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The Moderating Role of Genetic and Environmental Risk Factors for Schizophrenia on the Association Between Autistic Traits and Psychosis Expression in a General Population Twin Sample

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1. Abstract

This study aimed to investigate the moderating role of genetic and environmental risk factors for psychosis on the relationship between autistic traits (AT) and psychotic-like experiences (PLEs) in the general population. We analyzed the first-wave data from twins and siblings participating in the TwinssCan Project (n=792). PLEs and AT were assessed using the Community Assessment of Psychic Experiences and the Autism-Spectrum Quotient, respectively. The main effects of polygenic risk scores for schizophrenia and individual psychosis-associated environmental risk factors (i.e., childhood trauma (CT), bullying, negative life events, obstetric complications, cannabis use, winter birth, and hearing impairment) and their interacting effects with AT were tested in separate models, using multilevel linear regression. Confirming prior literature, the results showed that AT, all five CT subtypes, bullying, and negative life events were significantly associated with PEs (all $P < 0.004$). The interaction analyses revealed that 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 amplified the positive relationship between AT and PEs, whereas 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, $P = 0.04$) only showed a trend of interactions. No significant main or interacting effects of genetic and other risk factors were found. Such findings imply that CT might be a potential preventive target for psychosis expression in people with high AT.

2. Introduction

Symptoms of autistic traits and psychotic-like experiences often may overlap, suggesting underlying shared pathological mechanisms at work. Considering the vast exogeneous and

endogenous factors which might influence onsets of both conditions, as well as the aims of this study, the introduction will focus on describing both autism spectrum disorder and psychosis, with respect to autistic traits and psychotic-like experiences, together with environmental and genetic factors which might influence them and were used as moderating factors in this research.

2.1. Psychosis

The psychosis syndrome is marked by a disturbance of high mental functions. It encompasses a wide array of symptoms, including deficits in attention, memory, social cognition, and executive functions, but also delusional ideation, disorganized behavior and speech, affective flattening/loss of initiative, social and occupational impairment, and hallucinatory experiences (Kahn et al., 2015). Psychotic-spectrum disorders (also known as schizophrenia spectrum disorders, according to the international diagnostic classifications) include schizophrenia, affective psychosis, schizoaffective disorder, schizoid, schizotypal, and paranoid personality disorders, and psychotic disorder induced by substances (Pedrero, Debbané, 2017).

The DSM-5 mentions schizophrenia spectrum and other psychotic disorders as being defined by abnormalities in at least one of the following domains: hallucinations, delusions, grossly disorganized or abnormal motor behavior (including catatonia), disorganized thinking (speech), and negative symptoms (American Psychiatric Association, 2013). The defining characteristic of these disorders is psychosis. The ICD-10 and the DSM-5 state that psychosis diagnosis requires presence of either delusions or hallucinations (without insight into pathologic nature), or presence of both delusions and hallucinations (American Psychiatric Association, 2013; World Health Organization, 1992). Hallucinations are vivid perception-like experiences which take place without an external stimulus, and which are not under one's voluntary control. Hypnagogic and hypnopompic hallucinations are within the range of normal perceptive

experience, meaning that psychotic hallucinations must occur in the fully conscious state. The most common hallucinations in schizophrenia spectrum and other psychotic disorders are auditory hallucinations. These usually occur as voices which are distinguished from one's own thoughts (American Psychiatric Association, 2013). Delusions are fixed beliefs held with full subjective certainty even when an individual is presented with contradictory evidence. Most frequent delusions include nihilistic, erotomanic, referential, somatic, religious, grandiose, and persecutory delusions (American Psychiatric Association, 2013).

Besides being a main characteristic in schizophrenia spectrum, psychosis is also present in individuals with bipolar disorder (manic or depressive episodes), during withdrawal or intoxication from substances, and in individuals with obsessive-compulsive disorder (Arciniegas, 2015). Psychosis may also occur in individuals with neurocognitive disorders, such as Parkinson's disease, diffuse Lewy body disease, Huntington's disease, Alzheimer's disease, HIV, frontotemporal lobar degeneration, cerebrovascular disease, traumatic brain injuries, and substance abuse (Arciniegas, 2015). Ultra-high-risk individuals, as well as non-affected first-degree relatives, and healthy individuals with PLEs show negative symptoms and alterations in perceptual and cognitive functions in the prodromal phase (Evermann et al., 2020).

2.1.1. Psychotic-Like Experiences

Though psychosis first used to be seen as a bimodal construct (either no symptoms or clinically significant symptoms), today's theories suggest the existence of the psychosis continuum (Chapman et al., 2020). The continuum assumes that psychotic symptoms range continuously, from less severe symptoms that do not require care to more severe, significant symptoms that allow a clinical diagnosis. Psychotic-like Experiences (PLEs) make up the lowest end of the

psychosis continuum (Chapman et al., 2020). PLEs include both delusional experiences, and hallucinatory experiences (McGrath et al., 2015). There are six types of PLEs in the Composite International Diagnostic Interview (CIDI) Psychosis Module. Four types relate to delusional experiences. These include two paranoid delusional items (plot to harm/follow, ideas of reference), and two bizarre delusional items (thought withdrawal/insertion, mind control/passivity). Another two types included in the module regard the hallucinatory experiences, any they cover auditory and visual hallucinations (McGrath et al., 2015).

Both PLEs and schizotypal traits are seen as indicators for developing psychosis (Pedrero, Debbané, 2017). Van Os and colleagues proposed the persistent-proneness model to explain the connection between PLEs and clinical psychotic disorder. They state that PLEs are common and short-lived, but that they might persevere and progress via biological and psychological sensitizations which arise as a result of environmental stress. Exposure to long-term, severe environmental stress may cause the transformation of PLEs from transient to persistent, leading to severe impairment and clinical diagnosis (Van Os et al., 2009).

Besides psychosis, PLEs have been associated with the development of substance use disorders, anxiety and mood disorders, and suicidal ideation and suicidal intent (Varghese et al., 2011; Saha et al., 2011). The main characteristics of PLEs are that they usually disappear in adolescence and that they are unstable in their nature (Pedrero, Debbané, 2017). It should be highlighted that PLEs refer to abnormal experiences in perception within the positive dimension of psychosis – they include delusions and hallucinations. Unlike schizotypal traits which are stable in time and include abnormalities across Disorganized, Cognitive-Perceptual, and Interpersonal dimensions, PLEs contain subtypes of positive experiences that must not be viewed as a homogenous construct (Yung et al., 2009).

2.1.2. Prevalence

Around 2-3% of the population is affected by the psychosis syndrome (Perälä et al., 2007). The symptoms arise in late adolescence, two to five years before the clinical diagnosis, further progressing over time (Fusar-Poli et al., 2014). A general population study revealed that the lifetime prevalence (LTP) of all psychotic disorders is 3.06% (3.48% when the nonresponders' diagnoses were included). The found LTPs were as follows: 0.87% for schizophrenia, 0.42% for substance-induced psychotic disorders, 0.35% for major depressive disorder with psychotic features, 0.32% for schizoaffective disorder, 0.24% for bipolar I disorder, 0.21% for psychotic disorders due to a general medical condition, 0.18% for delusional disorder, and 0.07% for schizophreniform disorder (Perälä et al., 2007). When it comes to PLEs, a study which included 18 Western and non-Western countries, and 31 261 respondents found a lifetime prevalence of at least one PLE to be 5.8%. This prevalence was significantly higher among women (6.6%) in comparison to men (5%) (McGrath et al., 2015). Lifetime prevalence of hallucinatory experiences was 5.2%, while the LTP of delusional experiences has been found to be 1.3%. Gender differences had not been found for delusional experiences, whereas in hallucinatory experiences women had a higher LTP (5.9%) than men (4.3%) (McGrath et al., 2015).

Visual hallucinations are the most frequent type of PLEs, with a prevalence of 3.8%. The second most common type of PLEs are auditory hallucinations, with a prevalence of 2.5%. When it comes to numbers of PLE types in one's lifetime, 72% of participants reported one PLE type, 21.1% reported experiencing two types, and 6.8% of participants reported three or more PLE types (McGrath et al., 2015).

2.1.3. Neurobiology and Pathophysiology

Adolescence is a developmental period characterized by changes in puberty, social and environmental factors, and changes in neural structure and function. Around 75% of adults with mental disorders have had the onset of symptoms before age 25 (Kessler et al., 2005). Therefore, it is evident that said turbulent changes create a setting for potential development of mental illness, as they appear as a product of different neural maturational processes (Keshavan et al., 2014).

2.1.3.1. White and Grey Matters, and Functional Connectivity

Changes in grey matter during adolescence mostly include changes in cortical thickness due to synaptic pruning, which causes reductions in synaptic density. This density reaches its' highest level early in development, after which it progressively declines, reducing to about 60% of the maximum levels, with respect to each brain region (Huttenlocher et al., 1997; Patel et al., 2021). Pruning is a key characteristic of adolescent neurodevelopment, as it leads to maturation of the prefrontal cortex, brain area crucial for high-level cognitive functioning (Patel et al., 2021). In schizophrenia, reduced levels of cortical grey matter may appear due to intensive synaptic pruning which results in significantly low synaptic density. Postmortem studies done on patients with schizophrenia go hand-in-hand with this hypothesis (Sellgren et al., 2019). MRI has showed reduced levels of grey matter have been found in parietal, temporal, and frontal brain areas, and enlarged ventricles in patients with childhood-onset schizophrenia who have been treated with neuroleptics (Rapoport et al., 1999; McGlashan, Hoffman, 2000). Furthermore, functional abnormalities in the inferior and parietal cortical areas, as well as in the precuneus, have been found in healthy individuals prone to PLEs (Nenadic et al., 2015). Prefrontal network grey mater volume shows both cortical and subcortical alterations, as well

as altered functional connectivity between temporal, frontal, striatal, and hippocampal regions (Ettinger et al., 2012; Falkenberg et al., 2017).

Unlike the reducing grey matter, white matter in patients with psychotic disorders expands. Motor, sensory, and default network brain areas develop during childhood, while more complex functions, such as salience and executive networks, continue developing long into adolescence. It seems that increased white matter volume is a product of continuous myelination (Keshavan et al., 2014). A study using diffusion tensor imaging (DTI) showed structural abnormalities in fronto-temporo-parietal connection in individuals with ultra-high-risk of developing psychosis, even before the psychosis onset (Carletti et al., 2012). Functional connectivity of temporal and frontal regions is also affected (Diederen et al., 2013). The same study showed reduced fractional anisotropy in the splenium of the corpus callosum. Furthermore, ultra-high-risk individuals who later went on to develop psychosis showed alterations in the left anterior limb of the internal capsule, left superior fronto-occipital fasciculus, left corona radiata, and the anterior body of the corpus callosum, as well as oligodendrocyte abnormalities. The findings from this study shine a light on the role of the left frontal white matter alterations in the onset of psychosis (Carletti et al., 2012).

Parahippocampal, fronto-parieto-temporal network areas, and cingular gyri are brain regions that frequently show functional abnormalities, as well as abnormalities in both white and grey matter volumes (Goldstein et al., 2014; Wolter et al., 2016).

Degree certainty (DC) is a method used to study the number of immediate functional connections between a certain region and the rest of the brain. Cortical hubs are brain areas with high DC. In healthy brains, these hubs remain stable over time, unlike in the presence of underlying pathological processes. Studies showed a loss of spur of multimodal cortical hubs, as well as arising of peripheral hubs.

2.1.3.2. Cortical Gyrification

Cortical gyrification holds a key role in early brain development, and its' alterations play a crucial part as a neurological biomarker in schizophrenia (Evermann et al., 2020). Gyrification is a process of developing gyri and sulci folds, this way increasing the grey matter volume, and the overall cortical area. Folds formed via cortical gyrification allow efficient neural processing (Kinney et al., 2018). Altered brain gyrification has been found in the left temporal gyrus of individuals with PLEs, as well as reduced brain volumes in right prefrontal, and left occipital brain areas (Fonville et al., 2019). Decreased grey matter volumes in the precuneus, right prefrontal cortex, and the left supramarginal gyrus have been found in adults with PLEs, while the main affected areas in children with PLEs include the right orbitofrontal cortex, angular gyrus, and left superior temporal gyrus (increased grey matter volumes), and the left inferior temporal gyrus (reduced grey matter volume) (Jacobson et al., 2010; Pelletier-Baldelli et al., 2014; Drakesmith et al., 2016).

2.1.4. Genetics

The increase in risk for developing schizophrenia in children, as well as in people whos' siblings have diagnosed schizophrenia, is approximately ten-fold. Dizygotic concordances estimate at 0-28%, while the monozygotic concordances estimate at 41-65%. This amounts to an estimated broad heritability of 85% (Cardno, Gottesman, 2000).

An increased risk of severely distressing PLEs is associated with a heightened genomic risk for developing psychosis, as suggested by global brain volume metrics and PGS-proximal behaviors, thus showcasing an intricate, indirect effect of genomic risk to developing psychosis (Karcher et al., 2022).

Studies regarding psychosis highlighted neuregulin (NRG1), regulator of G-protein signaling 4 (RGS4), D-amino-acid oxidase (DAO), D-amino-acid oxidase activator (DAOA), and dysbindin (DTNBP1) as the prominent individual genes (Craddock et al., 2005). RGS4 has been found in postmortem studies of individuals with schizophrenia, and its postulated role in regulating metabotropic glutamatergic receptors, as well as serotonergic receptors, makes RGS4 a possible compelling factor in the development of psychosis (Mirnics et al., 2001; Chowdari et al., 2002). Additionally, studies done on brains of patients diagnosed with schizophrenia show a down-regulated expression of ErbB3, a neuregulin receptor 1, which interacts with RGS4. Neuregulin 1 (NRG1) encodes proteins and mRNA species. Encoding approximately 15 different proteins in brain, NRG1 participates in synaptogenesis, glial differentiation, myelination, axon guidance, neurotransmission, and cell-cell signaling. Behavioral studies done on hypomorphic mice show a certain association of function and/or expression of NRG1 and schizophrenia (Craddock et al., 2005; Thomas et al., 2016; Olaya et al., 2018). Research regarding dysbindin (DTNBP1), also known as dystrobrevin binding protein 1, shows inconsistent results, but there is plausible evidence of association between altered pre-synaptic glutamate function due to DTNBP1, and schizophrenia (Numakawa et al., 2004; Talbot et al., 2004). D-amino-acid oxidase (DAO) is oxidases an activator of NMDA glutamate receptor, D-serine. DAO has been associated with a primate-specific gene G72, which has later been renamed to D-amino-acid oxidase activator (DAOA). An in-vitro study showed G72 to enhance the DAO functioning. Though the evidence suggests a lesser influence of DAO and DAOA in comparison to NGR1 and DTNBP1 when it comes to schizophrenia, it seems that both the oxidase and oxidase activator heighten the risk of developing schizophrenia. It is postulated that this influence derives from altered functioning of NMDA receptors (Chumakov et al., 2002; Craddock et al., 2005).

When talking about schizophrenia, larger sample sizes provided new knowledge on the number of genome-wide DNA variants which cause it. Polygenic risk score for schizophrenia (PRS-SCZ) may be calculated using the data from alleles gathered in genome-wide association studies, thus researching the associations between genetic liability and disease phenotype (Mistry et al., 2018). Genome-wide association studies have now identified more than a hundred susceptibility loci for schizophrenia, showing that it is, indeed, a polygenic disorder whose effects spread on other psychiatric conditions, as shown in research done on different populations (Pantelis et al., 2014; Ikeda et al., 2019). The most recent version of the PRS-SCZ accounts for approximately 7% of the genetic variation in multiple disorder phenotypes, including non-psychiatric and psychiatric disorders, cognition, and schizophrenia symptoms, with significant associations between PLEs and the genetic risk of developing ASD, ADHD, bipolar disorders, and major depressive disorder, with common variant associations found at 287 different genomic loci (Turbetskoy et al., 2022). A higher number of copy number variations (CNVs) has been found in both neurodevelopmental disorders and schizophrenia, especially in individuals who have had previously experiences PLEs (Mistry et al., 2018; Legge et al., 2019).

Still, in cases of genetic research, a large research sample is mandatory in order to attain significant results when it comes to studying either genome-wide associations between different genetic variants and schizophrenia or polygenic scores, as discussed in articles by Sieradzka et al. (2014), Zammit et al. (2014), and Ikeda et al. (2019).

2.1.5. . Hearing Impairment

Hearing impairment has been identified as a risk factor for psychotic experiences and psychotic disorders (Stefanis et al., 2006; Linszen et al., 2016). Understanding the complex relationship

between hearing impairment and psychosis-related disorders has been a topic of interest for many researchers. As defined in an article from Stevens et al. (2013), hearing impairment includes both congenital and acquired types of hearing deficits. Individuals with hearing impairments show a greater risk for developing psychosis (Gevonden et al., 2014). In the same article, Gevonden et al. used the social defeat hypothesis to explain the association between hearing impairment in people with psychosis and the dopaminergic system. The social defeat hypothesis states that a long-term exclusion from the majority group might result in a greater activity and/or sensitization of the mesolimbic dopamine system, this way increasing the risk for schizophrenia (Selten et al., 2013). The PET study showed how the dopamine system is sensitized in socially excluded individuals. Results identified an increased striatal dopamine release in individuals with hearing impairment, a known risk factor for psychosis (Gevonden et al., 2014). Furthermore, children with hearing impairments who grew up in hearing households displayed a delay in the development of theory of mind, most probably due to limited exposure to social interaction, as well a limited opportunities for learning about different mental states, which consequently may lead to development of delusional experiences (Russell et al., 1998; Peterson et al., 2005; Stefanis et al., 2006). Additionally, because of a lack of external stimuli, individuals with hearing impairments have more troubles differentiating events in the world from their own mental events, therefore increasing risks of source monitoring failures (Stefanis et al., 2006). Source monitoring refers to one's ability to differentiate between externally and internally generated stimuli, and its disruption is often associated with hallucinatory experiences (Henquet et al., 2005; Stefanis et al., 2006).

In cases of non-clinical populations, a three-fold increase of a risk of developing positive psychotic experiences has been found in hearing-impaired individuals from 18 to 64 years of age (Thewissen et al., 2005). Another study found an association between hearing impairment in individuals of 19 years of age and positive psychotic experiences. It has been found that the

earlier the onset of hearing impairment is, the bigger is the risk of developing positive psychotic experiences (Stefanis et al., 2006).

2.1.6. Immune System Dysfunction

Immune system tends to be altered in individuals with psychotic disorders – certain subgroups of individuals with psychotic disorders show presence of chronic inflammatory, and autoimmune conditions (Bergink et al., 2014). An autoimmune disease may occur after various injuries, infections, or inflammation, causing a disruption of the blood-brain barrier, making it easier for brain-reactive antibodies to enter the brain (Benros et al., 2011). Even in cases of cancer, patients may show symptoms of psychiatric conditions before receiving a cancer diagnosis. As cancer increases blood-brain barrier permeability, it also activates the antibodies who fight the cancer, quite possibly leading to, and this way acknowledging the role of inflammation and antibodies in the development of psychosis (Benros et al., 2009; Kayser et al., 2010).

When talking about infection, studies show an elevated risk for developing schizophrenia in patients who have been hospitalized for infections. This has also been found in cases of hospitalization due to the presence of an autoimmune disease (Benros et al., 2011). As Bergink et al. (2014) report, psychosis can be caused by infectious agents in a direct or an indirect path. The direct mechanism supposes a noxious effect on both the neural structures, as well as neurons, while the indirect mechanism concerns the infectious agent's role on a microbe-specific activation of the immune system, mediated by the immune response. Furthermore, various genetic abnormalities can be caused due to genes being affected by different pathogens. These findings may also imply the existence of an indirect association between psychosis and infection (Carter, 2009). A study done on the Danish population revealed that the risk for

developing schizophrenia decreases from 45% to 29% after excluding individuals with a history of infections (Benros et al., 2011).

Just as research has been done on defining the exact relationship between infection and psychosis, certain studies have focused on the effects of autoimmunity on genesis and development of psychotic disorders. Another Danish study revealed a 45% higher risk of developing schizophrenia in individuals with a history of autoimmune diseases in themselves or in their relatives (Eaton et al., 2006). Furthermore, psychosis has been found to be a comorbidity in multiple autoimmune conditions, such as multiple sclerosis, systemic lupus erythematosus, autoimmune hepatitis, psoriasis, type 1 diabetes, rheumatoid arthritis, autoimmune diseases of the thyroid gland, and celiac disease (Benros et al., 2014).

2.1.7. Prenatal and Perinatal Factors

The neurodevelopmental model of psychosis emphasizes the importance of prenatal and postnatal factors on heightening the risk of psychosis in the offspring (Davies et al. 2020). Multiple studies have researched and shown the existing influence of said factors on offspring neurodevelopmental abnormalities.

Thirty significant prenatal and perinatal risk factors have been identified in a large meta-analysis comprising 152 studies, including age of both parents (paternal age lower than 20 years of age or older than 35 years of age, maternal age younger than 20 years of age or between 30 and 34 years of age), psychopathology in either of the two parents, three or more pregnancies, HSV-2, maternal infections, winter or winter-spring season birth in the northern hemisphere, negligible number of antenatal care visits, maternal stress NOS, famine or nutritional deficits during pregnancy, maternal hypertension, hypoxia, prematurely ruptured or ruptured membranes, polyhydramnios, obstetric complications, small size of the infant for gestational

age, premature birth, congenital malformations, length of the infant at birth being 49 cm or less, and birth weight (2000 g or less, and from 2500 g to 2999 g). (Davies et al., 2020).

Seasonal distribution of births has been hypothesized to have an effect on the chance of developing psychosis as one of the exogeneous risk factors. An increased risk of developing psychosis, but also PLEs is associated with winter births (Torrey et al., 1997; Mortensen et al., 1997; Davies et al., 2003; Polanczyk et al., 2010; Tochigi et al., 2013).

A study done by Zammit et al. (2009) displayed a number of important perinatal factors which may affect the development of PLEs. Both low and high birth weights are associated with an elevated risk of developing schizophrenia. A Finnish study discovered a 1.7-fold increase of the risk of schizophrenia in cases where the birth weight exceeded 4000 g, while a different study found an also 1.7-fold increase of the risk of schizophrenia in infants with a birth weight of 2500 g or less (Cannon et al., 2002; Wegelius et al., 2011). In infants with a later definite non-clinical psychosis-like symptoms (PLIKS), a five-minute Apgar score equal to six or less has been found to correlate with an increased risk of developing PLIKS. Another factor taken into consideration was resuscitation. Those infants who have been resuscitated developed an increased risk of developing definite, or suspected PLIKS. Out of the resuscitated infants, a smaller subgroup has been hospitalized. They showed an even slightly higher risk of later developing PLIKS when compared to infants who were resuscitated but did not require hospitalization, and to infants who were resuscitated and developed encephalopathy. The effects of the five-minute Apgar score and resuscitation were significant, but not large in this study. Another study found that women who will later become diagnosed with schizophrenia spectrum disorders had lower one-minute Apgar scores in comparison to the control group (Suvisaari et al., 2013). On this note, later research which included convulsions, rhesus incompatibility, not breathing at first, slow heartbeat, being born blue, being born jaundiced, requiring oxygen at birth, and blood transfusions were taken into consideration as perinatal

factors which might increase the risk of developing psychotic-like symptoms later in life. Still, the results of the study showed no significant effects of association of perinatal complications with later PLEs (Staines et al., 2024). Another study researching obstetric complications in schizophrenia cases have noted three subgroups of perinatal factors, including abnormal fetal growth and development (low birth weight, congenital malformations, small head circumference), complications of delivery (asphyxia, emergency Cesarean section, uterine atony), and complications of pregnancy (diabetes, preeclampsia, bleeding, rhesus incompatibility) (Cannon et al., 2002).

When talking about prenatal factors contributing to the development of PLEs, they usually include different medical complications and various environmental influences.

Both viral and bacterial infections play a role in developing psychosis in the offspring, Bacterial infections such as bacterial vaginosis and urinary tract infection (UTI) often go unnoticed during the pregnancy. Yet, they can heighten the chances of neurodevelopmental disorders in the offspring (Lee et al., 2020). The presence of UTIs in mothers may lead to an increased number of PLEs in children (Staines et al., 2024). Pneumonia, cystitis, bacterial venereal infection, tonsilitis, sinusitis, and pyelonephritis are also bacterial infections that elevate the risk for developing schizophrenia in offspring by more than a twofold (Sørensen et al., 2009). An interesting finding is that male offspring are more susceptible to develop psychosis after maternal exposure to bacterial infections during pregnancy, when compared to female offspring.

Furthermore, influenza, toxoplasma gondii (T. gondii) and herpes simples virus type 2 (HSV-2) have been found to correlate with the development of psychosis in offspring of mothers diagnosed with them (Brown, Derkits, 2010). Besides infections, severe anemia has been reported as an interesting factor for developing PLEs (Staines et al., 2024) Placenta has been proven to play a part in the fetal neurodevelopment, and its abnormalities appeared to be

relatively common in a Helsinki study of high-risk children who would later develop schizophrenia spectrum disorders – 75% of births of offspring with later diagnose schizophrenia spectrum disorders had placental abnormalities during birth (Bonnin et al., 2011; Suvisaari et al., 2013).

Maternal diabetes during pregnancy is also associated with an increased chance of psychiatric disorders, including psychosis, and it is hypothesized that the presence of maternal diabetes, together with an increased BMI in mothers, leads to an even more apparent neurodevelopmental disruptions in their offspring (Silva et al., 2021). Moreover, the risk of children having psychotic disorder diagnoses later in life is increased in cases of maternal severe obesity but without maternal diabetes by 67% to 88% (Kong et al., 2018).

2.1.8. Environmental Factors in the Prenatal Period

Though heritability explains a notable amount of the heightened risk of developing psychosis, environmental factors should be taken into consideration as well. As with most conditions, psychotic disorders ought not to be researched in the context of internal, genetic causes only, while excluding the many external influences, but rather as a byproduct of both the genes and one's environment, from as early as conception.

Antenatal environment has been identified as a period prone to "nudging" fetal neurodevelopment towards different conditions. In utero exposures to certain risk factors may contribute to psychosis onset in the offspring later in life.

Maternal nutrition emerged as an antenatal/prenatal environmental risk factor, with one of the first important findings stemming from the Dutch Hunger Winter studies, which examined the effects of famine during a Nazi blockade during the 1940s. Higher rates of hospitalization due to schizophrenia have been found in individuals whose mothers experienced famine during the

first trimester of their pregnancies (Susser et al., 1996). A later MRI study will reveal clinically abnormal neural structure in those who were exposed to famine during the first trimester, connected to early neurodevelopment of patients with schizophrenia (Hulshoff Pol et al., 2000). An even larger famine study, this time in the Wuhu region of Anhui Province in China, reported a two-fold increase of risk for developing schizophrenia after prenatal exposure to famine, similarly enough to the Dutch Hunger Winter studies (Neugebauer, 2005; Brown, Susser, 2008).

In addition to research regarding general caloric intake, efforts have been made to identify the role of micronutrients as well. Vitamin D deficiency is hypothesized to be a risk factor for schizophrenia, primarily due to winter births (low vitamin D intake), and urbanization (vitamin D deficiency is more common in city areas). In cases of adult schizophrenia in males, intake of vitamin D supplements was highlighted as a protective factor (McGrath et al., 2003). Findings suggest the importance of retinoids, such as vitamin A, in the CNS morphogenesis, as well as due to their antioxidative properties which guard the brain from injuries (Maden, 1999; Maden, 2002). Gene expression, cell proliferation, cell differentiation, and cell migration all call for an optimal amount of retinoids in the human organism (LaMantia, 1999). Iron is crucial in obtaining healthy myelination and the development and functioning of the dopaminergic neurotransmission, both of which are shown to be disrupted in schizophrenia (Rao et al., 1999; Davis et al., 2003). Low levels of maternal hemoglobin, which is tightly connected to iron, is also connected to a higher risk of adult schizophrenia in offspring (Insel et al., 2008). Folate deficiency plays a role by hindering both the synthesis and repair of the DNA, therefore increasing the risk of de novo mutations, methylation of the DNA, this way affecting the gene expressions related to neurodevelopment, as well as obstructing the conversion from homocysteine to methionine, thus leading to accumulated homocysteine which disrupts normal fetal neurodevelopment (Waterland, Jirtle, 2004; McClellan et al., 2006; Roffman et al., 2013).

Throughout history, efforts have been put into researching the effects of urbanization on development of schizophrenia. As early as 1939, research showed cases of manic-depressive psychosis as more frequent in urban areas than in rural ones, with the main explanation being social isolation as more common in the cities (Faris, Dunham, 1939). Later, the explanation of the effect of urbanization will be shifted to "drifting" of schizophrenic individuals from rural to city areas (Eaton et al., 2000). A Baltimore-based study done in 1974 identified the risk of being hospitalized due to schizophrenia to be three times higher for individuals living in urban areas in comparison to those living in rural areas (Eaton, 1974). Later studies further confirmed this pattern of the effect of urbanization, especially regarding schizophrenia in comparison to affective psychosis (Takei et al., 1995; Marcelis et al., 1998). There have been a few hypothesized explanations of this effect. As mentioned earlier, infections represent a hazard to developing psychotic disorders in offspring. In urban areas, urban households may be more crowded than rural households, resulting in a more effective spreading of infections among the members of the household (Yolken, Torrey, 1995). Building up on this hypothesis, zoonotic factors (infectious diseases transmittable from animals to humans) may add up to the risk of developing psychotic disorders, since domestic animals/pets tend to stay inside the home in urban areas, whilst usually animals in rural areas stay outside of the house (Tan, 1997; Yolken, Torrey, 1998). Considering the trend of urban hospitals being more advanced and equipped than rural ones, it is hypothesized that the perinatal survival chances may be higher in cities than in less urban areas, due to, usually, better equipment and medical staff (Speecheley, Avison 1995). Nutrition, and drug abuse are also seen as potentially crucial factors contributing to the effect of urbanization on psychosis development. Substance abuse may be more common in larger cities, and breast feeding may be less common than it is in smaller, rural areas, leading to deficits in infant's nutrition, especially important fatty acids (arachidonic acid) found in breast milk (Tien, Anthony, 1990; Horrobin et al., 1994). Sociocultural factors may also play a

role. Urban life is usually faster and in certain ways more challenging than rural life and adapting and navigating through it might appear more difficult and stressful to vulnerable individuals (Nurmi et al., 1996).

Allostatic load is a term defining the effect of cumulative burden the body experiences due to metabolic changes ascribable to heightened physiological activity and its recurrent ups and downs on disease genesis (McEwen, Stellar, 1998). A principal factor contributing to allostatic load is stress, as exposure to stressful events leads to disruption of neuroendocrine mechanisms, hippocampal function and structure, and immune system (VanItallie, 2002). Consequently, maternal stress has been considered as a potential in utero environmental factor adding to the increased risk of psychosis in offspring. A six-fold increase of risk for schizophrenia has been found in children whose fathers passed away during prenatal period, when compared to those children who have lost their fathers during their infancy (Huttunen, Niskanen, 1978). Alas, newer study of a Swedish sample of children born between 1973 and 1985 followed up to 2006 showed no significant effect of maternal bereavement stress in preconception and prenatal period on offspring neurodevelopment. The risk of children developing psychosis grew in cases of experiencing loss of a close family member from birth to adolescence, with the risk being higher in cases of loss of nuclear as opposed to extended family members, in cases of death by suicide, and if the loss of nuclear family member(s) happened earlier in childhood (Abel et al., 2014).

2.1.9. Childhood Environment

2.1.9.1. Bullying

According to Olweus (1996), bullying implies any behavior among peers that has the intent of causing distress or harm. It has been argued that bullying may be connected to an increased risk

of development of non-clinical psychotic outcomes later in life (Startup, 1999; Johns, Van Os, 2001; Lataster et al., 2006, Van Dam et al., 2012).

A review of ten general population studies offered consistent evidence of the association between non-clinical psychotic symptoms and bullying, with said association being stronger in cases of higher frequency, severity, and duration of bullying (Van Dam et al., 2012). Individuals at an ultra-high risk for developing psychosis had a higher prevalence of self-reported traumatic experiences, as reported by Spauwen et al. in 2006., whose findings suggest that individuals with an existing psychotic proneness have a higher risk of developing psychotic symptoms when having experienced psychological trauma. A two-fold increase of risk of developing psychotic symptoms in early adolescence has been reported for a non-clinical sample of 12-year-old children who have been victims of bullying between the ages of 8 and 10, with the correlation being stronger in cases of continuous and/or severe bullying (Schreier et al., 2009). The relationship between the frequency of bullying and psychotic outcome has also earlier been reported by Lataster et al. (2006), where it has been concluded that the risk of non-clinical PLEs is increased by 40.5% in adolescents who have experienced bullying. The same study identified a significant impact of bullying and victimization on the development of non-clinical psychotic symptoms, such as non-clinical delusional ideation and hallucinatory experiences.

Experienced stress may be a reason behind the connection between bullying and PLEs. Increased sensitivity to stress, stemming from increased cortisol levels and the disrupted function of the hypothalamic-pituitary-adrenal (HPA) axis is regarded as one of the symptoms of schizophrenia. Bullying implies continuous harassment, social-evaluative, and uncontrollable threats to one's safety, which in turn results in an overt activation of the HPA axis and cortisol release, leading to increased stress (Dickerson, Kemeny, 2004; Morgan et al., 2007). In the context of this hypothesis, it is plausible that stress affects the already existing genetic predisposition of developing PLEs, and/or that traumatic experiences, such as bullying,

may be severe enough to produce lasting effects on the activity of the HPA axis even without an apparent genetic predisposition (Read et al., 2001; Jones, Fernyhough, 2007).

Attributional biases, dysfunctional schemas, and altered cognitive, affective, and biological processing may link adverse interpersonal experiences to the development of PLEs (Crick et al., 1994; Camodeca et al., 2003; Collip et al., 2008).

The findings from mentioned studies imply an association between childhood bullying and victimization, and the development of both clinical and non-clinical psychotic experiences in adolescence and adulthood, with respect to chronicity, frequency, and severity of experienced bullying.

2.1.9.2. Childhood Trauma

Childhood trauma is an umbrella term for adverse childhood life experiences, including emotional and physical neglect, sexual, emotional, and physical abuse (Larkin, Read, 2008). The correlation between childhood trauma and psychosis has been replicated in multiple studies researching cases of non-clinical (subthreshold) samples as well (Ross et al., 1992; Startup, 1999). Individuals who have experienced childhood trauma present more severe clinical features of a first-episode psychosis in comparison to those who have not experienced childhood trauma, as well as slower improvements, as reported by Berg et al. (2016).

Positive psychotic symptoms have been found to be associated with experienced childhood trauma (Janssen et al., 2004). These symptoms include hallucinations, thought insertion, visual hallucinations, ideas of reference, paranoid ideation, hearing voices, and ideas of reading someone's mind (Heins et al., 1990; Ross et al., 1994; Ellason, Ross, 1997). An important finding further implying this correlation states that individuals suffering from post-traumatic stress disorder (PTSD) show higher levels of positive psychotic symptoms (Butler et al., 1996).

Results from other studies have concluded that the severity of the suffered abuse correlates with the risk of developing psychotic disorders later in life, implying a dose-response association – the more severe the experienced childhood abuse was, the more increased are the chances of psychotic disorders (Mullen et al., 1993; Fleming et al., 1999). Another study researching the relationship between childhood trauma and psychotic symptoms presented evidence further confirming a dose-response association between trauma and psychosis. Childhood trauma variable researched diverse types of traumatic experience, including physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. Results showed a strong association between childhood abuse and positive symptoms, as well a significant association between childhood neglect and both positive and negative psychotic symptoms. However, no significant associations had been identified between childhood trauma and the differential course of psychotic symptoms. The findings stemming out of this research do not assume that childhood trauma alone increases the risk of developing non-clinical psychotic symptoms, but rather that childhood trauma, including both neglect and abuse, is one of the factors which, together with other identified risk factors, increases vulnerability of developing PLEs (Van Dam et al., 2015).

2.1.9.3. Negative Life Events

Negative life events include those events that require individuals to either experience a change in their life, or to readjust (Coddington, 1972). Even though often described as environmental risk factors, one must not exclude the significant heritability of negative life events, making them genetic risk factors as well. In a review by Kendler and Baker from 2007, heritability of dependent negative life events has been reported as 31%, and for independent negative life events as 17%. The same review reported the average heritability of negative life events to be

28%. The environmental and genetic aspects of negative life events indicate an intricate bidirectional relationship between the genes and the environment, as it is postulated that genetic factors may impact one's exposure to certain environments, which then leads to heritability in said environments. This concept is also known as gene-environment correlation (rGE) (Jaffee, Price, 2007; Shakoor et al., 2016). Multiple studies confirm the association between negative life events and onset of PLEs (Janssen et al., 2004; Mackie et al., 2011; Varese et al.,2012; Kelleher et al., 2013; Gibson et al., 2019).

The number of negative life events positively correlates with a higher risk of developing psychotic symptoms in the general, non-clinical population of adults. A four-fold increase of a risk of developing PLEs has been found in adult individuals who have experienced two negative life events, with the said risk further increasing by a six-fold in adults who have experienced six of more negative life events (Johns et al., 2004; Wiles et al., 2006). When it comes to adolescents, studies show a higher risk in adolescent individuals who have experienced three or more negative life events (Bartels-Velthuis et al., 2012). Secondly, adolescents who have had a higher number of negative life events in three years faced a higher risk of persistent auditory hallucinations (Escher et al., 2002).

2.1.10. Cannabis Use

Cannabis is a (still commonly illegal) substance with the highest prevalence among young people, according to Reuter (2009). Numerous studies researched the association between cannabis use and PLEs, and psychotic disorders. Findings suggest that delta-9-tetrahydrocannabinol (THC) induces transient affective and PLEs, which dissolve after a few hours (D'Souza et al., 2004; D'Souza et al., 2005). A review of six longitudinal studies displays self-reported cannabis use as a significant predictor of psychotic symptoms, as well as a

predictor of higher risk of a schizophrenia diagnosis (Degenhardt, Hall, 2006). They propose two hypotheses of how cannabis might affect psychosis onset. First, it is hypothesized that the use of cannabis causes psychosis which would not have occurred if cannabis had not been used. On the other hand, the second hypothesis proposes that cannabis precipitates psychosis in cases of individuals who are already vulnerable to the condition.

A study by Anthony and Tien (1990) discovered that daily use of cannabis doubles the risk of self-reported psychotic experiences (seven types of delusional beliefs and four types of hallucinations were taken into consideration). Troublesome experiences, such as fears of persecution, fears of someone attempting to harm one, and hearing voices, have been reported in one out of seven people after cannabis use (Thomas, 1996). A study done on 3500 Greek 19-year-olds showed a positive correlation between cannabis use and positive and negative psychotic symptoms. The correlation has been found to be stronger if cannabis consumption manifested before 16 years of age, as opposed to cases where the use of cannabis started after the age of 15. The distress caused by PLEs, a variable that has been considered in this research, has not been found to impact this correlation (Stefanis et al., 2004). A review of 35 different studies concluded the existence of an increased risk of psychotic experiences in persons who have ever consumed cannabis. Furthermore, the results showed a dose-response effect – individuals who have used cannabis more frequently had a higher chance of experiencing psychotic outcomes (Moore et al., 2007). However, some individuals with psychosis and PLEs may continue abusing cannabis after the onset of psychotic symptoms. The reasoning behind this occurrence may lie in the notion that cannabis use reduces anxiety, boredom, and agitation, which are all associated with negative psychotic symptoms, while simultaneously increasing sociability and sleep. As cannabis use has no effect on positive psychotic symptoms, a decrease of negative psychotic symptoms remains as the main motivator for continued cannabis use in individuals with already occurred psychotic symptoms (Schofield et al., 2006).

2.2. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a heterogenous disorder which encompasses both neurodevelopmental and neurobehavioral conditions. It concerns persistent impairments in social communication and social interaction in a variety of contexts. These impairments include social reciprocity, nonverbal communication behaviors utilized in social situations, as well as understanding, building, and maintaining relationships with others. Additionally, it includes restrictive and repetitive patterns activities, behaviors, and interests (American Psychiatric Association, 2013).

The disorder commonly starts manifesting in infancy or in the first three years of one's life, by when social and developmental milestones have not yet been accomplished. The first perceivable sign that a child might suffer from ASD is not using words to communicate. Once the child is older and starts interacting with peers, social deficits become more apparent as there is a lack of interest in pursuing connections with others. Repetitive behaviors, hand and/or finger movements, difficulties with coordinating gestures and eye contact, and maintaining conversations are also some noticeable, core characteristics that advance as the child develops (Lord et al, 2000).

Along with the main symptoms, ASD patients often present other neurological and psychiatric disorders, with the most common ones being depression, anxiety, attention-deficit/hyperactivity disorder (Lord et al, 2022). Medical conditions, such as epilepsy, motor disturbances, obesity, circadian rhythm and sleep disturbances, gastrointestinal symptoms are also prominent features of autism spectrum disorder, alongside the core symptoms (Packer, 2016).

2.2.1. Autistic Traits

There is evidence that autistic traits (ATs) are distributed along a continuum in the general population in a manner of normal distribution, from the subclinical symptoms to extreme, clinical cases (Hoekstra et al., 2008). ATs manifest as restricted behaviors, activities and interests, and deficits in initiating and maintaining social interaction and communication, but under the threshold needed to diagnose ASD (Constantino, Todd, 2003). Sucksmith, Roth, and Hoekstra (2011) highlight initiation of and responding to joint attention, divergencies in gaze shift patterns, reduced requesting behavior, language delay, and visual disengaging from the stimuli as most frequent traits. When it comes to cognition, face processing strategy, basic emotion recognition, and complex mental state recognition are reported as common ATs, while social responsiveness, pragmatic language skills, and other subtypes of reciprocal social interaction are pointed out as atypicalities when considering behavior.

ATs may share certain genetic susceptibility factors with ASD, as was reported with attention to detail, rigidity, and childhood behavior ATs (Bralten et al., 2018). An increased risk of developing autistic symptoms in relatives of autistic individuals shines a light on the shared heritability of subclinical ATS and diagnosed ASD (Constantino et al., 2006; Ronald, Hoekstra, 2011).

2.2.2. Prevalence

There has been an observed increase in the prevalence of ASD in the last few decades. According to the Global Burden of Disease study from 2010., 1 in 132 people is diagnosed with autism spectrum disorder. This amounts to 52 million people across the world (Baxter et al., 2015). The most recent estimates of the Centers for Disease Control (CDC) reported that 1 in

36 8-year-old children in the United States might be on the autism spectrum (CDC, 2023). It has also been found that ASD is less common in females than in males, with a 1:4 ratio.

Years lived with disability (YLDs) and disability-adjusted life-years (DALYs) from 1990 to 2010 were both used as means of determining the burden. When it comes to years lived with disability, autism spectrum disorders are amongst the 20 of the most common causes for disabilities in children under 5 years of age. ASDs were the fourth leading cause of disabilities in children in the 5-14 age range (Baxter et al, 2015).

2.2.3. Autism Spectrum Disorder and Intellectual Disability

There seems to be a co-occurring connection between the ASD and intellectual disability. The severity of intellectual disabilities varies depending on the level of functioning and the development of ASD (Lecavalier et al., 2011). As mentioned earlier, one of the main characteristics of ASD is its heterogeneity, which therefore transfers to comorbidities of ASD as well. The intellectual developmental disorder, also known as intellectual disabilities (ID), represents an insufficiency of general mental abilities, which include academic learning, reasoning, problem solving, abstract thinking, planning, judgement, and learning from experience. Global developmental delay describes the inability to reach important developmental milestones in multiple domains of intellectual functioning. These intellectual disabilities lead to impaired adaptive functioning of an individual, where one has trouble with attaining and maintaining social participation and responsibility, one's independence, communication, and academic and/or occupational functioning (American Psychiatric Association, 2013).

It is reported that most people on the ASD spectrum do not have intellectual disabilities, when measured by standard tests of intelligence. Still, ID is associated with ASD in around 70% of

the cases, with 40% of cases having severe ID, and 30% mild to moderate ID (Bryson, Smith, 1998). Later studies report that the criteria for intellectual disabilities (IQ < 70) was met by 26% of preschool children already diagnosed with ASD. Furthermore, once the data had been regrouped according to subtypes of ASD, 69% of children who met criteria for ASD also met criteria for ID (Chakrabarti, Fombonne, 2001).

On the other hand, some studies focused on researching the proportion of ASD in individuals with ID. A study focusing on prevalence of ASD in adolescents with ID show that 28.2% of participants diagnosed with ID also position on the autism spectrum. Considering that the prevalence of ID is 7.18/1000, this research estimates that there are two individuals with both ASD and ID per thousand people in the general population (Bryson et al., 2008). Another study done on children attaining special education in the Netherlands showed that adaptive functioning depends on the levels of displayed autistic behaviors, and that these behaviors prohibit children from reaching expected levels of education, with respect to their IQs (De Bildt et al., 2005). It is clear that individuals with ASD carry knowledge and skills, but they are context specific. There may be difficulties with applying their skills and knowledge in a situation different from the one in which the skills have been attained. Due to this rigidity, individuals with ASD may find it hard to modify their behavior and use their knowledge and skills in new settings. These difficulties, along with the constantly changeable demands of the social world, often lead to stress and anxiety, which only further worsens the problem (Bryson, Smith, 1998).

2.2.4. Autism Spectrum Disorder and Communication

As with intellectual disabilities, language and communication skills vary across the spectrum. They usually manifest as one of the first symptoms of ASD as they are easily noticeable in the

first two years of a child's life. Arising so early in development, communication and language impairments persist during adolescence and affect other domains of development (Matson, Sturmey, 2011). Language-impaired children with ASD have a lower long-term outcome compared to language-impaired children with nonspectrum disorders (Howlin et al., 2000). General, social cognitive, and motor skills significantly correlate with the acquisition and development of expressive and receptive language, as well as non-verbal cognitive ability. Imitation skills, gesture use and non-verbal cognitive ability serve as predictors of expressive language, whereas gesture use, non-verbal cognitive ability, and response to joint-attention bids make for useful predictors of receptive language abilities (Luyster et al., 2008).

2.2.4.1. Spoken Language

Spoken language, also referred to as functional language, is affected in ASD. A longitudinal study reported that 28.6% of participants with ASD, aged 2 to 9 years of age, still have not spontaneously used words consistently by the age of nine. Another 23.8% of participants were regarded as fluent, and the same percentages of participants were found to speak in phrases or short sentences (not considered fluent), and to use single words but not in meaningful and spontaneous phrases (Anderson et al., 2007). Results from another longitudinal study showcase that developed nonverbal cognitive abilities by two or three years of age present as important predictors of functional language by ages five to nine (Thurm et al., 2007). Alas, the specific language impairments do not become apparent as soon as they manifest, but rather once the child reaches school age, making diagnosing and treating the impairment challenging (Matson, Sturmey, 2011).

2.2.4.2. Joint Attention and Nonverbal Communication

Joint attention and nonverbal communication represent important communication skills that develop prior to the functional language, and as such are relevant in predicting the development of later language abilities, as well as different cognitive, social, and behavioral outcomes (Cassel et al., 2007; Matson, Sturmey, 2011). Joint attention develops between nine and fifteen months of age as early means of infants communicating with intent. It refers to different behaviors aimed at directing and following other's attention towards an object or event of interest (Anderson et al., 2007). At this time, infants begin switching their gaze between people and objects, following another person's gaze, and pointing towards objects and people (Carpenter et al., 1998; Siller, Sigman, 2008). Abnormalities in joint attention emerge around the same time as ASD symptoms. Children of one year of age who would later become diagnosed with ASD showed deficits in declarative pointing (drawing attention to people and/or objects) (Werner et al., 2005).

Differences in joint attention deficits also vary depending on IQ – children with higher IQs and ASD showed deficient high-level joint attention skills, such as showing or pointing, while children with lower IQs and ASD showed deficient low-level joint attention skills, such as eye gaze and inability to follow head turn. This is especially noticeable in children with the mental age of 20 months or younger (Mundy et al., 1994).

Research implies of connection between joint attention and language acquisition and development. In children with ASD, frequency, and accuracy of joint attention initiation correlate with receptive language measures (Mundy et al., 1987). Furthermore, both joint attention initiation and responsiveness to others' joint attention bids correlate with language acquisition during a child's development (Bono et al., 2004).

2.2.5. Neurobiology and Pathophysiology

Autism spectrum disorder is a disorder of neuronal-cortical organization. It affects brain structures, neural pathways, and synaptic and dendritic organization (Geschwing et al, 2007). The altered structures explain the specific ways of communication, behavior and social interacting commonly found in individuals with autism spectrum disorder.

Structural and functional MRI studies and studies done on autopsied brains of individuals with ASD single out the cortex, the limbic system, and the cerebellum and the brainstem as the main neural structures affected by the disorder (Polleux, Lauder, 2004).

2.2.5.1. Brain Overgrowth

Morphometry and volumetry studies done by structural magnetic resonance imaging (sMRI) in people with autism spectrum disorder showcase brain overgrowth (Parellada et al, 2014). The weight of the brain in children diagnosed with autistic spectrum disorder, being 1451 g, is approximately the same as the average brain weight of a healthy adult (Courchesne, Redcay, 2005). What is especially interesting is the fact that some studies show that 90% to 95% of neonatal babies who would later be diagnosed with ASD had average or smaller-than-average head circumferences. The head circumference became evidently larger by the first or the second year (Courchesne et al, 2003). Once the child reaches four years of age, the brain volume becomes larger than the average brain volume by 10% (Dawson et al, 2007).

Studies have reported reduced volume of the corpus callosum, increased cortical thickness and folding in parietal lobes, and the increased cerebellar hemisphere volume (Stanfield et al., 2008). The amygdala, frontal and temporal lobes are areas of the most prominent overgrowth (Carper et al, 2002). An increased neuronal density has been found in brain networks important

for formation, maintenance, and memory retrieval, made up of the amygdala, together with subiculum, mammillary bodies, hippocampus, medial septal nuclei, and the entorhinal cortex (Courchesne, 1997).

2.2.5.2. Cerebellar Pathology

Yet, perinatal damage to the cerebellum remains the biggest non-genetic risk factor associated with ASD, since the children who have suffered these damages have a 36-fold increased risk of later developing autism spectrum disorder (Mosconi et al.,2015). Research shows that individuals with autism spectrum disorder have from 35% to 95% less cerebellar Purkinje cells compared to healthy individuals (Weigel et al., 2016). The deep cerebellar nucleus cells are enlarged in childhood but start to shrink in size and number as the child develops into adulthood (Mosconi et al., 2015).

The main cerebellar defects involved in neuropathology of ASD concern the white matter tract of the primary output pathway going from the cerebellum, known as the superior cerebellar peduncle, and the middle cerebellar peduncle (the primary cortical input pathway going into the cerebellum) (Sivaswamy et al.,2010).

Considering that both the middle and the superior cerebellar peduncles show alterations in their structures, a substantial portion of the cortical-pontine-cerebellar-thalamic-cortical loops are affected, therefore interfering with a healthy cognitive and behavioral development (Mosconi et al., 2015).

2.2.5.3. White and Grey Matter

When it comes to white and grey matter volumes, they are, as well, increased in patients with ASD. This abnormal increase of both white and grey matters might happen either due to reduced synaptic or dendritic pruning, or due to increased synaptogenesis and dendritic branching. Another hypothesis for increased white and grey matters is the dysregulation of the mechanisms of axonal outgrowth and/or dendritic arborizations or synaptic contacts between inhibitory and excitatory cortical neurons (Polleux, Lauder, 2004).

What is noteworthy to mention is the fact that the grey matter volume is not equally increased across the entire brain. As mentioned in articles by Bloss and Courchesne from 2007, and by Hazlett et al. from 2006, the grey matter volumes are the most enlarged in temporal and frontal lobes, while the occipital lobe suffers the least amount of enlargement. A study done in 2003 by Levitt et al. may have explained the significant enlargements of the grey matter in these areas. In older children with autism spectrum disorder, the temporal and frontal sulci were placed more superior and/or anterior in comparison to healthy children. This holds account for the abnormally large grey matter volumes in these areas. These regions of enlargement of the grey matter correspond the regions of cognitive functions affected in individuals suffering from the autism spectrum disorder. The larger the volume of the grey matter, the bigger the impairment in cognitive functions in affected structures.

The grey matter is connected in neural circuits by the white matter, which regulates both the speed and the timing of sending information across the brain (Courchesne et al., 2007). The emotional and social activities depend on good connectivity and activity supported by the white matter. The influence of the abnormal white matter and the issues of connectivity and functionality it brings may be divided into three main neural systems: the limbic system, the mirror neuron system, and the face processing system (Ameis, Catani, 2015).

The face processing system consists of the amygdala, the fusiform face area (inferior temporo-occipital cortex, and the superior temporal sulcus. The latter structure is prominent during eye

gazing and as a response to the biological motion. Amygdala is important when it comes to processing facial expressions and the fusiform face area has a key role in recognizing and identifying faces (Adolphs et al., 1999). These three structures are interconnected by the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus. The two white matter tracts, if damaged, correlate with impaired facial processing (Ameis, Catani, 2015).

Observing and imitating social interactions, other people's facial expressions and self-recognition activates the limbic system, as well as the mirror neuron system. The mirror neuron system is made up of the inferior frontal cortex and the right rostral inferior parietal lobule (Iacoboni, Dapretto, 2006). The white matter tract includes the arcuate fasciculus is crucial for language processing (left arcuate fasciculus) and visuo-spatial processing (right arcuate fasciculus (Lebel, Beaulieu, 2009).

The last of the three neural systems is the limbic system. There are three distinct levels of neural circuits in the limbic system which are beneficial when it comes to emotions, memory, and one's behavior (Catani et al.,2013). The first, antero-ventral circuit, with amygdala as its main point, integrates the emotional and visceral outputs with both cognition and behavior. Amygdala's main role is facilitating emotion recognition and recognizing unforeseeable visual stimuli. Other neural structures which make up this first circuit are orbito-frontal and anterior temporal regions. The white matter tract which connects the temporo-amygdalo-orbitofrontal neural network is called the uncinate fasciculus. This tract acts in cases of visual discrimination and complex emotion recognition, but it's also useful in social development since it can help predict behavioral responses to attention in babies (Browning, Gaffan, 2008; Ellison et al., 2013; Fujie et al., 2008).

The second circuit activates during attribution of emotions and personal reflection (the default mode network) and it comprises of precuneus ventromedial prefrontal cortex, temporal parietal junction, and the posterior cingulate cortex (Ellison et al., 2013). The abnormal function of this

white matter tract, the cingulum bundle, causes changes in motivational and psychosocial functions (Catani et al., 2002; Catani et al., 2008).

Lastly, the third circuit consists of the posterior precuneus, hippocampus, and retrosplenial cingulate gyrus. Here, the white matter tract is called the mammillo-thalamic tract, and its malfunction leads to issues with orientation in space, and facilitation of memory acquisition (Buckley et al., 2008).

2.2.5.4. Cortical Minicolumns

Abnormalities can also be found in minicolumns of excitatory and inhibitory neurons in the temporal and frontal lobes of patients diagnosed with autism spectrum disorder (Polleux, Lauder, 2004). These minicolumns have GABAergic interneurons, important for achieving inhibitory controls in various neural networks. Every minicolumn is made up of pyramidal neurons in layers 2, 3 and 5, whose dendrites reach the first layer of the column, and the pyramidal neurons in layer 6 with their dendrites reaching 4B layer.

A study from 1998 done by Bailey et al. on postmortem brain of patients with autism spectrum disorder revealed abnormally oriented dendrites in the fifth layer, ectopic neurons in the white matter of the first layer, and an unorganized organization of neurons in the superior temporal gyrus (Poleux, Lauder, 2004).

Dysfunction of the minicolumns may cause an abnormal laminar distribution of the mentioned interneurons, disrupt branching of pyramidal neurons and interneurons' dendrites and synapses, and create an imbalance between the numbers of pyramidal neurons and interneurons (Polleux, Lauder, 2004).

2.2.6. Genetics

Considering the high clinical heterogeneity of ASD, one can infer it derives from the high genetic heterogeneity. Today, we know that more than a hundred genomic regions and genes are associated with the development of autism spectrum disorder (Lord et al, 2022). The inherited risk for developing autism spectrum disorder is also associated ATs under the threshold of clinical ASD, showcasing how the disorder exists on a continuum (Parellada et al., 2013).

The concordance rate between dizygotic twins is 1%, and it ranges from 36% up to 91% between monozygotic twins. When it comes to non-twin siblings of patients with diagnosed ASD, the prevalence spans from 2.9% to 3.7% (Marotta et al, 2020). Essential autism has a recurrence rate of 35%, while the general recurrence rates of ASD in the family range between 10% to 18%. When it comes to ATs and language disorders, recurrence rate shows that approximately 20% to 25% of siblings of individuals with autism spectrum disorder show pragmatic language deficits (Constantino et al., 2010). Risk genes play important roles across different brain regions during the neurodevelopment. SCN2A and CHD8 present the highest confidence risk genes associated with idiopathic autism (Satterstrom et al., 2020). The abnormalities may appear as single base changes, or as copy number variations including millions of bases. Single gene mutations such as fragile X syndrome, Rett syndrome, and tuberous sclerosis complex, have been found to make up about 10% of ASD clinical cases (Devlin, Scherer, 2012). Approximately 20%-30% of clinical cases of autism spectrum disorder come from de novo rare point mutations or copy number variations (Sanders et al., 2015). On the other hand, individuals carrying small effect size variants, may never develop autistic-like symptoms at all (Lord et al., 2022).

The most important findings gathered from multiple studies showcase that most of the proteins that are encoded by risk genes play active roles in regulating gene expression, synaptic function and structure, and chromatin modification (Gilman et al., 2011). Studies done by Parikshak et al. in 2013, and Wilsey et al. in 2013, shine a light on the role of the glutamatergic neurons during the development of the cortex. The findings do vary between deep and superficial cortical layers. Post-mortem studies of brain tissue of patients with ASD noted changes in transcription in different cell types, especially the upper-layer cortical neurons (Velmeshev et al., 2019).

2.2.7. Neurotransmitters

The role of neurotransmitters in autism spectrum disorder has been supported by convincing evidence of altered development and function of GABAergic, glutamatergic, and serotonergic systems, and slightly weaker evidence of abnormal peptidergic, cholinergic, and catecholaminergic systems (Polleux, Lauder, 2004).

2.2.7.1. Glutamate

There are implications that glutamate, the primary excitatory neurotransmitter, plays a role in ASD. NMDARs (N-methyl-D-aspartate receptors) and AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazolepronic acid receptors), who together with metabotropic glutamate receptors make up the three primary groups of glutamate receptors, play a role in ASD (Marotta et al., 2020). Other genetic mutations in genes such as UBE3A, SHANK, NLGN3, NLGN4 may cause glutamatergic dysfunction and can cause autistic-like traits (Krishnan et al., 2017; Trobiani et al., 2018).

2.2.7.2. Gamma Aminobutyric Acid

GABA, derived from glutamate through the process of glutamate decarboxylase, is the main excitatory neurotransmitter. Its significance is prominent during brain development, as GABA influences migration, proliferation, differentiation, synapse maturation, and cell death (Marotta et al., 2020). In children diagnosed with autism spectrum disorder, plasma glutamine and glutamate/GABA ratios are lower, and plasma GABA and glutamate/glutamine ratios are higher, in comparison to healthy individuals (Al-Otaish et al., 2018; Marotta et al., 2020). Still, there seems to lack significant statistical relevance when it comes to treating ASD symptoms with GABA modulators by regulating the excitatory glutamatergic and inhibitory GABAergic pathway imbalance (Marotta et al., 2020).

2.2.7.3. Serotonin

Serotonin (5-HT, 5-hydroxytryptamine) plays a key role in neurodevelopmental processes, such as synaptogenesis, cortical plasticity, cell division proliferation, migration, and differentiation (Celada et al., 2013). Children with autism spectrum disorder have higher levels of serotonin or the serotonin transporter (5-HTT or SERT) in comparison to healthy individuals. Furthermore, the studies done on postmortem ASD brains show reduced bindings in 5-HT1A, and 5-HT2A (Muller et al., 2016; Abdulamir et al., 2018). When it comes to ASD treatment, SSRIs (selective serotonin reuptake inhibitors) did show slight efficacy in symptoms of repetitive and disruptive behaviors. Fluoxetine has shown the greatest efficacy in treating global ASD symptoms (West et al., 2009).

2.2.7.4. Dopamine

Dopamine alterations in the mesocorticolimbic pathway reflect on impaired social behaviors in individuals with ASD. Activation of D1 dopaminergic receptors lead to an increase of social behaviors (Gunaydin et al., 2014). Polymorphisms of DR3 and DR4 dopaminergic receptors, as well as the DAT (dopamine transporter) polymorphism are crucial factors for developing autism spectrum disorder (Staal, 2015). The DAT polymorphism causes autistic-like phenotypes in mice (DiCarlo et al., 2020). Impaired social skills, one of the core symptoms of ASD, are also caused by the haploinsufficiency of SHANK3 (Bariselli et al., 2016).

When it comes to the role of dopamine in treating ASD, risperidone and aripiprazole, dopamine receptor blockers, can be used in treating repetitive behaviors, and symptoms of irritability (Marcus et al., 2009; McDougle et al., 2005).

2.2.7.5. Acetylcholine

Acetylcholine is a neurotransmitter and a neuromodulator of the parasympathetic system (Marotta et al., 2020). Symptoms characteristic of ASD, such as anxiety and a disrupted sleep pattern, seem to be connected to nicotinic α4β2 acetylcholine receptors (Lena et al., 2004). Treatment using an nAChR agonist, ABT-418, alleviates these symptoms (Takechi et al., 2016). Increased levels of α7 nAChR in the frontal cortex and hippocampus are found in a number of psychiatric conditions, including ASD. These levels, if increased, alter attention, cognition, emotion, sensory processing, and working memory (De Jaco et al., 2017). When it comes to treating autistic-like symptoms by targeting the mentioned nAChRs, evidence from the study done by Ghaleiha et al. in 2014 show significant improvements of symptoms of lethargy, social withdrawal, and irritability after administration of galantamine.

2.2.8. Immune System Dysfunction

Inflammation is a homeostatic cellular response which occurs as to protect the organism from harmful environmental stimuli. The immunomodulatory mechanisms are present it the CNS and the peripheral system. These mechanisms function on down-regulation, or up-regulation of pro-inflammatory and/or anti-inflammatory cytokines, as well as their receptors (Serhan, Savill, 2005). Cytokines are proteins with both adaptive and innate inflammatory responses. They can penetrate the blood-brain barrier, thus enabling interaction between the immune system and the CNS. Their main roles include synaptic maturation, neuronal migration, and GABAergic and dopaminergic neuronal differentiation. If their functioning is disrupted, cytokines may influence degeneration, neuronal damage, and neuroinflammation (Curfs et al., 1997; Qin et al., 2007).

The immune system in patients with autism spectrum disorder is dysregulated, stemming from maternal immune activation, and genetic abnormalities. Findings suggest that an overly active immune response in pregnant mothers induces an inflammatory process, creating antibodies which disturb healthy fetal neurodevelopment (Onore et al., 2012). Research done on animals confirm the crucial role of maternal immune response in developing ASD. Autistic-like symptoms, including social deficits and other atypical behaviors characteristic of autism spectrum disorder, are found in rodents whose mothers had a heightened immune response (PATTERSON 2009). Comparable results have been found in both rhesus macaques (Martin et al., 2008), where the offspring showed stereotypic behavior and hyperactivity, and in dams (Singer et al., 2009). In these studies, IL-6 was the most prominent cause of abnormal behaviors in animal offspring (Hsiao, Patterson, 2011).

Several risk genes for developing ASD play an important part in obtaining and maintaining immune functions (Onore et al., 2012). Proteins in the PI3K pathway (phosphoinositide-3-

kinase), such as MET, PTEN, TSC1, and TSC2, play a key role in regulating IL-12 production in myeloid cells. These genes also regulate switching macrophage phenotypes from M1 (inflammatory) to M2 (alternative activated) subsets (Fukao et al., 2002). Macrophage inhibitory factor (MIF), complement 4B (C4B), and major histocompatibility complex type 2 haplotypes (MHC-II) partake in regulating one's immune system (Grigorenko et al., 2008; Odell et al., 2005; Lee et al., 2006).

2.2.9. Prenatal and Perinatal Factors

Besides the genetic influence, various environmental factors contribute to the development of autism spectrum disorder. Obstetric complications like maternal bleeding in early pregnancy, older maternal age and medication use in pregnancy increase the risk of developing ASD in children (Glasson et al., 2004).

A comprehensive study done by merging the Medical Birth Register and the Inpatient register in Sweden (Hultman et al., 2002) aimed to understand the correlations between antenatal, obstetric, and neonatal factors, and infantile autism. An increased risk for developing autism was found in pregnancies characterized by hypertensive diseases, daily cigarette smoking, bleeding, cesarean delivery, preterm birth (≤ 36 weeks), birth weight less than 2500 g, large or small size for gestational age. An Apgar score ranging from 0 to 6 at 5 minutes also contributes to an increased risk of developing autism. Genital, cardiologic, and palate and lip malformations were also present in newborns who would later develop autism (Hultman et al., 2002).

Mothers of children later diagnosed with autism spectrum disorder are more likely to experience a threatened abortion prior to 20 weeks' gestation. There was a larger number of epidural caudal anesthesia in comparison to control group deliveries (Glasson et al., 2004). Administering epidural caudal anesthesia decreases both the blood pressure and uterine blood flow in mothers.

This process may alter fetal heart rate and increase consumption of oxygen. In some cases, epidural caudal anesthesia causes intrapartum fever, which is considered to have adverse effects if the fetal core temperature becomes higher than maternal core temperature (Glosson et al., 2004). Postpartum hemorrhage, short duration of the labor (< 1 hour), parity, fetal distress during labor were also found as important characteristics of deliveries of babies later diagnosed with ASD (Glasson et al., 2004). In a study done by Boksa et al. (2002), the rats who were delivered via a cesarian section showed higher levels of dopamine D1 receptor binding in the nucleus accumbens. This increase is evident once the rats reach adulthood. Treating behavioral issues with dopamine inhibitors has been shown as useful in patients with autism spectrum disorder, especially those individuals who have abnormal ventral basal ganglia, a product of cerebral changes from birth (Buitelaar et al., 2000).

Maternal BMI and nutritional habits have also been found to contribute to an increased risk of developing ASD. Maternal undernutrition may cause a physiological stress response, further causing an abnormal release of proinflammatory factors (Georgieff et al., 2007), while maternal obesity may cause heightened maternal immune response and chronic inflammation of the uterus (Bugatto et al., 2010). Iron deficiency is also associated with a larger risk for developing ASD. Iron is important for immune function, myelination, and production of neurotransmitters. Therefore, its deficiency can disrupt the development of motor, cognitive, and language skills, as well as abnormalities in social behaviors (Gialoretti et al., 2019).

Furthermore, a lack of folic acid consumption leads to a higher risk of developing ASD (Gialloreti et al., 2019). On the other hand, another study showed an increased risk for developing ASD in children whose mothers used synthetic folic acid during pregnancy (Wiens et al., 2017). These opposing results can be explained by different structures between synthetic folic acid dietary supplements (pteroylmonoglutamic) and the folic acid from natural food resources (ormyl-tetrahydropteroylglutamates). Increased levels of the synthetic folic acid can

contribute to increased levels of unmetabolized folic acid in the blood, which further causes abnormalities in gene expression of ASD-risk genes, and in the brain synaptic transmission (Barua et al., 2014).

In this study, younger mothers had the lowest risk of their child being diagnosed with ASD, while the eldest mothers had the highest risk (Glosson et al., 2004). This may be explained with the weakened uterine muscles and blood supply that come with age. Besides the maternal age, paternal age also is of importance. The risk increases as the paternal age reaches 30, plateauing after 40, and increasing again after the age of 50 (Hultman et al., 2011). It appears the parental age, and/or reduced fertility causes changes in epigenetic DNA methylation, leading to an increased risk of developing ASD (Loke et al., 2015).

Assisted reproductive technologies (ART), such as in vitro fertilization (IVF), egg retrieval, hormonal induction, micro-manipulation of gametes, intra-cytoplasmic sperm injection (ICSI) and exposure to culture medium may create a stressful environment for the fetus, therefore resulting in different defects and low birth weight (Gialloreti et al., 2019). These technologies contribute to an increased risk of congenital anomalies, epigenetic, and imprinted disorders (Gosden et al., 2003). Research from 2017 described ART as an independent risk factor for developing autism spectrum disorder. This might be due to epigenetic changes happening due to hormone exposure, embryo and gamete freezing, culture media usage, delayed insemination, semen preparation, and different growth conditions (Iiu et al., 2017). The mentioned epigenetic changes can cause defects in genetic imprinting, which is known to contribute to the development of neuropsychiatric disorders, such as Fragile X syndrome and Rett syndrome, both of which include autistic-like traits (Loke et al., 2015).

An interesting study that shines a light on environmental factors included in developing ASD has been done by Zerbo et al. in 2011. They have examined different environmental factors in prenatal, perinatal, and postnatal developmental phases. Child's ethnicity, year of conception,

and maternal education were included as confounding variables. Winter conceptions bared a higher risk of developing autism in comparison with summer conceptions. The risk increases from August to March, decreases by April, and then plateaus until August. Conceptions in December, January, February, and March showed an increase in risk of autism (from 8% up to 26%). March conception is associated with the highest risk of autism (Zerbo et al., 2011).

When it comes to medications, using antidepressants and selective serotonin reuptake inhibitors (SSRIs)during pregnancy have been associated with an increased risk of developing ASD (Brown et al., 2017; Mezzacappa et al., 2017).

2.2.10. Environmental Factors in the Prenatal Period

Pesticides, air pollution, heavy metals, materials used in plastic industry may all contribute to the development of autism spectrum disorder (Gialoretti et al., 2019). Air pollution is the dominant chemical risk factor connected to onset of ASD. Distinctive characteristics of air pollution, such as time of exposure, metrics of exposure, type of air pollution all contribute to the development of ASD (Volk et al., 2011). Residential proximity to pesticides (organophosphates) is associated with a heightened risk of developing ASD (60%) (Shelton et al., 2014). The current most used pesticides are known to be neurotoxic, therefore causing disruptions in neurodevelopment, as well as causing oxidative stress (Wang et al., 2016).

Seasonal birth studies suggest a higher chance of ASD in children born in spring, and a lower risk for those born in autumn (Lee et al., 2019). On the other hand, there are findings which suggest an increased risks for summer birth months, with the peak being the months of June and July, which is hypothesized to happen due to earlier school enrollment, linked to relative physiological immaturity and the trend of overdiagnosing ASD in younger children (Hebert et al., 2020; Hsu et al., 2021). Interestingly enough, other studies report no association between

the season of birth and ASD (Mouridsen et al., 1994; Kolevzon et al., 2006; Atladottir et al., 2007).

Usage of antidepressants and antiepileptic drugs during pregnancy shows an association with the onset of ASD (Gialoretti et al., 2019). When talking about antiepileptic drugs, valproate showed the largest association with neurodevelopmental delay, disturbed cognitive functions, and ASD, as well as oxcarbazepine and lamotrigine (Roullet et al., 2013; Andrade et al., 2017).

Additionally, maternal eating behavior can affect the child's neurodevelopment. As mentioned earlier, folic acid, as well as low vitamin D levels, have been associated with development of ATs and autism spectrum disorder. These effects are the most prominent in the mid-gestational period (Suren et al., 2013). On the other hand, increased levels of aspartame and methanol in maternal diet might also be connected to development of ASD (Walton, Monte, 2015). Another nutritional factor that plays a role in ASD is a high-fat, low omega-3 diet. Mothers who eat high-fat food have the same highly activated inflammatory cytokines (IL-4, IL-5) as mothers of children who would later be diagnosed with autism spectrum disorder. Fatty foods disrupt the neural pathways involved in regulation of behavior, and this food mostly targets the serotoninergic system by suppressing it, therefore causing behavioral disorders (Gialoretti et al., 2019).

Regarding the exposure to prenatal infections, type of the infective agent, maternal immune response, and time of the gestational exposure are the main factors determining the risk of developing ASD ((Gialoretti et al., 2019). In the first trimester, viral infections cause the biggest risk of developing ASD, bacterial infections in the second trimester, and influenza and febrile episodes in the third semester. When it comes to fever, mothers who were administered anti-pyretic drugs had a higher ASD risk in comparison to mothers who did not take this medication (Zerbo et al., 2013).

Gestational diabetes causes disturbances in the motor development and learning and contributes to the development of ADHD by elevating oxidative stress and changing gene expression (Ornoy et al., 2001; Gardener et al., 2009).

2.2.11.Environmental Perinatal and Early Postnatal Period

The gut microbiome in individuals with autism spectrum disorder has a higher number of Clostridia, Desulfovibrio, Sutterella, and Bacteroidetes when compared to the gut microbiome of healthy individuals (Gialoretti et al., 2019). This explains the higher number of gastrointestinal disorders found in ASD patients. Numerous studies highlighted significant treatments of gastrointestinal issues of individuals with autism spectrum disorder. These treatments include microbiota transplantation, exclusion diets and diets rich in fibers and prebiotics, as well as galacto-oligosaccharides (GOS) (Yan et al., 2018; Grimaldi et al., 2018).

2.2.12. Childhood Environment

2.2.12.1. Bullying

Compared with the general population, adolescents with neurodevelopmental disabilities have higher rates of bullying (Zablotsky et al., 2014). The prevalence of bullying involvement in individuals with ASD is reported as higher than in individuals without ASD (46.3% for victimization, 14.8% for perpetration, and 8.9% for victimization/perpetration). Lower levels of academic performance, and higher levels of anxiety, loneliness, depression, negative affect, and negative thought about themselves are characteristic consequences of bullying involvement (Hawker, Boulton, 2000; Nansel et al., 2001; Poteat, Espelage, 2007). Children with diagnosed ASD show more internalizing symptoms after experiencing victimization, and more emotion

regulation problems after perpetrating bullying themselves. In cases of children with ASD who were both the victim and the bully, both internalizing and emotional regulation problems were present (Zablotsky et al., 2013). In a sample of children with ASD, 67% of the parents reported their child as having experienced cyber-bullying, verbal, physical, and/or social bullying, with 68% of the children experiencing more than one type of bullying. Furthermore, 46% of cases reported the victimization to occur once or more per week (Cappadocia et al., 2012).

The reason for the higher prevalence in ASD is most probably due to the core symptoms of ASD including social impairment and communication, making these individuals more susceptible to bullying due to the effect these symptoms have on peer interactions. It is reported that individuals with better social and communication skills have a lower risk of experiencing bullying (Martlew, Hodson, 1991; Cappadocia et al., 2012; Sterzing et al., 2012). Understanding the bullying behavior, as well as knowing how to respond to it, may appear more difficult for individuals with ASD (Jackson, 2002; Humphrey, Hebron, 2015). Children with ASD are oftentimes provided with teaching assistants in class, creating a distance between them and their peers by reducing the opportunities for social interaction amongst them (Symes, Humphrey, 2012).

2.2.12.2. Childhood Trauma

Children with ASD might be more prone to experience childhood trauma in comparison to children without neurodevelopmental disorders, as research suggests a 1.5 to 3 times higher risk of experiencing traumatic events in this population (Hibbard, Desch, 2007; Reiter et al., 2007; Sullivan, Knutson, 2000; Kerns et al., 2015).

Individuals with ASD are reported to experience stress more intensively and frequently than non-clinical samples, possibly due to having difficulties coping with change, social interaction,

and communication difficulties (Kerns et al., 2015). In her research, Fuld (2018) reports a significant interaction between adverse childhood experience in children aged 0 to 18 years of age and a higher risk of an ASD diagnosis. Furthermore, because of their dependence on other, they are at a higher risk of victimization and abuse. Social isolation, family stress, financial and psychological stressors for the members taking care of these children all represent risk factors contributing to an increased abuse of children with ASD and other neurodevelopmental disorders, further leading to experiences of childhood trauma (Sullivan, Knutson, 2000; Orsmond et al., 2004; Newschaffer et al., 2007). An analysis of the cases of child protective services in Minnesota, United States of America, reported a higher number of children with ASD than those without it, especially in cases of physical abuse (Hall-Lande et al., 2014). Additionally, children with ASD who have experienced sexual and physical abuse had a six-times higher risk of attempting suicide, and an eight-times higher risk of engaging in risky and abusive behaviors (Mandell et a., 2005). A study from Istanbul done on a sample of adolescents with ASD reported that 26% of the individuals have experienced childhood trauma, out of which 67% showed symptoms of PTSP (Mehtar, Mukaddes, 2011).

2.2.12.3. Negative Life Events

Adult individuals with diagnosed ASD have reported to have a wider range of negative, traumatic life events, which have been identified as mediators for probable PTSP diagnosis with both non-DSM 5 and DSM-5 criterions for traumas (Rumball et al., 2020). In the DSM-5, Criterion A for diagnosing PTSP includes one directly experiencing, witnessing, or learning that a close person experienced a traumatic event, as well as being exposed to extreme or continuous aversive details of traumatic events (American Psychiatric Association, 2013).

The results show a higher prevalence of probable PTSP than in the general population, with the probability being between 43% and 45% for both DSM-5 and non-DMS-5 criterions. When focusing on DSM-5 criteria, physical and sexual abuse have been found to be the most common, while bullying, bereavement, and traumas related to mental health problems are highlighted as most common non-DSM5 traumas (Rumball et al., 2020). The same study presented a finding that more than 60% of the participants reported to have experienced probable PTSP at one point in their lives, and more than 40% having showed symptoms of probable PTSP in the last month. When including more specific traumatic events, such as academic failure or parental divorce, more than a half of the sample of adults with ASD reported experiencing more than one traumatic life event during their lifetime (Taylor, Gotham, 2016).

A plausible explanation to higher occurrence of probable PTSP in individuals with diagnosed ASD may be that they experience anxiety and stress in higher intensities than the general population, even in cases of harmless situations (Pfeiffer et al., 2005; Rodgers et al., 2012).

2.2.13. Cannabis Use

The association between substance abuse and ASD has gaining a growing interest, but the number of existing research reporting on this relationship remains limited. Yet, it is hypothesized that the effects of cannabis might have a different effect on people with ASD in comparison to their peers with neurotypical developmental trajectories. Both CBD and THC components may lead to endocannabinoid dysregulation, as well as GABA/glutamate imbalances in autistic individuals. These abruptions could possibly increase the risk of development of psychotic disorders in these individuals (Al-Soleiti et al., 2021; Bortoletto, Colizzi, 2022). Furthermore, the prevalence of substance-use disorders is increased in the population of ASD individuals, as opposed to the general public, as reported in a study by

Butwicka et al. (2016). The heightened risks for developing a substance-use disorder are extended to full siblings of autistic individuals, half-siblings, and parents who do not have an ASD diagnosis. A number of studies offer explanations of the shared familial heritability, some of them being that both substance-use disorders and ASD possibly share the same genetic risk variants, that de novo mutations might arise as a results of parental substance abuse, and that a heightened risk of developing ASD may be caused by epigenetic modifications stemming from psychoactive substance abuse (Govorko et al., 2012; Sanders et al., 2012; Zuo et al., 2013).

2.3. Association Between Autistic Traits and Psychotic-Like Experiences

A growing body of evidence suggests an association between ATs and PLEs, with studies reporting ATs in childhood and adolescence as increasing the risk for psychotic-like experience later in life, as well as the presence of ASD symptoms in individuals with schizophrenia (Stahlberg et al., 2004; Morgan et al., 2008; Bevan Jones et al., 2012; Sullivan et al., 2013; Taylor et al., 2015).

A review of 45 studies with participants being between 11 and 96 years of age, reported a pooled prevalence of psychosis in ASD as 9.4%, with risk factors being divided into three subgroups: environmental (migrant status based on the parental country of birth), socio-demographic (male gender and age), and clinical (lower IQ, lower global functioning, higher empathizing bias, stability of autistic symptoms in adulthood) (Varcin et al., 2022).

A review of seven different studies identified a greater prevalence of ATs in individuals with psychosis in comparison to the general public. The co-occurrence of ATs and psychosis has been found to be greater than for psychosis and ASD (Kincaid et al., 2017). The pooled prevalence of PLEs in ASD is found to be 24%, with hallucinations being present in 6% of the

sample, and delusions in 45% (Kiyono et al., 2020). The same research identified the correlation between ATs and PLEs to be r = .34.

The overlaps between schizophrenia and ASD seem to be most pronounced on the non-clinical/subthreshold ends of both spectrums, implying an existence of the association between PLEs and ATs (Esterberg et al., 2008). Research conducted by Dardani et al. (2023) reported a correlation between ATs and PLEs in individuals up to the age of 24. Furthermore, the same study shines a light on the moderating role of traumatic experiences on the interplay between PLEs and ATs. The importance of stressful and traumatic experiences has been implied in other research, with results suggesting a potential psychosis-inducing effect of said experiences in autistic individuals (Bortoletto et al., 2023).

Schizophrenia and ASD share characteristics of disrupted neurodevelopment of language, and difficulties with verbal and nonverbal communication, and social interaction, cognition, and competence (Dickinson et al., 2007; Penn et al., 2008; Kincaid et al., 2017; Fusar-Poli et al., 2020); It is reported that ASD symptoms, such as speech delay, absence of speech, and difficulty with emotional reciprocity, overlap with negative psychotic symptoms, such as alogia, and blunting of affect. ATs are found to be connected to PLEs regarding disturbances of thought possession, perception, and delusions, visual hallucinations (Cederlof et al., 2016; Martinez et al., 2021).

A higher number of ATs, and ASD diagnoses are found in individuals with a diagnosed psychosis in comparison to the general population (Kincaid et al., 2017). After a three-year follow-up, schizotypal traits were found in adolescents with ATs, showing an association between autistic and schizotypal characteristics, especially regarding the domains of unusual behaviors and social impairment. The correlation was greater for ATs and negative psychotic symptoms, but the results were not negligible for positive, disorganized, and general psychotic symptoms as well (Esterberg et al., 2008; Pourcain et al., 2018). A longitudinal study done by

Jones et al. (2012) reported an association between parent-reported ATs at seven years of age and the occurrence of PLEs at twelve years of age. The results showed an increased risk of occurrence of PLEs at the age of twelve for children whose parents reported concerning ritualistic behaviors, social interaction problems, speech problems, and the number of parent-reported number of ATs.

Further improving the understanding of the relationship between the two subclinical phenomena is the finding of associations between ATs and peer victimization, and between peer victimization and occurrence of psychotic-like symptoms, implying a mediation effect of victimization between ATs and PLEs (Jones et al., 2012; Stanyon et al., 2022).

The association may be explained by a hypothesis that both PLEs and ATs represent symptoms of the same disorder, which presentive differently with respect to distinct phases of neurodevelopment. This concept is also known as heterotypic continuity and it assumes a continuity of the disorder with manifestations of the disorder (behavioral characteristics) changing with age (Rutter et al., 2006). Secondly, it is plausible that ATs may function as risk factors for developing stress sensitivity, social isolation and/or rejection, bullying, and academic stress, all of which may indirectly increase the risk of PLEs (Schreier et al., 2009; Arseneault et al., 2011). Another explanation may lie in the shared aetiological mechanisms for both ASD and schizophrenia, including overlapping genetic and neurodevelopmental influence, and similar spurring neurodevelopmental trajectories close to onset of both disorders (Rapoport et al., 2009; Toal et al., 2009; Jones et al., 2012). MRI revealed neuroanatomical similarities between ASD and psychosis, including abnormal anatomies of striatal, temporal lobe, and cerebellar regions, reduced gray matter in the right insular cortex, bilateral cerebellum, fusiform gyrus, occipital lobe and lingual gyrus, and reduced white matter in the cerebellum and left lingual gyrus (Toal et al., 2009).

When focusing on exogeneous factors contributing both to the development of ATs and PLEs, studies researching the effect of seasonal births highlight different seasons as risk factors for ATs and PLEs, respectively (Lee et al., 2008; Herbert et al., 2012, Brown, 2011). Summer months of birth (June – August) have been associated with an increased risk of ASD in children, while winter births contribute to a heightened risk of developing psychosis, as found in a meta-analysis comprising 51 different studies (Hsu et al., 2021).

When focusing on genetics and overlapping heritability of PLEs and ATs, genetically based risk factors have been reported as common for both psychosis and ASD (Crespi et al., 2010). Direct and indirect associations between schizophrenia and ASD have been identified, showing how both conditions share similar pathogenic mechanisms which disrupt the neurodevelopment (Burbach, Van der Zwaag, 2009; Crespi, Thiselton, 2011; Ionita-Laza et al., 2014).

All copy number variations (CNVs) associated with schizophrenia had also been found to be associated with ASD, with an even higher risk of penetrance. The burden of CNVs associated with both ASD and schizophrenia is increased in individuals with psychotic symptoms (Rees et al., 2016; Legge et al., 2019). A genetic-risk overlap has been found in altered folate metabolism (mediated by the TT genotype of the MTHFR C677T locus), down-regulated RELN signaling, increased levels of oxidative stress (partially mediated by GSTM1 deletion allele, reduced GAD1 expression, and deletions of the NRXN1 gene (Harada et al., 2001; Akbarian et al., 2006; Buyske et al., 2006; Persico et al., 2006; Rujescu et al., 2009).

3. Aim of the Thesis

Considering the fact that genetic and environmental risk factors for schizophrenia are shared across the psychosis continuum (Pries et al., 2020a), it is likely that the risk factors may also influence psychosis expression in the context of the autism spectrum. In the present thesis we,

therefore, aimed to examine the moderating role of genetic risk (i.e., polygenic risk score) 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 PLEs in a cohort of adolescents and young adults from the general population.

4. Methods

4.1. Participants

The participants were sampled from the East Flanders Prospective Twin Survey (EFPTS) registry of multiple births in East Flanders, Belgium. The EFPTS is a population-based, prospective registry of twin and higher-order multiple births (HOM) gathered at birth. Data regarding chorion type, zygosity, as well as placental data are gathered, and the placental biopsies get taken and frozen for further, future research (Derom et al., 2019). Establishing the prevalence of twin and HOM births in a certain, previously defined geographic area, all while identifying various obstetric and obstetric-pediatric complications and outcomes by creating a registry as is the EFPTS proved useful in understanding the causes of twin pregnancies, investigating the genetic predispositions and mechanisms behind different phenotypes, and environmental influences on such phenotypes. The Twin Survey enabled researching the effects of said prenatal environmental influences on individuals later in life, with respect to intelligence, behavior, stress, sexual maturation, learning and behavior in school, psychotic symptoms, blood pressure, and (sub)clinical depression (Derom et al., 2019).

This study used the data across three waves – baseline and two follow-ups. The baseline data was established from April 2010 to April 2014. This TwinssCan project included participants

from ages of 15 to 35 years. The data also included parents, twins, and the twins' siblings. Altogether, the first wave of the TwinssCan Project included 821 twins and their non-twin siblings. Out of the participants, 29 have been excluded from the Project due to the incomplete data. The twin participants' ages upon enrollment in the Project were between 15 and 18. With respect to sex, 316 participants (39%) were male, while the rest 61% of participants were female. Sequential analyses based on DNA fingerprints, fetal membranes, umbilical cord blood groups, sex, and placental alkaline phosphatase have been used in determining zygosity. All participants were informed on the study procedure and had given their written consent. The study was approved by the Commissie Medische Ethiek van de Universitaire ziekenhuizen KU Leuven ethics committee (Pries et al., 2017).

4.2. Measures

The measures used in this research were Autism Spectrum Quotient (AQ) for ATs, and Community Assessment of Psychic Experiences (CAPE) for PLEs. Polygenic Risk Score (PRS) for schizophrenia was used for assessing the moderating role of genes. Environmental moderators have been dichotomized based on previously validated methods and they include obstetric complications using the McNeil-Sjöström Obstetric Complications (OC) Scale, bullying, which was assessed via Retrospective Bullying Questionnaire (RBQ), childhood adversities (physical abuse, emotional abuse, sexual abuse, physical neglect, emotional neglect) with the use of Childhood Trauma Questionnaire- Short Form (CTQ-SF), hearing impairment (self-report), winter births, the use of cannabis (Composite International Diagnostic Interview – CIDI).

4.2.1. Autistic Traits

The Autism Spectrum Quotient (AQ) is a self-report measure consisting of 50 questions divided into five subgroups: social skill, attention switching, attention to detail, communication, and imagination. Items have been selected from the Triad of Impairments (restrictive and repetitive behaviors, impaired social functions, social communication difficulties). Each item scores one point if the participant self-reports the behavior as autistic-like: poor communication skills, poor imagination, poor social skills, poor attention-switching, strong attention to detail, and strong focus of attention In order to reduce bias, half of the items were formulated in a way that produces an "agree" response, while the other half was worded to entice a "disagree" response in a high-scoring individual with ASDA or high-functioning autism (HFA). To avoid false negatives which may happen due to HFA individuals rating their behavior as more appropriate than it ought to be, the included questions targeted the individual's preferences, as opposed to merely rating their own behavior (Baron-Cohen et al., 2001). The items were measured on a four-point Likert scale, with 1 being "definitely agree", and 4 being "definitely disagree". The scores were assessed by a dichotomous scale, with 50 being the maximum score. A score of 1 was assigned for each response indicative of ATs, as well as for opposite items with "slightly disagree" and "definitely disagree" responses.

4.2.2. Psychotic-Like Experiences

The Community Assessment of Psychic Experiences (CAPE) is a self-report questionnaire comprised out of 42 items, created to assess PLEs in the general population (Koning et al., 2006). It measures both frequency and level of distress regarding positive and negative psychotic experiences, as well as depressive experiences on four-point Likert scales, varying from "never (1)", "sometimes (2)", "often (3)", "nearly always (4)", and "not distressed (1)",

“a bit distressed (2)”, “quite distressed (3)”, “very distressed (4)”. This study focused on the frequency scores. Hypomania and disorganization are not included in the CAPE due to uncertainty of true and reliable self-reported answers in the general population (Konings et al., 2006). With respect to individuals with an ultra-high risk (UHR) for developing psychosis, the use of CAPE in screening of UHR individuals should be highlighted, as it does not require specifically skilled interviewers (Mossaheb et al., 2012).

4.2.3. Bullying

The Retrospective Bullying Questionnaire (RBQ) is a self-report measure of retrospective recollection of bullying before the age of 17, which evaluates bullying as a global construct, rather than assessing specific types of bullying (Cooper et al., 2013). The 44 items are mostly multiple-choice questions, and they regard psychological bullying (i.e., manipulating, threatening), relational (covert) bullying (i.e., spreading rumors, lying), physical bullying (i.e., pushing, shoving, hitting), and verbal bullying (i.e., insults, name calling). The questionnaire assesses six distinct types of bullying: two verbal, two physical, and two indirect types of victimization. One is ought to assess the frequencies, seriousness, and duration of victimization, together with the gender, number of bullies, and one’s participation in active bullying. Frequencies, as well as duration, and seriousness are expressed on a five-point Likert scales (Shafer et al., 2004). This study focused solely on the frequency scores. Bullying was dichotomized based on whether the participants experienced bullying, with a cutoff of two or more times (≥2).

4.2.4. Childhood Trauma

Childhood trauma has been evaluated via the Childhood Trauma Questionnaire – Short Form (CTQ-SF), which is a self-report measure assessing sexual, physical, and emotional abuse, as well as physical and emotional neglect. The short form provides five items for each type of mistreatment, together with three more items concerning the Minimization/Denial validity scale for detecting the underreporting of mistreatments (Bernstein et al., 2003). In total, there are 28 items divided into five before-mentioned subgroups, assessed on five-point Likert scales. The graveness of childhood trauma is divided into low, moderate, and severe trauma for each subgroup (Bernstein et al., 1998). For the purposes of this research, scores were dichotomized based on whether participants experienced childhood trauma, with the cutoffs being: ≥ 8 for physical abuse, ≥ 9 for emotional abuse, ≥ 6 for sexual abuse, ≥ 10 for emotional neglect, and ≥ 8 for physical neglect.

4.2.5. Obstetric Complications

Obstetric complications including prenatal, perinatal, and postnatal periods have been measured using McNeil-Sjöström Obstetric Complications Scale (MSS) which evaluates the possible chances for somatic damage, with the focus being on CNS damage (McNeil et al., 2000). The MSS scale is assessed by a six-point scale with 1 being “not relevant or harmful”, to six being “very great harm or deviation in offspring”. Obstetric complications scores have been dichotomized in line with a score of five (severe harm or deviation in offspring) on the MSS. For this study’s purposes, the participants with severe obstetric complications had to fit at least one of the following criteria: umbilical cord complications, version extraction delivery mode, face or forehead fetal presentation during delivery, birth weight not exceeding two kilograms, and/or birth weight being at least 20% lower than their siblings’.

4.2.6. Hearing Impairment

Meta-analyses show a certain association between hearing impairment and a risk of developing psychosis (Linszen et al., 2016). The hearing impairment variable has been dichotomized using participants' self-reports regarding their hearing with 0 being "absent", and 1 being "present".

4.2.7. Winter Birth

The meta-analysis of eight studies researching the role of the season of birth in developing schizophrenia shows a slightly heightened risk in children born in winter and early spring in the Northern Hemisphere (Davies et al., 2003). This variable has been dichotomized based on whether the participants have been born in the months between December and March, or not.

4.2.8. Cannabis Use

The use of cannabis has been dichotomized as using or not using cannabis during one's lifetime. This variable has been measured with the Composite International Diagnostic Interview (CIDI), a structured interview designed to aid in determining the fulfillment of diagnostic criteria, specifically the Substance Abuse Model which attends to the use of various substances including alcohol, cannabis, opiates, tobacco, sedatives, stimulants and others (Robins et al., 1988; Andrews et al., 1998).

4.2.9. Negative Life Events

Negative life events variable has been measured by using the semi-structured Interview for Recent Life Events (IRLE). It comprises 61 different life events. The events are separated in

ten categories, including migration, marital events, social and family relationships, bereavement, courtship and cohabitation, education, work, health, legal, and finance. The interview uses the five-point Likert scale. Month of occurrence, independence, and objective negative impact are attached for each of the 61 events. The month of occurrence is attained with the help of precise occasions such as public or religious holidays, independence is scored as the unlikeliness that the event in question is a result of a psychiatric condition, while the objective negative impact is scored by the participant's evaluation of the intensity of the negative impact with respect to the possible circumstances and threat the certain event carries with itself (Paykel et al., 1997). The total score is then calculated by summing the amount of experienced negative life events during one's lifetime.

4.2.10. Polygenic Risk Score for Schizophrenia

Polygenic risk score for schizophrenia (PRS-SZ) investigates the genetic risk for developing schizophrenia by acquiring data from alleles which have been previously identified in various genome-wide association studies (GWAS) (Mistry et al., 2018). The very creation and principles of GWAS derive from the notion that multiple genes with moderate, fair effects on the genotypes and phenotypes of different conditions may, together, account for a significant percentage of genetic variations (Purcell et al., 2007). PRS-SZ offers a calculated genetic risk of developing schizophrenia with respect to distinct stages of disease development, as well as different populations. By using GWAS, large copy number variations (CNVs) and single nucleotide polymorphisms (SNPs) are investigated in relation to the development of schizophrenia and are then selected in order to calculate the PRS-SZ (Wray et al., 2014).

4.2.10.1. Calculating the Polygenic Risk Score for Schizophrenia (PRS-SCZ)

As reported by Turbetskoy et al. in 2022, twelve polygenic risk scores were calculated using the GWAS-schizophrenia data. Considering the genetic variations between different ethnicities, this study used the summary statistics from the European population in assessing the PRS. Linkage disequilibrium reference panel, together with the summary statistics, have been used to acquire $PRS_{cs\text{-}auto}$ for improving data accuracy by means of a Python-based command line tool – PRC-CS, which utilizes the Bayesian approach. Operating along the Bayesian regression offers a quick acquisition of the global shrinkage parameter (Φ) from the gathered data. Employing the PRS-CS provides a better understanding of genetic architecture, together with its subtle disruptions and alterations, by utilizing the continuous shrinkage priors which function on the principle of marker-specific adaptive shrinkage. Furthermore, it updates the effect changes in SNPs for each linkage disequilibrium block, thus offering improved computing and modelling of linkage disequilibrium patterns (Ge et al., 2019).

A continuous shrinkage prior was placed on the SNP weights acquired via summary statistics, and was then integrated with the external linkage disequilibrium reference panel in the same manner as in the 1000 Genomes Project Phase III European Sample (https://github.com/getian107/PRScs), and with respect to the workings of PRS-CS-auto. The 1000 Genomes Project (1kGP) is the world's first GWAS, with the Phase III consisting of 2,504 unrelated samples offering a database of genetic variations (Byrska-Bishop et al., 2022).

To calculate posterior effect sizes, the PRS-CS-auto default parameters were utilized. After calculating the posterior effect sizes, the „—score“ function and the SUM modifier in PLINK 1.9 were used to compute the PRS-SZ. Following quality control, 3,366,081 variables were utilized in the PRS-SZ computation.

To calculate the sensitivity of the acquired results, we used the PRSice-2, a software aiming to both automate and simplify the PRS analyses. This software appears useful since it performs

PRS analyses on multiple phenotypes at the same time, computes p-values, provides multiple alternative options for imputing missing genotypes, permits using different inheritance models for calculating the PRS (Choi et al., 2019). P-values, beta-values, and effective alleles were extracted from the summary statistics to calculate the PRSice-2. The overlapping SNPs between the 1000 genomes (reference panel), GWAS summary statistics (training dataset), and the TwinssCan dataset (target) have been selected, while the deletions, insertions, SNPs located in complex linkage disequilibrium loci and long-range linkage disequilibrium loci, ambiguous SNPs, and those SNPs with a MAF of < 0.01 and/or imputation quality of R2 < 0.9 were excluded from the further analysis (Supplementary table 1). PLINK clump function (round 1: --clump-kb 250 --clump-r2 0.5; round 2: --clump-kb 5000 --clump-r2 0.2) was used in order to clump the remaining, selected SNPs. Supplementary table 2 offers a view of the number of alleles used in the PRS calculation.

When it comes to autosomal SNPs (summary statistics for neuroticism), their odd ratios were log-converted in beta-values. The PRS were then calculated using the PRSice-2 with respect to P-value thresholds (5×10^{-6}, 5×10^{-5}, 5×10^{-4}, 5×10^{-3}, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 and 1), while the p-threshold amounted to < 0.05.

4.3. Statistical analysis

The analyses were conducted using the Stata 16 (StataCorp, 2019). Considering the clustering was done within pairs of twins, multilevel linear regression models were used for analyzing the collected data. CAPE total scores were chosen as dependent variables, while AQ total scores were chosen as independent variables in multilevel linear regression models for investigating the connection between psychosis-like experiences and ATs. CAPE total scores were used as dependent variables also when analyzing the connection between PLEs, and genetic and environmental risk factors (negative life events, bullying, obstetric complications, winter birth,

cannabis use, PRS-SCZ, and childhood trauma), while the following were chosen as independent variables: binary CTQ subscores, RBQ, MSS, winter birth, cannabis use, continuous LEQ, and PRS-SCZ scores.

When examining the moderating roles of genetic and environmental risk factors on the relationship between PLEs and ATs, interactions between all independent variables and the AQ total score were, one by one, added to the multilevel linear regression models. The PRS-SCZ and AQ scores were standardized prior to being included in the multilevel linear regression model, so as to assist in the interpretation of the coefficients. Gender and age variables were chosen as covariates in all of the multilevel linear regression models, Furthermore, two principial genetic components, PC1 and PC2, were added to all multilevel linear regression models which used PRS-SCZ as a variable. Bonferroni correction was used for multiple testing corrections. The threshold of determining the statistical significance of the results was identified as $p < 0.05$.

5. Results

5.1. Sample Characteristics

The sample characteristics, as well as descriptive analyses of the risk factors are displayed in Table 1. In total, the dataset included 792 participants, including 274 monozygotic twins, 475 dizygotic twins, and 43 siblings. Approximately, 60% of the sample was made of females, with the mean age of 17.47 (±3.6). The mean AQ total score was 15.62 (±5.69), while the mean CAPE frequency total score was 1.56 (±0.26). When considering childhood trauma, approximately 43% of participants experienced emotional neglect, 31% experienced emotional abuse, 16% underwent physical neglect, 7% sexual abuse, and 4% physical abuse. Experiences of bullying victimization have been reported in around 62% of participants, out of which 20%

were exposed to serious bullying. Obstetric complications have been reported in around 22% of the participants. Almost 37% of the sample was born in winter season. Hearing impairment has been reported by 7 individuals, which makes up around 1% of the total sample. Consuming cannabis has been noted for 39 participants, which comes to approximately 6% of the sample. The mean of the PRS-SCZ score has been identified as -2.2×10^{8} ($\pm6\text{x}10^{7}$).

Table-1. Sample Characteristics (N = 792)

Characteristics	**N=792**
Age (years), M (SD)	17.47 (3.60)
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, 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 > 1	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, SD: Standard deviation, CAPE: The Community Assessment of Psychic Experiences, AQ: The Autism Spectrum Quotient, PRS-SZ: schizophrenia polygenic risk score.

5.2. Associations between autistic traits (ATs) and risk factors for schizophrenia with psychotic-like experiences (PLEs)

Table 2 shows a significant association of ATs with total CAPE (B: 0.12, 95% CI: 0.10 to 0.14, P < 0.001). Though PRS-SCZ was not found to be associated with total CAPE (B: 0.01, 95% CI: -0.01 to -0.03, P = 0.33), negative life events, bullying, and all childhood trauma subtypes showed significant positive associations with total CAPE (all P < 0.001). Other risk factors for schizophrenia and the total CAPE have not been shown to have significant associations (Table 2).

Table-2. Associations between psychosis-associated risk factors and autistic trait (ATs)s with psychotic-like experiences (PLEs)

	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

5.3. Moderations of risk factors for schizophrenia on the association between autistic traits (ATs) and psychotic-like experiences (PLEs)

Interaction analysis showed no moderating role of PRS-SCZ on the association between AQ total and CAPE total, indicating no role of genetic risk for schizophrenia in the association between ATs and PLEs. 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) all 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 corrected for multiple testing (Table 3). The positive associations between ATs and total CAPE according to childhood trauma subtypes has been depicted in marginal plots (Figure 1). No other significant results were found, meaning that winter birth, hearing impairment, cannabis use, bullying, and obstetric complications did not significantly interact with ATs in predicting total PLEs.

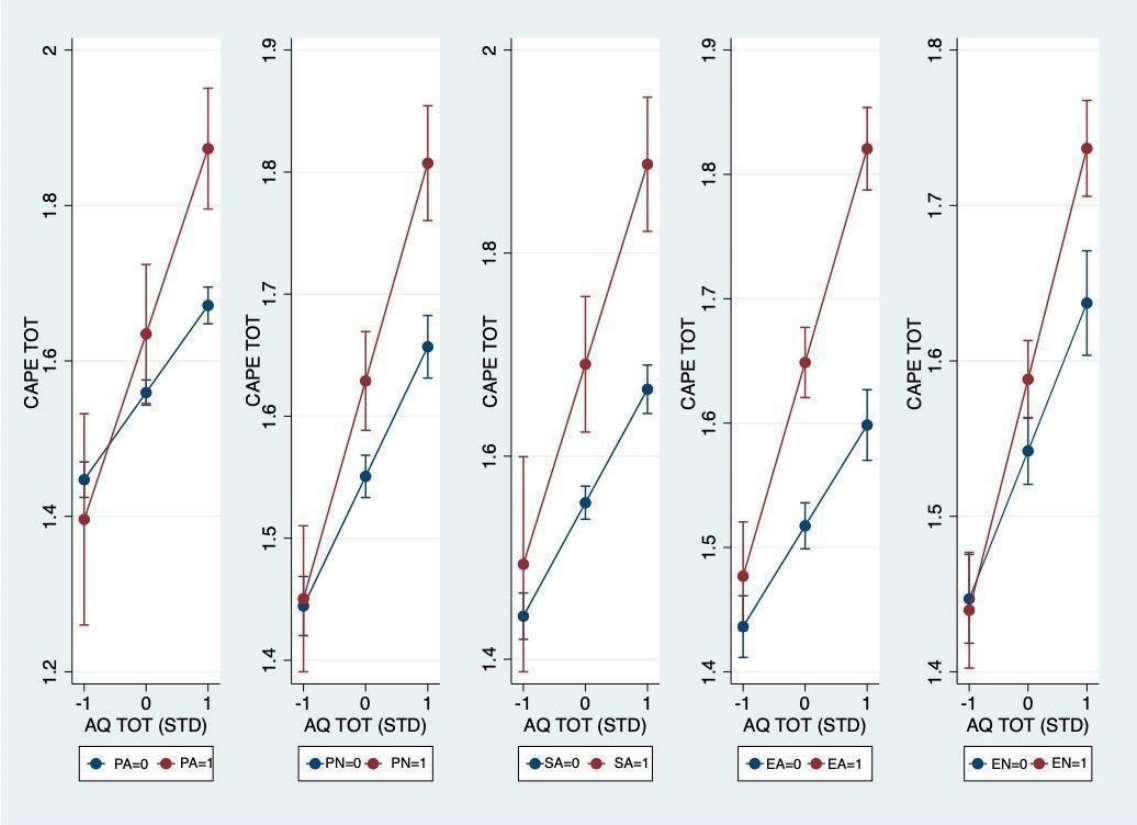
Table-3. Interaction effects of psychosis-associated risk factors and AT on Pes

	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

Figure-1. Interaction effects of childhood trauma subtypes and autistic traits (ATs) on psychotic-like experiences (PLEs)**.**



Marginal effect plots based on multilevel linear reression of the interaction between standardized total AQ score (x-axis) and different types of childhood trauma score on total CAPE frequency score(y-axis). CAPE TOT: Total CAPE frequency, AQ TOT (STD): Standardized Total AQ, PA:Physical abuse, PN: Physical neglect, SA:Sexual abuse, EA:Emotional abuse, EN:Emotional neglect

6. Discussion

The present thesis examined the factors moderating the association between ATs and PLEs in a general population twin sample, namely the TwinssCan cohort. We first tested the main associations of ATs and risk factors for schizophrenia with PLEs, finding hat ATs, all five childhood trauma subtypes, bullying, and negative life events were significantly associated with PLEs. Our main analyses revealed that AT significantly interacted with childhood traumas subtypes, particularly emotional abuse, physical abuse, sexual abuse, and physical neglect, on the expression of psychosis, although emotional neglect only showed a trend for significant interaction. However, genetic (i.e., PRS for schizophrenia) and other environmental risk factors for psychosis (i.e., bullying, obstetric complications, cannabis use, negative life events, winter birth, and hearing impairment) did not significantly moderate the relationship between ATs and PLEs.

As hypothesized and shown in previous studies, a statistically significant association between ATs and PLEs has been found. The already existing literature suggest a significant interplay between ASD and psychosis (Esterberg et al., 2008; Martinez et al., 2021). Increased risk of PLEs later in adolescence has been associated with a larger number of ATs in childhood and early life research (Bevan Jones et al., 2012; Martinez et al., 2021).

The results of this study show interactions between ATs and childhood trauma, especially emotional, sexual, and physical abuse, and physical neglect, on the expression of psychosis. Interaction with emotional neglect had a trend for significance ($p=0.007$). Nonetheless, hearing impairment, PRS-SCZ, negative life events, bullying, winter birth, cannabis use, nor obstetric complications were of statistical significance as moderating roles.

6.1. Childhood Trauma and Bullying

The results show that childhood trauma, but not bullying, significantly moderates the connection between ATs and PLEs. The same conclusions have been found in previous research which identified both bullying and childhood trauma as important factors contributing to the development of ATs, as well as the enduring consequences of these factors on autistic individuals (Berg et al., 2016; Fuld, 2018.; Roberts et al., 2015). To date, only a small number of studies had investigated the role of childhood trauma and bullying on the risk of psychosis development in individuals with an increased number of ATs. Two previous studies highlighted the mediating role of childhood trauma and bullying on the association between ATs and PLEs, this research identifies childhood trauma as having a greater moderating role as opposed to bullying (Dardani et al., 2023; Stanyon et al., 2022). The differences between moderating roles of bullying and childhood trauma may occur due to different timing and ways of victimization. Bullying usually occurs in school-aged children who have already, by that age, developed a number of coping mechanisms. Furthermore, children of school age possess external support systems which can help greatly in lowering the impact of bullying. On the other hand, childhood trauma usually occurs earlier in life, during crucial developmental stages, thus carrying the risk of more profound and chronic effects on the child. This is especially true for individuals with a higher number of ATs who may already have atypical neurodevelopmental trajectories. Considering the results of this study, in line with the literature and the results reported in previous research, childhood trauma emerges as an important factor in subclinical psychosis expression.

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6.2. Negative Life Events

The results of this study showed no interactions between the number of negative life events and ATs, regardless of the significant effect of the number of negative life events on PLEs. Individuals with ASD may be prone to experiencing more frequent and intensely perceived stressful life events, which could in turn further worsen their symptoms and subsequent psychopathology, as well as their general mental health (Berg et al., 2018; Fuld, 2018; Hoover, Kaufman, 2018; Schneider et al., 2019). The relationship between psychotic and manic symptoms in autistic people, and stressful and problematic family and school and/or work environments has recently been examined in just one research (Bortoletto et al., 2023). Unfortunately, it did not focus on examining the relationship between negative life events and ATs. The present thesis intended to expand on the mentioned research by investigating the interaction between the number of negative life events and ATs regarding PLEs but found no significant connection. There may be few reasons accounting for the lack of this relationship, with one being that individuals included in our sample -derived form the general population- may likely possess coping mechanisms which are more effective when coping with negative life events, in comparison to clinical samples of people with a full-blown diagnosis of ASD. Conversely, individuals with higher ATs may already have an elevated stress perception at baseline. Therefore, a higher number of negative life events may not necessarily increase their stress levels, nor lead to PLEs, thus leading to a less-pronounced effect of negative life events, and a weaker association with ATs. Taking the mentioned explanations in mind, future studies exploring the interaction between coping mechanisms and negative life events on PLEs across the autism spectrum are needed.

6.3. Obstetric Complications

The results of this study showed no significant interaction betweem obstetric complications and ATs on PLEs, meaning that obstetric complications do not seem to have a moderating role on the relationship between ATs and PLEs. Looking at previous studies, to the best of my knowledge, no research has been conducted on the association between obstetric complications and the risk of developing psychosis in clinical ASD, nor in the ATs in the general population. One might hypothesize that different types of severe obstetric complications might impact different brain areas, with respect to the severity threshold for obstetric complications. Depending on the subtype of said complications, affected brain regions might not be the same as those regions associated to PLEs in individuals with increased ATs. Nevertheless, the lack of research on this topic, as well as the findings of this study, call for further investigation of the role of obstetric complications in both larger clinical ASD samples, and in a larger general population.

6.4. Cannabis Use

Cannabis use has not been regarded as a significant moderating factor in the association between ATs and PLEs in this thesis. Still, the lack of research done on the topic of cannabis use-related psychosis in autistic individuals is noteworthy to mention. Findings from previous research done by De Alwis et al. (2014) imply a greater risk for developing cannabis use disorders in individuals with higher ADHD symptoms/ATs, even following controlling for conduct disorder. Another study revealed a two-fold increase in risk of developing substance use-related problems in autistic individuals (Butwicka et al., 2017). This study aimed at bridging the gap between these topics, and addressing the connection between cannabis use, PLEs, and ATs. However, it is important to note the low power of analysis in this research, since there was only a small number of cannabis users in the population sample (n=39). Most

existing research on cannabis use in ASD is focused primarily on medical use, as opposed to recreational use, limiting the knowledge on the relationship between non-medical cannabis use and psychosis expression in the context of ASD. Thus, more studies are needed to further understand this interplay.

6.5. Winter Birth

A significant association with PLEs, nor a significant interaction with ATs in predicting PLEs has not been found for the winter birth factor. Already existing research showcase inconsistent findings, with a number of studies reporting fall or spring births as risk factors, and others revealing no correlation (Mouridsen et al., 1994; Kolevzon et al., 2006; Atladottir et al., 2007; Hebert et al., 2010; Lee et al., 2019). Furthermore, research investigating psychotic traits in autistic children proposed a hypothesis stating that ASD with lower SST may be a homogenous form of autism. The results did not show an expected association between psychotic traits and winter birth, but rather an association between the group without psychotic traits and spring-summer births, disproving their hypothesis that winter births may be a risk factor for ASD with higher psychotic traits (Gadow, DeVincent, 2012).

Furthermore, results from already existing studies in which the connection between psychosis expression and winter birth has been identified are generally weak (Hsu et al., 2021; Tochigi et al., 2013). Keeping the reported results from aforementioned studies in mind, it is clear that more research must be done in order to further understand the interplay between the season of birth and the risks for developing psychosis and autism.

6.6. Hearing Impairment

The results of the present thesis do not suggest an association neither hearing impairment and ATs, nor and interaction between hearing impairment and ATs in further predicting PLes. This is in contrast with previously published research reporting an increased risk of psychotic symptoms to hearing impairment (Linszen et al., 2016). These different findings may be explained by a small number of individuals with hearing impairments in this study (n=7). Given that the prevalence of people with ASD who also have hearing impairments is estimated only around 9%, studies with larger sample sizes should be conducted in the future, therefore allowing a greater power to identify a statistically significant interaction between hearing impairment and ATs in predicting PLEs.

6.7. Genetic Risks

Multiple genetic studies have identified both direct and indirect connections between autism and schizophrenia (Burbach, Van der Zwaag, 2009; Crespi, Thiselton, 2011; Ionita-Laza et al., 2014). Yet, literature on the interaction between genetic risks for schizophrenia and ATs on psychosis expression still remains as limited. This thesis first examined the main effect of PRS-SCZ on PLEs, and then its interaction with ATs on PLEs. The results showed no significant connection between PLEs and PRS-SCZ, which does not go hand-in-hand with findings reported in earlier genetic studies (Karcher et al., 2022; Legge et al., 2019). These discrepancies may be attributed to the size of the population sample of this study, since the already existing studies done by Zammit et al. (2014) and Sieradzka et al. (2014), who also reported no significant association, also had smaller sample sizes. Keeping this reasoning in mind, it ought not to be surprising that no significant interactions has been found between ATs and PRS-SZ in predicting PLEs, since that would also require a sample size larger than the one used in this

study. Therefore, in order to truly identify the moderating role of PRS-SCZ when it comes to ATs and PLEs, future studies should include larger sample sizes.

7. Strengths and Limitations

The main strength of this thesis is that it assesses – for the first time - the role of environmental and genetic risk factors for schizophrenia, other than childhood trauma and bullying, as moderators in the relationship between ATs and PLEs. The study has been conducted in a large sample from the general population.

However, a few limitations should be considered. First, childhood adversities, negative life events, as well as bullying, were evaluated via self-report measures, which may be prone to recall bias. Yet, retrospective and prospective reports of childhood trauma, mentioned in earlier studies, have been shown to be connected to mental health problems during both adolescence and adult age, thus supporting the validity of our results (Newbury et al., 2018; Reuben et al., 2016).

The second limitation is that this study is susceptible to type II error when it comes to certain risk factors like genetic risk factors, cannabis use, and hearing impairment, with small effect sizes or low prevalences. Furthermore, type I error may also occur due to testing for multiple risk factors in schizophrenia. Bonferroni correction was used in order to avoid this, implying a lower chance of bias.

Third, ATs and PLEs were investigated as a continuum, which was allowed due to the general population sample which was used. Taking this into account, one should be aware of the limits this perspective carries in the context of generalization to individuals who meet the full criteria for ASD. Therefore, similar analyses should be conducted in clinical samples, granting the fact

that there still has not been developed a validated tool for assessing PLEs in autistic children (Hastings, 2020).

Finally, the cross-sectional nature of the present analysis does not allow to draw any conclusion about temporal or causal relationship between PLEs and risk factors. For identifying a causal inference, future studies should use a longitudinal design.

8. Conclusions

The findings reported in the present thesis highlight the intricate interaction between environmental and genetic factors in psychosis and autism, focusing particularly on subthreshold expressions. The results show that different types of childhood adversities may moderate the association between ATs and PLEs, increasing the risk of psychosis expression in people with elevated ATs. However, no meaningful interaction between other environmental risks, such as bullying, negative life events, and genetic risks, and ATs when it comes to predicting PLEs. Identifying those with greater ATs and screening them for early adversities might aid in the development of preventative interventions to protect them from subsequent environmental risk exposure.

These findings are relevant to improve the knowledge on the complex relationship between autism and psychosis. Additionally, they have clinical implications for implementing prevention strategies focused on vulnerable groups, developing personalized treatment regimens with respect to the person's individual risk profile, thus improving therapeutic outcomes. Future research studies should include larger samples and should be conducted with a longitudinal design in order to further understanding this association and the complex mechanisms behind the overlapping characteristics of ATs and PLEs.

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