45)	0.044
Δ high vs. low emotional neglect across groups						
Activity-related stress	0.09 (-0.03 – 0.20)	0.151	-0.28 (-0.55 – 0.01)	0.042	0.36 (0.11 – 0.62)	0.005
Δ high vs. low physical neglect across groups						
Activity-related stress	0.28 (0.17 – 0.39)	<0.001	-0.05 (-0.49 – 0.40)	0.827	0.33 (-0.11 – 0.77)	0.140
Social stress	0.10 (-0.03 – 0.24)	0.140	0.60 (0.12 – 1.08)	0.015	-0.49 (-0.96 – -0.03)	0.038

Table 5. Association between momentary stress and psychotic experiences, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interactionc	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ2 (df)	p
Outcome: psychotic experiences								
Event-related stress × sexual abuse × group[b]							0.65 (2)	0.723
Activity-related stress x sexual abuse x group[b]							3.44 (2)	0.179
Social stress x sexual abuse x group							1.08 (2)	0.582
Event-related stress × physical abuse × group[b]							14.24 (5)	0.014
Level of physical abuse								
High (mean+1 SD)	0.09 (0.08 - 0.11)	<0.001	-0.004 (-0.07 – 0.06)	0.912	0.07 (-0.01 – 0.16)	0.087		
Average (mean)	0.06 (0.04 – 0.08)	<0.001	0.01 (-0.02 – 0.04)	0.583	0.03 (0.01 – 0.06)	0.011		
Low (mean-1 SD)	0.03 (0.01 – 0.06)	0.018	0.02 (-0.04 – 0.08)	0.495	-0.01 (-0.07 – 0.05)	0.754		
High v. low[c]	0.06 (0.04 – 0.09)	<0.001	-0.02 (-0.14 – 0.09)	0.664	0.08 (-0.05 – 0.22)	0.232		
Activity-related stress x physical abuse x group[b]							1.42 (2)	0.491
Social stress x physical abuse x group[b]							0.50 (2)	0.779
Event-related stress × emotional abuse × group[b]							15.32 (5)	0.009
Level of emotional abuse								
High (mean+1 SD)	0.10 (0.08 – 0.12)	<0.001	-0.01 (-0.08 – 0.07)	0.799	0.07 (0.03 – 0.11)	0.001		
Average (mean)	0.05 (0.03 – 0.07)	<0.001	0.01 (-0.02 – 0.04)	0.586	0.03 (0.01 – 0.06)	0.002		
Low (mean-1 SD)	0.004 (-0.02 – 0.03)	0.748	0.03 (-0.04 – 0.10)	0.439	-0.001 (-0.03 – 0.03)	0.936		
High v. low[c]	0.10 (0.07 – 0.13)	<0.001	-0.04 (-0.17 – 0.09)	0.579	0.07 (0.01 – 0.13)	0.014		

Table 5. (continued) . Association between momentary stress and psychotic experiences, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interactionc	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ2 (df)	p
Outcome: psychotic experiences								
Activity-related stress x emotional abuse x group[b]							1.89 (2)	0.388
Social stress x emotional abuse x group[b]							0.22 (2)	0.897
Event-related stress × emotional neglect × group[b]							0.24 (2)	0.626
Activity-related stress x emotional neglect x group[b]							0.88 (2)	0.645
Social stress x emotional neglect x group[b]							1.16 (2)	0.561
Event-related stress × physical neglect × group[b]							1.25 (2)	0.284
Activity-related stress x physical neglect x group[b]							0.42 (2)	0.809
Social stress x physical neglect x group[b]							0.64 (2)	0.728

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of abuse (sexual, physical, and emotional) and neglect (physical and emotional) within and across groups (service users, siblings, controls))

[a] Adjusted for age, gender, ethnicity, and level of education

[b] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(TRAUMA_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times TRAUMA_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(TRAUMA_j \times GROUP_j) + \beta_7(STRESS_{ij} \times TRAUMA_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

Table 5. (continued) . Association between momentary stress and psychotic experiences, by trauma in service users, siblings, and controls[a]

[c] Difference in the magnitude of associations of momentary stress with psychotic experiences between those exposed to high v. low levels of abuse across groups (Δ high v. low):

	Service users v. controls		***Siblings v. controls***		***Service users v. siblings***	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: psychotic experiences			
Δ high vs. low physical abuse across groups						
Event-related stress	-0.02 (-0.16 – 0.12)	0.794	-0.11 (-0.28 – 0.07)	0.231	0.09 (-0.03 – 0.20)	0.129
Δ high vs. low emotional abuse across groups						
Event-related stress	0.03 (-0.03 – 0.09)	0.383	-0.11 (-0.25 – 0.03)	0.136	0.14 (0.003 – 0.27)	0.045

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Group comparisons (H3)

We next investigated differences in magnitude of associations between those exposed to high *v*. low levels of abuse across groups. The difference in magnitude of associations of event-related (*B*=0.23, *p*=0.075; *B*=0.15, *p*=0.011), activity-related (*B*=0.26, *p*=0.001; *B*=0.15, *p*=0.002), and social (*B*=0.26, *p*=0.020) stress with negative affect between those exposed to high *v.* low levels of physical and emotional abuse were greater in service users than in controls. Similarly, the difference in magnitude of associations of social (*B*=0.34, *p*=0.034) stress with negative affect between those exposed to high *v.* low levels of physical abuse was greater in siblings than in controls. Also, differences in magnitude of associations of activity-related (*B*=0.23, *p*=0.044) stress with (i) negative affect and event-related (*B*=0.14, *p*=0.045) stress with (ii) psychotic experiences between those exposed to high *v.* low levels of emotional abuse were greater in service users than in siblings.

Association between stress, negative affect, and psychotic experiences by emotional- and physical neglect and group [H2 & H3]

As shown in Table 4, the association of various types of momentary stress with negative affect was modified by emotional and physical neglect, as indicated by significant 3-way interaction effects. In contrast, no evidence was found that emotional and physical neglect modified the association between momentary stress and psychotic experiences.

Within groups (H2)

Activity-related (*B*=0.07, *p*=0.010; *B*=0.12, *p*<0.001) stress was associated with more intense negative affect in service users exposed to high *v.* low levels of emotional and physical neglect. In contrast, activity-related (*B*=-0.16, *p*=0.001) and social (*B*=-0.13, *p*=0.058) stress were associated with less intense negative affect in controls exposed to high *v.* low levels of physical neglect. A mixed pattern of findings emerged in siblings.

Group comparisons (H3)

We found, across groups, differences in magnitude of associations between those exposed to high *v*. low levels of neglect. The difference in magnitude of associations of activity-related (*B*=0.28, *p*<0.001) stress with negative affect between those exposed to high v. low levels of physical neglect was greater in service users than in controls. In contrast, a mixed pattern of findings on differences in the magnitude of associations between those exposed to high *v*. low levels of neglect were found in service users *v*. siblings and siblings *v*. controls.

Discussion

Main findings

Using a context-sensitive and ecologically valid experience sampling design, we found strong evidence that momentary stress was associated with increased (i) negative affect and (ii) psychotic experiences in service users and controls [H1]. In line with hypotheses [H2 & H3], prior experiences of childhood trauma (physical and emotional abuse and, partially, emotional and physical neglect, but not sexual abuse) was found to impact on the stress sensitivity in daily life by modifying the association between momentary stress and (i) negative affect and (ii) psychotic experiences within and across service users and controls. While in service users more intense (i) negative affect and (ii) psychotic experiences were found when high *v*. low levels of various types of abuse and neglect were compared, controls showed, intriguingly, either less intense negative affect (evident in physical abuse and neglect) or no marked differences in the magnitude of associations, suggesting more resilience to the detrimental effects of CT on the stress sensitivity in daily life. A less consistent pattern of findings was evident in siblings.

Methodological considerations

Several methodological considerations should be considered when interpreting our findings. First, the CTQ used in the study is a retrospective, self-report measure of CT. One concern is that recall bias and cognitive distortion might affect ratings [75]. However, in the current study, the potential impact was minimized due to the lower age of the sample and, thus, the reduced time that had passed between exposure to and assessment of trauma. Similarly, while ESM allows the assessment of variables with high ecological validity, all ESM ratings were based on subjective self-reports. Hence, our findings require triangulation including other levels of investigation (e.g. biological markers and other socio-environmental factors) [76, 77]. Nevertheless, ESM has recently been found to be a reliable and valid assessment method in a young nonclinical sample [78].

Second, ESM may be associated with assessment burden and, especially in the group of service users, selection bias cannot be ruled out. However, through an extensive ESM recruitment procedure there was, overall, a large proportion of participants with a sufficient number of valid responses (90.8% with, on average, more than 42 responses in each group). Third, the sample size of the sibling group was small and inconsistent findings might have occurred due to sampling error in this intermediate risk group. Fourth, cross-sectional modelling of ESM data did not allow for investigating temporality of stress, negative affect and psychotic experiences. Time-lagged analyses of ESM data [79, 80] are required to investigate temporality as an important criterion to establish causality [81]. Fifth, although several potential confounders (i.e. age, gender, ethnicity, level of education) were assessed, other unmeasured confounders (e.g. direct or indirect measures of genetic risk, other childhood adversities, direct measures of shared genetic and socio-environmental risk of siblings) may have influenced reported findings. Results remained largely unchanged, however, when we controlled for clustering of observations within families (see Supplementary Tables S1 and S2). Last, individuals with a DSM-IV diagnosis and relatively high scores in various psychopathology measures (i.e. BDI-II, CAPE, STAI) were included in the control group. The rationale was to increase ecological validity as diagnoses and symptoms represent general population risk of morbidity and to overcome disadvantages including only a “super-healthy” control group [82, 83]. Thus, passing the threshold to seek help in mental health services was the a priori defined exclusion criterion. However, when we performed a sensitivity analysis excluding all controls with DSM-IV diagnoses (*N*=8), findings remained largely unchanged (see Supplementary Tables S3, S4, and S5).

Comparison with previous research

In recent years, evidence has accumulated that links experiences of abuse and neglect during childhood with the aetiology of a number of psychopathologies, including psychosis. Elevated stress sensitivity, characterized by heightened emotional reactivity and more intense psychotic experiences in response to minor hassles in the flow of daily life, has been proposed to constitute a putative underlying mechanism through which CT impacts on mental health. However, the number of studies conducted to date and the generalisability of recent findings to a help-seeking adolescent and young adult population remained limited.

The present study found, for the first time, that, in help-seeking adolescents and young adults with, on average, high levels of depressive, anxiety, and psychotic symptoms, prior exposure to CT was associated with increased negative affect and psychotic experiences in response to momentary stress in daily life. This finding is in accordance with the proposition that CT may sensitize individuals to subsequent adversity and adds to recent findings [47-50]. In controls, when high *v*. low levels of CT were compared, momentary stress was, in contrast, associated with either less intense negative affect (evident in physical abuse and physical neglect) or no marked differences in the magnitude of associations. This finding of qualitative interaction in service users and controls represents an important finding, as it suggests that non-help seeking controls with higher levels of CT were less sensitive and more resilient towards minor stress in daily life. In siblings, however, we found no evidence that stress sensitivity was increased in daily life and findings on elevated stress sensitivity in those exposed to CT were less consistent in this group than in service users. This may in part be explained by the lower levels of CT (in particular, physical and emotional neglect) in siblings than in service user. Also, given only some of the siblings will go on to develop a mental disorder, they may have formed a group of resilient and non-resilient individuals, and, thus, only some evidence of elevated stress sensitivity in those with higher levels of CT was observed at a group level. However, the results should be interpreted with caution as the sample size of the sibling group was small and inconsistent, and, thus, findings may have occurred due to sampling error. Consistent with some ESM studies in help-seeking individuals and controls [48, 70, 84], we found no difference in aggregate ESM scores of momentary stress across groups, but elevated sensitivity to momentary stress in service users compared to controls and siblings. This tentatively suggests that it is not higher overall levels of perceived daily stress per se, but increased *sensitivity to* stress that is of relevance for mental health in help-seeking adolescents and young adults.

Reported findings in controls partly echoes findings in which adult controls exposed to high levels of sexual abuse reported less intense negative affect and psychotic experiences in response to minor socio-environmental stressors [50]. It corroborates, more generally, findings from previous research that a significant proportion of individuals exposed to childhood adversity do show resilience to develop any form of psychopathology and maintain psychosocial functioning [85-87]. Our findings suggest that CT does not inevitably lead to an increased sensitization to subsequent adversity. Instead, how CT impacts on mental health through stress sensitivity may depend on both individuals' vulnerability and various protective factors of biopsychosocial nature [87-89]. Several psychological, socio-environmental, and biological factors have been posited to contribute to offset the detrimental impact of adversity such as strong social networks and secure attachment, high-quality interpersonal relationships, good cognitive, social, and emotional skills, and a lower polygenic risk [85-87].

In line with observations of undefined clinical pictures and non-specific mental health symptoms at a developmentally early stage of psychopathology [2, 5], high levels of depressive, anxiety, and psychotic symptoms as well as high proportions of non-specific diagnoses and comorbidity were observed in the group of service users, which may further support previously proposed extended transdiagnostic phenotypes of psychopathology [11, 12, 14, 15, 90]. Notably, our study found that CT impacts more consistently on the association between momentary stress and negative affect and, thus, the emotional reactivity in daily life. This may be viewed, while speculative, in the context of proposed affective pathways to psychosis [91, 92] and recent integrated socio-developmental models [41, 43, 88, 93], in which the importance of premorbid anxiety and depressive symptoms and impairments in cognitive, motor, and social domains are posited to be manifest many years before prodromal symptoms and the first psychotic episode. Critically, and despite strong evidence from several studies, sexual abuse was not found to amplify individuals' stress sensitivity in our study. This may, in part, be explained by higher levels of trauma repression (i.e. amnesia for abuse memories) or impeded disclosure [94, 95], indicated by higher levels of self-reported sexual abuse in help-seeking adults compared to help-seeking adolescents and young adults and older and younger community samples [96-99].

Taken together, our findings suggest that stress sensitivity may be an important underlying risk or resilience mechanism of a transdiagnostic phenotype of depression, anxiety, and psychosis through which CT may impact on mental health in youth. While primary prevention of childhood trauma remains the ultimate – but difficult to achieve - goal, there is a need to carefully assess CT in youth mental health services and continue to strengthen the evidence on its impact (including the impact of clustering of CT within families) as basis for developing and evaluating evidence-based treatments in order to tackle the consequences of CT in help-seeking adolescents and young adults.

This may be addressed through developing and evaluating ecological momentary interventions that directly target elevated stress sensitivity in specific contexts in the real-world and real-time through interactive delivery schemes [100, 101] to prevent adverse clinical and social outcomes later in life.

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Supplementary material

Table S1. Association between momentary stress and negative affect controlled for clustering within families, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p
			Outcome: negative affect					
Event-related stress × sexual abuse × group[b]							3.88 (2)	0.144
Activity-related stress x sexual abuse x group[b]							3.04 (2)	0.219
Social stress x sexual abuse x group[b]							1.35 (2)	0.509
Event-related stress × physical abuse × group[b]							10.65 (5)	0.059
Level of physical abuse								
High (mean+1 SD)	0.21 (0.17 – 0.25)	<0.001	0.07 (-0.05 – 0.20)	0.248	0.07 (-0.09 – 0.23)	0.379		
Average (mean)	0.15 (0.11 – 0.19)	<0.001	0.09 (0.03 – 0.15)	0.002	0.13 (0.08 – 0.17)	<0.001		
Low (mean-1 SD)	0.08 (0.04 – 0.13)	0.001	0.11 (-0.01 – 0.22)	0.064	0.18 (0.08 – 0.29)	0.001		
High v. low[c]	0.13 (0.08 – 0.17)	<0.001	-0.03 (-0.24 – 0.18)	0.762	-0.11 (-0.37 – 0.14)	0.384		
Activity-related stress x physical abuse x group[b]							12.21 (2)	0.002
Level of physical abuse								
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	0.02 (-0.08 – 0.12)	0.685	0.05 (-0.05 – 0.14)	0.337		
Average (mean)	0.18 (0.15 – 0.22)	<0.001	0.05 (-0.02 – 0.12)	0.138	0.13 (0.09 – 0.17)	<0.001		
Low (mean-1 SD)	0.14 (0.09 – 0.18)	<0.001	0.08 (-0.04 – 0.19)	0.131	0.21 (0.13 – 0.28)	<0.001		
High v. low[c]	0.10 (0.05 – 0.15)	<0.001	-0.06 (-0.23 – 0.12)	0.520	-0.16 (-0.31 – -0.01)	0.037		

Table S1. (continued). Association between momentary stress and negative affect controlled for clustering within families, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ² (df)	p
			Outcome: negative affect					
Social stress x physical abuse x group[b]							5.86 (2)	0.054
Level of physical abuse								
High (mean+1 SD)	0.10 (0.07 – 0.14)	<0.001	0.08 (-0.06 – 0.23)	0.257	-0.07 (-0.20 – 0.06)	0.305		
Average (mean)	0.11 (0.07 – 0.14)	<0.001	0.05 (-0.02 – 0.11)	0.151	0.06 (0.02 – 0.11)	0.007		
Low (mean-1 SD)	0.11 (0.07 – 0.16)	<0.001	0.01 (-0.11 – 0.13)	0.882	0.19 (0.10 – 0.29)	<0.001		
High v. low[c]	-0.01 (-0.05 – 0.04)	0.708	0.07 (-0.16 – 0.30)	0.529	-0.26 (-0.47 – -0.05)	0.014		
Event-related stress × emotional abuse × group[b]							13.01 (5)	0.023
Level of emotional abuse								
High (mean+1 SD)	0.22 (0.19 – 0.26)	<0.001	0.15 (0.01 – 0.29)	0.035	0.15 (0.08 – 0.23)	<0.001		
Average (mean)	0.13 (0.09 – 0.17)	<0.001	0.10 (0.04 – 0.15)	0.001	0.14 (0.10 – 0.18)	<0.001		
Low (mean-1 SD)	0.04 (-0.01 – 0.09)	0.140	0.04 (-0.09 – 0.17)	0.522	0.13 (0.08 – 0.18)	<0.001		
High v. low[c]	0.19 (0.14 – 0.24)	<0.001	0.11 (-0.13 – 0.35)	0.377	0.03 (-0.08 – 0.13)	0.641		
Activity-related stress x emotional abuse x group[b]							11.91 (2)	0.003
Level of emotional abuse								
High (mean+1 SD)	0.25 (0.21 – 0.29)	<0.001	0.01 (-0.11 – 0.13)	0.882	0.14 (0.08 – 0.20)	<0.001		
Average (mean)	0.17 (0.13 – 0.21)	<0.001	0.05 (-0.02 – 0.11)	0.146	0.13 (0.09 – 0.17)	<0,001		
Low (mean-1 SD)	0.10 (0.04 – 0.15)	<0.001	0.09 (-0.04 – 0.22)	0.185	0.13 (0.08 – 0.19)	<0.001		
High v. low[c]	0.15 (0.10 – 0.21)	<0.001	-0.08 (-0.29 – 0.14)	0.470	0.00 (-0.08 – 0.08)	0.948		
Social stress x emotional abuse x group[b]							4.46 (2)	0.108
Event-related stress × emotional neglect × group[b]							0.12 (2)	0.803

Table S1. (continued). Association between momentary stress and negative affect controlled for clustering within families, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p
				Outcome: negative affect				
Activity-related stress x emotional neglect x group[b]							9.17 (2)	0.010
Level of emotional neglect								
High (mean+1 SD)	0.22 (0.18 – 0.26)	<0.001	-0.15 (-0.32 – 0.03)	0.106	0.13 (0.05 – 0.20)	0.001		
Average (mean)	0.18 (0.14 – 0.22)	<0.001	0.00 (-0.08 – 0.08)	0.994	0.13 (0.09 – 0.18)	<0.001		
Low (mean-1 SD)	0.15 (0.09 – 0.20)	<0.001	0.15 (0.04 – 0.25)	0.007	0.14 (0.08 – 0.20)	<0.001		
High v. low[c]	0.07 (0.02 – 0.13)	0.012	-0.29 (-0.54 – -0.04)	0.021	-0.01 (-0.11 – 0.09)	0.797		
Social stress x emotional neglect x group[b]							3.48 (2)	0.176
Event-related stress × physical neglect × group[b]							1.13 (2)	0.402
Activity-related stress x physical neglect x group[b]							27.69 (2)	<0.001
Level of physical neglect								
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	-0.11 (-0.42 – 0.21)	0.501	0.04 (-0.02 – 0.11)	0.196		
Average (mean)	0.17 (0.13 – 0.21)	<0.001	0.00 (-0.11 – 0.11)	0.988	0.12 (0.08 – 0.17)	<0.001		
Low (mean-1 SD)	0.11 (0.06 – 0.16)	<0.001	0.11 (-0.03 – 0.25)	0.126	0.21 (0.15 – 0.26)	<0.001		
High v. low[c]	0.12 (0.07 – 0.17)	<0.001	-0.22 (-0.65 – 0.22)	0.324	-0.16 (-0.26 – -0.06)	0.001		
Social stress x physical neglect x group[b]							6.82 (2)	0.033
Level of physical neglect								
High (mean+1 SD)	0.10 (0.06 – 0.14)	<0.001	0.37 (0.03 – 0.71)	0.033	0.00 (-0.08 – 0.09)	0.920		
Average (mean)	0.11 (0.08 – 0.15)	<0.001	0.15 (0.03 – 0.27)	0.018	0.07 (0.03 – 0.11)	0.001		
Low (mean-1 SD)	0.12 (0.07 – 0.17)	<0.001	-0.08 (-0.22 – 0.06)	0.267	0.14 (0.08 – 0.21)	<0.001		
High v. low[c]	-0.02 (-0.07 – 0.03)	0.367	0.45 (-0.01 – 0.92)	0.056	-0.14 (-0.27 – 0.01)	0.041		

Table S1. (continued). Association between momentary stress and negative affect controlled for clustering within families, by trauma in service users, siblings, and controls[a]

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of abuse (sexual, physical, and emotional) and neglect (physical and emotional) within and across groups (service users, siblings, controls))

[a] Adjusted for age, gender, ethnicity, and level of education

[b] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(TRAUMA_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times TRAUMA_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(TRAUMA_j \times GROUP_j) + \beta_7(STRESS_{ij} \times TRAUMA_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

[c] Difference in the magnitude of associations of momentary stress with negative affect between those exposed to high v. low levels of various forms of abuse and neglect across groups (Δ high v. low):

Table S1. (continued). Association between momentary stress and negative affect controlled for clustering within families, by trauma in service users, siblings, and controls[a]

	Service users v. controls		Siblings v. controls		Service users v. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: negative affect			
Δ high vs. low physical abuse across groups						
Activity-related stress	0.26 (0.10 – 0.42)	0.001	0.10 (-0.13 – 0.33)	0.376	0.16 (-0.03 – 0.34)	0.092
Social stress	0.26 (0.04 – 0.47)	0.020	0.34 (0.02 – 0.65)	0.034	-0.08 (-0.32 – 0.15)	0.491
Δ high vs. low emotional abuse across groups						
Event-related stress	0.16 (0.04- 0.28)	0.07	0.08 (-0.18 – 0.35)	0.533	0.08 (-0.17 – 0.32)	0.546
Activity-related stress	0.15 (0.05 – 0.25)	0.002	-0.08 (-0.31 – 0.15)	0.484	0.23 (0.01 – 0.45)	0.040
Δ high vs. low emotional neglect across groups						
Activity-related stress	0.09 (-0.03 – 0.20)	0.149	-0.28 (-0.55 – 0.01)	0.042	0.36 (0.11 – 0.62)	0.005
Δ high vs. low physical neglect across groups						
Activity-related stress	0.28 (0.17 – 0.39)	<0.001	-0.06 (-0.50 – 0.39)	0.798	0.34 (-0.10 – 0.78)	0.126
Social stress	0.11 (-0.02 – 0.25)	0.106	0.59 (0.11 – 1.07)	0.017	-0.47 (-0.94 – -0.01)	0.046

[c] Difference in the magnitude of associations of momentary stress with negative affect between those exposed to high v. low levels of various forms of abuse and neglect across groups (Δ high v. low):

Table S2. Association between momentary stress and psychotic experiences controlled for clustering within families, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction[c]	
	adj. β (95% CI)	p	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p
Outcome: psychotic experiences								
Event-related stress × sexual abuse × group[b]							0.66 (2)	0.719
Activity-related stress x sexual abuse x group[b]							3.46 (2)	0.177
Social stress x sexual abuse x group							1.10 (2)	0.576
Event-related stress × physical abuse × group[b]							13.31 (5)	0.021
Level of physical abuse								
High (mean+1 SD)	0.10 (0.08 - 0.12)	<0.001	-0.00 (-0.07 – 0.07)	0.991	0.07 (-0.01 – 0.16)	0.090		
Average (mean)	0.06 (0.04 – 0.08)	<0.001	0.01 (-0.02 – 0.04)	0.524	0.03 (0.01 – 0.06)	0.011		
Low (mean-1 SD)	0.03 (0.01 – 0.06)	0.016	0.02 (-0.04 – 0.08)	0.525	-0.01 (-0.07 – 0.05)	0.769		
High v. low[c]	0.06 (0.04 – 0.09)	<0.001	-0.02 (-0.13 – 0.09)	0.737	0.08 (-0.05 – 0.22)	0.239		
Activity-related stress x physical abuse x group[b]							1.58 (2)	0.455
Social stress x physical abuse x group[b]							0.41 (2)	0.815
Event-related stress × emotional abuse × group[b]							12.54 (5)	0.028
Level of emotional abuse								
High (mean+1 SD)	0.10 (0.08 – 0.12)	<0.001	-0.01 (-0.08 – 0.07)	0.859	0.07 (0.03 – 0.11)	0.001		
Average (mean)	0.05 (0.03 – 0.07)	<0.001	0.01 (-0.02 – 0.04)	0.511	0.03 (0.01 – 0.06)	0.003		
Low (mean-1 SD)	0.01 (-0.02 – 0.03)	0.719	0.03 (-0.04 – 0.10)	0.430	-0.00 (-0.03 – 0.03)	0.942		
High v. low[c]	0.10 (0.07 – 0.13)	<0.001	-0.03 (-0.16 – 0.10)	0.604	0.07 (0.01 – 0.13)	0.016		

Table S2. (continued). Association between momentary stress and psychotic experiences controlled for clustering within families, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction[c]	
	adj. β (95% CI)	p	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p
Outcome: psychotic experiences								
Activity-related stress x emotional abuse x group[b]							1.95 (2)	0.377
Social stress x emotional abuse x group[b]							0.22 (2)	0.898
Event-related stress × emotional neglect × group[b]							0.32 (2)	0.601
Activity-related stress x emotional neglect x group[b]							0.84 (2)	0.657
Social stress x emotional neglect x group[b]							1.35 (2)	0.508
Event-related stress × physical neglect × group[b]							5.64 (2)	0.060
Activity-related stress x physical neglect x group[b]							0.60 (2)	0.742
Social stress x physical neglect x group[b]							0.44 (2)	0.801

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of abuse (sexual, physical, and emotional) and neglect (physical and emotional) within and across groups (service users, siblings, controls))

Table S2. (continued). Association between momentary stress and psychotic experiences controlled for clustering within families, by trauma in service users, siblings, and controls[a]

[a] Adjusted for age, gender, ethnicity, and level of education
[b] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(TRAUMA_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times TRAUMA_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(TRAUMA_j \times GROUP_j) + \beta_7(STRESS_{ij} \times TRAUMA_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)
[c] Difference in the magnitude of associations of momentary stress with psychotic experiences between those exposed to high v. low levels of abuse across groups (Δ high v. low):

	Service users v. controls		Siblings v. controls		Service users v. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: psychotic experiences			
Δ high vs. low physical abuse across groups						
Event-related stress	-0.02 (-0.15 – 0.12)	0.809	-0.10 (-0.28 – 0.08)	0.263	0.08 (-0.03 – 0.20)	0.154
Δ high vs. low emotional abuse across groups						
Event-related stress	0.03 (-0.03 – 0.09)	0.357	-0.10 (-0.24 – 0.04)	0.150	0.13 (0.00 – 0.26)	0.048

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Table S3. Association between momentary stress, negative affect and psychotic experiences excluding controls with diagnoses, by group[a]

	Service users		Siblings		Controls		LR test for interactionb	
	adj. B (95% CI)	p	adj. B (95% CI)	p	adj. B (95% CI)	p	χ2 (df)	p
				Outcome: Negative affect				
Stress								
Event-related	0.10 (0.08 – 0.12)	<0.001	0.05 (0.02 – 0.08)	0.002	0.07 (0.05 – 0.10)	<0.001	6.77 (2)	0.034
Activity-related	0.14 (0.11 – 0.16)	<0.001	0.03 (-0.02 - 0.08)	0.212	0.10 (0.06 - 0.13)	<0.001	14.01 (2)	<0.001
Social	0.06 (0.04 – 0.08)	<0.001	0.02 (-0.01 – 0.06)	0.174	0.04 (0.02 – 0.07)	0.001	3.58 (2)	0.167
				Outcome: Psychotic experiences				
Stress								
Event-related	0.04 (0.03 – 0.05)	<0.001	0.01 (-0.01 – 0.02)	0.560	0.01 (0.001 – 0.03)	0.040	17.69 (2)	<0.001
Activity-related	0.07 (0.06 – 0.08)	<0.001	0.02 (-0.01 – 0.05)	0.138	0.04 (0.03 – 0.06)	<0.001	11.91 (2)	0.003
Social	0.03 (0.02 – 0.04)	<0.001	0.01 (-0.004 – 0.03)	0.126	0.02 (0.003 – 0.03)	0.018	3.20 (2)	0.202

Note: df, degrees of freedom; CI, confidence interval; LR, likelihood ratio; v., versus
[a] Adjusted for age, gender, ethnicity, and level of education
[b] Likelihood ratio test for stress × group interaction; difference in coefficients across groups:

	Service users v. controls		Siblings v. controls		Service users v. siblings	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
			Outcome: Negative affect			
Event	0.03 (-0.01 – 0.06)	0.108	-0.02 (-0.06 – 0.02)	0.299	0.05 (0.01 – 0.08)	0.014
Activity	0.04 (-0.003 – 0.08)	0.067	-0.06 (-0.12 - -0.01)	0.033	0.10 (0.05 – 0.16)	<0.001
Social	0.02 (-0.01 – 0.05)	0.298	-0.02 (-0.06– 0.02)	0.380	0.04 (-0.003 – 0.07)	0.070
			Outcome: Psychotic experiences			
Event	0.03 (0.01 – 0.05)	0.001	-0.01 (-0.03 – 0.01)	0.430	0.04 (0.02 – 0.06)	<0.001
Activity	0.03 (0.003 – 0.05)	0.028	-0.02 (-0.06 – 0.01)	0.153	0.05 (0.02 – 0.08)	0.001
Social	0.01 (-0.004 – 0.03)	0.145	-0.002 (-0.03 – 0.02)	0.840	0.02 (-0.01 – 0.04)	0.158

Table S4. Association between momentary stress and negative affect excluding controls with diagnoses, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p
Outcome: negative affect								
Event-related stress × sexual abuse × group[b]							3.99 (2)	0.136
Activity-related stress x sexual abuse x group[b]							2.96 (2)	0.228
Social stress x sexual abuse x group[b]							1.51 (2)	0.470
Event-related stress × physical abuse × group[b]							13.33 (5)	0.021
Level of physical abuse								
High (mean+1 SD)	0.21 (0.17 – 0.25)	<0.001	0.07 (-0.06 – 0.20)	0.285	0.06 (-0.11 – 0.23)	0.492		
Average (mean)	0.15 (0.11 – 0.18)	<0.001	0.09 (0.03 – 0.15)	0.002	0.12 (0.07 – 0.17)	<0.001		
Low (mean-1 SD)	0.08 (0.04 – 0.13)	0.001	0.11 (-0.004 – 0.22)	0.058	0.18 (0.06 – 0.30)	0.003		
High v. low[c]	0.13 (0.08 – 0.17)	<0.001	-0.04 (-0.25 – 0.17)	0.705	-0.12 (-0.39 – 0.15)	0.378		
Activity-related stress x physical abuse x group[b]							11.95 (2)	0.003
Level of physical abuse								
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	0.02 (-0.08 – 0.12)	0.702	0.04 (-0.05 – 0.14)	0.395		
Average (mean)	0.18 (0.15 – 0.22)	<0.001	0.05 (-0.02 – 0.11)	0.181	0.12 (0.08 – 0.17)	<0.001		
Low (mean-1 SD)	0.13 (0.09 – 0.18)	<0.001	0.07 (-0.04 – 0.19)	0.232	0.21 (0.12 – 0.29)	<0.001		
High v. low[c]	0.10 (0.05 – 0.15)	<0.001	-0.05 (-0.22 – 0.12)	0.572	-0.16 (-0.32 – -0.01)	0.037		
Social stress x physical abuse x group[b]							6.08 (2)	0.048
Level of physical abuse								
High (mean+1 SD)	0.10 (0.07 – 0.14)	<0.001	0.08 (-0.06 – 0.23)	0.254	-0.08 (-0.22 – 0.05)	0.230		
Average (mean)	0.11 (0.07 – 0.14)	<0.001	0.05 (-0.02 – 0.11)	0.147	0.05 (0.005 – 0.10)	0.031		

Table S4. (continued). Association between momentary stress and negative affect excluding controls with diagnoses, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ^2 (df)**	**p**
Outcome: negative affect								
Low (mean-1 SD)	0.11 (0.07 – 0.16)	<0.001	0.01 (-0.11 – 0.13)	0.876	0.19 (0.09 – 0.29)	<0.001		
High v. low[c]	-0.01 (-0.05 – 0.04)	0.711	0.07 (-0.16 – 0.30)	0.529	-0.27 (-0.49 – -0.06)	0.014		
Event-related stress × emotional abuse × group[b]							16.27 (5)	0.006
Level of emotional abuse								
High (mean+1 SD)	0.22 (0.19 – 0.26)	<0.001	0.15 (0.01 – 0.29)	0.043	0.16 (0.08 – 0.24)	<0.001		
Average (mean)	0.13 (0.09 – 0.17)	<0.001	0.09 (0.04 – 0.15)	0.001	0.14 (0.09 – 0.18)	<0.001		
Low (mean-1 SD)	0.04 (-0.01 – 0.09)	0.141	0.04 (-0.08 – 0.17)	0.501	0.11 (0.05 – 0.18)	<0.001		
High v. low[c]	0.19 (0.14 – 0.23)	<0.001	0.10 (-0.14 – 0.34)	0.410	0.04 (-0.07 – 0.16)	0.457		
Activity-related stress x emotional abuse x group[b]							10.03 (2)	0.006
Level of emotional abuse								
High (mean+1 SD)	0.25 (0.21 – 0.29)	<0.001	0.01 (-0.11 – 0.13)	0.895	0.13 (0.07 – 0.19)	<0.001		
Average (mean)	0.17 (0.13 – 0.21)	<0.001	0.05 (-0.02 – 0.11)	0.180	0.13 (0.08 – 0.17)	<0,001		
Low (mean-1 SD)	0.09 (0.04 – 0.14)	<0.001	0.08 (-0.05 – 0.21)	0.219	0.12 (0.06 – 0.18)	<0.001		
High v. low[c]	0.15 (0.10 – 0.21)	<0.001	-0.07 (-0.29 – 0.14)	0.499	0.01 (-0.07 – 0.10)	0.736		
Social stress x emotional abuse x group[b]							3.72 (2)	0.155
Event-related stress × emotional neglect × group[b]							0.00 (2)	0.966
Activity-related stress x emotional neglect x group[b]							8.94 (2)	0.011
Level of emotional neglect								
High (mean+1 SD)	0.22 (0.18 – 0.26)	<0.001	-0.15 (-0.33 – 0.03)	0.095	0.13 (0.05 – 0.20)	0.001		
Average (mean)	0.18 (0.14 – 0.22)	<0.001	-0.004 (-0.08 – 0.07)	0.904	0.13 (0.08 – 0.17)	<0.001		

Table S4. (continued). Association between momentary stress and negative affect excluding controls with diagnoses, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ^2 (df)**	**p**
			Outcome: negative affect					
Low (mean-1 SD)	0.14 (0.09 – 0.20)	<0.001	0.14 (0.03 – 0.25)	0.010	0.13 (0.07 – 0.20)	<0.001		
High v. low[c]	0.07 (0.02 – 0.13)	0.010	-0.29 (-0.54 – -0.04)	0.021	-0.01 (-0.12 – 0.10)	0.916		
Social stress x emotional neglect x group[b]							2.87 (2)	0.238
Event-related stress × physical neglect × group[b]							0.79 (2)	0.375
Activity-related stress x physical neglect x group[b]							26.02 (2)	<0.001
Level of physical neglect								
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	-0.11 (-0.42 – 0.21)	0.509	0.04 (-0.03 – 0.11)	0.228		
Average (mean)	0.17 (0.13 – 0.21)	<0.001	-0.003 (-0.12 – 0.11)	0.965	0.12 (0.08 – 0.17)	<0.001		
Low (mean-1 SD)	0.11 (0.06 – 0.16)	<0.001	0.10 (-0.04 – 0.24)	0.159	0.20 (0.14 – 0.26)	<0.001		
High v. low[c]	0.12 (0.07 – 0.17)	<0.001	-0.21 (-0.64 – 0.23)	0.348	-0.16 (-0.25 – -0.06)	0.002		
Social stress x physical neglect x group[b]							6.06 (2)	0.048
Level of physical neglect								
High (mean+1 SD)	0.10 (0.06 – 0.14)	<0.001	0.39 (0.04 – 0.73)	0.027	0.01 (-0.08 – 0.10)	0.834		
Average (mean)	0.11 (0.07 – 0.15)	<0.001	0.15 (0.03 – 0.27)	0.016	0.07 (0.02 – 0.11)	0.006		
Low (mean-1 SD)	0.12 (0.07 – 0.17)	<0.001	-0.09 (-0.23 – 0.05)	0.222	0.12 (0.05 – 0.19)	0.001		
High v. low[c]	-0.02 (-0.07 – 0.03)	0.373	0.47 (0.01 – 0.94)	0.045	-0.11 (-0.25 – 0.02)	0.104		

Note: SD, standard deviation; df, degrees of freedom; vs., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of abuse (sexual, physical, and emotional) and neglect (physical and emotional) within and across groups (service users, siblings, controls))

[a] Adjusted for age, gender, ethnicity, and level of education

Table S4. (continued). Association between momentary stress and negative affect excluding controls with diagnoses, by trauma in service users, siblings, and controls[a]

[b] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(TRAUMA_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times TRAUMA_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(TRAUMA_j \times GROUP_j) + \beta_7(STRESS_{ij} \times TRAUMA_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

[c] Difference in the magnitude of associations of momentary stress with negative affect between those exposed to high v. low levels of various forms of abuse and neglect across groups (Δ high v. low):

	Service users v. controls		Siblings v. controls		Service users v. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: negative affect			
Δ high vs. low physical abuse across groups						
Event-related stress	0.25 (-0.03 – 0.52)	0.077	0.08 (-0.26 – 0.43)	0.643	0.17 (-0.05 – 0.38)	0.129
Activity-related stress	0.26 (0.10 – 0.43)	0.001	0.11 (-0.12 – 0.35)	0.336	0.15 (-0.03 – 0.33)	0.106
Social stress	0.26 (0.04 – 0.48)	0.019	0.35 (0.03 – 0.66)	0.032	-0.08 (-0.32 – 0.15)	0.491
Δ high vs. low emotional abuse across groups						
Event-related stress	0.14 (0.02- 0.27)	0.026	0.06 (-0.21 – 0.33)	0.668	0.08 (-0.17 – 0.33)	0.512
Activity-related stress	0.14 (0.04 – 0.24)	0.007	-0.09 (-0.32 – 0.14)	0.451	0.23 (0.01 – 0.45)	0.043
Δ high vs. low emotional neglect across groups						
Activity-related stress	0.09 (-0.04 – 0.20)	0.201	-0.29 (-0.56 – -0.01)	0.039	0.37 (0.11 – 0.62)	0.005
Δ high vs. low physical neglect across groups						
Social stress	0.09 (-0.05 – 0.24)	0.214	0.59 (0.10 – 1.07)	0.017	-0.50 (-0.96 – -0.03)	0.037
Activity-related stress	0.28 (0.17 – 0.39)	<0.001	-0.05 (-0.50 – 0.39)	0.001	0.33 (-0.11 – 0.77)	0.137

Table S5. Association between momentary stress and psychotic experiences excluding controls with diagnoses, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p
				Outcome: psychotic experiences				
Event-related stress × sexual abuse × group[b]							0.62 (2)	0.735
Activity-related stress x sexual abuse x group[b]							3.38 (2)	0.185
Social stress x sexual abuse x group							1.05 (2)	0.591
Event-related stress × physical abuse × group[b]							14.01 (5)	0.016
Level of physical abuse								
High (mean+1 SD)	0.09 (0.07 - 0.12)	<0.001	-0.004 (-0.07 – 0.07)	0.917	0.08 (-0.01 – 0.17)	0.089		
Average (mean)	0.06 (0.04 – 0.08)	<0.001	0.01 (-0.02 – 0.04)	0.585	0.03 (0.01 – 0.06)	0.014		
Low (mean-1 SD)	0.03 (0.01 – 0.06)	0.021	0.02 (-0.04 – 0.08)	0.502	-0.01 (-0.07 – 0.06)	0.766		
High v. low[c]	0.06 (0.04 – 0.09)	<0.001	-0.02 (-0.14 – 0.09)	0.671	0.09 (-0.06 – 0.24)	0.240		
Activity-related stress x physical abuse x group[b]							1.36 (2)	0.506
Social stress x physical abuse x group[b]							0.89 (2)	0.642
Event-related stress × emotional abuse × group[b]							16.65 (5)	0.005
Level of emotional abuse								
High (mean+1 SD)	0.10 (0.08 – 0.12)	<0.001	-0.01 (-0.09 – 0.07)	0.800	0.07 (0.03 – 0.12)	0.001		
Average (mean)	0.05 (0.03 – 0.07)	<0.001	0.01 (-0.02 – 0.04)	0.590	0.03 (0.01 – 0.06)	0.008		
Low (mean-1 SD)	0.01 (-0.02 – 0.03)	0.750	0.03 (-0.04 – 0.10)	0.443	-0.01 (-0.04 – 0.03)	0.780		
High v. low[c]	0.10 (0.07 – 0.13)	<0.001	-0.04 (-0.17 – 0.10)	0.582	0.08 (0.01 – 0.14)	0.016		

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Table S5. (continued). Association between momentary stress and psychotic experiences excluding controls with diagnoses, by trauma in service users, siblings, and controls[a]

	Service users		Siblings		Controls		LR test for interaction	
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ^2 (df)**	**p**
				Outcome: psychotic experiences				
Activity-related stress x emotional abuse x group[b]							1.97 (2)	0.374
Social stress x emotional abuse x group[b]							0.07 (2)	0.965
Event-related stress × emotional neglect × group[b]							0.57 (2)	0.451
Activity-related stress x emotional neglect x group[b]							0.85 (2)	0.653
Social stress x emotional neglect x group[b]							1.11 (2)	0.573
Event-related stress × physical neglect × group[b]							0.92 (2)	0.338
Activity-related stress x physical neglect x group[b]							0.30 (2)	0.862
Social stress x physical neglect x group[b]							0.50 (2)	0.780

Note: SD, standard deviation; df, degrees of freedom; vs., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of abuse (sexual, physical, and emotional) and neglect (physical and emotional) within and across groups (service users, siblings, controls))
[a] Adjusted for age, gender, ethnicity, and level of education
[b] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(TRAUMA_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times TRAUMA_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(TRAUMA_j \times GROUP_j) + \beta_7(STRESS_{ij} \times TRAUMA_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

Table S5. (continued). Association between momentary stress and psychotic experiences excluding controls with diagnoses, by trauma in service users, siblings, and controls[a]

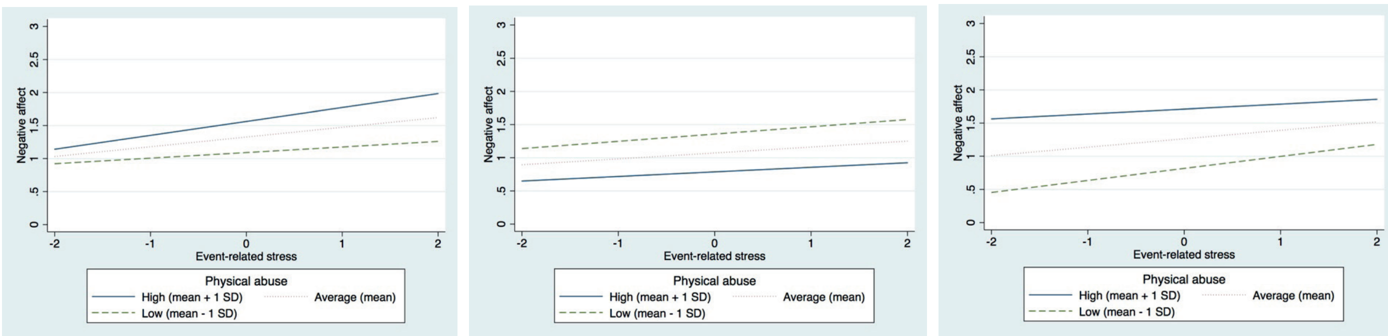
[c] Difference in the magnitude of associations of momentary stress with psychotic experiences between those exposed to high v. low levels of abuse across groups (Δ high v. low):

	Service users v. controls		Siblings v. controls		Service users v. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: psychotic experiences			
Δ high vs. low physical abuse across groups						
Event-related stress	-0.03 (-0.18 – 0.13)	0.743	-0.11 (-0.30 – 0.07)	0.234	0.09 (-0.03 – 0.21)	0.138
Δ high vs. low emotional abuse across groups						
Event-related stress	0.02 (-0.05 – 0.09)	0.532	-0.11 (-0.26 – 0.03)	0.127	0.14 (0.000 – 0.27)	0.049

Figures S1. Association between momentary stress, negative affect and psychotic experiences at high, average and low levels of abuse and neglect, by group

Supplementary Figure 1a. Association between event-related stress and negative affect at high (mean+1 SD), average (mean), and low (mean-1 SD) levels of physical abuse in service users, siblings, and controls[a,b]

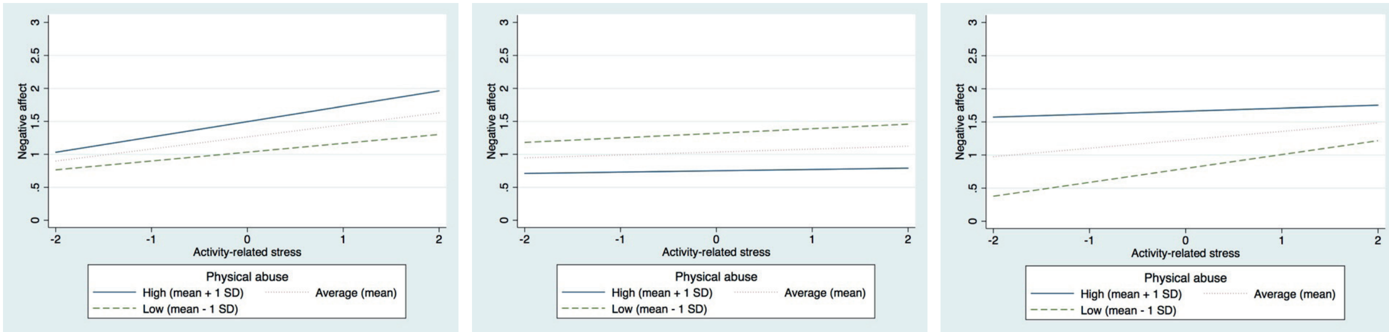
Service users | Siblings | Controls



Note: SD, standard deviation; df, degrees of freedom; vs., versus
[a] Adjusted for age, gender, ethnicity, level of education
[b] Event-related stress × physical abuse × group, χ^2=12.09, df=5, p=0.033; association between event-related stress and negative affect in each group by physical abuse:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ physical abuse						
High (mean+1 SD)	0.21 (0.17 – 0.25)	<0.001	0.07 (-0.06 – 0.20)	0.288	0.07 (-0.08 – 0.23)	0.359
Average (mean)	0.15 (0.11 – 0.18)	<0.001	0.09 (0.03 – 0.15)	0.003	0.13 (0.08 – 0.17)	<0.001
Low (mean-1 SD)	0.08 (0.04 – 0.13)	0.001	0.11 (-0.004 – 0.22)	0.059	0.18 (0.07 – 0.29)	0.001
High vs. low	0.13 (0.08 – 0.17)	<0.001	-0.04 (-0.25 – 0.17)	0.705	-0.11 (-0.36 – 0.15)	0.405

Supplementary Figure 1b. Association between activity-related stress and negative affect at high (mean+1 SD), average (mean), and low (mean-1 SD) levels of physical abuse in service users, siblings, and controls[a,b]



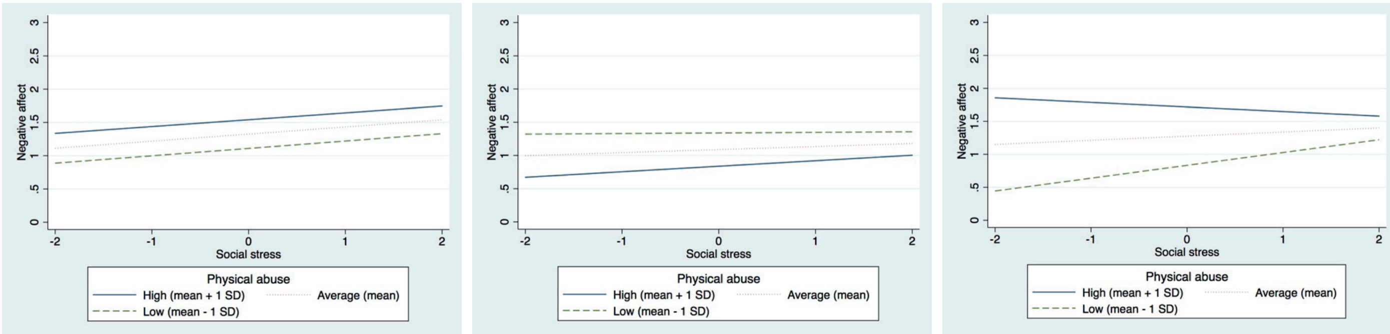
Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)

[a] Adjusted for age, gender, ethnicity, level of education

[b] Activity-related stress x physical abuse x group, χ^2=12.32, df=2, *p*=0.002; association between activity-related stress and negative affect in each group by physical abuse:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ physical abuse						
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	0.02 (-0.08 – 0.12)	0.705	0.04 (-0.05 – 0.14)	0.351
Average (mean)	0.18 (0.15 – 0.22)	<0.001	0.04 (-0.02 – 0.11)	0.186	0.13 (0.09 – 0.17)	<0.001
Low (mean-1 SD)	0.13 (0.09 – 0.18	<0.001	0.07 (-0.05 – 0.18)	0.238	0.21 (0.13 – 0.29)	<0.001
High vs. low	0.10 (0.05 – 0.15)	<0.001	-0.05 (-0.22 – 0.12)	0.577	-0.16 (-0.32 – -0.01)	0.033

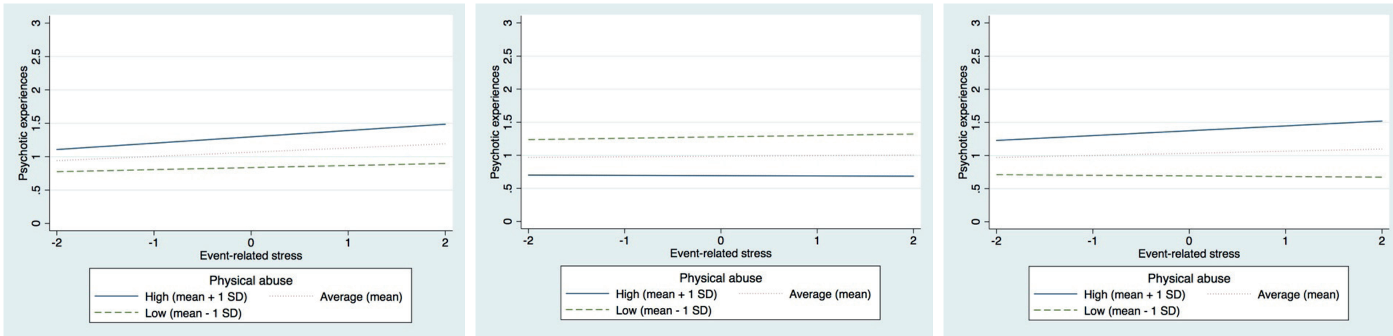
Supplementary Figure 1c. Association between social stress and negative affect at high (mean+1 SD), average (mean), and low (mean-1 SD) levels of physical abuse in service users, siblings, and controls[a,b]



Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)
[a] Adjusted for age, gender, ethnicity, level of education
[b] Social stress × physical abuse × group interaction, χ^2=5.99, df=2, *p*=0.050; association between social stress and negative affect in each group by physical abuse:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ physical abuse						
High (mean+1 SD)	0.10 (0.07 – 0.14)	<0.001	0.08 (-0.06 – 0.23)	0.257	-0.07 (-0.20 – 0.06)	0.305
Average (mean)	0.11 (0.07 – 0.14)	<0.001	0.05 (-0.02 – 0.11)	0.151	0.06 (0.02 – 0.11)	0.007
Low (mean-1 SD)	0.11 (0.07 – 0.16)	<0.001	0.01 (-0.11 – 0.13)	0.882	0.19 (0.10 – 0.29)	<0.001
High vs. low	-0.01 (-0.05 – 0.04))	0.708	0.07 (-0.16 – 0.30)	0.529	-0.26 (-0.47 – -0.05)	0.014

Supplementary Figure 1d. Association between event-related stress and psychotic experiences at high (mean+1 SD), average (mean), and low (mean-1 SD) levels of physical abuse in service users, siblings, and controls[a,b]



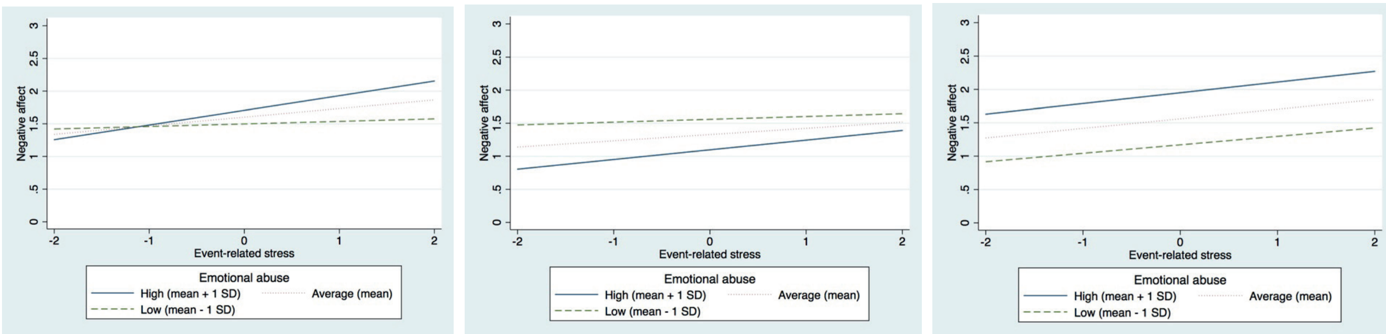
Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)
[a] Adjusted for age, gender, ethnicity, level of education
[b] event-related stress x physical abuse × group interaction, χ^2=14.24, df=5, *p*=0.014; association between event-related stress and psychotic experiences in each group by physical abuse:

	Service users		Siblings		Controls	
	adj. β (95% CI)	p	adj. β (95% CI)	p	adj. β (95% CI)	p
CTQ physical abuse						
High (mean+1 SD)	0.09 (0.08 - 0.11)	<0.001	-0.004 (-0.07 – 0.06)	0.912	0.07 (-0.01 – 0.16)	0.087
Average (mean)	0.06 (0.04 – 0.08)	<0.001	0.01 (-0.02 – 0.04)	0.583	0.03 (0.01 – 0.06)	0.011
Low (mean-1 SD)	0.03 (0.01 – 0.06)	0.018	0.02 (-0.04 – 0.08)	0.495	-0.01 (-0.07 – 0.05)	0.754
High vs. low	0.06 (0.04 – 0.09)	<0.001	-0.02 (-0.14 – 0.09)	0.664	0.08 (-0.05 – 0.22)	0.232

Supplementary Figure 2. Stress sensitivity as a putative mechanism linking emotional abuse and psychopathology

Supplementary Figure 2a. Association between event-related stress and negative affect at high (mean+1 SD), average (mean), and low (mean-1 SD) levels of emotional abuse in service users, siblings, and controls[a,b]

Service users Siblings Controls



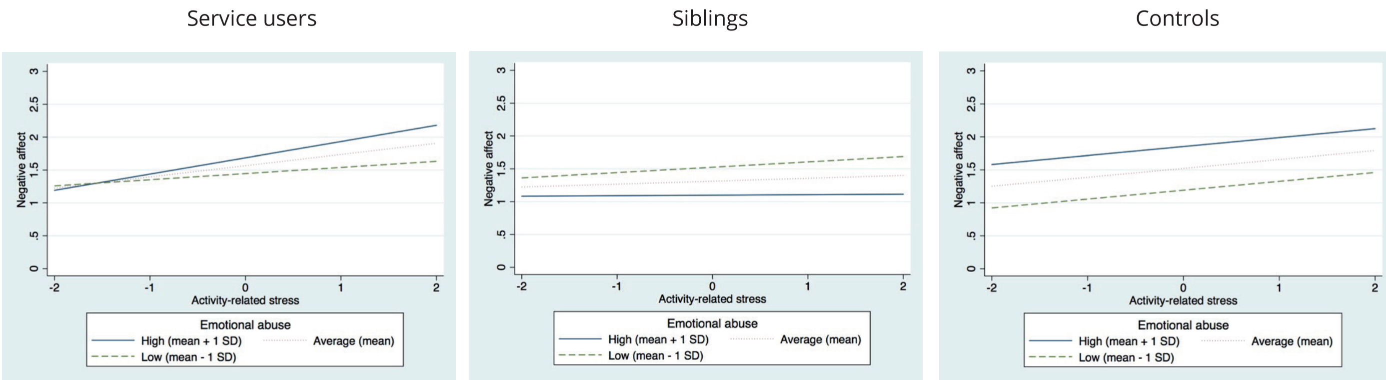
Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)

[a] Adjusted for age, gender, ethnicity, level of education

[b] Event-related stress x emotional abuse × group interaction, χ^2=16.15, df=5, *p*=0.006; association between event-related stress and negative affect in each group by emotional abuse:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ emotional abuse						
High (mean+1 SD)	0.22 (0.19 – 0.26)	<0.001	0.15 (0.01 – 0.29)	0.042	0.16 (0.08 – 0.24)	<0.001
Average (mean)	0.13 (0.09 – 0.17)	<0.001	0.09 (0.04 – 0.15)	0.001	0.14 (0.10 – 0.18)	<0.001
Low (mean-1 SD)	0.04 (-0.01 – 0.09)	0.142	0.04 (-0.09 – 0.17)	0.514	0.13 (0.07 – 0.18)	<0.001
High vs. low	0.19 (0.14 – 0.24)	<0.001	0.10 (-0.14 – 0.35)	0.402	0.03 (-0.07 – 0.14)	0.537

Supplementary Figure 2b. Association between activity-related stress and negative affect at high (mean + 1 SD), average (mean), and low (mean - 1 SD) levels of emotional abuse in service users, siblings, and controls[a,b]



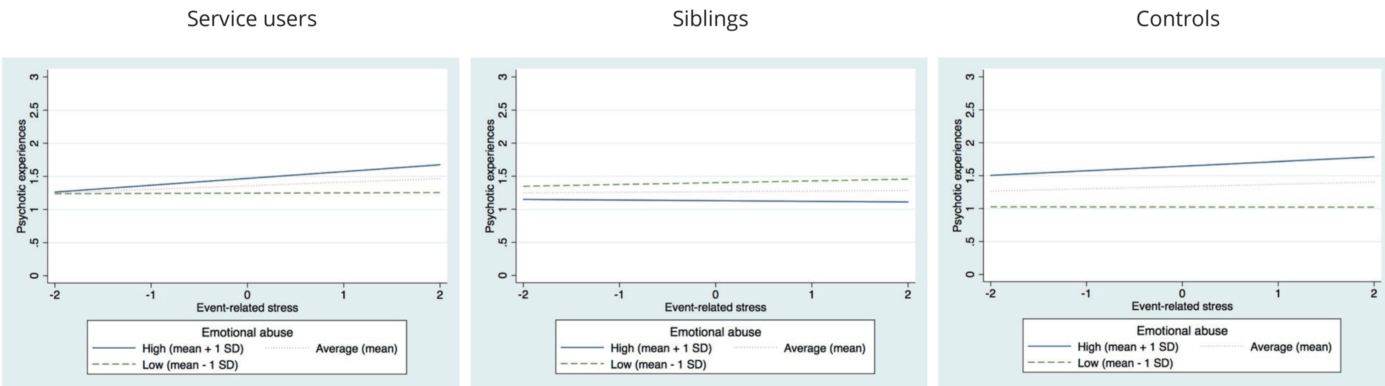
Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)

[a] Adjusted for age, gender, ethnicity, level of education

[b] Activity-related stress × emotional abuse × group interaction, χ^2=12.0, df=2, *p*=0.003; association between activity-related stress and negative affect in each group by emotional abuse:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ emotional abuse						
High (mean+1 SD)	0.25 (0.21 – 0.29)	<0.001	0.01 (-0.11 – 0.13)	0.899	0.14 (0.07 – 0.20)	<0.001
Average (mean)	0.17 (0.13 – 0.21)	<0.001	0.04 (-0.02 – 0.11)	0.183	0.14 (0.09 – 0.18)	<0,001
Low (mean-1 SD)	0.09 (0.04 – 0.15))	<0.001	0.08 (-0.05 – 0.21)	0.222	0.13 (0.08 – 0.19)	<0.001
High vs. low	0.15 (0.10 – 0.21)	<0.001	-0.07 (-0.29 – 0.14)	0.501	0.001 (-0.08 – 0.08)	0.980

Supplementary Figure 2c. Association between event-related stress and psychotic experiences at high (mean+1 SD), average (mean), and low (mean-1 SD) levels of emotional abuse in service users, siblings, and controls[a,b]

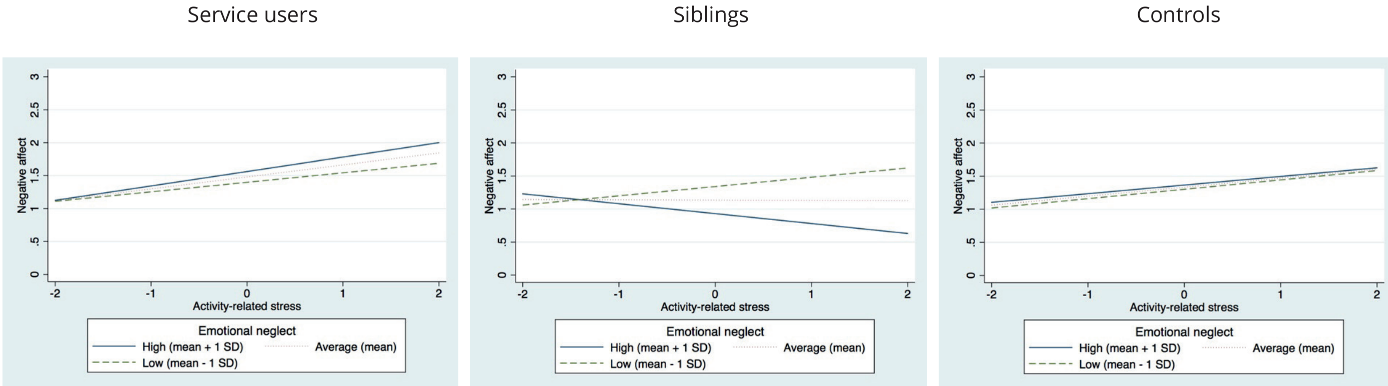


Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)
[a] Adjusted for age, gender, ethnicity, level of education
[b] event-related stress x emotional abuse x group, χ^2=15.32, df=5, *p*=0.009; association between event-related stress and psychotic experiences in each group by emotional abuse:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ emotional abuse						
High (mean+1 SD)	0.10 (0.08 – 0.12)	<0.001	-0.01 (-0.08 – 0.07)	0.799	0.07 (0.03 – 0.11)	0.001
Average (mean)	0.05 (0.03 – 0.07)	<0.001	0.01 (-0.02 – 0.04)	0.586	0.03 (0.01 – 0.06)	0.002
Low (mean-1 SD)	0.004 (-0.02 – 0.03)	0.748	0.03 (-0.04 – 0.10)	0.439	-0.001 (-0.03 – 0.03)	0.936
High vs. low	0.10 (0.07 – 0.13)	<0.001	-0.04 (-0.17 – 0.09)	0.579	0.07 (0.01 – 0.13)	0.014

Supplementary Figure 3. Stress sensitivity as a putative mechanism linking emotional neglect and psychopathology

Supplementary Figure 3a. Association between activity-related stress and negative affect at high (mean + 1 SD), average (mean), and low (mean - 1 SD) levels of emotional neglect in service users, siblings, and controls[a,b]

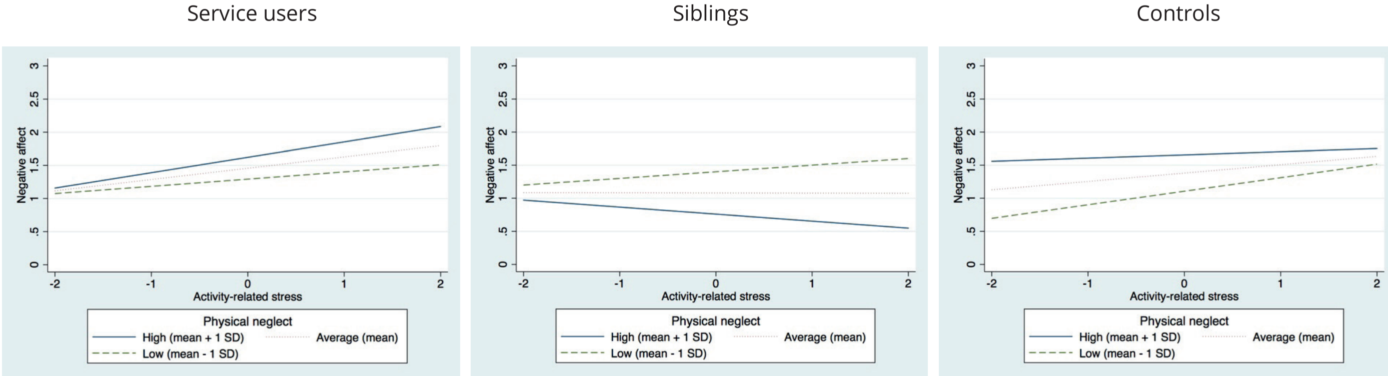


Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)
[a] Adjusted for age, gender, ethnicity, level of education
[b] activity-related stress × emotional neglect × group interaction, χ^2=9.16, df=2, *p*=0.010; association between activity-related stress and negative affect in each group by emotional neglect:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ emotional neglect						
High (mean+1 SD)	0.22 (0.18 – 0.26)	<0.001	-0.15 (-0.33 – 0.03)	0.097	0.13 (0.06 – 0.20)	<0.001
Average (mean)	0.18 (0.14 – 0.22)	<0.001	-0.004 (-0.08 – 0.07)	0.905	0.14 (0.10 – 0.18)	<0.001
Low (mean-1 SD)	0.14 (0.09 – 0.20)	<0.001	0.14 (0.03 – 0.25)	0.010	0.14 (0.08 – 0.20)	<0.001
High vs. low	0.07 (0.02 – 0.13)	0.010	-0.29 (-0.54 – -0.04)	0.022	-0.01 (-0.11 – 0.09)	0.830

Supplementary Figure 4. Stress sensitivity as a putative mechanism linking physical neglect and psychopathology

Supplementary Figure 4a. Association between activity-related stress and negative affect at high (mean + 1 SD), average (mean), and low (mean - 1 SD) levels of physical neglect in service users, siblings, and controls[a,b]



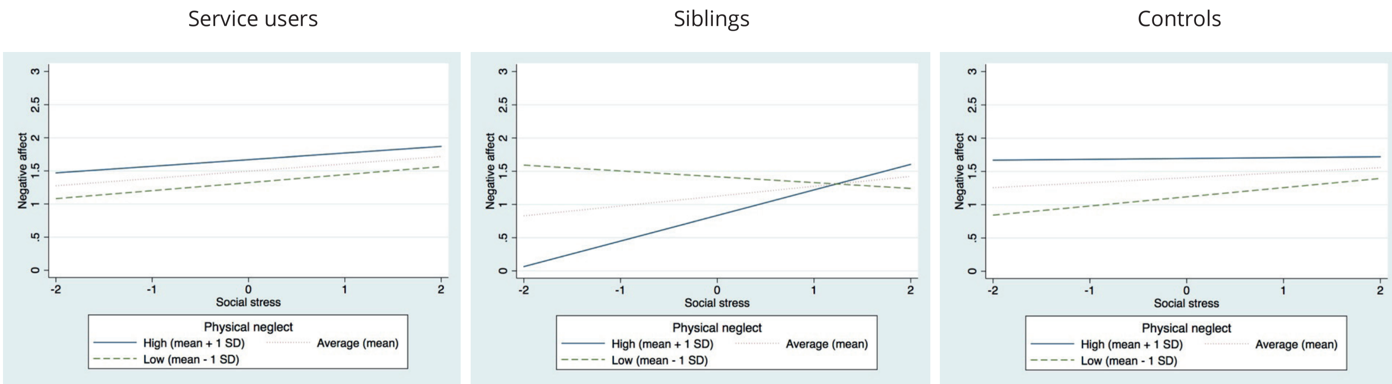
Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)

[a] Adjusted for age, gender, ethnicity, level of education

[b] activity-related stress × physical neglect × group interaction, χ^2=26.90, df=2, *p*=<0.001; association between activity-related stress and negative affect in each group by physical neglect:

	Service users		Siblings		Controls	
	adj. β (95% CI)	p	adj. β (95% CI)	p	adj. β (95% CI)	p
CTQ physical neglect						
High (mean+1 SD)	0.23 (0.19 – 0.27)	<0.001	-0.11 (-0.42 – 0.21)	0.512	0.05 (-0.02 – 0.12)	0.163
Average (mean)	0.17 (0.13 – 0.21)	<0.001	-0.003 (-0.12 – 0.11)	0.962	0.13 (0.09 – 0.17)	<0.001
Low (mean-1 SD)	0.11 (0.06 – 0.16)	<0.001	0.10 (-0.04 – 0.24)	0.164	0.20 (0.15 – 0.26)	<0.001
High vs. low	0.12 (0.07 – 0.17)	<0.001	-0.21 (-0.64 – 0.23)	0.353	-0.16 (-0.25 – -0.06)	0.001

Supplementary Figure 4b. Association between social stress and negative affect at high (mean + 1 SD), average (mean), and low (mean - 1 SD) levels of physical neglect in service users, siblings, and controls[a,b]



Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; LR, likelihood ratio; adj. β, standardized regression coefficients (continuous independent variables were standardized)

[a] Adjusted for age, gender, ethnicity, level of education

[b] Social stress × physical neglect × group interaction, χ^2=6.70, df=2, p=0.035; association between social stress and negative affect in each group by physical neglect:

	Service users		Siblings		Controls	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
CTQ physical neglect						
High (mean+1 SD)	0.10 (0.06 – 0.14)	<0.001	0.38 (0.04 – 0.73)	0.028	0.01 (-0.08 – 0.10)	0.783
Average (mean)	0.11 (0.07 – 0.15)	<0.001	0.15 (0.03 – 0.27)	0.016	0.08 (0.03 – 0.12)	0.001
Low (mean-1 SD)	0.12 (0.07 – 0.17)	<0.001	-0.09 (-0.23 – 0.05)	0.223	0.14 (0.07 – 0.20)	<0.001
High vs. low	-0.02 (-0.07 – 0.03)	0.373	0.47 (0.01 – 0.94)	0.046	-0.13 (-0.26 – 0.004)	0.058

CHAPTER 5

Bullying victimization and stress sensitivity in help-seeking youth: findings from an experience sampling study

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Abstract

Background: Bullying victimization confers risk for developing various mental disorders, but studies investigating candidate mechanisms remain scarce, especially in the realm of youth mental health. Elevated stress sensitivity may constitute a mechanism linking bullying victimization and mental health problems. In the current study, we aimed to investigate whether exposure to bullying victimization amplifies stress sensitivity in youth's daily life.

Methods: The Experience Sampling Method (ESM) was used to measure stress sensitivity (i.e. the association of momentary stress with (i) negative affect and (ii) psychotic experiences) in 42 help-seeking youths (service users), 17 siblings, and 40 comparison subjects (mean age 15 years). Before ESM assessments, bullying victimization at school as well as various psychopathological domains (i.e. depression, anxiety, psychosis) were assessed.

Results: Service users exposed to high levels of overall (primary hypotheses) as well as specific types (secondary hypotheses; physical and indirect, but not verbal) of bullying victimization experienced more intense negative affect and psychotic experiences in response to stress compared to those with low exposure levels (all $p<0.05$), whereas, in contrast, controls showed either less intense negative affect or no marked differences in stress sensitivity by exposure levels. In siblings, a less consistent pattern of findings was observed. **Conclusion:** Findings suggest that stress sensitivity may constitute a potential risk and resilience mechanism linking bullying victimization and youth mental health. Interventions that directly target individuals' reactivity to stress by providing treatment components in real-life using novel mHealth tools may be a promising novel therapeutic approach.

Keywords: Bullying; Stress, Psychological; Adolescent; Mental Health; Psychopathology; Ecological Momentary Assessment

Introduction

Bullying victimization is defined as an intentional misuse of power in which an individual or a group of individuals engage in repeated hostile behavior against peers who have difficulties to defend themselves [1]. The experience of being bullied has long been seen to reflect a normal pattern of interaction between peers that is transitory and important for individuals' social development [2]. As a consequence, exposure to bullying has not been considered to represent a particularly stressful experience and, therefore, not to be an important risk factor involved in the development of mental health problems [2, 3].

However, evidence has accumulated that exposure to bullying victimization is associated with a range of mental disorders (e.g. depression, anxiety, psychosis), general psychopathology, self-harm, and suicidality, amongst others [4-13], and has been found to predict the use of mental health services [14]. These findings suggest that exposure to bullying victimization may be an important non-specific risk factor for mental health problems, which is consistent with the detrimental, but non-specific effects reported for other adverse childhood experiences (e.g. childhood maltreatment) [15]. Recent estimates from the World Health Organization [16] are alarming: around two in ten children and adolescents are being exposed to bullying victimization at school, although prevalence estimates differ considerably across countries (e.g. in Europe: 4% in Italy, 30% in Lithuania). These findings have contributed to formal recognition of bullying as a risk factor for mental health problems in the Global Burden of Disease Study 2017 [17].

In recent years, there has been an increasing focus on dimensional and transdiagnostic approaches to psychopathology [18-20], resulting in classification frameworks (e.g. HiTOP) [21] that are based on patterns of symptom co-occurrence, cutting across traditional diagnostic boundaries. In support of these efforts and also based on frequent co-occurrence of more common psychopathological domains (e.g. anxiety, depression) with psychotic experiences, an extended and transdiagnostic psychosis spectrum phenotype has been proposed that is temporally and phenomenologically continuous across psychotic and non-psychotic disorders and shares socio-environmental risk factors, including bullying victimization [22].

Overall, high prevalence of bullying victimization in youth, and associations with immediate as well as prolonged mental health problems, which are often characterized by a number of co-occurring psychopathological domains (e.g. anxiety, depression, psychosis) [22, 23] that appear already early in life [24] underline the importance to develop early and transdiagnostic intervention strategies [25]. For this, an important step is to investigate candidate mechanisms that are relevant to linking exposure to bullying victimization and various mental health problems. Critically, however, the developmental processes and putative mechanisms involved remain largely under-researched, especially in the realm of youth mental health.

In contemporary models, exposure to socio-environmental risk (e.g., bullying victimization, childhood maltreatment, life events) is thought to impact on mental health through a progressive increase in individuals' stress response to subsequent adversity [26, 27]. This has often been referred to as a process of sensitization [28] which is thought to be mediated by a number of biological and psychological factors [29-34]. Although evidence remains limited, there is an ongoing debate [15] regarding the extent to which specific forms of adversity may be more strongly associated with specific forms of mental health outcomes (e.g., whether more intrusive types of adversity are specifically associated with psychosis). The Experience Sampling Methodology (ESM), a structured self-report diary technique [35], is particularly well suited to test these propositions at a behavioral level by investigating whether overall as well as specific types of bullying victimization is associated with an increased sensitivity to specific types of minor stressors in daily life.

In most studies using ESM, individuals' stress sensitivity has been conceptualized as the association of minor stressors with (i) negative affect and (ii) psychotic experiences in daily life and, thus, has also been referred to individuals' affective and psychotic reactivity, respectively. These studies have consistently found an increased stress sensitivity in adults who were exposed to childhood trauma and adult life events, including individuals with depression, an at-risk mental state for psychosis, and psychosis spectrum disorders [36-39]. Thus, findings suggest that stress sensitivity in the flow of daily life may play an important non-specific and transdiagnostic role linking childhood adversity and mental disorders in help-seeking individuals. In a recent experience sampling study, derived from the same sample as the current study, exposure to childhood trauma was, similarly, associated with elevated stress sensitivity in help-seeking youth [40]. Also, there is some evidence of specificity as some studies have reported that more intrusive forms of childhood trauma (e.g. sexual and physical abuse as well as physical neglect) were most consistently associated with an elevated stress sensitivity in help-seeking individuals [38, 40]. Consequently, more intrusive forms of bullying (i.e., physical bullying) may be particularly associated with an increased stress sensitivity in help-seeking youth.

To date, however, only one study has reported elevated stress sensitivity in a non-clinical sample of young adults exposed to bullying [41] and, to the best of our knowledge, no study has investigated the impact of bullying victimization on individuals' affective and psychotic reactivity to stress in a sample of help-seeking youth and whether effects of bullying exposure on stress sensitivity differ across individuals at differing liability to mental health conditions. To address current knowledge gaps, a sample of adolescents and young adults receiving help from a secondary mental health service (service users), their biological siblings, and controls were recruited in the current study. We included siblings of service users as they have an increased risk for developing a mental disorder and, hence, reflect an intermediate risk group (compared with service users and controls) and also share genetic and socio-environmental risk factors with service users [42-44].

Aims and hypotheses of the study

The aim of the current study was to determine whether bullying victimization modifies sensitivity towards stress in a sample of help-seeking youth (service users), their biological siblings, and comparison subjects (controls). More specifically, the study aimed to investigate the following primary hypotheses: First, within groups (service users, siblings, and controls), stress sensitivity (i.e., the association between momentary stress and (i) negative affect and (ii) psychotic experiences) is modified by bullying victimization, with greater associations in individuals exposed to high *vs.* those exposed to low exposure levels of bullying victimization (H1); second, the effect of bullying victimization on stress sensitivity differs across groups at differing liability to mental health problems, with a greater impact in service users *vs.* controls, service users *vs.* siblings, and siblings *vs.* controls (H2). In addition, to investigate whether some bullying types are specifically modifying stress sensitivity, the following secondary hypotheses were tested: First, within groups, exposure to specific bullying types (i.e. physical, verbal, indirect bullying) impact on stress sensitivity, with greater associations when high *vs.* low exposure levels are compared (H3); second, across groups, the impact of specific types of bullying victimization on stress sensitivity is greater in service users *vs.* controls, service users *vs.* siblings, and siblings *vs.* controls (H4). Lastly, to test whether specific bullying types modify specific forms of affective and psychotic reactivity, the following exploratory analyses were conducted: Within groups, individuals' response to specific stressors in daily life (i.e. event-related, activity-related, social stress) is modified by specific types of bullying victimization (i.e. physical, verbal, indirect bullying), with greater associations in individuals exposed to high *vs.* low exposure levels (H5).

Materials and methods

Sample

Data were derived from the Youth Experience Study (YES), a study conducted to investigate candidate mechanisms involved in linking adverse childhood experiences and youth mental health. Dataset version 1.1 was used for the current analysis. This version differs from version 1.0 used in earlier work [40] in the group status used for one individual. A sample of help-seeking youth (service users) were recruited from the Mutsaers Foundation (MF) by treatment coordinators and leaflets and posters were distributed in waiting areas of all outpatient locations of MF. The MF offers secondary mental health services for young individuals in Limburg, the Netherlands. The following broad inclusion criteria were used: aged 12-20 years; currently receiving treatment from MF. Exclusion criteria were: being diagnosed with an Autistic Spectrum Disorder according to DSM-IV with the exception of Pervasive Developmental Disorder Not Otherwise Specified; intellectual disability (IQ score below 70); insufficient knowledge of the Dutch language. Further, we recruited siblings of service users. Inclusion criteria were as follows: aged 12-20; participation of a biological sibling who is receiving treatment from MF. Exclusion criteria were the same as for service users with the addition of a lifetime history of receiving treatment from a mental health service. Lastly, a control sample of non-help-seeking individuals was recruited through schools from the same catchment area as MF mental health services. These schools were asked for permission to conduct the study and a letter accompanied by a leaflet was sent to parents, asking them whether their child is allowed to participate in the study. The YES was also introduced in form of an information session in class. Inclusion criteria were: aged 12-20 years, attending a school in the same catchment area as MF mental health services. Exclusion criteria were the same as for siblings. If a participant was older than 18, he/she was allowed to give written informed consent without asking the parents. The study was approved by the Medical Ethics Review Committee of Maastricht University Medical Centre in Maastricht, the Netherlands (approval number: NL37420.068.11).

Measures

Socio-demographic characteristics

Socio-demographic data (i.e. age, sex, ethnicity, and level of education) was collected using a socio-demographic schedule.

Bullying victimization

The Retrospective Bullying Questionnaire (RBQ), a 44-item self-report questionnaire [45], was used to assess bullying victimization. The questionnaire measures exposure to bullying at primary and secondary school, while the precise timing of exposure prior to assessment is not specified. Three types of bullying were assessed: physical (hit/punched, stolen property), verbal (called names, threatened), and indirect (spread lies, excluded) bullying. In addition to assessing exposure to bullying victimization, the RBQ asks more general questions about individuals' experiences at school (e.g. whether individuals were happy), details about the bullying incident (e.g. the number of bullies involved, reasons individuals believe they were bullied), and also bullying experiences at the workplace. For this study, we used 2 items asking for frequency and intensity of each bullying type (physical, verbal, indirect) for primary as well as secondary school resulting in 12 items rated on a 5-point scale ranging from 1-5 [45]. Frequency was assessed by asking participants how often they were exposed to bullying (1= 'never', 5='constantly') and intensity was assessed by asking to evaluate the seriousness (1='not at all', 5= 'extremely serious'). For primary hypotheses, sum scores were calculated by adding items assessing the frequency and intensity of bullying experiences (12 items; range sum score, 12-60, Cronbach's alpha, α = .90) and, for secondary and exploratory hypotheses, sum scores were calculated for three specific bullying types (4 items; range sum score 4-20; physical bulling, α = .77; verbal bullying, α = .84; indirect bullying, α = .87), respectively. Good psychometric properties have been reported for this measure [45].

Depressive, anxiety, and psychotic symptoms

The Beck Depression Inventory (BDI-II), a well-established questionnaire consisting of 21 items, was completed to assess depressive symptoms over the past 2 weeks (4-point scale ranging from 0-3). A Dutch version of the State-Trait Anxiety Inventory (STAI) was used to assess state and trait anxiety. The first part (STAI-DY1) measures trait (20 items) and the second part (STAI-DY2) assesses state (40 items) anxiety, both rated on a 4-point scale (ranging from 1-4; 1=not at all, 4=very much). The Community Assessment of Psychic Experiences (CAPE) was used to assess the frequency and distress of positive (20 items) and negative (14 items) sub-clinical psychotic and depressive (8 items) symptoms (rated on a 4-point scale ranging from 0-3; 0=not at all, 3=very much). For all measures, good psychometric properties have been [46-48] demonstrated.

Momentary stress, negative affect, and psychotic experiences

Momentary stress, negative affect, and psychotic experiences were assessed using the experience sampling method (ESM), an intensive self-assessment technique to assess subjective experiences and social contexts in real life, outside the research laboratory with high ecological validity [35]. A personal digital assistant (PsyMate) was used for data collection. In accordance with previous ESM studies [49, 50], the PsyMate beeped 10 times a day on 6 consecutive days at unpredictable moments between 7:30 am and 10:30 pm (scheduled at random within set time blocks of 90 minutes). Event-related, activity-related, and social stress were defined as unpleasant events, activities, and social situations occurring in daily life. Sufficient concurrent validity with other stress measures has been reported [51].

Momentary stress was calculated by computing the mean score of six items assessing event-related, activity-related, and social stress. Event-related stress was measured asking participants to report the pleasantness of the most important event that had happened since the last beep on a 7-point scale ranging from 'very unpleasant' (rating of -3) to 'very pleasant' (rating of 3). To ensure that higher ratings indicate higher levels of stress and pleasant events are excluded from analyses, the item was recoded (ratings of −3 were coded as 4, -2 as 3, -1 as 2, and neutral events as 1, while pleasant events were coded as 0). Activity-related stress was assessed by asking 'What am I doing (just before the beep)' (e.g. being at work/school, doing household, eating/drinking) and three additional items ('I would prefer doing something else', 'This activity is difficult for me', 'I can do this well' [reversed]) ranging from 'not at all' (rating of 1) to 'very much' (rating of 7). Social stress was measured by asking participants about their current social situation (e.g. 'I am alone', 'I am with my family', 'I am with my friends') and to rate this using the items 'I find the people I am with pleasant' [reversed] (if with someone) or 'I like to be alone' [reversed] (if alone) ranging from 'not at all' (rating of 1) to 'very much' (rating of 7).

Negative affect was assessed using five items asking participants to report the degree of feeling anxious, lonely, insecure, irritated, and down. Psychotic experiences were measured using eight items ('I see things that aren't really there', 'I hear things that aren't really there', 'I feel suspicious/paranoid', 'I feel harried', 'I feel unreal', 'My thoughts are influenced by other', 'I can't get these thoughts out of my head', 'I feel like I am losing control'). All items were rated on a 7-point scale (1='not at all', 7='very much') and mean scores were calculated to compute both variables. High levels of internal consistency and good concurrent validity with interviewer-rated measures has been previously reported [38].

Statistical analysis

First, we compared socio-demographic characteristics and psychopathological domains (i.e. standardized BDI-II, STAI-DY1/DY2, and CAPE scores) across groups using linear regression and χ^2-tests. Second, the MIXED command in Stata 15 was used to fit linear mixed models. This statistical modelling technique is needed as ESM data has a multilevel structure with multiple observations nested within participants. Maximum likelihood estimation of these models allows all available data to be used under the relatively unrestricted assumption that data is missing at random. We fitted models with momentary stress (event-related, activity-related, and social stress; primary and secondary hypotheses [H1-H4]: overall mean score including all stress items; exploratory analyses [H5]: mean score of specific stressors) as the continuous independent variable and (i) negative affect and (ii) psychotic experiences as the outcome variable, while controlling for potential confounders and variables associated with missing values (i.e. age, sex, ethnicity, level of education). To test whether associations between momentary stress and (i) negative affect and (ii) psychotic experiences are modified by exposure to bullying victimization at school (i.e. exposure at primary and secondary school combined; continuous total scores) and group (service users, siblings, and controls), two-way (stress x bullying, stress x group, bullying x group) and three-way (stress x bullying x group) interaction terms were simultaneously added into models. Wald tests were performed using the TESTPARM command to evaluate significance of three-way interaction terms to the model. The continuous stress and continuous bullying variables were standardized (mean=0, S.D.=1) for interpreting significant three-way interaction terms [52] and the LINCOM command was used to compute linear combinations of coefficients to test the hypotheses that, within each group, the association of momentary stress with (i) negative affect and (ii) psychotic experiences was greater in individuals exposed to high *vs.* those exposed to low levels of bullying victimization (+/- 1 S.D. of standardized continuous bullying victimization total scores; primary hypotheses [H1]: exposure to overall bullying; secondary and exploratory hypothesis [H3 and H5]: exposure to specific bullying types [53, 54]. Lastly, we investigated whether the impact of bullying victimization on stress sensitivity differed across groups by comparing the differences in the magnitude of associations of momentary stress with (i) negative affect and (ii) psychotic experiences between those exposed to high *vs*. low levels of bullying victimization (primary hypotheses [H2]: exposure to overall bullying; secondary hypotheses [H4]: exposure to specific bullying types) in service users compared to controls, service users compared to siblings, and siblings compared to controls. Separate models for momentary stress (overall as well as three specific stressors) and bullying exposure (overall as well as three specific types) were calculated, resulting in 2 models for primary hypotheses, 6 models for secondary hypotheses, and 24 models for exploratory analyses. We adjusted significance levels of Wald tests for three-way interactions to correct for Type-1 error proliferation using family-wise error-corrected p values (*p*FWE) by multiplying the unadjusted *p*-value by the total number of tests (*N*=8 for primary and secondary analyses and *N*=24 for exploratory analyses).

Results

Basic sample and clinical characteristics

In total, 109 individuals were eligible to participate. Of these, 99 youths (42 service users, 17 siblings, and 40 controls) completed the ESM with ≥20 valid responses over the 6-day assessment period as well as the BDI-II, STAI-DY1/DY2, CAPE, and RBQ. Thus, a high proportion of those initially assessed were included in the analysis (i.e. 90.8% of 109). There were, within groups, no differences between individuals who completed ESM assessments and those who did not with regard to socio-demographic characteristics and other variables. Groups did not differ in age, sex, or ethnicity (Table 1). However, there was evidence for higher levels of depression (BDI-II: β =0.71, p=0.001; B=1.08 p<0.001), state (β =0.50, p=0.025; β =0.59, p=0.40) and trait (β =0.59, p=0.004; B=0.95, p<0.001) anxiety, and negative (β =0.42, p=0.057; β =0.73, p=0.011) and positive (β =0.75, p<0.001; β =0.84, p=0.002) psychotic-like experiences in service users *vs.* controls and service users *vs.* siblings, respectively. As shown in Table 2, service users were exposed to higher overall levels of bullying victimization compared to controls (β =0.56, p=0.010) and siblings (β =0.60, p=0.034), while, in contrast, no differences were found comparing siblings and controls (β =-0.03, p=0.902). Further, service users reported higher levels of physical (β =0.86, p<0.001; β =0.77, p=0.005), but not verbal (β =0.29, p=0.188; β =0.42, p=0.150) and indirect (β =0.37, p=0.092; β =0.39, p=0.169) bullying compared to controls and siblings, respectively. Moreover, although not the primary aim of the current paper, it is worth mentioning that service users were more likely to report bullying-related mental health complaints, harmful behavior, and occupational problems when compared to controls and siblings (Table 2).

Table 1. Basic sample characteristics

	Service users (n=42)	Siblings (n=17)	Controls (n= 40)	Test statistic	p
Age (years), mean (S.D.)	15.4 (1.4)	15.3 (2.3)	15.6 (2.0)	F=0.24, df=2	0.785
Sex, n (%)					
Female	25 (59.5)	10 (58.8)	23 (57.5)	χ^2=0.04, df=2	0.983
Male	17 (40.5)	7 (41.2)	17 (42.5)		
Ethnicity, n (%)[a]					
White Dutch	26 (61.9)	11 (64.7)	25 (64.1)	χ^2=0.06, df=2	0.970
Other	16 (38.1)	6 (35.3)	14 (35.9)		
Level of education[b], n (%)					
School	30 (71.4)	7 (41.2)	17 (42.5)	χ^2=10.48, df=2	0.033
Further	12 (28.6)	8 (47.1)	20 (50.0)		
Higher	-	2 (11.8)	3 (7.5)		
Cannabis use, n (%)					
12-month	9 (21.4)	1 (5.9)	4 (10.0)	χ^2=3.36, df=2	0.187
lifetime	9 (21.4)	2 (11.8)	5 (12.5)	χ^2=1.50, df=2	0.473
Attempted suicide, n (%)					
During last year	6 (14.6)	-	-	-	-
Before age 17	8 (19.1)	-	-		
DSM-IV diagnoses, n (%)					
Pervasive developmental disorders NOS	10 (23.8)	-	5 (12.5)		
Attention-deficit and disruptive behaviour	6 (14.3)	3 (17.6)	-		
Adjustment disorders	4 (9.5)	-	-		
Anxiety disorders	2 (4.8)	-	-		
Depressive disorders	2 (4.8)	-	-		
Gender identity disorders	2 (4.8)	-	-		
Learning disorders	-	-	2 (5.0)		
Other disorders of infancy, childhood, or adolescence	5 (11.9)	-	-		
Parent-child relational problem	5 (11.9)	1 (5.9)	1 (2.5)		
Comorbid condition[c]	24 (57.1)	2 (11.8)	-		
None	6 (14.3)	13 (76.5)	32 (80.0)		
BDI-II sum sores, mean (S.D.)[d]	12.8 (9.2)	3.9 (3.3)	6.9 (7.0)	F=10.5, df=2	<0.001

Table 1. (continued). Basic sample characteristics

	Service users (n=42)	Siblings (n=17)	Controls (n= 40)	Test statistic	p
CAPE sum scores, mean (S.D.)[d]					
Positive	10.0 (9.4)	3.9 (3.2)	4.6 (3.9)	F=8.28, df=2	<0.001
Negative	9.9 (6.7)	5.6 (3.8)	7.4 (4.8)	F=3.88, df=2	0.024
Depressive	7.7 (4.0)	4.2 (1.8)	4.7 (3.4)	F=9.90, df=2	<0.001
STAI-DY1 (trait anxiety)[a] sum scores, mean (S.D.)[d]	35.5 (10.6)	30.2 (6.8)	31.1 (7.2)	F=3.47, df=2	0.035
STAI-DY2 (state anxiety)[a] sum scores, mean (S.D.)[d]	85.6 (20.8)	67.1 (9.2)	74.1 (16.4)	F=8.12, df=2	<0.001
Number of valid beeps Mean (range, min-max)	44.16 (25-59)	43.4 (23-57)	44.9 (24-58)	F=0.27, df=2	0.754

Note: S.D., standard deviation; df, degrees of freedom; β, standardized regression coefficients (mean score differences); CI, confidence interval;
[a] Missing values: ethnicity=1, BDI=1, STAI-DY1=1, STAI-DY2=2, [b] Categories defined as: school (primary education, LBO, MAVO, VMBO), further (MBO, HAVO, VWO), and higher (HBO, WO) of the Dutch educational system, [c] Consisting of the following diagnostic categories in the case group: Additional codes (Parent-child relational problem, 33.3%; Borderline intellectual functioning, 13.3%; Neglect of child, 6.7%), Attention-deficit and disruptive behaviour disorders (10%), Learning disorders (10%), Personality disorders (6.7%), Mild mental retardation (6.7%), Anxiety disorders (3.3%), Dissociative disorders (3.3%), Tic disorders (3.3%), Amphetamine related disorders (3.3%)[d] Standardized mean score differences across groups:

	Cases v. controls		Siblings v. controls		Cases v. siblings	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
BDI- II	0.71 (0.30 – 1.11)	0.001	-0.37 (-0.89 – 0.16)	0.168	1.08 (0.55 – 1.60)	<0.001
CAPE						
Positive	0.75 (0.34 – 1.17)	<0.001	-0.09 (-0.63 – 0.44)	0.735	0.84 (0.31 – 1.38)	0.002
Negative	0.42 (-0.01 – 0.85)	0.057	-0.31 (-0.87 – 0.25)	0.269	0.73 (0.17 – 1.29)	0.011
Depressive	0.80 (0.40 – 1.21)	<0.001	-0.12 (-0.64 – 0.41)	0.666	0.92 (0.39 – 1.45)	0.001
STAI-DY1	0.50 (0.06 – 0.93)	0.025	-0.09 (-0.65 – 0.47)	0.748	0.59 (0.03 – 1.14)	0.040
STAI-DY2	0.59 (0.19- 0.99)	0.004	-0.36 (-0.88 – 0.16)	0.170	0.95 (0.43 – 1.46)	<0.001

Table 2. Exposure to bullying victimization and related mental health complaints within and across groups

	Service users (n=42)	**Siblings (n=17)**	**Controls (n= 40)**	**Service users vs. controls**	**Service users vs. siblings**	**Siblings vs. controls**
Bullying victimization, n (%)						
Any	32 (76.2)	11 (64.7)	27 (67.5)	OR =1.5 (0.6 – 4.1)	OR =1.7 (0.5 – 5.9)	OR =0.9 (0.3 – 2.9)
Physical bullying	20 (47.6)	2 (11.8)	6 (15.0)	OR =5.2 (1.8 – 14.8)*	OR =6.8 (1.4 – 33.6)*	OR =0.8 (0.1 – 4.2)
Verbal bullying	24 (57.1)	10 (58.8)	23 (57.5)	OR =1.0 (0.4 – 2.4)	OR =0.9 (0.3 – 2.9)	OR =1.1 (0.3 – 3.3)
Indirect bullying	27 (64.3)	9 (52.9)	21 (52.5)	OR =1.6 (0.7 – 3.9)	OR =1.6 (0.5 – 5.0)	OR =1.0 (0.3 – 3.2)
Bullying victimization, only severe and frequent[a], n (%)						
Any	21 (50.0)	2 (11.8)	10 (25.0)	OR =3.0 (1.2 – 7.7)*	OR =7.5 (1.5 – 37.0)*	OR =0.4 (0.1 – 2.1)
Physical bullying	12 (28.6)	0 (0.0)	1 (2.5)	OR =15.6 (1.9 – 126.7)*	-	-
Verbal bullying	14 (33.3)	1 (5.9)	5 (12.5)	OR =3.5 (1.1 – 10.9)*	OR =8.0 (0.9 – 66.6)	OR =0.4 (0.0 – 4.1)
Indirect bullying	16 (38.1)	2 (11.8)	9 (22.5)	OR =2.1 (0.8 – 5.6)	OR =4.6 (0.9 – 22.9)	OR =0.5 (0.1 – 2.4)
Bullying victimization, mean (S.D.)						
Overall	24.6 (11.3)	18.8 (7.0)	19.1 (8.0)	β =0.56 (0.14 – 0.99)*	β =0.60 (0.05 – 0.15)*	β =-0.03 (-0.59 – 0.52)
Physical bullying	7.2 (3.7)	4.8 (2.4)	4.6 (1.6)	β =0.86 (0.46 – 1.26)**	β =0.77 (0.24 – 1.29)*	β =0.09 (-0.44 – 0.62)
Verbal bullying	8.5 (4.8)	6.8 (2.8)	7.3 (3.8)	β =0.29 (-0.15 – 0.73)	β =0.42 (-0.15 – 0.98)	β =-0.12 (-0.70 – 0.45)
Indirect bullying	8.9 (4.9)	7.2 (3.6)	7.3 (4.1)	β =0.37 (-0.06 – 0.81)	β =0.39 (-0.17 – 0.96)	β =-0.02 (-0.59 – 0.54)
Self-perceived long-term effects	17 (54.8)	1 (9.1)	5 (18.5)	OR =5.3 (1.6 – 17.8)*	OR =12.1 (1.4 – 106.8)*	OR =0.4 (0.0 – 4.3)
Bullying-related mental health complaints, n (%)						
Absence school	15 (46.9)	2 (18.2)	5 (18.5)	OR =3.9 (1.2 – 12.8)*	OR =4.0 (0.7 – 21.4)	OR =1.0 (0.2 – 6.0)
Suicidal thoughts	17 (53.1)	1 (9.1)	6 (22.2)	OR =4.0 (1.3 – 12.4)*	OR =11.3 (1.3 – 99.2)*	OR =0.4 (0.0 – 3.3)
Vivid memories	20 (62.5)	1 (9.1)	9 (33.3)	OR =3.3 (1.1 – 9.8)*	OR =16.7 (1.9 – 146.9)*	OR =0.2 (0.2 – 1.8)
Nightmares	9 (28.1)	0 (0.0)	3 (11.1)	OR =3.1 (0.8 – 13.0)	-	-
Re-living the event	13 (40.6)	0 (0.0)	4 (14.8)	OR =3.9 (1.1 – 14.1)*	-	-
Flashbacks	14 (43.8)	1 (9.1)	6 (22.2)	OR =2.7 (0.9 – 8.6)	OR =7.8 (0.9 – 68.2)	OR =0.4 (0.0 – 3.3)
Distressed in situations	16 (50.0)	0 (0.0)	3 (11.1)	OR =8.0 (2.0 – 32.0)*	-	-

Note: S.D., standard deviation; df, degrees of freedom; β, standardized regression coefficients (mean score differences); CI, confidence interval; OR, odds ratio; *$p<0.05$, **$p<0.001$

[a] defined as being bullied "sometimes" or more often (frequency) and the experience were evaluated as "quite serious" or "extremely serious" (intensity), for analyses all exposure levels were used

Association between momentary stress and negative affect by bullying victimization and group

There was evidence in support of primary and secondary hypotheses that exposure to overall bullying victimization as well as physical bullying, but not verbal and indirect bullying, modified the association of momentary stress with negative affect (Table 3). Evidence for effect modification by levels of bullying exposure within and across groups was evidenced by statistically significant 3-way interaction effects described below (Table 3).

Within-group comparisons

Within groups, momentary stress was associated with higher negative affect in service users (*adj.* β =0.09, p=0.002) and lower negative affect in controls (*adj.* β =-0.11, p=0.024) when high *vs.* low overall bullying victimization levels were compared, while no differences by exposure levels were found in siblings (*adj.* β =0.07, p=0.392) (see Table 3). Analyses to test secondary hypotheses revealed that stress was associated with lower negative affect in controls comparing those with high *vs.* those with low physical bullying levels (*adj.* β =-0.33, $p<0.001$), whereas higher negative affect was observed in service-users (*adj.* β =0.07, p=0.010) and, at trend level, siblings (*adj.* β =0.12, p=0.073). There was no evidence that verbal and indirect bullying modified the affective reactivity to stress in daily life. Results of exploratory analyses that test effect modification by levels of bullying exposure for associations of specific stressors (event-related, activity-related, and social) with negative affect are provided in Supplement 1 and Table S1.

Table 3. Association of stress with negative affect and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p	*p*FWE
Outcome: negative affect									
Momentary stress[b] × bullying × group									
Overall bullying exposure							12.83 (2)	0.002	0.013
High (mean+1 SD)	0.25 (0.21 – 0.29)	<0.001	0.11 (-0.00 – 0.23)	0.054	0.11 (0.04 – 0.18)	0.003			
Average (mean)	0.20 (0.17 – 0.24)	<0.001	0.08 (0.01 – 0.14)	0.018	0.16 (0.12 – 0.21)	<0.001			
Low (mean-1 SD)	0.16 (0.10 – 0.21)	<0.001	0.04 (-0.06 – 0.13)	0.412	0.22 (0.17 – 0.27)	<0.001			
High v. low[d]	0.09 (0.04 – 0.15)	0.002	0.07 (-0.10 – 0.24)	0.392	-0.11 (-0.21 – 0.01)	0.024			
Physical bullying							28.91 (2)	<0.001	<0.001
High (mean+1 SD)	0.24 (0.20 – 0.28)	<0.001	0.14 (0.04 – 0.24)	0.005	-0.05 (-0.15 – 0.06)	0.358			
Average (mean)	0.20 (0.16 – 0.24)	<0.001	0.08 (0.02 – 0.15)	0.010	0.12 (0.07 – 0.16)	<0.001			
Low (mean-1 SD)	0.17 (0.11 – 0.23)	<0.001	0.02 (-0.06 – 0.10)	0.615	0.28 (0.22 – 0.34)	<0.001			
High v. low[d]	0.07 (0.02 – 0.13)	0.010	0.12 (-0.01 – 0.26)	0.073	-0.33 (-0.47 – -0.19)	<0.001			
Verbal bullying							4.69 (2)	0.100	0.767
Indirect bullying							9.05 (2)	0.011	0.087
Outcome: psychotic experiences									
Momentary stress[b] × bullying × group[b]									
Overall bullying exposure							10.63 (2)	0.005	0.039
High (mean+1 SD)	0.14 (0.12 – 0.16)	<0.001	0.06 (-0.00 – 0.12)	0.051	0.04 (0.00 – 0.08)	0.029			
Average (mean)	0.10 (0.07 – 0.12)	<0.001	0.04 (0.00 – 0.07)	0.036	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.05 (0.02 – 0.08)	<0.001	0.01 (-0.04 – 0.06)	0.667	0.06 (0.03 – 0.09)	<0.001			
High v. low[d]	0.09 (0.05 – 0.12)	<0.001	0.05 (-0.04 – 0.14)	0.278	-0.01 (-0.07 – 0.04)	0.575			
Physical bullying							2.47 (2)	0.291	1.0
Verbal bullying							3.46 (2)	0.178	1.0
Indirect bullying							19.35 (2)	<0.001	<0.001

Table 3. (continued). Association of stress with negative affect and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p	*p*FWE
High (mean+1 SD)	0.15 (0.13 – 0.17)	<0.001	0.07 (0.01 – 0.12)	0.022	0.04 (0.00 – 0.07)	0.038			
Average (mean)	0.10 (0.08 – 0.12)	<0.001	0.04 (0.00 – 0.07)	0.039	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.05 (0.03 – 0.08)	<0.001	0.00 (-0.05 – 0.06)	0.883	0.06 (0.03 – 0.09)	<0.001			
High v. low[d]	0.10 (0.07 – 0.13)	<0.001	0.06 (-0.02 – 0.15)	0.153	-0.03 (-0.07 – 0.02)	0.241			

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; adj. β, standardized regression coefficients, continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of exposure to bullying victimization within and across groups (service users, siblings, controls); *p*FWE , family-wise error-corrected p values were computed by multiplying the unadjusted p value by the total number of tests (*N*=8) to adjust significance levels of likelihood ratio tests for three-way interactions.

[a] Adjusted for age, gender, ethnicity, level of education, 12-month use of cannabis

[b] Momentary stress was calculated by combining the ratings of six items assessing event-related, activity-related, and social stress by calculating mean scores

[c] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(BULLYING_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times BULLYING_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(BULLYING_j \times GROUP_j) + \beta_7(STRESS_{ij} \times BULLYING_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

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Table 3. (continued). Association of stress with negative affect and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls[a]

[d] Difference in the magnitude of associations of momentary stress with psychotic experiences between those exposed to high v. low levels of bullying victimization across groups (Δ high v. low):

	Service users vs. controls		Siblings vs. controls		Service users vs. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
Δ high vs. low exposure levels of bullying victimization across groups						
			Outcome: negative affect			
Momentary stress x bullying x group						
Overall bullying exposure	0.21 (0.09 – 0.32)	<0.001	0.19 (-0.01 – 0.38)	0.062	0.02 (-0.16 – 0.20)	0.822
Physical bullying	0.40 (0.25 – 0.56)	<0.001	0.45 (0.26 – 0.65)	<0.001	-0.05 (-0.19 – 0.10)	0.497
			Outcome: psychotic experiences			
Momentary stress x bullying x group						
Overall bullying exposure	0.10 (0.04 – 0.16)	0.001	0.07 (-0.04 – 0.17)	0.222	0.04 (-0.06 – 0.13)	0.470
Indirect bullying	0.12 (0.07 – 0.18)	<0.001	0.09 (-0.01 – 0.19)	0.070	0.03 (-0.06 – 0.12)	0.473

Between-group comparisons

To investigate whether the impact of exposure to bullying victimization on stress sensitivity differed across groups, differences in magnitude of associations between those exposed to high *vs.* low levels of bullying victimization were examined across groups. The difference in magnitude of associations between stress and negative affect was greater in service users than in controls when high *vs.* low levels of exposure to overall bullying victimization (*adj.* β =0.21, p<0.001) as well as physical (*adj.* β =0.40, p<0.001) bullying were compared. Further, there were differences in the magnitude of associations between stress and negative affect by physical (*adj.* β =0.45, p<0.001) and, at trend level, overall (*adj.* β =0.19, p=0.062) bullying comparing siblings *vs.* controls. No differences were found comparing service users *vs.* siblings.

Association between stress and psychotic experiences by bullying victimization and group

There was evidence that exposure to overall bullying victimization as well as indirect bullying, but not verbal and physical bullying, amplified the association of momentary stress with psychotic experiences, as evidenced by statistically significant 3-way interaction effects described below (Table 3).

Within-group comparisons

Within groups, momentary stress was associated with more intense psychotic experiences in service users (*adj.* β =0.09, p<0.001) exposed to high overall bullying victimization levels compared to those with low exposure levels, while no differences by bullying exposure were found in siblings (*adj.* β =0.05, p=0.278) and controls (*adj.* β =-0.01, p=0.575) (Table 3). Analyses of secondary hypotheses revealed that stress was associated with more intense psychotic experiences in service users (*adj.* β =0.10, p<0.001), but not in siblings (*adj.* β =0.06, p=0.153), and controls (*adj.* β =-0.03, p=0.241) comparing high *vs.* low levels of indirect bullying. There was no evidence that physical as well as verbal bullying modified the psychotic reactivity to stress in daily life. Results of exploratory analyses that test effect modification by levels of bullying exposure for associations of specific stressors (event-related, activity-related, and social) with psychotic experiences are provided in Supplement 1 and Table S2.

Between-group comparisons

There were differences in the magnitude of associations between momentary stress and psychotic experiences in those exposed to high *vs.* low exposure levels to overall bullying victimization comparing service users and controls (*adj.* β =0.10, p=0.001), but not service users and siblings (*adj.* β =0.04, p=0.470) and siblings and controls (*adj.* β =0.07, p=0.222). Further, there was evidence for differences in the magnitude of associations between stress and psychotic experiences by exposure levels to indirect bullying comparing service users and controls (*adj.* β =0.12, p<0.001), and, at trend level, siblings and controls (*adj.* β =0.09, p=0.070), but not service users and siblings (*adj.* β =0.03, p=0.473).

As groups differed considerably with regard to cannabis use, a sensitivity analysis is provided in Table S3 testing primary hypotheses while also controlling for 12-month prevalence of cannabis use. A similar pattern of findings emerged.

Discussion

Main findings

In line with primary and secondary hypotheses, our findings suggest that exposure to overall, as well as specific types of (i.e. physical and indirect, but not verbal), bullying victimization modifies individuals' affective and psychotic reactivity to minor stress in daily life. While there was strong evidence that service users who were exposed to high levels of bullying victimization reported more intense (i) negative affect and (ii) psychotic experience in response to stress compared to those with low exposure levels, controls showed either no marked differences or, intriguingly, less intense negative affect (evident for physical bullying) by exposure levels. In siblings, a less consistent pattern of findings was observed.

Methodological considerations

The current findings should be interpreted in light of potential limitations. First, bullying victimization was assessed retrospectively using a self-report measure. Thus, recall bias may have influenced reported findings [55] and recent studies also indicate that retrospectively assessed adverse childhood experiences, including bullying, may identify largely different groups of individuals [56]. However, potential effects may have been minimized due to the young age of the sample and the reduced time that had passed between exposure and assessment. Similarly, ESM measures were based on self-report. While this allows for ecologically valid assessment of experiences and contexts in real life, an important next step is to investigate how bullying victimization impacts on individuals' stress sensitivity on other levels of investigation, including biological markers [57-59] and passively assessed sensor data [60]. Second, due to potentially high assessment burden associated with ESM assessment for some participants, selection may have influenced our findings and possibly introduced bias, particularly if differential by bullying exposure. However, studies have shown that the ESM is a feasible and reliable assessment method in adolescent and adult populations [35]. In addition, extensive briefing on the ESM procedure resulted in a sufficient number of responses (i.e. ≥20 valid responses with, on average, 45 observations in each group) in most participants (90.8%). Also, there was no evidence that the number of valid responses differed across groups. Thus, as maximum likelihood estimations were used allowing for use of all available data, the potential impact of selection and sampling bias are kept at a minimum. Third, while we adjusted for potential confounders (i.e. age, sex, ethnicity, level of education), other unmeasured factors could have influenced reported findings (e.g. polygenetic risk for various psychopathologies and personality traits, other socio-environmental risk factors). Further, current mental health problems may influence reporting of bullying victimization and stress sensitivity and may, as a consequence, influence the interpretation of reported findings. Time-lagged analyses would be required to adjust for levels of symptoms in analyses of experience sampling data, which, in turn, would require a higher number of observations to conduct such analyses with sufficient power. Fourth, the sibling group was comparably small (N=17) and inconsistent findings may have occurred due to sampling error. Fifth, experience sampling data over the 6-day assessment period was used for cross-sectional modelling. Thus, the temporal order of stress, negative affect, and psychotic experiences were not specifically investigated. We therefore cannot rule out that reverse causality may have affected our findings. Similarly, using the RBQ and combining total scores of bullying exposure at primary and secondary school did not allow us for investigating the precise timing of the effects of bullying exposure on stress sensitivity. Thus, we cannot rule out that some participants may have been exposed to bullying during ESM assessments and hence timing of exposure, mechanism, and outcome could not be established. Future studies may investigate the effects of timing of bulling exposure on stress sensitivity by using time-lagged analyses potentially in combination with multilevel moderated mediation models and a cohort design to test for temporality as an important criterion for establishing causality [61]. Sixth, we combined all stress items to test primary and secondary hypotheses. However, using a composite measure of minor stressors may require further scrutiny by psychometric experience sampling studies. Last, we decided to recode a bipolar scale assessing event-related stress from “very unpleasant” (coded as -3) to “very pleasant” (coded as 3) into a unipolar scale including only unpleasant and neutral events that have happened since the last beep (sores ranging from 1-4). This may have resulted in potential underrepresentation of event-related stress in the composite stress score. We computed sensitivity analyses including the bipolar event-related stress scale and found no marked differences for reported associations (see Table S4).

Comparison with previous research

In recent years, evidence has accumulated that exposure to adverse childhood experiences, including bullying victimization [4-12], is associated with an increased risk of developing mental health problems. However, our understanding of candidate mechanisms remains limited, especially in youth. A process of sensitization that may ultimately lead to lasting changes in individuals’ responses to stress has been proposed to form a common mechanistic pathway that may partly explain associations between exposure to socio-environmental risk and psychopathology [28]. At a behavioral level, this proposition has been investigated using ESM and is largely supported by findings of an increased affective and psychotic reactivity in response to minor daily stressors in adults with various mental health problems and experiences of childhood trauma and adult life events [36-39].

In the current study, we found, for the first time, that young help-seeking individuals who were exposed to high levels of bullying victimization at elementary and/or secondary school responded with more intense negative affect and psychotic experiences to minor stress in their daily lives compared to those with low exposure levels. These findings are in accordance with reported effects of childhood trauma on stress sensitivity derived from the same sample [40] and may lend further support to behavioral sensitization as a process that emerges from adversity and that may contribute to push people along pathways to poor mental health outcomes in daily life in developmentally early stages of psychopathology.

In contrast, the response to stress was not differentially amplified by bullying exposure levels in controls. Specifically, controls exposed to high, but not low, exposure levels to physical bullying appeared to be resilient to its effects indicated by less intense negative affect in response to stress comparing high *vs.* low exposure levels. This is an interesting finding and parallels previous findings in which physical abuse and neglect [40] as well as sexual abuse [38] were found to be associated with lower negative affect in response to stress in controls. This may suggest that high levels of exposure to more intrusive forms of adversity may lead to the development of resilience towards subsequent stress in some individuals who do not develop help-seeking behavior, though some inconsistencies were observed in previous studies [38, 40] and direct replication studies are needed before firm conclusion can be drawn. We may speculate, however, that various protective factors may partly explain this finding, especially if they are differentially utilized and/or available in controls compared to service users, including good interpersonal relationships, social support, various personality characteristics, positive atmosphere at home, higher levels of neighborhood social cohesion, high self-esteem, low rumination tendencies, and low polygenetic risk [62, 63]. While tempting, this explanation needs to be carefully tested in future studies. It also corroborates, more generally, previous research that has shown that a large proportion of individuals exposed to socio-environmental risk do show resilience to its detrimental effects on mental health [64].

In siblings, a less consistent pattern of findings was observed with no differences in individuals' affective and psychotic reactivity to stress by exposure levels except some evidence for more intense negative affect in response to stress for those exposed to high *vs.* low levels of physical bullying. These results, however, should be interpreted with caution as the sample size was small and, therefore, findings may have occurred due to sampling error. In addition, as siblings represent an intermediate risk group, it may be speculated that only a small proportion develop a heightened sensitivity to stress while others are more resilient which leads to inconsistent findings at the group level. Notably, we found no evidence that verbal bullying modified the affective and psychotic reactivity in response to stress in all groups.

Interestingly, secondary analyses revealed that physical bullying at school was associated with more intense negative affect, whereas indirect bullying was associated with more intense psychotic experiences in response to stress in daily lives of help-seeking young individuals. These findings may be interpreted in light of cognitive models of psychosis [65, 66] in which various psychological factors and dysfunctional schemas are thought to be crucial in the development and maintenance of delusional ideations, one form of psychotic experiences. A core feature of delusions is thought to be an unfounded belief, and not a founded 'proof', that harm will occur from others. While speculative, indirect bullying may be more strongly associated with the development of persecutory beliefs of other people wanting to harm than other types of bullying which are more directly associated with physical violence, leading to an increased likelihood to respond with delusional ideations to daily life stressors. In following this line, one would expect that the psychotic reactivity to socially stressful situations is especially amplified by indirect bullying. This was, however, not the case in our exploratory analyses after we adjusted for multiple testing. Instead, indirect bullying was associated with an elevated psychotic reactivity to activity-related stress in service users. To the best of our knowledge, no study has specifically investigated differential associations of various bullying types with specific symptom domains of the psychosis spectrum.

Although strong evidence was found that bullying victimization modifies affective and psychotic reactivity to minor stress in help-seeking individuals, future studies should further investigate effects of poly- and re-victimization on stress sensitivity. Arguably, exposure to various adverse childhood experiences and other socio-environmental risk factors, the so-called exposome [67], may lead to an accumulation of risk by progressively increasing individuals' sensitivity to stress that may, in turn, contribute to the develop and maintenance of mental health problems. This approach would also account for findings that most risk factors are prone to cluster within a relatively small number of vulnerable individuals [2, 6] and tend to be associated with mental disorders in a dose-response fashion [15]. Additionally, more research is needed that focusses on investigating timing of bullying exposure, mechanism, and outcome by conducting well-controlled cohort studies to test whether elevated stress sensitivity mediates the association between exposure to and the onset of mental disorders. In using this study design, the potential buffering role of protective factors (e.g. number of close relationships, coping skills, personality traits) on stress sensitivity as well as potential complex interactions with other socio-environmental and genetic risk factors may be further investigated [62]. Lastly, in line with findings of frequently co-occurring psychopathological domains, especially at a developmentally early stage [23], we found high levels of depressive, anxiety, and psychotic symptoms and high proportions of non-specific diagnoses and comorbidity in service users. This further supports dimensional models of psychopathology [18, 19, 21] as well as notions of extended and transdiagnostic phenotypes [22].

Conclusion

Our findings suggest that individuals' response to minor stress in daily life may represent a putative risk or resilience mechanism through which exposure to bullying victimization may impact on mental health in youth. As dissipation of detrimental effects of bullying victimization on mental health has recently been reported to occur over time [7], programs that aim to prevent bullying victimization at school and inform teachers, parents, and the general public remain the ultimate goal. There is also a pressing need to directly assess bullying victimization in youth mental health services to integrate and directly tackle these adverse experiences in psychological interventions. Finally, to interrupt the process of prolonged sensitization to stress and alleviate individuals' mental health burden in daily life, novel mHealth tools (e.g. ecological momentary interventions) may be used to provide treatment components in real life using interactive delivery schemes to extend psychotherapy from clinical settings to individuals' everyday environment [35, 68, 69].

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Supplementary material

Supplement 1: Results of exploratory analyses

Results

Association between momentary stressors and negative affect by bullying victimization and group

We found no evidence that prior exposure to overall as well as specific types of bullying victimization modified the association of event-related with negative affect (Table S1). However, the association of activity-related stress and social stress with negative affect was amplified by physical bullying, but not by exposure to overall bullying victimization as well as other bullying types (i.e. verbal and indirect). Evidence for effect modification by levels of bullying exposure within and across groups was evidenced by statistically significant 3-way interaction effects (Table S1).

Within-group comparisons

Within groups, activity-related stress was associated with less intense negative affect in controls with high *vs.* low physical bullying levels (*adj.* β=-0.28, p<0.001), whereas no differences were observed in service-users (*adj.* β=0.05, p=0.120) and siblings (*adj.* β=0.04, p=0.619). In addition, social stress was associated with more intense negative affect in service users (*adj.* β=0.08, p=0.004) and less intense negative affect in controls (*adj.* β=-0.26, p=0.004), but no differences in siblings, when high *vs.* low physical bullying levels were compared.

Between-group comparisons

To investigate whether the impact of exposure to bullying victimization on stress sensitivity differed across groups, differences in magnitude of associations between those exposed to high *vs.* low levels of bullying victimization were examined across groups. The difference in magnitude of associations between activity-related stress and negative affect was greater in service users *vs.* controls (*adj.* β=0.33, p<0.001) and siblings *vs.* controls (*adj.* β=0.32, p=0.002), but not in service users *vs.* siblings (*adj.* β=0.01, p=0.891), when high vs. low levels of physical bullying were compared. In addition, there were significant differences in the magnitude of associations between social stress and negative affect by levels of physical bullying in service users vs. controls (*adj.* β=0.34, p<0.001) and siblings *vs.* controls (*adj.* β=0.39, p=0.001), but not service users *vs.* siblings (*adj.* β=-0.05, p=0.522).

Association between momentary stressors and psychotic experiences by bullying victimization and group

Within-group comparisons

We found no evidence that prior exposure to overall as well as specific types of bullying victimization modified the association of event-related and social stress with psychotic experiences (Table S2). However, we found evidence that activity-related stress was associated with more intense psychotic experiences in service users (*adj.* β=0.09, p<0.001), but not in siblings (*adj.* β=0.04, p=0.417) and controls (*adj.* β=-0.02, p=0.367) (Table S2) when high *vs.* low exposure levels to indirect bullying were compared, while no evidence for effect modification was found for overall bullying victimization as well as physical and verbal bullying.

Between-group comparisons

There were differences in the magnitude of associations of activity-related stress with psychotic experiences by high *vs.* low exposure levels to indirect bullying victimization comparing service users and controls (*adj.* β=0.11, p<0.001), but not service users and siblings (*adj.* β=0.05, p=0.280) and siblings and controls (*adj.* β=0.06, p=0.249).

Table S1. Association between momentary stressors and negative affect, by levels of bullying victimization in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction		
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ^2 (df)**	**p**	**pFWE**
			Outcome: negative affect						
Event-related stress × bullying × group[b]									
Overall exposure to bullying							0.13 (2)	0.936	1
Physical bullying							2.29 (2)	0.319	1
Verbal bullying							1.95 (2)	0.378	1
Indirect bullying							1.13 (2)	0.568	1
Activity-related stress × bullying × group[b]									
overall exposure to bullying							10.53 (2)	0.005	0.124
Physical bullying							18.35 (2)	<0.001	0.002
High (mean+1 SD)	0.20 (0.16 – 0.24)	<0.001	0.06 (-0.04 – 0.16)	0.250	-0.06 (-0.16 – 0.05)	0.290			
Average (mean)	0.17 (0.13 – 0.21)	<0.001	0.04 (-0.02 – 0.11)	0.194	0.09 (0.04 – 0.13)	<0.001			
Low (mean-1 SD)	0.15 (0.09 – 0.21)	<0.001	0.03 (-0.06 – 0.11)	0.564	0.23 (0.17 – 0.29)	<0.001			
High v. low[c]	0.05 (-0.01 – 0.10)	0.120	0.04 (-0.10 – 0.18)	0.619	-0.28 (-0.42 - -0.14)	<0.001			
Verbal bullying							7.08 (2)	0.029	0.696
Indirect bullying							6.64 (2)	0.036	0.867
Social stress × bullying × group[b]									
Overall exposure to bullying							4.62 (2)	0.100	1

Table S1. (continued). Association between momentary stressors and negative affect, by levels of bullying victimization in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction		
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ² (df)**	**p**	**pFWE**
Physical bullying							13.66 (2)	0.001	0.026
High (mean+1 SD)	0.13 (0.09 – 0.16)	<0.001	0.11 (0.01 – 0.20)	0.024	-0.10 (-0.24 – 0.04)	0.147			
Average (mean)	0.09 (0.05 – 0.12)	<0.001	0.05 (-0.01 – 0.11)	0.118	0.03 (-0.03 – 0.09)	0.283			
Low (mean-1 SD)	0.05 (-0.01 – 0.10)	0.095	-0.01 (-0.09 – 0.06)	0.709	0.16 (0.10 – 0.23)	<0.001			
High v. low[c]	0.08 (0.03 – 0.13)	0.004	0.12 (-0.00 – 0.25)	0.504	-0.26 (-0.44 - -0.08)	0.004			
Verbal bullying							0.59 (2)	0.744	1
Indirect bullying							3.39 (2)	0.183	1

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; adj. β, standardized regression coefficients, continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of exposure to bullying victimization within and across groups (service users, siblings, controls); *p*FWE , family-wise error-corrected p values were computed by multiplying the unadjusted p value by the total number of tests (*N*=24) to adjust significance levels of likelihood ratio tests for three-way interactions.

[a] Adjusted for age, gender, ethnicity, and level of education

[b] Three-way interaction as included in the following model (with y_{ij} for negative affect as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(BULLYING_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times BULLYING_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(BULLYING_j \times GROUP_j) + \beta_7(STRESS_{ij} \times BULLYING_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

[c] Difference in the magnitude of associations of momentary stress with negative affect between those exposed to high v. low levels of bullying victimization across groups (Δ high v. low):

	Service users vs. controls		Siblings vs. controls		Service users vs. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: negative affect			
Δ high vs. low exposure levels of bullying victimization across groups						
Activity-related stress × bullying × group						
Physical bullying	0.33 (0.18 – 0.48)	<0.001	0.32 (0.12 – 0.52)	0.002	0.01 (-0.14 – 0.16)	0.891
Social stress × bullying × group						
Physical bullying	0.34 (0.15 – 0.53)	<0.001	0.39 (0.17 – 0.61)	0.001	-0.05 (-0.18 – 0.09)	0.522

Table S2. Association between momentary stressors and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction		
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p	pFWE
Outcome: psychotic experiences									
Event-related stress × bullying × group[b]									
Overall exposure to bullying							3.01 (2)	0.222	1
Physical bullying							11.42 (2)	0.003	0.080
Verbal bullying							0.21 (2)	0.902	1
Indirect bullying							5.12 (2)	0.077	1
Activity-related stress × bullying × group[b]									
Overall exposure to bullying							6.37 (2)	0.041	1
Physical bullying							1.17 (2)	0.557	1
Verbal bullying							2.07 (2)	0.355	1
Indirect bullying							13.27 (2)	0.001	0.032
High (mean+1 SD)	0.13 (0.10 – 0.15)	<0.001	0.04 (-0.01 – 0.10)	0.131	0.03 (-0.00 – 0.07)	0.085			
Average (mean)	0.09 (0.07 – 0.11)	<0.001	0.03 (-0.01 – 0.06)	0.151	0.05 (0.02 – 0.07)	<0.001			
Low (mean-1 SD)	0.04 (0.01 – 0.07)	0.004	0.01 (-0.05 – 0.06)	0.803	0.06 (0.03 – 0.09)	<0.001			
High v. low[c]	0.09 (0.06 – 0.12)	<0.001	0.04 (-0.05 – 0.12)	0.417	-0.02 (-0.07 – 0.03)	0.367			
Social stress × bullying × group[b]									
Overall exposure to bullying							3.97 (2)	0.140	1
Physical bullying							0.90 (2)	0.634	1
Verbal bullying							2.57 (2)	0.280	1
Indirect bullying							6.45 (2)	0.040	0.952

Table S2. (continued). Association between momentary stressors and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls[a]

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; adj. β, standardized regression coefficients, continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of exposure to bullying victimization within and across groups (service users, siblings, controls); *p*FWE , family-wise error-corrected p values were computed by multiplying the unadjusted p value by the total number of tests (*N*=24) to adjust significance levels of likelihood ratio tests for three-way interactions.
[a] Adjusted for age, gender, ethnicity, level of education, and childhood trauma
[b] Three-way interaction as included in the following model (with y_{ij} for psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(BULLYING_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times BULLYING_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(BULLYING_j \times GROUP_j) + \beta_7(STRESS_{ij} \times BULLYING_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)
[c] Difference in the magnitude of associations of momentary stress with psychotic experiences between those exposed to high v. low levels of bullying victimization across groups (Δ high v. low):

	Cases vs. controls		Siblings vs. controls		Cases vs. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**P**	**adj. β (95% CI)**	**p**
			Outcome: psychotic experiences			
Δ high vs. low exposure levels of bullying victimization across groups						
Activity-related stress × bullying × group						
Indirect bullying	0.11 (0.05 – 0.17)	<0.001	0.06 (-0.04 – 0.16)	0.249	0.05 (-0.04 – 0.15)	0.280

Table S3. Sensitivity analysis: Association of stress with negative affect and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls, and also adjusted for cannabis use[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p	*p*FWE
Outcome: negative affect									
Momentary stress[b] × bullying × group									
Overall bullying exposure							11.02 (2)	0.004	0.031
High (mean+1 SD)	0.26 (0.22 – 0.30)	<0.001	0.12 (0.01 – 0.24)	0.035	0.13 (0.06 – 0.20)	<0.001			
Average (mean)	0.21 (0.17 – 0.25)	<0.001	0.08 (0.02 – 0.15)	0.009	0.17 (0.13 – 0.22)	<0.001			
Low (mean-1 SD)	0.16 (0.11 – 0.22)	<0.001	0.04 (-0.05 – 0.14)	0.350	0.22 (0.17 – 0.27)	<0.001			
High v. low[d]	0.10 (0.04 – 0.15)	0.001	0.08 (-0.09 – 0.24)	0.353	-0.09 (-0.19 – 0.00)	0.061			
Physical bullying							29.62 (2)	<0.001	<0.001
High (mean+1 SD)	0.25 (0.21 – 0.29)	<0.001	0.15 (0.06 – 0.25)	0.002	-0.04 (-0.15 – 0.06)	0.443			
Average (mean)	0.21 (0.17 – 0.25)	<0.001	0.09 (0.03 – 0.15)	0.005	0.12 (0.08 – 0.17)	<0.001			
Low (mean-1 SD)	0.17 (0.12 – 0.23)	<0.001	0.02 (-0.06 – 0.11)	0.562	0.29 (0.23 – 0.35)	<0.001			
High v. low[d]	0.07 (0.02 – 0.13)	0.006	0.13 (-0.00 – 0.26)	0.055	-0.33 (-0.47 – -0.19)	<0.001			
Verbal bullying							3.67 (2)	0.159	1.0
Indirect bullying							7.51 (2)	0.023	0.175
Outcome: psychotic experiences									
Momentary stress[b] × bullying × group[b]									
Overall bullying exposure							9.87 (2)	0.007	0.057
High (mean+1 SD)	0.14 (0.12 – 0.16)	<0.001	0.06 (-0.01 – 0.12)	0.066	0.05 (0.01 – 0.08)	0.018			
Average (mean)	0.10 (0.08 – 0.12)	<0.001	0.03 (0.00 – 0.07)	0.046	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.05 (0.02 – 0.08)	<0.001	0.01 (-0.04 – 0.06)	0.663	0.05 (0.03 – 0.08)	<0.001			
High v. low[d]	0.09 (0.05 – 0.12)	<0.001	0.05 (-0.04 – 0.14)	0.307	-0.01 (-0.06 – 0.04)	0.707			

Table S3. (continued). Sensitivity analysis: Association of stress with negative affect and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls, and also adjusted for cannabis use[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ^2 (df)**	**p**	***p*FWE**
Physical bullying							3.38 (2)	0.185	1.0
Verbal bullying							2.97 (2)	0.226	1.0
Indirect bullying							17.43 (2)	<0.001	0.001
High (mean+1 SD)	0.15 (0.13 – 0.17)	<0.001	0.07 (0.01 – 0.12)	0.024	0.04 (0.01 – 0.07)	0.021			
Average (mean)	0.10 (0.08 – 0.12)	<0.001	0.03 (0.00 – 0.07)	0.046	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.06 (0.03 – 0.08)	<0.001	0.00 (-0.05 – 0.05)	0.938	0.06 (0.03 – 0.09)	<0.001			
High v. low[d]	0.09 (0.06 – 0.12)	<0.001	0.06 (-0.02 – 0.15)	0.144	-0.02 (-0.07 – 0.02)	0.352			

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; adj. β, standardized regression coefficients, continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of exposure to bullying victimization within and across groups (service users, siblings, controls); *p*FWE , family-wise error-corrected p values were computed by multiplying the unadjusted p value by the total number of tests (*N*=8) to adjust significance levels of likelihood ratio tests for three-way interactions.

[a] Adjusted for age, gender, ethnicity, level of education, 12-month use of cannabis

[b] Momentary stress was calculated by combining the ratings of six items assessing event-related, activity-related, and social stress by calculating mean scores

[c] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(BULLYING_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times BULLYING_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(BULLYING_j \times GROUP_j) + \beta_7(STRESS_{ij} \times BULLYING_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request)

Table S4. Sensitivity analysis: Association of stress with negative affect and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls with bipolar event-related stress item[a]

	Service users		Siblings		Controls		Wald test for interaction [c]		
	adj. β (95% CI)	**P**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ^2 (df)**	**p**	***p*FWE**
			Outcome: negative affect						
Momentary stress[b] × bullying × group									
Overall bullying exposure							11.10 (2)	0.004	0.031
High (mean+1 SD)	0.26 (0.22 – 0.30)	<0.001	0.12 (0.01 – 0.24)	0.035	0.13 (0.06 – 0.20)	<0.001			
Average (mean)	0.21 (0.17 – 0.25)	<0.001	0.08 (0.02 – 0.15)	0.009	0.17 (0.13 – 0.22)	<0.001			
Low (mean-1 SD)	0.16 (0.11 – 0.22)	<0.001	0.04 (-0.05 – 0.14)	0.350	0.22 (0.16 – 0.27)	<0.001			
High v. low[d]	0.10 (0.04 – 0.15)	0.001	0.08 (-0.09 – 0.24)	0.353	-0.09 (-0.19 – 0.00)	0.062			
Physical bullying							29.70 (2)	<0.001	<0.001
High (mean+1 SD)	0.25 (0.21 – 0.29)	<0.001	0.15 (0.06 – 0.25)	0.002	-0.04 (-0.15 – 0.06)	0.443			
Average (mean)	0.21 (0.17 – 0.25)	<0.001	0.09 (0.03 – 0.15)	0.005	0.12 (0.08 – 0.17)	<0.001			
Low (mean-1 SD)	0.17 (0.12 – 0.23)	<0.001	0.02 (-0.06 – 0.11)	0.563	0.29 (0.23 – 0.35)	<0.001			
High v. low[d]	0.08 (0.02 – 0.13)	0.005	0.13 (-0.00 – 0.26)	0.055	-0.33 (-0.47 – -0.19)	<0.001			
Verbal bullying							3.67 (2)	0.159	1.0
Indirect bullying							7.61 (2)	0.022	0.178
			Outcome: psychotic experiences						
Momentary stress[b] × bullying × group									
Overall bullying exposure							9.99 (2)	0.007	0.054
High (mean+1 SD)	0.14 (0.12 – 0.16)	<0.001	0.06 (-0.01 – 0.12)	0.066	0.04 (0.01 – 0.08)	0.019			
Average (mean)	0.10 (0.08 – 0.12)	<0.001	0.03 (0.00 – 0.07)	0.046	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.05 (0.02 – 0.08)	0.001	0.01 (-0.04 – 0.06)	0.664	0.05 (0.03 – 0.08)	<0.001			

Table S4. (continued). Sensitivity analysis: Association of stress with negative affect and psychotic experiences, by levels of bullying victimization in service users, siblings, and controls with bipolar event-related stress item[a]

	Service users		Siblings		Controls		Wald test for interaction [c]		
	adj. β (95% CI)	P	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	p	*p*FWE
High v. low[d]	0.09 (0.06 – 0.12)	<0.001	0.05 (-0.04 – 0.14)	0.307	-0.01 (-0.06 – 0.04)	0.712			
Physical bullying							3.45 (2)	0.178	1.0
Verbal bullying							2.99 (2)	0.224	1.0
Indirect bullying							17.63 (2)	<0.001	0.001
High (mean+1 SD)	0.15 (0.13 – 0.17)	<0.001	0.07 (0.01 – 0.12)	0.024	0.04 (0.01 – 0.07)	0.022			
Average (mean)	0.10 (0.08 – 0.12)	<0.001	0.03 (0.00 – 0.07)	0.046	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.06 (0.03 – 0.08)	<0.001	0.00 (-0.05 – 0.05)	0.937	0.06 (0.03 – 0.09)	<0.001			
High v. low[d]	0.09 (0.06 – 0.12)	<0.001	0.06 (-0.02 – 0.15)	0.144	-0.02 (-0.07 – 0.02)	0.349			

Note: SD, standard deviation; df, degrees of freedom; v., versus; CI, confidence interval; adj. β, standardized regression coefficients, continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of exposure to bullying victimization within and across groups (service users, siblings, controls); *p*FWE , family-wise error-corrected p values were computed by multiplying the unadjusted p value by the total number of tests (*N*=8) to adjust significance levels of likelihood ratio tests for three-way interactions.

[a] Adjusted for age, sex, ethnicity, and level of education

[b] Momentary stress was calculated by combining the ratings of six items assessing event-related, activity-related, and social stress

[c] Three-way interaction term as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(BULLYING_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times BULLYING_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(BULLYING_j \times GROUP_j) + \beta_7(STRESS_{ij} \times BULLYING_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request

CHAPTER 6

Negative life events and stress sensitivity in youth's daily life: an ecological momentary assessment study

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Abstract

Background: Negative life events (LEs) are associated with mental health problems in youth. However, little is known about underlying mechanisms. The aim of the study was to investigate whether exposure to LEs modifies stress sensitivity in youth's daily life.

Methods: Ecological Momentary Assessment (EMA) was used to assess stress sensitivity (i.e. association of momentary stress with (i) negative affect and (ii) psychotic experiences) in 99 adolescents and young adults (42 service users, 17 siblings, and 40 controls; M_{age} 15 years). Before EMA, exposure to LEs (e.g., intrusive threats, experience of loss, serious illness) was assessed.

Results: Lifetime as well as previous-year exposure to LEs modified stress sensitivity in service users: they experienced more intense negative affect and psychotic experiences in response to stress when high vs. low exposure levels were compared. In contrast, controls showed no differences in stress sensitivity by exposure levels. Looking at specific types of LEs, controls showed less intense negative affect in response to stress when high vs. low exposure levels to threatening events during the last year, but not lifetime exposure, were compared. In siblings, no evidence was found that LEs modified stress sensitivity.

Conclusion: Stress sensitivity may constitute a putative risk and protective mechanism linking LEs and mental health in help-seeking youth, while unfavourable effects of LEs on stress sensitivity may attenuate over time or do not occur in controls and siblings. Targeting individuals' sensitivity to stress in daily life using novel digital interventions may be a promising approach towards improving youth mental health.

Keywords: Life Events; Stress Sensitivity; Youth Mental Health; Psychopathology; Ecological Momentary Assessment

Introduction

Most mental disorders manifest early (75% by age 24) and often increase in severity and specificity over time [1]. The onset of many mental disorders – e.g., psychotic, anxiety, mood, personality, eating, and substance-use disorders – fall into discrete time periods spanning from early adolescence (before age 14) to early adulthood (before age 25) [2]. Consequently, there has been a reform of youth mental health services [3] aimed at disrupting illness trajectories at developmentally early stages [4]. However, development and implementation of early intervention strategies are complicated by high comorbidity rates [2], and limited knowledge of underlying mechanisms, especially in the realm of youth mental health.

Mental health problems (e.g., depression, anxiety, psychosis) frequently co-occur during early stages of psychopathology [4] and share socio-environmental (e.g., negative life events) and genetic risk. This supports the notion of transdiagnostic phenotypes, including the extended psychosis spectrum phenotype [5], which are characterized by temporal and phenomenological continuity across developmental stages of clinical and subclinical mental health problems crossing traditional diagnostic boundaries. For instance, individuals reporting psychotic experiences are at increased risk of developing psychotic and affective disorders and the presence of psychotic experiences has been shown to predict greater illness severity as well as poorer treatment outcomes [5]. Thus, psychotic experiences may represent a severity marker of psychopathology [5], and subclinical as well as clinical expressions of affective dysregulation and psychosis may help elucidate putative underlying mechanisms through which socio-environmental risk factors, such as negative life events, impact on poor mental health.Life events (LEs) are situations with clear beginnings and endings that generate positive or negative changes within personal circumstances, and/or contain an element of immediate threat [6]. Widely studied LEs include exposure to serious illness, death of a family member, financial hardship, intrafamilial conflict, relationship conflicts and divorce, occupational changes, and legal problems [6]. Increasing evidence suggests exposure to LEs is, as other forms of adverse experiences, non-specifically associated with psychopathology [6-8] such as depression [9], schizophrenia [10], anxiety [11], attention-deficit/hyperactivity disorder [12], and suicidality [13]. Moreover, studies suggest a dose-response relationship in which higher numbers of LEs and the co-occurrence with other socio-environmental risk factors are associated with increased severity of psychopathology, including psychosis [14]. This is in accordance with a recent study demonstrating that individuals with first-episode psychosis (FEP) were almost four times more likely than healthy controls to have encountered both childhood and recent stressful LEs (e.g., death, divorce, sickness/accidents), in contrast to exposure to early LEs alone [15]. Considering that early adverse childhood adversities (ACEs) are linked to later psychopathology [2], and an increasing number of LEs exposure is suggested to increase odds of developing various mental health problems, including FEP [14], it is crucial to investigate LEs in the context of early-stage psychopathology.

Studies have also investigated associations of *specific types* of LEs with mental health problems. For instance, LeMoult and colleagues (2019) have shown that the death of a family member was associated with a higher risk of developing major depressive disorder before age 18. In youth, loss experiences have been linked to depressive symptoms, while events characterized by future threat were associated with anxiety [16]. Notably, there is a growing body of evidence suggesting the impact of LEs on mental health problems may be mediated by individuals' cognitive appraisal of and secondary to the event [17]. Thus, overall, there is evidence of an association between LEs exposure and mental health problems. Critically, however, underlying processes and mechanisms involved remain largely under-researched, especially in youth.

Elevated stress sensitivity in daily life has been proposed to be a transdiagnostic psychological mechanism contributing to the development and maintenance of mental health problems. Integrated models suggest that, as a consequence of exposure to socio-environmental risk (e.g., LEs), a process of gradual sensitization makes individuals more reactive to subsequent adversity as well as minor stressors in daily life (often referred to as elevated stress sensitivity or reactivity, which is partly related to other models, including the Diathesis-Stress Model or the Kindling hypothesis) [10, 18, 19]. It is thought that an increased sensitivity to minor stress in daily life may contribute to mental health problems and play a non-specific role in linking LEs and psychopathology in help-seeking individuals.

Context-sensitive ecological momentary assessment (EMA) - also known as experience sampling method - is a self-assessment diary technique that may be particularly well-suited to test the proposed role of stress sensitivity on a behavioural level by investigating whether exposure to LEs is associated with heightened stress sensitivity [20]. In recent EMA studies, derived from the same sample as the present study, exposure to childhood trauma and bullying victimization [21, 22] was associated with elevated stress sensitivity in help-seeking youth. To our knowledge, however, no study has investigated the modifying effects of negative LEs on stress sensitivity in help-seeking youth. To investigate the role of stress sensitivity in linking exposure to LEs and mental disorders at a developmentally early stage of psychopathology, help-seeking adolescents and young adults (service users), their biological siblings, and control subjects were recruited.

The current study aimed to investigate whether exposure to negative LEs modifies stress sensitivity in youth's daily life. Stress sensitivity was conceptualized as the associations between momentary stress (i.e., event-, activity-related and social stress combined) and (i) negative affect and (ii) psychotic experiences. We aimed to test the following primary hypotheses: First, we investigated whether overall lifetime as well as previous-year exposure to negative LEs (i.e., all LE exposure types combined) modifies individuals' stress sensitivity within groups (service users, siblings, and control group) with greater associations when high *vs.* low exposure levels are compared. Second, we tested whether differences exist in the magnitude of associations when modifying effects of LEs exposure on stress sensitivity are compared across groups, with greater differences in service users *vs*. controls, service users *vs*. siblings, and siblings *vs*. controls. Next, as secondary hypotheses, we examined whether lifetime and previous-year exposure to *specific types* of LEs (e.g., illness) modifies stress sensitivity within groups and whether there were differences of modifying effects across groups.

Materials and methods

Sample

Overall, 99 adolescents and young adults (age range 12-20 years) were recruited, consisting of help-seeking service users, their biological siblings, and controls. The help-seeking individuals were recruited from secondary youth mental health services provided by the Mutsaers Foundation (MF) in Limburg, the Netherlands. Service users were included if they were currently receiving treatment from MF, and excluded if they had a DSM-IV autism spectrum disorder diagnosis with the exception of pervasive developmental disorder not otherwise specified, IQ under 70, or insufficient command of Dutch. Moreover, biological siblings of participating service users were recruited. The same exclusion criteria applied, with the addition of lifetime history of receiving treatment from a mental health service. Lastly, individuals attending a school in the same catchment area as MF services were recruited as control subjects. Exclusion criteria were the same as for biological siblings.

Measures

Socio-demographic characteristics

We collected data on age, sex, ethnicity, and education level using a socio-demographic schedule.

Negative life events

A modified version of the List of Threatening Experiences questionnaire (LTE) [23, 24] was used to assess negative LEs. In the current study, 19 differing LEs were grouped into eight frequently used categories, which were based on the type of LEs exposure, including exposure to serious illness (e.g., “hospitalisation or other medical treatments”), experiences of loss (e.g., “death of a family member or friend”), and threatening events (e.g., “involved in a serious accident in which you and/or someone else got hurt seriously”). All items are provided in supplementary Table S1. In addition to asking whether individuals were exposed to LEs (dichotomous item), appraisal of LEs was also included. If an event has occurred (yes/no), participants were asked to rate the degree to which they perceived it as “unpleasant” or “pleasant” on a 5-point scale (from 1 = very unpleasant; to 5 = very pleasant). As our focus was on negative LEs, events appraised as neutral or pleasant were coded as 0, while events appraised as unpleasant or very unpleasant were coded as 1 and 2, respectively. All LTE items were used to calculate a total score (i.e., overall exposure of LEs). In the current study, the LTE was modified to assess LEs from the previous 12 months as well as before age 17. For participants younger than 17 years, the latter assessed LEs from birth to current age, excluding the previous year. The LTE has good discriminating power and test-retest reliability [24].

Depressive symptoms

The 21-item Beck Depression Inventory (BDI-II) [25] was used to assess depressive symptoms from the past 2-weeks on a 4-point scale (from 0 = not present; to 3 = severe). Good psychometric properties have been reported in clinical [26] and non-clinical [27] adolescent populations.

Anxiety symptoms

A Dutch version [28] of the State-Trait Anxiety Inventory (STAI-Y) [29] was used to measure state and trait anxiety. The STAI-DY consists of two parts and demonstrates good reliability and moderate validity [30]. The first 20-item part (STAI-DY1) assesses state anxiety (current intensity; ranging from 1 = not at all; 4 = very much), whereas the second 40-item part (STAI-DY2) assesses trait anxiety (pervasive frequency; ranging from 1 = rarely or never; to 4 = almost always).

Psychotic symptoms

The 42-item Community Assessment of Psychic Experiences (CAPE) was used to assess the frequency (from 0 = never; to 3 = nearly always) and distress (from 0 = not distressed; to 3 = very distressed) of negative (14 items), positive (20 items), and depressive (8 items) dimensions of non-clinical psychotic symptoms. CAPE has demonstrated good psychometric properties [31].

EMA measures

Daily changes in momentary stress (i.e., event-related, activity-related, and social stress), negative affect, and psychotic experiences were assessed using EMAs. This intensive self-assessment diary technique measures daily fine-grained subjective and social experiences with high ecological validity [20]. Data was collected outside the laboratory using a personal digital assistant (PDA), the “PsyMate”, which prompted participants with beeps ten times per day (between 7:30 am to 10:30 pm) at random intervals in set blocks of time for six consecutive days. A detailed description of used EMA items is shown in Table 1.

Table 1. EMA measures of stress, negative affect, and psychotic experiences

Domain	EMA Measure
Momentary stress	Mean scores of event-related, activity-related, and social stress items were calculated and combined in form of a composite stress score to represent individuals' momentary stress. Adequate concurrent validity with different stress measures has been reported [23].
Event	For event-related stress, participants had to rate the most important event since the last beep on a 7-point scale (from –3 = *very unpleasant*; to +3 = *very pleasant*). The item was reverse-coded such that higher ratings reflect higher levels of stress (–3 coded as 7; +3 coded as 1).
Activity	Activity-related stress was assessed by asking participants to identify what they were doing just before the beep (e.g., work or study, resting) and, subsequently, by asking whether they would "rather be doing something else", whether "this activity is difficult" for them, and whether they believe they "can do this well" [reversed] on a 7-point scale (from 1 = *not at all*; to 7 = *very much*).
Social	Participants were asked about their current social context (e.g., "I am alone", "I am with colleagues", "I am with friends"). Social stress was assessed by asking participants to rate the items "I find the people I am with pleasant" [reversed; if with someone] or "I like to be alone" [reversed; if alone] on 7-point scale (from 1 = *not at all*; to 7 = *very much*).
Negative affect	Participants reported the degree to which they felt anxious, lonely, down, irritated, and insecure on a 7-point scale (from 1 = *not at all*; to 7 = *very much*). The mean of these five items constitute the negative affect score. Good psychometric properties have been reported for the EMA measure of negative affect [24].
Psychotic experiences	The mean scores of eight items about mental states related to psychotic experiences were used (7-point scale from 1 = *not at all*; to 7 = *very much*). Participants were asked about the presence and intensity of hallucinations (e.g., "I hear things that aren't really there"), thought problems (e.g., "My thoughts are influenced by others", "It's hard to express my thoughts in words"), delusional ideations and other states (e.g., "I feel suspicious/paranoid", "I feel unreal", "I feel harried"). The EMA measure for psychotic experiences has demonstrated good concurrent validity [24].

Statistical analysis

In line with previous studies [21, 22] we first compared socio-demographic characteristics and standardized baseline scores (BDI-II, STAI-DY1/STAI-DY2, and CAPE) between groups (service users, biological siblings, and controls) using linear regression and χ^2-tests. To account for statistical dependencies in EMA data resulting from the multilevel data structure (multiple observations nested within participants), linear mixed models were computed using the MIXED command in STATA 15. Momentary stress and group status were added as independent variables and (i) negative affect and (ii) psychotic experiences as outcome variables, while controlling for age, sex, ethnicity, and level of education. To test primary and secondary hypotheses, we added two-way (Stress*X*LE, Stress*X*Group, LE*X*Group) and three-way (Stress*X*LE*X*Group) interaction terms into the models. After the three-way interaction terms were added, increase in model fit was tested using Wald tests (TESTPARM command). To account for multiple testing, the *p*-values of Wald tests were multiplied by the total number of tests to calculate family-wise error-corrected *p*-values (*p*FWE). Next, we computed linear combinations of coefficients with the LINCOM command to test whether, within-groups, associations between momentary stress and (i) negative affect and (ii) psychotic experiences were greater in individuals exposed to high *vs*. low levels of exposure to LEs (by calculating standardized LEs scores: +/- 1 *SD*, *M* = 0). Lastly, we explored whether effect moderation of LEs on stress sensitivity differs across groups by comparing differences in the magnitude of associations between momentary stress and (i) negative affect and (ii) psychotic experiences between individuals exposed to high *vs*. low levels of LEs exposure in service users *vs*. controls, service users *vs.* siblings, and siblings *vs*. controls.

Results

Sample characteristics

In total, 109 individuals were eligible to participate. Of these, 99 youths (42 service users, 17 siblings, and 40 controls) completed the EMA with ≥20 valid responses over the 6-day assessment period as well as the LTE, BDI-II, CAPE, and STAI-DY1/DY2. Groups did not significantly differ on age, sex, or ethnicity (Table 2). However, there was evidence for higher levels of depression, state and trait anxiety, and negative and positive psychotic experiences in service users *vs.* controls and service users *vs.* siblings, respectively. As shown in Table 3, service users were exposed to higher overall levels of LEs during the last year compared to controls and siblings, while no differences were found comparing siblings and controls. A similar pattern of findings was demonstrated for overall LEs before age 17, with service users exposed to higher overall levels of LEs as compared to controls and siblings, while no significant differences were found comparing siblings and controls. A similar pattern of findings was evident by looking at specific types of LEs during the last year and before the age of 17.

Table 2. Sample characteristics

	Service users (n=42)	Siblings (n=17)	Controls (n= 40)	Test statistic	*p*
Age (years), mean (S.D.)	15.4 (1.4)	15.3 (2.3)	15.6 (2.0)	F=0.24, df=2	0.785
Sex, n (%)					
Female	25 (59.5)	10 (58.8)	23 (57.5)	χ^2=0.04, df=2	0.983
Male	17 (40.5)	7 (41.2)	17 (42.5)		
Ethnicity, n (%)[a]					
White Dutch	26 (61.9)	11 (64.7)	25 (64.1)	χ^2=0.06, df=2	0.970
Other	16 (38.1)	6 (35.3)	14 (35.9)		
Level of education, n (%)[c]					
School	30 (71.4)	7 (41.2)	17 (42.5)	χ^2=10.48, df=2	0.033
Further	12 (28.6)	8 (47.1)	20 (50.0)		
Higher	-	2 (11.8)	3 (7.5)		
Cannabis use, n (%)					
12-months	9 (21.4)	1 (5.9)	4 (10.0)	χ^2=3.36, df=2	0.187
Lifetime	9 (21.4)	2 (11.8)	5 (12.5)	χ^2=1.50, df=2	0.473
Attempted suicide, n (%)					
During last year	6 (14.6)	-	-	-	-
Before age 17	8 (19.1)	-	-	-	-
DSM-IV diagnoses, n (%)					
Pervasive developmental disorders NOS	10 (23.8)	-	5 (12.5)	-	-
Attention-deficit and disruptive behaviour	6 (14.3)	3 (17.6)	-	-	-
Adjustment disorders	4 (9.5)	-	-	-	-
Anxiety disorders	2 (4.8)	-	-	-	-
Depressive disorders	2 (4.8)	-	-	-	-
Gender identity disorders	2 (4.8)	-	-	-	-
Learning disorders	-	-	2 (5.0)	-	-
Other disorders of infancy, childhood, or adolescence	5 (11.9)	-	-	-	-
Parent-child relational problem	5 (11.9)	1 (5.9)	1 (2.5)	-	-
Comorbid condition[b]	24 (57.1)	2 (11.8)	-	-	-
None	6 (14.3)	13 (76.5)	32 (80.0)	-	-
BDI-II sum sores, mean (S.D.)[a,d]	12.8 (9.2)	3.9 (3.3)	6.9 (7.0)	F=10.5, df=2	<0.001

Table 2. (continued). Sample characteristics

	Service users (n=42)	Siblings (n=17)	Controls (n= 40)	Test statistic	*p*
CAPE sum scores, mean (S.D.)[d]					
Positive	10.0 (9.4)	3.9 (3.2)	4.6 (3.9)	F=8.28, df=2	<0.001
Negative	9.9 (6.7)	5.6 (3.8)	7.4 (4.8)	F=3.88, df=2	0.024
Depressive	7.7 (4.0)	4.2 (1.8)	4.7 (3.4)	F=9.90, df=2	<0.001
STAI-DY1 (state anxiety)[a] sum scores, mean (S.D.)[d]	35.5 (10.6)	30.2 (6.8)	31.1 (7.2)	F=3.47, df=2	0.035
STAI-DY2 (trait anxiety)[a] sum scores, mean (S.D.)[d]	85.6 (20.8)	67.1 (9.2)	74.1 (16.4)	F=8.12, df=2	<0.001

SD: standard deviation; df: degrees of freedom; β: standardized regression coefficients (mean score differences); vs.: versus; CI: confidence interval.
[a] Missing values: ethnicity=1, BDI=1, STAI-DY1=1, STAI-DY2=2.
[b] Consisting of the following diagnostic categories in the service users group: Additional codes (Parent-child relational problem, 33.3%; Borderline intellectual functioning, 13.3%; Neglect of child, 6.7%), Attention-deficit and disruptive behaviour disorders (10%), Learning disorders (10%), Personality disorders (6.7%), Mild mental retardation (6.7%), Anxiety disorders (3.3%), Dissociative disorders (3.3%), Tic disorders (3.3%), Amphetamine related disorders (3.3%).
[c] Categories defined as: school (primary education, LBO, MAVO, VMBO), further (MBO, HAVO, VWO), and higher (HBO, WO) education of the Dutch educational system.
[d] Standardized mean score differences across groups:

	Service users vs. controls		Siblings vs. controls		Service users vs. siblings	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
BDI- II	0.71 (0.30 – 1.11)	0.001	-0.37 (-0.89 – 0.16)	0.168	1.08 (0.55 – 1.60)	<0.001
CAPE						
Positive	0.75 (0.34 – 1.17)	<0.001	-0.09 (-0.63 – 0.44)	0.735	0.84 (0.31 – 1.38)	0.002
Negative	0.42 (-0.01 – 0.85)	0.057	-0.31 (-0.87 – 0.25)	0.269	0.73 (0.17 – 1.29)	0.011
Depressive	0.80 (0.40 – 1.21)	<0.001	-0.12 (-0.64 – 0.41)	0.666	0.92 (0.39 – 1.45)	0.001
STAI-DY1	0.50 (0.06 – 0.93)	0.025	-0.09 (-0.65 – 0.47)	0.748	0.59 (0.03 – 1.14)	0.040
STAI-DY2	0.59 (0.19- 0.99)	0.004	-0.36 (-0.88 – 0.16)	0.170	0.95 (0.43 – 1.46)	<0.001

Table 3. Exposure to life events during the last year as well as before the age of 17 within and across groups

	Service users (n=42)	**Siblings (n=17)**	**Controls (n= 40)**	**Service users *vs.* controls**	**Service users *vs.* siblings**	**Siblings *vs.* controls**
Exposure to life events during the last year, mean (SD)						
Any	3.45 (3.67)	1.82 (2.21)	1.52 (1.96)	β=0.64 (0.22 – 1.06)*	β=0.54 (-0.001 – 1.09)*	β=0.10 (-0.45 – 0.65)
Illness	1.00 (1.49)	0.52 (0.87)	0.65 (0.83)	β=0.29 (-0.13 – 0.73)	β=0.40 (-0.16 – 0.96)	β=-0.10 (-0.67 – 0.46)
Loss	0.47 (0.89)	0.47 (0.87)	0.52 (0.90)	β=-0.05 (-0.49 – 0.38)	β=0.006 (-0.56 – 0.58)	β=-0.06 (-0.64 – 0.51)
Conflict	0.95 (1.48)	0.47 (0.87)	0.2 (0.51)	β=0.66 (0.24 – 1.08)*	β=0.42 (-0.12 – 0.97)	β=0.24 (-0.31 – 0.79)
Occupation	0.33 (0.72)	-	0.05 (0.22)	β=0.55 (0.13 – 0.98)*	β=0.65 (0.10 – 1.2)*	β=-0.09 (-0.65 – 0.45)
Finance	0.09 (0.43)	-	-	β=0.22 (-1.0 – 0.77)	β=0.33 (-0.23 – 0.90)	β=-0.00 (-0.57 – 0.57)
Housing						
Legal	0.14 (0.52)	0.05 (0.24)	-	β=0.39 (-0.03 – 0.83)	β=0.23 (-0.33 – 0.80)	β=0.16 (-0.40 – 0.73)
Threat	0.45 (0.94)	0.29 (0.98)	0.1 (0.44)	β=0.44 (0.008 – 0.87)*	β=0.19 (-0.36 – 0.76)	β=0.24 (-0.32 – 0.81)
Exposure to life events before the age of 17, mean (SD)						
Any	6.35 (3.27)	4.29 (2.08)	3.47 (2.47)	β=0.93 (0.54 – 1.33)**	β=0.67 (0.15 – 1.19)*	β=0.26 (-0.25 – 0.78)
Illness	1.64 (1.35)	1.47 (0.94)	1.00 (1.06)	β=0.53 (0.10 – 0.96)*	β=0.14 (-0.41 – 0.70)	β=0.39 (-0.17 – 0.95)
Loss	1.28 (1.21)	1.64 (1.45)	1.17 (1.23)	β=0.08 (-0.35 – 0.52)	β=-0.28 (-0.85 – 0.28)	β=0.37 (-0.20 – 0.94)
Conflict	1.64 (1.72)	0.82 (1.07)	0.62 (1.14)	β=0.68 (0.26 – 1.10)*	β=0.55 (0.009 -1.09)*	β=0.13 (-0.41 – 0.68)
Occupation	0.45 (0.80)	-	0.12 (0.46)	β=0.52 (0.10 – 0.94)*	β=0.72 (0.17 – 1.27)*	β=-0.20 (-0.75 – 0.35)
Finance	0.19 (0.59)	-	0.02 (0.15)	β=0.40 (-0.02 – 0.84)	β=0.46 (-0.09 – 1.03)	β=-0.06 (-0.62 – 0.50)
Housing						
Legal	0.21 (0.51)	-	-	β=0.60 (0.18 – 1.03)*	β=0.60 (0.05 – 1.15)*	β=-0.00 (-0.55 – 0.55)
Threat	0.92 (1.23)	0.35 (0.78)	0.52 (0.84)	β=0.38 (-0.04 – 0.81)	β=0.55 (-0.008 – 1.11)	β=-0.16 (-0.73 – 0.40)

SD: standard deviation; β: standardized regression coefficients (mean score differences); vs.: versus; CI: confidence interval; *p<0.05; **p<0.001

Association between momentary stress and negative affect by LEs exposure and group

There was evidence in support of the primary hypotheses that overall lifetime as well as previous-year exposure to LEs modified the association between momentary stress and negative affect (Table 4), as indicated by significant three-way interaction effects described below.

Within-group comparisons

Momentary stress was associated with increased negative affect in service users (*adj.* β=0.18, p<0.001) when high *vs.* low levels of exposure to overall LEs during the last year were compared, while no significant differences by exposure levels were found in siblings and controls. When comparing high *vs.* low levels of exposure to overall LEs before age 17, momentary stress was associated with increased negative affect in service users (*adj.* β=0.16, p<0.001), while no significant differences were found in siblings and controls. Analyses to test secondary hypotheses (Table 5) revealed that momentary stress was associated with lower negative affect in the control group when comparing high *vs.* low levels of exposure to threatening events (*adj.* β=-0.14, p=0.012). In contrast, increased negative affect in response to stress was observed in service users comparing high *vs.* low levels of exposure to loss experiences (*adj.* β=0.21, p<0.001), conflict events (*adj.* β=0.17, p<0.001), and threatening events (*adj.* β=0.09, p<0.001), while no significant differences were demonstrated in siblings.

Between-group comparisons

To investigate whether the modifying effects of exposure to LEs on stress sensitivity differed between groups, differences in magnitude of associations between those exposed to high *vs.* low levels of LEs were examined across groups. Specifically, the difference in magnitude of associations between stress and negative affect was greater in service users than in controls when comparing high *vs.* low levels of exposure to overall LEs during the last year (*adj.* β=0.21, p<0.001) and before age 17 (*adj.* β=0.16, p=0.011). Further, in testing secondary hypotheses (Table 5), we found significant differences in the magnitude of associations between those exposed to high *vs.* low levels of experience of loss (*adj.* β=0.26, p<0.001), conflict events (*adj.* β=0.18, p=0.026), and threatening events (*adj.* β=0.23, p<0.001) during the last year comparing service users *vs.* controls. Moreover, the difference in magnitude of associations between stress and negative affect was greater in service users than siblings comparing high *vs.* low exposure to conflict events during the last year (*adj.* β=0.26, *p*=0.002), and threatening events (*adj.* β=0.26, *p*=0.001) and, at trend level, experiences of loss (*adj.* β=0.13, *p*=0.054) before age 17. No significant differences were found comparing siblings *vs.* controls.

Association between stress and psychotic experiences by LEs exposure and group

There was evidence in support of the primary hypotheses that exposure to overall LEs modified the association between momentary stress and psychotic experiences (Table 4), as indicated by significant three-way interaction effects described below.

Within-group comparisons

Momentary stress was associated with more intense psychotic experiences in service users (*adj.* β=0.09, *p*<0.001) exposed to high levels of overall LEs compared to those with low exposure levels during the last year, while no differences were found in siblings and controls. When considering overall exposure to LEs before age 17, momentary stress was associated with more intense psychotic experiences in service users (*adj.* β=0.10, *p*<0.001) when high *vs.* low overall LEs levels were compared, while no significant differences were found in siblings and controls. Analyses of secondary hypotheses (Table 5) revealed that stress was significantly associated with more intense psychotic experiences during the last year when comparing service users exposed to high *vs.* low levels of experiences of loss (*adj.* β=0.10, *p*<0.001) and threatening events (*adj.* β=0.07, *p*<0.001). A similar pattern of findings was evident in service users with high *vs.* low exposure to threatening events (*adj.* β=0.06, *p*<0.001) before age 17. In contrast, stress was not significantly associated with more intense psychotic experiences across any type or level of LEs in neither the control group nor the sibling group (Table 5).

Between-group comparisons

There were differences in the magnitude of associations between momentary stress and psychotic experiences in those exposed to high *vs.* low levels of overall

LEs comparing service users *vs.* controls during the last year (*adj. β*=0.08, *p*=0.010) and before age 17 (*adj. β*=0.08, *p*=0.018). Moreover, the difference in magnitude of associations between momentary stress and psychotic experiences was greater in service users than in siblings when high *vs.* low levels of exposure to overall LEs during the last year (*adj. β*=0.12, *p*=0.012) as well as before age 17 (*adj. β*=0.11, *p*=0.031) were compared (Table 4). However, there was no difference when high *vs.* low levels of exposure to overall LEs were compared in siblings *vs.* controls. Analyses of secondary hypotheses (Table 5) showed differences in magnitude of associations between momentary stress and psychotic experiences comparing high *vs.* low exposure levels to experiences of loss (*adj. β*=0.10, *p*<0.001), but not threatening events (*adj. β*=0.04, *p*=0.211), during the last year in service users *vs.* controls. However, service users marginally differed from controls in the magnitude of associations between momentary stress and psychotic experiences by exposure levels to threatening events before age 17 (*adj. β*=0.06, *p*=0.053). Lastly, service users differed significantly from siblings in magnitude of associations between momentary stress and psychotic experiences comparing high *vs.* low levels of exposure to experiences of loss (*adj. β*=0.10, *p*=0.003) and threatening events *(adj. β*=0.09, *p*=0.004) during the last year. No significant differences were found comparing siblings *vs.* controls.

Table 4. Association of momentary stress with negative affect and psychotic experiences, by levels of exposure to life events in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ2 (df)**	**p**	**pFWE**
			Outcome: negative affect						
Momentary stress[b] × life events × group									
Overall exposure to life events during the last year							15.12 (2)	<0.001	0.004
High (mean+1 SD)	0.28 (0.24 – 0.31)	<0.001	0.08 (-0.02 – 0.19)	0.130	0.16 (0.09 – 0.24)	<0.001			
Average (mean)	0.19 (0.15 – 0.22)	<0.001	0.08 (0.02 – 0.14)	0.010	0.18 (0.14 – 0.22)	<0.001			
Low (mean-1 SD)	0.10 (0.05 – 0.15)	<0.001	0.07 (-0.03 – 0.17)	0.143	0.20 (0.14 – 0.25)	<0.001			
High *vs.* low[d]	0.18 (0.13 – 0.22)	<0.001	0.01 (-0.16 – 0.18)	0.903	-0.03 (-0.14 – 0.07)	0.539			
Overall exposure to life events before age 17							7.53 (2)	0.023	0.092
High (mean+1 SD)	0.28 (0.24 – 0.32)	<0.001	0.09 (-0.02 – 0.20)	0.116	0.19 (0.11 – 0.26)	<0.001			
Average (mean)	0.20 (0.16 – 0.24)	<0.001	0.08 (0.02 – 0.14)	0.011	0.18 (0.14 – 0.23)	<0.001			
Low (mean-1 SD)	0.11 (0.05 – 0.18)	<0.001	0.07 (-0.03 – 0.17)	0.164	0.18 (0.13 – 0.23)	<0.001			
High *vs.* low[d]	0.16 (0.09 – 0.23)	<0.001	0.02 (-0.15 – 0.19)	0.851	0.01 (-0.10 – 0.10)	0.916			
			Outcome: psychotic experiences						
Momentary stress[b] × life events × group									
Overall exposure to life events during the last year							11.75 (2)	0.003	0.012
High (mean+1 SD)	0.14 (0.12 – 0.16)	<0.001	0.01 (-0.05 – 0.07)	0.668	0.05 (0.01 – 0.10)	0.009			
Average (mean)	0.09 (0.07 – 0.11)	<0.001	0.03 (-0.00 – 0.06)	0.073	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.05 (0.02 – 0.08)	<0.001	0.05 (-0.01 – 0.10)	0.085	0.05 (0.02 – 0.08)	0.002			
High *vs.* low[d]	0.09 (0.06 – 0.11)	<0.001	-0.03 (-0.13 – 0.06)	0.466	0.01 (-0.05 – 0.06)	0.837			

Table 4. (continued). Association of momentary stress with negative affect and psychotic experiences, by levels of exposure to life events in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ2 (df)**	**p**	**pFWE**
Overall exposure to life events before age 17							8.36 (2)	0.015	0.06
High (mean+1 SD)	0.14 (0.12 – 0.16)	<0.001	0.03 (-0.03 – 0.08)	0.395	0.06 (0.02 – 0.10)	0.002			
Average (mean)	0.09 (0.07 – 0.12)	<0.001	0.03 (-0.00 – 0.06)	0.066	0.05 (0.03 – 0.08)	<0.001			
Low (mean-1 SD)	0.04 (0.01 – 0.08)	0.011	0.04 (-0.02 – 0.09)	0.187	0.04 (0.01 – 0.07)	0.002			
High *vs*. low[d]	0.10 (0.06 – 0.14)	<0.001	-0.01 (-0.10 – 0.08)	0.815	0.02 (-0.03 – 0.07)	0.456			

SD: standard deviation; df: degrees of freedom; vs.: versus; CI: confidence interval; adj. β: standardized regression coefficients, continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of exposure to life events within and across groups (service users, siblings, controls); *p*FWE: family-wise error-corrected *p* values were computed by multiplying the unadjusted *p* value by the total number of tests (primary hypotheses: *N*=4) to adjust significance levels of likelihood ratio tests for three-way interactions.

[a] Adjusted for age, sex, ethnicity, and level of education.

[b] Momentary stress was calculated by combining the ratings of items assessing event-related, activity-related, and social stress.

[c] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(\text{STRESS}_{ij}) + \beta_2(\text{LIFE EVENTS}_j) + \beta_3(\text{GROUP}_j) + \beta_4(\text{STRESS}_{ij} \times \text{LIFE EVENTS}_j) + \beta_5(\text{STRESS}_{ij} \times \text{GROUP}_j) + \beta_6(\text{LIFE EVENTS}_j \times \text{GROUP}_j) + \beta_7(\text{STRESS}_{ij} \times \text{LIFE EVENTS}_j \times \text{GROUP}_j) + \varepsilon_{ij}$ (full model not shown - available upon request).

Table 4. (continued). Association of momentary stress with negative affect and psychotic experiences, by levels of exposure to life events in service users, siblings, and controls[a]

[d] Difference in the magnitude of associations of momentary stress with psychotic experiences between those exposed to high *vs*. low levels of exposure to life events across groups (Δ high *vs*. low):

	Service users vs. controls		Siblings vs. controls		Service users vs. siblings	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
Δ high *vs*. low exposure levels of life events across groups						
Outcome: negative affect						
Momentary stress x life events x group						
Overall exposure to life events during the last year	0.21 (0.10 – 0.32)	<0.001	0.17 (-0.02 – 0.36)	0.083	0.17 (-0.01 – 0.34)	0.064
Overall exposure to life events before the age of 17	0.16 (0.04 – 0.28)	0.011	0.01 (-0.18 – 0.21)	0.912	0.15 (-0.04 – 0.33)	0.118
Outcome: psychotic experiences						
Momentary stress x life events x group						
Overall exposure to life events during the last year	0.08 (0.02 – 0.14)	0.010	-0.04 (-0.15 – 0.07)	0.466	0.12 (0.03 – 0.22)	0.012
Overall exposure to life events before the age of 17	0.08 (0.01 – 0.14)	0.018	-0.03 (-0.14 – 0.07)	0.571	0.11 (0.01 – 0.21)	0.031

Table 5. Association of momentary stress with negative affect and psychotic experiences, by levels of exposure to life events in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**	**χ2 (df)**	**p**	**pFWE**
Outcome: negative affect									
Momentary stress[b] × life events × group									
Exposure during the last year:									
Illness							0.71 (2)	n.s.	n.s.
Loss							24.59 (2)	<0.001	0.007
High (mean+1 SD)	0.34 (0.29 – 0.39)	<0.001	0.11 (0.04 – 0.18)	0.003	0.16 (0.10 – 0.21)	<0.001			
Average (mean)	0.23 (0.20 – 0.27)	<0.001	0.07 (0.01 – 0.13)	0.029	0.18 (0.14 – 0.22)	<0.001			
Low (mean-1 SD)	0.13 (0.08 – 0.18)	<0.001	0.03 (-0.06 – 0.12)	0.532	0.21 (0.15 – 0.26)	<0.001			
High *vs.* low[d]	0.21 (0.13 – 0.28)	<0.001	0.08 (-0.03 – 0.19)	0.149	-0.05 (-0.12 – 0.03)	0.195			
Conflict							13.18 (2)	0.002	0.014
High (mean+1 SD)	0.27 (0.23 – 0.31)	<0.001	0.04 (-0.06 – 0.14)	0.474	0.18 (0.07 – 0.28)	0.001			
Average (mean)	0.18 (0.15 – 0.22)	<0.001	0.08 (0.02 – 0.14)	0.012	0.18 (0.14 – 0.23)	<0.001			
Low (mean-1 SD)	0.10 (0.04 – 0.15)	<0.001	0.12 (0.02 – 0.22)	0.017	0.19 (0.12 – 0.26)	<0.001			
High *vs.* low[d]	0.17 (0.13 – 0.22)	<0.001	-0.08 (-0.24 – 0.08)	0.308	-0.01 (-0.16 – 0.14)	0.902			
Occupation							0.30 (1)	n.s.	n.s.
Finance	-		-		-		-	-	-
Housing	-		-		-		-	-	-
Legal problems	-		-		-		3.4 (1)	0.065	n.s.
Threat							15.38 (2)	<0.001	0.007
High (mean+1 SD)	0.26 (0.22 – 0.30)	<0.001	0.07 (-0.01 – 0.15)	0.083	0.11 (0.03 – 0.18)	0.005			
Average (mean)	0.22 (0.18 – 0.25)	<0.001	0.08 (0.02 – 0.14)	0.010	0.18 (0.14 – 0.22)	<0.001			
Low (mean-1 SD)	0.17 (0.12 – 0.22)	<0.001	0.09 (0.01 – 0.17)	0.030	0.25 (0.18 – 0.31)	<0.001			
High *vs.* low[d]	0.09 (0.04 – 0.14)	0.001	-0.02 (-0.12 – 0.09)	0.745	-0.14 (-0.25 – -0.03)	0.012			

Table 5. (continued). Association of momentary stress with negative affect and psychotic experiences, by levels of exposure to life events in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	p	adj. β (95% CI)	p	adj. β (95% CI)	p	χ2 (df)	p	pFWE
Exposure before age 17:									
Illness							2.48 (2)	n.s.	n.s.
Loss							0.27 (2)	n.s.	n.s.
Conflict							2.77 (2)	n.s.	n.s.
Occupation							0.39 (1)	n.s.	n.s.
Finance							0.40 (1)	n.s.	n.s.
Legal	-				-		-	-	-
Threat							16.14 (2)	<0.001	0.005
High (mean+1 SD)	0.29 (0.25 – 0.33)	<0.001	0.01 (-0.09 – 0.11)	0.800	0.16 (0.09 – 0.24)	<0.001			
Average (mean)	0.22 (0.18 – 0.25)	<0.001	0.07 (0.01 – 0.13)	0.024	0.18 (0.14 – 0.22)	<0.001			
Low (mean-1 SD)	0.15 (0.09 – 0.20)	<0.001	0.13 (0.04 – 0.22)	0.004	0.20 (0.14 – 0.25)	<0.001			
High *vs*. low[d]	0.14 (0.08 – 0.20)	<0.001	-0.12 (-0.26 – 0.03)	0.112	-0.03 (-0.14 – 0.07)	0.517			
Outcome: psychotic experiences									
Momentary stress[b] × life events × group									
Exposure during the last year:									
Illness							5.47 (2)	0.065	n.s.
Loss							16.13 (2)	<0.001	0.005
High (mean+1 SD)	0.17 (0.14 – 0.19)	<0.001	0.03 (-0.01 – 0.07)	0.136	0.05 (0.02 – 0.08)	0.001			
Average (mean)	0.12 (0.10 – 0.14)	<0.001	0.03 (-0.00 – 0.07)	0.064	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.07 (0.04 – 0.09)	<0.001	0.03 (-0.02 – 0.08)	0.183	0.05 (0.02 – 0.08)	0.001			
High *vs*. low[d]	0.10 (0.06 – 0.14)	<0.001	-0.00 (-0.06 – 0.06)	0.908	-0.00 (-0.04 – 0.04)	0.969			
Conflict							2.50 (2)	n.s.	n.s.
Occupation							0.26 (2)	n.s.	n.s.
Finance	-		-		-		-	-	-
Housing	-		-		-		-	-	-
Legal							3.32 (2)	0.069	n.s.

Table 5. (continued). Association of momentary stress with negative affect and psychotic experiences, by levels of exposure to life events in service users, siblings, and controls[a]

	Service users		Siblings		Controls		Wald test for interaction[c]		
	adj. β (95% CI)	p	adj. β (95% CI)	p	adj. β (95% CI)	p	χ2 (df)	p	pFWE
Threat							8.97 (2)	0.011	0.077
High (mean+1 SD)	0.14 (0.12 – 0.16)	<0.001	0.02 (-0.02 – 0.06)	0.408	0.06 (0.03 – 0.10)	0.001			
Average (mean)	0.10 (0.09 – 0.12)	<0.001	0.03 (-0.00 – 0.06)	0.062	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.07 (0.04 – 0.10)	<0.001	0.04 (0.00 – 0.09)	0.043	0.04 (0.01 – 0.07)	0.021			
High *vs*. low[d]	0.07 (0.04 – 0.09)	<0.001	-0.03 (-0.08 – 0.03)	0.361	0.02 (-0.03 – 0.08)	0.411			
Exposure before age 17:									
Illness							0.12 (2)	n.s.	n.s.
Loss							3.63 (2)	n.s.	n.s.
Conflict							5.13 (2)	0.077	n.s.
Occupation							0.04 (1)	n.s.	n.s.
Finance							0.14 (1)	n.s.	n.s.
Legal	-		-		-		-	-	-
Threat							5.66 (2)	0.059	n.s.
High (mean+1 SD)	0.14 (0.12 – 0.16)	<0.001	0.03 (-0.03 – 0.08)	0.350	0.05 (0.01 – 0.09)	0.012			
Average (mean)	0.11 (0.09 – 0.13)	<0.001	0.03 (-0.02 – 0.06)	0.072	0.05 (0.03 – 0.07)	<0.001			
Low (mean-1 SD)	0.08 (0.05 – 0.11)	<0.001	0.04 (-0.01 – 0.08)	0.142	0.05 (0.02 – 0.08)	0.002			
High *vs*. low[d]	0.06 (0.03 – 0.10)	<0.001	-0.01 (-0.09 – 0.07)	0.861	0.00 (-0.06 – 0.06)	0.977			

SD: standard deviation; df: degrees of freedom; vs.: versus; CI: confidence interval; adj. β: standardized regression coefficients, continuous independent variables were standardized (mean=0, SD=1) for interpreting significant three-way interaction terms and examining the difference in associations between high (mean + 1 SD), average (mean), and low (mean – 1 SD) levels of exposure to life events within and across groups (service users, siblings, controls); *p*FWE: family-wise error-corrected *p* values were computed by multiplying the unadjusted *p* value by the total number of tests (secondary hypotheses: *N*=7) to adjust significance levels of likelihood ratio tests for three-way interactions.
[a] Adjusted for age, se, ethnicity, and level of education.
[b] Momentary stress was calculated by combining the ratings of items assessing event-related, activity-related, and social stress.
[c] Three-way interaction as included in the following model (with y_{ij} for negative affect or psychotic experiences as outcome variable): $y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(LIFE\ EVENTS_j) + \beta_3(GROUP_j) + \beta_4(STRESS_{ij} \times LIFE\ EVENTS_j) + \beta_5(STRESS_{ij} \times GROUP_j) + \beta_6(LIFE\ EVENTS_j \times GROUP_j) + \beta_7(STRESS_{ij} \times LIFE\ EVENTS_j \times GROUP_j) + \varepsilon_{ij}$ (full model not shown - available upon request).

Table 5. (continued). Association of momentary stress with negative affect and psychotic experiences, by levels of exposure to life events in service users, siblings, and controls[a]

[d] Difference in the magnitude of associations of momentary stress with psychotic experiences between those exposed to high *vs*. low levels of exposure to life events across groups (Δ high *vs*. low):

	Service users vs. controls		**Siblings vs. controls**		**Service users vs. siblings**	
	adj. β (95% CI)	**p**	**adj. β (95% CI)**	**p**	**adj. β (95% CI)**	**p**
Δ high *vs*. low exposure levels of life events across groups						
Outcome: negative affect						
Momentary stress x life events x group						
During the last year:						
Loss	0.26 (0.15 – 0.36)	<0.001	0.13 (-0.00 – 0.26)	0.055	0.13 (-0.00 – 0.26)	0.054
Conflict	0.18 (0.02 – 0.35)	0.026	-0.07 (-0.29 – 0.15)	0.523	0.26 (0.09 – 0.42)	0.002
Threat	0.23 (0.11 – 0.35)	<0.001	0.12 (-0.03 – 0.27)	0.108	0.11 (-0.01 – 0.22)	0.066
Before age 17:						
Threat	0.18 (0.06 – 0.30)	0.004	-0.08 (-0.26 – 0.10)	0.367	0.26 (0.10 – 0.41)	0.001
Outcome: psychotic experiences						
Momentary stress x life events x group						
During the last year:						
Loss	0.10 (0.05 – 0.16)	<0.001	-0.00 (-0.07 – 0.07)	0.941	0.10 (0.03 – 0.17)	0.003
Threat	0.04 (-0.02 – 0.11)	0.211	-0.05 (-0.13 – 0.03)	0.220	0.09 (0.03 – 0.15)	0.004
Before age 17:						
Threat	0.06 (-0.00 – 0.13)	0.053	-0.01 (-0.11 – 0.09)	0.838	0.07 (-0.01 – 0.16)	0.082

Discussion

Main findings

There was strong evidence that lifetime as well as previous-year exposure to overall as well as specific types of LEs, modified stress sensitivity in help-seeking service users. Service users experienced increased negative affect and more intense psychotic experiences in response to minor daily stress when high *vs.* low exposure levels were compared. In siblings, however, we found no evidence that overall exposure to as well as specific types of LEs modified stress sensitivity. In controls, however, secondary analyses revealed decreased negative affect in response to stress comparing those exposed to high *vs.* low levels of threatening experiences. Thus, our findings tentatively suggest that individuals' response to minor stress in daily life represents a putative risk and resilience mechanism through which exposure to LEs may influence youth mental health.

Methodological considerations

The reported findings should be interpreted in view of potential limitations. First, the LTE is a retrospective measure of self-reported LEs. Consequently, recall bias and cognitive distortion may have influenced reported findings [25]. Moreover, it may have been difficult for participants to differentiate LEs from within the last 12 months from LEs before age 17. However, the low sample age likely minimized the impact of biases on reported LEs, as the time between exposure to and time of assessments of LEs was limited. Similarly, EMAs were based on self-report. While this allows for ecologically valid measurements of momentary stress, context, and experiences on the behavioural level, future research should consider triangulating the impact of LEs on individuals' stress sensitivity across other levels of investigation, such as biological markers [26] and passively collected digital sensor data [27]. Secondly, some of the LEs included in the current study (e.g., housing, financial, legal problems) were only prevalent in few or none of participating individuals. Consequently, we were not able to test modifying effects of all specific types of LEs on stress sensitivity in secondary analyses. Third, assessment burden associated with EMAs may have introduced selection bias. However, studies have demonstrated that EMAs are reliable and feasible in adult as well as adolescent clinical and community populations [20]. Additionally, extensive briefing on the "PsyMate" and EMA procedure ensured a high number of valid responses (90.8%).

Fourth, the group of siblings was relatively small (*n*=17) and findings that LEs did not modify stress sensitivity in this intermediate risk group may have occurred because of sampling error. Fifth, despite adjustment for potential confounders (i.e., age, sex, education level, and ethnicity), other unmeasured factors such as personality traits and polygenetic risk for psychopathologies could have influenced reported findings [28]. Lastly, the data collected over 6 days with EMA was modelled cross-sectionally and temporality of stress, negative affect, and psychotic experiences was not specifically investigated. It is recommended that future studies consider time-lagged and moderated mediation models to further investigate temporality as one important criterion important to inferring causality.

Comparison with previous research

Previous research suggests exposure to ACEs, including LEs [6-9, 11-14, 16, 29], is associated with an increased risk of developing mental health problems. However, candidate mechanisms remain poorly understood, particularly in youth. By contributing to lasting changes to the way an individual responds to stress, *stress sensitization* has been proposed to be a common mechanistic pathway that may help explain the relation between exposure to socio-environmental risk and psychopathology [18]. Notably, this proposition has already been investigated in adult populations. Adults with mental disorders (e.g., depression, psychosis) and a history of childhood trauma and LEs were found to have elevated affective and psychotic reactivity in response to minor daily stressors [24, 30]. Thus, stress sensitization may represent a putative mechanism underlying exposure to LEs and psychopathology. However, whether these findings can be generalized to young help-seeking individuals remained under-researched.

The current study is the first to report that young help-seeking individuals who were exposed to high levels of LEs responded to minor stressors in daily life with increased negative affect and psychotic experiences as compared to those with low exposure levels. Interestingly, these findings are in line with reported effects of childhood trauma [21] and bullying victimization [22] on stress sensitivity derived from the same sample, and with findings including individuals with at-risk mental state (ARMS) for psychosis and FEP exposed to childhood trauma [24]. Thus, in line with previous research, the present study suggests, although not directly tested, that behavioural sensitization in form of an increased stress sensitivity in daily life may be associated with exposure to ACEs and may have downstream contributions along multiple pathways leading to poor mental health.

In contrast, exposure to LEs before age 17 did not modify individuals' stress sensitivity in control subjects. However, in secondary analyses, controls exposed to high levels of more intrusive LEs (i.e., threatening experiences, serious accident) during the previous year responded with *decreased* negative affect as compared to those with low exposure to LEs. In other words, controls appeared to be more resilient to the detrimental effects of high exposure to more recent threatening LEs when compared to low exposure levels. This is interesting as it mirrors previous findings in which physical abuse and neglect [21], physical bullying [22], and sexual abuse [24] were associated with decreased negative affect in response to stress in controls. Taken together, high levels of exposure to more intrusive ACEs may result in resilience against subsequent minor stressors in daily life in individuals who do not develop help-seeking behaviour.

In biological siblings of service users, we found no evidence that exposure to LEs modifies stress sensitivity. Specifically, when comparing high *vs*. low exposure to LEs, siblings did not respond to minor stressors in daily life with an increased negative affect and psychotic experiences. However, with a small sample size, we have to be cautious when interpreting these findings. Moreover, findings at the group-level are possibly influenced by mixed resiliency to stress sensitivity at the person-level considering that siblings form an *intermediate* risk group and have a higher liability to psychopathology. Consequently, it may be that only some siblings developed an increased sensitivity to stress as service users, which may be not detectable at the group-level.

Secondary analyses revealed that, similar to exposure to overall LEs, loss, threat, and conflict events modified stress sensitivity in service users. In line with earlier findings reporting associations between the experience of loss and depressive symptoms in youth [16], we found that exposure to loss within the last year increased help-seeking individuals' negative affect in response to stress. Similarly, conflict events during the past year were associated with higher negative affect in response to stress in service users, while, in siblings, these effects were not found. This contrast between service users and their siblings is particularly interesting as these groups have probably been exposed to comparable levels of several assessed LEs (e.g., parental death, serious persistent quarrels with members within the family). Notably, service users and siblings do not only share genetic risk but also exposure to some socio-environmental risk.

The findings that exposure to LEs did not modify stress sensitivity in siblings and controls or resulted in lower affective reactivity to stress in controls may be partly explained by various protective factors. These may be differentially available in and/or used by controls and siblings compared to help-seeking individuals. Accumulating evidence suggests that social support, optimism, higher self-esteem, family/neighbourhood cohesion, parental involvement, positive atmosphere at home, low polygenetic risk, and low rumination tendencies contribute to helping individuals in light of ACEs [31-35]. It may be speculated that these processes protect individuals from an increased stress sensitivity by supporting helpful coping strategies and cognitive factors (e.g., greater cognitive flexibility [36]). A recent study demonstrated that psychological flexibility moderates the association between LEs and depressive symptoms and can therefore be considered a “buffer” against unfavourable impacts that LEs have on mental health [37].

Future studies may further explore the proposed transdiagnostic risk mechanism by considering the role of cognitive factors in individuals’ stress response (e.g., cognitive appraisal [17, 38], aberrant salience, jumping-to-conclusions bias, and theory of mind). Moreover, it is important to investigate whether the effects of ACEs on stress sensitivity accumulate over time (e.g., by using cohort designs and, for instance, calculating individuals’ environmental load) [39]. Lastly, exploring the contribution of stress sensitivity in symptom progression and persistence over time by using longitudinal EMA designs may be an important next step. In accordance with prior work that psychiatric symptoms frequently co-occur during developmentally early stages of psychopathology [4], high proportions of comorbid depressive, anxiety, and psychotic symptoms in service users further supports dimensional models of psychopathology [40] as well as transdiagnostic phenotypes, including an extended psychosis spectrum phenotype [5].

Conclusion

Our results suggest that stress sensitivity may reflect an important risk and resilience mechanism through which LEs negatively impact mental health in help-seeking youth. While we found no unfavourable effects of exposure to LEs on stress sensitivity in controls and siblings, service users appeared to be at greater risk of experiencing elevated stress sensitivity. Targeting sensitivity to stress in daily life with novel mHealth tools (e.g., ecological momentary interventions) by focusing on emotion regulation skills (e.g., mindfulness-based or compassion-focused therapies) may be a promising preventive as well as intervention strategy helping adolescents and young adults with mental health problems.

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Supplementary material

Table S1. Items used in the modified List of Threatening Events (LTE) questionnaire

Types of negative life events		
Illness		
	LE_001	"Serious illness, injury or assault to yourself?"
	LE_002	"Serious illness, injury or assault to a family member or friend?"
	LE_018	"Hospitalisation or other medical treatments?"
Loss		
	LE_003	"Death of a parent, partner, or child?"
	LE_004	"Death of a family member or friend?"
	LE_015	"Loss or theft of anything of value?"
Interpersonal/ Intra-familial conflicts		
	LE_005	"Break-up with partner (with whom you lived together)/ from parents?"
	LE_006	"Break-up committed relationship (not living together)/ of a parent?"
	LE_007	"Divorce/ of parents?"
	LE_008	"Cheating of spouse (one of the parents)?"
	LE_009	"Serious persistent problems (quarrel) with members within the family?"
	LE_010	"A serious problem with a friend, neighbour, or family member?"
Occupational conflicts		
	LE_011	"Serious problems at school/work (being suspended/ stopped/ fired/ finding no work)?"
Financial problems		
	LE_012	"Serious financial problems within the family (very serious debt, bankruptcy)?"
Housing problems		
	LE_013	"Serious housing problems (including homelessness)?"
Legal conflicts		
	LE_014	"A problem with the police and/or law (violation, court, prison / community service)?"
Threatening/ Intrusive incidents		
	LE_016	"Victim of threats, robbery, or burglary?"
	LE_017	"Witness to serious threat or another traumatic event?"
	LE_021	"Involved in a serious accident in which you and/or someone else got hurt seriously?"

PART 2

Digital interventions in
public mental health provision

CHAPTER 7

An ecological momentary compassion-focused intervention for enhancing resilience in help-seeking youth: a pilot study

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Abstract

Background: Digital interventions offer new avenues for low-threshold prevention and treatment in youth. Ecological momentary interventions (EMIs) represent a powerful approach that allows for adaptive, real-time, and real-world delivery of intervention components in daily life by real-time processing of multimodal Ecological Momentary Assessment (EMA) data. Compassion-focused interventions (CFIs) may be particularly amenable to translation into an EMI to strengthen emotional resilience and modifying putative risk mechanisms, including stress sensitivity, in daily lives of young help-seeking individuals.

Objective: We aimed to investigate feasibility, safety, and initial therapeutic effects of a novel, accessible, transdiagnostic, ecological momentary, compassion-focused intervention for improving emotional resilience to stress ('EMIcompass').

Methods: In an uncontrolled pilot study, help-seeking youth with psychotic, depressive, and/or anxiety symptoms were offered the EMIcompass intervention in addition to treatment as usual. EMIcompass consisted of three sessions with a trained psychologist (i.e., training session of CFI exercises, follow-up 'booster' session, and review session) and a 3-week EMI (i.e., consisting of enhancing, consolidating, and EMA-informed interactive tasks) administered through a mobile health (mHealth) app.

Results: In total, ten individuals (Mean age=20.3 years, range 14-25 years) were included in the study. Most participants were satisfied (80%) and reported low burden of app usage. No adverse events were observed. In around 1/3 of all EMAs, individuals scored high on stress, negative affect, or threat anticipation during the intervention period, resulting in real-time delivery of CFI intervention components in addition to weekly enhancing and daily consolidating tasks. Although findings should be interpreted with caution due to the small sample size, reduced stress sensitivity, momentary negative affect, and psychotic experiences as well as increased positive affect were found at post-intervention and 4-week follow-up. Further, reductions in psychotic, anxiety, and depressive symptoms were found (r=0.30-0.65).

Conclusions: Our findings provide evidence on feasibility and safety of the EMIcompass intervention in help-seeking youth and promising evidence of beneficial effects on stress sensitivity and psychopathological outcomes. An exploratory randomized controlled trial is warranted to establish feasibility and preliminary evidence of efficacy.

Keywords: Mental Health; Adolescent Psychopathology; Digital Interventions; Mobile Health; Self-Compassion; Ecological Momentary Assessment

Introduction

Most mental disorders first emerge in adolescence and young adulthood (three fourths by age 24 [1]), with an estimated lifetime prevalence of around 50% of any mental disorder in young age groups [1-5]. Further, the Global Burden of Disease study has reported that mental and substance use disorders in children and youth aged 10-24 years were the leading cause of overall disease burden in high-income countries [6-8]. Evidence further suggests that most mental disorders are continuous - phenomenologically and temporarily - and, in their early stages, non-specific in nature, often evolving in the form of transdiagnostic phenotypes associated with a range of exit psychopathologies [9-16]. Consequently, clinical staging models as an adjunct to formal diagnoses have been introduced [17-19], which highlight the importance of transdiagnostic (indicated) prevention and early intervention [20-24].

Recent transformations in our understanding of phenomenology, aetiology, and early course of mental disorders have contributed to a move towards early detection and prevention [10-13, 20, 25-31]. While conventional mental health services offer a range of therapeutic options, it has been widely documented that psychological help remains difficult to access, especially for young individuals in the early stages of mental health problems [21, 22, 32, 33]. Further, tailoring of therapeutic options to specific needs and preferences of youth remains a challenge [32-36] and likely contributes to the problem that only a fraction of young people in need of help access any mental health service. Hence, young individuals often experience a long duration of untreated mental health problems which has been identified an important marker of poor course and outcome [32].

There is increasing interest in using digital tools to deliver mental health services [37], which may help to extend access to and personalisation of mental health care [38, 39]. This has driven the development of novel mobile health (mHealth) interventions for various mental health problems [40-42], of which ecological momentary interventions (EMIs) [23, 34, 38, 39, 43], such as Acceptance and Commitment Therapy in Daily Life (ACT-DL) [34-36, 44], represent a very powerful approach. EMIs allow for adaptive, real-time, and real-world transfer of intervention components in individuals' daily lives. Thus, EMIs provide a unique opportunity to deliver personalized, precision interventions that are tailored to what young individuals need in a given moment and context through interactive sampling in real-time and the real-world. They are based on fine-grained ecological momentary assessment (EMA) data acquired through cutting-edge digital technology [21, 23, 24, 38, 39, 45, 46]. More recently, some authors have started to use the term Just-in-Time Adaptive Interventions (JITAIs) which emphasize EMI's capability of adapting the delivery of intervention components to person and context based on experience sampling or other, e.g. sensing data [47, 48].

One tangible prevention and early intervention strategy using digital tools is to identify and target transdiagnostic psychological mechanisms in daily life, which have been shown to be involved in the development of mental health problems [23, 38]. In recent years, research using EMA, a structured diary technique also known as Experience Sampling Methodology [43], has contributed to a better understanding of putative underlying mechanisms likely to be involved in impacting at different stages on, and increasing intensity of, mental health problems in individuals' daily lives, in real time and outside the research laboratory [21-23, 29, 43, 49, 50]. To date, the psychological mechanism most widely studied in daily life is elevated stress sensitivity, characterized by more intense negative affective and psychotic experiences in response to minor stressors and routine daily hassles [22, 24, 29, 43]. Findings from previous studies suggest that stress sensitivity is elevated in individuals with (1) higher familial or psychometric risk, (2) an Ultra-High Risk (UHR) state for psychosis, (3) other early mental health problems, (4) first-episode psychosis (FEP), (5) severe and enduring psychosis, and (6) depressive disorder [21, 22, 24, 28, 50-58]. In addition, heightened interpersonal sensitivity and threat anticipation have previously been reported to represent further candidate mechanisms in individuals with UHR, paranoia, and psychotic disorder [24, 29, 30, 59-62] as well as individuals with depression and anxiety [63-66]. Taken together, these transdiagnostic mechanisms reflect candidate targets to be modified by EMIs [21, 22, 24, 29].

Compassion-focused interventions (CFIs) are considered an important strand of transdiagnostic interventions for modifying emotion regulation systems [67, 68]. CFIs form part of third-wave Cognitive Behavioural Therapy (CBT) and previous meta-analytic evidence on third-wave CBT, including CFIs [69-73], suggests that these types of interventions may yield improvements in mental health outcomes of moderate to large effect size. CFIs have been successfully administered to and appraised positively by help-seeking individuals, including individuals with depression, anxiety, and psychosis [74-77]. Further, CFIs have been shown to induce reductions in negative affect and paranoia in moments of high stress in prior experimental work in the research lab [78, 79]. Further, positive imagery, an important component of CFIs, have been found to be effective for reducing various mental health problems, including depression, anxiety, and psychosis [76, 80, 81] as well as for increasing positive affect, optimism, and behavioural activation [79, 82-84]. Thus, CFIs are particularly well placed to be administered as an EMI to strengthen emotional resilience and modify putative risk mechanism of poor mental health in young individuals with psychological distress [72, 78, 85], including stress sensitivity and threat anticipation [21, 22]. However, the use of conventional CFIs under real-world conditions remains very limited [86].

As young individuals are ‘digital natives’, translating CFI components into an EMI administered through an mHealth app may be a particularly promising approach and offers entirely new avenues for low-threshold prevention and intervention in youth. As such, EMIs are fundamentally translational as they directly build on evidence on underlying momentary mechanisms in daily life and translate this into the development and evaluation of novel digital interventions by targeting these mechanisms in real-time and in the real-world, outside the research lab or clinic [23, 39, 43]. However, it remains to be established whether evidence on reductions in negative affect and paranoia in moments of high stress carried out in the research laboratory as well as effects on other mental health outcomes can indeed be translated to real-world and real-time delivery of EMIs that harness compassion-focused intervention techniques, especially in young help-seeking individuals, where accessible, youth-friendly translation of prevention and early intervention principles reflects a particular challenge.

The present study

This study aimed to establish the clinical feasibility, safety, and initial therapeutic effects of a novel, accessible, transdiagnostic, ecological momentary, compassion-focused intervention for improving emotional resilience to stress (‘EMIcompass’) in an uncontrolled phase I pilot study in help-seeking youth with psychotic, depressive, and/or anxiety symptoms. The EMIcompass intervention consisted of three sessions with a trained psychologist (i.e., training session, ‘booster’ session, review session) and a 3-week EMI. More specifically, the intervention offered widely used CFI techniques (e.g., compassionate and positive imagery, and writing; emotion as a wave). To facilitate the interactive, real-time, and real-world translation of the therapeutic content and techniques used in the initial training and booster sessions into individuals' daily lives, the EMI was administered through an mHealth app on a smartphone. The EMI consisted of i) enhancing, ii) consolidating, and iii) interactive EMI tasks that aim at ecological translation of CFI principles and techniques to daily life: participants were required to complete one 'enhancing task' per week, which allowed them to practice new compassion-focused exercises that were then extended throughout the study period. Additionally, they were required to practice learned CFI components once a day by completing 'consolidating tasks'. Each time an enhancing task was presented, the intervention components covered by consolidating tasks were expanded. Participants were also offered 'interactive tasks' if they scored high on stress, negative affect, or threat anticipation in daily EMA.

The primary objective of this study was to (1) assess the clinical feasibility of delivering the EMIcompass intervention to help-seeking youth based on successful recruitment, assessment of outcomes, compliance, satisfaction, and acceptability as well as safety by carefully documenting any serious adverse events throughout the entire study period. The secondary objectives were to examine (2) initial therapeutic effects of EMIcompass on reducing stress sensitivity, negative affect, and psychotic experiences, and increasing positive affect in daily life at the end of the 3-week intervention period ('post-intervention'), and after a 4-week follow-up period ('follow-up') and (3) the initial therapeutic effects of EMIcompass on reducing threat anticipation, psychotic, depressive, and anxiety symptoms as well as general psychopathology.

Methods

Study design

In an uncontrolled, phase I pilot study, help-seeking individuals with psychotic, depressive, and/or anxiety symptoms aged 14-25 referred to secondary mental health services in the Netherlands (i.e., Mondriaan Mental Health Trust; Virenze Mental Health Care) received the EMIcompass intervention in addition to treatment as usual. Data were collected before the intervention ('baseline'), at the end of the 3-week intervention period ('post-intervention'), and after a 4-week follow-up period ('follow-up'). Particularly close attention was paid to establishing clinical feasibility (e.g., pragmatic inclusion and exclusion criteria based on routine assessments) and safety (i.e., documentation of any serious adverse events) of this study. Our recruitment strategy drew on our previous and ongoing work with youth [22, 24, 29, 34-36, 44] as well as guidance for pragmatic randomised controlled trials [87] and, hence, was geared to reflect the heterogeneity of the population commonly encountered in routine care.

Sample

We recruited young individuals with psychotic, depressive, and/or anxiety symptoms who were seeking help from two secondary mental services (i.e., Mondriaan Mental Health Trust; Virenze Mental Health Care). The inclusion and exclusion criteria were equivalent in principle across the two services but were purposefully selected to be pragmatic and, hence, based on routine assessments for screening, diagnosis, formulation, and outcome measurement, which differed between the two services (see Table 1). This approach was adopted to ensure the aim of establishing of feasibility reflected the population actually encountered in clinical practice (rather than imposed by researchers) whilst keeping assessment burden at a minimum. The study was approved by the Ethics Review Committee Mondriaan Mental Health Trust and the Ethics Review Committee Psychology and Neuroscience, Maastricht University. A study flowchart is provided in Figure 1.

At Virenze, the Prodromal Questionnaire (PQ) [88, 89], which has been reported to be a very good screening measure in routine mental health services [89, 90], was used to screen for psychotic symptoms. Also, the Brief Symptom Inventory (BSI) [91, 92] was used to screen for anxiety, depressive and psychotic symptoms. At Mondriaan, the Symptom Questionnaire-48 (SQ-48) [93] was used in addition to the PQ to screen for anxiety and depressive symptoms.

Table 1. Inclusion and exclusion criteria by participating mental health services

	Mondriaan	**Virenze**
Inclusion criteria:	Aged between 18 and 25 years	Aged between 14 and 25
	PQ: score of 6 or above and/or **SQ-48:** score of 9 or above on social phobia subscale; or score of 8 or above on depression subscale; or score of 11 or above on anxiety subscale	**PQ:** score of 6 or above and/or **BSI:** T-score of 63 or above
	Willingness to participate in the compassion-focused ecological momentary intervention. Ability to give written informed consent independently, without help from others	
Exclusion criteria:	Insufficient command of Dutch, primary clinical diagnosis of alcohol or substance dependency, severe endocrine, cardiovascular or organic brain disease	

Notes: PQ, Prodromal Questionnaire; SQ49, Symptom Questionnaire-48; BSI, Brief Symptom Inventory

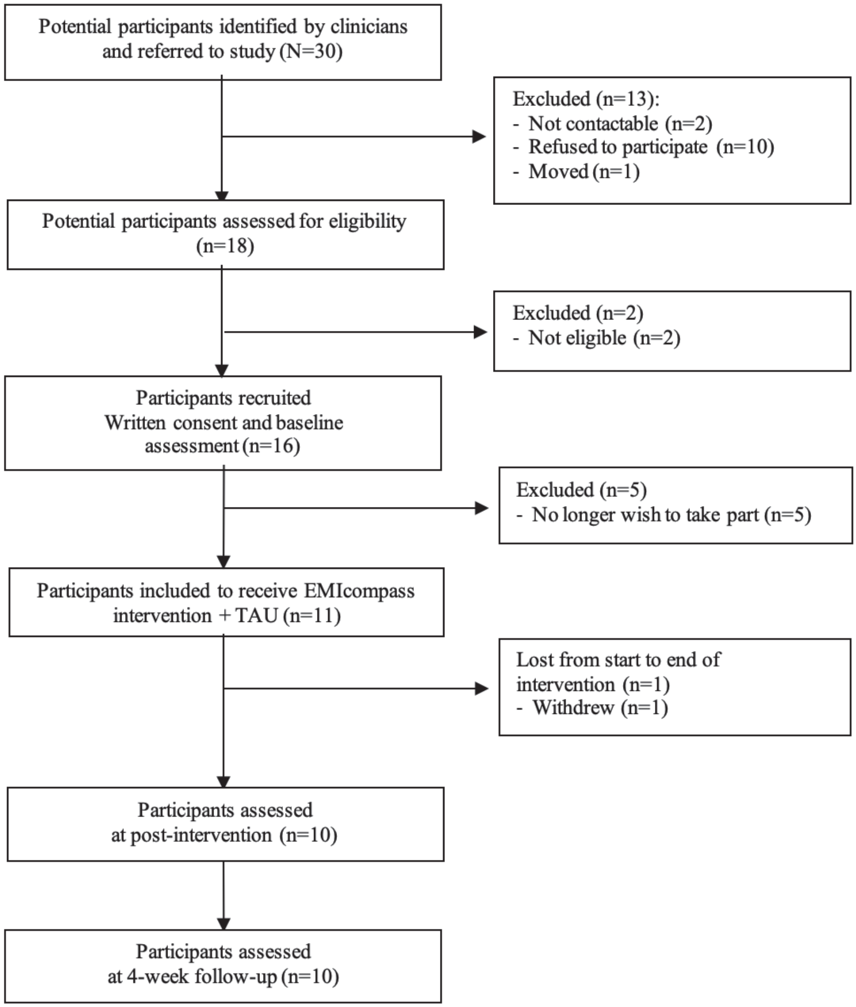

Figure 1. Study flowchart

The EMIcompass intervention

Development of the manual

The intervention was structured and manualised in order to ensure consistent delivery of the intervention. The manual was based on widely used CFI techniques (e.g., compassionate and positive imagery, and writing; emotion as a wave) and developed following a process of reviewing existing manuals and the extant CFI literature [67, 68, 73, 74, 78, 80], through the team's clinical experience of working with these approaches with clients, and through consultation with local experts in CFI and the wider research team. The intervention was designed based on principles of EMIs [23, 34-36, 39, 43, 44].

EMIcompass intervention + treatment as usual

In the current study, participants were offered the EMIcompass intervention in addition to treatment as usual, which included all the treatment they received prior to the start of the study (i.e., good standard care delivered according to local and national guidelines by their general practitioner, psychiatrist, and other health care professionals. This may include CBT, third-wave CBT, DBT, and other psychological interventions). The EMIcompass intervention consisted of three face-to-face sessions (one training session, one follow-up 'booster' session, and one review session) given by a trained psychologist, who was supervised by an expert clinical psychologist in compassion-focused therapy, and a 3-week EMI administered through an mHealth app on a smartphone (PsyMateTM). In addition, participants were offered on-demand e-mail and/or phone contact during the intervention period.

At the beginning of the 3-week intervention period, an initial face-to-face training session was offered to participants. This session was fully manualized based on previous research using compassion-focused interventions [67, 68, 74, 78, 94]. The goal of the first session was to train individuals in how to cope with negative emotions by applying a personal compassionate image that conveys compassion, care, and warmth to them based on Gilbert's (2010, pp. 187-189) descriptions and as applied by Lincoln et al. (2013). This was followed by inducing negative emotions using in-sensu exposure to a personally relevant social situation that participants remember having experienced as distressing. This method has been safely applied in individuals with mental health problems [74, 78] without any adverse consequences or health-related risks. Following induction of negative emotions, participants were asked to practice a 5-minute application of the compassionate image participants were trained in at the beginning of the session [67, 68, 78]. This step of actively using compassionate imagery subsequent to inducing negative emotions is considered essential for compassion-focused therapy to be efficacious in reducing stress sensitivity, threat anticipation, and psychotic, depressive and/or anxiety symptoms in daily life [67, 68]. Training the use of compassionate imagery was repeated and extended to imagery involving a 'compassionate self' [68] and 'emotion as a wave' [94] in the following booster session two weeks after the initial training session. In the review session at the end of the 3-week intervention period, the smartphone was returned, progress and satisfaction with, and acceptability of, the intervention were reviewed and assessed.

Table 2. Components of the EMIcompass intervention

	Week 1	**Week 2**	**Week 3**
Compassion-focused training sessions	Training session (compassionate image)	Booster session (day 11-15) (compassionate self-training, 'emotion as a wave')	Review session (after day 20)
Enhancing tasks	Task 1 (day 3 or 4): Compassionate self-validation	Task 2 (day 9 or 10): 'Emotion as a wave'	Task 3 (day 15 or 16): Self-compassionate writing
Consolidating tasks	Compassionate self-validation (from day 5, following enhancing EMI task 1)	Compassionate self-validation 'Emotion as a wave' (from day 11, following enhancing EMI task 2)	Compassionate self-validation 'Emotion as a wave' Self-compassionate writing (from day 17, following enhancing EMI task 3)
Interactive tasks	Compassionate image Compassionate self-validation (from day 5, following enhancing EMI task 1)	Compassionate image Compassionate self-validation 'Emotion as a wave' (from day 11, following enhancing EMI task 2)	Compassionate image Compassionate self-validation 'Emotion as a wave' Self-compassionate writing (from day 17, following enhancing EMI task 3)

Note: EMI, ecological momentary interventions

To allow for interactive, real-time, and real-world translation of the therapeutic content and techniques of initial and booster sessions into individuals' daily lives, participants were additionally offered a 3-week EMI delivered through an mHealth app. During the 3-week intervention period, the smartphone prompted a signalling sound from the smartphone seven times per day on six consecutive days per week to reduce burden associated with app usage. At each beep, participants were asked to complete a brief EMA on momentary stress, positive and negative affect, and threat anticipation in daily life (see section on used EMA measures). EMA was scheduled at random within set blocks of time. The EMI consisted of three different types of tasks (see Table 2): participants were asked to complete one 'enhancing task' per week, allowing them to practice new compassion-focused exercises, which were subsequently extended over the study period (e.g., discovering their own compassionate self, experiencing emotions as a wave). In addition, they were asked to practice learned CFI components once a day by completing 'consolidating tasks' at a predefined time. The components covered by consolidating tasks were extended each time an enhancing task was presented. Further, 'interactive tasks' were offered if participants scored high on stress, negative affect, or threat anticipation in the EMA (i.e., scores higher than 4 on a 7-point Likert scale). Given an essential element of compassion-focused therapy is for individuals to use compassionate imagery in moments of high stress, negative affect, or threat anticipation, these interactive tasks are thought to reflect a core active component of the 3-week compassion-focused EMI.

Measures

Socio-demographic characteristics

A socio-demographic schedule was used to assess age, gender, occupation, and level of education.

Clinical feasibility and safety

Feasibility was assessed based on successful recruitment, assessment of outcomes, compliance with the manual, satisfaction, and acceptability. For some of the domains of feasibility, a debriefing scale was used. Reasons for participants to decline to take part in the study were carefully recorded, and completeness of outcomes at each time point was documented. Acceptability was assessed in the review session of the EMIcompass intervention together with the trained psychologist by asking participants to complete a feedback form about the EMI tasks and sessions and to rate the extent to which they feel they benefit from, and are satisfied with, the intervention [74, 78]. In addition, the trained psychologist asked participants in the review session to report whether they perceived the face-to-face sessions, the compassion-focused exercises, and the EMI tasks as helpful. App usability was assessed by asking participants to rate the readability of the text shown on the screen, any difficulties to operate the app or technical problems, the clarity of provided instructions, and whether the app was perceived as burdensome. All items were rated on a 7-point Likert scale ranging from 'not at all' (rating of 1) to 'moderate' (rating of 4) and 'very' (rating of 7) which were subsequently grouped into three categories of 'not' (rating of 3 or lower), 'moderate' (rating of 4 or 5), and 'very' (rating of 6 or 7) for sake of interpretability of findings (given small numbers in each cell). Safety was assessed by carefully documenting any serious adverse events throughout the entire study period as well as potential negative effects of app usage on mental health in participants.

Stress sensitivity, negative and positive affect, and psychotic experiences in daily life

EMA was used to assess stress sensitivity, negative and positive affect, psychotic experiences, and threat anticipation in daily life. For this, the same app was used as for the EMIcompass intervention (PsyMateTM) and assessments were completed at baseline, post-intervention, and 4-week follow-up for a period of 6 consecutive days following the protocol from previous EMA studies [22, 24, 29, 46, 49]. Stress was operationalised as minor disturbances and distinctive unpleasant events, activities, and social situations that occur in the flow of daily life. Event-related stress was measured with one item asking participants to rate the most important event that has happened since the last beep on a 7-point Likert scale ranging from 'very unpleasant' (rating of -3) to 'very pleasant' (rating of 3) [54]. The item was recoded that higher ratings indicate higher levels of stress (with ratings of -3 coded as 7 and ratings of 3 coded as 1). Activity-related stress was measured by asking participants, first, to specify their current activity (e.g. resting, watching TV), which was followed by asking to rate the pleasantness of this activity on a 7-point Likert scale (1='very unpleasant', 7='very pleasant'). Social stress was measured by asking participants to specify categorically with whom they were spending time (e.g. nobody, partner, family) and to appraise the current social context using the items 'I find being with these people pleasant' [reversed], 'I feel accepted' [reversed], and 'I feel excluded (if with someone) or 'I find it pleasant to be alone' [reversed] and 'I would prefer to have company' (if alone) ranging from 'not at all' (rating of 1) to 'very much' (rating of 7). Good concurrent validity of these EMA stress measures has been reported [54, 55]. Further, a composite stress score was calculated by using the mean score of all seven stress items [21, 95]. Negative affect was assessed using five items by asking participants to rate the extent to which they feel anxious, down, insecure, uncomfortable, and guilty at each entry point [54] and positive affect was assessed by asking participants to rate the extent to which they feel cheerful and relaxed, all rated on a 7-point Likert scale ranging from 'not at all' (rating of 1) to 'very much' (rating of 7) [54, 55, 96]. Psychotic experiences were assessed using seven items ('I see things that aren't really there', 'I hear things that aren't really there', 'I feel suspicious/paranoid', 'I feel unreal', 'My thoughts are influenced by other', 'I can't get these thoughts out of my head', 'I feel like I am losing control') rated on a 7-point Likert scale ranging from 1 ('not at all') to 7 ('very much') [55, 96]. Threat anticipation was assessed by asking participants to think of what might happen in the next few hours and to rate the item 'I think that something unpleasant will happen' on a 7-point Likert scale (ranging from 1 ('not at all') to 7 ('very much')) [24, 29]. Negative and positive affect, psychotic experiences, and threat anticipation scores were assessed by computing mean scores, respectively. In line with earlier studies [22, 24, 29, 46, 49], items on stress, negative affect, and psychotic experiences were used as a proxy for individuals' stress sensitivity in daily life by modelling the association between stress and (i) negative affect and (ii) psychotic experiences. Thus, we conceptualized stress sensitivity in daily life as individuals' affective and psychotic reactivity to minor daily stressors.

Psychotic, depressive, and anxiety symptoms as well as general psychopathology

We used non-EMA outcome measures to assess psychotic, depressive, and anxiety symptoms as well as general psychopathology. First, the BSI was used to assess depressive and anxiety symptoms (based on the respective BSI subscales) and general psychopathology by computing the Global Severity Index (GSI; based on 53 BSI items). Participants rated each item on a 5-point scale ranging from 0 ('not at all') to 4 ('extremely') [91, 92]. Second, the Green et al. Paranoid Thoughts Scale

(GPTS), a reliable and valid scale, was used to assess psychosis [97]. The GPTS was modified to ask participants about paranoid ideation over the past week rather than the past month given the intervention period was only 3 weeks. A total score was computed using all 32 items (both with a 5-point scale; 1='not at all', 3='somewhat', 5='totally'). Third, the Threat anticipation measure (TAM) [98] was employed to measure threat anticipation by asking participants to estimate the future likelihood of a list of threatening, neutral, and positive events happening to themselves and to other people [62, 98, 99]. Items for threating and neutral events were used to compute total scores. Each event was rated separately for the likelihood that it will happen to oneself and to another person on a 7-point scale (1='not at all', 7='very likely'), resulting in four total sum scores (i.e., threat anticipation-self, threat anticipation-other, neutral anticipation-self, neutral anticipation-other) where higher scores indicate higher probability estimates. Finally, the Prodromal Questionnaire (PQ) [88, 89] was used to assess the presence of prodromal and attenuated psychotic symptoms (i.e., positive symptoms, disorganized symptoms, negative symptoms, and general symptoms). This measure consists of 16 items that assess the presence of psychotic symptoms (0=false, 1=true) which were used to compute a total score (range 0-16). Good psychometric properties have been reported for these measures [88, 97, 98, 100, 101].

Statistical analysis

STATA 15.1 was used to analyse the data. First, descriptive statistics was used, and confidence intervals constructed, as appropriate, to summarize findings on feasibility and safety. Second, as EMA data have a multilevel structure, such that multiple observations (level-1) are nested within subjects (level-2), linear mixed models were used to control for within-subject clustering of multiple observations using the "mixed" command in STATA. Thus, to examine the effects of the EMIcompass intervention on reducing stress sensitivity, EMA stress variables and time point were included as independent variables and (i) negative affect and (ii) psychotic experiences as the outcome variable in linear mixed models, which were fitted separately for each outcome variable. We then added two-way interaction terms for stress × time and used likelihood ratio tests ("lrtest" command) to evaluate improvement in model fit as well as the "lincom" command to compute linear combinations of coefficients for testing our hypotheses whether stress sensitivity was reduced at post-intervention and 4-week follow-up. We standardized continuous ESM and variables (mean = 0, S.D. = 1) for interpreting significant interaction terms. Family-wise error-corrected p-values were computed to control for multiple testing by multiplying the unadjusted p-values of the two-way interaction effects by the total number of tests (N=4) for each outcome. Third, to examine the effects of the EMIcompass intervention on other EMA outcome measures, time point was included as independent variable and negative affect, positive affect, psychotic experiences and threat anticipation as the outcome variable in separate linear mixed models. All models were controlled for potential confounders (i.e. age, gender, level of education). Lastly, we used Wilcoxon signed rank tests to examine the effects of EMIcompass on non-EMA outcome measures of threat anticipation, psychotic, depressive, and anxiety symptoms as well as general psychopathology at post-intervention and 4-week follow-up. Resulting Z-scores were used to calculate effect sizes displayed in r as described by Rosenthal [102].

Results

Socio-demographic characteristics

A study flowchart is shown in Figure 1. In total, 30 potential participants aged 14-25 years were referred to the study by clinicians from the two participating mental health services. Of these, 16 provided written informed consent and were eligible, of whom eleven completed the baseline assessment and were included to receive the EMIcompass intervention. One participant was lost during the 3-week intervention period, whereas 10 participants (mean age 20.3 years, range 14-24) completed the EMIcompass intervention and both post-intervention and 4-week follow-up assessments. The majority of participants were female (7/10; 70%) and currently at school/university (6/10; 60%). Half of the participants had a clinical diagnosis of major depressive disorder (5/10; 50%) and met criteria for a comorbid mental health condition. Most participants were of white Dutch ethnic background and some reported having used cannabis during the last 12 months (3/10; 30%).

Table 3. Basic sample characteristics

	Service users (n=10)
Age, mean (S.D.; range)	20.3 (3.8; 14-25)
Sex, n (%)	
Female	7 (70.0)
Male	3(30.0)
Ethnicity, n (%)	
White Dutch	6 (60.0)
Other	1 (10.0)
Missing value	3 (30.0)
Level of education, n (%)[a]	
School	2 (20.0)
Further	4 (40.0)
Higher	4 (40.0)
Occupation, n (%)	
School / Education	6 (60.0)
Employed (full-/part-time)	3 (30.0)
Unstructured activities	1 (10.0)
Cannabis use [a], n (%)	
12-months	3 (30.0)
Lifetime	4 (40.0)
DSM-IV diagnosis, n (%)	
Major depressive disorder	5 (50.0)
Attention-deficit hyperactivity disorder	1 (10.0)
Reactive attachment disorder	2 (20.0)
None	2 (20.0)
Comorbid condition [b]	5 (50.0)

Notes: S.D., standard deviation
[a] Categories defined as school (primary education, LBO, MAVO, VMBO), further (MBO, HAVO, VWO) and higher (HBO, HO, WO) of the Dutch educational system.
[a] Based on CIDI-L: Defined as having used cannabis more than 5 times on own initiative during the last 12-month or lifetime.
[b] Consisting of the following diagnostic categories: Panic disorder, Attention-deficit hyperactivity disorder, Intermittent explosive disorder, Borderline personality disorder, Parent-child relational problem.

Clinical feasibility and safety

Findings on clinical feasibility and safety are shown in Table 4. Almost all individuals (90%, 9/10) reported that taking part in the study did not interfere with their daily activities. Most individuals reported to be very (40-50%) or moderately satisfied (40-50%) with tasks delivered through the EMIcompass app as well as moderately (20%-30%) or very (60%) satisfied across face-to-face sessions. The majority of participants was also very (50%, 5/10) or moderately (20%, 2/10) successful in imagining a compassionate image. Some individuals reported that the intervention positively influenced social contacts (30%, 3/10 (ratings of 'moderate' and 'very' combined)) and levels of activity (40%, 4/10). All individuals were very satisfied with the face-to-face contact sessions with, and felt they were understood by, the trained psychologists. While all participants reported that they were able to follow the instructions shown on the screen, observer-ratings by trained psychologists, who also delivered the face-to-face sessions, indicated that some individuals may have had problems with this (10% at session 1 and 20% at session 3). Findings on app usability was satisfactory and the burden associated with app usage was perceived to be low or very low across all time points (70-90%), although some individuals (30%, 3/10) found the number of signals per day moderately burdensome. Also, some individuals perceived the items used in the PsyMateTM app as difficult or unclear (20%, 2/10). There were no severe adverse events recorded during the study period.

In-app usage data during the interventions period suggests high completion rates of EMA assessments. More specifically, the EMIcompass app triggered, in sum, 1260 signals asking participants to complete brief EMA assessments (126 for each person). Of these, individuals reacted to 467 (37.1%), although high variability between individuals was found (range 17% to 67%). In total, individuals scored high on stress, negative affect, or threat anticipation in 150 out of 467 EMA assessments (32.1%), resulting in real-time delivery of CFI intervention components in around 1/3 of all EMA assessments. When considering assessment of outcomes during the baseline, post-intervention, and follow-up, we found satisfactory completions rates (no missing data for outcome measures filled in in person as well as at least 30% of all EMA assessments). Thus, when combining self-reports and in-app usage data, assessment of outcomes and compliance with the manual was considered satisfactory. What is more, the conversation rate of recruitment was 3:1 (i.e., from identified to included individuals; see Figure 1), which is in line with previous research and considered successful recruitment.

Table 4. Findings on safety, feasibility, and app usability of the EMIcompass intervention

	Very [a]	Moderate [a]	Not [a]
Safety and feasibility			
Interference of study participation with daily activities	-	1 (10%)	9 (90%)
Satisfaction with face-to-face sessions	6 (60%)	2 (20%)	2(20%)
Session 1: compassionate image; inducing negative emotions	6 (60%)	3 (30%)	1 (10%)
Session 2: compassionate self; emotion as a wave	6 (60%)	3 (30%)	1 (10%)
Session 3: review session	6 (60%)	3 (30%)	1 (10%)
Satisfaction with tasks			
Task 1: compassionate self-validation	4 (40%)	5 (50%)	1 (10%)
Task 2: emotion as a wave	5 (50%)	3 (30%)	2 (20%)
Task 3: self-compassionate writing	5 (50%)	3 (30%)	2 (20%)
Self-reported success in making a compassionate image	5 (50%)	3 (30%)	2 (20%)
Taking part in the study positively affected activities [b]	2 (20%)	2 (20%)	5 (50%)
Taking part in the study affected social contacts			
Positively	1 (10%)	2 (20%)	7 (70%)
Negatively	-	-	10 (100%)
Satisfaction with contact with trained psychologist [b]	9 (100%)	-	-
Participant felt understood by trained psychologist [b]	9 (100%)	-	-
Self-reported level of understanding of instructions provided by trained psychologist? [b]	9 (100%)	-	-
Observer-rating by trained psychologists			
Compliance in session 1	7 (70%)	2 (20%)	1 (10%)
Compliance in session 2	7 (70%)	3 (30%)	-
Compliance in session 3	6 (60%)	2 (20%)	2 (20%)
EMIcompass app usability			
Readability of text on screen	10 (100%)	-	-
Difficulties to operate the app	-	-	10 (100%)
Clarity of instructions given on screen	10 (100%)	-	-
Difficulties understanding used items	-	2 (20%)	8 (80%)
EMIcompass app perceived as burdensome			
In terms of the number of signals per day	-	3 (30%)	7 (70%)
In terms of the number of items asked per signal	-	1 (10%)	9 (90%)
In terms of the signal sound	1 (10%)	1 (10%)	8 (80%)
Technical problems	-	1 (10%)	9 (90%)

[a] Items were rated on a 7-point Likert scale ranging from ‘not at all’ (rating of 1) to ‘moderate’ (rating of 4) and ‘very’ (rating of 7). The trained psychologist noted the answers. The answers were grouped into three categories of ‘not’ (rating of 3 or lower), ‘moderate’ (rating of 4 or 5), and ‘very’ (rating of 6 or 7) for sake of interpretability (given small numbers in each cell).
[b] Missing value for one participant.

Initial therapeutic effects

Stress sensitivity, negative and positive affect, and psychotic experiences in daily life

Findings on initial therapeutic effects of the EMIcompass intervention on stress sensitivity are provided in Table 5. We found preliminary evidence that participants experienced less intense negative affect in response to event-related and activity-related stress at post-intervention as well as in response to overall, event-related, activity-related, and social stress at follow-up than at baseline, as indicated by statistically significant two-way interaction effects for stress × time point. Further, participants reported less intense psychotic experiences in response to minor stressors in daily life (i.e., overall as well as specific types of stressors) at post-intervention and follow-up than at baseline.

Further, Table 6 shows findings of initial effects of EMIcompass on momentary negative affect, psychotic experiences, and positive affect. There was preliminary evidence that participants experienced less intense negative affect and psychotic experiences as well as more intense positive affect in daily life at post-intervention and 4-week follow-up than at baseline. There was also some evidence that individuals anticipated fewer threatening events in their daily lives at post-intervention and 4-week follow-up than at baseline.

Table 5. Initial therapeutic effects of EMIcompass on stress sensitivity in daily life

	Post-intervention *vs.* baseline		Follow-up *vs.* baseline		Follow-up *vs.* post-intervention		LR test for interaction[a]	
	adj. β (95% CI)	p	adj. β (95% CI)	p	adj. β (95% CI)	p	χ^2 (df)	pFWE
				Outcome: Negative affect				
Stress								
Overall	-0.12 (-0.27 – 0.03)	0.110	-0.51 (-0.63 - -0.40)	<0.001	-0.39 (-0.55 – -0.23)	<0.001	72.6 (2)	<0.001
Event-related	-0.41 (-0.56 - -0.25)	<0.001	-0.39 (-0.51 - -0.27)	<0.001	0.02 (-0.14 – 0.18)	0.831	51.6 (2)	<0.001
Activity-related	-0.25 (-0.40 - -0.09)	0.002	-0.35 (-0.47 - -0.23)	<0.001	-0.10 (-0.27 – 0.06)	0.216	32.5 (2)	<0.001
Social	0.05 (-0.10 – 0.20)	0.502	-0.41 (-0.53 - -0.28)	<0.001	-0.46 (-0.62 - -0.29)	<0.001	47.6 (2)	<0.001
				Outcome: Psychotic experiences				
Stress								
Overall	-0.15 (-0.25 - -0.04)	0.005	-0.28 (-0.36 – -0.20)	<0.001	-0.14 (-0.25 - -0.03)	0.013	48.7 (2)	<0.001
Event-related	-0.29 (-0.39 - -0.19)	<0.001	-0.19 (-0.27 - -0.11)	<0.001	0.10 (-0.01 – 0.20)	0.080	40.6 (2)	<0.001
Activity-related	-0.25 (-0.35 - -0.14)	<0.001	-0.20 (-0.28 - -0.12)	<0.001	0.05 (-0.06 – 0.16)	0.399	33.3 (2)	<0.001
Social	-0.01 (-0.11 – 0.09)	0.863	-0.24 (-0.32 - -0.16)	<0.001	-0.23 (-0.34 - -0.12)	<0.001	36.3 (2)	<0.001

Note: adj. β, standardized regression coefficients [continuous independent variables were standardized (mean = 0, S.D. = 1) for interpreting interaction terms; CI, confidence interval; df, degrees of freedom, LR, likelihood ratio test; pFWE, family-wise error-corrected p values were computed by multiplying the unadjusted p value by the total number of tests for each outcome (*N*=4) to adjust significance levels of likelihood ratio tests for two-way interactions. [a] Likelihood ratio test for stress × time interaction after inclusion in the following model: (for y_{ij} negative affect, psychotic experiences or positive affect as outcome variable):
$y_{ij} = \beta_0 + \beta_1(STRESS_{ij}) + \beta_2(TIME_j) + \beta_3(STRESS_{ij} \times TIME_j) + \varepsilon_{ij.}$

Table 6. Initial therapeutic effects of EMIcompass on individuals' momentary stress, negative affect, psychotic experiences, positive affect, and threat anticipation

	Baseline	Post-intervention	Follow-up	Post-intervention vs. baseline		Follow-up vs. baseline	
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	B (95% CI)	p	B (95% CI)	p
Positive affect	3.9 (1.8)	4.5 (1.5)	4.3 (1.6)	0.39 (0.16 – 0.62)	0.001	0.31 (0.10 – 0.52)	0.004
Negative affect	2.2 (1.3)	1.8 (1.1)	1.4 (0.7)	-0.44 (-0.59 – -0.30)	<0.001	-0.59 (-0.72 - -0.46)	<0.001
Psychotic experiences	1.7 (0.8)	1.4 (0.9)	1.3 (0.6)	-0.25 (-0.34 - -0.16)	<0.001	-0.36 (-0.44 - -0.28)	<0.001
Threat anticipation	2.7 (1.9)	2.2 (1.3)	1.6 (1.1)	-0.61 (-0.83 - -0.39)	<0.001	-0.96 (-1.15 – -0.76)	<0.001

Notes: S.D., standard deviation, CI, confidence interval

Psychotic, depressive, and anxiety symptoms as well as general psychopathology

Findings on the initial therapeutic effects of EMIcompass on non-EMA outcome measures are presented in Table 7. Overall, reductions in threat anticipation, psychotic, depressive, and anxiety symptoms as well as general psychopathology (as indexed by the GSI) of moderate to large effect size were found at the end of the 3-week intervention period ('post-intervention'), and after a 4-week follow-up period (r=0.30-0.65). There was initial evidence, despite small sample size and, hence, limited statistical power, that these reductions were beyond what would be expected by chance alone for psychotic symptoms at post-intervention and 4-week follow-up as well as, at trend level, for anxiety symptoms (post-intervention, 4-week follow-up) and anticipation of a positive future self (4-week follow-up). The intervention effects on depressive symptoms and general psychopathology were also of medium to large effect size but fell short of statistical significance. Reductions in threat anticipation (self, other) were only of small to moderate effect size and did not reach conventional levels of statistical significance.

Table 7. Initial therapeutic effects of EMIcompass intervention on psychotic, depressive and anxiety symptoms, general psychopathology, and threat anticipation

	Median scores (range)			Paired Wilcoxon signed ranks test (n=10)					
	Baseline	Post-intervention	Follow-up	Post-intervention vs. baseline		Follow-up vs. baseline		Follow-up vs. post-intervention	
				Z	Effect size (ra)	Z	Effect size (ra)	Z	Effect size (ra)
BSI									
Global Severity Index	81 (22 -146)	68.5 (5-158)	51 (7-142)	-1.02	-0.32	-1.17	-0.37	-1.53	-0.48
Depression	13.5 (1-23)	12 (0-23)	7 (1-21)	-1.02	-0.33	-1.03	-0.33	-1.38	-0.44
Anxiety	11.5 (4-16)	9.5 (0-17)	7 (2-14)	-1.74	-0.55†	-1.79	-0.57†	-0.82	-0.26
GPTS									
Total score	41 (32-73)	46.5 (32-83)	38 (32-70)	1.94	0.61*	-1.74	-0.55†	-2.50	-0.79*
PQ									
Total score	5 (1-10)	5 (0-9)	2 (0-10)	-1.32	-0.42	-2.05	-0.65*	-1.34	-0.42
TAM									
Future self (positive)	26.5 (17 – 37)	27 (16-37)	33 (7-42)	0.41	0.13	1.89	0.60†	1.79	0.57†
Future self (threatening)	15.5 (11-25)	16.5 (7-24)	13 (7-34)	-0.46	-0.15	-1.28	-0.40	-0.52	-0.16
Future others (positive)	31.5 (19-45)	31 (27-42)	33.5 (22-44)	0.21	0.07	1.33	0.42	1.74	0.55†
Future others (threatening)	15.5 (7-37)	14 (8-36)	13.5 (7-32)	-0.78	-0.25	-0.77	-0.24	-0.21	-0.07

*Notes: † $p < 0.10$; * $p < 0.05$;* BSI, Brief Symptom Inventory; GBTS, Green et al. Paranoid Thoughts Scale; PQ, Prodromal Questionnaire; IPSM, Interpersonal Sensitivity Measure; TAM, Threat Anticipation Measure

[a] effect size estimates are based on *r* described by Rosenthal, 2001 using the following formula: r = Z/√number of pairs.

Discussion

Principal findings

Findings of this uncontrolled phase I pilot study suggest initial findings on feasibility, safety, and preliminary therapeutic effects of a compassion-focused ecological momentary transdiagnostic intervention designed to improve emotional resilience to stress ('EMIcompass') in help-seeking youth with psychotic, depressive, and/or anxiety symptoms. First, individuals were satisfied with face-to-face and app-based intervention components, interference with daily activities was low, and observer-rated compliance with the treatment was high. Indicators of app usability were satisfactory. Also, no adverse effects were reported. Second, there was preliminary evidence of decreased stress sensitivity, negative affect, and psychotic experiences as well as increased positive affect in daily life at the end of the 3-week intervention period ('post-intervention'), and after a 4-week follow-up period ('follow-up') as compared to baseline. Third, there was initial evidence, despite the small sample size and limited statistical power, for reductions in threat anticipation, psychotic, anxiety, and depressive symptoms of medium to large effect size (r=0.30-0.65). Overall, this reflects promising preliminary evidence of clinical feasibility and safety of the EMIcompass intervention in help-seeking youth and some evidence on initial therapeutic effects, although findings on clinical outcomes should be interpreted with caution considering the small sample size of this pilot study.

Strengths and limitations

The strength of the current study is that principles of CFIs were, for the first time, translated into an EMI administered through an mHealth app as a new avenue for real-world and real-time prevention and intervention in youth. Further, EMIcompass transforms evidence on putative underlying mechanisms into an intervention that directly targets these mechanisms in daily life and, hence, is, at heart, translational. However, there are a number of limitations that have to be considered in interpreting our findings. First, in line with state-of-the-art guidance on developing and evaluating complex interventions [103], mHealth interventions in particular [104], the sample size (N=10) of this pilot study was selected to be small. Thus, the primary focus of this study was on investigating feasibility and safety as well as estimating the effect size of initial therapeutic effects rather than statistical significance to provide the basis for a feasibility randomised controlled trial (RCT) [105]. Nonetheless, while considering low statistical power and limitations associated with a small sample size, we found preliminary evidence (in terms of statistical significance) on effects of the EMIcompass intervention on stress sensitivity. These are promising findings as stress sensitivity is the primary target of this emotion regulation-focused intervention. Second, data on feasibility and acceptability were assessed together with or by the trained psychologist and not an independent person. Thus, we cannot rule out biases and underreporting of unhelpful experiences. Third, we used a debriefing scale to assess domains of feasibility. Thus, no established measure was used for classifying and assessing the quality of the EMIcompass app (e.g., MARS which is used to assess app engagement, functionality, aesthetics, and information quality) which limits reported findings. Fourth, due to the absence of a waiting-list or active control group, we cannot rule out that there may be no additive therapeutic effects of the EMIcompass intervention over and above the therapeutic effects of the face-to-face sessions with the trained psychologists or other therapeutic interventions participants received during the intervention period in form of treatment as usual. However, again, the primary aim of this pragmatic phase I pilot study was to provide the basis of a feasibility RCT by investigating feasibility and safety as well as generating initial effect sizes. It is now urgently warranted to further examine the efficacy of the EMIcompass intervention. Third, the majority of participants were female, and half of participants suffered from depression which may limit generalisability of findings as selection bias may have operated on our sampling procedure. Fifth, after written informed consent was obtained and baseline assessments were completed, five individuals decided not to participate in the study. The reasons for exclusion were not assessed which limits our findings on feasibility. Finally, the complex nature of investigated constructs, sample size, and study design exclude any form of causal inference.

Ideas for future work

The EMIcompass intervention aimed to augment current treatment options for young individuals seeking help for mental health problems. Most individuals reported to be satisfied with the intervention. While the small sample size has to be considered when interpreting findings, the preliminary therapeutic effects on candidate psychological mechanisms, including stress sensitivity, and on other psychopathological outcomes were promising. Importantly, no adverse effects have been reported and taking part in the study did not hinder individuals in their daily activities. Thus, overall, findings on feasibility, safety, and initial therapeutic effects may be considered to be encouraging.

This is one of the first studies to develop and pilot an ecological momentary intervention that incorporates an adaptive and context-dependent delivery scheme of intervention components in youth with mental health problems. The 'interactive-tasks' were triggered in around 1/3 of all EMA assessments when individuals experienced elevated levels of negative affect (e.g. feeling anxious, insecure, down; i.e. scores higher than 4 on a 7-point Likert scale) or momentary stress. Thus, real-time data processing was successfully applied based on EMA data to determine delivery of compassion-focused intervention components. This may represent not only an important step towards ecologically more valid and accessible psychological interventions in youth, but also a more personalised and contextualised clinical and preventive approach. In other words, principles of EMIs allow not only to translate intervention components targeting candidate momentary mechanisms and contexts to individuals' daily lives, but take also a personalized, adaptive approach informed by fine-grained real-time EMA data to produce sustainable change in the real world. Although a feasibility RCT is needed as a significant next step to investigate the efficacy of the intervention and feasibility as a basis for a confirmatory RCT [23, 34], the current pilot study of this novel EMI reflects an important steppingstone towards more personalized and accessible youth mental health care. Furthermore, in-app data analytics revealed a high variability in compliance between individuals. This suggests, that for some individuals the number of signals per day were too high (i.e., seven times per day on six consecutive days per week).

These findings hint towards potential avenues for improvement of the EMIcompass intervention to be iteratively incorporated. First, future versions of the EMIcompass intervention may offer adaptive intervention trajectories that vary in type of exercises depending on individual needs and preferences. Importantly, in doing so, potentially influencing factors (e.g. educational level, language skills, cultural peculiarities, subjective preferences) should be considered at an early stage of the design process and taken into account in optimizing EMIs further. Co-production with young service users is essential during these developmental processes

[106]. Second, sustained engagement in using digital tools remains an important challenge [107], which may be addressed through the use of gamification elements, especially in youth [108, 109]. However, in the current study, burden associated with app usage was low so far and problems with engagement have mainly been reported for standalone mHealth apps without components of blended care [110]. Third, in working towards more personalised mHealth apps, more sophisticated methods may be used to inform the timing and context of when intervention components are offered (e.g. by using mobile sensing data) and a broader range of intervention components delivered over a longer intervention period may help enhance effects of EMIcompass further and achieve sustainable change in individuals' daily life. Fourth, the type of intervention components may be personalised further by assessing effects of specific intervention components on individuals' mental health at the person-level. Fifth, it should be further examined whether and, if so, how the therapeutic alliance can be strengthened in the light of a limited number of face-to face sessions [111]. Finally, the number of signals per day triggered by the smartphone were perceived as burdensome by some participants. Thus, future versions of the EMIcompass app may lower the number of signals per day and/or shortening the number of items per signal [112].

Conclusions

Taken together, evidence on feasibility and safety as well as preliminary evidence on therapeutic effects of the EMIcompass intervention suggest that translating compassion-focused intervention components into individuals' daily life through an EMI delivered by an mHealth app may be a promising novel, accessible, and transdiagnostic treatment approach in help-seeking youth by strengthening emotional resilience and directly targeting candidate psychological mechanisms. As an important next step, an exploratory randomised controlled trial is warranted to demonstrate feasibility and preliminary evidence of efficacy of the EMIcompass intervention.

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CHAPTER 8

Digital interventions for psychosis

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Abstract

Digital technologies such as smartphones, smartwatches and head-mounted displays are increasingly available at low cost and have witnessed an unparalleled gain in computational power over the recent years. This has resulted in an increasing interest in, and steep upsurge in the possibilities of, using these technologies to deliver personalized, engaging and adaptive digital interventions for individuals with psychosis. In this chapter, different types of digital interventions will be described, recent examples of cutting-edge internet-based eHealth, app-based mHealth and virtual reality-based interventions provided and important challenges discussed. The chapter will conclude by discussing promising avenues for the future and clinical implications.

Keywords: Telemedicine; Mobile Health; Virtual Reality; Technology; Digital Psychiatry; Digital Intervention; eHealth; Monitoring; Feedback; Ecological Momentary Assessment; Ecological Momentary Interventions; Ecological Translation; Psychosis; Schizophrenia

Introduction

Although current routine mental health services offer various treatment options for individuals with psychotic symptoms, specialized support remains difficult to access and tailoring of interventions to service users' needs continues to be problematic. These limitations of existing mental health services likely contribute to an increased burden for individuals and their caregivers [1], considerably high dropout and relapse rates [2], treatment resistance [3] and low medication adherence [4]. Further, perceived stigma associated with mental health conditions, psychosis in particular [5], remains to be high and has been found to negatively influence individuals willingness to seeking help. This may ultimately lead to long durations of untreated psychosis [6, 7], an important predictor of poor prognosis and outcome [8]. Thus, modifying illness trajectories at early stages of psychosis is important [9, 10] and finding novel, easy-to-access and more engaging forms of delivering mental health services are urgently needed [11].

This chapter examines the clinical potential of emerging digital technologies for helping individuals with subclinical expressions of psychosis as well as psychosis spectrum disorders. For this, a selection of recently published studies and meta-analyses will be used to exemplary summarize recent developments. First, different types of digital interventions will be described, and examples of state-of-the-art applications provided. This will be followed by recent developments and studies that explore the potential of digital interventions to specifically target potential mechanisms underpinning psychosis. The chapter will conclude by discussing promising avenues for the future and clinical implications derived from the available evidence. Overall, the aim of the current chapter is to give interested readers a review on how digital interventions are currently being used to help individuals with psychosis at different clinical stages.

Differing types of digital interventions

Rapid technological advances, such as smartphones, smartwatches, fitness trackers and head-mounted displays, are increasingly available at low cost and have witnessed an unparalleled gain in computational power over the recent years. This has resulted in an increasing interest in, and steep upsurge in the possibilities of, using digital tools to deliver pioneering and truly integrative mental health services for individuals with psychosis and other mental disorders [12, 13]. In many countries, people have access to various of these information and communication technologies (e.g. mobile phone ownership rate among individuals with psychosis has been reported to be above 80% [14]) and are already accustomed to frequently use their wide-ranging functionalities. Consequently, digital interventions have great potential of bringing personalized, engaging and adaptive interventions to help individuals with mental health conditions, including psychosis [15-18].

There are differing types of digital interventions which are currently most widely studied for helping individuals with psychosis that can be roughly categorized in telemedical and internet-based (eHealth) [19, 20], app-based mobile health (mHealth) [15, 18, 21, 22] and virtual reality-based (VR) interventions [23, 24]. These digital tools offer a plethora of novel possibilities researchers and clinicians are only just beginning to explore, with the ultimate goal of enhancing mental health care. These tools differ greatly in terms of their content, complexity and functionality ranging from simple prompts sent via SMS or other messaging services, with the goal to remind users to do certain therapeutic tasks at home, to technologically very sophisticated interventions that include avatars - computer-generated virtual representation of humans - in VR environments that have the ability to respond to clients' verbal responses by using speech-recognition techniques and may even help individuals to guide through virtual therapy sessions. Importantly, digital interventions can either be used to supplement traditional face-to-face treatment (e.g. use of an mHealth app to practice certain intervention components to augment traditional cognitive behavior therapy) or to offer stand-alone services.

Digital interventions that have been developed and tested to support individuals with psychosis have primarily focused on five domains [25]:

(1) enabling remote *communication and social interactions* among service users, carers and mental health professionals (e.g. moderated online forums or online peer-support);

(2) allowing easy access to evidence-based *information* (e.g. modules delivered through mHealth apps that offer psychoeducation);

(3) supporting real-time and real-world *self-monitoring* and *management* of symptoms (e.g. use of mood trackers which are based on frequent self-reports on momentary mental states);

(4) delivery of person-tailored *feedback* (e.g. the use of fine-grained real-time data on behaviors, mental states and minor stressors that are actively used by clinicians during therapy sessions to help service users to gain meaningful insights about their mental health problems, including important determinants);

(5) delivery of psychological *interventions* in individuals' daily lives or in immersive virtual environments (e.g. exposure to fearful social stimuli to lower social anxiety in an interactive three-dimensional virtual environment).

In the following subsections, cutting-edge examples of eHealth platforms, mHealth apps and VR interventions will be discussed that offer one or more of aforementioned domains to help individuals with psychosis and are largely based on findings reported in recently published reviews [15, 17, 20, 22, 24, 26-33].

eHealth and mHealth interventions for psychosis

Studies have found that the frequency, availability and flexibility of contact with mental health professionals as well as peer-support are effective components of psychological interventions, which can be decisive for the reduction of relapse [34]. Digital interventions may help to increase the flexibility of contact with mental health professionals and peers through online chat, video calls and online platforms and may thereby optimize both treatment continuity and cost-effectiveness. In addition, giving individuals the right digital tools to inform themselves and others about their experiences, and to develop skills and strategies to better cope with mental health conditions they experience, have been found to contribute to empowering those in need of care, which may also support a more active role of individuals' recovery processes [35]. There are numerous digital interventions that improve communication among service users and health professionals and purposefully include components of peer-support components, easy-to-access evidence-based information and intervention components in form of online eHealth platforms or mHealth apps. In the following paragraphs, recent examples of cutting-edge applications will be provided (see also Table 1 and Table 2).

Schizophrenia Online Access to Resources ('*SOAR*') [36] is a web-based platform that gives individuals with psychosis spectrum disorders and their families access to modules on psychoeducation as well as modules that focus on practicing problem solving skills, coping strategies and promoting self-efficacy, amongst others. *SOAR* also includes moderated online support with trained health professionals and a peer discussion forum and has been found to reduce positive psychotic symptoms and improve knowledge about schizophrenia of medium to large effect when compared to treatment as usual (TAU). Another web-based and mobile platform is Moderated Online Social Therapy ('*MOST*'') that offers continuous, integrated face-to-face and digital care to young people which has been pioneered by the eOrygen team at Orygen, the National Centre of Excellence in Youth Mental Health, Australia. The elements of the MOST conceptual model have been applied to different interventions: '*HORYZON*' [37] includes an extensive psychosocial intervention that aims to increase social functioning in individuals with first episode psychosis, and has later been extended to helping individuals ultra-high-risk for psychosis ('*MOMENTUM*') [38]. These interventions were developed to increase self-efficacy, positive emotions and social support through online social environments. The interventions consist of an interactive online social therapy, peer-to-peer online social networking and expert and peer moderation. It also includes modules on helping individuals in defining their strength and doing mindfulness exercises to improve social functioning. In an uncontrolled single-group phase I pilot study, *MOMENTUM* has been found to be safe, feasible and engaging for young individuals with "ultra-high-risk" (UHR) state for psychosis. When comparing baseline and follow-up, an increased use of strengths, mindfulness skills and aspects of social support have been reported which was, in turn, associated with self-efficacy, life satisfaction and lower loneliness and depression scores, respectively. Overall, there was a large increase in social functioning [37, 38].

Table 1. Recent examples of eHealth applications with published feasibility/efficacy results.

Study	Name	Country of Origen	Targeted population	Main therapeutical targets
Rotondi et al., (2010)	SOAR	USA	Psychosis spectrum disorders	- Problem solving skills - Coping strategies - Self-efficacy
Alvarez-Jimenez et al., 2013	HORYZONS	Australia	FEP	- Social engagement - Self-efficacy - Wellbeing
Alvarez-Jimenez et al., 2018	MOMENTUM	Australia	CHR	- Social engagement - Self-efficacy - Wellbeing
Laine et al., 2019	Mental-net	Finland	Psychosis spectrum disorders	- Psychoeducation - Self-efficacy

Note: FEP: First Episode of Psychosis; CHR: Clinical High Risk of psychosis.

Table 2. Recent examples of mHealth (smartphone) applications with published feasibility/ efficacy results

Study	Name	Country of Origen	Targeted population	Main therapeutical targets
Ben-Zeev et al., 2014	FOCUS	USA	Psychosis spectrum disorders	- Coping strategies - Anxiety and depression management - Sleep disturbances - Social functioning - Medication management
Schlosser et al., 2016 and 2018	PRIME	USA	EIS individuals	- Reward-processing impairments
Kim et al., 2018	HYM	South Korea	Psychosis spectrum disorders	- Symptom monitoring (follow-up after CBT intervention)
Niendam et al., 2018	Ginger.io	USA	EIS individuals	- Assessment. - Symptom monitoring
Bucci et al., 2018	Actissist	United Kingdom	EIS individuals	- Psychoeducation - Symptom self-management skills
Depp et al., 2019	CBT2go	USA	Psychosis spectrum disorders	- Negative beliefs about the self/others - Attributions
Lim et al., 2019	+Connect	Australia	EIS	- Loneliness
Garety et al., 2017	SlowMo (blended therapy)	United Kingdom	Non-affective psychosis	- Reasoning biases - Paranoid attributions

Note: EIS: Early intervention services; FEP: First Episode of Psychosis; CHR: Clinical High Risk of psychosis.

'*Mental-Net*' [39], a web-based patient education intervention, offers a number of psychoeducational material and an online discussion forum. These psychoeducational modules are divided into 5 themes: information on mental disorders, evidence-based treatment options, well-being, patients' rights and ways to cope with challenges experienced in daily life (e.g. economic support, taking care of home). In a feasibility pilot study, service users diagnosed with schizophrenia accessed the website together with a mental health professional once per week (45-60 minutes). The acceptability has been found to be high as users were satisfied with the offered intervention components and also felt that provided information were useful to better cope with their mental health problems. In comparison to individuals in a waiting list control condition (TAU), the intervention group has also been found to have significantly higher scores in self-efficacy and lower scores in perceived hopelessness.

In addition to web-based eHealth platforms, there has been a recent increase of app-based digital interventions designed to help individuals with psychosis. '*FOCUS*' [40] is a multimodal digital intervention for people with serious mental illness, including psychosis spectrum disorders and consists of an mHealth app as well as a dashboard that can be assessed by clinicians. The app includes components which primarily target 5 domains, that is, (1) strategies to cope with auditory hallucinations (e.g. distraction, cognitive restructuring and hypothesis testing techniques); (2) managing anxiety and depression (e.g. relaxation techniques, behavioral activation and other supportive content); (3) sleep (e.g. sleep hygiene, wellness psychoeducation); (4) social functioning (e.g. anger management, activity scheduling); and (5) medication (e.g. reminders and psychoeducation). *FOCUS* has been found to be feasible and acceptable and initial therapeutic effects have been demonstrated in individuals with psychosis [40, 41], including those who were recently discharged [42]. Another pioneering mHealth app is Personalized Real-Time Intervention for Motivation Enhancement ('*PRIME*') [43]. *PRIME* is designed to target reward-processing impairments in individuals with recent onset schizophrenia and includes selecting goals that are being monitored over the course of the treatment, daily challenges, and social components with a trained online coach who assists users in the use of the app. Compared to a waitlist control condition, individuals in the *PRIME* condition showed greater improvements in depression, defeatist beliefs, self-efficacy and components of motivation [44].

Heal your Mind ('*HYM*') has been used after the completion of group-based Cognitive Behavioral Therapy for Psychosis to allow on-demand personal advice and support based on real-time monitoring of symptoms [45]. A case manager accessed users' responses and was able to provide real-time feedback which has been found to help personalizing case-management. In a survey study, including 24 people with early psychosis, more than 80% of the participants reported that the app was easy to use and around 70% perceived some benefit from having used it [45]. '*Ginger.io*' [46], a mobile app which works in combination with a web-based dashboard, has been used as part of early psychosis outpatient care. *Ginger.io* allows the assessment and monitoring of symptoms as well as passive data (e.g. physical movement, calls and texting pattern) and a clinician dashboard to provide feedback and alerts sent when responses indicate worsening of symptoms [46]. Longitudinal data (14 months) from 76 individuals from Early Intervention Services showed good feasibility of the integration of the app and the dashboard as a self-reported assessment of symptoms, providing data comparable to clinician-rate assessment ratings [46].

'*Actissist*' is an mHealth intervention that delivers cognitive behavioral therapy (CBT) through a smartphone app for individuals with early psychosis. It incorporates adaptive delivery of intervention components and does thus purposefully incorporate individuals' responses to short questionnaires that are prompted three times per day to ask participants about their current mental states. In addition, users also have the ability to access the therapeutic content of the app on demand [47]. Similarly, *'My Journey 3*' [48] is a smartphone delivered self-management tool for individuals with first episode psychosis recruited from Early Intervention in Psychosis services. The app includes key elements of self-management, including the ability to create a relapse prevention plan (e.g. identification of potential triggers, early warning signs, coping strategies), definition of recovery goals, listing of actions that can increase well-being and reminders to engage in these activities. Another mHealth app that has been recently developed and evaluated is '*CBT2go*' [49]. Again, this digital intervention is based on principles of CBT and consists of a single face-to-face session which is supplemented by an mHealth app. The app provides real-time thought-provoking interventions focusing on specific symptom domains (e.g. voice hearing) and beliefs which have been identified during face-to-face therapy session. The app also prompts individuals to complete modules on cognitive restructuring and other tasks. In a three-arm (i.e. CBT2go, self-monitoring, TAU) randomized single-blind controlled trial including 255 individuals with psychosis spectrum disorders, *CBT2go* has been found to be feasible and to have small to moderate effects on global psychopathology and community function as compared to TAU. However, *CBT2go* was not found to be more effective when compared to the active control condition (i.e. self-monitoring) for most of the primary and secondary outcomes [49]. Finally, the mobile app *'+Connect'* [50, 51] has been designed based on principles of positive psychology and focusses on the reduction of loneliness. The app offers peer and expert videos on demand, mood tracking and gamified challenges. Preliminary evidence of this mobile app showed significant reductions in loneliness (main intervention target) at post-treatment and in gain maintenance at 3-month follow-up [50]. See also Rus-Calafell and Schneider (2020) for a specific review on eHealth and mHealth applications designed to help people at early psychosis stages.

Future outlook on eHealth and mHealth interventions

In this section, a future outlook on eHealth and mHealth interventions is provided. For this, a selection of recently published trial protocols with pending efficacy or feasibility results is summarized.

A recent example of blended therapy, where face-to-face sessions with a therapist are combined with a mobile app, is the SlowMo Therapy [52]. SlowMo is a digital approach which employs technology to target the fast-thinking tendencies that have been associated with paranoia (e.g. jumping to conclusions, belief inflexibility). The therapy consists of eight individual, face-to-face sessions, delivered by trained therapists, assisted by a webapp with interactive personal accounts and daily scenarios. A smartphone app helps the person embed strategies into everyday life. As such, the SlowMo approach attempts to combine the best of existing talking therapies with novel digital technology to increase engagement, effectiveness and generalization to everyday life [53, 54]. Efficacy results from a large controlled randomized study (N=350) are expected to be published early 2021 [52].

'*EviBaS*' [55] is an internet-based 8-week online self-help intervention for people with psychosis that includes psychoeducational modules on delusional ideations, voice hearing, social competence and mindfulness. Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement and Recovery ('*EMPOWER*') [56, 57] is a digital mHealth intervention which will be offered as a supplement to TAU. *EMPOWER* focusses on early signs monitoring to prevent relapse in psychosis and promote well-being. '*EMBRACE*' [58] is a moderated 12-week online intervention to treat social anxiety in individuals with FEP and is, similar to MOMENTUM and HORYZONS, based on elements of the MOST conceptual model. '*Robin*' [59] integrates content of face-to-face treatment sessions with an mHealth app for individuals with clinical high risk for psychosis. The 'momentum trial' [60] is an mHealth app that aims to support self-perceived patient activation and shared decision making for people with psychosis spectrum disorders in outpatient treatment settings. Finally, in the context of symptom-focused interventions where a single-symptom of psychosis is the main target of the psychological therapy, a Dutch group has developed '*Temstem*' [61]. It is a mobile app that aims to help individuals who are hearing voices by offering motoric language games, tasks to improve self-esteem and imagery exercises.

In summary, there has been a recent surge of eHealth interventions and mHealth apps to help individuals with psychosis. Early pioneering work laid the foundation for a now rapidly evolving field, resulting in increasingly adaptive, multimodal digital interventions which aim to be engaging and tailored to what a person needs in a given moment and context. In doing so, a range of therapeutic approaches - most commonly CBT and third-wave CBT - have been used. In this section of the chapter, a selection of advanced eHealth and mHealth interventions were described and a future outlook provided to exemplify the current state of development. Overall, these interventions have been found to offer psychoeducational material and modalized digital interventions targeting established risk and resilience factors for psychosis as well as symptom domains (e.g. social functioning, self-efficacy, physical activity, auditory hallucinations, delusional ideations). Some interventions also enabled users to actively manage and monitor their symptoms in real-time, access broad set of skill trainings (e.g. relaxation techniques, helpful coping strategies) and to engage in various forms of remote communication with peers and service providers. Accumulating evidence suggests the feasibility, acceptability, and therapeutic effects of eHealth and mHealth interventions for psychosis. However, our understanding on candidate mechanisms, long-term effects, and cost-effectiveness remains very limited and the current use and implementation of digital tools in routine mental health services, outside the research context, is very limited.

VR interventions for psychosis

In addition to eHealth interventions and mHealth apps, the use of VR has great potential to offer completely new avenues for mental health care. Immersive VR in particular allows users to interact with a three-dimensional computer-generated virtual environment that is completely controllable by researchers or clinicians [62]. There has been a long tradition to use immersive VR environments to assess mental health problems as well as processes and mechanisms which have been found to be important for the development and persistence of psychosis in ecologically more valid ways with high external validity as compared to other lab-based assessment methods [23, 24, 33, 63-65]. More recently, VR has been used for the treatment of various mental health problems, including attention deficit hyperactivity disorder, autism, post-traumatic stress disorder and anxiety disorders [24, 29, 65-69]. VR-based interventions that are specifically designed to help individuals with psychosis are scarce, although, over the recent years, they have gained traction. Originally, VR interventions were mostly focusing on prevocational training and job interview training and have thus not been directly targeting psychosis symptomatology [24, 29, 33]. More recently, however, several studies have demonstrated initial therapeutic effects of VR intervention on putative mechanisms of symptoms of psychosis (see also Table 3).

One of the first studies considered to test a VR-based intervention for psychosis, is the one published by Freeman and colleagues (2016). This study included 30 individuals with psychosis who were randomized to VR-CBT or VR exposure. The VR-CBT condition was focusing on enabling patients to drop safety-seeking behaviors in computerized versions of feared social situations in virtual reality environments, while in the exposure condition individuals had solely to move in a VR environment while the number of avatars was increasing. In comparison with VR exposure, VR-CBT was found to reduce delusional conviction and real-world distress [70].

Table 3. Recent examples of Virtual Reality applications with published feasibility/efficacy results

Study	Name	Country of Origen	Targeted population	Main therapeutical targets
Freeman et al., 2016	VR-CBT	United Kingdom	Non-affective psychosis	- Safety behaviours - Social avoidance
Pot-Kolder et al., 2018	VR based CBT	Netherlands	Psychosis spectrum disorders	- Paranoid attributions -Social engagement
Nijman et al., 2019	DiSCoVR	Netherlands	Psychosis spectrum disorders	- Social cognition - General psychopathology
Vass et al., 2019	VR-ToMIS	Hungary	Psychosis spectrum disorders	- Negative symptoms - Theory of Mind - Language skills
Craig et al., 2018	AVATAR therapy	United Kingdom	Non-affective psychosis	- Distressing auditory hallucinations
duSert et al., 2018	Avatar therapy (immersive)	Canada	Psychosis spectrum disorders	- Distressing auditory hallucination

Note: VR: Virtual Reality.

A larger randomized study has found that a CBT-based VR intervention, aimed to improve paranoid thoughts and social involvement in people with psychosis, lowered paranoid ideation and anxiety as compared to TAU at post-treatment [71]. However, groups did not differ with regard to the amount of time spend with other people at post-treatment (i.e. increase of social activities). The treatment effects on paranoia were maintained at 6-month follow-up. Interestingly, individuals' safety behaviors and social cognition were found to mediate treatments effects on paranoid ideation [71]. The Dynamic Interactive Social Cognition Training in Virtual Reality ('*DiSCoVR*') was tested in a single-group feasibility pilot study investigating initial therapeutic effects of a 16-session training on social cognition and psychiatric symptoms [72]. In total, 17 individuals with psychosis spectrum disorders and problems in social cognition were included in this pilot study. Acceptability (e.g. satisfaction) has been reported to be high and most participants explicitly mentioned that the intervention was helpful because of the possibility to practice social interactions in VR environments. While the study has demonstrated changes in emotion perception of moderate effect, no effects were found on other outcomes measures such as social cognition and self-esteem [73]. In another randomized-controlled phase I feasibility pilot study [74], a VR-based intervention was designed to target Theory of Mind in outpatients with schizophrenia ('*VR-ToMIS*') [74]. The intervention consisted of 9-sessions of either VR-ToMIS or passive VR. In the passive VR condition, patients were able to freely explore the virtual environments, but not to contact any avatars. In the intervention group, improvements on negative symptoms, theory of mind and language skills were found as compared to the passive VR condition, but no differences on quality of life [74].

AVATAR therapy is an example of a more symptom-focused VR-based intervention for psychosis [75, 76]. The therapy allows a ‘face-to-face’ dialogue between the person and a computerized representation of their voice (or auditory hallucination). Although AVATAR therapy as originally developed by Leff and colleagues (2013) is not delivered using a complex immersive environment, the platform uses VR technology to create a virtual embodiment of the experience of hearing voices and to re-enact the relationship with the voice within a real-time dialogue (see also [77] for an independent pilot using a head mounted display to deliver the therapy). The embodiment of the voice is enhanced by the use of direct verbatim speech, and enactment of the ascribed character and background of the voice.

The efficacy of the therapy has now been demonstrated in two independent pilot studies [76, 77] and in a large fully-powered randomized controlled trial comparing AVATAR therapy and Supportive Counselling that showed AVATAR therapy to be more effective post-therapy in terms of reductions in the frequency, distress and omnipotence of voices after an average of 6 therapy sessions [75]. Interestingly, the interaction of sense of voice presence and reduction of anxiety was associated with two of the significant therapy outcomes (total severity and frequency of voices, see [78]).

Future outlook on VR interventions

Freeman and colleagues are currently working on automated psychological treatments delivered using VR [79]. In the '*gameChange*' trial, 432 patients with psychosis and avoidance of social situations will be recruited and randomized to receive either VR cognitive treatment (*gameChange*) additionally to their treatment as usual (TAU) or to continue solely with TAU. The intervention aims to reduce avoidance and to help individuals to feel more comfortable around other people by working on fear expectations and relearning feeling safe in social situations. In total, the intervention lasts for up to 6 sessions of 30 minutes and a computerized virtual coach will guide participants through 6 VR environments that include gamified social challenges of increasing difficulty. First results are expected to be published around mid 2021 [79].

THerapeutic Realistic Immersive Virtual Environments '*THRIVE*' [80] is another automated VR intervention that is currently investigated by the same research group and forms the basis of *gameChange* VR. Thus, it also focusses on individuals with psychosis and avoidance of social situations, although in this particular case the VR cognitive treatment will be compared with an active treatment condition (VR mental relaxation). Secondary outcomes include real-world distress, suicidal ideation and quality of life [80]. Further research on VR-based interventions for psychosis is currently being carried out at Dr Valmaggia's VR Lab at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN, King's College London). Among other work, this research group is testing the efficacy of a new VR-assisted therapy to help people improve social performance and manage paranoia thoughts while participating in social interactions (see [81] for a validation of the virtual environment designed for this purpose). An ongoing small feasibility trial is being carried out including people at first-episode psychosis (FEP). The same research group is working on the design and testing of a novel VR-based intervention to improve negative symptoms in people with psychosis (VR Therapy for Psychosis Negative Symptoms, *'V-NeST'*) (this work is led by Dr Matteo Cella).

Overall, VR interventions for psychosis have gained a great momentum. Similar to most eHealth and mHealth interventions, VR interventions often build on techniques commonly used in CBT as they are particularly amendable to translation into computer-generated virtual environments. So far, most VR interventions for psychosis aim to target factors which have been found to contribute to psychosis progression and persistence, including social anxiety and associated safety-seeking behaviors and theory of mind impairments as well as positive psychotic symptoms. Importantly, there is a growing number of high-end, all-in-one portable VR headsets available on the consumer market that can be used without expensive setups. This will likely further accelerate the use of VR intervention in clinical settings, outside the research laboratory.

From mechanistic research to novel treatment targets

As described earlier, digital interventions are well positioned to not only target psychotic symptoms in daily life, but also putative risk and resilience mechanisms which have been found to be important in the development and persistence of psychosis [18, 23, 82]. For instance, studies using Ecological Momentary Assessment (EMA) or synonymously Experience Sampling Methodology, a structured diary technique [83], have robustly found an elevated sensitivity towards stress in daily lives of individuals with an at-risk mental state for psychosis as well as psychosis spectrum disorders [84, 85]. Thus, these findings support the notion that individuals' stress sensitivity may constitute an important candidate psychological mechanism involved in the formation and maintenance of psychosis that could be a promising novel treatment target of digital interventions [18].

Building on advances in the field of mHealth interventions, an ecological interventionist causal model approach for targeting psychological mechanisms in daily life has been proposed [18]. This approach draws on Ecological Momentary Interventions (EMIs) which represent a promising digital intervention approach for targeting risk and resilience mechanisms as well as symptoms domains in the real-world and in real-time through cutting-edge mobile technologies [15, 18, 86]. EMIs allow the transfer of evidence-based intervention components (e.g. therapeutic techniques of cognitive-behavioral therapy, CBT, or third-wave CBT) that are particularly suitable to target putative mechanisms in daily lives of individuals with psychosis or individuals with a known clinical risk for developing psychosis. Two studies have recently been published that used principles of EMIs to target risk mechanisms, symptom domains and promoted helpful cognitions and behaviors. In the Acceptance and Commitment Therapy in Daily Life ('*ACT-DL*') trial [87, 88], principles and exercises of ACT were translated into an EMI and delivered through an mHealth app which aimed to target putative psychological mechanisms, including stress sensitivity, psychological flexibility and reward experience in individuals with UHR/FEP. ACT-DL includes modules on creative hopelessness, acceptance, cognitive difusion, self as context, committed action and defining values. The feasibility of the treatment protocol and evidence of efficacy has recently been demonstrated [88]. Further, in an uncontrolled pilot study [89], an ecological momentary, compassion-focused intervention for improving emotional resilience ('*EMIcompass*') was investigated including help-seeking youth with psychotic, depressive and/or anxiety symptoms. The intervention consisted of three sessions with a trained psychologist and a 3-week EMI administered through an mHealth app. Preliminary findings of this phase I pilot study suggest that using compassion-focused intervention components (e.g. compassionate image and writing, emotion as a wave, breathing exercises) delivered using an mHealth app following principles of EMIs may reduce stress sensitivity in daily life and various psychopathological domains in help-seeking youth [89]. The EMIcompass intervention is currently tested in an exploratory randomized controlled trial to establish clinical feasibility, candidate underlying mechanisms, and initial signals of efficacy. The results are expected to be published in 2021 [90].

Similarly, VR enables new opportunities for improving well established cognitive and behavioral techniques in an engaging and tailored way, as well as providing novel therapeutic contexts within which core psychological processes (Valmaggia et al., 2016) can be targeted in real time with immediate feedback. For example, in people with paranoia, VR scenarios are designed in which the degree of hostility that the virtual characters display can be manipulated (for example to be neutral, benign or hostile). This allows a more refined assessment of paranoia than self-report measures, at the same time that offers the opportunity to the person, for example, to drop key safety behaviors in a controlled and predictable setting (see Freeman et al., 2016 and Pot-Kolder et al., 2018) and to learn new emotional and behavioral responses to feared situations [81]. Crucially VR environments allow '*embodied*' cognitive processes to be targeted 'in action', potentially matching the dynamic conceptualization of appraisals (e.g. attributions of power and control about voices) with the ultimate aim that improvements made in VR environments will generalize to real-life contexts.

Quality from the user perspective

Findings from digital interventions included in this chapter suggest moderate to high acceptability and feasibility of eHealth, mHealth and VR interventions. However, some of the included studies did not specifically report data on users' perspective. Notably, acceptability as well as effectiveness on various health-related outcomes have been described to be particularly high if interventions were embedded in a therapeutic context and include some form of social contact with mental health professionals - commonly referred to as the blended care approach [14, 91, 92]. Furthermore, studies have shown that perceived quality increased if digital intervention include possibilities to socially interact with peers [93] and implement strategies to promote user engagement like gamification strategies [94].

Future research directions

Digital mental health services for psychosis, especially mHealth apps and VR interventions, are still at an early stage of their development and many interventions have only been tested in small feasibility trials. Thus, more well-powered randomized controlled trials are urgently needed to further investigate their efficacy, long-term effects, processes and mechanisms of action and cost-effectiveness. Furthermore, after careful testing, efforts should be made to bring evidence-based digital interventions into clinical practice as well as making them publicly available. In addition, most digital interventions which are currently developed and tested do arguably not fully harness the full potential of more recent technological advances. For example, integrating other technologies (e.g. sensors such as accelerometer, gyroscope, GPS to passively assess psychophysiological markers) may have additive effects on treatment outcomes and may also be used to further personalize the timing and context of when intervention components are delivered. Also, as engagement remains to be a problem [95], gamification features as well as other elements that aim to improve service users' motivation to use digital tools should be further investigated and incorporated [96]. In addition, it has become increasingly clear that fostering principles of co-design and co-production at an early stage of the developmental process of digital interventions is crucial for satisfying specific needs and preferences of service users as well as mental health professionals [13, 53] and has been found to be beneficial for implementing these tools into diverse clinical settings [94]. Finally, an important next step is to systematically investigate the role of relational components like the digital therapeutic alliance on health-related outcomes [97] and how to strengthen rapport and other unspecific treatment effects in light of potentially declining numbers of face-to face sessions [98, 99].

Clinical applications and recommendations

The use of telemedical and internet-based (eHealth), app-based mobile health (mHealth) and virtual reality (VR) interventions have been found to be safe among individuals with psychosis. Recent findings indicate feasibility and high acceptability ratings, and evidence on effectiveness is very promising although long-term effects have to be further investigated. Importantly, acceptability, feasibility and effectiveness are particularly high if digital interventions are used in clinical settings and thus include some form of social contact with a mental health professional. Thus, clinicians interested in the diverse possibilities of digital intervention may start using these tools in their everyday therapeutic work to gain important first-hand experience of the unique opportunities and current limitations of these tools and to supplement face-to-face treatment sessions.

Digital interventions hold great potential of bringing person-centered and adaptive interventions into individuals' everyday lives and, thereby, help to ecologically translate treatment components to contexts outside clinicians' office or specialized clinics. However, digital interventions developed by research groups are mostly neither routinely offered by health care professionals, nor integrated in established psychological treatments, and do also very scarcely find their way into major app stores. This strongly limits the current potential of digital interventions to alleviate mental health burden associated with psychosis and other mental and somatic health complaints. To address this problem, there have been recent efforts to systematically evaluate currently available digital interventions based on established criteria of digital mental health and mental health services research (e.g. National Health Service Apps Library in the UK; Platform for Digital health applications (DiGA) in Germany; App Evaluation Database by the Division of Digital Psychiatry, Beth Israel Deaconess Medical Center in the USA). Additionally, researchers and policy makers are working on national implementation strategies with the ultimate goal of making evidence-based digital interventions clinically and publicly available, and incorporating them in existing healthcare systems by, for example, enabling "health apps on prescription". These efforts allow individuals with psychosis and clinicians making more informed decisions on the quality of currently available digital interventions and to stay up to date in this rapidly evolving field.

Lastly, clinicians should be aware of possible barriers as well as social inequalities (e.g. disproportional distribution of ownership of required technologies, language skills, motor, or cognitive deficits) that must be taken into account when they are planning to use digital tools to supplement their services that may impact the access and abilities to use digital interventions in individuals with psychosis [100, 101].

Conclusion

This chapter explored the use of internet-based eHealth, app-based mHealth and virtual reality-based digital interventions to help individuals with psychosis. These differing types of digital interventions have been found to offer wide-ranging functionalities and therapeutic components, including remote communication, access to evidence-based information, digital self-monitoring and feedback as well as real-world and real-time delivery of psychological interventions*.* Overall, there is accumulating evidence on feasibility, acceptability and therapeutic effects of digital interventions for psychosis, especially if interventions are embedded in a therapeutic context (i.e. blended care approach). Thus, digital interventions signal great promise to help individuals who are experiencing psychotic symptoms and other commonly co-occurring mental health problems.

For most digital interventions described in this chapter, the theoretical base has been clearly stated and recent empirical evidence provided. Most interventions included intervention components that were informed by evidence-based recommendations and clinical guidelines (e.g. published by the National Institute for Health and Excellence, NICE) and primarily offered psycho-social interventions such as CBT, third-wave CBT and ACT. There were also a number of studies explicitly targeting cognitive factors described in integrated models of psychosis [82, 102-104]. Nevertheless, despite the promising results from clinical research on the use of these technologies described in this chapter, there are still important challenges to overcome. Lack of large randomized controlled trials, efforts to bridge the gap between research and clinical practice and the inclusion of the users' experience as an essential part of the interventions' evaluation, are among these challenges for the successful implementation of digital interventions for psychosis. To overcome these challenges, more efforts from the clinical research community and mental health services are needed in order to train clinicians to routinely offer, use and master digital interventions. There is also a need to further expand our knowledge on long-term effects, cost-effectiveness and the theoretical foundation of digital interventions, particularly on putative mediators and mechanisms of change and their potential causal link in the development and persistence of psychosis.

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CHAPTER 9

Social isolation, mental health, and use of digital interventions in youth during the COVID-19 pandemic: a nationally representative survey

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Abstract

Background: Public health measures to curb SARS-CoV-2 transmission rates may have negative psychosocial consequences in youth. Digital interventions may help to mitigate these effects. We investigated the associations between social isolation, COVID-19-related cognitive preoccupation, worries, and anxiety, objective social risk indicators, psychological distress as well as use of, and attitude towards, mobile health (mHealth) interventions in youth.

Methods: Data were collected as part of the 'Mental Health And Innovation During COVID-19 Survey' - a cross-sectional panel study including a representative sample of individuals aged 16 to 25 years (*N*=666; M_{age} 21·3) (assessment period: 07.05.-16.05.2020).

Results: Overall, 38% of youth met criteria for moderate or severe psychological distress. Social isolation worries and anxiety, and objective risk indicators were associated with psychological distress, with evidence of dose-response relationships for some of these associations. For instance, psychological distress was progressively more likely to occur as levels of social isolation increased (reporting 'never' as reference group: 'occasionally': adjusted odds ratio [aOR] 9.1, 95% confidence interval [CI] 4.3 – 19.1, p<0.001; 'often': aOR 22.2, CI 9.8 – 50.2, p<0.001;'very often': aOR 42.3, CI 14.1 – 126.8, p<0.001). There was evidence that psychological distress, worries, and anxiety were associated with a positive attitude towards using mHealth interventions, whereas psychological distress, worries, and anxiety were associated with actual use.

Conclusions: Public health measures during pandemics may be associated with poor mental health outcomes in youth. Evidence-based digital interventions may help mitigate the negative psychosocial impact without risk of viral infection given there is an objective need and subjective demand.

Keywords: COVID-19; Youth Mental Health; mHealth; Social isolation; Social risk

Introduction

As of March 2020, most European countries have adopted a range of public health measures to lower the transmission of SARS-CoV-2 coronavirus. Physical distancing and quarantine have been amongst the most important non-pharmacological measures to reduce infection rates of coronavirus disease 2019 (COVID-19). These preventive measures, however, may have a profound impact on public mental health. Studies investigating the psychosocial impact of earlier pandemics (e.g. SARS, MERS) have shown that physical distancing and quarantine have immediate as well as prolonged effects on individuals' mental health, including depression, anxiety, psychosis, and perceived stress [1-5]. Further, it has been found that these safety measures are associated with an increase of more distal risk factors for poor mental health such as social isolation, risk behaviours (e.g. cannabis and alcohol misuse), and lowered physical activity [1]. In line with findings on earlier outbreaks, accumulating evidence suggests negative psychosocial consequences of the current COVID-19 pandemic on public mental health, including increased levels of depression, anxiety, self-harm, and loneliness [6-27]. Although the increasing number of approved vaccines and potential breakthroughs in the pharmacological treatment of COVID-19 are reasons for optimism, health related outcomes may worsen at any time due to new virus variants (e.g. lineage B.1.1.7 or B.1.351) as well as economic uncertainties and recession which may occur secondary to the pandemic.

There is also evidence that the detrimental effects of pandemics are disproportionally distributed across communities: societal inequalities have been found to increase the risk of COVID-19 on various health domains. Those with inferior social position, for instance, have been found to have increased disease fatality and hospital admission rates as well as to experience more severe psychosocial and economic consequences [28] and initial findings from the UK suggest inequalities in adverse experiences during the early weeks of the lockdown [29]. Other studies have found that individuals with histories of migration and unemployment experience more severe depressive and anxiety symptoms, especially in youth [30].

Information and communication technologies may be particularly important in alleviating COVID-19-related psychosocial consequences [31]. For instance, smartphone applications (apps) help individuals to remotely interact with others (e.g. by using video conferencing software) and digital interventions, which do not require face-to-face contact (e.g. internet-based interventions [eHealth] and mobile health applications [mHealth apps]), may help to increase public mental health during health crises [31]. Previous studies have shown that digital tools available in major app stores, especially mHealth apps, are already frequently being used although most developers do not provide information on their evidence base, safety, and effectiveness [32-34]. While, in contrast, eHealth and mHealth interventions that have been developed and evaluated by research groups signal great promise on their safety, acceptability, and effectiveness across the whole spectrum of public mental health provision (i.e., mental health promotion, prevention and treatment of mental disorders), especially if embedded in social and therapeutic contexts (e.g. peer-support, blended care) [31, 35]. Thus, although mHealth apps available in app stores should be used with caution, digital interventions may be used to mitigate the negative impact of the COVID-19 pandemic [31]. If used purposefully, these tools may help to provide low-threshold, timely, and personalized public mental health care and can be tailored to the individual needs - even under the restrictive conditions of the COVID-19 pandemic and without the risk of viral infection [31, 36-38]. However, to the best of our knowledge, there has been no study to date which has specifically investigated the role of publicly available mHealth apps during public health crises, including the current COVID-19 pandemic, and the available evidence on the occurrence of psychological distress in young individuals and important correlates remain very limited.

In the current study, we aimed to investigate the associations between social isolation, COVID-19-related cognitive preoccupation, worries, and anxiety, objective social risk indicators and psychological distress as well as use of, and attitude towards, digital mHealth apps in a representative sample of youth aged 16-25 from the general population during the COVID-19 pandemic. Specifically, we sought to test the following hypotheses: First, (a) social isolation and lack of company, (b) COVID-19-related cognitive preoccupation, worries, and anxiety, and (c) objective indicators of social risk (e.g. unemployment, migrant or ethnic minority group position) are associated with occurrence of psychological distress. Second, these associations are consistent with a dose-response pattern. Third, current use of, and positive attitudes towards, mHealth apps are more common in those who experience psychological distress, more frequent social isolation and lack of company, COVID-19-related preoccupation, worries, and anxiety, and who are exposed to more objective indicators of social risk.

Methods

Design and participants

Data were drawn from the 'Mental Health And Innovation During COVID-19 Survey' —a cross-sectional panel study. This study was conducted as part of a living lab entitled "AI4U - Artificial Intelligence for personalized digital mental health promotion and prevention in youth", which aims to develop, optimize, evaluate, and implement digital AI-based interventions in routine public mental health provision by adopting a transdisciplinary approach involving users from the target population and relevant stakeholders in all stages of the research process. We recruited a representative sample of youth aged 16-25 from the German general population. The study commenced on May 7th and was completed on May 16th, 2020. Thus, data were collected at times of active lockdown measures to lower transmission rates. More specifically, during this time period, region-specific measures were enacted to prevent the spread of SARS-CoV-2, including the closure of schools, kindergartens, playgrounds, zoos, churches, sports clubs, services that require close physical contact (e.g. hairdressers), and non-essential shops. In addition, it was forbidden to leave the house without a good reason, and it was only allowed to have contact with one other person not living in the same household. Furthermore, keeping a physical distance of 1.5m and wearing face masks in public places as well as in public transportation was obligatory. Also, in order to reduce the effects of these measures on the population and the economy, many companies received state aid to be able to pay for running costs (e.g. personnel costs, rent).

For data collection, we used the Norstatpanel by Norstat Deutschland GmbH [39], which consists of a group of registered internet users who have agreed to take part in surveys and opinion polls and is certified according to ISO 26362 and ISO 9001 standards. To ensure the high quality of the panel, various quality assurance measures have been implemented and are frequently evaluated, such as, random selection, representativeness, diversified sources, and active recruitment of panellists as well as the absence of a public registration page, profile validation, plausibility testing, and cheater detection. The online panel operates in accordance with the applicable data protection laws (i.e., EU General Data Protection Regulation (GDPR); Federal Data Protection Act (BDSG)). Prior to assessments, informed consent was obtained from participants by Norstat in this general population sample. Participants were registered members of the Norstatpanel and selected at random. Selected individuals were invited by email to participate in the online survey. To ensure representativeness of the sample, individuals were stratified by gender, education, and population density data published by the Federal Statistical Office of Germany. Participation was incentivised through payments (i.e., around 0·10€ per minute) and other benefits (e.g. discounts). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research cofmmittee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Medical Ethics Review Committee II of Heidelberg University (Medical Faculty Mannheim; Ref. No. 529-20).

Measures

Social isolation/lack of company

Social isolation and lack of company were assessed using two items of Three-Item Loneliness Scale which has been developed based on the 20-item Revised UCLA Loneliness Scale [40] and has been specifically developed to assess loneliness in large-scale surveys [41]. However, as we were interested in measuring social isolation and lack of company, we excluded one item assessing the feeling of being left out. Subjective experiences of social isolation (‘*How often do you feel socially isolated?*’) and lack of company (‘*How often do you feel that you lack the company of others?*’) were both rated on a 6-point Likert scale ranging from 1 to 6 (1=‘never’, 3=‘rarely’, 6=‘very often’). A high internal consistency has been demonstrated for different versions of the UCLA Loneliness Scale, including the Three-Item Loneliness Scale [41, 42].

COVID-19-related cognitive preoccupation, worries, and anxiety

COVID-19-related cognitive preoccupation, worries, and anxiety were assessed using modified items from the COVID-19 Snapshot MOnitoring (COSMO) [30] survey in Germany. First, worries were assessed using 10 items introduced by the following sentence: *‘On a scale from 1 (no worries at all) to 7 (a lot of worries), how* *often did you worry last week that...'* which was followed by differing types of worries (e.g. about financial difficulties). For current analyses, we computed the overall mean score (Cronbach's alpha, α = 0.80). We also dichotomized the continuous score using median split of the continuous variable: <50. percentile was coded as 0 and ≥ 50. percentile coded as 1). Second, preoccupation and anxiety with the COVID-19 pandemic were assessed using three separate items rated on a 5-point scale *('The novel coronavirus is something I...'*, with ratings ranging from 1 *'...never think of'* to 5 *'...keep thinking about'*; *'The novel coronavirus is...',* with ratings ranging from 1 *'...not scary at all'* to 5 *'....scary'*; '*The novel coronavirus is...'*, with ratings ranging from 1 *'...not worrying'* to 5 *'...worrying')*.

Objective social risk indicators

Data on objective indicators of individuals' social circumstances and migrant/ethnic minority group position were assessed using a modified version of the Medical Research Council (MRC) Sociodemographic Schedule [43]. In total, six domains of social risk were included in the current study: (1) employment, (2) education, (3) relationship status, (4) living arrangements, (5) parental educational level as a proxy for lower socioeconomic status, (6) migrant or ethnic minority group position. To investigate the impact of social risk, we built on the work by Morgan et al.[44], and created an index by dichotomizing variables from each of the six domains to define the presence or absence of well-established indicators of social risk (i.e., [1] unemployment, unable to work, early retirement=1, other=0; [2] lower educational level [i.e., secondary school, no school-leaving qualification]=1, other=0; [3] being single=1, other=0; [4] living alone or alone with children=1, other=0; [5] lower parental educational level as a proxy for lower socioeconomic status [i.e., secondary school, no school-leaving qualification of both parents]=1, other=0; [6] foreign born or second generation migrant=1, other=0). This generated an index ranging from 0 to 6.

Current use of, and attitudes towards, mHealth apps

After providing a definition of mHealth apps participants were asked whether they are already using mHealth apps by asking the following question *'Do you already use mHealth apps (e.g. to relax or increase physical activity)?'*. This item was rated on a 6-point Likert scale and dichotomized (a rating of 1='never' coded as 0, and ratings of 2 ='very rarely', 4='occasionally' to 6='very often' were coded as 1). This item was followed by an item assessing the positive, negative, or neutral attitude towards the use of mHealth apps to help cope with the COVID-19 pandemic *('Do you think that an mHealth app could help you deal better with the corona situation?').* This item was rated on a 5-point Likert scale and dichotomized (with ratings of 1='strongly disagree' to 3='neither/nor' coded as 0, and ratings of 4='agree' to 5='strongly agree' coded as 1).

Psychological distress

The Kessler-10 (K10) [45], a well-established screening instrument for mental disorder in the general population, was used to assess psychological distress. The questionnaire was modified to assess psychological distress during the COVID-19 pandemic. That is, instead of asking about psychological distress experienced in the past 30 days, psychological distress experienced since the beginning of the pandemic was assessed ('*How often did you feel since the coronavirus outbreak…'* followed e.g. by *'…tired out for no good reason?'*). The 10 items were rated on a 5-point scale (1='none of the time', 3='some of the time', 5='all of the time'), yielding a minimum score of 10 and a maximum score of 50 (Cronbach's alpha, α = 0.93). For analyses including psychological distress as dependent variable, we dichotomized continuous distress scores based on an established cut-off score (absence of psychological distress: scores from 10-19 were coded as 0; presence of mild, moderate or severe psychological distress: scores from 20-50 were coded as 1). Good psychometric properties have been reported for this measure [46]. For analyses in which psychological distress was used as independent variable we used a categorical variable with four levels: 1) likely to be well (range score: 10 to 19), 2) mild mental disorder (range score: 20-24), 3) moderate mental disorder (range score: 25-29), 4) severe mental disorder (range score: 30-50), again, based on established and validated cut-off scores [45, 47].

Analysis

Descriptive statistics were used to report on basic sample characteristics. Logistic regression was used to, first, quantify the association of (1) social isolation/lack of company, (2) COVID-19-related cognitive preoccupation, worrying, and anxiety, and (3) objective indicators of social risk (separate as well as combined in form of a social risk index) as independent variables with psychological distress as outcome variable (hypotheses 1). This approach allows for examining dose-response relationships (hypotheses 2). Second, we investigated whether (1) psychological distress, (2) social isolation/lack of company, (3) COVID-19-related preoccupation, worries, and anxiety, and (4) the objective indicators of social risk as well as the social risk index are associated with the current use of, and attitude towards, mHealth apps (hypotheses 3). In all analyses, we adjusted for potential confounders (i.e., age, gender, educational level, migrant/ethnic minority group position, employment status), except in models that included social risk indicators as independent variable. Here, we adjusted for age and gender. We adjusted significance levels for Type-1 error proliferation using family-wise error-corrected p-values (*p*FWE) by multiplying the unadjusted p-value by the total number of independent variables (N=7 for models with psychological distress as dependent variable; N=8 for models with the use of, or attitude towards, mHealth apps as dependent variable). All analyses were performed using STATA version 15.1.

Results

Sample characteristics

In total, 1006 individuals were invited by email to participate. Of these, 685 youths completed the online survey and 19 individuals had to be excluded after completion of quality control checks (e.g. implausible response time and pattern of responses). Thus, 666 individuals were included in current analyses. There were no differences in variables between individuals with and without sufficient data quality (data not shown, available upon request). The sample characteristics are presented in Table 1, including frequencies of all assessed variables.

Social isolation and COVID-19-related preoccupation, worries, and anxiety by psychological distress

Individuals who reported subjective experiences of social isolation, lack of company, and COVID-19-related worries and anxiety were more likely to experience psychological distress during the COVID-19 pandemic. As shown in Table 2, there was evidence for dose-response relationships in that psychological distress was progressively more likely to occur as levels of reported social isolation, lack of company, and COVID-19-related worries and anxiety increased. For example, those

Table 1. Sample characteristics, psychological distress, and risk (*N*=666)

Age, mean (S.D.; range)	21·3 (2·6; 16-25)
Gender, n (%)	
Female	318 (47·8)
Male	346 (52·0)
Divers	2 (0·3)
Educational level, n (%)[a]	
Low	135 (20·3)
Middle	358 (53·7)
High	173 (26·0)
Migrant/ethnic minority group position, n (%)	
1st generation migrant	53 (7·9)
2nd generation migrant	156 (23·4)
Psychological distress [b], n (%)	
Likely to be well	287 (43·1)
Likely to have a mild disorder	130 (19·5)
Likely to have a moderate disorder	104 (15·6)
Likely to have a severe disorder	145 (21·8)
Psychological distress, mean (S.D.; range)	22·0 (8·6; 10-50)
Social isolation, n (%)	
Never	61 (9·2)
Very rarely	65 (9·8)
Rarely	135 (20·3)
Occasionally	212 (31·8)
Often	136 (20·4)
Very often	57 (8·6)
Lack of company, n (%)	
Never	34 (5·1)
Very rarely	43 (6·5)
Rarely	81 (12·2)
Occasionally	245 (36·8)
Often	178 (26·7)
Very often	85 (12·3)
COVID-19-related worries [c], n (%)	
<50th percentile	350 (52·6)
≥50th percentile	316 (47·4)
Mean (S.D.; range)	3·6 (1·2; 1-7)
Cognitive preoccupation with COVID-19 Item: *'The novel coronavirus is something I…',* n (%)	
… never think of	20 (3·0)
… don't think about very often	115 (17·3)
… think in part	245 (36·8)
… think about a lot	245 (36·8)
… keep thinking about	41 (6·2)

Table 1. (continued). Sample characteristics, psychological distress, and risk (*N*=666)

COVID-19-related anxiety Item: *'The novel coronavirus is…'*, n (%)	
… not scary at all	105 (15·8)
… rather not scary	187 (28·1)
… partly scary	219 (32·9)
… rather scary	133 (20·0)
… scary	22 (3·3)
COVID-19-related worrying Item*: 'The novel coronavirus is…'*, n (%)	
… not worrying	70 (10·5)
… rather not worrying	142 (21·3)
… partly worrying	207 (31·1)
… rather worrying	207 (31·1)
… worrying	40 (6·0)
Social risk index [d]	
0	160 (24·0)
1	270 (40·5)
2	174 (26·1)
3+	62 (9·3)
Current use of mHealth apps [e]	
Yes	473 (71·0)
No	193 (29·0)
Attitude towards the use of mHealth apps during the COVID-19 pandemic [f]	
Positive	170 (25·5)
Neutral/Negative	496 (74·5)

Notes: S.D., standard deviation.
[a] Educational levels were defined as follows: 'low' (i.e. lower secondary school certificate, secondary school certificate, no school-leaving qualification, or visiting respective school types), 'middle' (i.e. high-school diploma, completed vocational training, or visiting respective school type/doing an apprenticeship), 'high' (i.e. bachelor's, master's degree, or currently studying).
[b] The following K10 cut-offs were used to categories severity levels of psychological distress: 'none' (range score: 10 to 19); 'mild' (range score: 20-24); 'moderate' (range score: 25-29); 'severe' (range score: 30-50).
[c] Based on 10 items asking for potential worries related to the COVID-19 pandemic (e.g., health system overloaded, financial difficulties, completion of education/school) during the last week rated on a 7-point Likert scale (1='no worries at all'; 7='a lot of worries'). Items were dichotomized (i.e. median split of the continues variable: <50. percentile was coded as 0 and ≥50. percentile coded as 1).
[d] Defined as the number of objective indicators of social risk (i.e. unemployment/unable to work/early retirement; low education of both parents as a proxy for low socio-economic status; foreign born/second generation migration; living alone/alone with kids; being single; range social risk index: 0-6).
[e] Based on the following item 'Do you already use mHealth apps (e.g. to relax or increase physical activity)?' binary outcome variable: answering 'never' were coded as 0, whereas answering 'very rarely', 'rarely', 'occasionally', 'often', or 'very often' were coded as 1.
[f] Based on the following item 'Do you think that an mHealth app could help you deal better with the corona situation?'. This item was rated on a 5-point Likert scale and dichotomized (with ratings of 1='strongly disagree' to 3='neither/nor' coded as 0, and ratings of 4='agree' to 5='strongly agree' coded as 1).

Table 2. Social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index by psychological distress during COVID-19 pandemic (*N*=666)

Exposure	Outcome: Presence of mental distress during COVID-19 pandemic a									
	Total n (%)	Presence, n (%)	Absence, n (%)	Model 1 b		Model 2 c		Model 3 d		
				OR (95% CI)	p	OR (95% CI)	p	Adj. OR (95% CI)	p	pFWE
Social isolation										
Never	61 (9·2)	10 (16·4)	51 (83·6)	1		1		1		
Very rarely	65 (9·8)	21 (32·3)	44 (67·7)	2·4 (1·0 – 5·7)	0·041	2·5 (1.0 – 5·8)	0·039	2·6 (1·1 – 6·2)	0·029	0·205
Rarely	135 (20·3)	56 (41·5)	79 (58·5)	3·6 (1·7 – 7·7)	<0·001	3·6 (1·7 – 7·8)	<0·001	3·7 (1·7 – 8·1)	<0·001	0·006
Occasionally	212 (31·8)	132 (62·3)	80 (37·7)	8·4 (4·0 – 17·5)	<0·001	8·4 (4·0 – 17·5)	<0·001	9·1 (4·3 – 19·1)	<0·001	<0·001
Often	136 (20·4)	109 (80·2)	27 (19·8)	20·6 (9·3 – 45·7)	<0·001	21·0 (9·4 – 46·8)	<0·001	22·2 (9·8 – 50·2)	<0·001	<0·001
Very often	57 (8·6)	51 (89·5)	6 (10·5)	43·4 (14·7 – 128·2)	<0·001	43·8 (14·7 – 130·2)	<0·001	42·3 (14·1 – 126·8)	<0·001	<0·001
Lack of company										
Never	34 (5·1)	4 (11·8)	30 (88·2)	1		1		1		
Very rarely	43 (6·5)	20 (46·5)	23 (53·5)	6·5 (2·0 – 21·7)	0·002	6·5 (2·0 – 21·7)	0·002	7·7 (2·2 – 26·7)	0·001	0·009
Rarely	81 (12·2)	37 (45·7)	44 (54·3)	6·3 (2·0 – 19·5)	0·001	6·3 (2·0 – 19·5)	0·001	7·7 (2·4 – 24·8)	<0·001	0·004
Occasionally	245 (36·8)	125 (51·0)	120 (49·0)	7·8 (2·7 – 22·8)	<0·001	7·7 (2·6 – 22·6)	<0·001	9·3 (3·1 – 28·5)	<0·001	<0·001
Often	178 (26·7)	124 (69·7)	54 (30·3)	17·2 (5·8 – 51·3)	<0·001	16·9 (5·7 – 50·4)	<0·001	21·0 (6·7 – 65·3)	<0·001	<0·001
Very often	85 (12·3)	69 (81·2)	16 (18·8)	32·3 (10·0 – 104·9)	<0·001	31·7 (9·7–103·4)	<0·001	38·0(11·2–128·3)	<0·001	<0·001
Cognitive preoccupation with COVID-19										
The novel coronavirus is something I…										
… never think of	20 (3·0)	5 (25·0)	15 (75·0)	1		1		1		
… don't think about very often	115 (17·3)	46 (40·0)	69 (60·0)	2·0 (0·7 – 5·9)	0·208	1·9 (0·7 – 5·7)	0·229	2·4 (0·8 – 7·5)	0·134	0·935
… think in part	245 (36·8)	144 (58·8)	101 (41·2)	4·3 (1·5 – 12·1)	0·006	4·1 (1·4 – 11·7)	0·008	5·2 (1·7 – 15·9)	0·004	0·025
… think about a lot	245 (36·8)	157 (64·1)	88 (35·9)	5·4 (1·9 – 15·2)	0·002	5·1 (1·8 – 14·5)	0·003	6·6 (2·2 – 20·1)	0·001	0·007
… keep thinking about	41 (6·2)	27 (65·9)	14 (34·1)	5·8 (1·7 – 19·2)	0·004	5·4 (1·6 – 18·0)	0·006	7·1 (2·0 – 25·2)	0·003	0·018
COVID-19-related anxiety										

Table 2. (continued). Social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index by psychological distress during COVID-19 pandemic (*N*=666)

Exposure	Outcome: Presence of mental distress during COVID-19 pandemic a									
	Total n (%)	Presence, n (%)	Absence, n (%)	Model 1 b		Model 2 c		Model 3 d		
				OR (95% CI)	p	OR (95% CI)	p	Adj. OR (95% CI)	p	pFWE
The novel coronavirus is…										
… not scary at all	105 (15·8)	31 (29·5)	74 (70·5)	1		1		1		
… rather not scary	187 (28·1)	92 (49·2)	95 (50·8)	2·3 (1·4 – 3·8)	0·001	2·3 (1·4 – 3·8)	0·001	2·5 (1·5 – 4·1)	<0·001	0·006
… partly scary	219 (32·9)	140 (63·9)	79 (36·1)	4·2 (2·6 – 7·0)	<0·001	4·1 (2·5 – 6·9)	<0·001	4·3 (2·5 – 7·2)	<0·001	<0·001
… rather scary	133 (20·0)	97 (72·9)	36 (27·1)	6·4 (3·6 – 11·3)	<0·001	6·3 (3·6 – 11·2)	<0·001	6·6 (3·7 – 11·9)	<0·001	<0·001
… scary	22 (3·3)	19 (86·4)	3 (13·6)	15·1 (4·2 – 54·8)	<0·001	14·7 (4·0 – 53·5)	<0·001	13·8 (3·8 – 50·6)	<0·001	<0·001
COVID-19-related worrying										
The novel coronavirus is…										
… not worrying	70 (10·5)	26 (37·1)	44 (62·9)	1		1		1		
… rather not worrying	142 (21·3)	62 (43·7)	80 (56·3)	1·3 (0·7 – 2·4)	0·366	1·3 (0·7 – 2·3)	0·394	1·3 (0·7 – 2·4)	0·372	1·0
… partly worrying	207 (31·1)	126 (60·9)	81 (39·1)	2·6 (1·5 – 4·6)	0·001	2·6 (1·5 – 4·5)	0·001	2·5 (1·4 – 4·5)	0·001	0·010
… rather worrying	207 (31·1)	134 (64·7)	73 (35·3)	3·1 (1·8 – 5·5)	<0·001	3·0 (1·7 – 5·3)	<0·001	3·1 (1·7 – 5·6)	<0·001	<0·001
… worrying	40 (6·0)	31 (77·5)	9 (22·5)	5·8 (2·4 – 14·1)	<0·001	5·5 (2·2 – 13·5)	<0·001	5·6 (2·3 – 13·8)	<0·001	0·001
COVID-19-related worries [e]										
<50th percentile	350 (52·6)	140 (36.9)	210 (73.2)	1		1		1		
≥ 50th percentile	316 (47·4)	239 (63.1)	77 (26.8)	4·7 (3·3 – 6·5)	<0·001	4·6 (3·3 – 6·4)	<0·001	4·5 (3·2 – 6·3)	<0·001	<0·001
	Mean (S.D.)									
Continuous variable	3·6 (1·2)	NA	NA	2·3 (1·9 – 2·7)	<0·001	2·3 (1·9 – 2·7)	<0·001	2·2 (1·9 – 2·7)	<0·001	<0·001

Notes: df, degrees of freedom; CI, confidence interval; OR, odds ratio; S.D., standard deviation; *p*FWE, family-wise error-corrected p-values were computed by multiplying the unadjusted p-value by the total number of independent variables (*N*=7) to adjust significance levels; NA, not applicable.
[a] K10 cut-off of >19 has been used to index presence vs. absence of any mild, moderate or severe psychological distress as the outcome variable.
[b] Unadjusted model.
[c] Model adjusted for age and gender.
[d] Model adjusted for age and gender and social risk indicators (i.e. education, migrant/ethnic minority group position, employment status).
[e] Based on 10 items asking for potential worries related to the COVID-19 pandemic (e.g., health system overloaded, financial difficulties, completion of education/school) during the last week rated on a 7-point Likert scale (1='no worries at all'; 7='a lot of worries'). Items were dichotomized (i.e. median split of the continues variable: <50th percentile was coded as 0 and ≥ 50th percentile coded as 1)

who reported to be 'rarely', 'occasionally', 'often', and 'very often' socially isolated were around four, nine, 22 and 42 times, respectively, more likely to experience psychological distress (adjusted odds ratio [aOR] 3·7, 95% confidence interval [CI] 1·7 - 8·1, p=0·006; aOR 9·1, CI 4·3 - 19·1, p<0·001; aOR 22·2, CI 9·8 – 50·2, p<0·001; aOR 42·3, CI 14·1 – 126·8, p<0·001; respectively) as compared to those who reported to be 'never' socially isolated (see Figure 1).

Social risk indicators by psychological distress

We next investigated whether objective indicators of social risk were associated with psychological distress in young individuals during the COVID-19 pandemic. First, we investigated associations of all individual indicators of social risk and migrant/ethnic minority group position with psychological distress. We found that individuals from migrant and ethnic minority groups were more likely to experience psychological distress compared to those from the ethnic majority group (aOR 1·7, CI 1·2 – 2·4, p=0·041). However, after adjustment for multiple testing, there was no evidence that unemployment, being single, lower educational level, parental educational level, or living arrangements were associated with psychological distress (see Table 3). In testing associations between the social risk index and psychological distress we found that, compared to individuals in whom objective social risk indicators were absent, individuals with two objective indicators were at an increased risk to experience psychological distress during the COVID-19 pandemic (presence of two indicators: aOR 1·9, CI 1·2 - 3·0, p=0·034). By contrast, there was no strong evidence that, after adjustment for multiple testing, those exposed to only one social risk indicator or three or more indicators were at an increased risk for psychological distress (aOR 1·3, CI 0·9 – 1·9, p=1.0; aOR 2·1, CI 1·1 – 3·9, p=0·113, respectively). There was also no evidence of a dose-response relationship.

Psychological distress, COVID-19-related preoccupation, worries, anxiety, and social isolation by current mHealth app use

There was some evidence that psychological distress, perceived social isolation and lack of company as well as COVID-19-related cognitive preoccupation, worries, and anxiety were associated with current use of mHealth apps (Table 4).

Table 3. Objective social risk indicators by psychological distress during COVID-19 pandemic (*N*=666)

Exposure	Total n (%)	Presence, n (%)	Absence, n (%)	Outcome: Mental distress during COVID-19 pandemic [a]						
				Model 1 [b]		Model 2 [c]		Model 3 [d]		
				OR (95% CI)	*p*	Adj. OR (95% CI)	*p*	Adj. OR (95% CI)	*p*	*p*FWE
Employment status										
Absence	634 (95·2)	355 (56·0)	279 (44·0)	1		1		1		
Presence	32 (4·8)	23 (75·0)	8 (25·0)	2·4 (1·0 – 5·3)	0·039	2·5 (1·1 – 5·7)	0·029	2·5 (1·1 – 5·9)	0·032	0·227
Education [f]										
Absence	634 (95·2)	359 (56·6)	275 (43·4)	1		1		1		
Presence	32 (4·8)	20 (62·5)	12 (37·5)	1·3 (0·6 – 2·7)	0·513	1·3 (0·6 – 2·8)	0·449	1·1 (0·5 – 2·4)	0·801	1·0
Migrant/ethnic minority group position [g]										
Absence	505 (75·8)	272 (53·9)	233 (46·1)	1		1		1		
Presence	161 (24·2)	107 (66·5)	54 (33·5)	1·7 (1·2 – 2·5)	0·005	1·7 (1·2 – 2·5)	0·005	1·7 (1·2 – 2·4)	0·006	0·041
Socioeconomic status [h]										
Absence	573 (86·0)	328 (57·2)	245 (42·8)	1		1		1		
Presence	93 (14·0)	51 (54·8)	42 (45·2)	0·9 (0·6 – 1·4)	0·664	0·9 (0·6 – 1·4)	0·704	0·8 (0·5 – 1·3)	0·327	1·0
Living arrangements [i]										
Absence	542 (81·4)	307 (56·6)	235 (43·4)	1		1		1		
Presence	124 (18·6)	72 (58·1)	52 (41·9)	1·1 (0·7 – 1·6)	0·773	1·1 (0·7 – 1·6)	0·658	1·1 (0·7 – 1·7)	0·644	1·0
Relationship status [j]										
Absence	288 (43·2)	151 (52·4)	137 (47·6)	1		1		1		
Presence	378 (56·8)	228 (60·3)	150 (39·7)	1·4 (1·0 – 1·9)	0·042	1·5 (1·1 – 2·1)	0·017	1·5 (1·1 – 2·0)	0·024	0·169

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Table 3. (continued). Objective social risk indicators by psychological distress during COVID-19 pandemic (*N*=666)

Exposure	Total n (%)	Presence, n (%)	Absence, n (%)	Outcome: Mental distress during COVID-19 pandemic [a] Model 1 [b] OR (95% CI)	*p*	Model 2 [c] Adj. OR (95% CI)	*p*	Model 3 [d] Adj. OR (95% CI)	*p*	*p*FWE
Social risk index [k]										
0	160 (24·0)	79 (49·4)	81 (50·6)	1		1		NA		
1	270 (40·5)	149 (55·2)	121 (44·8)	1·3 (0·9 – 1·9)	0·244	1·3 (0·9 – 1·9)	0·223	NA		1·0
2	174 (26·1)	110 (63·2)	64 (36·8)	1·8 (1·1 – 2·7)	0·011	1·9 (1·2 – 3·0)	0·005	NA		0·034
3+	62 (9·3)	41 (66·1)	21 (33·9)	2·0 (1·1 – 3·7)	0·026	2·1 (1·1 – 3·9)	0·016	NA		0·113

Notes: df, degrees of freedom; CI, confidence interval; OR, odds ratio; *p*FWE, family-wise error-corrected p-values were computed by multiplying the unadjusted p-value by the total number of independent variables (*N*=7) to adjust significance levels; NA, not applicable.

[a] K10 cut-off of >19 has been used to index presence vs. absence of any mild, moderate or severe psychological distress as the outcome variable.

[b] Unadjusted model.

[c] Model adjusted for age and gender.

[d] Model adjusted for age and gender and social risk indicators (i.e. education, migrant/ethnic minority group position, employment status, depending on depending variable).

[e] Binary variable: defined as unemployment, unable to work, early retirement (coded as 1) *vs.* other (coded as 0).

[f] Binary variable: defined as low education level, that is, secondary school qualification as well as no school-leaving qualification (coded as 1) *vs.* other (coded as 0).

[g] Binary variable: defined as being foreign born or second-generation migrant (coded as 1) *vs.* other (coded as 0).

[h] Binary variable: defined as low educational level (i.e. secondary school qualification, no school-leaving qualification) of both parents as a proxy for low socioeconomic status (coded as1) *vs.* other (coded as 0).

[i] Binary variable: defined as living alone or alone with children (coded as 1) *vs.* other (coded as 0).

[j] Binary variable: defined as being single (coded as 1) *vs.* other (coded as 0).

[k] Defined as the number of objective indicators of social risk (i.e. unemployment/unable to work/early retirement; low education of both parents as a proxy for low socio-economic status; foreign born/second generation migration; living alone/alone with kids; being single; range social risk index: 0-6).

Table 4. Current use of mHealth apps by psychological distress, social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index (*N*=666)

Exposure	Total, n (%)	Yes, n (%)	No, n (%)	Outcome: Current use of mHealth apps [a] Model 1 [b] OR (95% CI)	*p*	Model 2 [c] Adj. OR (95% CI)	*p*	Model 3 [d] Adj. OR (95% CI)	*p*	*p*FWE
Psychological distress [e]										
None	287 (43·1)	183 (63·8)	104 (36·2)	1		1		1		
Mild	130 (19·5)	101 (77·7)	29 (22·3)	2·0 (1·2 – 3·2)	0·005	2·0 (1·2 – 3·2)	0·006	1·9 (1·2 – 3·2)	0·008	0·061
Moderate	104 (15·6)	75 (72·1)	29 (29·9)	1·5 (0·9 – 2·4)	0·125	1·4 (0·8 – 2·2)	0·221	1·4 (0·9 – 2·4)	0·166	1·0
Severe	145 (21·8)	114 (78·6)	31 (21·4)	2·1 (1·3 – 3·3)	0·002	2·1 (1·3 – 3·3)	0·002	2·3 (1·4 – 3·6)	<0·001	0·007
COVID-19-related worries [f]										
<50th percentile	350 (52·6)	235 (67.1)	115 (32.9)	1		1		1		
≥50th percentile	316 (47·4)	238 (75.3)	78 (24.7)	1·5 (1·1 – 2·1)	0·021	1·5 (1·0 – 2·1)	0·026	1·5 (1·1 – 2·2)	0·014	0·114
	Mean (S.D.)									
Continuous variable	3·6 (1·2)	NA	NA	1·3 (1·1 – 1·5)	0·001	1·3 (1·1 – 1·5)	0·002	1·3 (1·1 – 1·5)	0·001	0·010
	Total, n (%)									
Social isolation										
Never	61 (9·2)	33 (54·1)	28 (45·9)	1		1		1		
Very rarely	65 (9·8)	43 (66·2)	22 (33·8)	1·7 (0·8 – 3·4)	0·168	1·7 (0·8 – 3·6)	0·142	1·6 (0·8 – 3·3)	0·211	1·0
Rarely	135 (20·3)	94 (69·6)	41 (30·4)	1·9 (1·0 – 3·6)	0·036	2·0 (1·1 – 3·8)	0·031	1·8 (1·0 – 3·5)	0·065	0·518
Occasionally	212 (31·8)	162 (76·4)	50 (23·6)	2·7 (1·5 – 5·0)	0·001	2·7 (1·5 – 4·9)	0·001	2·7 (1·4 – 4·9)	0·002	0·014
Often	136 (20·4)	106 (77·9)	30 (22·1)	3·0 (1·6 – 5·7)	0·001	3·0 (1·6 – 5·8)	<0·001	2·9 (1·5 – 5·5)	0·002	0·016
Very often	57 (8·6)	35 (61·4)	22 (38·6)	1·3 (0·6 – 2·8)	0·423	1·3 (0·6 – 2·7)	0·517	1·2 (0·6 – 2·6)	0·614	1·0
Lack of company										
Never	34 (5·1)	13 (38·2)	21 (61·8)	1		1		1		
Very rarely	43 (6·5)	31 (72·1)	12 (27·9)	4·2 (1·6 – 10·9)	0·004	4·3 (1·6 – 11·2)	0·003	3·7 (1·4 – 10·0)	0·009	0·070
Rarely	81 (12·2)	56 (69·1)	25 (30·9)	3·6 (1·6 – 8·4)	0·003	3·7 (1·6 – 8·6)	0·002	3·3 (1·4 – 7·7)	0·007	0·057
Occasionally	245 (36·8)	182 (74·3)	63 (25·7)	4·7 (2·2 – 9·9)	<0·001	4·6 (2·1· – 9·7)	<0·001	4·2 (2·0 – 9·1)	<0·001	0·002
Often	178 (26·7)	133 (74·7)	45 (25·3)	4·8 (2·2 – 10·3)	<0·001	4·5 (2·1 – 9·8)	<0·001	4·1 (1·8 – 9·0)	<0·001	0·004

Table 4. (continued). Current use of mHealth apps by psychological distress, social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index (*N*=666)

				Outcome: Current use of mHealth apps [a]						
Exposure	**Total, n (%)**	**Yes, n (%)**	**No, n (%)**	**Model 1 [b]**		**Model 2 [c]**		**Model 3 [d]**		
				OR (95% CI)	***p***	**Adj. OR (95% CI)**	***p***	**Adj. OR (95% CI)**	***p***	***p*FWE**
Very often	85 (12·3)	58 (68·2)	27 (31·8)	3·5 (1·5 – 7·9)	0·003	3·3 (1·4 – 7·7)	0·006	3·0 (1·3 – 7·2)	0·010	0·086
Cognitive preoccupation with COVID-19 The novel coronavirus is something I...										
... never think of	20 (3·0)	7 (35·0)	13 (65·0)	1		1		1		
... don't think about very often	115 (17·3)	71 (61·7)	44 (38·3)	3·0 (1·1 – 8·1)	0·030	2·9 (1·1 – 7·9)	0·037	2·4 (0·8 – 6·8)	0·103	0·820
... think in part	245 (36·8)	180 (73·5)	65 (26·5)	5·1 (2·0 – 13·5)	0·001	4·9 (1·9 – 13·0)	0·001	4·2 (1·5 – 11·5)	0·005	0·042
... think about a lot	245 (36·8)	188 (76·7)	57 (23·3)	6·1 (2·3 – 16·1)	<0·001	5·7 (2·2 – 15·2)	<0·001	4·9 (1·8 – 13·5)	0·002	0·018
... keep thinking about	41 (6·2)	27 (65·9)	14 (34·2)	3·6 (1·2 – 11·0)	0·026	3·2 (1·0 – 10·0)	0·045	2·6 (0·8 – 8·6)	0·105	0·840
COVID-19-related anxiety The novel coronavirus is...										
... not scary at all	105 (15·8)	59 (56·2)	46 (43·8)	1		1		1		
... rather not scary	187 (28·1)	129 (69·0)	58 (31·0)	1·7 (1·1 – 2·8)	0·029	1·7 (1·0 – 2·8)	0·035	1·6 (0·9 – 2·6)	0·075	0·600
... partly scary	219 (32·9)	165 (75·3)	54 (24·7)	2·4 (1·5 – 3·9)	0·001	2·3 (1·4 – 3·7)	0·001	2·1 (1·3 – 3·6)	0·003	0·026
... rather scary	133 (20·0)	105 (79·0)	28 (21·0)	2·9 (1·7 – 5·2)	<0·001	2·7 (1·5 – 4·9)	<0·001	2·6 (1·5 – 4·7)	0·001	0·009
... scary	22 (3·3)	15 (68·2)	7 (31·8)	1·7 (0·6 – 4·4)	0·303	1·5 (0·6 – 4·1)	0·410	1·5 (0·6 – 4·2)	0·400	1·0

Table 4. (continued). Current use of mHealth apps by psychological distress, social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index (N=666)

Exposure	Total, n (%)	Yes, n (%)	No, n (%)	Outcome: Current use of mHealth apps [a] Model 1 [b] OR (95% CI)	p	Model 2 [c] Adj. OR (95% CI)	p	Model 3 [d] Adj. OR (95% CI)	p	pFWE
The novel coronavirus is…										
… not worrying	70 (10·5)	38 (54·3)	32 (45·7)	1		1		1		
… rather not worrying	142 (21·3)	94 (66·2)	48 (33·8)	1·6 (0·9 – 3·0)	0·094	1·6 (0·9 – 2·8)	0·133	1·5 (0·8 – 2·7)	0·198	1·0
… partly worrying	207 (31·1)	150 (72·5)	57 (27·5)	2·2 (1·3 – 3·9)	0·005	2·1 (1·2 – 3·7)	0·010	2·0 (1·1 – 3·6)	0·017	0·138
… rather worrying	207 (31·1)	165 (79·7)	42 (20·3)	3·3 (1·9 – 5·9)	<0·001	3·2 (1·8 – 5·7)	<0·001	3·0 (1·6 – 5·4)	<0·001	0·003
… worrying	40 (6·0)	26 (65·0)	14 (35·0)	1·6 (0·7 – 3·5)	0·275	1·3 (0·6 – 3·0)	0·500	1·3 (0·6 – 3·0)	0·509	1·0
Social risk index [g]										
0	160 (24·0)	123 (76·9)	37 (23·1)	1		1		NA		
1	270 (40·5)	194 (71·9)	76 (28·1)	0·8 (0·5 – 1·2)	0·253	0·8 (0·5 – 1·3)	0·422	NA	0·423	1·0
2	174 (26·1)	117 (67·2)	57 (32·8)	0·6 (0·4 – 1·0)	0·051	0·7 (0·4 – 1·1)	0·138	NA	0·138	1·0
3+	62 (9·3)	39 (62·9)	23 (37·1)	0·5 (0·3 – 1·0)	0·037	0·5 (0·3 – 1·0)	0·055	NA	0·080	0·437

Notes: df, degrees of freedom; CI, confidence interval; OR, odds ratio; S.D., standard deviation; *p*FWE, family-wise error-corrected p-values were computed by multiplying the unadjusted p-value by the total number of independent variables (N=8) to adjust significance levels; NA, not applicable.
[a] Based on the following item "Do you already use mHealth apps (e.g. to relax or increase physical activity)?" binary outcome variable: answering 'never' were coded as 0, whereas answering 'very rarely', 'rarely', 'occasionally', 'often', or 'very often' were coded as 1.
[b] Unadjusted model.
[c] Model adjusted for age and gender.
[d] Model adjusted for age and gender and objective indicators of social risk (e.g. low education, migrant/ethnic minority group position, unemployment).
[e] The following K10 cut-offs were used to categories severity levels of psychological distress: 'none' (range score: 10 to 19); 'mild' (range score: 20-24); 'moderate' (range score: 25-29); 'severe' (range score: 30-50).
[f] Based on 10 items asking for potential worries related to the COVID-19 pandemic (e.g., health system overloaded, financial difficulties, completion of education/school) during the last week rated on a 7-point Likert scale (1='no worries at all'; 7='a lot of worries'). Items were dichotomized (i.e. median split of the continues variable: <50. percentile was coded as 0 and ≥50. percentile coded as 1).
[g] Defined as the number of objective indicators of social risk (i.e. unemployment/unable to work/early retirement; low education of both parents as a proxy for low socio-economic status; foreign born/second generation migration; living alone/alone with kids; being single; range social risk index: 0-6).

Table 5. Attitude towards mHealth apps by psychological distress, social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index (N=666)

Exposure	Total, n (%)	Positive, n (%)	Neutral/ Negative, n (%)	Outcome: Attitude towards the use of mHealth apps [a] Model 1 [b] OR (95% CI)	p	Model 2 [c] Adj. OR (95% CI)	p	Model 3 [d] Adj. OR (95% CI)	p	pFWE
Psychological distress [e]										
None	287 (43·1)	45 (15·7)	242 (84·3)	1		1		1		
Mild	130 (19·5)	39 (30·0)	91 (70·0)	2·3 (1·4 – 3·8)	0·001	2·3 (1·4 – 3·8)	<0·001	2·2 (1·3 – 3·6)	0·002	0·013
Moderate	104 (15·6)	39 (37·5)	65 (62·5)	3·2 (1·9 – 5·4)	<0·001	3·2 (1·9 – 5·4)	<0·001	3·2 (1·9 – 5·4)	<0·001	<0·001
Severe	145 (21·8)	47 (32·4)	98 (67·6)	2·6 (1·6 – 4·1)	<0·001	2·6 (1·6 – 4·1)	<0·001	2·5 (1·6 – 4·0)	<0·001	0·002
COVID-19-related worries [f]										
<50th percentile	350 (52·6)	70 (20.0)	280 (80.0)	1		1		1		
≥50th percentile	316 (47·4)	100 (31.7)	216 (68.3)	1·9 (1·3 – 2·6)	<0.001	1·9 (1·3 – 2·7)	<0·001	1·8 (1·3 – 2·6)	<0·001	0·007
	Mean (S.D.)									
Continuous	3·6 (1·2)	NA	NA	1·4 (1·2 – 1·7)	<0·001	1·4 (1·2 – 1·7)	<0·001	1·4 (1·2 – 1·7)	<0·001	<0·001
	Total, n (%)									
Social isolation										
Never	61 (9·2)	13 (21·3)	48 (78·7)	1		1		1		
Very rarely	65 (9·8)	12 (18·5)	53 (81·5)	0·8 (0·3 – 2·0)	0·689	0·8 (0·4 – 2·0)	0·703	0·8 (0·3 – 2·0)	0·678	1·0
Rarely	135 (20·3)	25 (18·5)	110 (81·5)	0·8 (0·4 – 1·8)	0·647	0·8 (0·4 – 1·8)	0·657	0·8 (0·4 – 1·7)	0·562	1·0
Occasionally	212 (31·8)	51 (24·1)	161 (75·9)	1·2 (0·6 – 2·3)	0·656	1·2 (0·6 – 2·4)	0·634	1·2 (0·6 – 2·4)	0·645	1·0
Often	136 (20·4)	48 (35·3)	88 (64·7)	2·0 (1·0 – 4·1)	0·052	2·1 (1·0 – 4·3)	0·042	2·0 (1·0 – 4·2)	0·052	0·418
Very often	57 (8·6)	21 (36·8)	36 (63·2)	2·2 (1·0 – 4·9)	0·065	2·3 (1·0 – 5·1)	0·052	2·1 (0·9 – 4·8)	0·083	0·663

Table 5. (continued). Attitude towards mHealth apps by psychological distress, social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index (*N*=666)

Exposure	Total, n (%)	Positive, n (%)	Neutral/ Negative, n (%)	Outcome: Attitude towards the use of mHealth apps [a] Model 1 [b] OR (95% CI)	p	Model 2 [c] Adj. OR (95% CI)	p	Model 3 [d] Adj. OR (95% CI)	p	pFWE
Lack of company										
Never	34 (5·1)	5 (14·7)	29 (85·3)	1		1		1		
Very rarely	43 (6·5)	10 (23·3)	33 (76·7)	1·8 (0·5 – 5·7)	0·350	1·8 (0·5 – 5·9)	0·335	1·7 (0·5 – 5·8)	0·364	1·0
Rarely	81 (12·2)	14 (17·3)	67 (82·7)	1·2 (0·4 – 3·7)	0·734	1·2 (0·4 – 3·7)	0·711	1·2 (0·4 – 3·8)	0·728	1·0
Occasionally	245 (36·8)	54 (22·0)	191 (78·0)	1·6 (0·6 – 4·4)	0·330	1·7 (0·6 – 4·6)	0·306	1·7 (0·6 – 4·7)	0·302	1·0
Often	178 (26·7)	59 (33·2)	119 (66·9)	2·9 (1·1 – 7·8)	0·038	3·0 (1·1 – 8·1)	0·034	3·0 (1·1 – 8·2)	0·035	0·282
Very often	85 (12·3)	28 (32·9)	57 (67·1)	2·8 (1·0 – 8·2)	0·051	3·0 (1·0 – 8·7)	0·041	3·0 (1·0 – 8·7)	0·045	0·356
Cognitive preoccupation with COVID-19 The novel coronavirus is something I…										
… never think of	20 (3·0)	2 (10·0)	18 (90·0)	1		1		1		
… don't think about very often	115 (17·3)	11 (9·6)	104 (90·4)	1·0 (0·2 – 4·7)	0·951	1·0 (0·2 – 4·8)	0·986	1·0 (0·2 – 5·2)	0·963	1·0
… think in part	245 (36·8)	56 (22·9)	189 (77·1)	2·7 (0·6 – 11·8)	0·197	2·8 (0·6 – 12·5)	0·175	3·1 (0·7 – 14·0)	0·150	1·0
… think about a lot	245 (36·8)	81 (33·1)	164 (66·9)	4·4 (1·0 – 19·6)	0·049	4·8 (1·1 – 21·2)	0·040	5·3 (1·2 – 24·2)	0·032	0·255
… keep thinking about	41 (6·2)	20 (48·8)	21 (51·2)	8·6 (1·8 – 41·8)	0·008	9·4 (1·9 – 46·1)	0·006	10·5 (2·1 – 53·1)	0·005	0·038

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Table 5. (continued). Attitude towards mHealth apps by psychological distress, social isolation, lack of company, cognitive preoccupation, worrying, anxiety, and social risk index (*N*=666)

Exposure	Total, n (%)	Positive, n (%)	Neutral/ Negative, n (%)	Outcome: Attitude towards the use of mHealth apps [a] Model 1 [b] OR (95% CI)	*p*	Model 2 [c] Adj. OR (95% CI)	*p*	Model 3 [d] Adj. OR (95% CI)	*p*	*p*FWE
COVID-19-related anxiety										
The novel coronavirus is…										
… not scary at all	105 (15·8)	13 (12·4)	92 (87·6)	1		1		1		
… rather not scary	187 (28·1)	43 (23·0)	144 (77·0)	2·1 (1·1 – 4·1)	0·029	2·1 (1·1 – 4·2)	0·027	2·2 (1·1 – 4·3)	0·026	0·211
… partly scary	219 (32·9)	56 (25·6)	163 (74·4)	2·4 (1·3 – 4·7)	0·008	2·5 (1·3 – 4·9)	0·006	2·5 (1·3 – 4·8)	0·008	0·066
… rather scary	133 (20·0)	47 (35·3)	86 (64·7)	3·9 (2·0 – 7·6)	<0·001	4·0 (2·0 – 7·9)	<0·001	4·0 (2·0 – 8·0)	<0·001	<0·001
… scary	22 (3·3)	11 (50·0)	11 (50·0)	7·1 (2·6 – 19·6)	<0·001	7·4 (2·6 – 20·6)	<0·001	6·9 (2·5 – 19·5)	<0·001	0·002
COVID-19-related worrying										
The novel coronavirus is…										
… not worrying	70 (10·5)	6 (8·6)	64 (91·4)	1		1		1		
… rather not worrying	142 (21·3)	35 (24·7)	107 (75·4)	3·5 (1·4 – 8·8)	0·008	3·5 (1·4 – 8·8)	0·008	3·5 (1·4 – 8·9)	0·008	0·062
… partly worrying	207 (31·1)	50 (24·2)	157 (75·9)	3·4 (1·4 – 8·3)	0·007	3·5 (1·4 – 8·5)	0·007	3·4 (1·4 – 8·4)	0·008	0·063
… rather worrying	207 (31·1)	67 (32·4)	140 (67·6)	5·1 (2·1 – 12·4)	<0·001	5·3 (2·2 – 13·0)	<0·001	5·4 (2·2 – 13·2)	<0·001	0·002
… worrying	40 (6·0)	12 (30·0)	28 (70·0)	4·6 (1·6 – 13·4)	0·006	4·8 (1·6 – 14·2)	0·005	4·8 (1·6 – 14·2)	0·005	0·040
Social risk index [g]										
0	160 (24·0)	37 (23·1)	123 (76·9)	1		1		NA		
1	270 (40·5)	68 (25·2)	202 (74·8)	1·1 (0·7 – 1·8)	0·631	1·1 (0·7 – 1·8)	0·562	NA		1·0
2	174 (26·1)	45 (25·9)	129 (74·1)	1·2 (0·7 – 1·9)	0·562	1·2 (0·7 – 2·0)	0·511	NA		1·0
3+	62 (9·3)	20 (32·3)	42 (67·7)	1·6 (0·8 – 3·0)	0·164	1·6 (0·8 – 3·0)	0·161	NA		1·0

Notes: df, degrees of freedom; CI, confidence interval; OR, odds ratio; S.D., standard deviation; *p*FWE, family-wise error-corrected p-values were computed by multiplying the unadjusted p-value by the total number of independent variables (*N*=8) to adjust significance levels; NA, not applicable.

[a] Based on the following item "Do you think that an mHealth app could help you deal better with the corona situation?" binary variable: answering 'strongly disagree', 'disagree', or 'neither nor' were coded as 0, whereas answering 'agree' or 'strongly agree' were coded as 1. Thus, individuals who had a negative or neutral attitude towards using an mHealth app were compared to those with a positive attitude.

[b] Unadjusted model.

[c] Model adjusted for age and gender.

[d] Model adjusted for age and gender and objective indicators of social risk (e.g. low education, migrant/ethnic minority group position, unemployment).

[e] The following K10 cut-offs were used to categories severity levels of psychological distress: 'none' (range score: 10 to 19); 'mild' (range score: 20-24); 'moderate' (range score: 25-29); 'severe' (range score: 30-50).

[f] Based on 10 items asking for potential worries related to the COVID-19 pandemic (e.g., health system overloaded, financial difficulties, completion of education/school) during the last week rated on a 7-point Likert scale (1='no worries at all'; 7='a lot of worries'). Items were dichotomized (i.e. median split of the continues variable: <50. percentile was coded as 0 and ≥50. percentile coded as 1).

[g] Defined as the number of objective indicators of social risk (i.e. unemployment/unable to work/early retirement; low education of both parents as a proxy for low socio-economic status; foreign born/second generation migration; living alone/alone with kids; being single; range social risk index: 0-6).

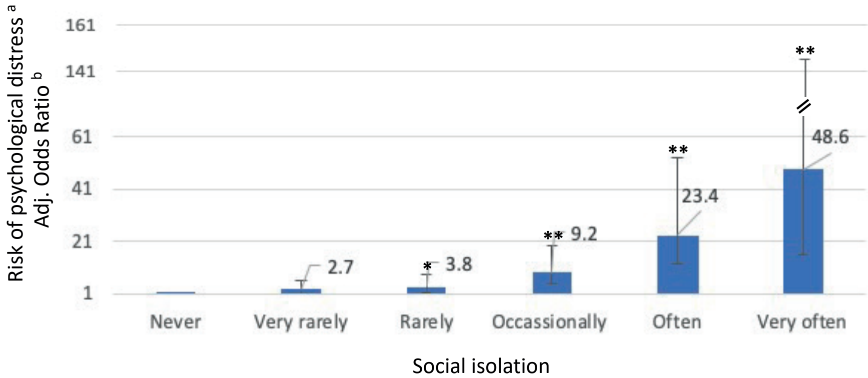

Figure 1. Associations of social isolation with psychological distress
Notes: Odds ratios and 95% confidence intervals are shown.
* p<0.05, ** p<0.001
a K10 cut-off of >19 has been used to index presence vs. absence of any mild, moderate or severe psychological distress as the outcome variable.
b Model adjusted for age, gender, educational level, migrant/ethnic minority group position, employment status.

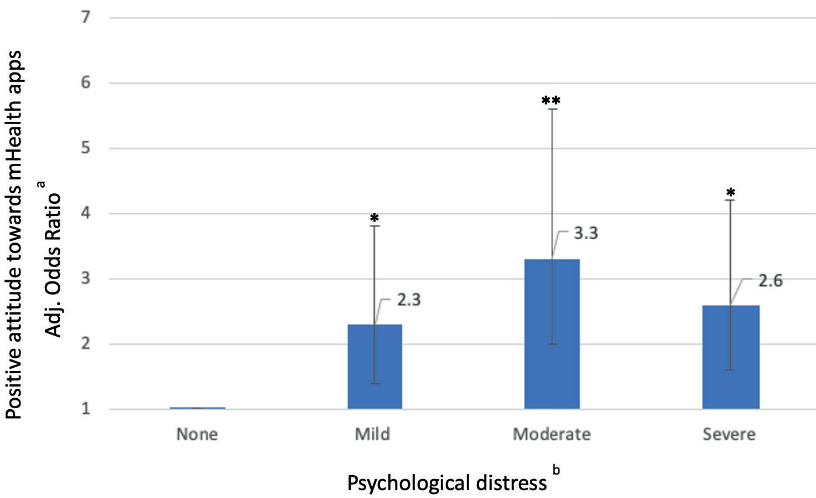

Figure 2. Associations of psychological distress with the positive attitude towards using mHealth apps
Notes: Odds ratios and 95% confidence intervals are shown.
* p<0.05, ** p<0.001
a Model adjusted for age and gender and social risk indicators (i.e. education, migrant/ethnic minority group position, employment status).
b The following K10 cut-offs were used to categories severity levels of psychological distress: 'none' (range score: 10 to 19); 'mild' (range score: 20-24); 'moderate' (range score: 25-29); 'severe' (range score: 30-50).

For example, those with severe levels of psychological distress were two times more likely to use mHealth apps compared to those without psychological distress (aOR 2·3, CI 1·4 – 3·6, *p*=0·007). However, those with mild and moderate levels of psychological distress were as likely to use mHealth apps as those without psychological distress after adjustments for multiple testing. Further, youth who perceived a lack of company were more likely to use mHealth apps ('occasionally': aOR 4·2, CI 2·0 – 9·1, *p*=0·002; 'often': aOR 4·1, CI 1·8 – 9·0, *p*=0·004; respectively) as compared to those who reported to 'never' experience a lack of company during the COVID-19 pandemic although some inconsistencies were found. In contrast, there was no evidence that objective indicators of social risk were associated with the use of mHealth apps.

Psychological distress, COVID-19-related worries, anxiety, and social isolation by attitude towards mHealth apps

As shown in Table 5 and Figure 2, individuals who experienced psychological distress were, across all levels of severity, more likely to report a positive attitude towards the use of mHealth apps (mild psychological distress: aOR 2·2, CI 1·34 – 3·6, *p*=0·013; moderate: aOR 3·2, CI 1·9 – 5·4, *p*<0·001; severe: aOR 2·5, CI 1·6 – 4·0, *p*=0·002) than those who did not report psychological distress. Similarly, those with more pronounced COVID-19-related worries (≥50. percentile : aOR 1·8, CI 1·3 – 2·6, *p*=0·007), anxiety ('The novel coronavirus is rather scary': aOR 4·0, CI 2·0 – 8·0, *p*<0·001; 'The novel coronavirus is scary': aOR 6·9, CI 2·5 – 19·5, *p*=0·002), or high levels of cognitive preoccupation with COVID-19 ('The novel coronavirus is something I keep thinking about': aOR 10·5, CI 2·1 – 53·1, *p*=0·038) were more likely to report a positive attitude towards the use of mHealth apps. However, social isolation, lack of company, and objective indicators of social risk were not associated with individuals' attitudes towards the use of mHealth apps to address psychosocial consequences of the COVID-19 pandemic after adjustments for multiple testing.

Discussion

This study investigated whether social isolation, lack of company, COVID-19-related worries and anxiety as well as objective social risk indicators were associated with psychological distress during the COVID-19 pandemic in a representative sample of adolescents and young adults. In addition, associations with current use of, and attitude towards, mHealth apps were investigated. First, there was evidence that social isolation, lack of company, and COVID-19-related cognitive preoccupation, worries, and anxiety were associated with psychological distress. Second, we found evidence of dose-response relationships as psychological distress was progressively more likely to occur as the level of reported social isolation, lack of company, and COVID-19-related preoccupation, anxiety, and worrying increased - although some inconsistencies were observed. Third, an association between migrant/ethnic minority group position and psychological distress was found, while other objective indicators of social risk were not associated with psychological distress. Similarly, associations of levels of the social risk index and psychological distress were inconsistent. Fourth, there was evidence that psychological distress and high levels of COVID-19-related cognitive preoccupation, worries, and anxiety were associated with a more positive attitude towards the use of mHealth apps to help overcome negative consequences of the COVID-19 pandemic. Finally, the actual use of mHealth apps was more likely to be evident in those with severe psychological distress, frequent social isolation and lack of company as well as COVID-19-related preoccupation, anxiety, and worries, though some inconsistencies were found by levels of respective variables.

An important strength of this study is that findings are based on a representative sample of adolescents and young adults who participated in this survey during active lockdown in Germany. However, several limitations should be taken into account before interpreting reported findings. First, the cross-sectional design of the study did not allow us to investigate temporal order and, thus, we cannot rule out that reverse causality may have operated on our findings and, importantly, the complex nature of investigated constructs and the study design exclude any form of causal inference [48]. Also, as we have not assessed variables before the pandemic, we are not able to disentangle the unique additive effects of the pandemic on reported associations. However, longitudinal cohort studies have found that the prevalence of psychological distress and various mental health conditions was considerably higher during the pandemic as compared to time periods before the pandemic [18, 20, 23, 26, 27, 45], although some inconsistencies were reported [21]. Also, participants were explicitly asked to report levels of psychological distress *during* the COVID-19 pandemic. Second, the very dynamic development of the pandemic may limit the generalizability of findings to later stages of the ongoing pandemic or subsequent pandemics. Although strong evidence was found that social isolation, worrying, and other psychosocial factors related to public health measures for minimising transmission rates were strongly associated with psychological distress, it is possible that the withdrawal of restrictions quickly decreases subjective feelings of social isolation and worrying and, thus, may contribute to a reduction of psychological distress for most individuals [20]. However, the survey was conducted after the peak of new cases per day had occurred during the first wave of the pandemic in Germany and some infection control measures were already beginning to be lifted. Thus, our findings may also underestimate prevalence of psychological distress as compared to moments of strict lockdown and high rates of new cases. That said, mental health outcomes may worsen due to ongoing and expected economic uncertainties and, hence, it may be argued that further negative psychosocial consequences are yet to come. Furthermore, we used a conservative method to minimize type I error rate inflation, which further supports robustness of our findings. Third, some of the indicators used to conceptualize social risk may - although frequently being used in social epidemiological studies - apply to young people only to a limited extent. For instance, living alone may not be perceived as indexing social adversity. Also, some social risk indicators may only be contributing to poor mental health later in life (e.g. lower educational level). Fourth, we used a short screening measure (i.e. K10) to assess psychological distress. As the K10 is arguably largely focussing on depressive symptoms (e.g. feeling hopeless/worthless), other potentially important psychopathological domains (e.g. positive psychotic symptoms) have been largely neglected. Lastly, due to time constraints, the study was not pre-registered before data collection and data on the psychometric properties of COVID-19 related measures (i.e., COSMO worry scale) is very limited. However, we tested a-priori defined hypotheses and findings on internal consistency are reported.

Overall, there is accumulating evidence on the negative consequences of the COVID-19 pandemic on public mental health. A number of cross-sectional and longitudinal cohort studies have found detrimental effects of the pandemic on various mental health domains, including psychological distress, depression, anxiety, and an increase of more distal risk factors such as cannabis and alcohol misuse and loneliness [6-24]. These findings are largely in line with findings from this nationally representative survey, i.e., high levels of social isolation, lack of company, COVID-19-related worrying, and anxiety have been reported and found to impact psychological distress in youth during active lockdown in Germany. Although migrant/ethnic minority group position was found to be associated with psychological distress, we found no evidence that an increased number of social risk indicators was associated with increased levels of psychological distress. Thus, our findings partly differ from other studies which have found that psychosocial consequences of the current pandemic are disproportionally distributed in the society and may especially affect those with more inferior social positions or minority status. However, our findings are in line with findings demonstrating more pronounced effects in youth [23, 24] and one study has shown associations between loneliness and COVID-19 related distress [25]. Further, positive attitudes towards the use of mHealth apps to help alleviate the psychosocial consequences of the pandemic was highly prevalent and associated with an objective need (e.g. more severe levels of psychological distress, higher levels of worrying). There have been also other studies which have reported that individuals have a positive attitude towards, and increasingly use, digital interventions during the current COVID-19 pandemic across the whole spectrum of public mental health provision (i.e., mental health promotion, prevention and treatment of mental disorders) [36-38, 49, 50], and alterations of telemedicine regulations have been reported [51]. However, mHealth apps provide the opportunity of delivering low-threshold, personalized mental health care in daily life.

The present findings suggest that there is a pressing demand for evidence-based public mental health interventions that aim to specifically target the negative consequences of the COVID-19 pandemic [1]. Digital interventions, including eHealth interventions and mHealth apps, may help to mitigate the negative psychosocial consequences by providing evidence-based information, reliably monitoring symptoms, or delivering intervention components in individual`s daily lives [31, 36, 37, 52, 53]. Furthermore, digital interventions may be used to ensure continuity of care in the provision of mental health services in case of repeated outbreaks and lockdowns during the pandemic, and for providing and extending digital interventions to the area of mental health promotion and prevention to mitigate the negative impact of the pandemic especially in youth. Digital mHealth interventions may be particularly suited to help achieve this goal, as they have the potential, once developed and evaluated, to be scaled up and broadly offered at the population level.

To conclude, digital interventions may help to mitigate the negative impact of the COVID-19 pandemic on youth mental health as there is a subjective demand and objective need. Smartphone-based mHealth apps are particularly suited to provide low-threshold and timely public mental health care in times of physical distancing and quarantine. As the quality of evidence of currently available apps in major app stores is often unknown or very limited [54-59] there is an urgent need to (1) develop and evaluate digital interventions specifically designed to address social isolation and poor mental health to actively prepare for a potential worsening of the current pandemic as well as future health crises, (2) make these evidence-based digital interventions publicly available to improve public mental health, and (3) develop digital strategies for continued mental health care as well as mental health promotion and prevention of mental disorders. Finally, decision-makers and stakeholders in the area of public mental health should work on systematically evaluating currently available digital interventions to support young users to find evidenced-based digital tools which are most helpful for their individual preferences and current needs [60-62].

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CHAPTER 10

Evidence synthesis of digital Interventions to mitigate the negative impact of the COVID-19 pandemic on public mental health: a rapid meta-review

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Abstract

Background: Accumulating evidence suggests negative effects of the COVID-19 pandemic on public mental health. Digital interventions that have been developed and evaluated in recent years may be used to mitigate negative consequences of the COVID-19 pandemic. However, evidence-based recommendations on the use of existing telemedicine and internet-based (eHealth) and app-based mobile Health (mHealth) interventions are lacking.

Objective: The aim was to investigate the theoretical and empirical base, user perspective, safety, effectiveness, and cost effectiveness of digital interventions in public mental health provision (i.e. mental health promotion, prevention and treatment of mental disorders) that may help to reduce the consequences of the current COVID-19 pandemic.

Methods: A rapid meta-review was conducted. MEDLINE, PsycINFO, and CENTRAL databases were searched on May 11, 2020. Study inclusion criteria were broad and considered systematic reviews and meta-analyses that investigated digital tools for health promotion, prevention, or treatment of mental health conditions likely affected by the COVID-19 pandemic.

Results: Overall, 815 peer-reviewed systematic reviews and meta-analysis were identified of which 83 met inclusion criteria. The present findings suggest that there is good evidence on the usability, safety, acceptance/satisfaction, and effectiveness of eHealth interventions while evidence on mHealth apps is promising, especially if social components (e.g. blended care) and strategies to promote adherence are incorporated. Although most digital interventions focus on the prevention or treatment of mental disorders, there is some evidence on mental health promotion. However, evidence on process quality, cost-effectiveness, and long-term effects is very limited.

Conclusions: There is evidence that digital interventions are particularly suited to mitigating psychosocial consequences at the population level. In times of physical distancing, quarantine, and restrictions on social contacts, decision-makers should develop digital strategies for continued mental health care and invest time and efforts in the development and implementation of mental health promotion and prevention programs.

Keywords: COVID-19; mHealth; eHealth; prevention; mental health promotion; intervention; digital mental health; telemedicine

Introduction

Measures to prevent and control infections in the COVID-19 pandemic such as physical distancing, quarantine, and restrictions on social contacts can have a negative impact on public mental health [1]. This includes an increase in depression, anxiety, loneliness, and perceived stress [2] as well as in risk behaviours, such as cannabis and alcohol use [3] in the population. In addition to the immediate effects of the infection control measures, further negative consequences for mental health are to be expected due to more direct deleterious effects of COVID-19 (e.g. illness anxiety, contamination fears) and the economic downturn and recession [4]. Recently reported restrictions in access to, and continuity of, care for individuals with mental disorder caused by infection prevention and control measures in some countries are an additional cause for concern [3, 5, 6].

Digital interventions, which do not require face-to-face contact, may play an important role in improving public mental health at times of infection prevention and control measures. They can be broadly grouped in telemedicine and internet-based interventions (hereafter eHealth intervention) [7], and app-based mobile Health (mHealth) interventions delivered using smartphones or other mobile devices [8]. These interventions provide a unique opportunity for delivering low-threshold, public mental health care tailored to individual needs and contexts in daily life, outside the clinic [9], even under the restrictive conditions of the COVID-19 pandemic. As smartphones are mostly in close proximity to users, and accessible whenever and wherever convenient, the use of mHealth apps in particular represents a powerful approach that allows the real-time and real-world delivery of intervention components in individuals daily lives.

Digital tools may help to mitigate the negative psychosocial consequences most effectively if intervention strategies are not only targeted at vulnerable individuals with a clinically high-risk state or mental disorder, but also at the population level. More specifically, following the seminal 'population strategy' advocated by Geoffrey Rose [10], even a small shift in the population mean of mental health, which is continuously distributed in the population, may lead to a substantial reduction of the prevalence of mental health problems. If applied to the current pandemic, a scalable, digital public mental health approach may contribute to lower rates of mental disorders by targeting important determinants and shifting the mean level of mental health in the population.

In order to minimize the negative impact of the COVID-19 pandemic on mental health of the population, digital interventions can be used in the following areas of public mental health provision: primary prevention strategies, including a) mental health promotion and literacy at the population level; b) indicated, selective, or universal prevention targeting high-risk individuals, subpopulations, or the entire population, respectively as well as secondary and tertiary prevention strategies, including c) treatment and preventive services for people with mental disorders. Indeed, evidence from ad-hoc surveys suggests that digital interventions for improving public mental health are urgently needed to address the psychosocial consequences of the COVID-19 pandemic [1-3, 11, 12]. For example, findings from the German COVID-19 Snapshot Monitoring (COSMO [13]), a repeated representative cross-sectional survey, suggest strong concerns about the economy, social inequalities, and the healthcare system as well as high levels of psychological distress in the adult general population, and in young people in particular [14, 15]. Another representative survey (Norstatpanel) found that a staggering 39% of youth met criteria for moderate mental health problems, even after the most restrictive infection control measures had been lifted [16]. Furthermore, the reported social isolation during the COVID-19 pandemic was associated with levels of psychological distress in a dose-response fashion [16]. Recent evidence also suggests a high subjective demand for digital mental health interventions in the general population and people with mental disorder [17, 18], which is matched with a high and rapidly growing number of mHealth apps available in major app stores, with the strongest growth having been noted for mHealth apps[19]. It has further been reported that the demand for mHealth apps has increased globally by 49% during the COVID-19 pandemic [20], with 73% of psychologically distressed and socially isolated youth in the Norstatpanel survey indicating the use of mHealth apps to be helpful in coping with the ongoing COVID-19 pandemic [16].

Taken together, based on the evidence presented, there is an urgent need for, and high potential in, using digital interventions to improve public mental health and mitigate the negative psychosocial impact of the COVID-19 pandemic. However, evidence-based recommendations for the use of digital interventions during public health crises, including this ongoing pandemic, is currently lacking. The present meta-review aimed to synthesise the available evidence on the theoretical and empirical base of interventions, quality from the user perspective (i.e., acceptability, usability, satisfaction), safety, effectiveness, and cost effectiveness of digital interventions in the area of public mental health provision (i.e., mental health promotion, prevention of, and treatment for mental disorder).

Methods

A rapid meta-review of systematic reviews on digital public mental health interventions was conducted. For this, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA;[21]) was used as a guideline for reporting findings. In line with the current state of the art in the development and evaluation of complex digital mental health interventions [8], the following criteria to review the available evidence were used: theoretical and evidence base, quality from the user perspective (i.e., acceptability, usability, satisfaction), safety, effectiveness, and cost effectiveness.

Search strategy and selection criteria

The databases Medical Literature Analysis and Retrieval System Online (MEDLINE), PsycINFO, and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched for systematic reviews and meta-analyses published in English and German language from inception to April 2020. An extensive search of bibliographic databases was performed using queries that combined search terms on mental health, public mental health provision, digital eHealth/mHealth interventions (see Multimedia Appendix 1) and high-quality reviews (i.e. systematic review, meta-analysis) using logical operators. In doing so, database-specific queries were used to ensure semantic equivalence. The queries were launched on May 11, 2020, covering results until April 2020. The results were obtained and duplicates were removed. References written in English and German language were included. No other filters or restrictions were applied.

The search criteria were purposefully broad and considered systematic reviews that investigated digital tools for health promotion, prevention, or treatment of mental health conditions and determinants likely affected by the COVID-19 pandemic (e.g. depression, anxiety, psychosis, substance misuse, self-harm, well-being, quality of life, self-esteem, loneliness). Titles and abstracts were screened for inclusion by one reviewer (NM). Studies were included if they were published in a peer-reviewed journal, contained original findings examining the theoretical

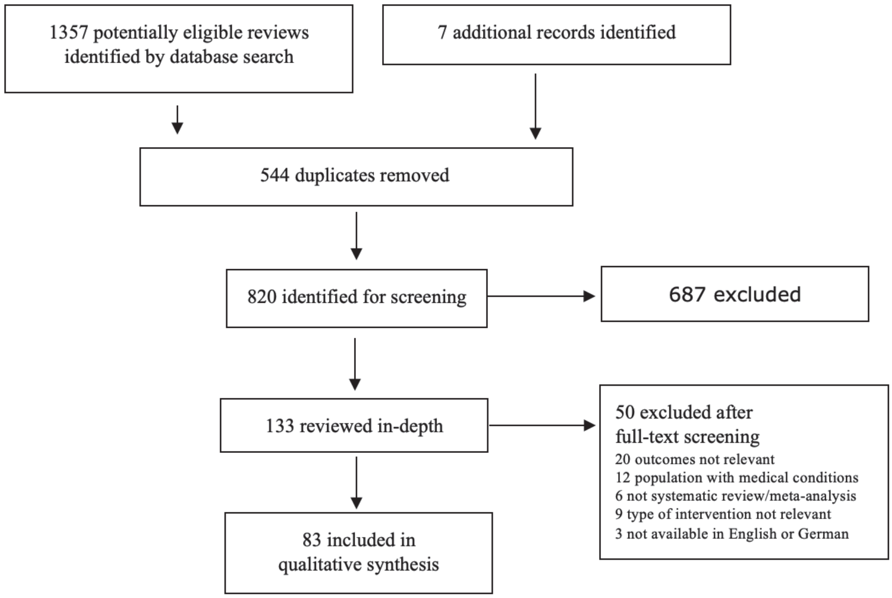

Figure 1. Study selection

and evidence base, quality from the user perspective (i.e., acceptability, usability, satisfaction), safety, effectiveness, or cost effectiveness of digital mHealth and eHealth interventions. Due to the rapid meta-review format of the current study, conclusions drawn by the included authors are reported. The included articles had to be systematic reviews and/or meta-analysis that followed established reporting guidelines (e.g. PRISMA; [21]). Because of time constraints and the rapid meta-review format of the current study, a second reviewer (CR) independently screened a randomly selected subset (40%) of identified studies. The references were categorized as 'eligible', 'query', and 'not eligible'. Inclusion and exclusion criteria were applied to references that were queried or eligible. Reviewers were blinded and potential discrepancies in selection decisions were discussed with another member of the research team. There has been a pilot screening of a randomly selected subset of identified studies (around 5%) to discuss decisions on categorising studies at an early stage. As inclusion criteria were purposefully broad, discrepancies between the reviewers (CR and NM) were very low. Full texts of potentially relevant articles were obtained, read, and assessed by one reviewer (CR), and data extraction was performed by three reviewers (CR as well as research assistants NM and VP under close supervision by CR; see acknowledgments).

Reviews and meta-analysis on preprint servers and grey literature were not included. EndNote reference management software [22] was used to record reviewers' decisions, including reasons for exclusion. The study selection process was documented using the PRISMA flow diagram (see Figure 1).

Results

The search strategy of our meta-review on digital interventions yielded 815 peer-reviewed systematic reviews and meta-analysis (Figure 1). Of these, 83 references were included in the meta-review (Table 1-3). Overall, 44 of the included reviews have summarized findings on eHealth interventions of which 19 focused on interventions targeting depression, 22 focused on anxiety, 11 focused on problematic substance use and two focused on eating disorders. Several reviews included interventions that targeted several mental health problems (see Table 1). In total, 16 reviews have summarized findings on mHealth interventions. Of these, two focused on depression, one focused on anxiety and one focused on problematic substance use and another on eating disorder. Similarly, the majority of included reviews focused on various mental health domains (see Table 2). Furthermore, 23 of the included reviews jointly reported effects of eHealth and mHealth interventions on various mental health outcomes (see Table 3). A complete summary of included reviews on eHealth, mHealth, and mixed interventions are shown in the Supplements, including secondary outcomes, quality from the user perspective, safety, and cost effectiveness. Here, findings on intervention components, theoretical and evidence base on process and outcomes, primary outcomes, and quality of evidence are shown.

Quality from the user perspective

Evidence from the included systematic reviews suggest moderate to high levels of acceptance, feasibility and user satisfaction of eHealth and mHealth interventions for mental health promotion and prevention [30, 31] as well as the treatment of mental health problems [32-41]. This applies, in particular, for interventions including social components [32, 42], strategies to promote user adherence [33, 43], symptom monitoring [44, 45], or a blended care approach [46].

Safety: Data sharing and data safety regulations as well as aspects of eHealth/mHealth and clinical safety of interventions were often not explicitly reported or systematically investigated in the identified systematic reviews [47-49]. The descriptions of many eHealth interventions do not make explicit reference to prevailing regulations and clinical guidelines [50]. Furthermore, there is evidence that mHealth apps available in major app stores use problematic data sharing and privacy practices (e.g. monetization of sensitive user data through analytics and advertising) [8, 27, 28].

Effectiveness of eHealth interventions

There was good evidence on the effectiveness of telemedical and other eHealth interventions in the field of mental health promotion and prevention as well as the treatment of mental health conditions.

Mental health promotion and prevention

There have been a number of systematic reviews that aimed to investigate the effectiveness of telemedical and eHealth interventions for mental health promotion and prevention. These interventions have primarily been shown to improve mental health [34], physical activity [34, 35], well-being [36, 37], stress [23, 38], depression [23, 36, 38, 51, 52], anxiety [23, 36, 38, 51, 52], alcohol use [24, 53-56] and cannabis use [57, 58] in the general population as well as dysfunctional cognition and self-esteem in at-risk populations [59, 60]. Importantly, effectiveness has been demonstrated across differing age groups, including adults [24, 54, 59] as well as adolescents from the general population [34, 52, 56, 61-63], and effect sizes mostly ranged from small to medium. However, evidence on the use of eHealth intervention for the elderly is scarce, although findings from the identified reviews indicated some evidence on the effectiveness of eHealth interventions for reducing social isolation and increasing social participation of people aged 65 and older [64] which may be of particular interest for the current COVID-19 pandemic.

Treatment of mental health conditions

There was also strong evidence on the effectiveness of telemedical and eHealth interventions in the provision of treatment and services for people with mental disorder.

This included anxiety disorders [65-68], depression [60, 61, 65-67, 69-73], substance abuse [54, 74-76], eating disorders [77], and severe mental illness [78], with overall small to medium effect sizes, not only with regard to the reduction of relevant symptoms but also the improvement of dysfunctional cognition [60], self-esteem [60] and quality of life [66]. Some of the identified studies have even reported medium to large effect sizes for cognitive-behavioural eHealth interventions that aimed to reduce symptoms of depression [79].

The effectiveness of telemedicine interventions which use videoconference tools or the telephone has also been well documented in depressive [80-83], anxiety [80, 83-85] and psychotic disorders [86], with comparable effects of online group and individual therapy sessions [87, 88], compared with conventional (offline) therapy sessions. Superior effectiveness was observed for interventions adopting a blended-care approach combining eHealth with conventional intervention components [46, 54, 71].

Overall, findings suggest that the evidence on long-term effects and non-inferiority compared to conventional therapy and active control conditions remains limited [79, 81, 82, 86, 87] and there is only limited evidence of telemedical and eHealth interventions on underlying processes and mechanisms of action [89].

Effectiveness of mHealth interventions

While there is some, initial evidence on the effectiveness of mHealth interventions to improve physical activity [90-95], stress appraisal [96, 97], depression [26, 96-100], anxiety [25, 26, 96, 97] and alcohol and substance use [55, 96, 98, 101-103], with small to medium effect sizes in all areas of public mental health provision, the amount of research to investigate this issue remains, overall, limited [104-108]. Only a minority of mHealth interventions were found to use more advanced techniques (accelerometer, GPS) to inform the delivery of intervention components [25, 89, 92]. In addition, a substantial difference was found between mHealth apps available in major app stores, for which there is no or only very limited evidence on their effectiveness [29, 108-111], and mHealth interventions developed by research groups. As for eHealth interventions, evidence on long-term effects and on underlying processes and mechanisms of action remains very limited.

Cost effectiveness

There is some evidence on the cost effectiveness of eHealth interventions for depression and anxiety in primary care settings when compared to care as usual and waiting list control conditions [51] as well as for a range of mental disorders when compared to conventional CBT [112, 113]. However, as only a few systematic reviews have systematically investigated the cost-effectiveness of digital interventions to date, these findings should be interpreted with caution. While there is some evidence on the cost effectiveness of mHealth interventions (e.g. for digital monitoring and feedback in depression) from individual studies [18], evidence summarized at the level of systematic reviews is very limited.

Table 1. Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Mental Health Promotion and Prevention					
Alkhaldi et al. (2016) [33]	Yes	Adult general population	Technology-based engagement promotion strategies (e.g. text messages, self-monitoring, F, support)	Not reported	Small to moderate positive effects on technology-based strategies for promoting engagement with digital interventions as compared to no strategy; quality of evidence: moderate (assessed using Cochrane risk-of-bias tool)
Elaheebocus et al. (2018) [32]	No	Adult general population	Identity representation, communication, peer grouping, data sharing, competition/gamification, activity data viewing, online social network	Social Behavior Change Technique	Positive effects on outcomes (e.g. increased PA, lower alcohol intake) in most behavioral interventions that included social media features, 28% no effect; quality of evidence: low (e.g. small samples, heterogeneous interventions); no standardized approach was used to assess the quality of included studies

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Cotie et al. (2018) [35]	Yes	Adult general population	Multimodal/unimodal websites: information, PA tracking tools, online discussion forums; prompts (e.g. reminders to exercise, track movement)	Social Cognitive Theory, Transtheoretical Behavioral Theory	Moderate improvement in PA; no improvement in obesity-related outcomes; quality of evidence: moderate (assessed using the GRADE approach)
Deady et al. (2017) [59]	Yes	Adult general population	Behavioral and problem-solving therapy, mindfulness, situational analysis, skills program, relaxation self-help program, persuasive framing, PE	CBT, third wave CBT, ACT, PE	Small positive effects on depression and anxiety; similar effect sizes for universal and indicated/selective interventions; quality of evidence: moderate (assessed using the Downs and Black checklist)
Heber et al. (2017) [23]	Yes	Adult general population	Mindfulness, stress and mood management, problem solving, ER, coping with stress, ACT, skills, relaxation	CBT, third wave CBT, ALT	Small effect on stress, depression and anxiety; guided interventions more effective than unguided interventions; small effects for short interventions (≤4 weeks), moderate effects for medium-long interventions (5-8 weeks; small-moderate effect for CBT and third wave CBT; small effect for alternative interventions; small-moderate effect up to 6 months follow-up for computer-based stress-management interventions; quality of evidence: low (assessed using the Cochrane risk-of-bias tool)

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Ennis et al. (2018) [31]	No	Trauma-exposed individuals	PE, interactive games, cognitive and behavioral principles, peer support, MI	CBT	No effects on various symptom domains for selected interventions, significant effects for indicated interventions as compared to active control conditions; quality of evidence: fair to good (assessed using the Downs and Black checklist)
Pennant et al. (2015) [52]	Yes	Young individuals (aged 5-25 years) with risk of developing anxiety disorder or depression; young individuals from the general population	Supportive text, animation, photographs, videos, rewards, games, homework, web pages with reading, quizzes, F, phone calls, interactive fantasy adventure game, depression monitor, diary, counter-thought generator	CBT	Medium effects on anxiety and depression in populations at risk; small effects on anxiety and depression in general population; inconsistent findings in children; quality of evidence: low (assessed using the GRADE approach)
Fleming et al. (2014) [61]	No	Young individuals (aged 9-25 years) with depressive symptoms	Serious games: supported and fully self-help interventions; F, conflict/ competition, interaction, PE	CBT	Small treatment effects on depressive symptoms; quality of evidence: low (e.g. small samples, heterogeneous interventions); no standardized approach was used to assess the quality of included studies
Flujas-Contreras et al. (2019) [37]	Yes	Parents of children with mental or physical health problems	PE, self-care, positive parenting, coping strategies, children´s contingency management, problem solving games	CBT, Triple P	Moderate effect sizes on various mental health domains; small effect size on parental self-efficacy, no effects on parental stress; Triple P: small effect size; quality of evidence: high (assessed using the Cochrane risk-of-bias tool and the Moncrieff Scale)

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Boumparis et al. (2019) [57]	Yes	School and high school students (aged 12-20); problematic cannabis users (aged 16-40)	Parent-involvement-program, climate school course, MI, brief interventions, solution focused approaches, skills-based prevention programs, community reinforcement approach	CBT, Person-centered Therapy, Social Influence Theory	Small effects on cannabis use in students and problematic cannabis users as compared to controls; effects maintained in students at 12-month follow-up but not in problematic cannabis users; quality of evidence: low (assessed using the Cochrane risk-of-bias tool)
Hadjistav-ropoulos et al. (2020) [54]	Yes	Adults general population; service users with alcohol use disorder recruited from specialized mental health services	Information on alcohol, preparing for change exercises, skills training, drinking diary, online discussion forum, automated motivational text or email prompts, blood-alcohol-concentration calculator	CBT	Self-guided iCBT significantly more effective in reducing alcohol consumption when compared to information about alcohol and waitlist control conditions; therapist-guided iCBT more effective as compared to waitlist (medium-large effect) control condition; quality of evidence: moderate (assessed using the Cochrane risk-of-bias tool)
Tait et al. (2010)[56]	No	Young people with substance misuse	Interactive assignments, video clips, personalized normative F, information, interactive online alcohol education, assessment	Not reported	Small effect in preventing development of alcohol-related problems among people who were non-drinkers at baseline; effects similar to brief in-person interventions; quality of evidence: low (e.g. small sample sizes, mostly short-term effects investigated, considerable heterogeneity), no standardized approach was used to assess the quality of included studies

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Treatment					
Arguel et al. (2018) [50]	Yes	Adults with various mental disorders	Social network interventions (e.g. social networks and forums, discussion groups)	Social Cognitive Theory; Theory of Planned Behavior, Technology Acceptance Model. Perceived Risk Influence	Most common theory for online social network interventions is Social Cognitive Theory, quality of evidence: low (assessed using the Cochrane risk-of-bias tool)
Lin et al. (2019) [75]	No	General population, patients with substance use disorder, primary care patients	Psychotherapy: SC, MI, individual counselling sessions, group therapy focused on relapse prevention, ME, combination of videoconference & methadone treatment, PE	CBT, CBI	Superior treatment retention for telemedicine in one study; lower dropout rate in one study; quality of evidence: moderate (e.g. retrospective studies, moderate risk of bias) (assessed using the Cochrane risk-of-bias tool)
Simon et al. (2019) [39]	No	Adults with PTSD	PE; stress management techniques; cognitive restructuring/trauma processing; relapse prevention.	CBT	High levels of acceptability; quality of evidence: moderate (assessed using the Cochrane risk-of-bias tool)
Richards et al. (2012) [70]	Yes	Adults with symptoms of depression	CBT-ID, Beating the Blues (BTB), MoodGym, Sadness Program, Overcoming Depression on the Internet (ODIN), Color your Life 5	CBT	Overall medium effect size; large effect and greater retention for therapist-supported studies; small effect for studies without support; quality of evidence: high, but high risk of missing data (assessed using the Cochrane risk-of-bias tool)

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Sierra et al. (2018) [79]	Yes	Individuals with depression	Behavioral activation, acceptance and commitment therapy	third wave CBT	Medium to large effect sizes comparing online intervention vs. waitlist or TAU; quality of evidence: low (e.g. high attrition to post-measure in some studies, high variability in sample size), no standardized approach was used to assess the quality of included studies
Erbe et al. (2017) [46]	No	Adults with depression, anxiety, and/ or substance abuse	Blended Interventions: treatment programs that use elements of both face-to-face and internet-based interventions; web-based programs with modules such as cognitive, behavioral and emotion-focused interventions, email support, PE, group chats	CBT	Blended interventions are feasible and more effective than waiting list control conditions; quality of evidence: low; no standardized approach was used to assess the quality of included studies
Lau et al. (2016) [62]	Yes	Population (aged 7-80) with symptoms of depression, PTSD, autism, ADHD, alcohol use disorder	Goal-oriented, cognitive training games (physical, emotional, cognition, skills), PE	Goal-oriented, Problem-Solving, Cognition Training, and Games	Moderate effect on various symptom domains; quality of evidence: moderate, risk of bias unclear (incomplete reporting) (assessed using the Cochrane risk-of-bias tool)
Irvine et al. (2020) [88]	Yes	Hetero-genous sample (e.g. students, adults with and without diagnoses of mental disorders, adults referred to mental health services)	Counselling, CBT techniques used by therapist, solution focused therapy, peer counselling, Employee Assistant Program	CBT	Telephone sessions shorter than face-to-face sessions; no significant difference in therapeutic alliance, disclosure, empathy, attentiveness; more active participation in telephone mode; quality of evidence: low (e.g. small sample sizes, observational studies, high levels of inconsistency), no standardized approach was used to assess the quality of included studies

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Gentry et al. (2019) [87]	No	Veterans with PTSD, opioid-dependents; women with HIV; cancer patients, inmates in seclusion, smokers, diabetes patients	Group therapy via VTC services e.g. relapse control therapy, coping skills, healthy relationship educational program, cognitive processing therapy, relaxation response resilience program, mindfulness, SC, self-management education, chat group, video group, psychosocial support	CBT, ACT, PE	No differences between VTC and face-to-face group sesstions on treatment outcomes (e.g. PTSD symptoms); effects of VTC comparable to face-to-face treatment; mild decreases of therapeutic alliance in VTC; quality of evidence: moderate (assessed using the quality of evidence criteria of the US Preventive Services Task Force)
Grist et al. (2013) [65]	Yes	Participants with common mental disorders	e.g. Beating the Blues, MoodGYM, Panic Online, Color Your Life, DE-STRESS, FearFighter, Coping With Depression; support via email, phone, web forum, text messages	CBT	Medium effect size of iCBT on various mental health outcomes, comparable to face to face CBT; iCBT significantly more effective than waitlist and active control; quality of evidence: moderate (assessed using the Cochrane risk-of-bias tool)
Axelsson et al., (2019) [112]	Yes	Adult patients with health anxiety	Cognitive restructuring, exposure-based techniques	CBT	Moderate to large effects of iCBT on health anxiety (superior to active controls in two studies), small effect on QoL; comparable effects of iCBT to face-to-face-CBT; quality of evidence: moderate (e.g. small effect of publication bias, substantial heterogeneity), low risk of bias (assessed using the Cochrane risk-of-bias tool)

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Berryhill et al. (2019) [80]	No	Adult patients with anxiety disorder	Video-conferencing psychological therapy	CBT, ACT, Metacognitive Therapy	Small to large improvements on anxiety; quality of evidence: moderate (assessed using the Effective Public Health Practice Project quality assessment tool)
Bolton et al. (2015) [82]	Yes	Adults with traumatic experience	Hybrid design: internet and real-time (telephone calls, initial face-to-face introductory meeting) delivery of intervention components or asynchronous (email) communication	CBT	Medium-large improvements in cognitive and behavioral symptoms of depression, generalized anxiety and posttraumatic stress; quality of evidence: moderate (e.g. underpowered, rare blinded group allocation) (assessed using the Quality Index)
Castro et al. (2020) [81]	Yes	Depressed adults with no comorbid somatic disorders	Workbook including exercises, skills trainings and coping strategies, information about local mental health services, pedometer	CBT	Large reduction in depressive symptoms compared to control; non-significant small effect of telephone-administered psychotherapy compared to active comparators; quality of evidence: low (assessed using the Cochrane risk-of-bias tool)

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Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Stech et al. (2020) [68]	Yes	Adults with an at-risk mental state or a diagnosis of panic disorder	PE, cognitive restructuring, relapse prevention, exposure techniques	CBT	Large improvements for panic and agoraphobia severity for iCBT compared to waitlist and information controls; similar results of iCBT and face-to-face CBT in reducing panic and agoraphobia symptoms; large within-group improvements for panic, medium for agoraphobia symptom severity; quality of evidence: low-moderate (assessed using the Cochrane risk-of-bias tool and ROBINS-I tool)
Rees et al. (2015) [83]	No	Participants with anxiety disorders (e.g., PTSD, obsessive-compulsive, social phobia) and/or depression	Treatment components based on CBT principles delivered using video conferencing software	CBT	Treatment effective in reducing anxiety symptoms (moderate – large effect sizes), comparable to face-to-face treatment; quality of evidence: low (e.g. partly no controls or case studies, small sample sizes), no standardized approach was used to assess the quality of included studies

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Richardson et al. (2010) [60]	No	Children and adolescents with depression	Stressbusters; Master your Mood online (group therapy via online chat room), Catch It (CBT principles with aspects of interpersonal therapy and behavioral activation); MoodGYM (CBT- based, delivered online); iCBT: Cool Teens, BRAVE; including intervention components such as PE, quizzes, homework assignments, case vignettes, narration, cartoons, educational and training videos	CBT	30% - 78% of included participants no longer met diagnostic criteria for primary diagnoses; improvements in depressive symptoms only in participants completing ≥3 sessions; quality of evidence: low (e.g. 50% case studies, studies without control groups, possibility of publication bias, small number of databases), no standardized approach was used to assess the quality of included studies
Rost et al. (2017) [41]	No	Individuals with depression	Mindfulness-based cognitive therapy, behavioral activation, MI	CBT	Effectiveness of digital interventions on depressive symptoms; drop-out rates comparable to face-to-face treatment; quality of evidence: low (e.g. high heterogeneity, possibility of biases), no standardized approach was used to assess the quality of included studies due to high variability in study type
Pasarelu et al. (2017) [66]	Yes	Non-clinical and clinical population (depressive and anxiety symptoms)	iCBT: transdiagnostic/ tailored, clinician guided with interview/ self-guided with interview/ self-guided, 4-25 modules	CBT	Medium-large effect for iCBT on anxiety and depression outcomes; medium effect on QoL; large effect on generic outcome measures; no differences on anxiety and QoL compared to disorder-specific treatments; quality of evidence: moderate to high (assessed using the Cochrane risk-of-bias tool)

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Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Pittock et al. (2018) [77]	No	Patients with symptoms of bulimia nervosa	Weekly emails, F, tasks, manuals, email support, messaging with coach, face-to-face evaluations, group online setting	CBT	Large effects for iCBT in binge eating and purging reduction; sustained at follow-up; no overall significant superiority to controls; quality of evidence: moderate (assessed using the Cochrane risk-of-bias tool)
Massoudi et al. (2019) [51]	Yes	Patients in primary care with depressive/ anxiety symptoms/ disorders	Monitoring, PE, relaxation, behavioral activation, intensive disease management, mindfulness, ACT, medication management, assessment of symptoms, email reminder	CBT, Trans-theoretical Model of Behavioural Change	Small effect of e-health interventions for depression compared to control groups/ TAS, moderate effect compared to waitlist; effects maintained in long-term; no evidence for effectiveness for anxiety; quality of evidence: low-moderate (assessed using the Cochrane risk-of-bias tool)
Lewis et al. (2019) [85]	Yes	Adults with PTSD	PTSD-Coach, trauma-focused PE, skills training, imaginal exposure, cognitive restructuring	CBT	Clinically relevant reduction in PTSD symptoms as compared to waiting list control; quality of evidence: low (assessed using Cochrane risk-of-bias tool)
Harrer et al. (2019) [38]	Yes	University students with symptoms of depression, anxiety, stress, sleep problems, and eating disorders	Mindfulness based intervention, Talk to Me, eating disorder prevention, Moodgym, problem solving simulator, PE, present control intervention, eating and stress management, ACT based intervention, cognitive bias modification	CBT, CBM, third wave CBT, Emotional Disclosure, Skills Training, Personalized F	Small effect on depression, stress and anxiety; moderate effect on eating disorder symptoms and role functioning; no significant effect on well being; quality of evidence: moderate, high risk of bias in 50% of studies (assessed using the Cochrane risk-of-bias tool)

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Hedman et al. (2012) [113]	No	Adult patients (e.g. with depression, social phobia, panic disorder, PTSD)	Online bibliotherapy, therapist contact over the internet (text messages, email), PE	CBT	Large effect sizes on reducing depression, panic disorder, social phobia, small-moderate effect sizes on lowering chronic pain; quality of evidence: high for depression, panic disorder and social phobia (assessed with APA criteria for evidence)
Grist et al. (2019) [63]	Yes	Children and adolescents with anxiety and depression symptoms	films, text, animations, interactive fantasy game, computerized spider exposure therapy, interactive presentation, workbook, self-help manual, anxiety management, dot probe task, problem solving	CBT, computer-delivered Attention Bias Modification programs (ABM), Cognitive Bias Modification programs (CBM), video games utilizing Neurofeedback, Biofeedback, ER Training, internet-based ACT program, Problem-Solving Therapy	Small effect of technology delivered interventions compared to waitlist; CBT medium effect, ABM small effect; no significant benefit over control groups; quality of evidence: high risk of detection bias, low risk of attrition bias (assessed using the Cochrane risk-of-bias tool)
Davies et al. (2014) [36]	Yes	University students with symptoms of de-pression, anxiety, psy-chological distress	Stress management, improving relationship functioning, decreasing elevated levels of perfectionism, mindfulness, social support, increasing use of lucid dreaming,	CBT, Mindfulness, Stress Management Theory, Cognitive Learning Theory, Lucid Dreaming	Improvements in anxiety, depression, stress compared to inactive control; no support for either condition for anxiety or depression compared to active controls; quality of evidence: low (e.g. skewed data), moderate risk of bias (assessed using the Cochrane risk-of-bias tool)

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Coughtrey et al. (2018) [82]	No	Population with depression and other medical conditions (e.g. HIV/ AIDS, multiple sclerosis, parkinson's disease)	Telephone-based Interventions, cognitive and behavioral components	CBT, Interpersonal Psychotherapy, Behavioral Activation, Exposure and Response Prevention, Applied Relaxation	Small to high effects on reducing symptoms of depression or anxiety (greater for uncontrolled compared to controlled studies); but significant change in only 4/14 studies; quality of evidence: moderate to high (assessed using the Effective Public Health Practice Project Quality Assessment Tool)
Asuzu et al. (2019) [58]	Yes	Adolescents and young adults (<24 years) with cannabis misuse	Cannabis specific and non-specific; prevention program tailored to mother-daughter-dyad, RealTeen, Climate Schools, Computer brief intervention	Family Interaction Theory; Personalized and Corrective Normative F; Harm Reduction; Social Competency and Skills Building; Motivational Enhancement Model	Small-medium effects in reduction of cannabis use (7/11); quality of evidence: low (assessed using the National Institute of Health quality rating tool)
Baker et al. (2018) [86]	Yes	Adults with psychotic disorders	Telephone Intervention: relapse prevention, medication adherence, reduction of smoking and cardiovascular disease risk behaviors	Not reported; person-delivered interventions (spoken word and psychological strategies)	Relapse prevention (n=5/8), medication adherence (n=1/3); at least half of outcomes in favor of the telephone intervention, comparable levels of improvement; quality of evidence: low (e.g., high variation in quality, many uncontrolled studies), no standardized approach was used to assess the quality of included studies

Table 1. (continued). Summary of included reviews on eHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Chebli et al. (2016) [53]	No	Pathological gamblers, problem drinkers, smokers, opioid dependent outpatients	Support calls via telephone (positive F, encouragement, answer questions), SMS, email prompts, voice respond messages; peer based social support; behavioral approaches, internet-based modules/ assignments, face-to-face meetings, internet-based forum, information, self-help kit	CBT, MI	Consistent evidence for positive treatment outcomes for addictive behavior (effect size not reported); positive behavioral changes through reduction of problematic behaviors; quality of evidence: moderate (assessed using the Downs and Black checklist)
Danielsson et al. (2014) [74]	Yes	Adults with substance misuse (i.e. cigarettes, alcohol) and/ or pathological gambling	E.g. Online SC training, digital multimedia intervention, emails, SMS; Gambling & Alcohol misuse: Internet intervention with emails, telephone helplines, drinking journal, decision making modules, individual/group intervention, self-help booklet, craving helpline	MI, F, PE, CBT	Telephone helplines can reduce tobacco smoking; inconsistent effects for alcohol use and gambling; all together inconsistent evidence of eHealth on tobacco/ alcohol/ gambling; quality of evidence: low (e.g. lack of controls, very high attrition rates), no standardized approach was used to assess the quality of included studies
Gilmore et al. (2017) [76]	No	Patients with co-occurring PTSD/ trauma symptoms and substance use disorder	Web-based modules, telehealth treatment, skill training, symptom management, MI, expert advice	Behavioral therapy	eHealth efficacious in reducing substance use and trauma symptoms: significant decrease in trauma symptoms in 3/4 studies; significant decrease in substance use in 4/6 studies; quality of evidence: moderate-high (assessed using the GRADE approach)

Notes: CBT= Cognitive Behavioral Therapy; PE=psychoeducation; PA=physical activity; F=feedback; ME=motivation enhancement; MI=motivational interviewing; ER=emotion regulation; SC=smoking cessation; QoL=quality of life; TAU=treatment as usual; VTC=video teleconferencing.

[a] Complete summary of included reviews on eHealth and mHealth are shown in the Supplements, including findings on secondary outcomes, quality from the user perspective, safety, and cost effectiveness.

Table 2. Summary of included studies on mHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary Outcome & quality of evidence
Mental Health Promotion and Prevention					
Sucala et al. (2016) [110]	No	Not reported	Meditation, breathing exercises, digital diary, cognitive restructuring, emotional ratings, problem solving, rational statements, goal setting, hypnosis, physical exercise	No information for 63,5% of the apps, 26,9% with Cognitive Behavioral Approach, 7,7% using mixed approach	Great majority of the mHealth apps do not offer evidence-based interventions; quality of evidence: low (e.g. no information on evidence-base in 96,2% of the apps; none of the 14 apps reported studies on effectiveness); no standardized approach was used to assess the quality of included studies/apps
Edwards et al. (2016) [114]	No	Not reported	Gamification: F, monitoring, reward and threat, goals and planning; individual techniques: self-monitoring of behavior, non-specific reward, social support unspecified, non-specific incentive and focus on past success	Behavior Change Technique	Median number of techniques per app was 14; Common combinations: goal setting, self-monitoring, non-specific reward and non-specific incentive; goal setting, self-monitoring and focus on past success; no correlation between number of techniques and user ratings or price; no standardized approach was used to assess the quality of included studies/apps
Böhm et al. (2019) [90]	No	Healthy Children and adolescents (aged 6-18 years)	F, self-monitoring, goal setting, strategies to overcome barriers, information	Social Cognitive Theory, Behavior Change Technique,	No statistically significant effects on PA-related outcomes with mHealth tools; quality of evidence: low (e.g. small number of studies, inadequate use of validated measures, missing RCTs, heterogeneity of interventions); no standardized approach was used to assess the quality of included apps/ studies

Table 2. (continued). Summary of included studies on mHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary Outcome & quality of evidence
Kim et al. (2019) [93]	Yes	Adults (e.g. overweight university staff and students)	Lifestyle intervention, education and coaching to promote PA, dietary counseling, education related to health behavior, F	Transtheoretical model, Theory of Planned Behavior	Significant increase in PA, significant weight loss in the intervention groups; quality of evidence: moderate (low risk of bias assessed using the Cochrane risk-of-bias tool), but only 5 studies included
Song et al. (2019) [102]	No	General population with unhealthy alcohol use	Motivation (encouraging messages, peer support, monetary compensation), general and personalized information, reminder, and warning	Behavioral change theories (e.g. Theory of Planned Behavior, Health Belief Model, Theory of Reasoned Action, Social Learning, Theory)	63% mHealth interventions brought significant positive outcomes in improving participants' health compared to traditional methods; quality of evidence: high (assessed using Mixed Methods Appraisal Tool)
Feter et al. (2019) [92]	Yes	Not reported	PA interventions with SMS or App promotion using accelerometer, pedometer, questionnaire, daily diary,	Not reported	Efficient in increasing minutes and steps per day in adults when compared to baseline; quality of evidence: moderate-high (assessed using the Downs and Black scale)
Bort-Roig et al. (2014) [91]	No	General population, special populations (e.g. obese patients)	Smartphone strategies to influence PA; PA profiles, goal setting, real-time F, social support networking, and online expert consultation	Behavior Change Theories, including Social Cognitive Theory and the Trans-theoretical Model	PA increases and one study reported PA maintenance over 3 months; quality of evidence: low (e.g. small sample sizes, short study periods), no standardized approach was used to assess the quality of included studies
Muntaner et al. (2016) [95]	No	General population	Monitoring, F, information, interactive voice response system, questionnaire, messages with helpful hints, goal setting, motivational messages, reminders	Social Cognitive Theory, Protection Motivation Theory, Transtheoretical Model, Theory of Planned Behavior, Goal Setting Theory, Problem Solving Theory	6/12 studies reported significant increases in PA levels; quality of evidence: low-moderate (e.g. lack of information provided by studies) (assessed using the Downs and Black scale)

Table 2. (continued). Summary of included studies on mHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary Outcome & quality of evidence
Rathbone et al. (2017) [99]	No	General population	Self-monitoring, SMS, PE, podcast, journal	CBT	Significant decrease in anxiety and stress with medium to large effect sizes, quality of evidence: low to moderate (assessed using Cochrane risk-of-bias tool); 8 of the studies without control groups
Alyami et al. (2017) [29]	No	Not reported	PE, symptom management, therapeutic treatment, self-assessment, supportive resources, multi-purpose	CBT, mobile-based Interpersonal Psychotherapy, smartphone-based CBM for Attention	Over 60% of apps exclusively focused on social anxiety, remainder targeted social anxiety and related conditions; most developers did not provide information on organizational affiliations or content source; most apps used multimedia while 17 apps used text only; quality of evidence not reported
Treatment					
Sander et al. (2020) [109]	No	Soldiers or veterans, family members (of people with PTSD, Clinicians, Children, Police officers or public safety professionals)	63.8% of apps offered elements of mindfulness, relaxation, breathing, or body exercises; information/ PE, assessment, monitoring and tracking, F, skill training, exposure, mindfulness, relaxation, breathing, body exercises, resource orientation, tips and advices	CBT, Behavior Therapy, Systemic Therapy, third wave CBT, Psychodynamic therapy	Overall app quality based on the MARS was medium. Most offered a wide range of content, including established psychological PTSD treatment methods (processing of trauma-related emotions and beliefs, relaxation exercises, and PE); quality of evidence not reported
Terhorst et al. (2018) [111]	No	Patients with depression	Assessment, PE, monitoring and tracking	third wave CBT, CBT, Behavioral Therapy, Alternative Medicine	Overall quality was average. Four high-quality apps were identified and recommended with reservations for practical use; quality of evidence not reported

Table 2. (continued). Summary of included studies on mHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary Outcome & quality of evidence
Ilagan et al. (2020) [108]	Yes	Adults with borderline personality disorder (BPD)	Positive stimuli paired with self, personalized safety-plan, PE on suicidal thoughts, symptom monitoring, digital hope kit, self-help skills, anger management exercises, mindfulness meditation exercises	CBT	No significant effect of apps on BPD symptoms and general psychopathology, quality of evidence: moderate (assessed using Cochrane Collaboration Risk of Bias Assessment Tool)
Loo Gee et al. (2016) [97]	No	General population and patients (aged 17-55 years)	Integrative EMIs: self-monitoring of symptoms, delivery of automated or therapist-delivered psychotherapy content	CBT	EMIs may be a promising treatment for generalized anxiety and may be effective for reducing stress; quality of evidence: low-moderate (assessed using the Cochrane Effective Practice and Organization of Care Group criteria)
Rootes-Murdy et al. (2018) [100]	No	Patients with mood disorders	Apps, phone calls, SMS, mobile web-based surveys; electronic pill dispenser, face-to-face conversation with animated agent	Not reported	Overall satisfaction and feasibility of mobile technology, reduction in mood symptoms; few examined effectiveness of mobile technology improving medication adherence through RCTs; results represent approximately 10% higher mean medication adherence rates when compared to observational studies; quality of evidence: low (e.g. mostly observational studies, technologies only used for short period), no standardized approach was used to assess the quality of included studies

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Table 2. (continued). Summary of included studies on mHealth interventions [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary Outcome & quality of evidence
Miralles et al. (2020) [25]	No	Not reported	Psychological interventions for mental disorders delivered via smartphone, plus SMS and phone calls	CBT, Behavior Therapy, third wave CBT	72.7% of the papers focused on six mental disorders: depression, anxiety, trauma and stressor-related, substance-related and addiction, schizophrenia spectrum, and other psychotic disorders, or a combination of disorders; quality of evidence: low (e.g. little percentage of RCTs, few studies asses effect of mHealth on symptomatology), no standardized approach was used to assess the quality of included studies

Notes: CBT=Cognitive Behavioral Therapy; PE=psychoeducation; PA=physical activity; F=feedback; EMIs=ecological momentary interventions.
[a] Complete summary of included reviews on eHealth and mHealth are shown in the Supplements, including findings on secondary outcomes, quality from the user perspective, safety, and cost effectiveness.

Table 3. Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Mental Health Promotion and Prevention					
Rose et al. (2017) [94]	No	General population of adolescents (aged 10-19 years); specific at-risk populations	Diet and PA education, goal setting, monitoring, parental involvement; counselling; health information, assessment of behavior, skill building, reward system, F, pedometer, self-monitoring, cycling video game, fruit promotion via email, family involvement	Not reported	Significant improvements in behaviour in 8/22; significant improvement in diet and/or PA for majority of interventions with goal setting; self-monitoring less effective without goal setting; significant improvement in behaviour in most interventions with family involvement; quality of evidence: low-moderate (e.g. poor handling of confounding factors, participant selection bias), assessed using a checklist based on quality assessment criteria by the Centre for Reviews and Dissemination
Baker et al. (2018) [64]	No	Older adults	ICT based interventions: using devices with touchscreen, social network services	Social concepts often poorly defined	No evaluation of efficacy due to insufficient attention to social concepts; quality of evidence: low (e.g. very small sample sizes, poorly defined outcomes), Multiple tools were used to assess the quality of included studies (i.e. Cochrane Collaboration Risk of Bias Assessment Tool; PEDro scale, Downs and Black scale)

Table 3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Kreuze et al. (2017) [106]	No	Hetero-geneous, including adults, adolescents, university students	Virtual Hope Box (support, comfort, distract or relax using audio, video, pictures, games, mindfulness exercises, messages, inspirational quotes and coping statements), coping strategies, behavioural activation, interpersonal psychotherapy, community resiliency concepts, problem solving, F	CBT, Cognitive Therapy, Dialectic Behaviour Therapy, Mindfulness-based Cognitive Therapy, Problem-solving Therapy	Participants improved significantly on depression, anxiety, hopelessness, self-esteem, and negative automatic thoughts; promising evidence for reduction of suicidal ideation and mental health co-morbidities; quality of evidence: low (e.g. unprecise study effects, small sample sizes, low engagement); no standardized approach was used to assess the quality of included studies
Lau et al. (2011) [34]	No	Children and adolescents	Goal setting, tips, comic stories, social support emails, self-monitoring, quizzes, games, charts to plan activities, motivational reminder, F, tailored information, online counselling	Health Behaviour Change Theory, Social Cognitive Theory, Transtheoretical Model, Relapse Prevention Model	Evidence supporting efficacy of interventions on improving psychosocial outcomes vs. conventional or no treatment, less consistent for behavioural outcomes; quality of evidence: 7/9 studies good methodological quality; assessed using the Cochrane risk-of-bias tool
Yonker et al. (2015) [103]	No	Adolescents and young adults (aged 11-25 years)	Observation, providing health information, engaging in community, recruiting research participants	Not reported	Positive impact on mental health outcomes; mixed results for community engagement; quality of evidence: low (e.g. 62% of studies with sampling bias, 24% with incomplete datasets, 19% with small sample size); no standardized approach was used to assess the quality of included studies

Table 3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Treatment					
Berry et al. (2016) [115]	No	Individuals with severe mental health problems (e.g. bipolar disorder, schizoaffective disorder, psychotic disorder, schizophrenia)	Medication reminders, information, advice, helpline for crisis intervention, decision making tools, coping skills, check-ins	CBT	High acceptability of online and mobile phone-delivered interventions; acceptability was higher for interventions delivered via mobile phones as compared to online formats; quality of evidence: low (e.g. varied findings, limited number of studies, inaccurate measurement of acceptability), no standardized approach was used to assess the quality of included studies
Walsh et al. (2016) [47]	No	Population with variety of mental illnesses e.g. anxiety, depression, bipolar disorder, eating disorder	Technology based symptom-monitoring, F	Self-monitoring, CBT	Acceptability of monitoring is related to perceived validity, ease of practice, convenient technology, appropriate frequency, helpfulness of F, impact of monitoring on participants' ability to manage health and personal relationships; quality of evidence: low (e.g. descriptive results, high heterogeneity), no standardized approach was used to assess the quality of included studies due to low quality of data

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Table 3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Rice et al. (2014) [69]	No	Young people with depression	PE, behavioural activation, thought monitoring, skills training, online support group postings	CBT	Most intervention studies demonstrated superiority of online intervention vs. comparison treatment (treatment as usual, waitlist, brief PE); no standardized approach was used to assess the quality of included studies
Aref-Adib et al. (2019) [43]	No	Patients with schizo-phreniform disorders and/or bipolar disorder	Web-based computer program, Telecare, online platform, mHealth, peer-run web-based computer program; e.g. mindfulness, shared decision making, aid to build relationships and to communicate.	Not reported	Factors that affect implementation: e.g. lack of motivation, poor information technology skills, language problems, poor mental state, labour-intensive scheduling, availability of telehealth space, equipment, attitudes/beliefs about digital interventions; quality of evidence: low, no standardized approach was used to assess the quality of included studies as research is in early stages
Biagianti et al. (2018) [42]	No	Adults with psychotic disorder	Internet peer-support, peer-support bulletin board, PE, therapy groups, moderated peer discussion forums, psychosocial interventions, social networking, SMS based motivational coaching, goal setting, computerized social cognition training, group texting	Social Cognition Training	Digital interventions+ peer-to-peer communication associated with good retention rates (78,4%), + mental health providers improved engagement, peer-to-peer communication highly engaging; quality of evidence: low (e.g. small samples, no control groups); no standardized approach was used to assess the quality of the included studies

Table 3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Faurholt-Jepsen et al. (2016) [45]	No	In- and outpatients with bipolar disorder type 1	Computer, ChronoRecord, PDA, Prism, Smartphone, MONARCA, Personal Life Chart App, Paper Pencil, Moodswings, Websites on healthy lifestyle; self-monitoring of mood, medications, self-management, PE, F	CBT	Consistent evidence for validity of electronic self-monitored mood for depression; no consistent evidence for validity of electronic self-monitored mood for mania; quality of evidence: moderate (e.g. possible risks of biases) (assessed using the Cochrane risk-of-bias tool)
Goldberg et al., (2018) [44]	No	Patients with mental disorders (e.g. depression, bulimia, psychotic disorder, substance use, bipolar disorder)	Remote measurement-based care as part of treatment e.g. biofeedback, self-guided intervention, psychotherapy, remote therapist support	Remote measurement-based care (RMBC)	Positive effects of the intervention for RMBC as part of multicomponent intervention; inconsistent evidence for clinical effectiveness of intervention alone (effective in 1/3 studies, but not as effective as part of multicomponent intervention); quality of evidence: low (meta-analysis could not be conducted due to high heterogeneity of outcomes and study design), no standardized approach was used to assess the quality of included studies
Perry et al. (2016) [107]	No	Young people (aged 12 – 25 years) with suicidal thoughts	Cognitive restructuring, behavioural activation, focus on problem solving around suicidal ideation, video diaries, message board	CBT	Significant reductions in suicidality, depression and hopelessness (small-moderate effect sizes); quality of evidence: low (only one study, small sample, high attrition rate, no control group); no standardized approach was used to assess the quality of the included studies

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Table 3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Wright et al. (2019) [71]	Yes	Population (≥16 years) with diagnosed depression	Multimedia, text (with images) via computer or app	CBT	Small to moderate effects of ICBT compared to control conditions; significantly larger effects for studies with support from clinician (moderate effect) than for studies without support (small effect); quality of evidence: moderate-high (assessed using the CLEAR NPT)
Xiang et al. (2019) [73]	No	Older adults (≥50 years) with symptoms or diagnosis of depression	Therapist- or self-guided CBT: Beating the Blues, Sadness Program, Manage your Mood, Wellbeing Plus Course, MoodTech,	CBT	Large within-group and between-group effect sizes; quality of evidence: low (assessed using the Cochrane risk-of-bias tool)
Alvarez-Jimenes et al. (2014) [40]	No	≥ 80% of participants diagnosed with schizophrenia-spectrum disorders	Web-based PE; moderated forums for patients and supporters; integrated web-based therapy, social networking and peer and expert moderation; personalized advice based on clinical monitoring; text messaging interventions	CBT	Efficient use in about 80% of patients; high perception as positive and useful, little dropout in follow-up (≤30%); quality of evidence: low (e.g. poor description of methodology/results) (assessed using the Cochrane risk-of-bias tool)
Arshad et al. (2020) [104]	Yes	Adults with suicide attempts/ meeting criteria for NSSI disorder, PTSD, depression, suicidal ideation	Dialectical behavioral therapy techniques, individual ER therapy, toolbox of support (e.g. coping skills, strategies, crisis support)	CBT, DBT, individual ER therapy	Limited evidence for efficacy of internet- and mobile-based interventions for self-injurious thoughts and behaviours, reductions in SB in single-arm noncontrolled studies; beneficial effect on suicidal ideation compared to TAU, not when compared to active controls; quality of evidence: low (assessed using the Cochrane risk-of-bias tool)

Table 3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
Domhardt et al. (2020) [26]	Yes	Children and adolescents with mental and somatic disorders	Internet- and mobile based Interventions (IMIs): webpages, email, chat, videoconferencing, mobile app, instant messaging; psychotherapeutic orientation	CBT	Large effect for IMIs across mental disorders, medium effect of IMIs for somatic conditions compared to nonactive controls; quality of evidence: moderate (assessed using the AMSTAR-2 checklist)
Meyer et al. (2018) [78]	Yes	Population with major depressive disorder, borderline personality disorder, variety of diagnoses	Monitoring, adherence promotion, PE, self-management, relapse prevention	CBT	Larger RCTs showed beneficial effects on symptoms and functioning (effect size not reported); quality of evidence: low (e.g. small sample sizes, unreliable differentiation between on- and offline available software), no standardized approach was used to assess the quality of included studies
Ye et al. (2014) [67]	Yes	Children and adolescents with anxiety and/or depressions	Self-monitoring of moods, stress, alcohol and cannabis use, SMS and phone call support, online self-help sessions, email, SMS, phone calls, family/ group/ teacher support	CBT	Medium effect size in reducing anxiety symptom severity compared to waitlist control, increased remission rate; non-significant reduction of depression symptom severity; no difference in anxiety/ depression symptoms between internet-based intervention and face-to-face intervention; no superiority of usual care; quality of evidence: moderate-high (assessed using a modified version of Quality Assessment Tool for Quantitative Studies)

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Table 3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed) [a]

Reference	Meta analyses	Population	Intervention components	Theoretical and evidence base on process/outcomes	Primary outcomes & quality of evidence
O.Rourke et al. (2016) [55]	No	Hazardous young drinkers	Behavioural interventions; web-based, email, text messages, social network sites; personalized F, monitoring, social norms F (SNS), PE, improving knowledge, self-efficacy and awareness of social norms	Not reported	Interactive approaches (text messaging, email, SNS) significantly reduce frequency of drinking; personalized electronic F reduces alcohol consumption, frequency of binge drinking, and drinking in a non-risky way; quality of evidence: moderate (assessed using the Cochrane risk-of-bias tool)
Dick et al. (2019) [101]	No	Third level students	F, descriptive norm correction, self-affirmation manipulation, theory-based messages, implementation intention tasks, motivational brief intervention, messages based on social cognitive theory	Social Cognitive Theory, little to no detail about design and development process of the intervention	Reduction of substance misuse and initiation (effect size not reported); quality of evidence: low (assessed using the Quality Assessment Tool for Quantitative Studies by the Effective Public Health Practice Project)
Giroux et al. (2017) [24]	No	Adults with high school education and high risk or problematic alcohol/drug use	PE, F, Craving and relapse management, behaviour change, alcohol use journal, control strategies, social skills learning, chat with therapist	CBT, Theory of Planned Behaviour, Solution focused, Self-control, Relapse Prevention	Significant decrease in substance use in 3/4 of studies; long term (12-month follow-up, investigated by only 2 studies): effects maintained for women; quality of evidence: moderate (assessed using the Cochrane criteria checklist)

Notes: CBT=Cognitive Behavioural Therapy; DBT=Dialectical behaviour therapy; PE=psychoeducation; PA=physical activity; F=feedback; ER=emotion regulation; TAU=treatment as usual.

[a] Complete summary of included reviews on eHealth and mHealth are shown in the Supplements, including findings on secondary outcomes, quality from the user perspective, safety, and cost effectiveness.

Discussion

Research in context

Evidence before this study

Digital interventions may help to mitigate the negative psychosocial impact of pandemics. We therefore searched for original papers investigating the use of digital interventions to help alleviate negative psychosocial consequences in earlier coronavirus and influenza outbreaks. On May 3, 2020, we searched Medline, CENTRAL, and PsycINFO with no date and language restrictions using the following keywords: Previous epi-/pandemics (e.g. 'Corona' OR 'SARS' OR 'MERS' OR 'Influenza') AND mental health (e.g. 'Mental dis*' OR 'Depress*') OR social isolation ('Lonel*') AND digital interventions (e.g. 'mHealth' OR 'eHealth' OR 'Telemed*'). A priori defined inclusion criteria were applied (e.g. papers on need, acceptability, usability, safety, and effectiveness). 264 articles were identified and none of the studies met inclusion criteria. Thus, we found no studies on the use of digital interventions during earlier outbreaks.

Added value of this study

For the first time, this meta-review systematically examined the current evidence on feasibility, safety, and effectiveness of digital interventions relevant for improving public mental health by mitigating reported negative psychosocial consequences of epi-/pandemics. It shows that the evidence on eHealth interventions is robust and mHealth interventions very promising if developed and evaluated in context of scientific research projects but very low or non-existing for mHealth apps available in major app Stores.

Implications of all the available evidence

Evidence-based digital interventions may help to mitigate the negative impact of the COVID-19 pandemic on public mental health. Digital interventions are particularly suited to provide low-threshold and timely public mental health care in times of physical distancing and quarantine. As the quality of evidence of currently available apps in app Stores is often unknown or very limited, there is an urgent need to 1) develop and evaluate digital interventions specifically designed to address social isolation and poor mental health during public health crises and

2) make evidence-based digital interventions publicly available to improve public mental health.

Principal findings

Evidence-based eHealth and mHealth interventions may play a central role in areas of public mental health provision (i.e., mental health promotion, prevention of, and treatment for mental disorder) to mitigate the negative consequences of the current COVID-19 pandemic. To date, however, evidence-based recommendations on existing digital interventions that have been developed and evaluated in recent years were still lacking. This meta-review was the first to review the available evidence on the theoretical and empirical base, quality from the user perspective (i.e., acceptability, usability, satisfaction), safety, effectiveness, and cost effectiveness of digital interventions in the area of public mental health provision, that is, mental health promotion at the population level, indicated, selective, or universal prevention targeting at-risk, sub-, or the entire population as well as treatment and services for people with mental disorders.

First, there was robust evidence on effectiveness of telemedical internet-based or eHealth interventions and initial evidence on the effectiveness of mHealth interventions in relation to mental health outcomes likely affected by the current COVID-19 pandemic (e.g., anxiety, depression), especially if interventions are informed by clinical guidelines and co-designed by service users and mental health professionals. Second, effectiveness, acceptability, feasibility, and user satisfaction have been described to be particularly high if digital interventions are embedded in a therapeutic context and include some form of social interaction with a mental health professional (blended-care approach). Third, some of the included systematic reviews and meta-analyses suggest non-inferiority of effectiveness for some eHealth interventions as compared to traditional face-to-face therapy, but further replication is needed before firm conclusions can be drawn. Thus, in order to exclude the risk of infection in the current public health crisis, clinicians and other health professionals may consider combining differing types of digital interventions (e.g. counselling or psychotherapy using videoconference software augmented by a smartphone-based mHealth app) as this approach may be particularly promising given the current evidence base and reflects a novel digital version of the blended-care approach. However, more research is needed to investigate long-term treatment effects and effects of symptom monitoring on mental health outcomes. Notably, the evidence on the use of digital interventions for elderly as well as children is very limited. This is an important finding as these age groups may be more strongly challenged by the current pandemic. Fourth, most studies to date do not specifically investigate the additive effects on health-related outcomes when using more advanced techniques (e.g., accelerometer, GPS) to further personalize the delivery of intervention components, gamification elements as well as the integration of other technologies such as wearables although it has been described to be potentially beneficial in some of the included reviews [25, 89, 92, 114]. Fifth, the theoretical basis of most digital interventions that have been described in previous reviews were found to be CBT or third-wave CBT as they may be particularly amendable to translation into digital intervention components [23, 25, 26]. Thus, clinicians with an expertise in CBT techniques may find it easier to purposefully incorporate intervention components delivered using digital tools in their daily clinical routines. However, findings suggest that there is a need to further improve the theoretical foundation of digital intervention, particularly mHealth interventions publicly available in major app stores. Sixth, the data available on process quality and cost-effectiveness of eHealth and mHealth interventions is very limited. Seventh, users frequently report concerns about data safety and privacy [115]. While eHealth and mHealth interventions developed and evaluated by research groups generally comply with the General Data Protection Regulation (GDPR; in European countries) and work in accordance with Good Clinical Practice (GCP) standards, the contents of many mHealth apps currently available in major app stores, do not explicitly refer to existing clinical guidelines and recommendation by learned societies [50, 116]. There are a number of reviews that have concluded that mHealth apps use problematic data sharing and privacy practices [8, 27, 28] and that there may not only be a lack of quality of offered content but even harmful intervention components. Also, although not specifically reported in included systematic reviews and meta-analysis, the recent surge in the use of popular and freely available platforms (e.g. Zoom, Skype) to provide online mental health services rather than secured platforms may be another cause of concern [117] as these platforms do mostly not comply with national standards for sensitive patient data protection. In order to demonstrate user safety, clinical guidelines should be explicitly taken into account and advice by mental health professionals, learned societies, and IT professionals actively incorporated.

Overall, existing apps available in app stores should be used with caution due to the existing risks in data and clinical safety as well as lack of evidence on their effectiveness.

Limitations

This meta-review has several limitations. Because of time constraints and the rapid meta-review format of the current study, the quality of included systematic reviews was not evaluated using established assessment tools (e.g. AMSTAR 2 checklist [118]). Along similar lines, the conclusions drawn in this meta-review on the quality of evidence are largely based on quality assessments undertaken in the included systematic reviews and meta-analysis. However, if the quality of evidence was not systematically evaluated using a standardized approach it is indicated in Tables 1-3. Also, only one reviewer screened identified articles while a second reviewer independently screened a randomly selected subset (40%) of studies. However, this meta-review was conducted in line with the state of the art of conducting rapid reviews [119]. Furthermore, the World Health Organization has explicitly recommended rapid reviews for evidence synthesis during the ongoing public health crisis, given these are urgently needed for policy makers and the public [120].

In considering the urgent need of continued access to mental health care for vulnerable individuals during the COVID-19 pandemic, and the importance of developing and implementing public mental health prevention and promotion strategies, digital interventions should be provided by public health services and routinely offered during infection control measures of pandemics. Since there is currently no direct evidence on digital interventions that aim to minimize the psychosocial impact of previous corona and influenza virus outbreaks, digital interventions should be developed and evaluated by research groups in close collaboration with relevant stakeholders to ensure established standards for investigating quality from the user perspective, effectiveness, and cost effectiveness are met. Importantly, evidence-based digital interventions are rapidly deliverable and scalable at the population level. This may facilitate delivering personalized care and minimizing the negative impact of the COVID-19 pandemic on public mental health.

Conclusions

Decision-makers and stakeholders, including policymakers, technology companies, and public health professionals, should join forces to develop evidence-based strategies for mental health care in the area of public mental health provision, especially in moments of public health crises. As studies from previous pandemics as well as accumulating evidence from the COVID-19 pandemic suggest a negative impact on public mental health, the development and implementation of mental health promotion and prevention strategies at the population level may be an important measure to improve public mental health. As shown in earlier studies, digital interventions which incorporate contact with mental health staff in a blended-care approach may be particularly suited to alleviate mental health burden in help-seeking individuals. At times of COVID-19 and physical distancing measures, this may be translated into a digital blended care approach by combining telemedical with internet-based eHealth or smartphone-based mHealth interventions. Furthermore, efforts should be made to systematically evaluate currently available digital interventions based on established criteria of digital mental health and mental health services research (e.g., National Health Service Apps Library in the UK; Platform for Digital health applications in Germany; App Evaluation Database provided by the Division of Digital Psychiatry, Beth Israel Deaconess Medical Center in the USA) [121-123]. This would systematize the search for evidence-based mHealth apps and thus allow clinicians and interested users to make more informed decisions on the quality of currently available digital interventions. There is also a need to carefully examine the role of social inequalities and the related digital divide as well as possible barriers (e.g. disproportional access to necessary technologies, educational requirements, language skills, cultural peculiarities, motor, or cognitive impairments), which can influence the access to and use of information platforms of digital mental health interventions.

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10

Supplementary material

Supplement 1. Search strategy: MEDLINE

Database: Ovid MEDLINE(R) <1946 to April Week 4 2020>

Search Strategy:

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1 exp Mental Health/ (37303)
2 exp Psychopathology/ (7194)
3 exp Mental Disorders/ (1225111)
4 "mental health".tw. (113359)
5 "mental dis*".tw. (37183)
6 psychopatholog*.tw. (35952)
7 "mental ill*".tw. (25880)
8 "psychiatric dis*".tw. (41201)
9 SMD.tw. (6004)
10 exp Depression/ (116762)
11 exp Depression, Postpartum/ (5418)
12 exp Depressive Disorder, Major/ (29572)
13 exp Depressive Disorder/ (107891)
14 exp Dysthymic Disorder/ (1135)
15 exp Mood Disorders/ (120656)
16 exp Affect/ (32941)
17 exp Emotions/ (237356)
18 exp Emotional Regulation/ (195)
19 depress*.tw. (394544)
20 dysthymi*.tw. (2850)
21 melanchol*.tw. (2736)
22 mood*.tw. (63196)
23 affect*.tw. (1563493)
24 emotion*.tw. (160488)
25 sad.tw. (8270)
26 lonel*.tw. (5604)
27 exp Anxiety/ (83635)
28 exp Anxiety Disorders/ (78672)
29 exp Phobic Disorders/ (11222)
30 exp Agoraphobia/ (2581)
31 exp Performance Anxiety/ (140)
32 exp Panic Disorder/ (6843)
33 exp Panic/ (2598)
34 exp Fear/ (32507)
35 anxi*.tw. (172074)
36 agoraphobi*.tw. (3157)
37 GAD.tw. (7875)
38 panic*.tw. (16859)
39 fear*.tw. (68150)
40 phobi*.tw. (10167)
41 fright*.tw. (2288)
42 exp Obsessive Behavior/ (1404)
43 exp Obsessive-Compulsive Disorder/ (14429)

44 OCD.tw. (7833)
45 obsessive*.tw. (15408)
46 exp Psychotic Disorders/ (51615)
47 exp Paranoid Disorders/ (4078)
48 exp Schizophrenic Psychology/ (33207)
49 exp Schizophrenia/ (103737)
50 exp Schizophrenia, Disorganized/ (538)
51 exp Schizophrenia, Paranoid/ (4110)
52 exp Schizophrenia, Catatonic/ (576)
53 exp Prodromal Symptoms/ (1578)
54 exp Schizophrenia, Childhood/ (1549)
55 psycho*.tw. (537844)
56 schizo*.tw. (124146)
57 paranoi*.tw. (7341)
58 hallucinat*.tw. (12064)
59 delusion*.tw. (9419)
60 exp Bipolar Disorder/ (39900)
61 bipolar*.tw. (53604)
62 mani*.tw. (498873)
63 hypomani*.tw. (2534)
64 exp Personality Disorders/ (41057)
65 exp Borderline Personality Disorder/ (6757)
66 exp Antisocial Personality Disorder/ (9455)
67 exp Dependent Personality Disorder/ (226)
68 exp Schizoid Personality Disorder/ (593)
69 exp Histrionic Personality Disorder/ (3993)
70 "personality disorder*".tw. (17440)
71 histrionic.tw. (598)
72 borderline.tw. (37356)
73 dependen*.tw. (1444582)
74 exp Narcissism/ (2862)
75 narci*.tw. (3641)
76 exp Attention Deficit Disorder with Hyperactivity/ (28293)
77 exp "Attention Deficit and Disruptive Behavior Disorders"/ (32289)
78 exp Attention/ (77279)
79 ADHD.tw. (20249)
80 attention.tw. (325691)
81 exp Child Behavior Disorders/ (20188)
82 exp Conduct Disorders/ (3363)
83 "callous unemotional".tw. (597)
84 "dysfunction of behavio*".tw. (275)
85 "social behavio*".tw. (11306)
86 antisocial.tw. (7625)
87 "anti-social".tw. (354)
88 dyssocial.tw. (34)
89 dissocial.tw. (175)
90 "aggressive behavio*".tw. (13076)
91 defiant.tw. (2087)
92 delinquen*.tw. (6130)
93 "conduct disorder*".tw. (4095)
94 exp Autistic Disorder/ (20200)
95 autis*.tw. (37691)

96 exp Adjustment Disorders/ (4204)
97 exp Social Adjustment/ (23204)
98 adjustment.tw. (139354)
99 exp Cognition Disorders/ (92327)
100 exp Intellectual Disability/ (95241)
101 cognition*.tw. (57240)
102 intellect*.tw. (34165)
103 disabilit*.tw. (153891)
104 learning.tw. (225885)
105 exp "Sleep Initiation and Maintenance Disorders"/ (13034)
106 exp Sleep Disorders, Circadian Rhythm/ (2269)
107 exp Sleep/ (78550)
108 sleep.tw. (138836)
109 insomnia.tw. (16769)
110 nightmares.tw. (1547)
111 exp Stress Disorders, Traumatic/ (35714)
112 exp Stress Disorders, Post-Traumatic/ (32062)
113 exp Stress, Psychological/ (129346)
114 exp Stress, Physiological/ (214074)
115 stress.tw. (611314)
116 distress*.tw. (103640)
117 "post-trauma*".tw. (26218)
118 PTSD.tw. (19272)
119 exp Substance-Related Disorders/ (275494)
120 "substance disorder*".tw. (310)
121 (substance adj3 abus*).tw. (23317)
122 addict*.tw. (53307)
123 cannabis.tw. (13262)
124 tobacco.tw. (84037)
125 exp Alcoholism/ (74611)
126 exp Alcohol Drinking/ (68175)
127 alcohol*.tw. (279470)
128 amphetamine.tw. (20830)
129 hallucinogens.tw. (1264)
130 exp "Feeding and Eating Disorders"/ (30305)
131 exp Anorexia Nervosa/ (12849)
132 exp Binge-Eating Disorder/ (1420)
133 exp Bulimia Nervosa/ (2321)
134 exp Eating/ (71950)
135 exp Bulimia/ (5444)
136 exp Anorexia/ (4933)
137 "eating disorder*".tw. (16385)
138 "body-imag*".tw. (10541)
139 "binge-eating".tw. (4751)
140 bulimi*.tw. (7600)
141 anorexi*.tw. (29319)
142 exp Sexual Dysfunctions, Psychological/ (26480)
143 sexual.tw. (166394)
144 orgasm.tw. (2590)
145 desire.tw. (27818)
146 erectile.tw. (18047)
147 ejaculation.tw. (6367)

148 dyspareunia.tw. (3342)
149 exp Self-Injurious Behavior/ (69868)
150 "self-injur*".tw. (3839)
151 "self-harm".tw. (4156)
152 suicid*.tw. (66400)
153 "at risk*".tw. (147796)
154 "high risk*".tw. (236307)
155 ARMS.tw. (49756)
156 UHR.tw. (712)
157 vulnerab*.tw. (107836)
158 exp Anhedonia/ (959)
159 anhedon*.tw. (3456)
160 exp Motivation/ (167764)
161 exp Reward/ (21181)
162 motivation.tw. (49856)
163 exp Developmental Disabilities/ (19858)
164 exp Personality Development/ (153603)
165 exp Adaptation, Psychological/ (125798)
166 development*.tw. (2017494)
167 internali*.tw. (54249)
168 externali*.tw. (12204)
169 "quality of life".tw. (225450)
170 happiness.tw. (5276)
171 satisfact*.tw. (227385)
172 "social support".tw. (31355)
173 pleasure.tw. (5782)
174 gratitude.tw. (1050)
175 compassion*.tw. (7850)
176 well-being.tw. (60119)
177 resilien*.tw. (22733)
178 or/1-177 (8415847)
179 exp Telemedicine/ (27662)
180 exp Internet-Based Intervention/ (89)
181 internet.tw. (39914)
182 ehealth.tw. (1775)
183 "web-based".tw. (23543)
184 "e-health".tw. (1709)
185 telemed*.tw. (8716)
186 telehealth*.tw. (2984)
187 teletherap*.tw. (1266)
188 uhealth.tw. (1)
189 "u-health".tw. (19)
190 eTherap*.tw. (9)
191 "e-Therap*".tw. (373)
192 exp mobile application/ (5560)
193 exp Smartphone/ (4124)
194 "mobile health".tw. (1928)
195 mHealth.tw. (1600)
196 m-health.tw. (279)
197 app.tw. (19176)
198 "app-based".tw. (242)
199 "mobile app*".tw. (2150)

200 "mobile-based".tw. (245)
201 "phone-based".tw. (773)
202 smartphone.tw. (5176)
203 "smartphone-based".tw. (910)
204 "digital tool".tw. (45)
205 "digital assist*".tw. (965)
206 apps.tw. (3316)
207 or/179-206 (115779)
208 exp Primary Prevention/ (150004)
209 exp Secondary Prevention/ (20087)
210 exp Health Promotion/ (75852)
211 exp Early Intervention, Educational/ (2987)
212 exp Internet-Based Intervention/ (89)
213 exp Early Medical Intervention/ (2920)
214 prevention.tw. (462307)
215 intervention*.tw. (812225)
216 "health promotion*".tw. (25265)
217 treatment*.tw. (3843362)
218 "health service".tw. (39081)
219 therap*.tw. (2375507)
220 counselling.tw. (22841)
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Supplement 2

Table S1. Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Mental Health Promotion and Prevention				
Alkhaldi et al. (2016) [33]	Not reported	Possible increase of engagement with technology-based strategies	No adverse events reported	Not reported
Elaheebocus et al. (2018) [32]	Social media features might be relevant for improving variety of health outcomes	Lowered helpfulness, increased satisfaction, and motivation reported	No adverse events reported	Not reported
Cotie et al. (2018) [35]	eHealth intervention as a tool for promotion of lifestyle improvements highly accessible, time efficient	Not reported	Not reported	Cost effectiveness reported; no data on savings provided
Deady et al. (2017) [59]	Inadequate evidence on medium to long-term effect and reduction of incidence of mental disorders	Not reported	Not reported	Not reported
Heber et al. (2017) [23]	Not reported	Not reported	Not reported	Cost effectiveness reported; no data on savings provided
Ennis et al. (2018) [31]	No long-term follow-up data, heterogeneity of studies and outcomes	Not reported	Adverse events reported in one study	Potential low cost; no data on savings provided
Pennant et al. (2015) [52]	Sparse evidence for other computerized interventions (computerized but not cCBT)	Not reported	Not reported	Not reported
Fleming et al. (2014) [61]	Not reported	Promising findings on adherence, but moderate satisfaction	Not reported	Not reported

Table S1. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Flujas-Contreras et al. (2019) [37]	Positive effects on parenting and emotional wellbeing of parents and Children; increased attendance and participation level in technology-based treatment (compared with traditional interventions)	Not reported	Not reported	Not reported
Boumparis et al. (2019) [57]	Not reported	Not reported	Not reported	eHealth intervention significantly more cost-effective than therapist-delivered intervention; no data on savings reported
Hadjistavropoulos et al. (2020) [54]	Guided ICBT can be useful for patients at risk for treatment failure	Not reported	Not reported	Not reported
Tait et al. (2010)[56]	Insufficient data to assess utility of SC interventions	Not reported	Not reported	Not reported
Treatment				
Arguel et al. (2018) [50]	Lack of guidelines for online social network interventions; no reference to health psychology theories	Not reported	Not reported	Not reported
Lin et al. (2019) [75]	Telemedicine interventions are promising; especially useful when other treatments are less available; high satisfaction; substantial methodological limitations	High satisfaction; comparable to in-person treatment; technical challenges	Not reported	Higher costs for videoconference than treatment via phone; no data on savings provided

Table S1. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Simon et al. (2019) [39]	Greater dropout from ICBT than waitlist; no difference in dropout between ICBT and I-non-CBT	High satisfaction in experimental treatment groups; moderate to high acceptability	Two participants in intervention condition reported clinically significant increase in depression, one in anxiety symptoms (both experienced death of family member during treatment)	ICBT for individuals with PTSD offers potential as a cost-effective, timely and accessible treatment choice; no data on savings provided
Richards et al. (2012) [70]	Similar effect for administrative-supported studies; support only significantly different between studies with no support vs therapist support	70-80% reported general satisfaction, perceived benefit, program equaled or was better than a usual therapy; 95% recommended intervention	Not reported	Unsupported programs have the potential to increase access, at minimal cost, especially where human resources are limited; no data on savings provided
Sierra et al. (2018) [79]	Not reported	Not reported	Not reported	Cost effectiveness reported; no data on savings provided
Erbe et al. (2017) [46]	Blended therapy time effective; lower dropout rates and/or greater abstinence rates of patients with substance abuse, may help maintain effects of inpatient therapy, may increase effects of psychotherapy	Blended Interventions can lead to lower dropout rates and greater abstinence rates of patients with substance abuse	Not reported	Cost effectiveness reported; no data on savings provided
Lau et al. (2016) [62]	Not reported	Not reported	Not reported	Not reported
Irvine et al. (2020) [88]	Not reported	No significant differences in alliance	Going out to engage in a face-to-face appointment may be essential for therapeutic process	Cost effectiveness reported; no data on savings provided

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Table S1. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Gentry et al. (2019) [87]	VTC is feasible	High satisfaction, generally positive F from participants (despite technical challenges)	Not reported	Not reported
Grist et al. (2013) [65]	Moderators: mean age of study sample (negative correlation of age and effectiveness), type of control group	Not reported	Not reported	Cost effectiveness reported; no data on savings provided
Axelsson et al., (2019) [112]	2/3 responded to ICBT, 1/2 achieve remission; control condition as moderator of effect size; effects in routine care, effects mostly sustained at 12-month follow-up	Not reported	Not reported	Therapist-guided ICBT cost-effective when compared to passive controls and internet-delivered behavioral stress management; no data on savings provided
Berryhill et al. (2019) [80]	No differences between videoconferencing and face-to-face groups	Not reported	Not reported	Not reported
Bolton et al. (2015) [82]	No superiority of telepsychology to face-to-face psychotherapy in long-term maintenance, eHealth as potential short-term treatment option; contributes to immediate, positive changes in 1/3 physical outcomes and 10/20 psychosocial outcomes	High consumer satisfaction and treatment acceptance, participation rate (83%) comparable to face-to-face psychotherapy, participants favored short-term treatment conditions	Not reported	Not reported
Castro et al. (2020) [81]	Not reported	Mean adherence: 73%	Not reported	Not reported

Table S1. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Stech et al. (2020) [68]	No impact of program length, inclusion or arousal reduction techniques, degree of clinician support	Not reported	Not reported	Not reported
Rees et al. (2015) [83]	Lack of comparison with active control groups	Not reported	Not reported	Cost effectiveness reported; no data on savings provided
Richardson et al. (2010) [60]	Reduction in clinical symptoms and improvements in behavior, self-esteem and cognitions in all studies; preliminary evidence for ICBT as acceptable and effective for children/ adolescents	Moderate-high satisfaction with treatment from children and parents despite often high levels of drop out and non-completion	Not reported	Not reported
Rost et al. (2017) [41]	Not reported	High level of acceptance	Not reported	Not reported
Pasarelu et al. (2017) [66]	Moderate effect on comorbidities; differences in depression outcomes compared to disorder-specific; treatment small-moderate heterogeneity	Not reported	Not reported	Not reported
Pittock et al. (2018) [77]	Not reported	Not reported	Not reported	Not reported

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Table S1. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Massoudi et al. (2019) [51]	Internet-based interventions as useful and acceptable for users as common treatment	Not reported	Not reported	Guided and self-guided e-health interventions more cost-effective than TAU; usual primary care provision for depression more cost-effective than guided e-health interventions and primary care; guided e-health intervention 94% likely to be cost-effective compared to waitlists; no data on savings provided
Lewis et al. (2019) [85]	No evidence to support maintenance of symptom improvement at follow-up (3–6 months)	Not reported	Not reported	Not reported
Harrer et al. (2019) [38]	Not reported	Not reported	Not reported	Not reported
Hedman et al. (2012) [113]	ICBT tested for 25 different clinical disorders; ICBT produces equivalent effects compared to conventional CBT	Not reported	Not reported	57% average probability of ICBT being cost-effective at willingness to pay of zero; cost-effective intervention compared with no treatment

Table S1. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Grist et al. (2019) [63]	CBT based technology delivered interventions are useful when access to traditional psychotherapies is limited/delayed; type of control condition, problem severity, therapeutic support, parental support, and continuation of other ongoing treatment as moderators	Engagement was improved by therapeutic support	Not reported	Low cost alternative treatment when face to face treatments are not available or feasible; no data on savings provided
Davies et al. (2014) [36]	Not reported	Interventions are highly useable, satisfactory, and perceived as moderately to highly useful and helpful	Not reported	Not reported
Coughtrey et al. (2018) [82]	Not reported	Not reported	Not reported	Not reported
Asuzu et al. (2019) [58]	e-Health can overcome barriers to access care; longer duration of intervention adherence	Not reported	Not reported	Not reported
Baker et al. (2018) [86]	Telephone interventions were feasible and effective for improving health outcomes	Not reported	Not reported	Not reported
Chebli et al. (2016) [53]	Reduces barriers of access	High satisfaction with SC intervention; preference for Internet-based service in opioid users	Not reported	Time-efficient and cost-effective, compared to face-to face treatment methods; no data on savings provided
Danielsson et al. (2014) [74]	Lack of studies with control groups	Not reported	Not reported	Not reported
Gilmore et al. (2017) [76]	Technology-based interventions are feasible; moderate-high quality of studies	Not reported	Not reported	Not reported

Notes: CBT= Cognitive Behavioral Therapy; PE=psychoeducation; F=feedback; SC=smoking cessation; TAU=treatment as usual; VTC=video teleconferencing.

Table S2. Included studies on mHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Mental Health Promotion and Prevention				
Sucala et al. (2016) [110]	Only 3,8% of the apps have been rigorously tested	Not reported	Possible damaging consequences for people suffering from anxiety, who may use untested apps instead of specialized care	Not reported
Edwards et al. (2016) [114]	Few health apps employ gamification: wide variation in the use of behavior change techniques, which may limit potential to improve health outcomes; no correlation between user rating (possible proxy for health benefits) and game content or price	Not reported	Not reported	Not reported
Böhm et al. (2019) [90]	No effect of activity trackers on PA	81% interested in trying various PA-apps, 92% enjoyed requirement of being active	Not reported	Not reported
Kim et al. (2019) [93]	Smartphone-based health interventions significantly affect weight loss and increase PA; modest evidence for using smartphone health programs to improve young adults' PA, weight control and body mass index	Not reported	Not reported	Not reported

Table S2. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Song et al. (2019) [102]	33% cognitive changes significantly improved	Not reported	Significant negative outcome reported for male participants in intervention arm in one study	Cost effectiveness reported; no data on savings provided
Feter et al. (2019) [92]	Mobile phone-based PA interventions were effective to increase minutes and steps per day in adults; promotion of engagement through curiosity	Not reported	Not reported	Not reported
Bort-Roig et al. (2014) [91]	Validity of phone-based assessment rarely considered; measurement properties found average-to-excellent levels of accuracy for different behaviors; smartphone apps have potential for PA promotion	PA profiles, real-time F, social networking, expert consultation, and goal setting were identified as key features that facilitated PA engagement	Not reported	Not reported
Muntaner et al. (2016) [95]	Important tool for disease prevention and interventions affecting health behavior	Not reported	Important to evaluate safety and effectiveness before launching an app	Mobile devices are inexpensive tools; no data on savings provided
Rathbone et al. (2017) [99]	Significant increase in step count, moderate effects on moods, moderate to large effects on depression, large effect on increased positivity	High satisfaction with texting intervention, individuals perceive mHealth to be effective	Not reported	Cost effectiveness reported; no data on savings provided

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Table S2. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Alyami et al. (2017) [29]	Social anxiety apps have potential to overcome barriers to accessing treatment; none of the apps identified have had studies on their effectiveness published; evidence base is lacking, currently not possible to recommend their use	Not reported	Not reported	Not reported
Treatment				
Sander et al. (2020) [109]	Users are confronted with great difficulties in identifying useful high-quality apps, most apps lack an evidence-base	Not reported	Inadequate data protection and privacy declarations: passwords and logins were required in only 10% of apps, 17% provided a privacy statement	Not reported
Terhorst et al. (2018) [111]	Depression apps available in German showed an average quality; general lack of evidence; identified apps can only be recommended with reservations	Not reported	Lack of evidence	Not reported
Ilagan et al. (2020) [108]	Evidence on BPD-related interventions delivered via smart-phone apps is still weak; too early to recommend them	Dropout rates ranging from 0 – 56,7%; smartphone applications reported to be user-friendly	Some studies reported suicide attempts or slower reduction of suicide risk compared to control group	Not reported

Table S2. (continued). Included reviews on eHealth interventions

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Loo Gee et al. (2016) [97]	EMIs are associated with a small, but significant reduction in generalized anxiety symptoms; EMIs targeting stress may be effective; few studies examined EMIs targeting other anxiety-related conditions: mixed results	Not reported	Not reported	Not reported
Rootes-Murdy et al. (2018) [100]	Mobile technologies have potential to improve medication adherence, can be utilized for symptom tracking, side effects tracking, direct links to prescription refills, and provide patients with greater ownership over their treatment progress	Improvements in medication adherence could not be conclusively attributed to intervention due to the observational study designs and lack of comparison groups	Not reported	Not reported
Miralles et al. (2020) [25]	Depression and anxiety disorders are primarily covered, in line with their real-world prevalence	Not reported	31%-49% of included mental health apps do not include a privacy policy; data can be distributed to (third-party) services for storage and analysis; risk that data is being transmitted over insecure networks	Not reported

Notes: PA=physical activity; F=feedback; EMIs=ecological momentary intervention.

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Table 3. Summary of included reviews on interventions including eHealth and mHealth interventions (mixed)

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Mental Health Promotion and Prevention				
Rose et al. (2017) [94]	Lack of evidence on medium to long term effects	Not reported	Not reported	Not reported
Baker et al. (2018) [64]	Poorly defined social outcomes; limited methodologies to evaluate interventions	Not reported	Not reported	Not reported
Kreuze et al. (2017) [106]	Not reported	Not reported	Elevated suicide risk at follow-up	The mean incremental cost-effectiveness ratio was US$37,985; willingness to pay for a favorable treatment response was high
Lau et al. (2011) [34]	Not reported	Not reported	Not reported	Not reported
Yonker et al. (2015) [103]	75 of included studies were observational, only 12 including an intervention	One study found that adolescents did not feel comfortable having an unknown health care provider screen their social media accounts	Privacy and confidentiality issues	Cost effective recruitment strategy; no data on savings provided
Treatment				
Berry et al. (2016) [115]	No significant relationship between clinical characteristics and acceptability	Many participants satisfied with clarity and appearance of interventions	Concerns about safety, privacy and confidentiality in some studies	Not reported
Walsh et al. (2016) [47]	Not reported	Moderate-strong rates of participation in 2/3 of studies, lower rates in 1/3; overall positive experience; perceived lack of support for unguided participants (F messages unhelpful)	Not reported	Not reported

Table S3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed)

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Rice et al. (2014) [69]	There are young individuals who may be more willing to disclose information digitally than in person	Some interventions report relatively low levels of engagement	Privacy concerns reported	Cost effectiveness reported; no data on savings provided
Aref-Adib et al. (2019) [43]	No single factor identified as key barrier/facilitator; majority of factors centered at level of individual or intervention; complexity of digital interventions as barrier for people with psychiatric symptoms, low premorbid intelligence quotient, or low IT skills	Easy and flexible access to digital interventions; possibility of sharing intervention with others	A minority of people with psychosis became paranoid or experienced an increase in symptoms	Costs for developing interventions and delivery as barriers; no data on savings provided
Biagianti et al. (2018) [42]	All interventions feasible and acceptable for broad spectrum of mental health problems though significant variation in their effects on health-related outcomes has been found	Acceptability high for online social networking integrated in evidence-based therapies	Increased anxiety, low self-esteem, psychological distress, and depression in young people with frequent social media use	Cost effective; no data on savings provided
Faurholt-Jepsen et al. (2016) [45]	Not reported	Not reported	Not reported	Not reported
Goldberg et al., (2018) [44]	Not reported	Moderate-high adherence/ acceptability for daily, weekly and monthly assessment with tendency to higher adherence for less frequent assessment; moderate-high satisfaction with RMBC as stand-alone assessment and part of a multicomponent intervention	Not reported	Not reported

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Table S3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed)

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Perry et al. (2016) [107]	Not reported	Not reported	Potential risk of cyber-bullying, unknown safety of vulnerable information	Potential cost reduction; no data on savings provided
Wright et al. (2019) [71]	Lower effect sizes for studies with lower completion rates and studies in primary care practices	Not reported	Not reported	Not reported
Xiang et al. (2019) [73]	Participant's age as moderator of effect size (negative correlation); larger effects for studies excluding participants with severe symptomatology	Not reported	Not reported	Not reported
Alvarez-Jimenes et al. (2014) [40]	Online and mobile-based interventions can improve positive psychotic symptoms, hospital admissions, socialization, social connectedness, depression, medication adherence	Feasible and acceptable to patients with schizophrenia (80% completed the majority of sessions); 26% had difficulties with online PE, 12% found online CBT not helpful	Need of careful evaluation of new interventions (engagement rates, intervention/patient factors)	Not reported
Arshad et al. (2020) [104]	Not reported	Text message-based services: high perceived helpfulness, good way to stay in touch with services; mobile phone apps: high perceived helpfulness and satisfaction with content; internet-delivered CBT and DBT approaches: high perceived helpfulness and utility	Not reported	Not reported

Table S3. (continued). Summary of included reviews on interventions including eHealth and mHealth interventions (mixed)

Reference	Secondary outcomes	Quality from user perspective	Safety	Cost effectiveness
Domhardt et al. (2020) [26]	Age, symptom severity and source of outcome assessment as moderators	Not reported	Not reported	Not reported
Meyer et al. (2018) [78]	No study focused on well-being of relatives; identified studies mainly target mood disorders	SMART: app perceived as useful and helpful for self-management, significant associations between clinician-rated mood symptoms and daily self-ratings; DBT-Coach: easy to use and helpful for ER	Not reported	Not reported
Ye et al. (2014) [67]	Not reported	Not reported	Not reported	Not reported
O.Rourke et al. (2016) [55]	No impact of intervention length on effectiveness	Interactive approaches increase ease of engaging in intervention with high acceptability	Not reported	Not reported
Dick et al. (2019) [101]	Low study quality (lack of blinding, self-report measures)	Lack of engagement	Increase in substance misuse in one study	Not reported
Giroux et al. (2017) [24]	Online interventions are accepted by people in workforce who seek help for the first time	Not reported	Not reported	eHealth presents a better cost-efficacy ratio; online interventions have potential to cover large areas at low costs and reach populations that are harder to reach; no data on savings provided

Notes: CBT=Cognitive Behavioural Therapy; DBT=Dialectical behaviour therapy; PE=psychoeducation; PA=physical activity; F=feedback; ER=emotion regulation.

CHAPTER 11

General discussion

This thesis builds upon the available literature by (1) examining the role of the jumping to conclusions reasoning (JTC) bias and working memory performance (WMP) in the development and persistence of an extended transdiagnostic psychosis phenotype in individuals with co-occurring affective dysregulation and psychotic experiences (PEs) in the general population (**Part 1; chapters 2-3**), (2) investigating stress sensitivity in daily life as a putative transdiagnostic mechanism involved in linking adverse childhood experiences (ACEs) and mental health outcomes in a sample of young service users with depression, anxiety, and psychosis using an experience sampling study design (**Part 1; chapters 4-6**), (3) exploring new avenues for digital interventions, such as smartphone-based ecological momentary interventions (EMIs) and other mobile health (mHealth) intervention, internet-based (eHealth) interventions, and virtual-reality (VR) based interventions, in diverse settings across the whole spectrum of public mental health (**Part 2; chapters 7-8**), (4) investigating the effects of the COVID-19 pandemic on youth mental health as well as young individuals' use of, and attitude towards, digital interventions in a nationally representative sample, and (5) examining the potential use of existing digital intervention for mitigating negative consequences of the COVID-19 pandemic (**Part 2; chapters 9-10**).

This concluding chapter will be centered around the aims of this thesis specified in the introduction and a critical appraisal of all chapters' principal findings and methodological considerations. This will be followed by a broader discussion on future directions and potential clinical implications in light of existing and newly generated evidence.

Cognitive factors and the extended transdiagnostic psychosis phenotype

There has been an increasing interest in investigating transdiagnostic phenotypes as evidence suggests that many mental disorders, including psychosis spectrum and affective disorders, are considerably overlapping on a genetic, biological, and symptom level. However, whether risk and resilience factors that have been proposed to be involved in the development and maintenance of specific psychopathological domains in various aetiological models generalise to transdiagnostic phenotypes remained largely unknown.

The aim of chapter 2 was to investigate whether well-established cognitive risk factors proposed in contemporary models of psychosis [1-3], that is, the JTC bias and lowered WMP, are associated with a transdiagnostic phenotype of co-occurring affective disorders and PEs in the general population. In line with a priori defined hypotheses, we found that the JTC bias was more likely to occur in individuals with co-occurring affective dysregulation and PEs. This suggests, for the first time, that the role of the JTC bias extends to transdiagnostic phenotypes if they are accompanied by PEs. Second, a lower WMP was found in individuals who reported any mental health problems, including the sole presence, or co-occurrence, of affective dysregulation and PEs. Third, there was some evidence of dose–response relationships, as the JTC bias and decreased WMP were more likely to be present in individuals with affective dysregulation as the level of PEs increased or psychosis-related help-seeking behaviour was reported, although some inconsistencies were observed. Overall, these findings support previous evidence on the specificity of the JTC bias in subclinical and clinical expressions of psychosis which appears to be independent from the presence or absence of other co-occurring mental health problems. Moreover, as has been shown in previous studies, lowered WMP has been found to be a more broadly distributed cognitive risk factor across various psychopathological domains.

In chapter 3, we sought to investigate whether the JTC bias contributes to psychosis progression and persistence over time, building on cross-sectional associations demonstrated in chapter 2. In accordance with recent aetiological models [1, 2], we found some evidence that individuals with low levels of PEs (i.e., conceptualized to represent a state of aberrant salience) were more likely to progress to high levels of psychosis (i.e., conceptualized to represent frank psychosis) over a period of around 3 years if the JTC bias was present. We also found that the JTC bias may not only be associated with the progression, but also the persistence of high levels of psychosis over time. This suggests, to some degree, that the JTC bias may contribute to the progression and persistence of psychosis in individuals with a transdiagnostic psychosis phenotype. It is quite unlikely, however, that the presence of the JTC bias does inevitably lead to higher levels of psychosis in individuals with affective dysregulation, given the high prevalence of the JTC bias in clinical and general population samples. It is more likely that the JTC bias combines with, or elevates the risk of, other biopsychosocial cognitive and socio-environmental risk factors, including belief inflexibility, negative attribution bias,

bias against disconfirmatory evidence, maladaptive cognitive schemas, prior exposure to adversity, and high polygenetic risk [2, 4, 5]. Although speculative, the JTC bias may contribute to the development of full-threshold paranoia by influencing individuals' immediate response to ambiguous or neutral stimuli in the environment (e.g., a passing car), making it more likely to be interpreted as dangerous if pre-existing vulnerabilities and tendencies to perceive the world as threatening exist. In other words, the tendency to make hasty decisions based on insufficient information in a standardized cognitive test (e.g., the beads task) may manifest in real-world settings by influencing how external stimuli are interpreted, and, when combined with malfunctional schemas, biases, and other biopsychosocial risk factors, may contribute to transitional processes from subclinical to clinical severity. Although intriguing, these propositions have never been tested, and additional research is needed to elucidate the role of JTC bias in the development and persistence of psychosis spectrum disorder.

There are important methodological considerations that must be taken into account. First, significance levels remained below conventional alpha for some of the tested hypotheses. In particular, the prospective modelling applied in chapter 3 led to low statistical power and imprecise estimates. Thus, the results should be interpreted with caution and replication is strongly needed before firm conclusions on the role of the JTC bias on psychosis progression and persistence can be drawn. Additionally, there were conceptual limitations regarding the transdiagnostic psychosis phenotype, states of aberrant salience, and frank psychosis. A more sophisticated methodological approach would be desirable, which may include the use of recently proposed dimensional models [6, 7] or psychosis spectra [8]. Recent efforts have been made to develop novel quantitative classification frameworks that are more data-driven and are specifically based on patterns of symptom co-occurrence (e.g., the Hierarchical Taxonomy Of Psychopathology; HiTOP [9, 10]).

Stress sensitivity as a candidate mechanism linking adversity and youth mental health

In the chapters 4, 5, and 6 we have investigated whether exposure to ACEs, including childhood trauma, bullying victimisation, and negative life events, amplifies individuals’ sensitivity to stress in a sample of young help-seeking individuals with high levels of depressive, anxiety and psychotic symptoms, their biological sibling, and comparison subjects. We found consistent evidence that service users exposed to high levels of various types of ACEs experienced more intense negative affect and psychotic experiences in response to stress compared to those with low exposure levels. Thus, young help-seeking individuals were found to be more sensitive towards minor stressors in daily life if they were exposed to ACEs. Contrary to these findings, controls showed less intense negative affect or no differences in stress sensitivity by levels of exposure to ACEs in some of the tested comparisons, while findings in biological siblings remained inconclusive. This suggests, as demonstrated in samples of help-seeking adults [11-13], that stress sensitivity may constitute a putative risk and resilience mechanism linking ACEs and youth mental health. Thus, targeting individuals' stress sensitivity may be a promising novel intervention strategy in youth with the goal of interrupting the process of stress sensitization and thereby alleviating individuals' mental health burden and enhancing emotional resilience in daily life.

There are several methodological limitations that must be considered when interpreting these chapters of the thesis. Most importantly, the effects of ACEs on stress sensitivity were examined independently. Given the high prevalence of poly-victimization [14, 15], an important next step is to determine whether ACEs have an accumulating effect in modifying stress sensitivity when the number of exposures increases. Furthermore, due to the study design, we were unable to examine whether stress sensitivity contributes to poor mental health outcomes over time [16]. There are also a number of limitations to retrospectively assessing ACEs, including recall bias [17]. Thus, there is an urgent need to conduct additional research on putative underlying mechanisms that influence mental health outcomes in youth daily lives, outside of the research laboratory, with a high degree of ecological validity.

From candidate mechanism to novel treatment targets

In chapter 7, we aimed to investigate the feasibility, safety, and preliminary therapeutic effects of a transdiagnostic, ecological momentary, compassion-focused intervention for enhancing emotional resilience to stress (‘EMIcompass’) in a phase I pilot study in young help-seeking individuals with psychotic, depressive, and/or anxiety symptoms. Our findings provide evidence on the feasibility and safety of the EMIcompass intervention in help-seeking adolescents as well as initial effects on stress sensitivity and various psychopathological domains. More specifically, as hypothesized, we found some evidence that an EMI may be well-suited to target candidate mechanisms in daily life and that delivering compassion-focused intervention components to help-seeking youth via a smartphone is feasible and safe.

This study is among the first to develop and pilot an EMI in youth with mental health problems that actively incorporates an adaptive and context-sensitive delivery scheme for intervention components [18]. Interestingly, approximately a third of all EMA assessments in daily life triggered the delivery of 'interactive tasks'. This type of task was only offered if individuals experienced elevated levels of negative affect (e.g., feeling anxious, insecure, or down), threat anticipation, or momentary stress. Thus, these findings suggest that young help-seeking individuals frequently encounter difficult moments throughout the day and that real-time processing of EMA data may successfully be used to determine when intervention components are most needed. This could be a significant step toward developing more ecologically valid and accessible psychological interventions for youth, as well as more individualized contextualized clinical and preventive care [18, 19].

However, these findings must be interpreted within the context of methodological limitations, including the pilot study's small sample size (N=10), the absence of a waiting list or active control group, and the fact that some of the findings on initial therapeutic effects on psychopathological domains remained below conventional alpha. A feasibility RCT is now required, and is currently underway [20], to ascertain the interventions' efficacy and feasibility, and to lay the groundwork for a confirmatory RCT.

Digital intervention in public mental health provision

The rapidly growing body of evidence on the use of digital technologies in the treatment of individuals suffering from mental health conditions, as well as areas of mental health promotion and prevention, is remarkable. In chapters 8, 9, and 10, we examined these recent developments from a variety of perspectives. First, we narratively reviewed the available evidence and clinical potential of emerging digital technologies (i.e., mHealth, eHealth, and VR intervention delivered via smartphones, wearables, and head-mounted displays) for helping individuals experiencing subclinical expressions of psychosis as well as psychosis spectrum disorder. Second, we examined whether public health measures to reduce SARS-CoV-2 infection rates had a negative effect on youth mental health in a general population sample and whether there was a subjective demand for using digital tools to improve mental health during the COVID-19 pandemic. Finally, we conducted a rapid meta-review to investigate the theoretical and empirical foundations, user perspectives, safety, effectiveness, and cost-effectiveness of digital interventions in public mental health provision (i.e., mental health promotion, prevention, and treatment of mental disorders) that may aid in mitigating the negative psychosocial consequences of the COVID-19 pandemic.

Overall, the evidence reported in chapters 8 and 10 suggests high acceptability and feasibility of eHealth, mHealth, and VR interventions in areas of public mental health provision. There was convincing evidence for the effectiveness of telemedical and other eHealth interventions in promoting and preventing mental health problems, as well as in treating mental health conditions, including psychosis spectrum disorder. There was, in contrast, preliminary, but very promising, evidence on the effectiveness of mHealth interventions [21]. More generally, the effectiveness of digital interventions utilizing a blended-care approach was found to be superior as compared to stand-alone digital interventions, especially in individuals with more severe mental health problems [22, 23] and the evidence for long-term effects and noninferiority to standard therapy and active control conditions have been found to be limited. Similarly, there is a paucity of evidence regarding the underlying processes and mechanisms of change, which largely parallels findings in other areas of intervention research. The theoretical and empirical foundations for most eHealth, mHealth, and VR interventions that have been developed by research groups are explicitly stated, whereas popular mHealth apps available in major app stores (e.g., Google Play Store, Apple App Store) as well as eHealth platforms do frequently not disclose the theoretical or empirical foundations and evidence-base of their content, while those who do only cite uncontrolled pilot studies. The publicly available apps have also been found to employ questionable data sharing and privacy practices for monetarizing user data [24, 25].

Most digital interventions that have been developed to date were found to primarily focus on four overarching domains of technology enabled mental health services [18, 26], that is, (1) remote communication, continuity of care, and flexibility through online chat and video call (i.e., telehealth); (2) monitoring of symptoms and behaviours in daily life; (3) personalized feedback on subjective experience and behavioural patterns as well as (4) static (e.g., on-demand access to psychoeducational modules) and adaptive interventions (e.g., EMIs) that apply real-time processing of data to inform the delivery of intervention components in daily life.

In chapter 9, we investigated whether public health measures implemented during the COVID-19 pandemic, such as physical distancing and quarantine, had a negative effect on youth mental health and young individuals' use of, and attitude towards, digital interventions during this unprecedented public health crisis. We have found strong evidence that social isolation, COVID-19-related cognitive preoccupation, worries, and anxiety were associated with psychological distress in youth. There was also evidence of dose–response relationships for some of these associations, as psychological distress was found to be more likely as reported social isolation and COVID-19-related preoccupation, anxiety, and worrying increased — although some inconsistencies were observed.

In line with hypotheses, there was also some evidence that psychological distress and high levels of COVID-19-related cognitive preoccupation, worries, and anxiety were associated with a more favourable attitude toward, and the current use of, mHealth apps to assist in overcoming the pandemic's negative consequences. This suggests that there is an objective need and subjective demand for digital intervention during public health crises, and that young people already use digital tools to work on their mental and physical health.

There are various methodological considerations which are important to be considered when interpreting this thesis' findings on digital interventions. First, in chapter 8 and 10, we conducted a narrative review and rapid meta-review, respectively. As a result, the representativeness of identified studies may be limited, as standard procedures for conducting systematic-reviews and meta-analyses were not followed (e.g., two independent reviewers who are blinded to each other's decisions). Second, in chapter 9, a questionnaire to assess psychological distress was used (i.e., Kessler-10) which has been developed as a brief screening tool to identify levels of distress. Thus, no validated semi-structured clinical interview was used to determine individual's subclinical and clinical symptoms. Further, the findings were based on an online panel which consisted of a group of registered internet users who had agreed to take part in surveys. Thus, selection bias cannot be ruled out. Further, the cross-sectional design of the survey did not allow us to compare findings on psychological distress and other variables with times before the COVID-19 pandemic.

Concluding remarks

There has been a recent shift towards a more dimensional understanding of mental disorders, crossing traditional diagnostic boundaries. This includes studying concepts of mental ill-health continua, spectra, and transdiagnostic phenotypes, as well as identifying transdiagnostic candidate mechanisms affecting mental health in everyday life, outside the research laboratory, and developing, evaluating, and implementing transdiagnostic intervention strategies. This thesis contributes to the body of knowledge by taking a transdiagnostic approach to mental health and linking adversity, cognition, candidate mechanisms, and novel digital intervention.

Taken together, the findings presented in this thesis suggest that stress sensitivity may be a critical transdiagnostic risk or resilience mechanism linking ACEs and youth mental health. While primary prevention of ACEs, including childhood trauma, bullying victimization, and negative life events, remains the most important goal, there is an urgent need to carefully assess ACEs in youth mental health services and to continue strengthening the evidence on their impact on youth mental health (e.g., their cumulative and long-term effects via stress sensitivity) as a basis for developing and evaluating evidence-based treatments in order to tackle their negative consequences. Building on these findings, we demonstrated that translating compassion-focused intervention components into individuals' daily life through an EMI delivered by an mHealth app may be a promising novel, accessible, and transdiagnostic treatment approach in help-seeking youth by strengthening emotional resilience and directly targeting candidate mechanisms in daily life. Our findings also underscore the critical need for additional research into the extent to which risk and resilience factors associated with the development and persistence of specific psychopathological domains generalise to transdiagnostic phenotypes to improve contemporary etiological models [27].

The use of digital mental health services in routine mental health care as well as mental health promotion and prevention of mental disorders is still in its infancy. There is a need to conduct well-powered randomized controlled trials to further investigate their efficacy, long-term effects, and processes and mechanisms of change before they can be recommended for widespread use in routine clinical care [21]. Additionally, it has become increasingly clear that early adoption of co-design and co-production principles is critical for meeting the unique needs and preferences of users and mental health professionals [21, 28, 29]. However, findings indicate that digital interventions have the potential to bring person-centered and adaptive interventions into individuals' daily lives, enabling the ecological translation of evidence-based interventions across areas of public mental health provision [18, 21]. There is also a strong need to conduct systematic evaluations of currently available digital interventions in major app stores using established criteria of mental health services research. There have been global initiatives (e.g., the National Health Service Apps Library in the United Kingdom; the Platform for Digital Health Applications in Germany; and the Division of Digital Psychiatry's App Evaluation Database in the USA) with the goal of evaluating and making evidence-based digital interventions clinically and publicly available, as well as integrating them into existing healthcare systems. These efforts must be accelerated in the coming years to enable individuals with a range of needs and preferences to access the most appropriate evidence-based digital mental health service.

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CHAPTER 12

Summary

The current thesis adopted a transdiagnostic approach to mental health, with the objectives of (1) examining the role of the jumping to conclusions reasoning (JTC) bias and working memory performance (WMP) in the development and persistence of an extended transdiagnostic psychosis phenotype, (2) determining whether individuals' stress sensitivity in daily life may form a transdiagnostic candidate mechanism involved in linking adverse childhood experiences (ACEs) and mental health outcomes in young service users, (3) exploring new avenues for digital interventions, such as smartphone-based ecological momentary interventions (EMIs) and other mobile health (mHealth) intervention, internet-based (eHealth) interventions, and virtual-reality (VR) based interventions, in diverse clinical and non-clinical settings across the whole spectrum of public mental health provision, (4) examining the effects of the COVID-19 pandemic on youth mental health as well as young individuals' use of, and attitude towards, digital interventions, and (5) investigating the potential use of available digital intervention for mitigating negative consequences of the COVID-19 pandemic in youth.

In **chapter 2** we investigated whether well-established cognitive risk factors, such as the JTC bias and a decreased WMP, are associated with a transdiagnostic phenotype of co-occurring affective disorders and psychotic experiences (PEs) in the general population. We found that the JTC bias was more likely to occur in individuals with co-occurring affective dysregulation and PEs. There was also some evidence of dose–response relationships, as the JTC bias and decreased WMP were more likely to be present in individuals with affective dysregulation when levels of PEs increased or psychosis-related help-seeking behavior was reported. These findings corroborate previous research demonstrating the JTC bias's specificity in subclinical and clinical manifestations of psychosis, which appears to be independent of the presence or absence of other co-occurring mental health problems. **Chapter 3** builds on these findings and examined whether the JTC bias contributes to the progression and persistence of psychosis over time. We found some evidence that individuals with low levels of PEs were more likely to progress to high levels of psychosis over a three-year period if the JTC bias was present. Additionally, we found that the JTC bias may be associated with not only the progression of psychosis, but also with the persistence of high levels of psychosis over time. This suggests that the JTC bias may play a role in the progression and persistence of psychosis in individuals with a transdiagnostic psychosis phenotype.

In **chapters 4, 5, and 6**, we examined whether exposure to ACEs, such as childhood trauma, bullying victimization, and negative life events, increases individuals' sensitivity to stress in a sample of young help-seeking individuals with high levels of depressive, anxiety, and psychotic symptoms, as well as their biological sibling and comparison subjects. We found consistent evidence that service users exposed to high levels of various ACEs had more intense negative affect and psychotic experiences in response to stress than those exposed to low levels. Thus, when exposed to ACEs, young help-seeking individuals were found to be more sensitive to minor stressors in daily life. In contrast to these findings, controls demonstrated less intense negative affect or no differences in stress sensitivity when ACE exposure levels were compared, while findings in biological siblings remained inconclusive. This suggests that stress sensitivity may serve as a putative risk and resilience mechanism linking ACEs and poor mental health in youth.

Chapter 7 explored the feasibility, safety, and preliminary therapeutic effects of a transdiagnostic, ecological momentary, compassion-focused intervention for enhancing emotional resilience to stress ('EMIcompass') in a phase I pilot study with young help-seeking individuals experiencing psychotic, depressive, or anxiety symptoms. The findings suggest EMIcompass intervention's feasibility and safety in help-seeking adolescents, as well as its initial effects on stress sensitivity and a variety of psychopathological domains. There was, therefore, some evidence that an EMI may be well-suited to directly target candidate mechanisms in daily life.

The body of evidence on the use of digital technologies to assist people with mental illnesses, as well as in areas of mental health promotion and prevention, is remarkable. We studied these recent developments from a number of angles in **chapters 8, 9, and 10**. To begin, in chapter 8, we summarized the available evidence and clinical potential of emerging digital technologies (i.e., mobile health, eHealth, and virtual reality interventions delivered via smartphones, wearables, and head-mounted displays) for supporting individuals experiencing subclinical manifestations of psychosis as well as psychosis spectrum disorder. Second, in chapter 9, we investigated if public health measures to lower SARS-CoV-2 infection rates had a detrimental effect on youth mental health in a general population sample and whether there was a subjective need for using digital technologies to promote mental health during the COVID-19 pandemic. Finally, in chapter

10, we conducted a rapid meta-review to examine the theoretical and empirical foundations, user perspectives, safety, effectiveness, and cost-effectiveness of digital interventions in public mental health provision that may help mitigate the negative psychosocial consequences of the COVID-19 pandemic.

Overall, the findings described in chapters 8 and 10 indicate that eHealth, mHealth, and VR interventions in the domains of public mental health provision are feasible and accepted by most users. Telemedical and other eHealth treatments were found to be beneficial in promoting and preventing mental health problems, as well as treating mental health conditions. In contrast, there was preliminary, but highly encouraging, evidence on the efficacy of mHealth interventions. Furthermore, the effectiveness of hybrid digital interventions was found to be superior to stand-alone interventions, especially in people with more severe mental health problems, and the evidence for long-term effects and non-inferiority to standard therapy and active control conditions was found to be limited.

In chapter 9, we found evidence that social isolation, cognitive preoccupation, fears, and worry were all associated with psychological distress in adolescents during the COVID-19 pandemic. There was also evidence of dose–response relationships for some of these associations, with psychological distress becoming more likely as reported social isolation and COVID-19-related preoccupation, anxiety, and worrying increased. Additionally, there was some evidence that psychological distress and high levels of cognitive preoccupation, and worry about COVID-19 were associated with a more favorable attitude towards, and use of, mHealth apps. This indicates, to some degree, that there was an objective need and subjective demand for digital interventions during a public health crisis, and that young people are already utilizing digital technologies to manage their mental and physical health.

APPENDIX

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Impact paragraph

In this section, the scientific and societal impact of the research presented in this thesis will be discussed.

Scientific impact

Despite extensive research on mental health, significant individual suffering, and high societal costs, treatment effectiveness has remained relatively stable in recent years, especially for severe mental disorders [1]. These findings contrast sharply with significant advances in other medical disciplines and a wide variety of somatic diseases, where treatment options and effectiveness have significantly improved. Some of the current difficulties in mental health research in finding better treatment options may partly be explained by fundamental difficulties in applying the dominant traditional medical model to mental health conditions. The long-held belief that mental disorders are distinct disease entities with unambiguous phenotypic representation and biological correlates as well as disease-specific mechanisms and risk factors is increasingly being challenged by mounting evidence indicating a high degree of overlap between mental disorders on the genetic [2], neuroscientific [3], and behavioural level [4]. This implies that studying mental disorders in isolation introduces inherent problems that may obstruct significant progress towards developing novel therapeutic approaches as well as understanding important determinants of poor mental health and underlying mechanisms.

The primary objective of this thesis was to take a transdiagnostic approach to mental health by examining how cognitive factors, adverse childhood experiences, and candidate mechanisms contribute to an increased risk for developing transdiagnostic phenotypes of depression, anxiety, and psychosis. The thesis also sought to determine the extent to which digital interventions have the potential to target transdiagnostic candidate mechanisms and outcomes, as well as to alleviate mental health burden in various areas of public mental health provision (i.e., mental health promotion, prevention of, and treatment for mental disorder).

We found that the jumping to conclusions (JTC) reasoning bias - the most widely studied cognitive bias in psychosis - was more likely to occur and associated with an increased risk for psychosis progression and persistence in individuals with a transdiagnostic phenotype of co-occurring affective dysregulation and psychotic experiences in a large prospective cohort study. This suggests, for the first time, that the JTC bias extends to transdiagnostic phenotypes. Moreover, stress sensitivity has been found to constitute a putative transdiagnostic risk and resilience mechanism linking adverse childhood experiences and mental health in youth at a developmental early stage of psychopathology using an ecologically valid experience sampling study design. We have also demonstrated that a compassion-focused ecological momentary intervention may be effective in directly targeting candidate mechanisms, including stress sensitivity, and strengthening resilience in young help-seeking service users. Finally, digital interventions have been found to increasingly being used, and hold great promise for, mental health promotion and the prevention and treatment of mental disorders.

These findings emphasize the importance of conducting additional research to determine whether psychological processes and mechanisms involved in the development and maintenance of psychopathologies extend to transdiagnostic phenotypes in order to overcome current limitations in mental health research and to corroborate contemporary aetiological models (e.g., the integrated socio-developmental-cognitive model of psychosis [5]). This may ultimately improve prediction of onset, course, and outcome, and to help develop and implement more effective and person-tailored interventions. Studies that do not exclude but purposefully allow for comorbidities and multidimensional psychopathology are urgently needed to advance progress in research, treatment, and aetiological models as well as dimensional and transdiagnostic approaches to mental health [6, 7].

Anticipated societal impact

> *"The time will come when diligent research over long periods will bring to light things which now lie hidden. A single lifetime, even though entirely devoted to the sky, would not be enough for the investigation of so vast a subject (...) And so this knowledge will be unfolded only through long successive ages. There will come a time when our descendants will be amazed that we did not know things that are so plain to them (...) Many discoveries are reserved for ages still to come, when memory of us will have been effaced."*
>
> *Lucius Annaeus Seneca (c. 4 BC – AD 65), Naturales quaestiones.*

According to the Global Burden of Disease study, an estimated 792 million people worldwide suffered from a mental disorder in 2017 [8]. This is slightly more than one in every ten people on the planet (10.7 percent). The majority of these individuals suffered from anxiety or depression. When substance use disorders are included, the numbers rise even higher: approximately one-in-seven people (15 percent) worldwide. There is strong evidence that individuals with mental health or substance use disorders are at an increased risk of committing suicide [9] and the immense individual suffering associated with mental illness can hardly be expressed in numbers. The economic cost of psychopathologies has been estimated to be 600 billion euros a year, or more than 4% of GDP, in the European Union. This figure includes 190 billion euros (1.3 percent of GDP) for direct care, 170 billion euros (1.2 percent) for social security programs, and 260 billion euros (1.6 percent) for indirect public spending on unemployment and decreased productivity among people with mental disorders [10].

These staggeringly high rates of mental disorders and tremendous costs clearly demonstrate the critical need to improve support for people experiencing mental health difficulties, identify important risk factors early, and strengthen the population's resilience. The thesis contributes to a better understanding of how exposure to adversity, which millions of people face on a daily basis, and cognitive factors increase the risk of developing multidimensional mental health problems. Moreover, reported findings on the COVID-19 pandemic indicate that public health measures to reduce infection rates had detrimental effects on youth mental health. This is a significant finding that requires careful consideration when making decisions about how to properly manage this and future pandemics effectively.

The reported findings on the use of digital interventions are encouraging. We demonstrated that digital intervention, mHealth apps in particular, hold great potential to enable the delivery of highly personalized interventions that are tailored to an individual's specific needs in a given moment and context. They are especially well-suited for improving public mental health because they are easily scaled up and the devices required to deliver evidence-based interventions in daily life are readily available to most people. Additionally, the thesis may aid in a better understanding of the current state of evidence-based mental health services and in assisting decision makers in developing and implementing digital strategies during public health crises.

The research topics covered in this thesis have the potential to enhance the reputation and impact of the regional academic community in the field of mental health. The findings from the studies presented in this thesis have been featured in news outlets, and they may help service users, the public, and policymakers make more informed decisions about the use of technology to enable mental health services, as well as contribute to a broader discussion about their potential and limitations.

However, as Seneca so beautifully stated, scientific discoveries typically take time to reach their full potential for societal benefit, and the findings presented in this thesis represent yet another step forward in the long process of improving societies' mental health.

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Curriculum Vitae

Christian Rauschenberg was born in Bad Nauheim, Germany, on 25 June 1990. After completing his secondary school education (2006) and a three-year training as an administrative assistant, he decided to return to school to complete his high school education. He graduated from the Berta Jourdan School in Frankfurt a.M. (2010) and completed his civilian service at Bürgerhilfe Sozialpsychiatrie Frankfurt e.V., a non-profit organization that helps people with enduring mental health conditions. He then studied psychology (B.Sc.) at the Justus Liebig University Giessen, Germany, from 2011-2015. As part of his studies, he spent one semester at the Fatih Universitesi in Istanbul. During the time of his undergraduate studies, he gained valuable experiences through a variety of internships (including at the Free University of Berlin and the Bender Institute of Neuroimaging) and positions as a student assistant (including the Departments of Psychotherapy and Systems Neuroscience, Biological Psychology and Developmental Psychology at the University of Giessen). He also served as chairperson of STOFF e.V. from 2012 to 2015, a non-profit organisation dedicated to organizing lectures, workshops, and the acquisition of academic books. After graduating in Psychology, he studied a Research Master in Cognitive and Clinical Neuroscience with the specialisation in Psychopathology at Maastricht University, which he completed in 2017. During this time, he was able to lay the groundwork for his research interests during a research internship at the School for Mental Health and Neuroscience, Department of Psychiatry and Neuropsychology, Maastricht University, which resulted in a subsequent position as PhD Candidate under the supervision of Prof Jim van Os and Prof Ulrich Reininghaus. He spent four months as a Visiting Researcher at King's College London's Virtual Reality Lab, where he worked under the supervision of Dr Lucia Valmaggia. Christian Rauschenberg began working part-time in February 2020 and full-time in May 2021 in the Department of Public Mental Health at the Central Institute of Mental Health, Heidelberg University, where he is conducting research on the use of digital monitoring, feedback, and ecological momentary interventions in areas of public mental health provision. This includes working on the research projects "Living lab AI4U - artificial intelligence for personalized digital mental health promotion in youth" and "DiSERVE@home - digital forms of service delivery in crisis resolution and home treatment for people with severe mental health problems". He will continue to work on these projects as a postdoctoral research fellow.

List of publications

Scientific publications in international peer-reviewed journals

Schick, A., Paetzold, I., **Rauschenberg, C.**, Hirjak, D., Banaschewski, T., Meyer-Lindenberg, A., Boehnke, J. R., Boecking, B., Reininghaus, U. (2021). The effects of a novel, transdiagnostic, hybrid ecological momentary intervention for improving resilience in youth (EMIcompass): study protocol for an exploratory randomized controlled trial. *JMIR Research Protocols.*

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Submitted and in progress articles

Rauschenberg, C.*, Schulte-Strathaus, J.C.C.*, van Os, J., Goedhart, M., Schieveld, J. N. M. & Reininghaus, U. Negative life events and stress sensitivity in youth’s daily life: an ecological momentary assessment study.

Goetzl, C., Hiller, S., **Rauschenberg, C.**, Schick, A., Koppe, G., Durstewitz, D., Reininghaus, U., Krumm, S. AI-Based Mobile Mental Health Apps for Young People: A Mixed-Methods Approach on Users' and Stakeholders' Perspectives.

Schick, A., **Rauschenberg, C.**, Ader, L., Daemen, M., Wieland, L., Paetzold, I., Postma, M. R., Schulte-Strathaus, J.C.C., Reininghaus, U. Methods for gathering intensive time series data in mental health research: Scoping review of a rapidly evolving field (invited review, *Psychological Medicine*).

Paetzold, I., Schick, A., **Rauschenberg, C.**, Hirjak, D., Banaschewski, T., Meyer-Lindenberg, A., Boehnke, J. R., Boecking, B., Reininghaus, U. Exploring putative therapeutic mechanisms and processes of change in a hybrid compassion-focused, ecological momentary intervention: Findings from the EMIcompass study.

Paetzold, I., Schick, A., **Rauschenberg, C.**, Hirjak, D., Banaschewski, T., Meyer-Lindenberg, A., Boehnke, J. R., Boecking, B., Reininghaus, U. An ecological momentary compassion-focused intervention for enhancing resilience in help-seeking youths: Findings on the effects of baseline characteristics from the EMIcompass trial.

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Book chapters

Schulte-Strathaus, J.C.C., **Rauschenberg, C.**, Baumeister, H., Reininghaus, U. (2022). Ecological Momentary Interventions in Public Mental Health Provision. In: Baumeister, H. & Montag C., ed. *Digital Phenotyping and Mobile Sensing: New Developments in Psychoinformatics.* 2nd ed. Cham, Switzerland: Springer Nature Switzerland.

Rauschenberg C., Rus-Calafell M., Reininghaus U., Valmaggia L. (2022). Digital Interventions for Psychosis. In: Asmundson GJ, ed. *Comprehensive Clinical Psychology*. 2nd ed. Amsterdam, Netherlands: Elsevier Ltd.

Other publications

Reininghaus U. & **Rauschenberg C.** (2020) Digitale Public Mental Health Ansätze zur Verminderung der psychosozialen Folgen der COVID-19 Pandemie (Policy

Brief; carried out as part of the *COVID-19 Public Health Research Network*, an ad hoc consortium of more than 25 scientific societies and organizations that are active in the field of public health).

Scientific communications related to this thesis

Oral presentation. 14th European Public Health Conference (Online, 2021).

Oral presentation. Kongress der Deutschen Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN) (Berlin, 2021).

Oral presentation. 24. Bundeskongress für Schulpsychologie, Sektion Schulpsychologie des Berufsverbands Deutscher Psychologinnen und Psychologen (BDP) (Online, 2021).

Oral presentation. Jahrestagung der Landesarbeitsgemeinschaft für Erziehungsberatung Baden-Württemberg (Online, 2021).

Oral presentation. 8th European Conference on Schizophrenia Research (Online, 2021).

Oral presentation. 56. Jahrestagung der Deutschen Gesellschaft für Sozialmedizin und Prävention (DGSMP) (Online, 2021).

Oral presentation. 19. Deutscher Kongress für Versorgungsforschung (Online, 2021).

Oral presentation. 25. Mallorca-Treffen deutschsprachiger SozialpsychiaterInnen (Online, 2021).

Oral presentation. 1st ESRC Centre for Society and Mental Health (King's College London) annual conference (Online, 2021).

Poster presentation. 38. Symposium der Fachgruppe Klinische Psychologie und Psychotherapie der Deutschen Gesellschaft für Psychologie (DGPs) (Online, 2021).

Oral presentation. 36th San Diego International Conference on Child and Family Maltreatment (San Diego, 2020).

Poster presentation. NIHR MindTech MedTech Co-operative National Symposium: New Frontiers for Digital Mental Health: Implementation & Impact (London, 2019).

Oral presentation. 7th European Conference on Schizophrenia Research (Berlin, 2019).

Oral presentation. Annual Meeting of the Belgian Association for Psychological Sciences (Liège, 2019).

Poster presentation. 6th Biennial Schizophrenia International Research Society Conference (Florence, 2018).

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