The role of the exposome in the association between autism and psychosis

Melike Karaçam Doğan



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De rol van het exposoom in de associatie tussen autisme en psychose

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Table of Contents

Chapter 1 **General Introduction** 9

Chapter 2 **The Moderating Role of Genetic and Environmental Risk Factors for Schizophrenia on the Relationship between Autistic Traits and Psychosis Expression in the General Population** 27

Chapter 3 **Examining psychological protective mechanisms as moderators of the association between autistic traits and psychosis expression in a general population twin sample** 67

Chapter 4 **Sex differences in the effect of childhood adversity and coping strategies on psychosis expression: A TwinssCan study** 103

Chapter 5 **Examining the association between autistic traits and psychopathology in the general population: are there sex differences?** 151

Chapter 6 **Discussion** 183

Chapter 7 **Summary** 199

Samenvatting 202

Chapter 8 **Impact** 205

Appendix **Curriculum Vitae** 214

List of Publications 215

Acknowledgements 221

Chapter 1

General Introduction

1.1 From Psychosis to Neurodevelopment: A Historical Overview of the Concept of Autism

The concept of autism has undergone substantial changes since its earliest appearance in psychiatric literature, and its origins are closely tied to the study of schizophrenia rather than developmental disorders. Eugen Bleuler first introduced the term "autism" in 1911 to characterize a profound withdrawal from the shared external world, which he considered central to the schizophrenia phenotype. In his framework, autism constituted one of the fundamental symptoms of schizophrenia (Bleuler, 1911). Bleuler described autism primarily as a withdrawal from external reality, characterized by diminished affective engagement, rigid and idiosyncratic modes of thinking and a marked reduction in spontaneous social contact.

Following Bleuler's description, Eugène Minkowski proposed in the late 1920s and early 1930s that autistic withdrawal did not reflect intentional avoidance but indicated a primary loss of the natural, immediate, and intuitive contact with reality. Minkowski referred to this disruption as a breakdown of the "vital contact with reality" (*le contact vital avec la réalité*), a condition in which the person no longer navigates interpersonal situations with the spontaneous attunement that characterizes ordinary social life (Minkowski, 1927; 1933). He described recurring experiential patterns such as "morbid rationalism," an overly abstract and excessively logical mode of interpreting human events, and "geometrism" an excessive focus on symmetry, spatial order and numerical relations. Minkowski also differentiated between "poor autism" which involved emotional flatness, experiential impoverishment and disengagement, and "rich autism" characterized by intense inner fantasy and imaginative elaboration. Later phenomenological scholarship has built on these ideas by showing that schizophrenic autism reflects coordinated alterations in basic self-awareness, intentionality and intersubjective relatedness. These disruptions contribute to a loss of natural common sense and a weakening of the basic experiential structures that organize everyday reality. Such alterations can emerge before overt psychotic symptoms and may reflect early vulnerability to schizophrenia spectrum disorders (Parnas et al., 2002).

Only later did autism take on a neurodevelopmental meaning. In the 1940s, Leo Kanner and Hans Asperger independently described children with marked difficulties in social reciprocity, restricted and repetitive patterns of behavior and atypical sensory responses (Kanner, 1943; Asperger, 1944). These descriptions formed the foundation of what is now understood as the autism spectrum. Autism was still considered related to childhood psychosis for many years, and it was not until DSM-III (1980) that it was formally separated from schizophrenia and reclassified under pervasive developmental disorders (APA, 1980). Subsequent revisions, including DSM-5 and ICD-11, consolidated earlier subtypes into the dimensional construct of autism spectrum disorder (ASD), emphasizing its heterogeneity and developmental trajectory (APA, 2022; World Health Organization, 2022). Despite this diagnostic separation, contemporary research demonstrates that autism and psychosis share multiple areas of overlap that include genetic susceptibility, neurocognitive profiles, early neurodevelopmental pathways and several environmental risk factors (Lai et al., 2014; Chisholm et al., 2015; Sullivan et al., 2013; Reininghaus et al., 2016; Ribolsi et al., 2022).

1.2 The Challenges of Studying Autism Spectrum and Dimensional Psychopathology

Beyond clinical diagnoses of ASD, autistic traits (ATs) are continuously distributed in the general population (Constantino & Todd, 2003). These traits include social communication differences, cognitive rigidity, increased attention to detail, attention shifting difficulties and atypical sensory processing.

Research on autism spectrum conditions and their relationship with broader psychopathology has traditionally relied on clinical samples. However, this approach presents several methodological, ethical, and conceptual challenges, especially when investigating co-occurring mental health problems and etiological mechanisms across the lifespan. Clinical populations often consist of individuals who have already received a diagnosis and typically present with more pronounced symptoms or greater support needs, limiting the generalizability of findings. Such samples may not accurately represent the full heterogeneity of the autism spectrum. For instance,

diagnostic ascertainment is influenced by factors such as caregiver concern, healthcare access, and systemic bias related to gender, race, and socioeconomic status, resulting in the overrepresentation of certain subgroups (e.g., white males from higher-income families) and the under recognition of others (e.g., girls, ethnic minorities, or individuals without intellectual disability) (Hus Bal et al., 2025). This creates a critical blind spot: a substantial portion of the neurodiverse population and their mental health needs remain underrepresented in autism research.

To address these limitations, researchers have increasingly adopted dimensional, general population-based approaches. Investigating ATs as quantitatively distributed characteristics in the general population allows for the exploration of transdiagnostic mechanisms and this approach aligns with frameworks such as the Research Domain Criteria (Insel et al., 2010), which emphasize the importance of understanding shared and unique mechanisms linking neurodevelopmental traits to diverse psychopathological presentations. Importantly, general population samples reduce referral bias and allow for the study of risk and protective factors before clinical thresholds are crossed.

1.3 Autistic Traits and Psychopathology

There is growing evidence that individuals with elevated ATs may be at increased risk for co-occurring psychopathology, such as depression, anxiety, obsessive–compulsive symptoms, and psychosis expression (Bevan Jones et al., 2012; Carpita et al., 2023; Dell'Osso et al., 2019; Dell'Osso et al., 2018; Demartini et al., 2024; Liew et al., 2015; Lundström et al., 2011; Martinez et al., 2021). However, this association is far from deterministic: Not all individuals with high ATs develop psychiatric problems, highlighting the importance of contributing factors in shaping mental health outcomes.

1.4 Autistic Traits and Psychosis Expression: A Complex Subdomain of Psychopathology

Among the various mental health outcomes associated with elevated ATs, psychosis expression has gained particular research interest.

1.4.1 Psychosis Expression in the General Population

According to the DSM-5, schizophrenia is a severe mental disorder marked by disruptions in thought, perception, and behavior, requiring the presence of at least two core symptoms (such as hallucinations, delusions, disorganized speech, disorganized or catatonic behavior, or negative symptoms) over the course of one month, with at least one being hallucinations, delusions, or disorganized speech (APA, 2022). However, schizophrenia represents only the most severe clinical endpoint of a much broader psychosis spectrum. To address this limitation, the concept of psychosis spectrum disorder has been introduced as a dimensional framework capturing psychosis expression along a severity continuum, ranging from subtle, non-clinical psychotic experiences to full-blown psychotic disorders (Guloksuz & Van Os, 2018).

Psychotic experiences (PEs), such as hallucination-like perceptions or delusion-like ideation, exist along a continuum in the general population and are particularly common during adolescence and young adulthood (van Os et al., 2009). Although these experiences are often transient and non-clinical, persistent and distressing PEs are predictive of increased risk for psychiatric disorders, including schizophrenia and affective psychoses (van Os & Reininghaus, 2016).

In this thesis, psychosis is considered as one possible manifestation of broader psychopathology, particularly where ATs intersect with environmental risk factors and neurodevelopmental vulnerability. Psychosis expression is defined broadly to encompass not only positive symptoms but also negative and depressive symptoms (Reininghaus et al., 2013; Stefanis et al., 2002), aligning with multidimensional models of subclinical psychosis and transdiagnostic frameworks of psychopathology (van Os & Reininghaus, 2016).

1.4.2 Association Between Autistic Traits and Psychosis Expression

Recent research has highlighted overlaps between autism and psychotic disorders in genetic findings, neuroimaging, clinical characteristics, cognitive profiles and environmental risk factors (Ribolsi et al., 2022). Both conditions may share underlying neurodevelopmental vulnerabilities, including mentalizing difficulties (Chung et al., 2014) and executive dysfunctions such as impaired cognitive flexibility (Aumer et al., 2024; Hill, 2004). These shared features have contributed to increasing interest in the relationship between ATs and psychosis expression beyond categorical diagnoses.

Considering that both conditions are viewed as spectra within the general population, the association between ATs and psychosis expression has been examined in large non-clinical cohorts. For instance, data from the Avon Longitudinal Study of Parents and Children (ALSPAC) revealed that parent-reported ATs at age 7 were associated with psychotic experiences at age 12 (Bevan Jones et al., 2012). Similarly, analyses from the Adult Psychiatric Morbidity Survey (APMS) demonstrated a robust association between ATs and psychotic experiences in the general population (Martinez et al., 2021). These findings suggest that ATs and psychosis expression frequently co-occur across the general population.

Several conceptual models have been proposed to interpret this observed association. One account conceptualizes the relationship in terms of shared neurodevelopmental vulnerability, suggesting that partially overlapping genetic, cognitive and developmental mechanisms may give rise to both autistic and psychotic features (Lai et al., 2014; Chisholm et al., 2015; Ribolsi et al., 2022). At the same time, this interpretation raises important methodological considerations. Core characteristics such as social withdrawal, cognitive rigidity, and atypical perceptual experiences may be captured by both autism and psychosis related self-report instruments, implying that part of the observed association may reflect phenotypic or measurement overlap rather than a fully shared etiopathology, particularly in population-based studies (Chisholm et al., 2015).

Beyond descriptive overlap, psychosis is a frequent co-occurring condition in individuals with autism, yet it remains unclear whether psychosis emerging in this context follows the same etiopathological pathways as psychosis in neurotypical individuals. Moreover, it is not well understood which specific ATs most strongly increase vulnerability to psychosis expression. One possibility is that elevated ATs heighten sensitivity to environmental stressors, thereby indirectly increasing psychosis risk through stress sensitization mechanisms (van Os & Reininghaus, 2016). In contrast, alternative theoretical accounts such as the diametric hypothesis propose opposing alterations in social cognition across the autism and psychosis spectra, emphasizing reduced mentalizing in autism and hyper-mentalizing in psychosis (Crespi & Badcock, 2008). Consequently, it cannot be assumed that risk or protective factors operate in the same direction or with the same extent in individuals with elevated ATs as they do in neurotypical populations, making it particularly important to examine these associations empirically. Taken together, these perspectives underscore the need to move beyond descriptive co-occurrence and to examine how individual traits and environmental exposures interact to shape psychosis risk in individuals with elevated ATs.

1.4.3 The Role of Risk and Protective Factors

1.4.3.1 Genetic Risk Factors

There is growing evidence for shared genetic underpinnings between autism spectrum disorder and schizophrenia. Several studies have identified common risk loci, including both chromosomal rearrangements and single-gene variants (Burbach & van der Zwaag, 2009). For instance, rare copy number variants in synaptic genes such as NRXN1, NLGN4, SHANK3, and CNTNAP2 have been implicated in both conditions (Carroll & Owen, 2009). These genes encode proteins critical for synaptic development, adhesion, and plasticity, and their disruption contributes to synaptic dysfunction seen in both disorders. However, conflicting findings also exist. For instance, Vorstman et al. found no substantiating evidence for shared genetic risk loci between schizophrenia and autism (Vorstman et al., 2013), and contradictory findings have been reported for the HLA-DRB1 locus, which plays a key role in immune system regulation: DRB1*13 alleles

have been associated with protection against autism but increased risk of schizophrenia (Crespi & Thiselton, 2011).

Schizophrenia polygenic risk scores (PRS-SZ) are traditionally used to represent the genetic liability for psychosis. PRS-SZ aggregates the weighted effects of many related single-nucleotide polymorphisms identified in the genome-wide association studies (Trubetskoy et al., 2022). In this thesis, PRS-SZ is used to assess genetic risk for psychosis, which will be further discussed in **Chapter 2.**

1.4.3.2 Environmental Factors

The exposome, which covers cumulative environmental exposures over the life course (Wild, 2005), provides a promising lens to examine how risk and protective factors interact with neurodevelopmental vulnerabilities.

Environmental risk factors (such as trauma, bullying, obstetric complications, and cannabis use) have long been implicated in the development of psychotic disorders (Erzin et al., 2021; Pries et al., 2020). Childhood trauma, bullying, stressors, and obstetric complications have been associated with a clinical diagnosis of ASD (Bortoletto et al., 2023; Glasson et al., 2004; Kerns et al., 2015). However, we still know very little about how such risk factors operate in individuals with high ATs. Do they interact with ATs to amplify psychosis expression? This thesis addresses this question by integrating the exposome framework in a study detailed in **Chapter 2**.

1.4.3.3 Protective Factors

Psychiatric research has long focused on risks, but resilience frameworks remind us that many people thrive despite adversity. Protective factors, ranging from social support and healthy life-style routines to neighborhood cohesion, help explain why not everyone exposed to stress develops psychopathology. Yet, as umbrella reviews show, most psychosis research has concentrated on risks, while protective influences remain understudied (Radua et al., 2018).

Integrating resilience into exposome-based approaches fits with the salutogenesis model, which prioritizes building health and well-being rather than only treating illness (Karaçam Doğan & Guloksuz, 2025; van Os & Guloksuz, 2024). Beyond environmental resources, psychological factors like personality traits, adaptive coping, and positive parenting experiences may foster resilience, especially in individuals with elevated ATs. While much research has focused on these mechanisms in the general population or clinical high-risk groups (Crush et al., 2018; González-Pinto et al., 2011; Pruessner et al., 2011; Radua et al., 2018), relatively little is known about how such protective factors operate in individuals with elevated ATs. Given that individuals with high ATs may experience higher baseline levels of stress, social difficulties, or sensory overload, understanding what fosters resilience in this population is particularly important. Do psychological protective factors reduce the likelihood of psychosis expression despite underlying neurodevelopmental vulnerabilities? The second study in this thesis (**Chapter 3**) addresses this gap by investigating the moderating role of psychological protective mechanisms in the relationship between ATs and psychosis expression.

These resilience mechanisms might also differ by sex or gender, given known differences in socialization, emotional processing, and psychotic symptom expression (Barry et al., 1957; Domes et al., 2010; Grossman et al., 2008; Grossman & Wood, 1993). Complementing this, **Chapter 4** takes a broader transdiagnostic approach by examining how different coping styles interact with childhood adversity to influence psychosis expression, with a specific focus on sex differences. Although ATs are not directly included in this model, the study provides essential insight into coping as a key resilience mechanism under adverse developmental conditions, highlighting the importance of sex-specific approaches to fostering adaptive coping strategies.

1.5 Sex-Specific Manifestations of Autistic Traits and Psychopathology

Although transdiagnostic and resilience-focused frameworks offer critical insight into the general pathways linking ATs to psychopathology, they may not fully capture the differences in these processes across sexes. ATs are expressed heterogeneously, and growing evidence suggests that these manifestations are sex-dependent in both form and clinical consequences (Lai et al., 2015). While males with high ATs may display more externalizing symptoms, females are often under-recognized due to camouflaging behaviors and internalizing symptomatology such as anxiety or depression (Fusar-Poli et al., 2022; Hull et al., 2021; Vadukapuram et al., 2022). These sex-based differences in phenotypic presentation may also shape the relationship between ATs and broader psychopathology. For example, females with high ATs may experience a stronger association with affective symptoms compared to their male counterparts, yet this remains underexplored in population-based cohorts. **Chapter 5** contributes to this gap by examining sex-specific associations between ATs and a broad range of psychopathological symptoms, aiming to uncover potential mechanisms that may explain differential mental health outcomes across sexes.

1.6 Thesis Outline

The main aim of the current thesis is to examine how ATs relate to PE in the general population, focusing on the moderating role of environmental risk factors and psychological protective mechanisms. Drawing from large-scale epidemiological cohorts, this work integrates multiple lines of evidence within an exposome framework, with additional attention to sex differences in transdiagnostic psychopathology. **Chapter 2** investigates whether environmental and genetic risk factors for psychosis moderate the association between ATs and psychosis expression. **Chapter 3** tests whether psychological protective factors buffer the relationship between ATs and PE. **Chapter 4** explores the interaction between coping styles and childhood adversity in shaping PE, with a particular focus on sex differences. **Chapter 5** analyzes sex differences in the relationship between ATs and a broad spectrum of psychopathological symptoms.

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Chapter 2

The Moderating Role of Genetic and Environmental Risk Factors for Schizophrenia on the Relationship between Autistic Traits and Psychosis Expression in the General Population

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Abstract

Background: Psychosis-related environmental risks in autism, along with genetic overlaps between autism and psychosis, have been well-established. However, their moderating roles in the relationship between autistic traits (ATs) and psychotic experiences (PEs) remain underexplored.

Methods: First-wave data from 792 twins and siblings (mean age: 17.47±3.6, 60.23% female) in the TwinssCan Project were analyzed. PEs and ATs were assessed using the Community Assessment of Psychic Experiences and the Autism-Spectrum Quotient, respectively. Polygenic risk scores for schizophrenia and psychosis-associated environmental factors (i.e., childhood trauma (CT), bullying, negative life events, obstetric complications, cannabis use, winter birth, and hearing impairment) were tested for their independent effects on PEs and their interaction effects with ATs in moderating the relationship between ATs and PEs using separate multilevel linear regression models with Bonferroni's correction.

Results: ATs, all CT subtypes, bullying, and negative life events were positively associated with PEs (all $P<0.004$). Moderation analyses revealed that the association between ATs and PEs was amplified by emotional abuse (B:0.08, 95% CI:0.05-0.11, $P<0.001$), physical abuse (B:0.11, $P=0.001$), sexual abuse (B:0.09, 95% CI:0.03-0.15, $P=0.002$), and physical neglect (B:0.06, 95% CI:0.03-0.10, $P=0.001$), emotional neglect (B:0.04, 95% CI:0.01-0.07, $P=0.007$), and negative life events (B:0.007, 95% CI:0.0005-0.014, $P=0.04$), although the latter two risks did not survive Bonferroni's correction. No significant main or interacting effects of genetic and other risk factors were found.

Conclusions: People with high ATs were more likely to have PEs when exposed to CT. Trauma screening and early interventions might be warranted in this at-risk population.

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and social interaction along with restricted, repetitive patterns of behaviors, interests, and/or activities (APA, 2022). The prevalence of ASD has recently been estimated to be 1 in 36 children in the United States (Maenner et al., 2023). Psychiatric comorbidity is common in ASD. The prevalence of comorbid conditions has been estimated to be 28% for attention-deficit hyperactivity disorder (ADHD), 20% for anxiety disorders, 11% for depressive disorders, and 9% for schizophrenia spectrum disorders (SSD)(Lai et al., 2019). Recent meta-analyses consistently reported an increased prevalence of not only clinical psychosis (9.4%) (Varcin et al., 2022) but also subthreshold psychosis (24%) (Kiyono et al., 2020) in autistic people. On the other hand, the prevalence of ASD is also high (9%) in patients with first-episode psychosis (Ferrara et al., 2024), and its symptoms are associated with poor cognitive and psychosocial function in people with SSD (Nibbio et al., 2022), highlighting an intricate, bidirectional link between psychosis expression and ASD.

In the past two decades, autism has increasingly been recognized as a true spectrum with varying degrees of traits existing on a continuum in the general population. According to such a concept, autistic traits (ATs), such as social communication difficulties and repetitive behaviors, could also be present among individuals who do not meet the formal diagnostic criteria for ASD. Similar to clinical ASD, ATs have been shown to be associated with an increased vulnerability to multiple psychopathologies, including subclinical psychosis expression (Bevan Jones et al., 2012; Lundström et al., 2011; Martinez et al., 2021; Salmela et al., 2019). A recent meta-analysis has identified multiple demographic and clinical characteristics, such as older age, male gender, lower intellectual quotient, and less stereotyped interests/behaviors, as risk factors for developing clinical psychosis among autistic individuals (Varcin et al., 2022). Nevertheless, evidence on risk factors for subclinical psychosis among people with subthreshold autism is lacking.

Considering that genetic and environmental risk factors for schizophrenia are shared across the psychosis continuum (Pries, Dal Ferro, et al., 2020) and throughout a neurodevelopmental trajectory also enclosing other conditions emerging earlier in life (Owen & O'Donovan, 2017), it is likely that the risk factors may also influence psychosis expression in the context of the autism spectrum. Notably, childhood trauma, bullying, stressors, and obstetric complications have been associated with a clinical diagnosis of ASD (Bortoletto et al., 2023; Glasson et al., 2004; Kerns et al., 2015). Moreover, genetic studies have identified several direct and indirect links between autism and schizophrenia, highlighting shared vulnerabilities between these conditions (Burbach & van der Zwaag, 2009; Carroll & Owen, 2009). In the present study, we, therefore, aimed to examine the moderating role of polygenic risk and well-established environmental risk factors for schizophrenia (i.e., childhood trauma, bullying, negative life events, obstetric complications, cannabis use, winter birth, and hearing impairment) on the relationship between ATs and PEs in the general population of twins and non-twin siblings. We hypothesized that the presence of genetic and environmental risk factors for schizophrenia would strengthen the association between ATs and PEs and their influences on PEs would vary within the autism spectrum.

Methods

Participants

Analyses were conducted on the dataset obtained from the first wave of the TwinssCan Project. The details of participant enrollment and data collection have been previously described elsewhere (Pries et al., 2019). Briefly, the TwinssCan cohort comprises twins, non-twin siblings, and parents recruited from the East Flanders Prospective Twin Survey (EFPTS), a prospective population-based registry of multiple births from East Flanders, Belgium (Derom et al., 2019). The twins were between 15 and 18 years old upon enrollment, while their non-twin siblings were from 15 to 35 years old. The first assessment of the TwinssCan Project began in April 2010 and concluded in April 2014 (Pries et al., 2017). Written informed consent was obtained from all participants. The exclusion criteria were: (1) lack of parental or caregiver consent for those under 18 years old and (2) having a

pervasive mental disorder. The study was approved by the local ethics committee (Commissie Medische Ethiek van de Universitaire Ziekenhuizen KU Leuven, Nr. B32220107766). In this study the data of 821 twins and siblings were included. However, 29 participants were excluded due to missing data, leaving 792 participants for further analysis.

Measures

Psychotic Experiences

PEs were assessed with the Community Assessment of Psychic Experiences (CAPE), a widely used 42-item self-report questionnaire consisting of three subscales (i.e., positive, negative, and depressive) (Stefanis et al., 2002). The CAPE has demonstrated stability, reliability, and validity in evaluating PEs in the general population (Konings et al., 2006). Four-point Likert scales were used to measure the frequency and distress levels of the symptoms. The average scores from these scales give total and subscale scores (positive, negative, depressive). In our analysis, we specifically used the frequency scores as an indicator of PEs.

Autistic Traits

The Autism-Spectrum Quotient (AQ), a 50-item self-report questionnaire, was used to assess ATs (Baron-Cohen et al., 2001). It is widely used to measure ATs in the general population and has good psychometric properties through comprehensive research (Baron-Cohen et al., 2001; Hoekstra et al., 2008). The scale consists of 5 subdomains, each with 10 items: imagination, social skills, communication, attention to detail, and attention shifting. For items in line with ATs, "definitely agree" and "slightly agree" responses were scored 1, and "definitely disagree" and "slightly disagree" responses were scored 0. For the other items, "definitely disagree" and "slightly disagree" were reversely scored 1; otherwise, 0. The total score ranges from 0 to 50 with higher AQ scores indicating higher ATs (Baron-Cohen et al., 2001).

Childhood Trauma

Childhood trauma (CT) was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), a 28-item self-report instrument rated on a 5-point Likert scale to measure five subtypes of childhood adversity: emotional, physical, and sexual abuse, as well as emotional and physical neglect. In the manual of CTQ, three severity cut-off scores (low, moderate, and severe) were suggested for each CTQ subscale (Bernstein & Fink, 1998). Aligning with previous research (Guloksuz et al., 2019; Pries, Dal Ferro, et al., 2020), we binarized the variable into the presence or absence of each CT subtype by employing the low severity cut-off threshold based on the manual of the CTQ (≥ 9 for emotional abuse, ≥ 8 for physical abuse, ≥ 6 for sexual abuse, ≥ 10 for emotional neglect, and ≥ 8 for physical neglect). These cut-off scores were used to maintain consistency and increase comparability across studies.

Bullying

The Retrospective Bullying Questionnaire (RBQ) was used to assess the experiences of bullying before the age of 17 (Schäfer et al., 2004). It is a 44-item self-rated questionnaire examining different aspects of bullying, including verbal, physical, and relational aggression, experienced across settings like school, neighborhood, and online platforms. The severity of different kinds of bullying was rated on a 5-point Likert scale (1=not being bullied, 2=not serious at all, 3=just a little, 4=quite serious, 5=extremely serious). Aligning with prior research, bullying victimization was considered present if they had encountered any type of bullying (cut-off score≥ 2) (Pries et al., 2019).

Negative life events

Negative life events were assessed with the Life Events Questionnaire (LEQ), a 61-item self-report of major life events such as job loss, illness, death of a loved one, and financial changes (Paykel, 1997). Participants indicated if these incidents had ever happened to them. The total score was calculated by summing the number of negative life events experienced over a lifetime.

Obstetric complications

Adverse events during pregnancy, labor, and postpartum period were measured with the McNeil-Sjöström Obstetric Complications (OC) Scale (MSS) (McNeil, 1995). The severity of OC was scored on a 6-point scale (1 = not harmful or relevant to 6 = very great harm or deviation in offspring). Aligning with prior research (Guloksuz, 2015), a dichotomous OC variable was generated using an MSS cut-off score of 5 or more to indicate severe OC. In other words, severe OC was defined as 1) birth weight lower than 2 kilograms, 2) birth weight more than 20% lower than that of the sibling, 3) version extraction delivery mode, 4) face or forehead presentation of the fetus during delivery, or 5) umbilical cord complication.

Cannabis use

Lifetime cannabis use was assessed by the L section of Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). A dichotomous variable was generated to indicate cannabis use over a lifetime.

Winter birth

The high-risk birth period was defined as the winter solstice (December-March) based on previous studies investigating the link between birth season and schizophrenia spectrum disorders in the Northern Hemisphere (Davies et al., 2003). A dichotomous variable was generated to indicate winter birth.

Hearing impairment

Hearing impairment was evaluated based on the participants' self-reported current hearing status.

Genotyping and quality control

As previously reported (Pries, Dal Ferro, et al., 2020), genotypes of the twins and their siblings were generated on two platforms: the Infinium CoreExome-24 and Infinium PsychArray-24 kits. Quality control (QC) procedures were performed using PLINK v1.9 in both datasets

separately (Purcell et al., 2007). Single-nucleotide polymorphisms (SNPs) and participants with call rates below 95% and 98%, respectively, were removed. A strict SNP QC was conducted only for subsequent sample QC steps. This involved a minor allele frequency (MAF) threshold >10% and a Hardy–Weinberg equilibrium (HWE) P-value $>10^{-5}$, followed by linkage disequilibrium (LD)-based SNP pruning ($R^2<0.5$). This resulted in ~58K SNPs to assess sex errors (n=8), heterozygosity [F < mean - 5× the standard deviation (SD), n = 3], homozygosity (F > mean + 5× SD), and relatedness by pairwise identity by descent (IBD) values (monozygotic $p < 0.9$, dizygotic and full siblings: $p > 0.65$ or $p < 0.35$, $n = 5$). The ancestry-informed principal component (PC) analyses were conducted using EIGENSTRAT (Price et al., 2006). The ethnic outliers of which the first 4 PCs diverged >10× SD from Utah residents with Northern and Western European ancestry from the Centre d'Etude du Polymorphisme Humain (CEPH) collection (Central EUrope, CEU) and Toscani in Italia (TSI) samples (n=5), and >3× SD of the TwinssCan samples (n=7) were excluded (see also supplementary figure 1). After removing these subjects, a regular SNP QC was performed (SNP call rate >98%, HWE P-value > 1e-06, MAF > 1%, and strand ambiguous SNPs and duplicate SNPs were removed).

The two QCed datasets were imputed on the Michigan server (Das et al., 2016), using the Haplotype Reference Consortium r1.1 2016 reference panel with European samples after phasing with Eagle v2.3. Post-imputation QC involved removing SNPs with imputation quality (R^2) < 0.8, with an MAF < 0.01, SNPs that had a discordant MAF compared to the reference panel (MAF difference with HRC reference > 0.15), as well as strand ambiguous AT/CG SNPs and multi-allelic SNPs. The two chips were merged, and an additional check for MAF > 0.01, HWE P > 1e-06 was executed, which resulted in 3,407,392 SNPs for 688 individuals. The general imputation quality is shown in Supplementary Figure 1.

PRS calculation

Polygenic risk score of schizophrenia (PRS-SZ) was calculated based on the genome-wide association study (GWAS) results for schizophrenia (Trubetskoy et al., 2022) with the clumping and

threshold (C+T) methods using PRSice2 (Choi et al., 2020). To ensure the ethnicity match between training and target datasets, we selected the summary statistics from the European population. To calculate PRS-SZ, the beta-values, effective allele, and P-values were extracted from all schizophrenia GWAS summary statistics. Insertions and deletions, ambiguous SNPs, SNPs with a MAF<0.01 and imputation quality R2<0.9, as well as SNPs located in complex-LD regions and long-range LD regions were excluded from TwinssCan dataset (Supplementary Table 1). Overlapping SNPs between GWAS summary statistics (training dataset), 1000 genomes (reference), and our TwinssCan dataset (target) were selected. These SNPs were clumped in two rounds using PLINK's clump function (round 1: --clump-kb 250 --clump-r2 0.5; round 2: --clump-kb 5000 --clump-r2 0.2). The numbers of alleles for PRS calculation are listed in Supplementary Table 2. We selected all independent SNPs at the P-threshold of < 0.05 to calculate PRS-SZ since this threshold accounted for the most of the variation in the phenotype according to the analysis conducted by the Psychiatric Genomics Consortium (Trubetskoy et al., 2022).

Statistical analysis

All analyses were performed using Stata 16 (StataCorp, 2019). Participants were clustered within twin pairs, necessitating the use of multilevel analyses. Multilevel regression models are recommended for analyzing data with observations at multiple levels, as they account for variability associated with each level of nesting (Snijders & Bosker, 2011). These models are particularly suitable for twin studies and have been commonly employed in twin studies using PRS analyses to adjust for relatedness (Carlin et al., 2005; Den Braber et al., 2016; Pain et al., 2018; Vink et al., 2014). The number of predictors included was carefully considered to ensure adequate statistical power, adhering to the literature regarding sample size relative to the number of predictors (Green, 1991; Harris, 2001; Van Voorhis & Morgan, 2007). Firstly, to examine the main association between risk factors with PEs, multilevel linear regression analyses were performed using total CAPE as the dependent variable and AQ scores, PRS-SZ, CT subtypes, bullying, negative life events, obstetric complications, cannabis use, or winter birth as an independent variable tested in separate models. To examine whether the psychosis-associated genetic and environmental

risk factors moderate the association between ATs and symptoms, a full interaction of total AQ and genetic or each environmental risk factor on total CAPE was tested using multilevel linear regression analyses. To facilitate the interpretation of the coefficients, AQ scores, negative life events, and PRS-SZ were standardized to have a mean of 0 and standard deviation (SD) of 1. All models were adjusted for age and gender. In the PRS models, the first two ancestry PCs, capturing 82.4% of genetic variation related to population structure in the TwinssCan cohort, were included as covariates to adjust for major effects of population stratification in accordance with previous research in this sample (Klingenberg et al., 2023; Pries, Klingenberg, et al., 2020). The statistical significance threshold was set at Bonferroni-corrected $P< 0.004$. In case of significant interaction, marginal effects analysis was performed to estimate the differential influences of the ATs (i.e., mean, mean – 1SD, and mean + 1SD) at different levels of risk factors using the STATA 'margins' command, and the results were visualized using the STATA 'marginsplot' command.

As exploratory analyses, similar multilevel linear regression analyses were conducted to investigate potential differential effects of risk factors on psychotic subdomains (CAPE positive, negative, and depressive subscales as dependent variables) to capture the detailed relationships that may not be apparent in aggregate measures.

Results

Sample characteristics

A total of 792 participants, including 274 monozygotic twins, 475 dizygotic twins, and 43 siblings, were included in the current analyses. Participant characteristics are displayed in Table 1.

Table-1. Sample Characteristics

Characteristics	**N=792**
Age (years), M (SD)	17.47 (3.60)
Sex, n (%)	
Female	477 (60.23)
Male	315 (39.77)
Zygosity, n (%)	
MZ	274 (34.60)
DZ	475 (59.97)
Sibling	43(5.43)
CAPE – frequency, M (SD) Total score	1.56 (0.26)
Positive subscore	1.41 (0.28)
Negative subscore	1.67 (0.34)
Depressive subscore	1.76 (0.36)
AQ, M (SD) Total score	15.62 (5.69)
Imagination subscore	2.77 (1.77)
Social skills subscore	2.03 (1.93)
Communication subscore	2.55 (1.82)
Attention to detail subscore	4.44 (2.07)
Attention shifting subscore	3.81 (1.85)
Childhood trauma, n (%)	
Emotional abuse	248 (31.31)
Physical abuse	35 (4.42)
Sexual abuse	55 (6.94)
Emotional neglect	340 (42.93)
Physical neglect	129 (16.29)
Bullying, n (%)	
Severity ≥ 2	487 (61.88)
Severity ≥ 3	344 (43.71)
Severity ≥ 4	161 (20.46)
Winter birth, n (%)	290 (36.62)
Cannabis use, n (%)	39 (5.60)
Obstetric complications, n (%)	162 (22.47)
Negative life events, M (SD)	3.03 (1.86)
Hearing impairment, n (%)	7 (0.88)

M: mean, SD: standard deviation, MZ: monozygotic, DZ: dizygotic, CAPE: The Community Assessment of Psychic Experiences, AQ: The Autism Spectrum Quotient, PRS-SZ: schizophrenia polygenic risk score

Associations of ATs and psychosis-associated risk factors with PEs

Autistic traits were significantly associated with total CAPE (Table 2, B: 0.12, 95% CI: 0.10 to 0.14, P < 0.001). While PRS-SZ was not associated with total CAPE (B: 0.01, 95% CI: -0.01 to 0.03, P = 0.33), all five CT subtypes, bullying, and negative life events showed significant positive associations with total CAPE (all P < 0.001). No significant associations between other psychosis risk factors and total CAPE were found (Table 2).

Table-2. Associations between psychosis-associated risk factors and ATs with PEs

	B (95% CI)	**p**
Autistic traits	0.12 (0.10 – 0.14)	**<0.001**
PRS-SZ	0.01 (-0.01 – 0.03)	0.33
Winter birth	0.02 (-0.02 – 0.06)	0.40
Hearing impairment	0.08 (-0.11 – 0.26)	0.41
Emotional abuse	0.18 (0.14 - 0.22)	**<0.001**
Physical abuse	0.22 (0.14 – 0.31)	**<0.001**
Sexual abuse	0.21 (0.14 - 0.28)	**<0.001**
Emotional neglect	0.08 (0.04 - 0.11)	**<0.001**
Physical neglect	0.11 (0.07 - 0.16)	**<0.001**
Bullying	0.09 (0.06 - 0.13)	**<0.001**
Obstetric complications	0.01 (-0.03 – 0.06)	0.54
Negative life events	0.07 (0.05 – 0.09)	**<0.001**
Cannabis use	0.001 (-0.08 – 0.08)	0.98

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval

Similar to the main analysis, exploratory analyses of CAPE subscales showed significant positive associations of ATs, all CT subtypes, bullying, and negative life events with all three CAPE subscale scores (Supplementary Tables 3-5).

Moderations of psychosis-associated risk factors on the associations between ATs and PEs

An interaction analysis revealed that PRS-SZ did not moderate the association between ATs and total CAPE. However, emotional abuse (B: 0.08, 95% CI: 0.05 to 0.11, P < 0.001), physical abuse (B: 0.11, 95% CI: 0.05 to 0.18, P = 0.001), sexual abuse (B: 0.09, 95% CI: 0.03 to 0.15, P = 0.002), and physical neglect (B: 0.06, 95% CI: 0.03 to 0.10, P = 0.001) significantly interacted with ATs in predicting total CAPE. Emotional neglect (B: 0.04, 95% CI: 0.01 to 0.07, P = 0.007) and negative life events (B: 0.007, 95% CI: 0.0005 to 0.014, P = 0.04) significantly interacted with ATs in predicting total CAPE at a nominal level, but the statistical significance was lost after correction for multiple testing (Table 3).

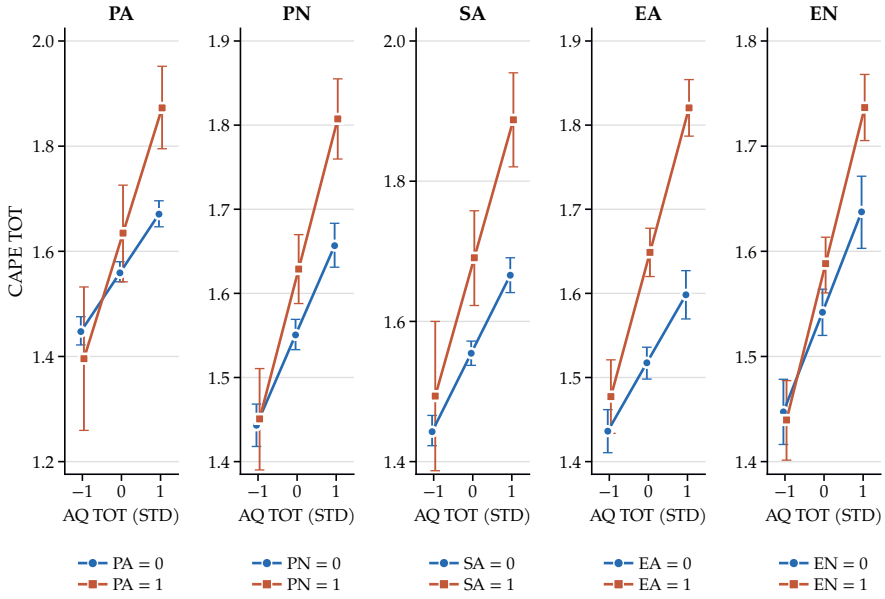
Table-3. Interaction effects of psychosis-associated risk factors and ATs on PEs

	B (95% CI)	**p**
PRS-SZ	-0.004 (-0.025 - 0.017)	0.70
Winter birth	0.03 (-0.002 – 0.06)	0.07
Hearing impairment	0.05 (-0.19 - 0.30)	0.69
Emotional abuse	0.08 (0.05 - 0.11)	**<0.001**
Physical abuse	0.11 (0.05 - 0.18)	**0.001**
Sexual abuse	0.09 (0.03 - 0.15)	**0.002**
Emotional neglect	0.04 (0.01 - 0.07)	0.007
Physical neglect	0.06 (0.03 - 0.10)	**0.001**
Bullying	0.02 (-0.01 - 0.05)	0.22
Obstetric complications	-0.001 (-0.040 - 0.038)	0.94
Negative life events	0.007 (0.0005 - 0.014)	0.04
Cannabis use	-0.04 (-0.12 - 0.03)	0.27

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval

Marginal effects analysis revealed that the positive association between ATs and total CAPE increased in the presence of CT subtypes (Supplementary Table 6 & Figure 1).

Figure 1. Marginal Effect Plots Based on Multilevel Linear Regression of the Interaction Between Standardized Total AQ Score (*X*-Axis) and Different Types of CT Score on Total CAPE Frequency Score (*Y*-Axis).



AQ TOT (STD), standardized total AQ; CAPE TOT, total CAPE frequency; EA, emotional abuse; EN, emotional neglect; PA, physical abuse; PN, physical neglect; SA, sexual abuse.

No significant moderations of other psychosis risk factors on the relationship between ATs and total CAPE were found. Exploratory analyses of CAPE subscales showed similar significant interactions between CT subtypes and ATs for CAPE positive subscale (Supplementary Table 7). However, emotional abuse was the only risk factor significantly interacting with ATs in determining CAPE negative and depressive subscales (Supplementary Tables 8 & 9).

Discussion

The present study aimed to evaluate the role of psychosis-associated risk factors in moderating the association between ATs and PEs in a general population twin sample. Our primary analyses revealed that ATs significantly interacted with the CT subtypes, particularly

emotional abuse, physical abuse, sexual abuse, and physical neglect, on the expression of psychosis, whereas genetic and the other tested environmental risk factors for psychosis did not. Exploratory analyses of psychosis subdomains yielded similar positive interactions between CT subtypes and ATs for positive symptoms, but only emotional abuse significantly interacted with ATs on the expression of depressive and negative symptoms.

We found that CT, but not bullying, significantly moderates the relationship between ATs and PEs. This is partially aligned with the previous research. To date, only a few studies have addressed the impact of CT and bullying on the risk of psychosis among individuals with elevated ATs. Two studies have consistently shown that both CT and bullying can mediate the relationship between ATs and PEs (Dardani et al., 2023; Stanyon et al., 2022). Adding to prior evidence, our study suggests that CT, but not bullying, moderates the relationship between ATs and PEs. A possible explanation for this discrepancy between the impact of CT and bullying could be that the perpetrators of CT are usually parents, family members, or relatives (U.S. Department of Health & Human Services, 2025), who could have a more profound impact on a child's life and emotional development than the perpetrators of bullying, who are often peers. External support systems might also be available to help lessen the impact of bullying. Additionally, bullying tends to be more episodic, whereas chronic and insidious CT may involve prolonged exposure without immediate access to support, possibly leading to a more pervasive and enduring impact. Another speculation could be that CT might contribute to the development of maladaptive coping strategies such as avoidance and rumination (O'Mahen et al., 2015), as well as an increased threat anticipation (Reininghaus et al., 2016), that could potentially lead to PEs, especially in autistic individuals who already tend to misinterpret threats. While bullying may also have similar effects, its impact may be more prevalent in certain social contexts compared to the broader and more internalized effect of CT.

Our exploratory analyses revealed significant interactions between various CT subtypes and ATs on positive symptoms similar to the overall psychosis expression. However, emotional abuse was the only form of CT that also interacted with ATs in determining negative and

depressive symptoms. This is in line with the literature reporting that emotional abuse is a chronic, widespread type of CT and has been found to cause more severe developmental consequences into adulthood, than those caused by other types of CT (Dye, 2019). Altogether, these findings implied that all forms of CT could amplify the risk of subclinical psychosis, especially positive symptoms in people with high ATs, whereas emotional abuse may exert a broader influence on multiple domains of psychosis expression in this population. Indeed, literature has acknowledged emotional abuse as the form of abuse most frequently linked to mental health problems (Ackner et al., 2013).

The number of negative life events did not interact with ATs, despite its significant effect on PEs. A recent study found that exposure to family problems and conflicts with peers was associated with increased occurrence of psychotic/manic symptoms in autistic inpatients (Bortoletto et al., 2023); however, the relationship between ATs and life events was not studied in non-clinical samples. One possible explanation for this discrepancy is that individuals from our general population sample with high ATs levels, but do not meet the formal criteria for an ASD diagnosis, may cope better with negative life events than those from clinical samples. On the other hand, individuals with higher ATs might already have an elevated baseline of stress perception. Consequently, an increased number of negative life events may not significantly raise their stress levels or lead to PEs, resulting in a less pronounced effect of these events and a weaker association with ATs.

Winter birth, obstetric complications, hearing impairment, and cannabis use were not significantly associated with PEs and did not interact with ATs in predicting PEs. To the best of our knowledge, no studies have ever explored interactions of these factors with ATs on PEs before. First, while some studies suggest a seasonal effect on autism, the findings have been inconsistent, with various studies reporting different seasons of birth, such as fall (Lee et al., 2019) or spring births (Hebert et al., 2010; Mouridsen et al., 1994) as potential risk factors or no association at all (Atladóttir et al., 2007; Kolevzon et al., 2006). Considering that the previously reported association between winter birth and psychosis expression is generally weak (Hsu

et al., 2021; Tochigi et al., 2013), such mixed findings might simply reflect the complex relationship between the season of birth and the risks for psychosis and autism. The level of complexity might require a larger study to detect more subtle effects. Similarly, our limited number of participants with hearing impairment (n=7) and cannabis use (n=39) might offer low statistical power. To this extent, given that ASD and hearing problems frequently co-occur, with a reported ASD prevalence of 9% in children with hearing impairment (Do et al., 2017), further studies on the effect of hearing impairment on psychosis expression in the context of the autistic spectrum are warranted. Also, while existing research on cannabis use in ASD primarily focuses on medical use (da Silva Junior et al., 2022), the pro-psychotic impact of recreational cannabis exposure among autistic individuals and people with high ATs should not be overlooked, due to disruptive epigenetic effects potentially implicated in pathophysiology of schizophrenia (Bortoletto & Colizzi, 2022; Colizzi et al., 2022).

We did not find a significant association between PRS-SZ and PEs, which might be attributed to the relatively small sample size of our study. Some large population-based studies such as Adolescent Brain Cognitive Development Study (n=4650) and UK Biobank (n=127966) have found an association between PRS-SZ and PEs (Karcher et al., 2022; Legge et al., 2019), while others, with smaller sample sizes (n = 2152 and n = 3483) have shown no significant relationships (Sieradzka et al., 2014; Zammit et al., 2014), that might be due to an inadequate statistical power to detect a potentially weak effect of PRS-SZ on PEs. Given that our sample size (n = 792) is even smaller, our study might arguably be underpowered to detect an association between PRS-SZ and PEs, such that the magnitude of the association of PRS-SZ with PEs was weaker than that with a clinical diagnosis for schizophrenia (Zammit et al., 2014). In addition, subclinical psychotic symptoms often co-occur with other psychopathology, creating a transdiagnostic and overlapping symptom representation (McGorry & Van Os, 2013; Van Os & Reininghaus, 2016). Moreover, environmental factors may have a stronger influence than genetic predisposition as measured by PRS-SZ on the development of PEs. Methodological differences, particularly in the assessment protocol of PEs, might also explain the inconsistencies.

The interaction between ATs and PRS-SZ was not significantly associated with PEs, as well. To the best of our knowledge, this is the first study to specifically test PRS-SZ as a potential moderator between AT and PEs. Consequently, direct comparisons with prior research are limited. The lack of a significant interaction between ATs and PRS-SZ on PEs might be attributable to several factors, including the limitations mentioned above (small sample size, potential weaker impact of PRS-SZ on subclinical symptoms). Additionally, although several studies have demonstrated a substantial genetic overlap between schizophrenia and autism (Carroll & Owen, 2009), it is important to note that PRS-SZ accounts only for common genetic variants. Other genetic factors, such as rare variants, copy number variations, and chromosomal anomalies, may also play a role in contributing to PEs in individuals with higher ATs.

Our findings hold important clinical and research implications. Screening for childhood trauma in individuals with elevated ATs could help identify those at a heightened risk of developing psychosis and facilitate early intervention. Trauma-focused therapies and resilience-building programs may provide effective strategies to decrease psychosis risk and improve long-term outcomes. However, research on the screening, treatment, and prevention of childhood trauma in autistic populations remains limited. Available research suggests that trauma screening, psychoeducation, and psychotherapy (such as trauma-focused cognitive behavioral therapy) should be adapted to meet the unique needs of autistic children (Peterson et al., 2019). Future studies should explore this relationship, particularly focusing on how trauma contributes to psychosis and treatment of trauma-related symptoms in autism. To advance our understanding, future research should use longitudinal designs to investigate the causal pathways linking psychosis expression to environmental risk factors, particularly childhood trauma. Moreover, investigating potential intermediate mechanisms, such as affective dysregulation, cognitive biases or salience attribution, could help identify the shared vulnerabilities underlying these conditions. Additionally, studies involving larger and more diverse samples are essential to better understand the genetic and environmental mechanisms driving the autism–psychosis continuum.

Limitations

The present study investigates, for the first time, the moderating role of schizophrenia-related genetic and environmental risk factors in the association between ATs and PEs, leveraging data from a large general population sample. However, several limitations should be considered. First, childhood adversities, bullying, and life events were evaluated using self-report measures, which may be subjected to recall bias. However, both retrospective and prospective reports of childhood trauma were demonstrated to be linked to mental health issues during adolescence and adulthood (Newbury et al., 2018; Reuben et al., 2016), supporting the validity of our findings based on retrospective reports. Second, our general population sample allowed us to investigate ATs and PEs as a continuum. However, it limits the generalization to those meeting the full criteria of ASD. Similar analyses in clinical samples should be conducted even though a validated tool for assessing PEs in autistic children remains to be developed (Hastings, 2020). Furthermore, the generalizability of our findings might be influenced by the composition of the TwinssCan cohort, which primarily included twins. In this regard, it should be noted that twins experience unique genetic and shared environmental factors, such as specific prenatal conditions and family dynamics, that may differ from those of singletons and could shape the observed associations. Third, while the sample size of 792 participants provided sufficient power for detecting some significant moderate effects, the study may still be prone to type II error for certain risk factors with low prevalence or small effect sizes, including hearing impairment, cannabis use, and obstetric complications. The limited representation of these factors might have reduced our ability to identify the interaction effects, which are usually smaller than the main effects. Future research with larger cohorts is necessary to confirm these findings. Furthermore, our sample may have been underpowered to detect significant associations between PRS-SZ and PEs. Moreover, the age range of our sample may limit the detection of PEs that could emerge later in adulthood. However, it is important to note that the onset of psychopathology often occurs in adolescence and young adulthood, both in the general population (Solmi et al., 2021), and among individuals with autism (Fusar-Poli et al., 2024), supporting the significance of the findings from the current sample. Lastly, our study

was a cross-sectional analysis, precluding a temporal relationship between the risk factors and PEs to be drawn. Therefore, further investigation using a longitudinal design is needed for causal inference.

Conclusions

Our findings underscore the significant role of environmental risks in shaping the complex continuum of autism and psychosis. Identifying individuals with higher ATs and screening them for childhood adversity could be a promising measure to safeguard them from further environmental risk exposure and facilitate early intervention to prevent psychosis expression.

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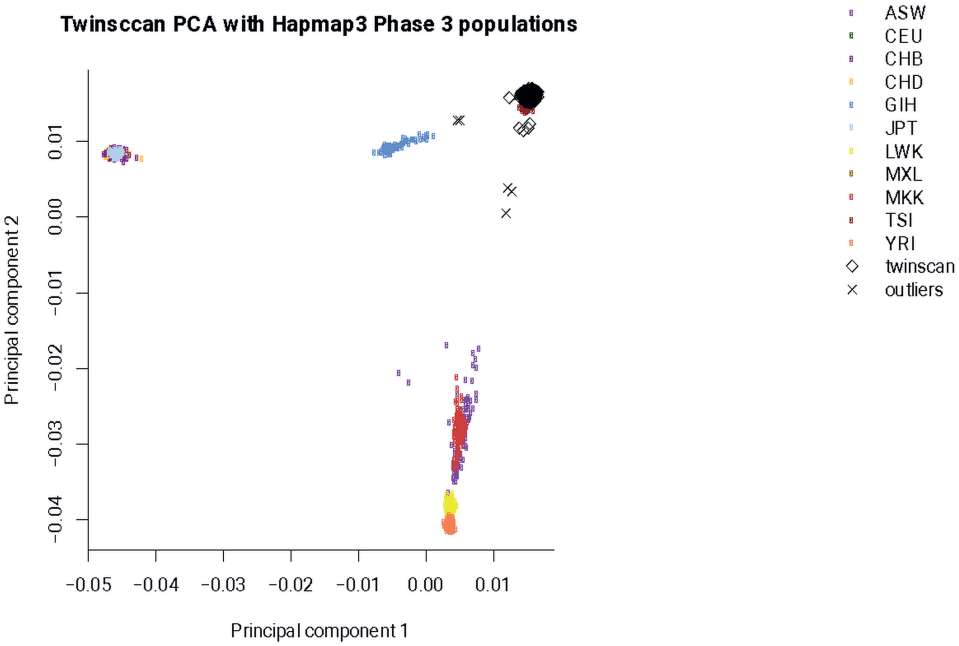
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Conflicts of Interest

Marco Colizzi has been a consultant/advisor to GW Pharma Limited, GW Pharma Italy SRL and F. Hoffmann-La Roche Limited, outside of this work.

Supplementary Material

Supplementary Figure 1. The first and second principal component of TwinssCan data (with identified ethnic outliers) along with hapmap3 population



Supplementary Table 1. 20 Complex-LD regions and long-range LD regions excluded from PRS analysis.

	B (95% CI)
Chromosome	**Base pair position (start point to end point)**
1	48000000-52000000
2	86000000-100500000
2	183000000-190000000
3	47500000-50000000
3	83500000-87000000
5	44500000-50500000
5	129000000-132000000
6	25500000-33500000
6	57000000-64000000
6	140000000-142500000
7	55000000-66000000
8	8000000-12000000
8	43000000-50000000
8	112000000-115000000
10	37000000-43000000
11	87500000-90500000
12	33000000-40000000
20	32000000-34500000
8	8135000-12000000
17	40900000-45000000

Supplementary Table 2. The number of alleles used for PRS calculation for the TwinssCan data at different P-value thresholds using the different cohorts

Level	*P*-value threshold	Number of SNPs
1	$5x10^{-8}$	168
2	$5x10^{-7}$	302
3	$5x10^{-6}$	567
4	$5x10^{-5}$	1236
5	$5x10^{-4}$	2900
6	$5x10^{-3}$	8144
7	0.05	26635
8	0.1	38852
9	0.2	56596
10	0.3	70225
11	0.4	81110
12	0.5	89965
13	1	113020

Supplementary Table 3. Associations between psychosis-associated risk factors and ATs with CAPE positive subscores

	B (95% CI)	p
Autistic traits	0.10 (0.08 - 0.12)	**<0.001**
PRS-SZ	0.01 (-0.01- 0.03)	0.28
Winter birth	0.01 (-0.19 - 0.20)	0.28
Hearing impairment	0.03 (-0.02- 0.07)	0.96
Emotional abuse	0.16 (0.12 - 0.20)	**<0.001**
Physical abuse	0.25 (0.16 - 0.34)	**<0.001**
Sexual abuse	0.23 (0.14 - 0.32)	**<0.001**
Emotional neglect	0.06 (0.04 - 0.07)	**0.004**
Physical neglect	0.12 (0.06 - 0.13)	**<0.001**
Bullying	0.10 (0.06 - 0.14)	**<0.001**
Obstetric complications	0.03 (-0.02 - 0.08)	0.25
Negative life events	0.07 (0.05 - 0.08)	**<0.001**
Cannabis use	-0.05 (-0.14 - 0.04)	0.27

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. CAPE: The Community Assessment of Psychic Experiences, PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval

Supplementary Table 4. Associations between psychosis-associated risk factors and ATs with CAPE negative subscores

	B (95% CI)	**p**
Autistic traits	0.16 (0.14 - 0.18)	**<0.001**
PRS-SZ	0.00 (-0.03- 0.03)	0.99
Winter birth	0.03 (-0.02- 0.07)	0.28
Hearing impairment	0.16 (-0.09 - 0.40)	0.21
Emotional abuse	0.18(0.13 - 0.23)	**<0.001**
Physical abuse	0.19(0.08 - 0.31)	**0.001**
Sexual abuse	0.16(0.07 - 0.26)	**<0.001**
Emotional neglect	0.10(0.05 - 0.14)	**<0.001**
Physical neglect	0.12 (0.05 - 0.18)	**<0.001**
Bullying	0.09 (0.04 - 0.14)	**<0.001**
Obstetric	-0.002 (-0.06- 0.06)	0.94
Negative life events	0.07 (0.04 - 0.09)	**<0.001**
Cannabis use	0.03 (-0.08- 0.15)	0.59

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. CAPE: The Community Assessment of Psychic Experiences, PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval

Supplementary Table 5. Associations between psychosis-associated risk factors and ATs with CAPE depressive subscores

	B (95% CI)	**p**
Autistic traits	0.11 (0.09 - 0.14)	**<0.001**
PRS-SZ	0.02 (0.00- 0.05)	0.07
Winter birth	0.03 (-0.02- 0.09)	0.25
Hearing impairment	0.15 (-0.11 - 0.41)	0.25
Emotional abuse	0.23 (0.18 - 0.28)	**<0.001**
Physical abuse	0.24 (0.12 - 0.36)	**<0.001**
Sexual abuse	0.26 (0.17 - 0.36)	**<0.001**
Emotional neglect	0.11 (0.06 - 0.16)	**<0.001**
Physical neglect	0.10 (0.03 - 0.17)	**0.004**
Bullying	0.10 (0.05 - 0.15)	**<0.001**
Obstetric	0.01 (-0.05- 0.07)	0.76
Negative life events	0.10 (0.07 - 0.12)	**<0.001**
Cannabis use	0.09 (-0.03- 0.21)	0.15

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. CAPE: The Community Assessment of Psychic Experiences, PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval

Supplementary Table 6. Marginal effects for the relationship between ATs and PEs by presence of CT Subtypes

Childhood Trauma (1 = Present, 0 = Absent)		dy/dx (95% CI)	p
Emotional abuse	1	0.16 (0.13 – 0.18)	**<0.001**
	0	0.08 (0.06 – 0.10)	**<0.001**
Physical abuse	1	0.22 (0.15 – 0.28)	**<0.001**
	0	0.11 (0.09 – 0.12)	**<0.001**
Sexual abuse	1	0.20 (0.14 – 0.25)	**<0.001**
	0	0.10 (0.09 – 0.12)	**<0.001**
Emotional neglect	1	0.14 (0.11 – 0.16)	**<0.001**
	0	0.09 (0.07 – 0.12)	**<0.001**
Physical neglect	1	0.17 (0.13 – 0.20)	**<0.001**
	0	0.10 (0.08 – 0.12)	**<0.001**

Marginal effects analysis was performed to estimate the differential influences of the ATs at different levels of CT subtypes. ATs: autistic traits, PEs: psychotic experiences, CT: childhood trauma.

Supplementary Table 7. Interaction effects of psychosis-associated risk factors and ATs on CAPE positive subscores

	B (95% CI)	p
PRS-SZ	-0.01 (-0.02- 0.01)	0.25
Winter birth	0.03 (0.00- 0.07)	0.08
Hearing impairment	-0.10 (-0.38- 0.18)	0.48
Emotional abuse	0.12 (0.08 - 0.15)	**<0.001**
Physical abuse	0.15 (0.07 - 0.22)	**<0.001**
Sexual abuse	0.10 (0.03 - 0.16)	**0.003**
Emotional neglect	0.05 (0.02 - 0.09)	0.005
Physical neglect	0.07 (0.03 - 0.11)	**0.002**
Bullying	0.02 (-0.02 - 0.06)	0.27
Obstetric complications	0.01 (-0.04 - 0.05)	0.79
Negative life events	0.01 (-0.004 - 0.02)	0.17
Cannabis use	-0.06 (-0.14 - 0.03)	0.20

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. ATs: autistic traits, CAPE: The Community Assessment of Psychic Experiences PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval

Supplementary Table 8. Interaction effects of psychosis-associated risk factors and ATs on CAPE negative subscores

	B (95% CI)	**p**
PRS-SZ	-0.01 (-0.03 - 0.01)	0.39
Winter birth	0.02 (-0.02 - 0.07)	0.35
Hearing impairment	0.21 (-0.11 - 0.54)	0.20
Emotional abuse	0.09 (0.04 - 0.13)	**<0.001**
Physical abuse	0.08 (-0.01 - 0.17)	0.08
Sexual abuse	0.10 (0.02 - 0.18)	0.01
Emotional neglect	0.03 (-0.01 - 0.07)	0.15
Physical neglect	0.06 (0.01 - 0.11)	0.03
Bullying	0.03 (-0.02 - 0.07)	0.21
Obstetric complications	-0.02 (-0.07 - 0.04)	0.45
Negative life events	0.02 (0.003 - 0.04)	0.02
Cannabis use	-0.03 (-0.13 - 0.08)	0.60

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. ATs: autistic traits, CAPE: The Community Assessment of Psychic Experiences PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval

Supplementary Table 9. Interaction effects of psychosis-associated risk factors and ATs on CAPE depressive subscores

	B (95% CI)	**p**
PRS-SZ	-0.01 (-0.03 - 0.01)	0.37
Winter birth	0.04 (-0.01 - 0.09)	0.09
Hearing impairment	0.21 (-0.15 - 0.58)	0.26
Emotional abuse	0.09 (0.04- 0.14)	**<0.001**
Physical abuse	0.11 (0.01- 0.21)	0.04
Sexual abuse	0.05 (-0.03 - 0.14)	0.22
Emotional neglect	0.05 (0.01 - 0.10)	0.02
Physical neglect	0.08 (0.02 - 0.13)	0.009
Bullying	0.01 (-0.04 - 0.06)	0.58
Obstetric complications	0.02 (-0.04 - 0.07)	0.56
Negative life events	0.01 (-0.004 - 0.03)	0.12
Cannabis use	-0.05 (-0.17 - 0.06)	0.38

Age and gender were covariates. Statistical significance is p<0.004 after Bonferroni correction. ATs: autistic traits, CAPE: The Community Assessment of Psychic Experiences PRS-SZ: schizophrenia polygenic risk score, B: unstandardized regression coefficient, CI: confidence interval.

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Chapter 3

Examining psychological protective mechanisms as moderators of the association between autistic traits and psychosis expression in a general population twin sample

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Abstract

Background: Psychological protective factors, such as coping styles, extraversion, and optimal parenting, may reduce the risk of psychosis. However, their role in moderating the association between autistic traits (ATs) and psychosis expression (PE) remains understudied.

Methods: This study analyzed the first-wave data from the TwinssCan Project (n=792 twins and siblings, 60.2% female, mean age=17.4±3.6). ATs and PE were assessed using the Autism-Spectrum Quotient and the Community Assessment of Psychic Experiences (CAPE), respectively. Multilevel linear regression models were used to evaluate the moderating effects of seven coping styles (active coping, avoidance, reassuring thoughts, expressing emotions, seeking social support, palliative-reacting, and passive-reacting coping), extraversion, and optimal parenting.

Results: Seeking social support (B[95%CI]:-0.005[-0.009,-0.001]), reassuring thoughts (B[95%CI]:-0.005[-0.009,-0.001]), extraversion (B[95%CI]: -0.03[-0.04,-0.01]) and optimal parenting (B[95%CI]: -0.02[-0.03,0]) weakened the associations between ATs and CAPE total frequency scores, suggestive of protective mechanisms, whereas passive-reacting coping (B[95%CI]:0.007[0.004,0.010]) strengthened this, suggestive of a risk factor. Additionally, avoidance (B[95%CI]: 0.09[0.02,0.16]) emerged as a risk factor in confirmatory analyses by significantly interacting with ATs in predicting CAPE total severity scores.

Conclusions: Engagement coping, extraversion, and optimal parenting may mitigate psychosis vulnerability in individuals with higher ATs, while passive-reacting coping and avoidance may heighten psychosis vulnerability. Although further research is needed, our findings provide a rationale for developing and testing targeted preventive strategies aimed at enhancing resilience in individuals with ATs.

Keywords: autistic traits, psychosis expression, coping styles, parenting, personality, prevention

Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by difficulties in social communication, restricted interests, and repetitive behaviors (APA, 2022). Autistic traits (ATs) exist on a continuum in the general population, including individuals without a clinical diagnosis of ASD. ATs have been linked to an increased vulnerability to develop various psychopathological conditions, including psychosis (Bevan Jones et al., 2012; Lundström et al., 2011; Martinez et al., 2021). Recent studies show that individuals with higher ATs are at greater risk for experiencing subclinical psychotic symptoms (Bevan Jones et al., 2012; Martinez et al., 2021), even though the factors that might moderate this relationship remain understudied.

Few studies have examined the role of risk factors for schizophrenia as potential moderators in the association between clinical ASD and psychosis (Varcin et al., 2022). Recently, we analyzed the moderating role of various environmental risk factors on the relationship between ATs and psychosis expression (PE) (Karaçam Doğan et al., 2025). In this context, PE is defined broadly, to encompass not only positive symptoms but also negative and depressive symptoms (Reininghaus et al., 2013; Stefanis et al., 2002). In accordance with the existing literature, childhood trauma was regarded as a significant moderator that strengthened the association between ATs and PE as a risk factor (Dardani et al., 2023; Stanyon et al., 2022). A growing body of research has identified several protective factors that may reduce the risk of psychosis expression, including psychological variables such as personality traits (e.g., extraversion, openness, and agreeableness), adaptive coping styles, and higher premorbid intelligence quotient (IQ). Additionally, positive family environment, physical activity, and neighborhood characteristics such as cohesive communities and access to green spaces) have also been identified as protective factors (Crush et al., 2018; González-Pinto et al., 2011; Ku et al., 2024; Pruessner et al., 2011; Radua et al., 2018; Thakkar et al., 2023; Zhang et al., 2024). However, the role of these factors in the association between ATs and PE remains underexplored. This gap becomes particularly relevant in the context of higher ATs, since internal resilience factors like coping mechanisms may be underdeveloped and perceived stress levels are

higher compared to neurotypical adults (Hirvikoski & Blomqvist, 2015), possibly making them more vulnerable. Furthermore, social isolation and peer rejection can lead to loneliness, which is associated with a decline in perceived social support in autistic individuals (Lasgaard et al., 2010). Therefore, a broader approach that emphasizes building resilience is crucial to enhance the mental health outcomes of neurodiverse people.

Adopting a salutogenic perspective in mental health care has been increasingly recognized as a proactive strategy (Karaçam Doğan & Guloksuz, 2025; van Os & Guloksuz, 2024). In this framework, identifying protective factors becomes important for promoting population-wide health and preventing the negative outcomes associated with ATs and PE. By focusing on these protective factors, we can increase individual resilience while also paving the way for preventive public mental health strategies.

Therefore, guided by the salutogenesis framework, we aimed to investigate whether potentially protective psychological factors for psychosis (i.e., extraversion, coping styles, and optimal parenting) might moderate the relationship between ATs and PE in a large general population cohort of adolescent and young adult twins and siblings. We hypothesized that these factors may buffer the adverse effects of elevated ATs on PE, offering valuable insights into increasing resilience to reduce the risk of psychosis in this vulnerable population.

Methods

Participants

Analyses were performed using data from the first wave of the TwinssCan Project. The process of participant recruitment and data collection has been detailed in prior publications (Pries et al., 2019). The TwinssCan cohort consists of twins, non-twin siblings, and their parents, who were recruited through the East Flanders Prospective Twin Survey (EFPTS), a prospective population-based registry of multiple births in East Flanders, Belgium (Derom et al., 2019). For this study, we studied twins and siblings only and excluded parents. The twins enrolled were aged 15 to 18, while the non-twin siblings ranged from 15 to 35 years old. All participants provided written informed

consent. Exclusion criteria included lack of parental or caregiver consent for participants under 18, and the presence of a severe and chronic psychiatric disorder, as reported by caregivers, consistent with the Dutch consensus definition of severe mental illness (SMI) (Delespaul, 2013), such as schizophrenia, other psychotic disorders, bipolar disorder with psychotic features, autism spectrum disorders, or substance use disorders, when these conditions substantially impaired functioning and required coordinated care. The study was approved by the local ethics committee (Commissie Medische Ethiek van de Universitaire Ziekenhuizen KU Leuven, Nr. B32220107766). A total of 821 twins and siblings participated, but 29 were excluded due to missing data, leaving 792 participants for the final analysis.

Measures

Psychosis Expression

Psychosis expression was evaluated using the Community Assessment of Psychic Experiences (CAPE), a widely used, reliable, valid, and stable 42-item self-report questionnaire for assessing psychosis expression in the general population (Konings et al., 2006; Stefanis et al., 2002). CAPE consists of three subscales: positive, negative, and depressive. Responses are gathered using a four-point Likert scale, which measures both the frequency, and the level of distress associated with the symptoms. From these responses, overall and subdomain scores (positive, negative, depressive) were generated. For our analysis, we first focused on the frequency scores to quantify PE, consistent with our previous work using the TwinssCan cohort data (Drukker et al., 2024; Karaçam Doğan et al., 2025; Pinckaers et al., 2019; Pries et al., 2017). To explore the robustness of our findings, we additionally analyzed an alternative outcome score, the CAPE total severity score, calculated by multiplying the frequency score of an item by its corresponding distress score (Jaya et al., 2018; Jaya et al., 2021). For instance, a person who reports hearing voices "sometimes" (assigned a frequency score of 2) and experiencing "quite distressed" as a result (assigned a distress score of 3) would receive a combined severity score of 6. Furthermore, we employed the five-dimensional scoring approach of the CAPE positive subdomain for our exploratory analyses (Wigman et al., 2011), based on prior evidence suggesting

that the presentation of positive symptoms may differ among individuals with autism (Kiyono et al., 2020; Ribolsi et al., 2022). This model includes 5 subscales: hallucinations, delusions, paranoia, grandiosity, and paranormal beliefs. Importantly, this five-factor structure was replicated in young adult women from the same East Flanders Prospective Twin Survey and demonstrated excellent model fit (Wigman et al., 2012).

Autistic Traits

The Autism-Spectrum Quotient (AQ) is a 50-question self-assessment tool designed to evaluate autistic traits within the general population (Baron-Cohen et al., 2001). The AQ has good psychometric reliability, and the Dutch version was used for this study (Hoekstra et al., 2008). It consists of five subscales, each containing 10 questions: imagination, social skills, communication, attention to detail, and attention switching. Based on the mostly used scoring approach, responses of "definitely agree" and "slightly agree" were scored as 1 for items reflecting ATs, while "definitely disagree" and "slightly disagree" were scored as 0 (Baron-Cohen et al., 2001; Woodbury-Smith et al., 2005). For other items, the scoring was reversed, with disagreement scored as 1 and agreement as 0. Therefore, the total possible score ranged from 0 to 50, with higher scores indicating higher ATs.

Coping Styles

The Utrecht Coping List (UCL) is a 44-item self-report questionnaire commonly used in psychological research to assess coping styles (Schreurs et al., 1993). These include active coping (7 items), avoidance (8 items), reassuring thoughts (5 items), expressing emotions (3 items), palliative-reacting coping (8 items), passive-reacting coping (7 items), and seeking social support (6 items). Responses are rated on a 4-point Likert scale ranging from 1 (never) to 4 (very often). Active coping emphasizes problem-solving, while reassuring thoughts involves maintaining a positive attitude. Expressing emotions refers to openly displaying feelings such as anger or fear. Palliative-reacting coping involves behaviors aimed at distraction, such as smoking or drinking, while passive-reacting coping reflects self-isolation and feelings of helplessness. Seeking social support measures the tendency to seek assistance from others. We categorized coping styles based on

orientation to the stressor into engagement (i.e., active coping, seeking social support, and reassuring thoughts) and disengagement coping styles (i.e., palliative-reacting coping, avoidance, and passive-reacting coping) (Dijkstra & Homan, 2016). The last UCL subscale, expressing emotions, does not fit into either category (Dijkstra & Homan, 2016).

Optimal parenting

The Parental Bonding Instrument (PBI) is a 25-item self-report questionnaire assessing two parenting styles: care (12 items) and overprotection (13 items), separately for mothers and fathers (Parker et al., 1979). Responses are rated on a 4-point Likert scale from 0 (very unlikely) to 3 (very likely). For overprotection items, the scoring is reversed. Optimal parenting scores were calculated to represent high care and low overprotection. In our analysis, we used a combined parenting score as it best captures the parenting with a holistic approach without focusing on one parent, aligning with the evidence that having two supportive parents provides best child cognitive outcomes, while having one supportive parent, irrespective of which parent and regardless of parent's sex, provides significant advantages over having none (Martin et al., 2007; Ryan et al., 2006). Optimal parenting scores range from 0 to 75 for each parent; therefore, the combined score ranges from 0 to 150.

Extroverted personality traits

The Dutch translation of the extraversion subdomain of the Eysenck Personality Questionnaire Revised Short Scale (EPQ-RSS) was used to assess extroverted personality traits (Sanderman et al., 1991). The EPQ-RSS comprises 12 binary questions to evaluate extraversion, where responses are scored as either 0 (no) or 1 (yes). A total score, ranging from 0 to 12, is calculated based on the Dutch manual (Sanderman, 2012).

Statistical analysis

Analyses were carried out using Stata 16 (StataCorp, 2019). We used multilevel linear regression models to assess the effects of the independent variables on PE, accounting for potential clustering of participants within family. Multilevel regression models are recommended for analyzing data with multiple levels of observations, as they capture variability at each hierarchical level (Snijders & Bosker,

2011). All continuous variables (total AQ scores and the protective factors) were standardized to a mean of 0 and a standard deviation (SD) of 1 to ensure comparability and facilitate the interpretation of the regression coefficients.

As the main analyses, the independent associations of total AQ scores and each protective factor (i.e., coping styles, extraversion and parenting) with CAPE total frequency scores were tested in separate multilevel linear regression models. Then, the interaction between total AQ and each protective factor in predicting CAPE total frequency scores were tested to see whether the protective factors moderated the relationship between AQ scores and CAPE total scores. In the case of significant interaction, follow-up marginal effect analyses were subsequently performed to examine how the association between the moderator and PE varied across different levels of ATs (–1 SD, 0, +1 SD), using the STATA 'margins' command. To aid interpretation of significant interaction effects, the STATA 'marginsplot' command was used to visualize the effect of ATs on PE at different levels (–1 SD, 0, +1 SD) of the moderator. As a confirmatory analysis, the CAPE total severity score was used as an alternative outcome to test the robustness of findings based on the CAPE total frequency score. Similar analytical approaches were also applied to the CAPE negative, positive, and depressive subdomain frequency scores as secondary analyses. We repeated similar analytical approaches using individual CAPE positive symptom subdomains as the outcome in the exploratory analyses. Age and gender were covariates in all models. The nominal statistical significance level was set at $P = 0.05$. No multiple testing correction was applied to maximize the power of analyses, given the explorative nature of our study to avoid an increase in Type II error (Rothman, 1990).

Results

Participants

The current analyses included 792 participants, comprising 274 monozygotic twins, 475 dizygotic twins, and 43 siblings. The mean age was 17.5 ± 3.6, and 60.2% of the participants were female. *Table 1* reports the descriptive characteristics.

Table 1. Sample Characteristics

Characteristics	N=792	Range
Age (years), M (SD)	17.47 (3.60)	15-34
Gender, n (%)		
Female	477 (60.23)	
Male	315 (39.77)	
Zygosity, n (%)		
MZ	274 (34.60)	
DZ	475 (59.97)	
Sibling	43 (5.43)	
CAPE frequency scores, M (SD)		
Total score	1.56 (0.26)	1.04-3.02
Positive score	1.41 (0.28)	1-3.15
Negative score	1.67 (0.34)	1-3.28
Depressive score	1.76 (0.36)	1-3.62
Total CAPE severity score, M (SD)	4.69 (1.29)	2-12.48
CAPE positive subdomain scores, M (SD)		
Hallucinations	1.14 (0.32)	1-4
Delusions	1.28 (0.30)	1-3
Paranoia	1.68 (0.41)	1-3.8
Grandiosity	1.56 (0.61)	1-4
Paranormal beliefs	1.45 (0.55)	1-4
Total AQ score, M (SD)	15.62 (5.69)	2-40
UCL scores, M (SD)		
Expressing emotions	6.81 (1.77)	3-12
Engagement coping		
Active coping	17.34 (3.30)	8-27
Seeking social support	14.41 (3.78)	6-24
Reassuring thoughts	12.53 (2.53)	5-20
Disengagement coping		
Avoidance	16.62 (3.39)	8-29
Passive-reacting coping	12.29 (3.41)	7-27
Palliative-reacting coping	18.29 (3.38)	10-29
PBI optimal parenting score, M(SD)	108.68(18.59)	41-149
EPQ-RSS extraversion subscale score, M(SD)	8.53 (2.88)	0-12

Descriptive statistics for the study sample, including demographic variables and psychometric measures. Data were presented as mean or frequency with ranges indicated where applicable. M: mean, SD: standard deviation, MZ: monozygotic, DZ: dizygotic, SD: Standard deviation, CAPE: The Community Assessment of Psychic Experiences, AQ: The Autism Spectrum Quotient, UCL: Utrecht Coping List, PBI: Parental Bonding Instrument, EPQ-RSS: The Eysenck Personality Questionnaire Revised Short Scale

Associations of ATs and protective factors with psychosis expression

Main analyses showed that ATs (B[95%CI]: 0.12[0.10,0.14]), expressing emotions (B[95%CI]: 0.018[0.008,0.028]), and all three disengagement coping strategies (avoidance B[95%CI]: 0.016[0.01,0.02]; passive-reacting coping B[95%CI]: 0.04[0.03,0.04]; and palliative-reacting coping B[95%CI]: 0.007[0.002,0.012]) were positively associated with CAPE total frequency scores.

Confirmatory analyses revealed similar significantly positive associations of CAPE total severity scores with ATs and the four coping strategies (Table 2). For engagement coping strategies, active coping (B[95%CI]: -0.006[-0.010,0]) and seeking social support (B[95%CI]: -0.006[-0.011,-0.001]) were negatively associated with CAPE total frequency but not with CAPE total severity scores, whereas reassuring thoughts were associated with neither outcome (Table 2).

Optimal parenting (B[95%CI]: -0.07[-0.09,-0.05]) and extroverted personality traits (B[95%CI]: -0.08[-0.10,-0.06]) were significantly negatively associated with CAPE total frequency scores, also replicated in the confirmatory analyses (Table 2).

Table 2. Associations between psychological factors and ATs with PE

	Total CAPE frequency	**Total CAPE severity**
	B (95% CI)	**B (95% CI)**
Autistic traits	**0.12 (0.10 to 0.14)**	**0.46 (0.37 to 0.54)**
Coping styles		
Expressing emotions	**0.018 (0.008 to 0.028)**	**0.25 (0.16 to 0.34)**
Engagement coping		
Active coping	**-0.006 (-0.01 to 0)**	-0.06 (-0.15 to 0.03)
Seeking social support	**-0.006 (-0.011 to -0.001)**	-0.01 (-0.11 to 0.08)
Reassuring thoughts	-0.004 (-0.011 to 0.003)	-0.08 (-0.17 to 0.01)
Disengagement coping		
Avoidance	**0.016 (0.01 to 0.02)**	**0.23 (0.14 to 0.32)**
Passive-reacting coping	**0.04 (0.03 to 0.04)**	**0.71 (0.63 to 0.78)**
Palliative-reacting coping	**0.007 (0.002 to 0.012)**	**0.14 (0.05 to 0.23)**
Optimal parenting	**-0.07 (-0.09 to -0.05)**	**-0.31 (-0.40 to -0.22)**
Extraversion	**-0.08 (-0.10 to -0.06)**	**-0.36 (-0.44 to -0.27)**

Age and gender were covariates. B: unstandardized regression coefficient, CI: confidence interval

Secondary analyses of the CAPE subdomains revealed that ATs, avoidance, and passive-reacting coping were significantly positively associated with all three CAPE subdomains, whereas expressing emotions and palliative-reacting coping were significantly associated with the CAPE positive and depressive, but not negative, subdomains. None of the engagement coping strategies were associated with CAPE positive scores. However, active coping and seeking social support were negatively associated with CAPE negative scores, whereas active coping and reassuring thoughts were negatively associated with CAPE depressive scores. Additionally, optimal parenting and extraversion were negatively associated with all CAPE subdomains (Supplementary Table 1).

Exploratory analyses of individual CAPE positive symptom subdomains showed that ATs and passive-reacting coping were positively associated with all positive symptom subdomains. The other two disengagement coping strategies (i.e., avoidance and palliative-reacting coping) were positively associated with delusions, but not hallucinations, while optimal parenting and extraversion were negatively associated with both delusions and hallucinations. Other psychological factors showed mixed results across positive symptom subdomains (Supplementary Table 2).

Interactions of protective factors with ATs on PE

Main analyses revealed that passive-reacting coping was the only disengagement coping strategy significantly interacting with ATs in predicting CAPE total frequency scores (B[95%CI]:0.007[0.004,0.010]). For engagement coping strategies, seeking social support (B[95%CI]:-0.005[-0.009,-0.001]) and reassuring thoughts (B[95%CI]: -0.008[-0.014,-0.002]) significantly negatively interacted with ATs in predicting CAPE total frequency scores. Similarly, negative interactions with ATs were observed for extraversion (B[95%CI]: -0.03[-0.04,-0.01]), and optimal parenting (B[95%CI]: -0.02[-0.03,0]). No significant interactions were found for other coping strategies (Table 3). The marginal plots showed that the association between ATs and CAPE total frequency scores was attenuated at higher levels of reassuring thoughts, social support seeking, extraversion, and optimal parenting, but the association amplified at higher levels of passive-

reacting coping (Figure 1). Follow-up marginal effect analyses revealed that passive-reacting coping and optimal parenting were associated with increased and decreased PE, respectively, across all levels of ATs, with a trend toward stronger associations at higher AT levels. In contrast, reassuring thoughts were positively associated with PE only at lower AT levels, while extraversion was negatively associated with PE only at higher AT levels. The association between seeking social support and PE was not significant across AT levels (Supplementary Table 3). Consistent with the main analyses, confirmatory analyses of CAPE total severity scores revealed positive interactions between ATs and passive-reacting coping, as well as negative interactions between ATs and seeking social support and extraversion (Table 3). However, avoidance coping, but not reassuring thoughts and optimal parenting, significantly interacted with ATs in predicting CAPE total severity scores (Table 3).

Table 3. Interaction effects of psychological factors and ATs on PE

	Total CAPE frequency	**Total CAPE severity**
	B (95% CI)	**B (95% CI)**
Coping styles		
Expressing emotions	-0.002 (-0.011 to 0.006)	0.02 (-0.06 to 0.10)
Engagement coping		
Active coping	-0.001 (-0.006 to 0.004)	0.05 (-0.04 to 0.14)
Seeking social support	**-0.005 (-0.009 to -0.001)**	**-0.13 (-0.21 to -0.05)**
Reassuring thoughts	**-0.008 (-0.014 to - 0.002)**	-0.07 (-0.15 to 0.01)
Disengagement coping		
Avoidance	0.003 (-0.001 to 0.008)	**0.09 (0.02 to 0.16)**
Passive-reacting coping	**0.007 (0.004 to 0.010)**	**0.09 (0.03 to 0.15)**
Palliative-reacting coping	-0.002 (-0.007 to 0.002)	-0.01 (-0.09 to 0.08)
Optimal parenting	**-0.02 (-0.03 to 0)**	-0.07 (-0.16 to 0.01)
Extraversion	**-0.03 (-0.04 to -0.01)**	**-0.09 (-0.16 to -0.02)**

Regression coefficients (B) with 95% confidence intervals demonstrating the moderating effects of coping styles, parenting, and extraversion on the relationship between ATs and PE. Age and gender were covariates. B: unstandardized regression coefficient, CI: confidence interval. Statistical significance $p<0.05$ is shown in bold.

Figure 1. Interaction effects of the moderators and ATs on PE

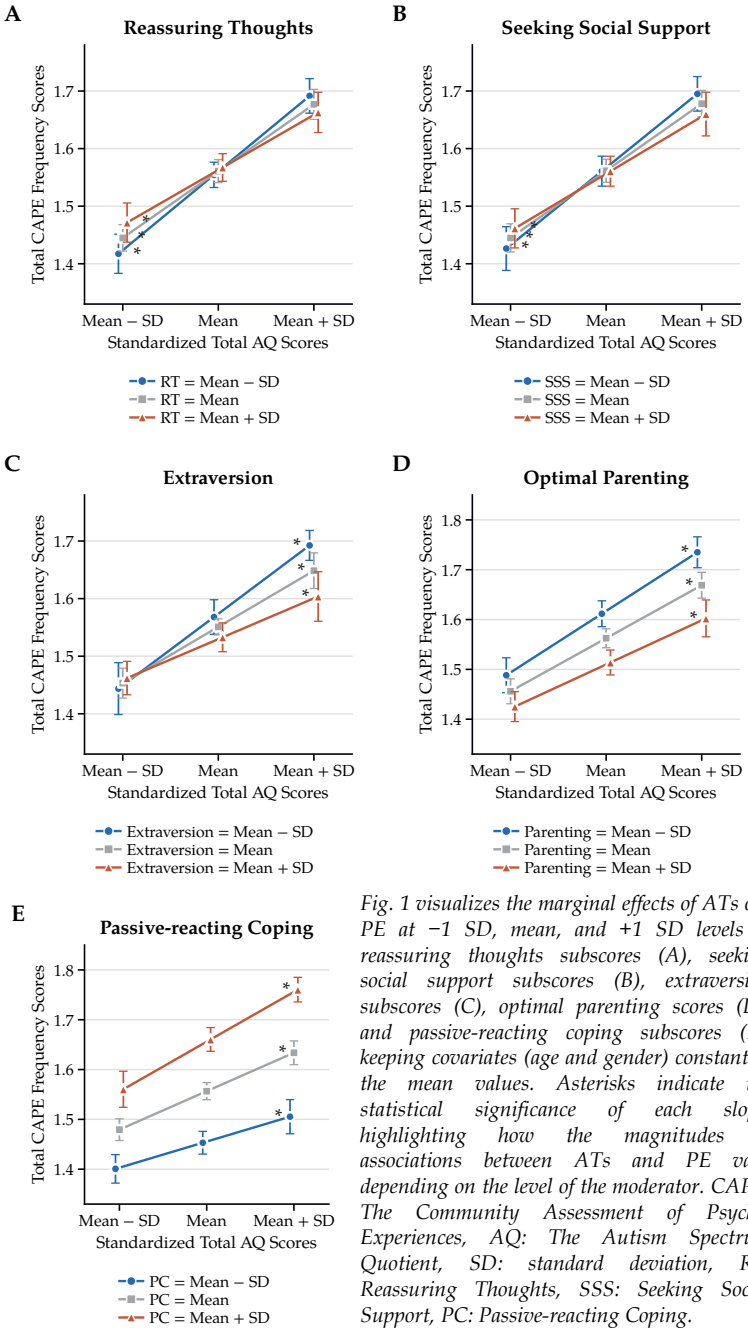


Fig. 1 visualizes the marginal effects of ATs on PE at −1 SD, mean, and +1 SD levels of reassuring thoughts subscores (A), seeking social support subscores (B), extraversion subscores (C), optimal parenting scores (D), and passive-reacting coping subscores (E), keeping covariates (age and gender) constant at the mean values. Asterisks indicate the statistical significance of each slope, highlighting how the magnitudes of associations between ATs and PE vary depending on the level of the moderator. CAPE: The Community Assessment of Psychic Experiences, AQ: The Autism Spectrum Quotient, SD: standard deviation, RT: Reassuring Thoughts, SSS: Seeking Social Support, PC: Passive-reacting Coping.

Secondary analyses of the CAPE subdomains revealed positive interactions between ATs and avoidance specifically for negative symptoms, and between ATs and passive-reacting coping for both positive and negative symptoms. All three engagement coping strategies negatively interacted with ATs in predicting positive symptoms, with seeking social support additionally showing a significant negative interaction for depressive symptoms. While optimal parenting significantly negatively interacted with ATs in predicting depressive symptoms only, extraversion showed negative interactions with ATs consistently for all CAPE subdomains (Supplementary Table 4). Exploratory analyses of individual CAPE positive symptom subdomains revealed that ATs significantly interacted with passive-reacting coping, seeking social support, reassuring thoughts, optimal parenting, and extraversion in predicting hallucinations, consistent with findings of the primary analyses using the CAPE total frequency scores. In contrast, no significant interaction effects were observed for delusions (Supplementary Table 5).

Discussion

To the best of our knowledge, this is the first study that investigated the role of potential protective factors in moderating the relationship between ATs and PE in the general population. Our results indicate that engagement coping strategies, such as seeking social support and reassuring thoughts, significantly weakened the association between ATs and PE, whereas disengagement coping strategies, including passive-reacting coping and avoidance, strengthened the association. Similar to engagement coping strategies, optimal parenting and extraversion significantly negatively moderated this association, suggesting their potential mitigating role in buffering AT-associated psychosis vulnerability.

Despite an abundance of studies on coping among parents of autistic children, research in individuals with high ATs or ASD diagnosis is limited. Our findings align with prior evidence showing that engagement coping is linked to higher well-being (Muniandy et al., 2022) and moderates the relationship between stress and well-being in autism (Muniandy et al., 2023), whereas disengagement coping is associated with several psychopathological outcomes (Khor et al.,

2014; Muniandy et al., 2022). Specifically, we found that reassuring thoughts were significantly positively associated with PE only at low AT levels, implying maladaptive coping among this group. Interestingly, prior research showed that autistic people with co-occurring substance use disorders tend to score lower on this coping strategy than their non-autistic counterparts, which can be increased by cognitive behavioral therapy with accompanying improved clinical outcomes (Kronenberg et al., 2015; Walhout et al., 2022). Taken together, these findings suggest that individuals with higher ATs may need to rely on reassuring thoughts more than neurotypical people, possibly due to heightened stress sensitivity and sensory overload. In contrast, passive-reacting coping consistently showed a positive association with PE across all levels of AT. The increasing strength of its association at higher AT levels suggests that this coping strategy may exacerbate PE even further in those with higher ATs.

When examining PE subdomains, we found that all engagement coping strategies mitigated the association between ATs and positive symptoms. This pattern may reflect the more distressing nature of positive symptoms, which may require more active engagement to manage associated distress (Rollins et al., 2010). Interestingly, the interaction effect patterns observed for hallucinations were similar to those found for the CAPE total frequency scores, whereas none of the coping styles interacted with ATs in predicting delusions. This aligns with the view that delusions are challenging to assess in autism, as they may be difficult to differentiate from imaginative thinking and can manifest differently due to social impairments and distinct attributional styles (Ribolsi et al., 2022). Altogether, these findings highlight the differential influences of coping strategies on the multidimensionality of PE in the background of autistic continuum. Further studies in larger samples might be warranted.

Of personality traits, extraversion appeared to be significantly negatively associated with PE only at high levels of AT. This suggests a potential protective role of extraversion in people with higher ATs, likely by fostering social engagement and mitigating the social isolation often experienced, thereby challenging the common assumption that autistic individuals are entirely asocial (Davidson & Smith, 2009). Extraversion also emerged as a protective factor across

all CAPE subdomains with the broadest effects on positive symptoms, including hallucinations, paranoia, and grandiosity. These findings align with previous evidence highlighting the protective role of extraversion in general psychopathology among individuals with autism (Baranova et al., 2022; Grella et al., 2022; Lodi-Smith et al., 2018; Shirayama et al., 2022). Interestingly, personality traits, including extraversion, can be modified with intervention, not only early in life but also throughout young adulthood to old age (Hill et al., 2012; Mõttus et al., 2012; Robins et al., 2001). Meta-analyses indicate that interventions can significantly impact personality, with extraversion and emotional stability showing the most substantial changes in both clinical and nonclinical settings (Roberts et al., 2017). Therefore, intervention aiming at enhancing extraversion could be another potential strategy to prevent PE in people with high ATs.

Finally, optimal parenting was negatively associated with PE across all AT levels. This finding aligns with prior evidence showing consistent associations between parent-child interactions and psychosis (Barnes et al., 2021). Although literature specifically addressing such associations in autism is limited, research highlights the importance of parent-child relationships on mental health outcomes in autism. For instance, parental warmth and stronger parent-child relationships have been linked to reduced behavioral and emotional difficulties, as well as fewer autism symptoms (Midouhas et al., 2013; Smith et al., 2008), while poor mother-child relationships have been associated with behavioral and emotional difficulties in autistic children (Bilgiç & Uzun, 2016). Evidence suggests that attachment-based interventions could enhance bonding and reduce emotional problems and parental intrusiveness in autism (Kubo et al., 2021; Poslawsky et al., 2015). In that respect, as the strength of the association between optimal parenting and PE increased as a function of AT levels in our sample, we speculate that family interventions aimed at improving parent-child relationship may be particularly beneficial for those with high ATs.

Limitations

Some limitations should be acknowledged. First, although this study demonstrated a moderating role of potential protective factors on the

association between ATs and PE, the cross-sectional design precludes causal inference. Second, our findings were derived from general population data. Therefore, longitudinal studies in clinical populations are required to increase the generalizability and translational relevance of our findings. Nevertheless, our findings provide important insights into the subclinical spectrum of autism and psychosis, which might pave the way for early intervention and prevention of clinical disorders among at-risk populations. Third, PE in the TwinssCan dataset was assessed using self-report questionnaires, which might be prone to false-positive responses. However, a recent systematic review has found that self-reported PE is linked to similar negative outcomes as interview-based PE (Healy et al., 2019). Moreover, evidence suggests that presumed false-positive self-reported PE also predicts subsequent psychiatric disorders (Van Der Steen et al., 2019), further supporting the clinical relevance of our findings. Also, the coefficients in our models are modest; however, their cumulative impact may still be clinically meaningful over time, given the bidirectional relationship between maladaptive coping and psychosis (Lin et al., 2011; Riera-López de Aguileta et al., 2020). Finally, we only focused on psychological protective factors but did not explore other potential protective factors, such as premorbid IQ, sociodemographic characteristics, or neighborhood variables that might moderate the association between ATs and PE. Therefore, future studies should also include a vast array of socio-environmental factors that encompass the exposome (Arias-Magnasco et al., 2025) to expand our understanding.

Conclusion

Our study offers several insights that may guide future research on psychological protective factors and inform strategies to reduce psychosis expression in individuals with high ATs. Overall, our findings emphasize the importance of fostering engagement coping skills, especially reassuring thoughts, as a promising target for reducing psychosis expression. Addressing maladaptive coping styles, particularly passive-reacting coping, might help lower the risk for PE in this population. Furthermore, the negative moderating roles of extraversion and optimal parenting on AT-associated PE highlight the potential utility of personality-focused interventions and family-

based interventions to decrease psychosis vulnerability. Importantly, our findings align with the resilience framework, which suggests that both biological and environmental factors play a crucial role in enhancing the ability to withstand stress and reducing susceptibility to psychopathology (Snijders et al., 2018). Although longitudinal studies are required to establish causality, our findings provide a rationale for developing and testing targeted preventive strategies aimed at enhancing resilience in individuals with ATs.

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Declaration of competing interest

Marco Colizzi has been a consultant/advisor to GW Pharma Limited, GW Pharma Italy SRL and F. Hoffmann-La Roche Limited, outside of this work. All the other authors have nothing to declare.

Supplementary Material

Supplementary Table 1. Associations between psychological factors and ATs with CAPE subdomain scores

	Positive **B (95% CI)**	**Negative** **B (95% CI)**	**Depressive** **B (95% CI)**
Autistic traits	**0.10 (0.08 to 0.12)**	**0.16 (0.14 to 0.18)**	**0.11 (0.09 to 0.14)**
Coping styles			
Expressing emotions	**0.03 (0.01 to 0.05)**	0.02 (0.00 to 0.04)	**0.06 (0.03 to 0.08)**
Engagement coping			
Active coping	0.004 (-0.02 to 0.02)	**-0.04 (-0.07 to -0.02)**	**-0.05 (-0.07 to -0.02)**
Seeking social support	-0.01 (-0.03 to 0.01)	**-0.06 (-0.08 to -0.03)**	0.00 (-0.03 to 0.02)
Reassuring thoughts	0.0004 (-0.02 to 0.02)	-0.02 (-0.04 to 0.01)	**-0.03 (-0.05 to 0.00)**
Disengagement coping			
Avoidance	**0.03 (0.01 to 0.05)**	**0.10 (0.08 to 0.12)**	**0.05 (0.03 to 0.07)**
Passive-reacting coping	**0.09 (0.08 to 0.11)**	**0.16 (0.14 to 0.18)**	**0.21 (0.19 to 0.23)**
Palliative-reacting coping	**0.03 (0.01 to 0.04)**	0.02 (-0.01 to 0.04)	**0.03 (0.01 to 0.05)**
Optimal parenting	**-0.06 (-0.08 to -0.04)**	**-0.07 (-0.09 to -0.05)**	**-0.10 (-0.13 to -0.08)**
Extraversion	**-0.03 (-0.05 to -0.01)**	**-0.15 (-0.18 to -0.13)**	**-0.09 (-0.11 to -0.07)**

Regression coefficients (B) with 95% confidence intervals demonstrating the association of coping styles, parenting, extraversion, and ATs with CAPE subdomain scores. Age and gender were covariates. CAPE: The Community Assessment of Psychic Experiences, B: unstandardized regression coefficient, CI: confidence interval. Statistical significance $p<0.05$ is shown in bold.

Supplementary Table 2. Associations between psychological factors and autistic traits with CAPE positive subdomain scores

	Hallucinations	Delusions	Paranoia	Grandiosity	Paranormal Beliefs
Autistic traits	**0.08 (0.06 to 0.11)**	**0.08 (0.06 to 0.11)**	**0.14 (0.11 - 0.17)**	**0.09 (0.05 to 0.13)**	**0.08 (0.04 to 0.11)**
Coping styles					
Expressing emotions	0.02 (0.00 to 0.04)	0.01 (-0.01 to 0.03)	**0.06 (0.03 to 0.09)**	0.03 (-0.01 to 0.07)	**0.05 (0.02 to 0.09)**
Engagement coping					
Active coping	-0.004 (-0.03 to 0.02)	-0.01 (-0.03 to 0.01)	-0.01 (-0.04 to 0.01)	**0.10 (0.06 to 0.14)**	0.01 (-0.03 to 0.05)
Seeking social support	-0.02 (-0.05 to 0.001)	-0.02 (-0.04 to 0.01)	-0.03 (-0.06 to 0.00)	0.03 (-0.01 to 0.07)	-0.01 (-0.05 to 0.02)
Reassuring thoughts	-0.02 (-0.04 to 0.00)	0.00 (-0.02 to 0.02)	-0.01 (-0.04 to 0.01)	**0.04 (0.00 to 0.08)**	0.02 (-0.02 to 0.06)
Disengagement coping					
Avoidance	0.01 (-0.01 to 0.03)	**0.04 (0.02 to 0.06)**	**0.03 (0.01 to 0.06)**	0.01 (-0.03 to 0.05)	0.02 (-0.02 to 0.05)
Passive-reacting coping	**0.06 (0.03 to 0.08)**	**0.08 (0.06 to 0.10)**	**0.14 (0.11 to 0.17)**	**0.10 (0.06 to 0.15)**	**0.08 (0.04 to 0.12)**
Palliative-reacting coping	0.002 (-0.02 to 0.02)	**0.02 (0.003 to 0.04)**	0.02 (0.00 to 0.05)	**0.06 (0.01 to 0.10)**	**0.04 (0.01 to 0.08)**
Optimal parenting	**-0.05 (-0.07 to -0.03)**	**-0.05 (-0.07 to -0.02)**	**-0.09 (-0.12 to -0.07)**	-0.02 (-0.06 to 0.02)	**-0.06 (-0.10 to -0.02)**
Extraversion	**-0.05 (-0.07 to -0.03)**	**-0.02 (-0.04 to 0.00)**	**-0.07 (-0.10 to -0.04)**	0.02 (-0.02 to 0.06)	0.01 (-0.03 to 0.05)

Regression coefficients (B) with 95% confidence intervals demonstrating the association of coping styles, parenting, extraversion, and ATs with CAPE positive subdomain scores. Age and gender were covariates. CAPE: The Community Assessment of Psychic Experiences, B: unstandardized regression coefficient, CI: confidence interval. Statistical significance $p<0.05$ is shown in bold.

Supplementary Table 3. Marginal effect estimates showing the association between moderators and PE at different levels of ATs

Variable	Standardized AQ Level	dy/dx (95% CI)
Seeking social support	-1	0.02 (−0.00, 0.04)
	0	0.001 (−0.02, 0.02)
	1	−0.02 (−0.04, 0.01)
Reassuring thoughts	-1	**0.03 (0.00, 0.05)**
	0	0.006 (−0.01, 0.02)
	1	−0.015 (−0.04, 0.01)
Passive-reacting coping	-1	**0.08 (0.06, 0.10)**
	0	**0.10 (0.09, 0.12)**
	1	**0.13 (0.11, 0.15)**
Optimal parenting	-1	**−0.03 (−0.05, −0.01)**
	0	**−0.05 (−0.07, −0.03)**
	1	**−0.07 (−0.09, −0.04)**
Extraversion	-1	0.01 (−0.02, 0.04)
	0	−0.02 (−0.04, 0.00)
	1	**−0.04 (−0.07, −0.02)**

Marginal effects (dy/dx) with 95% confidence intervals showing the estimated change in PE at low (−1 SD), mean (0 SD), and high (+1 SD) levels of ATs for each moderator. Age and gender were included as covariates. dy/dx: marginal effect estimate, CI: confidence interval. Statistical significance at $p < 0.05$ is shown in bold.

Supplementary Table 4. Interaction effects of psychological factors and ATs on CAPE subdomain scores

	Positive B (95% CI)	**Negative B (95% CI)**	**Depressive B (95% CI)**
Coping styles			
Expressing emotions	-0.004 (-0.02 to 0.01)	-0.004 (-0.02 to 0.02)	0.00 (-0.02 to 0.02)
Engagement coping			
Active coping	**-0.02 (-0.04 to 0.00)**	0.02 (0.00 to 0.04)	0.01 (-0.02 to 0.03)
Seeking social support	**-0.02 (-0.04 to 0.00)**	-0.02 (-0.04 to 0.00)	**-0.02 (-0.05 to 0.00)**
Reassuring thoughts	**-0.03 (-0.05 to -0.01)**	-0.01 (-0.03 to 0.01)	-0.02 (-0.04 to 0.00)
Disengagement coping			
Avoidance	0.002 (-0.01 to 0.02)	**0.02 (0.00 to 0.04)**	0.02 (0.00 to 0.04)
Passive-reacting coping	**0.03 (0.01 to 0.04)**	**0.02 (0.01 to 0.04)**	0.01 (0.00 to 0.03)
Palliative-reacting coping	-0.02 (-0.03 to 0.00)	-0.001 (-0.02 to 0.02)	0.00 (-0.02 to 0.02)
Optimal parenting	-0.01 (-0.02 to 0.01)	-0.02 (-0.04 to 0.00)	**-0.04 (-0.06 to -0.02)**
Extraversion	**-0.03 (-0.05 to -0.02)**	**-0.02 (-0.04 to 0.00)**	**-0.03 (-0.05 to -0.01)**

Regression coefficients (B) with 95% confidence intervals demonstrating the moderating effects of coping styles, parenting, and extraversion on the relationship between ATs and CAPE subdomain scores. Age and gender were covariates. AT: autistic traits, CAPE: The Community Assessment of Psychic Experiences, B: unstandardized regression coefficient, CI: confidence interval. Statistical significance $p<0.05$ is shown in bold.

Supplementary Table 5. Interaction effects of psychological factors and ATs on CAPE positive subdomain scores

	Hallucinations	Delusions	Paranoia	Grandiosity	Paranormal Beliefs
Coping styles					
Expressing emotions	**0.03 (0.01 to 0.05)**	-0.01 (-0.03 to 0.01)	0.01 (-0.01 to 0.04)	-0.03 (-0.07 to 0.01)	**-0.05 (-0.08 to -0.01)**
Engagement coping					
Active coping	-0.02 (-0.04 to 0.01)	-0.02 (-0.04 to 0.00)	-0.01 (-0.04 to 0.01)	-0.01 (-0.06 to 0.03)	**-0.05 (-0.09 to -0.01)**
Seeking social support	**-0.03 (-0.05 to -0.01)**	-0.02 (-0.04 to 0.00)	-0.02 (-0.04 to 0.01)	0.00 (-0.04 to 0.04)	-0.03 (-0.07 to 0.004)
Reassuring thoughts	**-0.05 (-0.07 to -0.03)**	-0.01 (-0.03 to 0.00)	**-0.05 (-0.08 to -0.03)**	-0.01 (-0.05 to 0.03)	-0.03 (-0.07 to 0.002)
Disengagement coping					
Avoidance	-0.01 (-0.03 to 0.01)	0.01 (-0.01 to 0.02)	0.00 (-0.02 to 0.02)	0.01 (-0.03 to 0.05)	0.00 (-0.03 to 0.03)
Passive-reacting coping	**0.05 (0.03 to 0.07)**	0.02 (0.00 to 0.03)	**0.04 (0.02 to 0.06)**	0.03 (-0.001 to 0.07)	0.02 (-0.01 to 0.05)
Palliative-reacting coping	-0.02 (-0.04 to 0.01)	-0.01 (-0.03 to 0.01)	-0.02 (-0.04 to 0.01)	-0.01 (-0.05 to 0.03)	**-0.04 (-0.08 to -0.01)**
Optimal parenting	**-0.04 (-0.06 to -0.02)**	0.00 (-0.02 to 0.02)	-0.02 (-0.04 to 0.01)	0.01 (-0.04 to 0.05)	0.03 (-0.01 to 0.07)
Extraversion	**-0.05 (-0.07 to -0.03)**	(-0.03 to 0.001)	**-0.04 (-0.06 to -0.02)**	**-0.05 (-0.09 to -0.02)**	-0.02 (-0.05 to 0.01)

Regression coefficients (B) with 95% confidence intervals demonstrating the moderating effects of coping styles, parenting, and extraversion on the relationship between ATs and CAPE positive subdomain scores. Age and gender were covariates. AT: autistic traits, CAPE: The Community Assessment of Psychic Experiences, B: unstandardized regression coefficient, CI: confidence interval. Statistical significance $p<0.05$ is shown in bold.

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Chapter 4

Sex differences in the effect of childhood adversity and coping strategies on psychosis expression: A TwinssCan study

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Abstract

Background: Sex differences in psychosis pathoetiology are insufficiently understood. This study explores how childhood adversity (CA) and coping mechanisms relate to psychosis expression (PE) across males and females in the general population.

Method: Data from the TwinssCan project (males: n=312; females: n=478) were used. The Childhood Trauma Questionnaire assessed CA domains. The Utrecht Coping List assessed coping strategies. Psychosis expression was assessed using the Community Assessment of Psychic Experiences (CAPE). Mixed linear regression analyses examined sex-stratified associations of CAPE scores with CA, coping strategies, and their interactions.

Results: Emotional abuse (EA) was associated with increased total CAPE scores (T-CAPE), explaining the greatest variance among CA across sexes. Sex-specific effects showed that sexual abuse (SA) and physical abuse (PA) were linked to higher T-CAPE in females, whereas physical neglect (PN) was linked to higher T-CAPE in males. Passive-reacting was associated with increased T-CAPE, explaining the greatest variance among coping styles across both sexes. Sex-specific effects showed that, in females, seeking social support was linked to decreased T-CAPE, while emotional expression increased it. The only sex-shared interaction effect was between reassuring thoughts and emotional neglect (EN), associated with decreased T-CAPE. In females, social support (× PA/PN/EA), reassuring thoughts (× PA/PN), and palliative-reacting (× PN/PA) were associated with decreased T-CAPE, while passive-reacting (× EN) increased it. In males, avoidance (× SA/PA) and passive-reacting (× PN) were associated with increased T-CAPE.

Conclusion: Sex differences in the associations of PE with CA and coping underscore the necessity for sex-specific interventions that promote adaptive coping strategies.

Keywords: Sex Differences, Childhood Adversity, Coping Strategies, Psychosis Expression, General Population

Introduction

Psychosis expression (PE) in the general population can precede the development of severe psychotic and non-psychotic disorders (Guloksuz & Van Os, 2018). Therefore, understanding the factors associated with PE in the general population is crucial for implementing prevention strategies and developing effective interventions.

Childhood adversity (CA) has been identified as a significant transdiagnostic risk factor affecting mental health, from subtle symptoms to chronic and severe conditions (Arias-Magnasco et al., 2025). Some researchers propose a dimensional model of CA, categorizing subtypes into two domains, each linked to unique biological processes. The threat domain includes subtypes such as sexual abuse (SA), physical abuse (PA), or emotional abuse (EA), while the deprivation domain refers to the absence of essential cognitive, social, or emotional input (i.e., emotional neglect (EN) and physical neglect (PN)) (McLaughlin et al., 2019; Sheridan & McLaughlin, 2014; Thomas et al., 2023). Furthermore, studies have shown a dose-response relationship between the number of childhood adversities and mental health outcomes (Steine et al., 2017). Moreover, research has recently suggested that specific CA subtypes may have distinct impacts on mental health, especially when considering sex-specific effects (Alameda et al., 2021; Pence et al., 2022; Prachason et al., 2024; Zhou et al., 2025).

Incorporating sex differences into research (Wierenga et al., 2024) and clinical care (e.g., early psychosis clinics) (Ferrara & Srihari, 2021), is essential to improve mental health outcomes and reduce disparities. Emerging evidence indicates that sex differences shape the impact of CA subtypes on psychosis (Pence et al., 2022; Zhou et al., 2025). Some studies suggest that especially SA and PA may have stronger associations with psychosis and mental health in females (Enthoven et al., 2023; Gallo et al., 2018; Pence et al., 2022; Zhou et al., 2025). A recent meta-analysis found a link between SA and psychosis in females but not in males (Zhou et al., 2025). Another meta-analysis reported stronger associations of PA and SA with anxiety or depression in females (Gallo et al., 2018). However, follow-up comparisons showed no significant sex differences. This may reflect the limited number of studies examining subtype-specific effects by sex. Additionally, many

studies fail to account for the co-occurrence and interdependence of these subtypes.

Adding to its complexity, the impact of CA on mental health is influenced not only by the nature and severity of exposure but also by coping strategies. Researchers propose that coping strategies may be either adaptive or maladaptive, depending on the subjective experience, the contextual demands, and the resulting outcomes (Skinner et al., 2003). Notably, individuals at clinical high risk for psychosis tend to rely on maladaptive coping strategies (Jalbrzikowski et al., 2014), potentially worsening symptoms. Furthermore, sex differences in coping are evident. Females typically utilize a broader range of strategies, favoring social support and emotional expression (Bucci et al., 2023; Day & Livingstone, 2003; Eschenbeck et al., 2007; Tamres et al., 2002), while males often adopt avoidant strategies (Eschenbeck et al., 2007). Despite these insights, the sex-specific effects of coping strategies on PE remain insufficiently explored (Bucci et al., 2023; Lin et al., 2011; Riera-López de Aguileta et al., 2020), particularly in the general population. Lin et al. reported that females use a broader range of coping strategies, but the pathways linking coping strategies to PE were similar across sexes (Lin et al., 2011). Other studies examining the role of sex in the association between coping strategies and PE have focused on case-control comparisons, such as psychosis-prone groups versus healthy controls, without considering the dimensional conceptualization of the psychosis phenotype (Dangelmaier et al., 2006; Schuldberg et al., 1996). Therefore, further research is needed.

This study aims to explore sex differences in how CA and coping strategies influence PE, and whether coping strategies moderate the relationship between CA and PE in the general population.

Methods

Participants

This study utilized data from the TwinssCan Project, a general population cohort that includes monozygotic and dizygotic twins, their siblings (15–35 years), and parents. Recruitment was conducted through the East Flanders Prospective Twin Survey (EFPTS), a

population-based registry of multiple births in Belgium (Derom et al., 2019). Detailed information on participant recruitment is available in previous reports (Pries, Snijders, et al., 2019). All participants provided written informed consent, and parental consent was obtained for those under 18. Participants were excluded if caregivers reported a severe psychiatric condition impairing functioning and study participation. The local ethics committee (Commissie Medische Ethiek van de Universitaire Ziekenhuizen KU Leuven, Nr. B32220107766) approved the study. The current analyses included data from 790 participants, twins and their non-twin siblings, with relevant information.

Measurements

Psychosis Expression

PE was assessed using the Community Assessment of Psychic Experiences (CAPE), a validated 42-item self-report questionnaire (Stefanis et al., 2002). CAPE is widely used for evaluating PE in the general population and has demonstrated strong reliability and validity (Konings et al., 2006). It provides a total and three subdomains: positive, negative, and depressive. The questionnaire measures both the frequency of experiences and the distress associated with them, using a four-point Likert scale. Total and subscale mean scores range from 1 to 4. Consistent with previous studies using this cohort (Karaçam Doğan et al., 2025), the analyses focused on frequency scores.

Coping strategies

Coping strategies were assessed using the Utrecht Coping List (UCL), a 44-item self-report questionnaire designed to evaluate seven coping strategies (Sanderman & Ormel, 1992; Schreurs et al., 1993). Participants rated each item on a four-point Likert scale ranging from 1 (never) to 4 (very often). Active coping (7 items) reflects proactive problem-solving strategies to address stressors. Seeking social support (6 items) measures the extent to which individuals turn to others for emotional or practical assistance. Reassuring thoughts (5 items) involve maintaining a positive mindset or reframing negative situations. Emotional expression (3 items) refers to openly displaying emotions such as anger or fear. Passive-reacting coping (7 items)

captures feelings of being overwhelmed, helpless, and withdrawn in response to stress. Palliative-reacting coping (8 items) focuses on distraction-based behaviors, such as smoking or drinking, to alleviate distress. Avoidance (8 items) reflects the tendency to ignore or deny stressful situations rather than confronting them directly.

Childhood adversity

CA was assessed using the Childhood Trauma Questionnaire (CTQ), a 28-item self-report measure that evaluates adverse experiences before the age of 17 (Bernstein et al., 2003). Each item was rated on a five-point Likert scale, covering five subtypes: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. To obtain a total CA score, responses to all items were summed. In line with the CTQ manual and following our consistent approach in previous studies (Bernstein & Fink, 1998; Guloksuz et al., 2019; Prachason et al., 2024; Pries, Lage-Castellanos, et al., 2019), subtypes were dichotomized based on predefined cut-off scores: ≥9 for EA, ≥8 for PA, ≥6 for SA, ≥10 for EN, and ≥8 for PN.

Statistical Analyses

All statistical analyses were conducted using Stata version 18.0 (StataCorp, 2023). To explore sex-specific associations, mutually adjusted stratified linear regression analyses were conducted to examine the association of PE with CA and coping strategies, which included all adversity subtypes and all coping strategies, respectively. The CAPE total score was the primary outcome, while the CAPE negative, positive, and depressive subscales were analyzed as secondary outcomes. Sensitivity analyses were conducted to assess the robustness of the findings by testing the associations between total CA, its subtypes, and the coping strategies in independent models. The explained variance (adjusted R^2) for the independent regression models was also calculated. Additionally, exploratory interaction analyses investigated whether coping strategies moderated the association between CA and PE (total CAPE and its subdomains) in independent models. Post-hoc analyses examined sex differences in significant associations by comparing regression coefficients between males and females using Chow's test (Chow, 1960). In all models, to account for intrafamily correlation, standard errors were adjusted for

sibling clustering using Stata's "cluster" option. All analyses were adjusted for age. Statistical significance was corrected for multiple comparisons using Bonferroni correction (see the Results section and Supplementary Table 1).

Results

Sample characteristics are reported in Table 1, and missing data are reported in Supplementary Table 2. After excluding participants with missing data in any variables, the final sample consisted of 790 twins and siblings (312 males, 478 females). The mean age was 17.45 ± 3.58 years.

Table 1. Sample Characteristics

	Males	**Females**
Age (years), M (SD)	16.89 (±2.76)	17.82 (±3.98)
Zygosity, n (%)		
MZ	98 (31.41%)	176 (36.82%)
DZ	201 (64.42%)	272 (56.90%)
Sibling	13 (4.17%)	30 (6.28%)
Psychosis expression M (SD)		
Total CAPE	1.56 (±0.26)	1.57 (±0.27)
Positive subdomain	1.42 (±0.28)	1.41 (±0.28)
Negative subdomain	1.72 (±0.36)	1.65 (±0.34)
Depressive subdomain	1.67 (±0.34)	1.82 (±0.37)
Coping Strategies, M (SD)		
Active coping	17.87 (±3.48)	16.99 (±3.14)
Seeking social support	12.83 (±3.10)	15.42 (±3.84)
Reassuring thoughts	12.23 (±2.55)	12.72 (±2.50)
Emotional expression	6.86 (±1.77)	6.78 (±1.78)
Passive-reacting coping	11.80 (±3.17)	12.62 (±3.53)
Palliative-reacting coping	18.23 (±3.07)	18.32 (±3.57)
Avoidance	16.88 (±3.45)	16.45 (±3.34)
Total CA, M (SD)	34.69 (±8.17)	33.81 (±8.84)
CA subtypes, n (%)		
Emotional abuse	101 (32.37%)	146 (30.54%)
Physical abuse	20 (6.41%)	14 (2.93%)
Sexual abuse	18 (5.77%)	37 (7.74%)
Emotional neglect	163 (52.24%)	177 (37.03%)
Physical neglect	54 (17.31%)	74 (15.48%)

Means (M) and standard deviations (SD) are reported for continuous variables. For categorical variables, counts (n) and percentages (%) are provided. MZ: monozygotic, DZ: dizygotic

Childhood adversity and psychosis expression

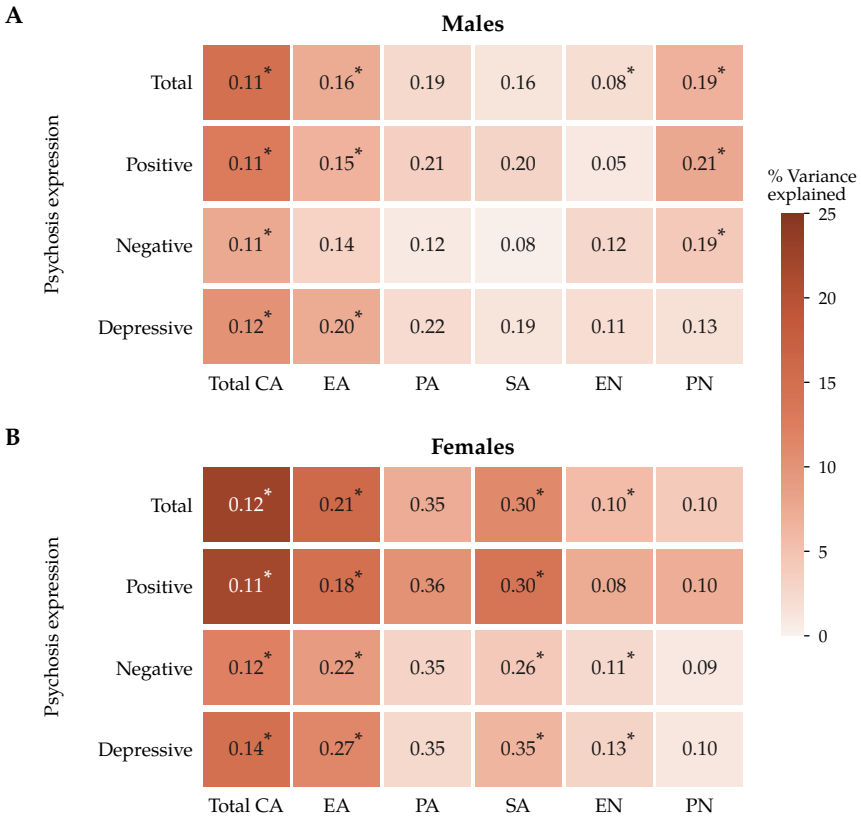
Association between CA and CAPE total

In males, EA and PN were significantly associated with increased CAPE total score in the mutually adjusted model ($p<0.05$; Table 2). Independent regression analyses confirmed these associations and additionally showed significant associations of total CA and EN with CAPE total scores (Bonferroni corrected $p<0.05/6$). The model including EA had the highest R^2 (7.5%) among the adversity subtypes (Figure 1A).

In females, EA, PA, and SA were significantly associated with increased CAPE total score in the mutually adjusted model ($p<0.05$; Table 2). Independent regression analyses confirmed the associations with EA and SA and additionally showed significant associations of total CA and EN with the CAPE total score ($p<0.05/6$). The model including EA had the highest R^2 (15.8%) among the adversity subtypes (Figure 1B).

Follow-up sex comparisons ($p<0.05$) using coefficients from the mutually adjusted model indicated an association between PN and CAPE total specifically in males ($\chi^2 = 6.12$, $p = 0.01$; Table 2).

Figure 1. Sex-stratified variance in psychosis expression explained by childhood adversity subtypes



The heatmaps show the variance in psychosis expression explained by each childhood adversity subtype in males (A) and females (B) from the independent models. Unstandardized regression coefficients (Beta) are shown, with significant associations marked by asterisks. All models were adjusted for age. EA, emotional abuse; EN, emotional neglect; PN, physical neglect; PA, physical abuse; SA, sexual abuse.

Table 2. Main effects of childhood adversity and coping strategies on CAPE total in mutual models

	Males (n=312)			Females (n=478)			Sex Differences	
	Beta	95% CI	p-value	Beta	95% CI	p-value	χ^2	p-value
Childhood adversity[a]								
Emotional abuse	0.11	0.05 to 0.17	**<0.001**	0.16	0.11 to 0.21	**<0.001**	1.75	0.19
Physical abuse	0.05	-0.06 to 0.17	0.368	0.20	0.07 to 0.33	**0.003**	0.60	0.44
Sexual abuse	0.02	-0.11 to 0.15	0.749	0.18	0.11 to 0.26	**<0.001**	3.40	0.07
Emotional neglect	0.03	-0.02 to 0.09	0.227	0.02	-0.03 to 0.07	0.483	N/A	N/A
Physical neglect	0.12	0.04 to 0.19	**0.002**	0.00	-0.06 to 0.06	1.000	6.12	**0.01**
Coping strategies[b]								
Active coping	-0.017	-0.044 to 0.010	0.221	-0.002	-0.024 to 0.021	0.891	N/A	N/A
Seeking social support	0.014	-0.017 to 0.046	0.378	-0.051	-0.072 to -0.031	**<0.001**	11.0	**0.001**
Reassuring thoughts	0.017	-0.012 to 0.047	0.250	-0.013	-0.036 to 0.010	0.285	N/A	N/A
Emotional expression	-0.022	-0.049 to 0.004	0.101	0.028	0.007 to 0.048	**0.008**	7.62	**0.006**
Passive-reacting	0.140	0.111 to 0.170	**<0.001**	0.125	0.105 to 0.146	**<0.001**	0.35	0.552
Palliative-reacting	-0.015	-0.047 to 0.017	0.357	0.001	-0.021 to 0.023	0.945	N/A	N/A
Avoidance	0.016	-0.012 to 0.043	0.274	0.017	-0.005 to 0.039	0.127	N/A	N/A

[a]p value threshold was accepted as < 0.05 for one mutually adjusted model including all childhood adversity subtypes on CAPE total
[b] p value threshold was accepted as < 0.05 for one mutually adjusted model including all coping strategies on CAPE total

Association between CA and CAPE subdomains

In males, PN was significantly associated with increased scores in the positive and negative subdomains, while EA was significantly associated with increased scores in the positive and depressive subdomains in the mutually adjusted models ($p<0.05/3$; Supplementary Table 4). These associations were confirmed in the independent models ($p<0.05/18$; Supplementary Table 5, Figure 1A). Total CA was associated with higher scores across all CAPE subdomains, with the model including the positive subdomain having the highest R^2 (12.8%; Figure 1A).

In females, EA and SA were significantly associated with increased scores across all subdomains in the mutually adjusted models ($p<0.05/3$; Supplementary Table 4). These associations were confirmed in the independent models ($p<0.05/18$; Supplementary Table 5, Figure 1B). Additionally, EN was associated with higher scores in the negative and depressive subdomains. Total CA was associated with higher scores across all CAPE subdomains, with the model including the positive subdomain having the highest R^2 (21.8%; Figure 1B).

Follow-up sex comparisons ($p<0.05$) using coefficients from the mutually adjusted model indicated associations between PN and the positive and negative subdomains specifically in males (Supplementary Table 4).

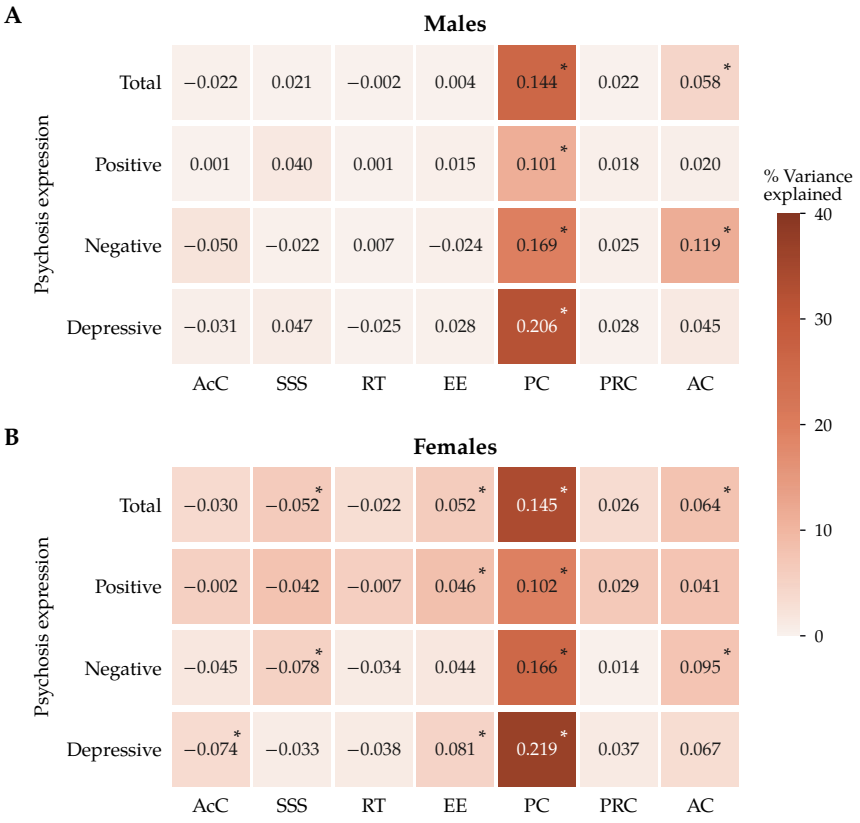
Coping strategies and psychosis expression

Association between coping strategies and CAPE total

In males, passive-reacting was significantly associated with increased CAPE total in the mutually adjusted model ($p<0.05$; Table 2). The association was confirmed in the independent models, which additionally showed that avoidance was significantly associated with increased CAPE total. The model with passive-reacting had the highest R^2 ($p<0.05/7$; 26.1%; Figure 2A).

In females, seeking social support was significantly associated with decreased CAPE total scores, whereas passive-reacting and emotional

Figure 2. Sex-stratified variance in psychosis expression explained by coping strategies



The heatmaps show the variance in psychosis expression explained by each coping strategy in males (A) and females (B) from the independent models. Unstandardized regression coefficients (Beta) are shown, with significant associations marked by asterisks. All models were adjusted for age. AcC, active coping; AC, avoidance coping; EE, emotional expression; PC, passive-reacting coping; PRC, palliative-reacting coping; RT, reassuring thoughts; SSS, seeking social support.

expression were associated with increased CAPE total scores ($p<0.05$; Table 2). The associations were confirmed in the independent models ($p<0.05/7$), which additionally showed that avoidance was significantly associated with increased CAPE total. The model with passive-reacting had the highest R^2 (33.9%; Figure 2B).

Follow-up sex comparisons ($p<0.05$) using coefficients from the mutually adjusted model indicated female-specific associations between CAPE total and seeking social support as well as emotional expression (Table 2).

Association between coping strategies and CAPE subdomains

In males, passive-reacting was associated with higher CAPE scores across all subdomains, while avoidance and emotional expression were associated with higher and lower scores in the negative subdomain, respectively ($p<0.05/3$; Supplementary Table 6). The independent models confirmed these associations, except for the association with emotional expression, which was not significant ($p<0.05/21$; Supplementary Table 7). The model including passive-reacting on the depressive domain had the highest R^2 (32.1%; Figure 2A).

In females, passive-reacting was associated with higher CAPE scores across all subdomains in the mutually adjusted models, and avoidance with higher scores in the negative subdomain. Seeking social support was associated with lower scores in the positive and negative subdomains, while active coping was associated with lower scores in the depressive subdomain ($p<0.05/3$; Supplementary Table 6). In the independent models, these associations were confirmed, except for social support in the positive subdomain, which was not significant. In addition, emotional expression was associated with higher scores in the positive and depressive subdomains ($p<0.05/21$; Supplementary Table 7). The model including passive-reacting on the depressive subdomain had the highest R^2 (36.9%; Figure 2B).

Follow-up sex comparisons ($p<0.05$) using coefficients from the mutually adjusted model indicated that seeking social support was associated with lower positive and negative subdomain scores specifically in females, whereas emotional expression was associated

with lower negative subdomain scores specifically in males (Supplementary Table 6).

Exploratory interaction analyses between coping strategies and CA on psychosis expression

Interaction effects on CAPE total

In males, interactions including avoidance (x total CA/SA/PA) and passive-reacting (x PN) were associated with increased CAPE total scores, whereas the interaction including reassuring thoughts (x EN) was associated with decreased CAPE total scores (Supplementary Table 8).

In females, interactions including seeking social support (x total CA/EA/PA/PN), reassuring thoughts (x total CA/PA/EN/PN) and palliative-reacting (x total CA/PA/PN) were associated with decreased total CAPE scores. In contrast, passive-reacting interacted with total CA and EN, which was associated with increased total CAPE scores (Supplementary Table 8).

Follow-up sex comparisons revealed significant differences. Specifically, in females, seeking social support and reassuring thoughts weakened the effects of both PA and PN, while palliative-reacting coping weakened the effect of PN on total CAPE scores. In males, avoidance strengthened the effects of SA and PA on total CAPE scores (Figure 3, Supplementary Table 8).

Interaction effects on CAPE subdomains

For CAPE subdomains, interaction patterns largely mirrored those observed for CAPE total scores, with some additional subdomain-specific effects (Supplementary Tables 9-11).

Follow-up sex comparisons indicated several significant differences. Seeking social support (× total CA/PA/PN), reassuring thoughts (× PA/PN), and palliative-reacting (× PN) were associated with lower subdomain scores, whereas emotional expression (× SA) was associated with higher positive scores particularly in females. Avoidance (× SA/PA) was associated with higher negative and

Figure 3. Interaction effects of CA subtypes and coping strategies on psychosis expression

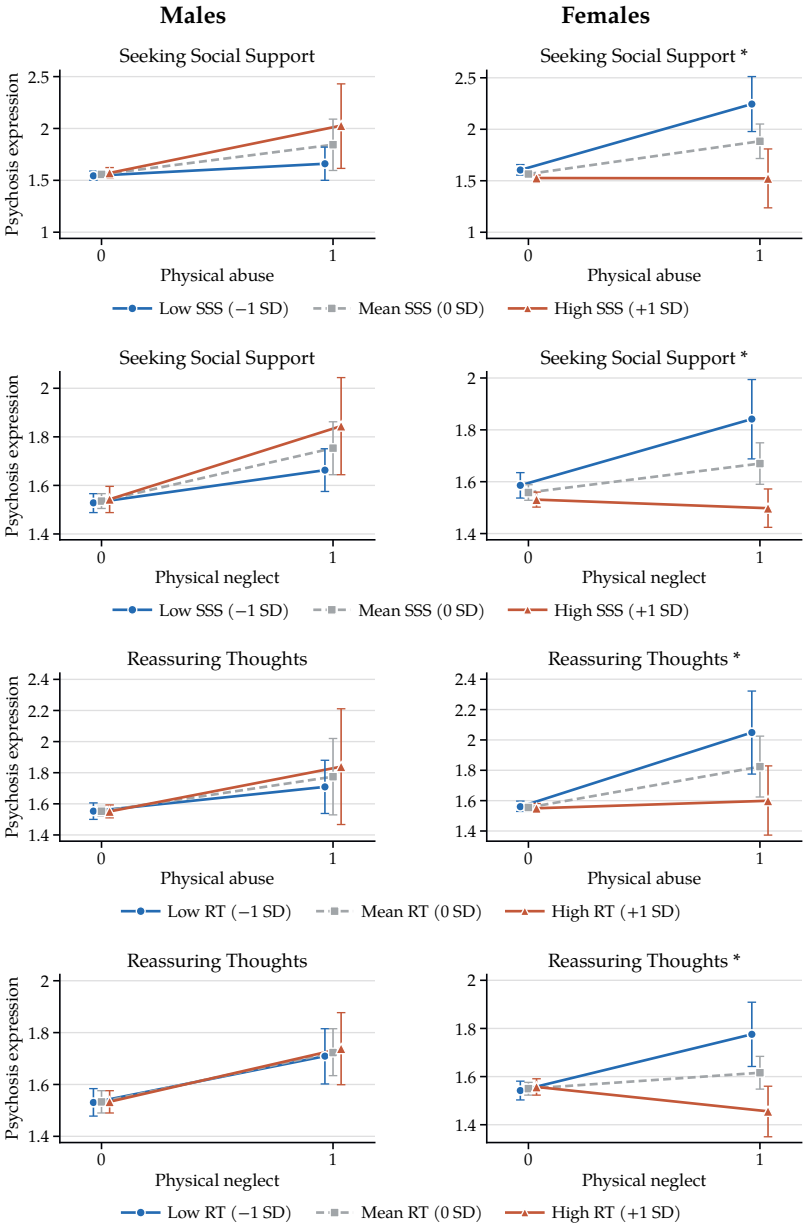
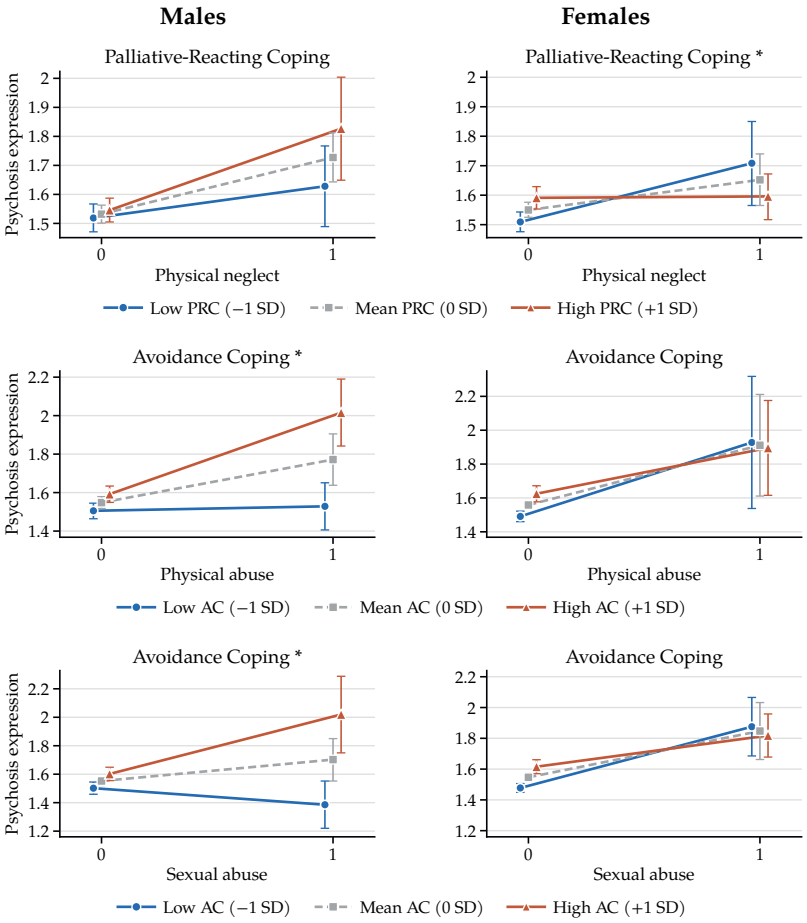


Figure 3 (continued).



The figure illustrates the interaction effects between adversity subtypes and coping strategies on total CAPE that were significantly different in males and females (indicates the significant model). Sex-stratified margin plots show the linear prediction of total CAPE frequency scores at specified values of childhood adversity subtypes and coping strategies, including seeking social support, reassuring thoughts, palliative-reacting, and avoidance, while keeping age constant at the mean value. AC, avoidance coping; CAPE, Community Assessment of Psychic Experiences; PRC, palliative-reacting coping; RT, reassuring thoughts; SD, standard deviation; SSS, seeking social support.*

depressive scores particularly in males. Notably, avoidance showed a sex-divergent pattern in the context of SA, being significantly associated with lower scores in females (Supplementary Tables 9-11).

Discussion

This study examines sex-specific associations of PE with CA and coping strategies in the general population. CA was linked to PE in both sexes, with notable differences for specific subtypes. In males, EA and PN showed significant associations with PE, whereas in females, EA, PA and SA were associated with PE. Coping strategies also differed. Passive-reacting was associated with increased PE in both sexes. Additionally, seeking social support and emotional expression were linked to decreased and increased PE, respectively, in females. Furthermore, interaction analyses indicated that these associations were not uniform but depended on the combination of adversity type, coping strategy, and sex.

Total CA was significantly associated with CAPE total and subdomain scores in both sexes, supporting prior research identifying CA as an important environmental risk factor for psychosis (Arias-Magnasco et al., 2025; Zhou et al., 2025). EA emerged as a trans-syndromal risk factor across sexes, explaining the highest variance in total CAPE scores among the CA subtypes, consistent with prior studies that show its broad impact (Kirchhoff et al., 2024; Toutountzidis et al., 2018). Sex-specific patterns also emerged. The association between PN and PE in males may reflect heightened sensitivity to deprivation-related stressors (Prachason et al., 2024), aligning with prior findings on its specific impact in males (Hilberdink et al., 2023) and sex-stratified research linking it to negative symptoms in males (Enthoven et al., 2023; Kirchhoff et al., 2024; Pruessner et al., 2019). The unique association between SA and all the PE dimensions in females aligns with evidence suggesting greater vulnerability to abuse-related adversity (Betz et al., 2023; Enthoven et al., 2023; Gallo et al., 2018; Pence et al., 2022; Stanton et al., 2020; Zarchev et al., 2024; Zhou et al., 2025). Neurodevelopmental evidence supports these findings, showing sex-specific effects of early adversity on brain development; for example, hippocampal volume relates to neglect in males and abuse in females at different developmental stages (Teicher et al.,

2018). Our findings underscore the complexity of adversity's impact, as exposures are often interdependent and interconnected (Guloksuz et al., 2018). Future research should replicate these findings in larger cohorts and explore additional adversities that may exhibit sex-specific effects (Andreu-Bernabeu et al., 2025).

Coping strategies play a crucial role in linking adversity to mental health outcomes. Consistent with previous research, females in our sample utilized a broader range of coping strategies (Lin et al., 2011). Although a prior study did not identify sex-specific pathways between coping strategies and PE in the general population (Lin et al., 2011), we observed both shared and sex-specific associations. Passive-reacting consistently emerged as a maladaptive strategy. This finding is generally in line with previous research indicating that maladaptive coping contributes to psychosis across sexes (Chisholm et al., 2018; Ered et al., 2017; Fonseca-Pedrero et al., 2012). Passive-reacting has been shown to be associated with an increased impact of stressful life events and poorer clinical outcomes, particularly in individuals with psychosis spectrum disorders and their unaffected relatives (Schirmbeck et al., 2020; van Dijk et al., 2019). Sex-specific associations with coping styles also emerged. The association between seeking social support and reduced psychosis expression in females is consistent with prior literature (Crush et al., 2018; Eschenbeck et al., 2007; Kendler et al., 2005; Willhite et al., 2008), highlighting its role in emotional regulation and stress reduction (Cohen & Wills, 1985). Conversely, while previous research indicates that males have a greater tendency toward emotional suppression, emotional expression could be beneficial (Gross & John, 2003; Haga et al., 2009).

Interaction analyses of coping strategies and CA on PE underscored further sex differences. The use and effect of some coping strategies depended on the specific stressor (Tamres et al., 2002). Females' broader repertoire (Tamres et al., 2002), including seeking social support, palliative-reacting, and reassuring thoughts, was generally protective, while passive-reacting was maladaptive. Notably, avoidance showed associations with lower levels of depressive and negative symptoms among females when interacting with SA, suggesting that in some contexts it may provide temporary relief from distressing thoughts or emotions (Angelakis & Gooding, 2021). This

interpretation is consistent with evidence that females report higher levels of rumination (Johnson & Whisman, 2013) and that rumination may partly mediate the association between childhood adversity and affective symptoms (Kim et al., 2017). In contrast, and consistent with prior research (Felsten, 1998; Woodhead et al., 2014), avoidance was associated with poorer outcomes in males, especially in interaction with PA or SA. In males, avoidance may reflect emotional suppression and social disengagement, contributing to less favorable outcomes. Psychosocial perspectives, such as social role theories of gender differences, further emphasize women's greater reliance on social support (Barbee et al., 1993) and men's tendency toward emotional suppression and avoidance (Matud, 2004). Conversely, reassuring thoughts were beneficial for males, suggesting potential pathways for resilience, particularly against EN. Clinically, these insights underscore both the broad utility of trauma-focused interventions across sexes and the need for sex-sensitive approaches tailored to distinct coping tendencies.

Limitations

Although this study provides important insights into sex differences, several limitations should be noted. The relatively small sample size may have limited statistical power, particularly in stratified analyses, reducing sensitivity to subtle effects. The relatively young mean age of the sample corresponds to a developmental period in which subclinical PE is common (Staines et al., 2023) and may represent an early transdiagnostic marker for later psychopathology (McGorry et al., 2018). While this enhances the developmental relevance of the findings, it may also limit their generalizability to older populations, underscoring the need for replication across broader age ranges. Post-hoc analyses did not consistently confirm sex differences observed in stratified analyses, consistent with prior meta-analyses, suggesting these effects may be modest. However, small effects may still be meaningful within the broader exposome framework, as they can accumulate and interact with biological, psychological, and social factors over time. Larger studies incorporating additional factors are needed. Including twins and siblings increased statistical power but may have introduced bias due to shared genetic and environmental influences; to address this, intrafamily correlation was accounted for

and standard errors were adjusted for sibling clustering. Prior literature suggests that including all siblings, rather than one per pair, improves statistical power (Krull, 2007). While the mutually adjusted models accounted for other childhood adversity subtypes, individual coefficients should be interpreted with caution, as confounding by unmeasured factors cannot be fully excluded. Finally, the cross-sectional design precludes causal inferences, as coping strategies may both shape and be shaped by PE (Lin et al., 2011), and could mediate the association between adversity and psychosis-related outcomes (Chang et al., 2025; Ered et al., 2017), as well as the link between PE and later functioning (Chisholm et al., 2018). Longitudinal studies are essential to clarify these dynamics.

Conclusion

This study shows that CA and coping strategies are associated with PE through both shared and sex-specific patterns. CA, particularly EA, emerged as a trans-syndromal risk factor in both sexes, while other subtypes showed sex-specific associations, with SA in females and PN in males. Coping further shaped these relationships, with passive-reacting explaining the greatest variance across sexes. Males more often relied on maladaptive strategies, whereas females particularly benefited from supportive approaches such as seeking social support. Overall, coping effects varied by adversity type and sex, underscoring the need to move beyond one-size-fits-all care models. Integrating sex-sensitive frameworks that consider adversity histories and coping profiles may improve early intervention strategies.

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Supplementary Table 1. Bonferroni corrections

Analyses	Explanation	p-value
Main analyses on CAPE total		
Childhood adversity	1 mutually adjusted model including all childhood adversity subtypes on CAPE total	<0.05
Coping strategies	1 mutually adjusted model including all coping strategies on CAPE total	<0.05
Secondary analyses on CAPE subdomains		
Childhood adversity	3 mutually adjusted models including all childhood adversity subtypes on 3 CAPE subdomains	<0.016
Coping strategies	3 mutually adjusted models including all coping styles on 3 CAPE subdomains	<0.016
Sensitivity analyses on CAPE total		
Childhood adversity	6 independent models for total childhood adversity and its subtypes on CAPE total	<0.0083
Coping strategies	7 independent models for coping styles on CAPE total	<0.0071
Sensitivity analyses on CAPE subdomains		
Childhood adversity	18 independent models for 6 total childhood adversity and its subtypes on 3 CAPE subdomains	<0.0027
Coping strategies	21 independent models for 7 coping styles on 3 CAPE subdomains	<0.0023
Explorative analyses	Bonferroni correction was not applied for the interaction analyses	<0.05
Follow-up comparisons	Bonferroni correction was not applied	<0.05

Supplementary Table 2. The number of missing reports in males and females

	Males	Females
Age	0	0
Psychosis expression		
Total CAPE	15	11
Positive subdomain	15	11
Negative subdomain	15	11
Depressive subdomain	15	11
Coping Strategies		
Active coping	15	7
Seeking social support	15	7
Reassuring thoughts	15	7
Emotional expression	15	7
Passive-reacting coping	15	7
Palliative-reacting coping	15	7
Avoidance	15	7
Childhood adversity		
Total CA	15	10
Emotional abuse	15	10
Physical abuse	14	10
Sexual abuse	15	10
Emotional neglect	15	10
Physical neglect	15	10

Supplementary Table 3. Sensitivity analyses of childhood adversity and coping strategies on CAPE total in independent models

	Males (n=312)				Females (n=478)				Sex Differences	
	Beta	95% CI	*p*	Adjusted R^{2*}	Beta	95% CI	*p*	Adjusted R^{2*}	χ^2	*p*
Childhood adversity[a]										
Total CA	0.11	0.07 to 0.15	**<0.001**	14.7%	0.12	0.09 to 0.15	**<0.001**	22.7%	0.13	0.71
Emotional abuse	0.16	0.09 to 0.22	**<0.001**	7.5%	0.21	0.15 to 0.27	**<0.001**	15.8%	1.55	0.21
Physical abuse	0.19	-0.01 to 0.39	0.069	2.5%	0.35	0.08 to 0.62	0.011	7.3%	N/A	N/A
Sexual abuse	0.16	-0.05 to 0.37	0.140	1.3%	0.30	0.18 to 0.41	**<0.001**	11.2%	1.26	0.26
Emotional neglect	0.08	0.02 to 0.14	**0.008**	1.9%	0.10	0.04 to 0.15	**0.001**	5.6%	0.15	0.70
Physical neglect	0.19	0.10 to 0.28	**<0.001**	6.8%	0.10	0.01 to 0.18	0.029	4.1%	2.03	0.15
Coping strategies[b]										
Active coping	-0.02	-0.05 to 0.01	0.137	0.2%	-0.03	-0.06 to -0.001	0.042	3.6%	N/A	N/A
Seeking social support	0.02	-0.01 to 0.06	0.247	-0.2%**	-0.05	-0.08 to -0.02	**0.001**	6.3%	9.82	**0.002**
Reassuring thoughts	-0.002	-0.04 to 0.03	0.896	-0.6%**	-0.02	-0.05 to 0.01	0.157	3.1%	N/A	N/A
Expressing emotions	0.004	-0.03 to 0.04	0.785	-0.5%**	0.05	0.02 to 0.08	**0.001**	6.1%	4.60	**0.03**
Passive-reacting coping	0.14	0.11 to 0.18	**<0.001**	26.1%	0.15	0.12 to 0.17	**<0.001**	33.9%	0.01	0.94
Palliative-reacting coping	0.02	-0.01 to 0.06	0.218	-0.04%**	0.03	0.001 to 0.05	0.039	3.4%	N/A	N/A
Avoidance	0.06	0.02 to 0.09	**0.001**	4.5%	0.06	0.03 to 0.10	**<0.001**	7.9%	0.07	0.80

Comparison analyses were conducted only when stratified analyses revealed significant results (after Bonferroni correction) in either males or females, or both. The models were adjusted for:

[a] Bonferroni correction applied for 6 models examining total childhood adversity (CA) and its subtypes ($p<0.0083$).

[b] Bonferroni correction applied for 7 models testing different coping strategies ($p<0.0071$).

**Adjusted R^2 values are presented to demonstrate the proportion of variance explained by each respective model including adjustments for age and family relatedness.*

*** Adjusted R^2 values were negative, indicating that the included variables explained less variance in psychosis expression than the mean-only model.*

Supplementary Table 4. Secondary analyses of childhood adversity on CAPE subdomains in mutually adjusted models

	Males (n=312)			**Females (n=478)**			**Sex Differences**	
	Beta	95% CI	*p*	Beta	95% CI	*p*	χ^2	*p*
CAPE positive								
Emotional abuse	0.11	0.03 to 0.19	**0.005**	0.14	0.09 to 0.20	**<0.001**	0.49	0.49
Physical abuse	0.09	-0.07 to 0.25	0.276	0.19	-0.06 to 0.44	0.132	N/A	N/A
Sexual abuse	0.05	-0.12 to 0.23	0.545	0.23	0.12 to 0.33	**<0.001**	2.57	0.11
Emotional neglect	-0.01	-0.08 to 0.05	0.669	0.0002	-0.05 to 0.05	0.994	N/A	N/A
Physical neglect	0.16	0.07 to 0.26	**0.001**	0.02	-0.05 to 0.09	0.571	5.78	**0.02**
CAPE negative								
Emotional abuse	0.09	0.001 to 0.19	0.046	0.18	0.10 to 0.26	**<0.001**	1.85	0.17
Physical abuse	0.02	-0.21 to 0.25	0.838	0.19	-0.09 to 0.47	0.179	N/A	N/A
Sexual abuse	-0.06	-0.30 to 0.18	0.625	0.17	0.04 to 0.30	**0.008**	2.92	0.09
Emotional neglect	0.07	-0.01 to 0.16	0.080	0.02	-0.05 to 0.09	0.497	N/A	N/A
Physical neglect	0.16	0.05 to 0.26	**0.004**	-0.01	-0.10 to 0.08	0.825	5.57	**0.02**
CAPE depressive								
Emotional abuse	0.16	0.07 to 0.25	**<0.001**	0.22	0.15 to 0.30	**<0.001**	1.16	0.28
Physical abuse	0.09	-0.15 to 0.32	0.467	0.13	-0.14 to 0.40	0.342	N/A	N/A
Sexual abuse	0.04	-0.21 to 0.28	0.775	0.26	0.12 to 0.40	**<0.001**	2.54	0.11
Emotional neglect	0.05	-0.03 to 0.12	0.240	0.03	-0.04 to 0.10	0.391	N/A	N/A
Physical neglect	0.06	-0.06 to 0.18	0.322	-0.01	-0.11 to 0.09	0.858	N/A	N/A

** p value threshold was accepted as <0.016 for 3 mutually adjusted models including all childhood adversity subtypes on 3 CAPE subdomains*

Supplementary Table 5. Sensitivity analyses of childhood adversity on CAPE subdomains in independent models

	Males				Females				Sex Differences	
	Beta	95% CI	*p*-value[a]	Adjusted R^{2b}	Beta	95% CI	*p*-value[a]	Adjusted R^{2b}	χ^2	*p*-value
CAPE positive										
Total CA	0.11	0.07 to 0.15	**<0.001**	12.8%	0.11	0.07 to 0.15	**<0.001**	21.8%	0.02	0.89
Emotional abuse	0.15	0.08 to 0.23	**<0.001**	6.7%	0.18	0.12 to 0.25	**<0.001**	14.7%	0.39	0.53
Physical abuse	0.21	0.01 to 0.42	0.038	3.6%	0.36	0.06 to 0.65	0.019	10.1%	N/A	N/A
Sexual abuse	0.20	-0.02 to 0.42	0.072	2.9%	0.30	0.17 to 0.43	**<0.001**	13.8%	0.58	0.45
Emotional neglect	0.05	-0.02 to 0.11	0.140	0.9%	0.08	0.02 to 0.14	0.006	7.5%	N/A	N/A
Physical neglect	0.21	0.10 to 0.31	**<0.001**	7.8%	0.10	0.01 to 0.18	0.022	7.2%	2.53	0.11
CAPE negative										
Total CA	0.11	0.05 to 0.16	**<0.001**	7.6%	0.12	0.08 to 0.15	**<0.001**	12.1%	0.1	0.76
Emotional abuse	0.14	0.05 to 0.23	0.003	3.2%	0.22	0.14 to 0.29	**<0.001**	8.9%	1.91	0.17
Physical abuse	0.12	-0.11 to 0.36	0.289	0.7%	0.35	0.05 to 0.65	0.022	3.0%	N/A	N/A
Sexual abuse	0.08	-0.15 to 0.30	0.509	0.2%	0.26	0.12 to 0.40	**<0.001**	4.2%	1.81	0.18
Emotional neglect	0.12	0.03 to 0.20	0.007	2.7%	0.11	0.04 to 0.18	**0.0026**	2.4%	0.04	0.84
Physical neglect	0.19	0.09 to 0.30	**<0.001**	4.2%	0.09	-0.02 to 0.19	0.106	0.9%	1.99	0.16
CAPE depressive										
Total CA	0.12	0.06 to 0.18	**<0.001**	10.1%	0.14	0.10 to 0.18	**<0.001**	14.8%	0.41	0.52
Emotional abuse	0.20	0.12 to 0.29	**<0.001**	7.5%	0.27	0.19 to 0.36	**<0.001**	11.4%	1.38	0.24
Physical abuse	0.22	-0.01 to 0.46	0.064	2.2%	0.35	0.06 to 0.63	0.017	2.5%	N/A	N/A
Sexual abuse	0.19	-0.03 to 0.41	0.092	1.3%	0.35	0.20 to 0.50	**<0.001**	6.4%	1.38	0.24
Emotional neglect	0.11	0.03 to 0.18	0.006	2.0%	0.13	0.05 to 0.21	**<0.001**	2.9%	0.23	0.63
Physical neglect	0.13	0.01 to 0.25	0.040	1.6%	0.10	-0.01 to 0.21	0.065	1.0%	N/A	N/A

[a]p value threshold was accepted as <0.0027 for 18 models examining total childhood adversity and its subtypes

[b]Adjusted R^2 values are presented to demonstrate the proportion of variance explained by each respective model including adjustments for age and family relatedness.

Supplementary Table 6. Secondary analyses of coping strategies on CAPE subdomains in mutually adjusted models

	Males			**Females**			**Sex Differences**	
	Beta	95% CI	*p*-value*	Beta	95% CI	*p*-value*	χ^2	*p*-value
CAPE positive								
Active coping	0.002	-0.032 to 0.036	0.902	0.021	-0.009 to 0.051	0.168	N/A	N/A
Seeking social support	0.029	-0.011 to 0.068	0.152	-0.056	-0.085 to -0.027	**<0.001**	12.31	**<0.001**
Reassuring thoughts	0.008	-0.029 to 0.046	0.668	-0.011	-0.046 to 0.023	0.519	N/A	N/A
Emotional expression	-0.010	-0.044 to 0.023	0.536	0.031	0.005 to 0.057	0.022	N/A	N/A
Passive-reacting coping	0.106	0.056 to 0.157	**<0.001**	0.090	0.054 to 0.126	**<0.001**	0.604	0.60
Palliative-reacting coping	-0.008	-0.045 to 0.029	0.674	0.016	-0.012 to 0.043	0.259	N/A	N/A
Avoidance coping	-0.009	-0.042 to 0.023	0.571	-0.001	-0.032 to 0.030	0.949	N/A	N/A
CAPE negative								
Active coping	-0.044	-0.084 to -0.004	0.029	-0.002	-0.033 to 0.028	0.873	N/A	N/A
Seeking social support	-0.015	-0.062 to 0.031	0.509	-0.070	-0.097 to -0.043	**<0.001**	3.948	**0.047**
Reassuring thoughts	0.033	-0.006 to 0.072	0.097	-0.021	-0.053 to 0.011	0.195	N/A	N/A
Emotional expression	-0.050	-0.087 to -0.013	**0.009**	0.025	-0.006 to 0.056	0.117	9.086	**0.003**
Passive-reacting coping	0.159	0.117 to 0.202	**<0.001**	0.143	0.114 to 0.172	**<0.001**	0.403	0.53
Palliative-reacting coping	-0.026	-0.075 to 0.024	0.314	-0.018	-0.047 to 0.011	0.227	N/A	N/A
Avoidance coping	0.076	0.030 to 0.122	**0.001**	0.052	0.019 to 0.085	**0.002**	0.731	0.39
CAPE depressive								
Active coping	-0.019	-0.056 to 0.018	0.309	-0.045	-0.078 to -0.011	**0.009**	1.096	0.295
Seeking social support	0.031	-0.007 to 0.070	0.112	-0.024	-0.057 to 0.009	0.158	N/A	N/A
Reassuring thoughts	0.001	-0.040 to 0.041	0.978	-0.012	-0.046 to 0.021	0.463	N/A	N/A
Emotional expression	-0.012	-0.055 to 0.031	0.577	0.028	-0.003 to 0.059	0.080	N/A	N/A
Passive-reacting coping	0.211	0.165 to 0.258	**<0.001**	0.209	0.174 to 0.243	**<0.001**	0.007	0.931
Palliative-reacting coping	-0.016	-0.055 to 0.024	0.434	0.008	-0.021 to 0.037	0.599	N/A	N/A
Avoidance coping	-0.009	-0.048 to 0.029	0.629	-0.010	-0.046 to 0.025	0.574	N/A	N/A

* p value threshold was accepted as <0.016 for 3 mutually adjusted models including all coping styles on 3 CAPE subdomains

Supplementary Table 7. Sensitivity analyses of coping styles on CAPE subdomains in independent models

	Males				Females				Sex Differences	
	Beta	95% CI	*p*-value[a]	Adjusted R^{2b}	Beta	95% CI	*p*-value[a]	Adjusted R^{2b}	χ^2	*p*-value
CAPE positive										
Active coping	0.001	-0.030 to 0.031	0.960	0.1%	-0.002	-0.033 to 0.029	0.889	5.6%	N/A	N/A
Seeking social support	0.040	0.004 to 0.076	0.028	1.5%	-0.042	-0.077 to -0.008	0.016	7.9%	N/A	N/A
Reassuring thoughts	0.001	-0.039 to 0.040	0.980	0.1%	-0.007	-0.041 to 0.027	0.686	5.7%	N/A	N/A
Emotional expression	0.015	-0.017 to 0.047	0.369	0.4%	0.046	0.019 to 0.073	**<0.001**	8.3%	2.1	0.147
Passive-reacting coping	0.101	0.055 to 0.147	**<0.001**	11.3%	0.102	0.068 to 0.135	**<0.001**	19.5%	0.001	0.981
Palliative-reacting coping	0.018	-0.020 to 0.055	0.350	0.4%	0.029	0.002 to 0.057	0.036	6.8%	N/A	N/A
Avoidance coping	0.020	-0.013 to 0.053	0.229	0.6%	0.041	0.007 to 0.075	0.019	7.7%	N/A	N/A
CAPE negative										
Active coping	-0.050	-0.091 to -0.009	0.017	2.1%	-0.045	-0.080 to -0.010	0.012	1.6%	N/A	N/A
Seeking social support	-0.022	-0.072 to 0.028	0.385	0.2%	-0.078	-0.112 to -0.044	**<0.001**	5.3%	3.34	0.068
Reassuring thoughts	0.007	-0.034 to 0.047	0.744	-0.002%*	-0.034	-0.069 to 0.001	0.055	1.0%	N/A	N/A
Emotional expression	-0.024	-0.064 to 0.016	0.239	0.4%	0.044	0.006 to 0.081	0.022	1.7%	N/A	N/A
Passive-reacting coping	0.169	0.125 to 0.213	**<0.001**	19.6%	0.166	0.133 to 0.199	**<0.001**	25.8%	0.01	0.911
Palliative-reacting coping	0.025	-0.021 to 0.072	0.282	0.4%	0.014	-0.014 to 0.042	0.337	0.2%	N/A	N/A
Avoidance coping	0.119	0.073 to 0.165	**<0.001**	11.5%	0.095	0.057 to 0.133	**<0.001**	7.8%	0.61	0.435
CAPE depressive										
Active coping	-0.031	-0.071 to 0.009	0.122	0.5%	-0.074	-0.113 to -0.035	**<0.001**	3.5%	2.36	0.124
Seeking social support	0.047	-0.003 to 0.097	0.065	0.8%	-0.033	-0.076 to 0.010	0.131	0.8%	N/A	N/A
Reassuring thoughts	-0.025	-0.067 to 0.017	0.246	0.1%	-0.038	-0.076 to 0.000	0.052	1.0%	N/A	N/A
Emotional expression	0.028	-0.013 to 0.069	0.182	0.2%	0.081	0.040 to 0.121	**<0.001**	4.7%	3.35	0.067
Passive-reacting coping	0.206	0.163 to 0.250	**<0.001**	32.1%	0.219	0.181 to 0.257	**<0.001**	36.9%	0.2	0.658
Palliative-reacting coping	0.028	-0.017 to 0.074	0.221	0.1%	0.037	0.005 to 0.068	0.021	1.1%	N/A	N/A
Avoidance coping	0.045	-0.002 to 0.093	0.063	1.4%	0.067	0.024 to 0.110	0.003	3.2%	N/A	N/A

[a] p value threshold was accepted as <0.0023 for 21 independent models for 7 coping styles on 3 CAPE subdomains.

[b] Adjusted R^2 values are presented to demonstrate the proportion of variance explained by each respective model including adjustments for age and family relatedness.

*Adjusted R2 value was negative, indicating that the included variables explained less variance in psychosis expression than the mean-only model.

Supplementary Table 8. Interaction between childhood adversity subtypes and coping strategies on CAPE total

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Active coping								
Total CA	-0.004	-0.05 to 0.04	0.866	-0.01	-0.04 to 0.02	0.587	N/A	N/A
Emotional abuse	-0.02	-0.09 to 0.04	0.473	0.004	-0.06 to 0.07	0.893	N/A	N/A
Physical abuse	0.05	-0.21 to 0.32	0.698	-0.19	-0.40 to 0.03	0.085	N/A	N/A
Sexual abuse	-0.11	-0.39 to 0.16	0.414	-0.01	-0.11 to 0.08	0.762	N/A	N/A
Emotional neglect	-0.03	-0.08 to 0.03	0.337	-0.02	-0.07 to 0.03	0.457	N/A	N/A
Physical neglect	-0.01	-0.10 to 0.09	0.909	-0.04	-0.13 to 0.05	0.360	N/A	N/A
Seeking social support								
Total CA	0.01	-0.04 to 0.06	0.673	-0.04	-0.06 to -0.02	**<0.001**	3.43	0.064
Emotional abuse	-0.02	-0.11 to 0.06	0.599	-0.10	-0.17 to -0.03	**0.003**	2.18	0.14
Physical abuse	0.17	-0.02 to 0.35	0.078	-0.32	-0.54 to -0.10	**0.005**	13.19	**<0.001**
Sexual abuse	-0.04	-0.24 to 0.16	0.708	-0.07	-0.23 to 0.09	0.370	N/A	N/A
Emotional neglect	0.00	-0.07 to 0.07	0.917	-0.06	-0.13 to 0.01	0.071	1.94	0.16
Physical neglect	0.08	-0.03 to 0.20	0.154	-0.14	-0.24 to -0.05	**0.002**	9.01	**0.003**
Reassuring thoughts								
Total CA	-0.01	-0.05 to 0.03	0.535	-0.03	-0.04 to -0.01	**0.001**	0.35	0.56
Emotional abuse	-0.05	-0.11 to 0.01	0.126	-0.05	-0.12 to 0.02	0.162	N/A	N/A
Physical abuse	0.07	-0.09 to 0.22	0.408	-0.22	-0.37 to -0.07	**0.005**	7.32	**0.01**
Sexual abuse	0.09	-0.03 to 0.21	0.127	-0.08	-0.22 to 0.05	0.223	N/A	N/A
Emotional neglect	-0.09	-0.15 to -0.04	**0.001**	-0.07	-0.14 to -0.01	**0.027**	0.20	0.65
Physical neglect	0.01	-0.08 to 0.11	0.772	-0.17	-0.27 to -0.07	**0.001**	6.88	**0.01**
Emotional expression								
Total CA	-0.02	-0.05 to 0.01	0.109	0.01	-0.04 to 0.05	0.764	N/A	N/A
Emotional abuse	-0.06	-0.13 to 0.00	0.068	0.01	-0.06 to 0.08	0.721	N/A	N/A
Physical abuse	-0.11	-0.24 to 0.02	0.087	-0.01	-0.23 to 0.21	0.954	N/A	N/A
Sexual abuse	-0.08	-0.24 to 0.08	0.340	0.14	-0.01 to 0.28	0.064	N/A	N/A
Emotional neglect	-0.01	-0.07 to 0.05	0.664	0.01	-0.05 to 0.07	0.659	N/A	N/A
Physical neglect	0.01	-0.09 to 0.11	0.860	0.09		0.141	N/A	N/A

Supplementary Table 8. Interaction between childhood adversity subtypes and coping strategies on CAPE total *(continued)*

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Passive-reacting coping								
Total CA	0.02	-0.01 to 0.04	0.231	0.04	0.01 to 0.06	**0.002**	1.27	0.26
Emotional abuse	0.00	-0.07 to 0.06	0.941	0.06	-0.01 to 0.12	0.071	N/A	N/A
Physical abuse	0.08	-0.06 to 0.22	0.266	0.14	-0.13 to 0.41	0.298	N/A	N/A
Sexual abuse	0.05	-0.11 to 0.21	0.532	0.04	-0.11 to 0.19	0.566	N/A	N/A
Emotional neglect	0.04	-0.03 to 0.11	0.213	0.07	0.02 to 0.12	**0.008**	0.36	0.55
Physical neglect	0.08	0.01 to 0.15	**0.031**	0.07	-0.03 to 0.16	0.157	0.03	0.86
Palliative-reacting coping								
Total CA	-0.003	-0.05 to 0.04	0.873	-0.03	-0.05 to -0.02	**<0.001**	1.36	0.243
Emotional abuse	-0.06	-0.15 to 0.03	0.166	-0.04	-0.09 to 0.01	0.150	N/A	N/A
Physical abuse	0.05	-0.21 to 0.31	0.683	-0.21	-0.37 to -0.05	**0.010**	3.16	0.08
Sexual abuse	-0.11	-0.28 to 0.06	0.200	-0.08	-0.21 to 0.06	0.248	N/A	N/A
Emotional neglect	-0.04	-0.11 to 0.03	0.289	-0.03	-0.08 to 0.02	0.187	N/A	N/A
Physical neglect	0.09	-0.05 to 0.22	0.225	-0.10	-0.17 to -0.02	**0.018**	5.42	**0.02**
Avoidance coping								
Total CA	0.02	0.00 to 0.04	**0.048**	-0.004	-0.04 to 0.03	0.783	1.55	0.21
Emotional abuse	-0.02	-0.10 to 0.06	0.556	0.04	-0.04 to 0.12	0.336	N/A	N/A
Physical abuse	0.20	0.13 to 0.27	**<0.001**	-0.08	-0.32 to 0.15	0.498	4.90	**0.03**
Sexual abuse	0.27	0.10 to 0.44	**0.002**	-0.10	-0.23 to 0.03	0.146	11.47	**<0.001**
Emotional neglect	0.04	-0.02 to 0.11	0.202	-0.02	-0.09 to 0.04	0.486	N/A	N/A
Physical neglect	0.06	-0.05 to 0.18	0.282	-0.02	-0.13 to 0.08	0.674	N/A	N/A

** Bonferroni correction was not applied for the interaction analyses, as these findings are exploratory in nature*

Supplementary Table 9. Interaction between childhood adversity subtypes and coping strategies on CAPE positive

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Active coping								
Total CA	-0.03	-0.06 to 0.01	0.110	-0.02	-0.05 to 0.02	0.286	N/A	N/A
Emotional abuse	-0.04	-0.10 to 0.03	0.308	0.01	-0.06 to 0.09	0.698	N/A	N/A
Physical abuse	-0.03	-0.25 to 0.18	0.760	-0.25	-0.42 to -0.08	**0.004**	2.55	0.11
Sexual abuse	-0.17	-0.45 to 0.12	0.244	0.04	-0.08 to 0.16	0.499	N/A	N/A
Emotional neglect	-0.05	-0.11 to 0.01	0.088	-0.03	-0.09 to 0.03	0.386	N/A	N/A
Physical neglect	-0.04	-0.13 to 0.06	0.454	-0.06	-0.15 to 0.02	0.144	N/A	N/A
Seeking social support								
Total CA	0.01	-0.03 to 0.06	0.521	-0.05	-0.07 to -0.03	**<0.001**	8.10	**0.004**
Emotional abuse	0.00	-0.09 to 0.09	0.979	-0.10	-0.18 to -0.03	**0.008**	3.18	0.07
Physical abuse	0.14	-0.04 to 0.32	0.136	-0.38	-0.60 to -0.16	**0.001**	13.70	**<0.001**
Sexual abuse	-0.06	-0.26 to 0.15	0.595	-0.07	-0.24 to 0.10	0.397	N/A	N/A
Emotional neglect	0.01	-0.07 to 0.08	0.891	-0.07	-0.15 to 0.00	0.055	N/A	N/A
Physical neglect	0.08	-0.06 to 0.22	0.242	-0.16	-0.26 to -0.06	**0.002**	7.51	**0.01**
Reassuring thoughts								
Total CA	-0.01	-0.05 to 0.03	0.655	-0.03	-0.05 to -0.02	**<0.001**	1.03	0.31
Emotional abuse	-0.05	-0.13 to 0.02	0.140	-0.05	-0.12 to 0.03	0.238	N/A	N/A
Physical abuse	0.09	-0.09 to 0.28	0.321	-0.31	-0.46 to -0.15	**<0.001**	11.71	**<0.001**
Sexual abuse	0.08	-0.05 to 0.21	0.245	-0.06	-0.23 to 0.11	0.485	N/A	N/A
Emotional neglect	-0.07	-0.14 to 0.00	0.057	-0.04	-0.11 to 0.03	0.298	N/A	N/A
Physical neglect	0.02	-0.08 to 0.13	0.653	-0.17	-0.29 to -0.05	**0.007**	5.65	**0.02**
Emotional expression								
Total CA	-0.02	-0.04 to 0.01	0.206	-0.01	-0.05 to 0.03	0.619	N/A	N/A
Emotional abuse	-0.06	-0.14 to 0.01	0.074	-0.02	-0.09 to 0.05	0.646	N/A	N/A
Physical abuse	-0.10	-0.20 to 0.00	**0.049**	-0.02	-0.23 to 0.19	0.830	0.43	0.51
Sexual abuse	-0.12	-0.27 to 0.03	0.110	0.15	0.02 to 0.28	**0.027**	7.25	**0.01**
Emotional neglect	-0.02	-0.09 to 0.04	0.439	-0.01	-0.07 to 0.05	0.745	N/A	N/A
Physical neglect	0.03	-0.07 to 0.13	0.582	0.03	-0.07 to 0.14	0.560	N/A	N/A

Supplementary Table 9. Interaction between childhood adversity subtypes and coping strategies on CAPE positive *(continued)*

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Passive-reacting coping								
Total CA	0.02	-0.01 to 0.05	0.170	0.04	0.01 to 0.07	**0.004**	1.20	0.27
Emotional abuse	-0.02	-0.11 to 0.07	0.632	0.03	-0.05 to 0.10	0.506	N/A	N/A
Physical abuse	0.08	-0.05 to 0.22	0.218	0.21	-0.04 to 0.46	0.101	N/A	N/A
Sexual abuse	0.07	-0.13 to 0.26	0.487	0.05	-0.11 to 0.20	0.570	N/A	N/A
Emotional neglect	0.04	-0.04 to 0.13	0.318	0.08	0.01 to 0.14	**0.018**	0.41	0.52
Physical neglect	0.12	0.03 to 0.21	**0.011**	0.08	-0.01 to 0.17	0.079	0.32	0.57
Palliative-reacting coping								
Total CA	-0.03	-0.06 to 0.01	0.205	-0.04	-0.06 to -0.02	**<0.001**	0.58	0.45
Emotional abuse	-0.08	-0.18 to 0.01	0.081	-0.02	-0.09 to 0.04	0.473	N/A	N/A
Physical abuse	-0.03	-0.25 to 0.19	0.783	-0.26	-0.44 to -0.08	**0.004**	2.75	0.10
Sexual abuse	-0.11	-0.31 to 0.09	0.265	-0.03	-0.19 to 0.13	0.725	N/A	N/A
Emotional neglect	-0.06	-0.14 to 0.01	0.078	-0.04	-0.09 to 0.02	0.212	N/A	N/A
Physical neglect	0.08	-0.03 to 0.20	0.158	-0.11	-0.19 to -0.02	**0.016**	7.00	**0.01**
Avoidance coping								
Total CA	0.01	-0.01 to 0.03	0.501	-0.003	-0.04 to 0.03	0.833	N/A	N/A
Emotional abuse	-0.07	-0.15 to 0.01	0.099	0.04	-0.05 to 0.12	0.380	N/A	N/A
Physical abuse	0.17	0.05 to 0.29	**0.005**	-0.06	-0.30 to 0.19	0.653	2.67	0.10
Sexual abuse	0.22	-0.01 to 0.46	0.062	-0.02	-0.18 to 0.14	0.822	N/A	N/A
Emotional neglect	0.04	-0.03 to 0.10	0.242	-0.01	-0.08 to 0.06	0.711	N/A	N/A
Physical neglect	0.06	-0.06 to 0.18	0.322	0.01	-0.09 to 0.11	0.844	N/A	N/A

** Bonferroni correction was not applied for the interaction analyses, as these findings are exploratory in nature*

Supplementary Table 10. Interaction between childhood adversity subtypes and coping strategies on CAPE negative

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Active coping								
Total CA	0.02	-0.05 to 0.08	0.616	-0.003	-0.04 to 0.04	0.877	N/A	N/A
Emotional abuse	-0.03	-0.12 to 0.06	0.563	0.01	-0.07 to 0.09	0.866	N/A	N/A
Physical abuse	0.17	-0.15 to 0.48	0.300	-0.19	-0.43 to 0.05	0.122	N/A	N/A
Sexual abuse	-0.06	-0.36 to 0.23	0.665	-0.08	-0.18 to 0.02	0.107	N/A	N/A
Emotional neglect	0.00	-0.07 to 0.08	0.904	0.00	-0.07 to 0.07	0.896	N/A	N/A
Physical neglect	0.02	-0.09 to 0.14	0.707	-0.05	-0.16 to 0.06	0.408	N/A	N/A
Seeking social support								
Total CA	0.001	-0.07 to 0.08	0.958	-0.03	-0.05 to -0.01	**0.006**	0.73	0.39
Emotional abuse	-0.05	-0.17 to 0.07	0.405	-0.10	-0.17 to -0.02	**0.008**	0.38	0.54
Physical abuse	0.22	-0.02 to 0.46	0.069	-0.26	-0.52 to 0.01	0.058	N/A	N/A
Sexual abuse	0.02	-0.22 to 0.26	0.883	-0.10	-0.27 to 0.07	0.239	N/A	N/A
Emotional neglect	0.00	-0.10 to 0.10	0.942	-0.04	-0.11 to 0.03	0.213	N/A	N/A
Physical neglect	0.07	-0.05 to 0.20	0.247	-0.14	-0.24 to -0.04	**0.008**	6.51	**0.01**
Reassuring thoughts								
Total CA	-0.02	-0.08 to 0.03	0.397	-0.03	-0.05 to -0.01	**0.01**	0.01	0.91
Emotional abuse	-0.06	-0.14 to 0.02	0.117	-0.03	-0.11 to 0.05	0.453	N/A	N/A
Physical abuse	0.06	-0.10 to 0.22	0.485	-0.15	-0.34 to 0.04	0.124	N/A	N/A
Sexual abuse	0.09	-0.05 to 0.24	0.219	-0.12	-0.26 to 0.02	0.087	N/A	N/A
Emotional neglect	-0.13	-0.20 to -0.06	**<0.001**	-0.11	-0.18 to -0.04	**0.002**	0.12	0.73
Physical neglect	-0.01	-0.10 to 0.09	0.899	-0.19	-0.29 to -0.08	**0.001**	6.23	**0.01**
Emotional expression								
Total CA	-0.03	-0.07 to 0.01	0.134	0.02	-0.03 to 0.07	0.346	N/A	N/A
Emotional abuse	-0.07	-0.16 to 0.02	0.107	0.04	-0.05 to 0.12	0.423	N/A	N/A
Physical abuse	-0.13	-0.30 to 0.04	0.125	0.00	-0.24 to 0.23	0.970	N/A	N/A
Sexual abuse	-0.06	-0.27 to 0.15	0.592	0.10	-0.10 to 0.29	0.329	N/A	N/A
Emotional neglect	0.00	-0.08 to 0.07	0.942	0.03	-0.05 to 0.11	0.434	N/A	N/A
Physical neglect	0.00	-0.12 to 0.12	0.978	0.14	-0.01 to 0.28	0.069	N/A	N/A

Supplementary Table 10. Interaction between childhood adversity subtypes and coping strategies on CAPE negative *(continued)*

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Passive-reacting coping								
Total CA	0.01	-0.04 to 0.06	0.710	0.03	0.01 to 0.06	**0.019**	0.84	0.36
Emotional abuse	0.02	-0.07 to 0.11	0.678	0.09	0.02 to 0.16	**0.017**	1.22	0.27
Physical abuse	0.06	-0.16 to 0.28	0.616	0.11	-0.19 to 0.41	0.480	N/A	N/A
Sexual abuse	0.06	-0.09 to 0.21	0.423	0.02	-0.16 to 0.20	0.837	N/A	N/A
Emotional neglect	0.02	-0.08 to 0.12	0.651	0.06	0.00 to 0.12	0.056	N/A	N/A
Physical neglect	0.02	-0.08 to 0.13	0.640	0.06	-0.06 to 0.18	0.328	N/A	N/A
Palliative-reacting coping								
Total CA	0.01	-0.05 to 0.07	0.710	-0.03	-0.05 to -0.01	**0.006**	1.35	0.24
Emotional abuse	-0.06	-0.17 to 0.05	0.280	-0.05	-0.11 to 0.01	0.134	N/A	N/A
Physical abuse	0.15	-0.14 to 0.44	0.306	-0.14	-0.32 to 0.03	0.111	N/A	N/A
Sexual abuse	-0.08	-0.23 to 0.07	0.309	-0.13	-0.27 to 0.00	0.051	N/A	N/A
Emotional neglect	-0.02	-0.11 to 0.07	0.709	-0.03	-0.08 to 0.03	0.359	N/A	N/A
Physical neglect	0.08	-0.12 to 0.29	0.431	-0.10	-0.19 to -0.01	**0.035**	2.52	0.11
Avoidance coping								
Total CA	0.02	0.00 to 0.05	**0.049**	-0.01	-0.05 to 0.03	0.580	2.38	0.12
Emotional abuse	0.03	-0.07 to 0.13	0.606	0.05	-0.04 to 0.13	0.313	N/A	N/A
Physical abuse	0.21	0.14 to 0.27	**<0.001**	-0.08	-0.35 to 0.19	0.560	4.21	**0.04**
Sexual abuse	0.29	0.15 to 0.43	**<0.001**	-0.15	-0.29 to -0.01	**0.034**	19.43	**<0.001**
Emotional neglect	0.04	-0.05 to 0.13	0.347	-0.03	-0.11 to 0.05	0.412	N/A	N/A
Physical neglect	0.05	-0.07 to 0.18	0.406	-0.05	-0.19 to 0.09	0.450	N/A	N/A

* *Bonferroni correction was not applied for the interaction analyses, as these findings are exploratory in nature*

Supplementary Table 11. Interaction between childhood adversity subtypes and coping strategies on CAPE depressive

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Active coping								
Total CA	0.02	-0.04 to 0.09	0.525	0.003	-0.05 to 0.06	0.901	N/A	N/A
Emotional abuse	0.01	-0.07 to 0.10	0.778	-0.02	-0.12 to 0.07	0.609	N/A	N/A
Physical abuse	0.07	-0.30 to 0.43	0.717	-0.04	-0.38 to 0.31	0.839	N/A	N/A
Sexual abuse	-0.07	-0.35 to 0.21	0.643	-0.03	-0.17 to 0.10	0.624	N/A	N/A
Emotional neglect	-0.02	-0.09 to 0.05	0.561	-0.03	-0.11 to 0.04	0.421	N/A	N/A
Physical neglect	0.02	-0.11 to 0.15	0.744	0.02	-0.10 to 0.15	0.694	N/A	N/A
Seeking social support								
Total CA	0.02	-0.06 to 0.09	0.639	-0.02	-0.06 to 0.02	0.228	N/A	N/A
Emotional abuse	-0.03	-0.15 to 0.09	0.606	-0.12	-0.21 to -0.02	**0.015**	1.28	0.26
Physical abuse	0.14	-0.12 to 0.41	0.281	-0.29	-0.52 to -0.07	**0.010**	8.82	**0.003**
Sexual abuse	-0.09	-0.29 to 0.11	0.371	-0.02	-0.19 to 0.16	0.868	N/A	N/A
Emotional neglect	0.01	-0.08 to 0.11	0.789	-0.07	-0.17 to 0.02	0.117	N/A	N/A
Physical neglect	0.11	-0.06 to 0.27	0.215	-0.12	-0.23 to -0.01	**0.034**	4.91	**0.03**
Reassuring thoughts								
Total CA	-0.004	-0.06 to 0.06	0.894	-0.01	-0.04 to 0.02	0.529	N/A	N/A
Emotional abuse	-0.01	-0.09 to 0.07	0.812	-0.08	-0.16 to 0.00	**0.042**	1.67	0.20
Physical abuse	0.01	-0.18 to 0.21	0.906	-0.13	-0.30 to 0.04	0.146	N/A	N/A
Sexual abuse	0.13	-0.03 to 0.30	0.116	-0.08	-0.22 to 0.05	0.236	N/A	N/A
Emotional neglect	-0.09	-0.17 to -0.02	**0.019**	-0.09	-0.17 to -0.01	**0.032**	0.00	0.97
Physical neglect	0.02	-0.12 to 0.16	0.769	-0.13	-0.24 to -0.03	**0.013**	3.20	0.07
Emotional expression								
Total CA	-0.03	-0.09 to 0.03	0.300	0.02	-0.04 to 0.08	0.463	N/A	N/A
Emotional abuse	-0.04	-0.13 to 0.06	0.467	0.05	-0.05 to 0.14	0.361	N/A	N/A
Physical abuse	-0.12	-0.34 to 0.11	0.309	0.03	-0.23 to 0.29	0.816	N/A	N/A
Sexual abuse	-0.01	-0.21 to 0.19	0.891	0.17	-0.02 to 0.35	0.076	N/A	N/A
Emotional neglect	0.00	-0.09 to 0.08	0.935	0.04	-0.05 to 0.13	0.380	N/A	N/A
Physical neglect	-0.02	-0.17 to 0.13	0.784	0.14	-0.02 to 0.30	0.076	N/A	N/A

Supplementary Table 11. Interaction between childhood adversity subtypes and coping strategies on CAPE depressive *(continued)*

	Males			Females			Sex Differences	
Interaction	Beta	95% CI	*p**	Beta	95% CI	*p**	χ^2	*p*
Passive-reacting coping								
Total CA	0.02	-0.02 to 0.07	0.317	0.03	-0.003 to 0.06	0.076	N/A	N/A
Emotional abuse	0.00	-0.08 to 0.09	0.915	0.08	0.01 to 0.16	**0.032**	1.74	0.19
Physical abuse	0.10	-0.08 to 0.28	0.288	0.04	-0.28 to 0.36	0.824	N/A	N/A
Sexual abuse	-0.02	-0.14 to 0.10	0.753	0.08	-0.08 to 0.25	0.327	N/A	N/A
Emotional neglect	0.08	0.00 to 0.17	**0.046**	0.07	0.00 to 0.14	0.065	0.10	0.75
Physical neglect	0.06	-0.05 to 0.18	0.294	0.04	-0.09 to 0.17	0.561	N/A	N/A
Palliative-reacting coping								
Total CA	0.02	-0.05 to 0.10	0.551	-0.03	-0.06 to 0.004	0.095	N/A	N/A
Emotional abuse	-0.01	-0.13 to 0.10	0.834	-0.07	-0.13 to 0.00	**0.038**	0.78	0.38
Physical abuse	0.10	-0.28 to 0.48	0.619	-0.20	-0.35 to -0.05	**0.007**	2.34	0.13
Sexual abuse	-0.15	-0.35 to 0.05	0.152	-0.11	-0.23 to 0.02	0.101	N/A	N/A
Emotional neglect	0.00	-0.10 to 0.09	0.917	-0.04	-0.11 to 0.03	0.227	N/A	N/A
Physical neglect	0.10	-0.11 to 0.30	0.352	-0.06	-0.15 to 0.03	0.169	N/A	N/A
Avoidance coping								
Total CA	0.04	0.01 to 0.07	**0.010**	0.004	-0.03 to 0.04	0.827	2.38	0.12
Emotional abuse	0.00	-0.10 to 0.11	0.928	0.03	-0.07 to 0.13	0.530	N/A	N/A
Physical abuse	0.26	0.14 to 0.37	**<0.001**	-0.15	-0.37 to 0.07	0.180	9.82	**<0.001**
Sexual abuse	0.34	0.17 to 0.52	**<0.001**	-0.19	-0.32 to -0.06	**0.003**	24.14	**<0.001**
Emotional neglect	0.05	-0.05 to 0.14	0.333	-0.03	-0.12 to 0.06	0.519	N/A	N/A
Physical neglect	0.10	-0.10 to 0.30	0.328	-0.05	-0.20 to 0.09	0.468	N/A	N/A

** Bonferroni correction was not applied for the interaction analyses, as these findings are exploratory in nature*

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Chapter 5

Examining the association between autistic traits and psychopathology in the general population: are there sex differences?

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Abstract

Introduction: Autistic traits (ATs) are linked to increased vulnerability to psychopathology. While sex differences are studied in clinical autism, little is known about these associations in the general population. This study examines sex-specific associations between ATs and psychopathology in a community sample of adolescents and young adults.

Methods: Data from 788 participants (475 females), aged 15–35 years (mean = 17.48 ± 3.60) in the TwinssCan cohort were used. ATs were assessed using Autism Spectrum Quotient (AQ), while psychopathology and psychosis expression were measured with the Symptom Checklist-90 Revised (SCL-90) and Community Assessment of Psychic Experiences (CAPE). Sex-stratified linear regression models examined associations with SCL-90 and CAPE scores. Chow's test was used for exploratory sex comparisons.

Results: In both sexes, total AQ scores were positively associated with the total SCL-90 score and all its subscales, as well as with total CAPE and all its subscales. No significant sex difference was found for either total SCL-90 or total CAPE. In exploratory post-hoc comparisons, a nominally statistically significant sex difference was observed for the obsessive–compulsive SCL-90 subscale ($p = 0.03$), where AQ accounted for 5.6% of the variance in males compared to 15.86% in females. A nominally statistically significant sex difference was found in the CAPE depressive subscale as well ($p = 0.03$), where AQ explained 4.78% of the variance in males versus 13.53% in females.

Discussion: The findings highlight that ATs relate to broad psychopathology across sexes, whereas domain-specific sex differences emerged in exploratory post-hoc comparisons. Future studies should replicate findings in clinical and longitudinal samples.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by persistent social communication deficits, along with the presence of repetitive behaviors and/or restricted interests (APA, 2022). Its prevalence has been steadily increasing (Solmi et al., 2022), being currently estimated around 1% in the general population worldwide (Zeidan et al., 2022) and 1 in 36 children in the United States (Maenner et al., 2023).

Epidemiological studies have evidenced a marked male-to-female ratio of approximately 4:1 for ASD diagnosis (Maenner et al., 2023), raising significant questions about underlying biological, social, and clinical factors contributing to this disparity. Hypotheses include a higher genetic vulnerability threshold in females, protective effects of X chromosome genes, hormonal differences, as well as behavioral, social, and diagnostic biases that may delay recognition in females (Fusar-Poli et al., 2022; Werling & Geschwind, 2013). Autistic females often present with more internalizing symptoms, such as anxiety and depression, while males tend to exhibit more externalizing behaviors, such as hyperactivity or aggression (Fusar-Poli et al., 2022; Vadukapuram et al., 2022). These differences not only influence the diagnostic process but may also affect the identification of co-occurring psychiatric conditions. For instance, autistic females have higher rates of mood and anxiety disorders, while males are more likely to be diagnosed with attention-deficit/hyperactivity disorder and conduct disorders (Hsu et al., 2024; Vadukapuram et al., 2022).

Beyond clinical ASD, there is growing recognition that autistic traits (ATs) exist on a continuum in the general population (Constantino & Charman, 2016). The overlap between ATs and psychopathology is particularly intriguing as it provides valuable insights into transdiagnostic vulnerabilities. Studies have consistently reported associations between ATs and various domains of psychopathology, such as anxiety, depression, psychotic experiences, bipolar disorder, and eating disorders (Carpita et al., 2023; Concerto et al., 2021; Dell'Osso et al., 2019; Dell'Osso et al., 2018; Demartini et al., 2024; Fusar-Poli et al., 2024; Karaçam Doğan, Prachason, et al., 2025; Liew et al., 2015; Lundström et al., 2011; Martinez et al., 2021). Recent research

has hypothesized that ATs in the general population may contribute to distinct sex-specific psychopathological outcomes. For example, ATs in males have been more frequently linked to behaviors such as pathological video gaming (Carpita et al., 2024), while in females, they are more likely to be associated with eating disorders, including anorexia nervosa or orthorexia nervosa (Carpita et al., 2022). While these findings are in line with a general scenario regardless of ATs, some evidence suggests that ATs might override the sex-dependent influence on certain psychopathology. Specifically, it was reported that even though trauma and stress-related symptoms were generally more severe in females than males, this difference disappeared in individuals with elevated levels of ATs (Carpita et al., 2019). Such evidence highlights the need to consider sex-dependent influences on psychopathology in the realm of autistic continuum.

Findings from the literature underline the importance of studying ATs not only as a subthreshold domain of ASD, but also as a relevant factor associated with the broader psychopathological spectrum in clinical and subclinical populations (Carpita et al., 2023; Concerto et al., 2021; Dell'Osso et al., 2019; Dell'Osso et al., 2018; Demartini et al., 2024; Fusar-Poli et al., 2024; Karaçam Doğan, Prachason, et al., 2025; Liew et al., 2015; Lundström et al., 2011; Martinez et al., 2021). At the same time, the functional significance of ATs may vary across individuals and contexts. Although elevated ATs may confer vulnerability in some domains, they have also been associated with potentially adaptive characteristics, such as ability to hyperfocus, good memory, creativity, honesty and loyalty (Russell et al., 2019). This heterogeneity raises the possibility that the psychopathological correlates of ATs may also differ across individual characteristics, including sex. However, little is known about whether associations between ATs and psychopathology differ between males and females. Furthermore, it remains unclear whether such differences are autism specific or reflect normative sex differences in psychopathology. Therefore, the present study primarily aims to investigate the sex-specific differences in the associations between ATs and psychopathological dimensions in a large general population sample of adolescent/young adult twins and their siblings. Furthermore, we aim to investigate the association between specific autistic domains and psychopathology in the general population as exploratory analyses.

Methods

Participants

Participants were recruited from the East Flanders Prospective Twin Survey, a prospective population-based, multi-birth registry situated in Flanders, Belgium (Derom et al., 2019). Those fulfilling the inclusion criteria were invited to participate in the TwinssCan project (Pries et al., 2019), a longitudinal study collecting data of twins aged 15–35 years as well as their siblings and parents. The first assessment was performed from April 2010 to April 2014. All participants gave written informed consent. For participants below the age of 18, parents also signed informed consent. Participants were excluded if they had a severe and persistent psychiatric condition that was identified by caregivers and aligned with the Dutch consensus definition of severe mental illness (Delespaul, 2013). These conditions included schizophrenia, other psychotic disorders, bipolar disorder with psychotic features, ASD, or substance use disorders, provided that these significantly impaired daily functioning and necessitated coordinated care. The local ethics committee (Commissie Medische Ethiek van de Universitaire ziekenhuizen KU Leuven, Nr. B32220107766) approved the study. Data of 821 twins and siblings collected at the first wave of the TwinssCan project were included in the present study. Thirty-three participants were excluded from our analysis due to missing information regarding psychopathology or ATs, leaving 788 participants for the analyses.

Measurements

Autistic traits

The Autism Spectrum Quotient (AQ-50) is a self-report tool that measures the degree to which an adult with average or above-average intelligence has the traits associated with the autistic spectrum (Baron-Cohen et al., 2001). The Dutch translation of the AQ was used for this study (Hoekstra et al., 2008). It consists of 50 items, grouped into five subdomains: imagination, social skills, communication, attention to detail, and attention switching. Responses were given on a 4-point Likert scale ranging from 'definitely agree' to 'definitely disagree.'

Following the most widely used scoring method (Baron-Cohen et al., 2001; Woodbury-Smith et al., 2005), each item was dichotomized and scored as 0 or 1. For items consistent with ATs, 'definitely agree' and 'slightly agree' were scored as 1, while 'definitely disagree' and 'slightly disagree' were scored as 0; for the remaining items, the scoring was reversed. This yielded a total score ranging from 0 to 50, with higher scores on both the total and subscales reflecting higher levels of ATs.

General Psychopathology

The Symptom Checklist-90 Revised (SCL-90) (Derogatis et al., 1976), a 90-item self-report questionnaire, was used to assess overall psychopathology and nine symptom domains: psychoticism, paranoid ideation, anxiety, depression, somatization, obsessive–compulsive, interpersonal sensitivity, hostility, and phobic anxiety. Respondents were asked to rate the extent to which they were bothered by each symptom in the past week based on a 5-point Likert scale ranging from 'not at all' to 'very much'. The SCL-90 Global Severity Index (hereafter: total SCL-90), ranging from 0 to 4, was derived by averaging the scores of all SCL-90 items (Derogatis et al., 1976). The nine symptom domain scores were similarly derived by averaging all items per symptom domain (Derogatis et al., 1976).

Psychosis Expression

Psychosis expression was evaluated using the Community Assessment of Psychic Experiences (CAPE), a widely used, reliable, valid, and stable 42-item self-report questionnaire for assessing psychotic experiences in the general population (Konings et al., 2006; Stefanis et al., 2002). The CAPE consists of three subscales: positive, negative, and depressive. Responses were gathered using a four-point Likert scale, which measures both the frequency and the level of distress associated with the symptoms. From these responses, overall and subscale scores (positive, negative, and depressive) were generated. For our analysis, we specifically focused on the frequency scores to measure psychosis expression, consistent with our previous work using the TwinssCan cohort data (Karaçam Doğan, Fusar-Poli, et al., 2025; Karaçam Doğan, Prachason, et al., 2025).

Statistical analyses

Data analyses were performed using Stata version 17 (Stata, 2021).

For our primary objective, we first tested sex-specific associations between total AQ and psychopathology scores (i.e., total SCL-90 and total CAPE) using linear regression analyses stratified by sex. Total AQ was modelled as the independent variable and psychopathology scores as dependent variables. As secondary analyses, we conducted sex-stratified linear regression to investigate the association of SCL-90 and CAPE subdomains with total AQ.

For our exploratory aim, we performed sex-stratified linear regression analyses similar to the primary analyses, using each of the five AQ subscales as the independent variable in separate models and the total SCL-90 as well as the total CAPE as dependent variables.

Because the sample includes monozygotic and dizygotic twin pairs and siblings, standard errors (SE) were adjusted for the non-independence of observations within the same family using the Stata 'cluster' option in all models, which produces cluster-robust variance estimates that account for intra-pair dependence irrespective of zygosity. Total SCL-90 and the symptom dimension scores were transformed using a square-root function, and all analyses were adjusted for age. To capture the relative contribution of each explaining variable in the model, the Stata "Shapley2" post-estimation command (Wendelspiess Chávez Juárez, 2015) was used to calculate the Shorrocks–Shapley decomposition of R^2 (Shorrocks, 2013). The Chow's test (Chow, 1960) was used for post-hoc analyses to compare the regression coefficients of the two sexes.

Statistical significance was set at $p < 0.05$ for the analyses using total SCL-90 and total CAPE scores as the outcome. Bonferroni-corrected $p < 0.006$ and $p < 0.02$ were used for secondary analyses using SCL-90 and CAPE subdomains as outcomes, respectively. Due to the exploratory nature of the analyses, we did not apply a Bonferroni correction for post-hoc sex comparisons and AQ subscale analyses.

Table 1. Characteristics of participants

	Males (n=313)	**Females (n=475)**	**Total (n=788)**
Age (y), *M* (SD)	16.92 (2.84)	17.84 (3.99)	17.48 (3.60)
Zygosity, *n* (%)			
Monozygotic twins	97 (30.99)	175 (36.84)	272 (34.52)
Dizygotic twins	203 (64.86)	270 (56.84)	473 (60.03)
Sibling	13 (4.15)	30 (6.32)	43 (5.46)
Total AQ, *M* (SD)	16.50 (5.58)	15.00 (5.62)	15.60 (5.65)
Social skills	2.21 (1.97)	1.92 (1.90)	2.04 (1.93)
Attention switching	4.01 (1.83)	3.68 (1.85)	3.81 (1.85)
Attention to detail	4.34 (2.09)	4.51 (2.06)	4.44 (2.07)
Communication	2.64 (1.88)	2.48 (1.78)	2.54 (1.82)
Imagination	3.31 (1.87)	2.42 (1.62)	2.77 (1.78)
Total SCL-90, *M* (SD)	0.44 (0.40)	0.50 (0.44)	0.48 (0.43)
Phobic anxiety	0.17 (0.37)	0.22 (0.44)	0.20 (0.42)
Anxiety	0.36 (0.46)	0.45 (0.54)	0.41 (0.51)
Depression	0.46 (0.51)	0.58 (0.58)	0.53 (0.55)
Interpersonal sensitivity	0.53 (0.51)	0.67 (0.58)	0.62 (0.56)
Somatization	0.44 (0.45)	0.53 (0.51)	0.49 (0.49)
Obsessive-compulsive	0.68 (0.55)	0.69 (0.59)	0.68 (0.58)
Paranoid ideation	0.44 (0.54)	0.46 (0.58)	0.45 (0.56)
Hostility	0.42 (0.46)	0.42 (0.49)	0.42 (0.48)
Psychoticism	0.26 (0.40)	0.26 (0.37)	0.26 (0.38)
Total CAPE frequency, *M* (SD)	1.57 (0.26)	1.56 (0.26)	1.56 (0.26)
Positive symptoms	1.42 (0.28)	1.40 (0.27)	1.41 (0.28)
Negative symptoms	1.72 (0.36)	1.64 (0.33)	1.67 (0.35)
Depressive symptoms	1.67 (0.34)	1.82 (0.37)	1.76 (0.36)

CAPE: Community Assessment of Psychic Experiences, SCL-90: Symptom Checklist-90 Revised, M: mean, SD: standard deviation

Results

Characteristics of participants

The characteristics of the participants are reported in **Table 1**. Data from 272 monozygotic twins, 473 dizygotic twins, and 43 siblings from 384 families were used in this analysis. About 60% of the participants were female, and the age range of the dataset was 15–34 years old.

Sex-stratified association between total autistic traits and psychopathology

Total AQ explained 10.11% and 18.73% of the variance of total SCL-90 in males (B[95%CI]: 0.09[0.06, 0.12], $p < 0.001$) and females (B[95%CI]: 0.12[0.10, 0.15], $p < 0.001$), respectively (**Table 2**). No significant sex differences in the association between total AQ and total SCL-90 were found ($\chi2 = 2.84$, $p = 0.09$). The sequential analyses of the psychopathology subdomains revealed that total AQ was significantly associated with all symptom domains in males and females (all Bonferroni-corrected $p < 0.006$, **Table 2**). However, the order of hits from the largest to lowest explained variance differed for males and females (**Figure 1**). In males, the variances explained by total AQ (Shapley value) ranged from 3.08% to 10.40%. It explained the largest variances for interpersonal sensitivity (10.40%) and phobic anxiety (9.48%), followed by paranoid ideation (9.19%), depression (8.60%), psychoticism (7.83%), obsessive-compulsive (5.60%), anxiety (4.93%), hostility (4.70%), and somatization (3.08%). In females, the explained variance ranged from 8.77% to 17.57%. Total AQ explained the largest variances for interpersonal sensitivity (17.57%), followed by obsessive-compulsive (15.86%), psychoticism (15.04%), paranoid ideation (13.53%), depression (13.05%), hostility (12.59%), phobic anxiety (12.29%), anxiety (9.42%), and somatization (8.77%). Exploratory post-hoc sex comparison indicated a nominally statistically significant difference in the association between total AQ and the obsessive-compulsive domain of SCL-90, with a stronger association in females ($\chi2 = 4.89$, $p = 0.03$) (**Table 2**).

For psychosis expression, total AQ explained 16.74% of the variance of total CAPE in males (B[95%CI]: 0.11 [0.08, 0.14], $p < 0.001$) and 23.9% of the variance in females (B[95%CI]: 0.13[0.10, 0.16], $p < 0.001$) (**Table 3**). We did not find any significant sex differences in the association between total AQ and total CAPE ($\chi2 = 0.77$, $p = 0.38$).

The sequential analyses of the psychosis expression subdomains revealed that total AQ was positively and significantly associated with positive, negative, and depressive symptoms in both males and females (all Bonferroni-corrected $p < 0.02$, **Table 3**). Total AQ scores explained the largest variances for negative symptoms in both males (16.49%) and females (24.52%), and smaller variances for positive symptoms (males:

10.75%; females: 12.65%) and depressive symptoms (males: 4.78%; females: 13.53%). Exploratory post-hoc sex comparison revealed a nominally statistically significant difference for the CAPE depressive subdomain, with a stronger association in females ($\chi 2 = 4.69$, $p = 0.03$) (**Table 3**). Differences in the percentages of variance explained by total SCL-90 and CAPE scores, as well as their subscales, are presented in **Figure 1**.

Table 2. Sex-stratified associations between total autistic traits and psychopathology

Outcome	Males			Females			Sex difference	
	B (95% CI)	p-value	%Variance explained	*B* (95% CI)	p-value	%Variance explained	χ^2, df(1)	p-value
Total SCL-90	0.09 (0.06 – 0.12)	**<0.001**	10.11	0.12 (0.10 – 0.15)	**<0.001**	18.73	2.84	0.09
Phobic anxiety	0.10 (0.06 – 0.14)	**<0.001**	9.48	0.13 (0.09 – 0.17)	**<0.001**	12.29	0.81	0.37
Anxiety	0.08 (0.04 – 0.12)	**<0.001**	4.93	0.12 (0.08 – 0.16)	**<0.001**	9.42	1.78	0.18
Depression	0.11 (0.07 – 0.15)	**<0.001**	8.60	0.14 (0.10 – 0.17)	**<0.001**	13.05	0.95	0.33
Interpersonal s.	0.12 (0.07 – 0.16)	**<0.001**	10.40	0.16 (0.13 – 0.19)	**<0.001**	17.57	2.80	0.09
Somatization	0.06 (0.02 – 0.10)	**0.002**	3.08	0.10 (0.07 – 0.14)	**<0.001**	8.77	3.22	0.07
Obsessive-compulsive	0.09 (0.05 – 0.13)	**<0.001**	5.60	0.15 (0.11 – 0.18)	**<0.001**	15.86	4.89	**0.03**
Paranoid ideation	0.13 (0.08 – 0.18)	**<0.001**	9.19	0.16 (0.12 – 0.21)	**<0.001**	13.53	1.12	0.29
Hostility	0.08 (0.04 – 0.12)	**<0.001**	4.70	0.13 (0.09 – 0.16)	**<0.001**	12.59	2.54	0.11
Psychoticism	0.10 (0.06 – 0.14)	**<0.001**	7.83	0.13 (0.10 – 0.17)	**<0.001**	15.04	1.79	0.18

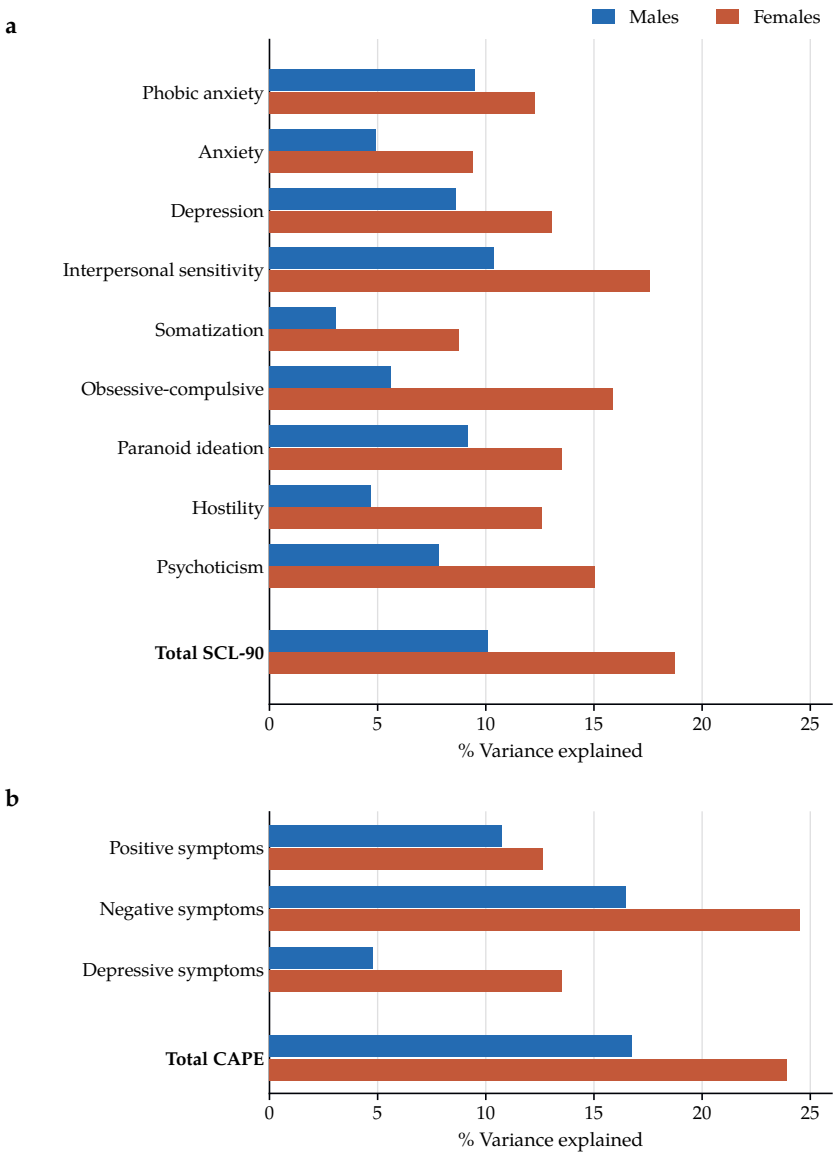
Age was added as a covariate in all models. Statistical significance (Bonferroni-corrected $p < 0.006$) is presented in bold. Bonferroni was not applied for post-hoc sex comparisons ($p<0.05$). SCL-90 Symptom Checklist-90 Revised, B unstandardized regression coefficient, SE clustered standard error, df: degrees of freedom

Table 3. Sex-stratified association between total autistic traits and psychosis expression

Outcome	Males			Females			Sex difference	
	B (95% CI)	p-value	%Variance explained	*B* (95% CI)	P value	%Variance explained	χ^2, df(1)	p-value
Total	0.11 (0.08 – 0.14)	**<0.001**	16.74	0.13 (0.10 – 0.16)	**<0.001**	23.90	0.77	0.38
Positive	0.09 (0.06 – 0.13)	**<0.001**	10.75	0.10 (0.06 – 0.13)	**<0.001**	12.65	0.02	0.90
Negative	0.15 (0.11 – 0.19)	**<0.001**	16.49	0.17 (0.13 – 0.20)	**<0.001**	24.52	0.46	0.50
Depressive	0.07 (0.03 – 0.12)	**0.001**	4.78	0.14 (0.10 – 0.18)	**<0.001**	13.53	4.69	**0.03**

Age was added as a covariate in all models. Statistical significance (Bonferroni-corrected $p < 0.02$) is presented in bold. Bonferroni was not applied for post-hoc sex comparisons ($p<0.05$). CAPE Community Assessment of Psychic Experiences, B unstandardized regression coefficient, SE clustered standard error, df degrees of freedom

Figure 1. % of variance of psychopathological domains and psychosis expression explained by total autistic traits in males and females



This figure displays the sex-stratified associations of autistic traits with psychopathology and psychosis expression: ***a*** *% variance of each symptom domain explained by total AQ;* ***b*** *% variance of each CAPE subdomain explained by total AQ*

Sex-stratified associations between AQ subscales and psychopathology

Exploratory analyses of the association between AQ subscales and psychopathology are reported in the Supplementary Material. The attention switching, communication, attention to detail, and socialization subscales showed associations with both total SCL-90 and CAPE scores across sexes. The imagination subscale was not significantly related to either total SCL-90 or CAPE in either sex. Exploratory post-hoc comparisons indicated a nominally statistically significant sex difference only for the association between attention switching and total SCL-90 ($\chi^2 = 4.87$, $p = 0.03$), with a stronger association in females.

Discussion

This study explored sex differences in the association between ATs and psychopathology in a large, general population sample of adolescents and young adults. In our primary analyses, ATs were significantly associated with increased general psychopathology (i.e., total SCL-90) and psychosis expression (i.e., total CAPE) in both males and females. No significant sex differences emerged for these associations. In the secondary analyses examining specific symptom domains, ATs were significantly associated with all SCL-90 and CAPE subdomains across sexes. However, exploratory post-hoc between-sex comparisons revealed two nominally statistically significant sex differences: ATs showed stronger associations with CAPE depressive and SCL-90 obsessive-compulsive (OC) subdomains among females compared to males. Adding to our previous report on sex-specific influence of childhood adversity in this dataset (Karaçam Doğan et al., 2026), the current study further underscores the importance of a sex-sensitive approach in gaining more insights into the development of psychopathology across the autistic continuum.

In terms of general psychopathology, our findings on significant associations of ATs with the overall and multiple subdomains of SCL-90 in both sexes support the role of ATs as a vulnerability factor for the development of a range of psychopathological conditions (Carpita et al., 2023; Dell'Osso et al., 2019; Dell'Osso et al., 2018; Demartini et al., 2024; Liew et al., 2015; Lundström et al., 2011; Martinez et al., 2021).

This also aligns with the growing hypothesis that neurodevelopmental alterations associated with autism may overlap with those underlying several other mental disorders (Carpita et al., 2023), which could account for the increased co-occurrence of various psychopathologies among individuals with high ATs. Although post-hoc analyses did not find significant sex differences in the associations of ATs with total SCL-90, a nominally statistically significant sex difference in the OC subdomain was found in the exploratory post-hoc analyses. A recent meta-analysis found that males with obsessive-compulsive disorder (OCD) are significantly more likely to meet diagnostic criteria for ASD than females (Aymerich et al., 2024). Furthermore, some studies demonstrated that patients with OCD+ASD comorbidity were more likely to be male (Martin et al., 2020), and OCD comorbidity in autistic males was higher than in autistic females (Croen et al., 2015). However, our findings in a general population sample suggest a different dynamic. One possible explanation is that studies on co-occurring conditions rely on formal clinical diagnoses of ASD, where autistic females may be under-identified due to camouflaging behaviors; this possibly explains the less likelihood to find comorbid OCD and ASD among females compared to males in clinical samples. In contrast, self-report measures in the general population may capture greater female insight, as they are more likely to acknowledge repetitive thoughts or behaviors when these cause distress. Speculatively, this could account for discrepancies in the patterns of ASD co-occurring conditions between clinical and general population samples. Furthermore, when ATs are masked, the remaining behaviors, such as rigidity, repetitive actions, or distress over disrupted routines, may be interpreted by individuals or clinicians as OC symptoms, which could partly explain the stronger association observed in females in the current study. On the other hand, the higher prevalence of OCD+ASD comorbidity reported in males (Aymerich et al., 2024; Croen et al., 2015; Martin et al., 2020) may reflect a distinct autistic OCD subtype characterized by greater severity (Bejerot, 2007). Moreover, repetitive and restrictive behaviors, which have been shown to correlate with OCD severity (Derin et al., 2025), may also be more pronounced in males. These patterns could have been underrepresented in our general population sample. Future longitudinal research, ideally combining diagnostic assessments with dimensional self-report measures, is needed to clarify whether these sex-specific patterns reflect true comorbidity or

differences in the perception and reporting of ATs.

Focusing on psychosis expression, ATs were significantly associated with total CAPE scores and all three dimensions in both females and males. Consistent with prior research, we did not find significant sex differences in the associations of ATs with positive and negative psychotic-like symptoms (Bevan Jones et al., 2012; Taylor et al., 2015). However, a nominally statistically significant sex difference emerged in the depression subdomain, with greater variance explained in females. This finding aligns with previous research suggesting that females with higher levels of ATs tend to report more frequently internalizing symptoms like depression. Notably, Kreiser and White (2015), in a general population sample, found that ATs more strongly predicted mood disorders in females than in males (Kreiser & White, 2015), supporting the notion of a sex-specific vulnerability even outside of clinically diagnosed autism. This observation is in line with clinical ASD populations, where autistic females exhibit higher rates of depression compared to autistic males (Oswald et al., 2016). Furthermore, camouflaging behaviors are more commonly reported in autistic females and have been associated with adverse mental health outcomes, including increased risk for depression and suicidality (Cassidy et al., 2020; Hull et al., 2021), potentially contributing to this heightened vulnerability. However, since camouflaging was not assessed in this sample, its contribution to higher rates of depression among females remains speculative.

Considering the SCL-90 and CAPE findings together, a notable pattern emerged across the two measures: interpersonal sensitivity was the SCL-90 domain for which AQ explained the greatest proportion of variance in both sexes (**Table 2**), while the CAPE negative dimension showed the strongest association with AQ (**Table 3**). Both dimensions capture aspects of social engagement and interpersonal functioning that are conceptually related to the social skills and communication domains of the AQ. This convergence may be understood within transdiagnostic accounts that conceptualize social difficulties as dimensions of functioning cutting across conventional diagnostic boundaries, rather than as features belonging exclusively to individual disorders (Schilbach, 2016). From this perspective, the present pattern may reflect a broader dimension of social functioning

expressed across ATs and multiple psychopathological domains. Given the heterogeneity of ATs (Barańczuk et al., 2024), and the possibility that different trait dimensions may show distinct sex-specific associations with psychopathology, we conducted exploratory analyses of AQ subscales and found a nominally stronger association between attention switching difficulties and general psychopathology in females. This is an interesting finding as sex-differences in the associations between different AT dimensions and psychopathology are largely unexplored. However, its interpretation might not be straightforward and could be complicated by the conceptual overlap between the measured constructs. Specifically, stronger associations between attention switching and overall psychopathology, as well as between total AQ and OC symptoms, among females might merely represent a common covariance between these overlapping constructs underlain by cognitive inflexibility rather than independent evidence for distinct female specific mechanisms. Alternatively, the attention switching finding may reflect a genuinely stronger association with psychopathological symptoms in females or sex-related differences in the perception and reporting of both ATs and psychological distress. Future research combining item-level analyses with neurocognitive measures of cognitive flexibility is needed to clarify the observed pattern.

Finally, ATs should not be viewed as uniformly disadvantageous, as particular autistic characteristics may have context-dependent adaptive implications. For instance, in an adult sample, attention to detail attenuated, rather than strengthened, the association between psychotic traits and depressive symptoms (Sampson et al., 2021). Autistic adults have also shown reduced susceptibility to framing effects in decision-making (De Martino et al., 2008), as well as greater generosity towards socially distant others and more consistent fairness-based allocations (Forbes et al., 2024). Moreover, higher levels of ATs have been associated with lower sensitivity to antisocial peer influence in a male adolescent cohort (Van Hoorn et al., 2017). As the present analyses focused exclusively on symptom dimensions and included no measures of strengths or adaptive functioning, future studies should examine how such characteristics relate to psychopathology and whether these associations differ by sex.

Limitations

To the best of our knowledge, this is the first study to systematically examine sex differences in the association between ATs and psychopathology in the general population, while considering a wide range of psychopathological domains. However, several limitations should be acknowledged. First, our sample was drawn from the general population, predominantly consisting of adolescents and young adults, while individuals with severe and persistent psychiatric conditions were excluded by design. The findings therefore could not be generalized to the broader adult population and to people with more severe psychopathology, including individuals with a clinical ASD diagnosis. Second, this study utilized self-report data, which may be subject to biases related to self-awareness, leading to under- or over-reporting of symptoms. Moreover, the fact that autism may manifest differently in females, particularly with lower social-communication problems than males (Wood-Downie et al., 2021), could result in under-identification of ATs using a screening tool. While the AQ is a useful instrument for preliminary screening, it does not fully capture the autistic phenotypes, particularly restricted and repetitive behaviors. Similarly, although the SCL-90 effectively assesses a range of psychopathological domains, it does not cover certain externalizing symptoms, such as hyperactivity, which is more commonly observed in autistic males and may therefore have influenced the observed sex differences. Furthermore, the use of twins and siblings' data in this study may limit the generalizability of our findings to a broader population. Nonetheless, prior research supports the inclusion of all related individuals, rather than selecting one sibling per pair, as a valid strategy for maximizing the statistical power in population-based studies (Krull, 2007). A further limitation is the potential conceptual and item-level overlap between the AQ and psychopathology measures, although previous research using the AQ and CAPE found modest and comparable correlations across all three CAPE dimensions, suggesting that overlap with negative or social withdrawal content is unlikely to fully account for the observed associations (Ziermans et al., 2021). Lastly, the cross-sectional design of our study precludes any conclusions regarding causal relationships between variables. Therefore, longitudinal studies are needed to clarify whether high ATs prospectively increase the risk of developing

psychopathology or are rather stably correlated with psychiatric symptoms due to their shared underlying neurobiology.

Conclusion

In this large general population sample, ATs were robustly associated with a broad range of psychopathological domains in both sexes, supporting their transdiagnostic role. While overall associations were comparable between males and females, exploratory post-hoc comparisons pointed to possible sex-specific patterns, with nominally stronger relationships of ATs with depressive and obsessive-compulsive symptoms in females. Similarly, attention switching difficulties were nominally more strongly associated with general psychopathology in females. These findings highlight the importance of considering sex-related differences when examining the mental health correlates of ATs, even in non-clinical populations. Considering the cross-sectional design and the exploratory nature of the domain-specific findings, future longitudinal and clinically enriched studies, ideally incorporating objective neurocognitive measures, are needed to replicate these findings, clarify their causal pathways, and explore the mechanisms underlying the observed sex-related differences.

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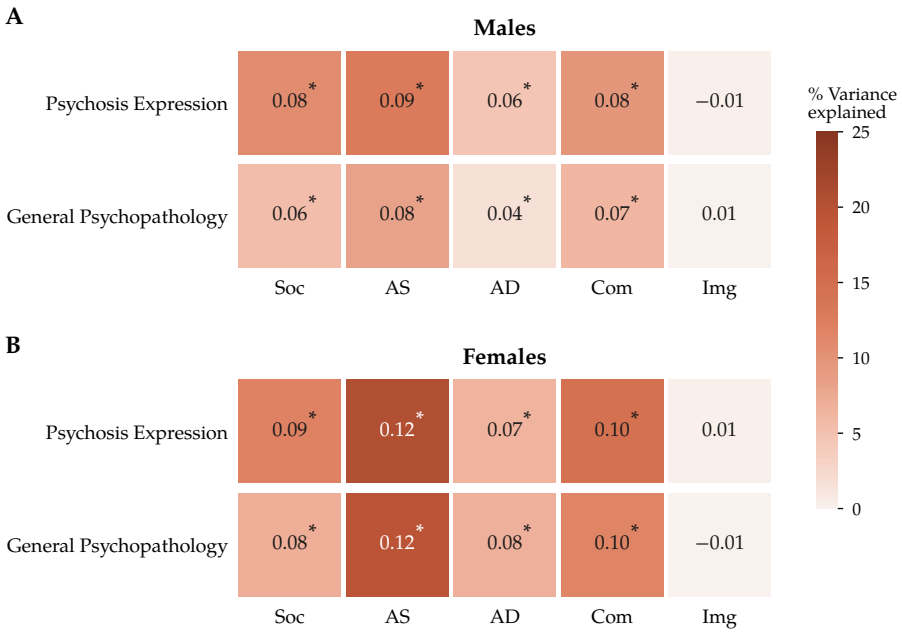
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Supplementary Table 1. Association between AQ subscales and psychopathology.

Predictor (AQ subscale)	Outcome	Males				Females				Sex difference	
		B	SE	p-value	% variance explained by AQ subscales	*B*	SE	P value	% variance explained by AQ subscales	χ^2, df(1)	p-value
Socialization	**Total SCL-90**	0.06	0.02	**<0.001**	5.54	0.08	0.01	**<0.001**	7.10	0.48	0.49
	Total CAPE	0.08	0.02	**<0.001**	10.76	0.09	0.02	**<0.001**	11.96	0.13	0.72
Attention switching	**Total SCL-90**	0.08	0.02	**<0.001**	8.23	0.12	0.01	**<0.001**	19.52	4.87	**0.03**
	Total CAPE	0.09	0.02	**<0.001**	12.90	0.12	0.01	**<0.001**	20.54	1.15	0.28
Attention to detail	**Total SCL-90**	0.04	0.01	**0.02**	1.73	0.08	0.01	**<0.001**	6.87	3.72	0.05
	Total CAPE	0.06	0.01	**<0.001**	4.74	0.07	0.01	**<0.001**	6.51	0.38	0.54
Communication	**Total SCL-90**	0.07	0.02	**<0.001**	6.20	0.10	0.01	**<0.001**	11.80	2.53	0.11
	Total CAPE	0.08	0.02	**<0.001**	9.76	0.10	0.01	**<0.001**	14.57	0.74	0.39
Imagination	**Total SCL-90**	0.01	0.01	0.67	0.06	-0.01	0.02	0.66	0.05	0.37	0.54
	Total CAPE	-0.01	0.01	0.58	0.13	0.01	0.02	0.60	0.11	0.65	0.42

Age was added as a covariate in all models. Statistical significance (Bonferroni-corrected $p < 0.03$) is presented in bold. Bonferroni was not applied as these analyses were exploratory ($p<0.05$). CAPE Community Assessment of Psychic Experiences. SCL-90 Symptom Checklist-90 Revised. B unstandardized regression coefficient. SE clustered standard error.

Supplementary Figure 1. % Variance explained by AQ subscales in psychosis expression and psychopathology by sex



The figures display the variance in psychosis expression (CAPE total scores) and general psychopathology (SCL-90 total scores) accounted for by each AQ subscale in males (A) and females (B). Unstandardized regression coefficients (Beta) are presented, with significant associations indicated by asterisks. All analyses were adjusted for age. Abbreviations: Soc = socialization, AS = attention switching, AD = attention to detail, Com = communication, Img = imagination.

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Chapter 6

Discussion

This thesis aims to investigate the role of environmental exposures (both risk and protective factors) in shaping the association between autistic traits (ATs) and psychopathology, by integrating results from four empirical studies.

It contributes to this field in four main ways. First, it evaluates how childhood trauma and other environmental risks moderate the relationship between ATs and psychosis expression (PE) in the general population **(Chapter 2)**. Second, it investigates psychological protective factors, such as coping, extroverted personality traits, and optimal parenting, as potential buffers in this association, thereby extending the scope of the thesis to resilience frameworks **(Chapter 3)**. Third, it examines sex-specific pathways on PE, with attention to sex differences in both risk (e.g., childhood trauma types) and resilience (e.g., coping strategies) factors **(Chapter 4)**. Finally, it investigates sex differences in the association between ATs and psychopathological domains **(Chapter 5)**. By combining these perspectives, this thesis provides novel analyses on exposome to clarify the complex, multidimensional relationship between ATs and PE **(Chapters 2–3),** a PE-focused sex-differences study (Chapter 4), and a broader investigation of sex differences in AT–psychopathology associations beyond the exposome framework (Chapter 5).

6.1 Dimensional, Transdiagnostic, and Spectrum Approaches to Autism and Psychosis

A central theme of our findings is that they align with dimensional and transdiagnostic models of psychopathology. Rather than treating autism, psychosis, and other disorders as discrete, unrelated categories, our results support the view that there are continuous dimensions of risk and expression. We observed associations between ATs and a broad range of symptoms (such as psychotic, affective, obsessive-compulsive) in the general population. This pattern aligns well with transdiagnostic frameworks, such as the NIMH's Research Domain Criteria (RDoC) (Insel et al., 2010), and evidence supporting the conceptualization of psychosis and autism as spectrum conditions (Guloksuz & Van Os, 2018; Lord et al., 2018).

The RDoC initiative proposes studying mental health phenomena in terms of multidimensional constructs (e.g., social communication, cognitive control, perception/understanding of self) across the general and clinical populations, rather than within a traditional categorical diagnosis (Cuthbert, 2014). We also treated autism-related characteristics (such as social/communication problems and attention difficulties) and psychotic experiences (such as mild hallucination-like perceptions and paranoid thoughts) not as separate entities but rather as interrelated dimensions present at varying degrees across the whole population. Accordingly, the observed association between ATs and PE may reflect shared underlying transdiagnostic processes (such as social/communication problems or cognitive inflexibility) that align with RDoC constructs, while shared environmental risk factors (such as trauma, bullying, or stressful life events) and protective factors may further shape these associations.

The results reported in **Chapters 2–4** are in line with the concept of a psychosis continuum in the population (Guloksuz & Van Os, 2018). We found that subclinical psychotic experiences (like mild hallucinations or delusional ideation reported on the CAPE) are associated with higher ATs. These experiences share risk factors with clinical psychosis, such as childhood trauma (Janssen et al., 2004). It also underlines that these mental phenomena can arise from the interaction of dimensional traits and life stress in the general population, a perspective that helps destigmatize these experiences as part of a spectrum of human experiences under certain conditions. This thesis also suggests that environmental risk factors may represent promising targets for preventive strategies aimed at improving outcomes. Rather than seeing psychosis risk as fixed or only relevant once a threshold is crossed, a continuum view combined with our findings implies that we might reduce PE and prevent its progression by acting early on environmental factors, especially among people with high ATs.

6.2 The Role of Childhood Trauma as Moderator

Autistic individuals are known to be disproportionately exposed to childhood adversity compared to their typically developing peers (Hoover & Kaufman, 2018). **Chapter 2** of this thesis demonstrated that

certain childhood trauma subtypes amplify the association between ATs and PE in the general population. Among these, emotional abuse emerged as the only adversity type that interacted with ATs across all PE dimensions, suggesting a transdiagnostic role.

These findings support a shift toward integrative theories of psychopathology that bridge neurodevelopmental and environmental perspectives. The evidence that ATs (a neurodevelopmental factor) and childhood trauma (an environmental factor) interact to influence psychosis risk suggests that diathesis–stress models remain highly relevant (Pruessner et al., 2017). Autism-related characteristics may represent a developmental diathesis that, when met with significant stress, increases risk for severe outcomes, like psychosis.

In autistic individuals, increased vulnerability to childhood trauma stems both from autism-specific characteristics (e.g., social communication difficulties, sensory hypersensitivity, and elevated stress responsivity) and from external factors such as exclusionary social attitudes and limited support systems (Kerns et al., 2022; Peterson et al., 2019). Importantly, trauma in autism may not follow the classical PTSD symptom profile. Instead, it can manifest through behavioral changes, increased stereotypies, regression in social skills, or sleep and eating disturbances. These atypical expressions risk being misinterpreted as part of the autism phenotype itself, thereby obscuring trauma histories (Brenner et al., 2018). Although it is well recognized that identifying and addressing trauma in autistic individuals is challenging, the literature on this subject remains limited. Current findings highlight the necessity of adapting trauma-focused psychoeducation and psychotherapeutic interventions to the specific needs of autistic individuals. Early awareness and screening, parent education programs that promote secure attachment, collaboration with educational and healthcare systems, and social skills training have been highlighted as promising preventive strategies (Peterson et al., 2019).

Overall, this thesis demonstrates that childhood trauma is not merely a background risk but also a moderator of how ATs shape vulnerability to psychosis. Building on this, **Chapter 3** took a preventive and protective perspective by focusing on coping,

personality traits, and parenting as moderators of the AT–PE association, although trauma itself was not directly assessed.

6.3 Psychological Protective Factors

Most psychiatric research has traditionally focused on risk factors; however, our findings emphasize that protective factors also deserve attention, particularly within a transdiagnostic framework. **Chapter 3** showed that several modifiable psychological factors buffered the impact of ATs on PE. In particular, engagement coping mechanisms (e.g. seeking social support), extraversion and optimal parenting significantly weakened the AT–PE association. Conversely, maladaptive coping strategies (notably avoidance and passive-reacting) strengthened the AT–PE association.

Our observations are consistent with classic resilience models, which emphasize that individuals facing significant challenges or predispositions can nonetheless achieve positive outcomes if protective resources are present (Masten, 2014). Conversely, the exacerbating effect of maladaptive coping strategies aligns with the diathesis–stress framework and the concept of stress reactivity as a psychosis vulnerability marker (Myin-Germeys et al., 2001; Nuechterlein & Dawson, 1984; Pruessner et al., 2017). Individuals with neurodevelopmental predispositions and poor coping capacities may exhibit heightened sensitivity to stress, making them more prone to psychotic experiences under lower levels of stress. Indeed, one interpretation of our moderation results is that engagement coping might raise the threshold for psychosis expression by making individuals more resilient to stress, whereas passive-reacting and avoidance lower that threshold. Notably, some of the identified protective factors, such as extraversion, are broadly beneficial and not disorder-specific, supporting the notion that resilience processes operate transdiagnostically. For instance, extroverted personality traits may reduce the likelihood of multiple adverse outcomes (e.g., psychosis and depression) among individuals with high ATs. Moreover, integrating the findings from **Chapter 4**, we observed that resilience (e.g., coping) and risk (e.g., trauma) factors influence PE differently across sexes, underscoring the importance of considering sex-specific resilience mechanisms in psychosis research. As a

conclusion, the presence of resilience factors may thus help explain why many individuals with elevated ATs do not develop serious psychopathology.

In practical terms, these findings highlight the clinical relevance of systematically assessing not only risk but also protective factors within the autism–psychosis continuum. While traditional assessments often focus on established psychosis risk factors (e.g., family history, childhood trauma), our results emphasize the value of evaluating resilience-related domains such as coping strategies, social support, and personality traits. Incorporating these dimensions into clinical practice may contribute to more integrative prevention and intervention strategies, for example, by promoting adaptive coping styles or strengthening social skills to enhance resilience in individuals with elevated ATs.

6.4 Studying Sex Differences in Autism-Psychosis Research

According to the Sex and Gender Equity in Research (SAGER) guidelines (Heidari et al., 2016), researchers are encouraged to explicitly account for sex and gender in study design, analysis, and interpretation to improve reproducibility and equity in scientific evidence. In line with SAGER principles, the present thesis incorporated sex-stratified analyses to investigate potential differences in how ATs, environmental risk factors, and psychological mechanisms contribute to psychopathology. This approach acknowledges that sex might shape developmental trajectories and risk–resilience profiles.

6.4.1 Are there any sex differences in the association of childhood trauma and coping with psychosis expression?

Evidence across psychiatric epidemiology indicates pronounced sex differences in the onset, expression, and course of psychotic disorders. Males typically present earlier, with more severe negative symptoms and poorer functional outcomes, whereas females often show later onset and greater affective involvement (Abel et al., 2010). At the subclinical level, males tend to exhibit more pronounced negative symptoms than females and they also report poorer premorbid functioning and lower levels of social support. By contrast, female sex

has been identified as an independent predictor of affective psychotic presentations (Barajas et al., 2015).

Females are more frequently exposed to childhood sexual abuse (Stoltenborgh et al., 2015), whereas childhood neglect appears more strongly associated with mental health outcomes in males (Prachason et al., 2024). Resilience factors (such as coping) show notable sex differences as well. Females generally employ a wider repertoire of coping strategies, especially emotion-focused coping like seeking social support and expressing emotions (Bucci et al., 2023; Eschenbeck et al., 2007; Tamres et al., 2002), whereas males are more likely to rely on avoidance coping (Eschenbeck et al., 2007). Our findings (**Chapter 4**) supported this pattern: sexual abuse was linked to higher psychosis expression in females, and physical neglect in males. Moreover, coping moderated these associations differently by sex. Seeking social support, reassuring thoughts and palliative-reacting buffered adversity effects in females, while avoidance amplified the impact of sexual and physical abuse in males.

These differences likely reflect the interplay of biological vulnerability and psychosocial processes. Biological accounts emphasize chromosomal, hormonal, and neurobiological mechanisms. For instance, neuroimaging evidence suggests that childhood sexual abuse in psychosis is most strongly associated with auditory hallucinations in females, potentially mediated by greater limbic gray matter volume, possibly pointing to a sex-linked neurobiological pathway (Millman et al., 2022). Conversely, male hippocampal volume has been linked to neglect rather than abuse, whereas in females, abuse (but not neglect) during adolescence shows stronger hippocampal associations (Teicher et al., 2018).

Psychosocial explanations complement this view by emphasizing gendered socialization. From early childhood, girls are typically encouraged toward more emotional communication and tenderness, whereas boys are socialized toward more physical exploration and toughness (Christiansen et al., 2022; Rosario et al., 1988). Structural models propose that socially defined gender roles expose individuals to distinct types of stressors and challenges, each eliciting different coping strategies (Christiansen et al., 2022; Ptacek et al., 1992). These

patterns might shape both vulnerability and resilience to trauma and may partly account for sex differences in mental health outcomes.

Taken together, these observations underscore that integrating both risk and resilience mechanisms within sex-informed models is therefore essential to understand how childhood trauma and coping shape psychosis risk in the general population.

6.4.2 Sex Differences in the Association of ATs and Psychopathology

In autism spectrum conditions, sex differences are similarly profound yet historically understudied. However, recent "female autism phenotype" literature emphasizes that ATs in females may be subtler, manifesting as internalizing distress, social mimicry, or camouflaging strategies (Hull et al., 2021; Lai et al., 2015). Consequently, females are often under-diagnosed or misdiagnosed, and their specific needs remain insufficiently addressed. Understanding these differences is essential not only for diagnostic accuracy but also for clarifying how ATs relate to broader psychopathology across sexes.

Chapter 5 demonstrated sex differences in the association between ATs and psychopathology. While both sexes showed significant associations, certain dimensions (particularly depressive and obsessive-compulsive symptoms) were more strongly linked to ATs in females. This accords with prior work showing autistic girls and women tend to experience more internalizing problems, such as depression (Fusar-Poli et al., 2022; Vadukapuram et al., 2022). The finding regarding obsessive-compulsive symptoms seems counterintuitive given that clinically, autism co-occurring with OCD is often reported more in males (Aymerich et al., 2024; Martin et al., 2020); yet our result may reflect that subclinical OC tendencies in high-AT females are under-recognized but contribute strongly to their psychopathology.

Integrating these findings within psychosis-spectrum frameworks, our study suggests that ATs in females might be explained more closely by an "affective dysregulation" pathway (Myin-Germeys & van Os, 2007), as the association between ATs and the CAPE depressive subdomain was stronger in females than in males, whereas no comparable sex differences were observed for the other CAPE

subdomains. From a transdiagnostic perspective, the results highlight that some mechanisms tied to ATs can transcend diagnoses, increasing risk for various mental health problems rather than a single comorbid disorder. This is important because it suggests that interventions targeting those mechanisms (for example, interventions to improve emotion regulation or flexibility in autistic individuals) might confer protection against multiple forms of psychopathology simultaneously, rather than requiring separate interventions for each potential disorder.

Altogether, these patterns highlight that ATs elevate risk across a spectrum of mental health outcomes, but the manifestation of that risk can be sex-specific. Recognizing these differences is important for tailoring interventions such as addressing internalizing distress in autistic females, and monitoring repetitive/compulsive behaviors that might otherwise be overlooked as mere autistic routines.

6.5 Methodological Concerns and Future Directions

In this thesis, I examined how environmental and psychological factors interact with ATs to influence psychopathology, thereby contributing to the growing literature on the exposome framework in neurodevelopmental and psychosis research. However, several methodological considerations should be acknowledged.

First, all studies employed a cross-sectional design, which restricts the ability to make causal inferences. Although the findings suggest that childhood trauma **(Chapter 2)** and protective factors (coping, parenting, and extraversion) (**Chapter 3**) moderate the relationship between ATs and PE, it is not possible to determine the temporal sequence of these associations. Longitudinal studies following individuals from early development into adulthood are warranted to identify critical periods when environmental exposures exert the strongest influence on mental health trajectories, specifically psychosis.

Second, the reliance on self-report measures introduces potential recall and reporting biases. Retrospective assessments may be influenced by current emotional states, and self-reported ATs might not fully capture the social-communication difficulties of individuals who camouflage,

particularly females. Incorporating informant reports, clinical interviews, and objective behavioral or biological measures would strengthen the validity for future studies.

Third, some caution is warranted regarding potential measurement overlap between the instruments used to assess ATs and PE. Although some conceptual overlap exists between autism and psychosis-related measures (Chisholm et al., 2015), the most substantial overlap is generally considered to involve autistic social/communicative deficits and negative symptoms (Zhou et al., 2020). In the present study, this is most likely between the AQ social skills subscale and the social withdrawal items of the CAPE negative dimension. Although such similarity may contribute to the observed association between ATs and PE, several findings suggest that it is unlikely to account for the results. Previous studies using the same instruments have reported comparable correlations across the positive, negative, and depressive CAPE dimensions (r=0.32–0.36) (Ziermans et al., 2021), arguing against shared measurement content as the primary explanation. Moreover, in the present thesis these associations and moderation effects were also evident for the CAPE positive dimension and its five-factor structure. In Chapter 3 they further held when PE was weighted by distress, an appraisal dimension that the AQ does not assess at all, making it unlikely that the findings merely reflect shared item wording. Nevertheless, future studies would benefit from item-level analyses, instruments specifically designed to distinguish autistic and psychotic traits, and clinician- or informant-rated assessments.

Fourth, the characteristics of the sample limit the generalizability of our findings. Participants were mainly adolescent twins and siblings from the general population, predominantly of White European background. This design provides a valuable opportunity to study traits and symptoms dimensionally, yet it may not reflect clinical or ethnically diverse populations. Nonetheless, previous research has shown that including all individuals, rather than restricting analyses to one sibling per twin pair, represents a valid approach to maximize statistical power in population-based studies (Krull, 2007). In this thesis, I followed this recommendation while accounting for the non-independence of

twin data through appropriate statistical methods and corrections. However, future studies should aim to confirm these findings in larger, more heterogeneous cohorts and in individuals at different points along the autism–psychosis continuum.

Finally, longitudinal and experimental designs are needed to test causal hypotheses. Prospective cohort studies could clarify mediation pathways, while intervention trials (such as programs teaching adaptive coping to high-AT adolescents with trauma histories) could directly examine whether strengthening protective factors alters outcomes. Taken together, these methodological and conceptual directions will move the field beyond correlational evidence toward identifying causal mechanisms and modifiable targets. Such progress will refine theoretical models of the autism-psychosis continuum and inform preventive, resilience-oriented interventions for neurodivergent populations.

6.6 Conclusion

The first part of this thesis demonstrates that environmental adversity, particularly childhood trauma, plays a significant role in shaping the association between ATs and PE in the general population. The second part highlights the importance of psychological protective mechanisms that buffer this association and promote resilience despite neurodevelopmental vulnerability. The third and fourth parts investigate potential sex differences in these relationships, showing that the impact of exposures may manifest differently in males and females, emphasizing the need for sex-sensitive approaches in future research. These results highlight that ATs do not operate in isolation but within a broader exposomic and psychosocial context. Integrating environmental and psychological dimensions thus provides a more comprehensive understanding of the autism–psychopathology continuum and offers potential targets for preventive and resilience-oriented interventions in neurodivergent populations.

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Chapter 7

Summary
Samenvatting

Grounded in dimensional and transdiagnostic frameworks, the work conceptualized both autism and psychosis as continuously distributed phenomena rather than discrete diagnostic categories, and adopted an exposome perspective to investigate how genetic, environmental, and psychological factors influence mental health outcomes. **Chapter 2** investigated whether genetic liability for schizophrenia and established environmental risk factors moderate the association between autistic traits (ATs) and psychosis expression (PE). The findings demonstrated that childhood trauma (CT) strengthened the association between ATs and PE, whereas polygenic risk for schizophrenia and other environmental risk factors did not substantially modify this relationship. Analyses across psychosis subdomains (positive, negative, and depressive) showed that CT subtypes interacted with ATs on positive symptoms, while emotional abuse emerged as the only CT subtype that significantly strengthened the association of ATs with all psychosis domains.

Chapter 3 shifted the focus from risk to resilience by examining psychological protective mechanisms. It investigated whether coping strategies, extroverted personality traits, and perceived parenting quality buffered the association between ATs and PE. The results indicated that engagement coping styles (such as seeking social support and reassuring thoughts), extraversion, and optimal parenting attenuated this association, whereas disengagement coping strategies, including passive-reacting coping and avoidance, were associated with a stronger association.

Chapter 4 investigated sex differences in the associations between childhood adversity, coping strategies, and psychosis expression. Several shared and sex-specific patterns were identified. Emotional abuse emerged as a trans-syndromal risk factor in both sexes, while the association between physical neglect and PE was observed specifically in males. Passive-reacting coping was linked to higher levels of PE in both sexes. Among females, seeking social support, reassuring thoughts, and palliative-reacting coping were more strongly associated with lower symptom levels, whereas in males maladaptive coping patterns, such as avoidance, were associated with worse outcomes.

Chapter 5 investigated sex differences in the association between ATs and a broad range of psychopathological symptoms in the general population. Higher levels of ATs were associated with increased psychopathology domains in both sexes; however, the associations for depressive and obsessive–compulsive symptom domains were more pronounced in females.

Op basis van dimensionele en transdiagnostische kaders conceptualiseert dit werk autisme en psychose als continu verdeelde fenomenen, in plaats van als discrete diagnostische categorieën. Dit werk hanteert een exposoomperspectief om te onderzoeken hoe genetische, omgevings- en psychologische factoren mentale gezondheidsuitkomsten beïnvloeden. **Hoofdstuk 2** onderzoekt of genetische kwetsbaarheid voor schizofrenie en gevestigde omgevingsrisicofactoren de associatie tussen autistische trekken (AT's) en psychose-expressie (PE) modereren. De bevindingen tonen aan dat jeugd trauma (JT) de associatie tussen AT's en PE versterkt, terwijl polygenetisch risico voor schizofrenie en andere omgevingsrisicofactoren deze relatie niet substantieel beïnvloeden. Analyses van de psychose-subdomeinen (positief, negatief en depressief) laten zien dat subtypen van JT met AT's een interactie hebben ten aanzien van positieve symptomen, terwijl emotionele mishandeling naar voren komt als het enige JT-subtype dat de associatie tussen AT's en alle psychosedomeinen significant versterkt.

Hoofdstuk 3 verlegt de focus van risico naar veerkracht door psychologische beschermende mechanismen te onderzoeken. Het onderzoekt of copingstrategieën, extraverte persoonlijkheidstrekken en ervaren kwaliteit van opvoeding de associatie tussen AT's en PE bufferen. De resultaten geven aan dat het opzoeken van sociale steun , geruststellende gedachten, extraversie en optimale opvoeding deze associatie verzwakken, terwijl een passief reactiepatroon en vermijden geassocieerd zijn met een sterkere associatie tussen AT's en PE.

Hoofdstuk 4 onderzoekt sekseverschillen in de associaties tussen JT, copingstrategieën en psychose-expressie. Zowel gedeelde als seksespecifieke patronen worden vastgesteld. Emotionele mishandeling komt naar voren als een transsyndromale risicofactor bij beide seksen, terwijl de associatie tussen lichamelijke verwaarlozing en PE specifiek bij mannen wordt waargenomen. Een passief reactiepatroon is bij beide seksen geassocieerd met hogere niveaus van PE. Bij vrouwen zijn het opzoeken van sociale steun, geruststellende gedachten en een palliatieve reactie sterker geassocieerd met lagere symptoomniveaus, terwijl bij mannen maladaptieve copingstrategieën, zoals vermijden, geassocieerd zijn met ongunstigere uitkomsten.

Hoofdstuk 5 onderzoekt sekseverschillen in de associatie tussen AT's en een breed scala aan psychopathologische symptomen in de algemene bevolking. Hogere niveaus van AT's zijn bij beide seksen geassocieerd met verhoogde niveaus van psychopathologie; de associaties met depressieve en obsessief-compulsieve symptomen zijn echter meer uitgesproken bij vrouwen.

Chapter 8

Impact

The prevalence of autism spectrum disorder (ASD) has shown a consistent increase over time (Solmi et al., 2022), with current global estimates suggesting it affects about 1% of the general population (Zeidan et al., 2022), approximately 1 in every 36 children in the United States (Maenner et al., 2023). Subclinical autistic traits (ATs) are increasingly recognized in the general population as well (Constantino & Charman, 2016), with growing awareness that these traits, even below diagnostic thresholds, may increase susceptibility to a range of mental health problems (Carpita et al., 2023; Liew et al., 2015; Lundström et al., 2011; Martinez et al., 2021).

Traditionally, autism and psychosis have been investigated in isolation. This thesis aims to bridge these domains by demonstrating that ATs and psychosis expression (PE) are meaningfully connected within a shared, dimensional framework. It further highlights how environmental exposures (both risk and protective factors) shape these associations. This work also deepens this framework by applying a sex-sensitive perspective, demonstrating that vulnerability and resilience processes relevant to PE can differ by sex. Moreover, it assesses sex differences in the associations between ATs and broader psychopathology domains, adopting a transdiagnostic perspective. Integrating evidence from developmental psychopathology and exposome research, this work contributes to a more unified understanding of how neurodevelopmental vulnerability interacts with environmental exposures to shape mental health trajectories.

This thesis has several implications for clinical practice. For one, our findings encourage proactive mental health monitoring in individuals with high ATs, even if they do not meet full ASD criteria. Clinicians working with autistic or high-AT youth should be aware that these individuals may be at elevated risk not only for social or behavioral difficulties, but also for other psychiatric problems (such as anxiety, depression) and even psychotic symptoms, especially if they have a history of childhood trauma. These findings support the consideration of structured screening and monitoring approaches in this population. Evidence indicates that subthreshold psychotic symptoms are frequently underdetected due to symptom overlap and diagnostic overshadowing, supporting the value of psychosis risk screening in this population (Mammarella et al., 2024).

Similarly, assessment of childhood trauma may help identify individuals who could benefit from further trauma-informed evaluation and support. However, translating such approaches into routine clinical practice involves several challenges. Trauma-related symptoms may overlap with ATs and be influenced by developmental and communication differences, while psychosis risk screening may be complicated by difficulties in distinguishing true risk from false positives, as well as by limited clinician confidence and barriers to referral (Kerns et al., 2023; Quinton et al., 2024; Radez et al., 2023). Screening should therefore be followed by a more detailed assessment and, when needed, referral to appropriate services, especially because autism and psychosis can be difficult to distinguish in routine clinical practice (Keeshin et al., 2020; Watson et al., 2026). When clinically significant trauma-related difficulties are identified, autistic children and adolescents should receive interventions that address those experiences, such as trauma-focused cognitive behavioral therapy, rather than having their difficulties attributed solely to autism (Peterson et al., 2019).

In terms of interventions, the moderators we identified highlight several targets such as enhancing social support and teaching adaptive coping strategies. For example, social skills training groups for adolescents with ATs and therapies that explicitly coach engagement coping might be particularly beneficial. This also suggests that sex differences should be considered when designing trauma-focused interventions, to account for sex-specific coping profiles and symptom expression. Recognizing sex differences in autism-related presentations, such as the greater internalizing vulnerability and camouflaging in autistic females, is further needed for personalized preventive interventions.

From a public health perspective, this thesis highlights the importance of addressing modifiable social and environmental factors to prevent the onset and persistence of psychopathology. Reducing child abuse and neglect is an obvious societal goal in itself, but our findings emphasize that doing so, especially in neurodevelopmentally susceptible individuals, could have compounded benefits in preventing the cascade that leads to serious mental illness. The findings reinforce the value of integrating preventive strategies (such as parenting support, school-based resilience programs, and trauma-

responsive educational practices) into mental health policy. Importantly, the observed sex differences also underline the need for sex-sensitive prevention and early intervention approaches, as risk and resilience profiles may differ by sex. Sex-sensitive and neurodiversity-informed service planning may reduce stigma and access barriers, enabling more equitable and individualized care. The ultimate clinical takeaway is optimistic: it suggests that even when risk factors like neurodevelopmental vulnerabilities and trauma are present, positive environmental and psychological influences can shift outcomes toward a healthier trajectory.

In conclusion, the impact of this thesis is multifaceted. It contributes to a future in which autism and psychosis are not seen as disparate phenomena, but as part of a complex continuum of human experiences influenced by the environment we live in. Moreover, it shows that people may benefit from support that is adapted to sex-specific patterns of vulnerability and resilience. Ultimately, this work advances a broader goal of contemporary psychiatry: to move beyond reactive treatment toward proactive, resilience-oriented, and sex-sensitive strategies that promote mental well-being and personalized care.

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Appendix

Curriculum Vitae
List of Publications
Acknowledgements

Curriculum Vitae

Melike Karaçam Doğan was born on July 16th, 1992, in Ankara, Türkiye. She received her medical degree from Hacettepe University Medical School in 2016 and completed her psychiatry residency at the Department of Psychiatry, Hacettepe University, from 2017 to 2021. Since 2022, she has worked as a psychiatrist, and in 2026, she returned to the Department of Psychiatry at Hacettepe University as an Assistant Professor.

Melike joined the Mental Health and Neuroscience Research Institute at Maastricht University as a visiting researcher through the TÜBİTAK 2219 International Postdoctoral Research Fellowship Program and subsequently enrolled as a PhD candidate. She received the Excellence Award from the European College of Neuropsychopharmacology in 2025 and the Early Career Award from the Schizophrenia International Research Society in 2026. Under the supervision of Dr. Sinan Gülöksüz, her PhD project investigated the role of the exposome in the association between autistic traits and psychosis in the general population.

List of Publications

Peer-reviewed publications

Karaçam Doğan M, Prachason T, Scalmati S, Lin BD, Pries LK, Klingenberg B, Arias-Magnasco A, Menne-Lothmann C, Decoster J, van Winkel R, Collip D, Delespaul P, De Hert M, Derom C, Thiery E, Jacobs N, Wichers M, Rutten B, van Os J, Fusar-Poli L, Guloksuz S. (2026). Examining the association between autistic traits and psychopathology in the general population: are there sex differences? *European Archives of Psychiatry and Clinical Neuroscience*, Advance online publication.

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Research Awards and Other Recognitions

2026 SIRS Early Career Award

2025 ECNP Excellence Award

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2019 EFPT Exchange Programme

2014 Şeref Zileli Intern of the Year Award

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