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Environmental Risk Factors and Cognitive Outcomes in Psychosis: Pre-, Perinatal, and Early Life Adversity

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Abstract

Risk for psychosis begins to accumulate as early as the fetal period through exposure to obstetric complications like fetal hypoxia, maternal stress, and prenatal infection. Stressors in the postnatal period, such as childhood trauma, peer victimization, and neighborhood-level adversity, further increase susceptibility for psychosis. Cognitive difficulties are among the first symptoms to emerge in individuals who go on to develop a psychotic disorder. We review the relationship between pre-, perinatal, and early childhood adversities and cognitive outcomes in individuals with psychosis. Current evidence shows that the aforementioned environmental risk factors may be linked to lower overall intelligence and executive dysfunction, beginning in the premorbid period and persisting into adulthood in individuals with psychosis. It is likely that early life stress contributes to cognitive difficulties in psychosis through dysregulation of the body's response to stress, causing changes such as increased cortisol levels and chronic immune activation, which can negatively impact neurodevelopment. Intersectional aspects of identity (e.g., sex/gender, race/ethnicity), as well as gene–environment interactions, likely inform the developmental cascade to cognitive difficulties throughout the course of psychotic disorders and are reviewed below. Prospective studies of birth cohorts will serve to further clarify the relationship between early-life environmental risk factors and cognitive outcomes in the developmental course of psychotic disorders. Specific methodological recommendations are provided for future research.

Keywords

Childhood trauma; Cognition; Obstetric complications; Psychosis

1 Introduction

Although psychotic disorders, such as schizophrenia, tend to emerge during later adolescence/early adulthood, substantial evidence points to its neurodevelopmental origins beginning as early as the fetal period. Specifically, repeated studies have linked pre- and

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perinatal complications (Davies et al. 2020) and postnatal childhood adversity (Varese et al. 2012) to increased risk of psychosis (Brown 2011), and worsened course (Walker et al. 2008), and earlier onset of illness (Verdoux et al. 1997; Cannon et al. 2002a; Neill et al. 2020). Furthermore, signs of brain compromise in a large subgroup of patients with psychosis have been observed well before the onset of the disorder, with premorbid cognitive difficulties in approximately 40–50% of cases (Khandaker et al. 2011; Mollon and Reichenberg 2018). Cumulatively, these findings suggest that disruptions in neurodevelopment, particularly from pre- and postnatal adverse events, can lead to observable changes in behavior before any symptoms of the disorder emerge.

This review summarizes human literature linking prenatal, perinatal, and early childhood risk factors for cognitive outcomes across the developmental course of psychosis spectrum disorders. Furthermore, this review examines the relationship between these early environmental risk factors, cognition, and intermediate phenotypes of these disorders. Various mechanistic underpinnings of these relationships, including dysregulation of the hypothalamic-pituitary adrenal (HPA) axis, inflammation, and structural and functional brain changes, are explored. Specificity of these relationships to psychosis spectrum disorders is also considered.

2 Obstetric Complications and Cognition in Psychosis

Obstetric complications (OCs) refer to a broad range of difficulties during pregnancy and at birth and are among the most well-replicated environmental risk factors for psychosis (Cannon et al. 2002a; Ellman and Cannon 2008; Mittal et al. 2008). Namely, prenatal infection (Brown and Derkits 2010), maternal stress (Lipner et al. 2019), and fetal hypoxia (Mittal et al. 2008) are among the most well-studied OCs associated with psychosis risk. Maternal health behaviors (e.g., nutrition, nicotine use) have also been linked with psychosis outcomes (Brown and Susser 2008; Scott et al. 2018), and act transactionally with other co-occurring OCs linked to psychosis, including stress (Lipner et al. 2019). Subtle neurodevelopmental changes conferred by these prenatal adversities can prime offspring to be more susceptible to postnatal challenges and/or lead to a cascade of other cognitive, social, and behavioral outcomes. This paper will discuss the aforementioned OCs and their relationship to cognitive functioning in the course of psychotic disorders. Given recall bias evident in retrospective reporting of OCs (McIntosh et al. 2002), only studies that prospectively collected information about OCs were included.

2.1 Prenatal Infection

Exposure to infections during pregnancy (e.g., influenza, rubella, genital/reproductive infections) has been associated with an increased risk for psychotic disorders in offspring (Brown and Derkits 2010; Karlsson and Dalman 2020). Ecologic studies were among the first to establish this relationship. In one such study, offspring of women pregnant during the 1957 influenza epidemic were more likely to develop schizophrenia than those who were pregnant in a different time (Mednick et al. 1988). Although useful in preliminarily understanding the link between prenatal infection and psychosis risk, ecologic studies include mothers who did not actually incur the infection themselves and may not adequately

demonstrate the strength of the relationship between exposure and psychosis outcomes (Brown 2011). Individual-level evidence from birth cohort studies or population-based studies from countries with national health registries provide more specific evidence about the relationship between prenatal infection and offspring outcomes utilizing prospectively collected measures of infection, such as serologic determination or physician diagnoses from medical records. Often using a nested case–control design, birth cohort studies have also compared outcomes between psychosis cases and controls, with or without exposure to various types of infections (Ellman and Susser 2009).

A handful of birth cohort studies examine the relationship between prenatal infection exposure and premorbid cognition within offspring who did and did not go on to develop a psychotic disorder. One such cohort, the Collaborative Perinatal Project (CPP), provided evidence of associations between serologically determined prenatal infection and impairments in cognitive function at age 7 (Ellman et al. 2009). Maternal influenza B infections during the third trimester, but not influenza A infections, were associated with significant decreases in verbal IQ and performance on the Information subtest of the Wechsler Intelligence Scale for Children (WISC) in those who went on to develop schizophrenia, but not controls (Ellman et al. 2009). Findings from the Rubella Birth Defects Evaluation Project also demonstrated a relationship between serologically determined prenatal rubella exposure and diminished IQ among those who went on to develop a schizophrenia spectrum disorder (Brown et al. 2001). Exposed offspring who developed schizophrenia spectrum disorders, but not rubella-exposed controls, also demonstrated a significant decline in IQ from childhood to adolescence. These studies demonstrate that prenatal infection may account for poorer cognitive performance prior to the onset of psychotic disorders and highlight that the type, and even strain, of infection may impact the cognitive difficulties that arise following infection exposure.

To our knowledge, only two additional studies examine the relationship between prenatal infection and cognitive deficits in adults with psychosis. In the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) cohort, prenatal exposure to genital/reproductive infections, confirmed by either medical records or seropositivity to immunoglobulin antibody for herpes simplex virus-2, was examined with respect to cognitive outcomes in adulthood (Brown et al. 2011). Significantly poorer verbal memory performance, measured by the California Verbal Learning Test (CVLT), was observed in exposed, compared to unexposed, offspring with schizophrenia. Verbal memory findings were only significant in offspring born to Black mothers (Brown et al. 2011). In the same cohort, cases with serologically documented exposure to influenza and toxoplasmosis showed impaired performance on the Wisconsin Card Sorting Test (WCST) and Trails B assessments in adulthood, indicating poorer executive functioning, specifically in cognitive set shifting (Brown et al. 2009). In sum, these findings suggest that prenatal infection is associated with both general and specific (e.g., verbal memory, executive function) cognitive difficulties beginning as early as age 7 that persist into the full disorder. Maternal and offspring demographics, and qualities of the infection, are also likely meaningful moderators of these relationships.

The mechanisms by which infection confers risk to the fetus vary by infection type and gestational timing. Some infections, like rubella, can cross the placenta and fetal blood-brain barrier, directly impacting neurodevelopment (Brown et al. 2001). Genital and reproductive infections may impact the fetus by way of microbes present in the placenta or vagina, proximal to the fetus itself (Engman et al. 2008; Brown 2011). Alternatively, most prenatal infections (e.g., influenza) do not appear to cross the placenta and likely impact the developing fetus by mechanisms co-occurring with infections, such as the maternal proinflammatory response (Fineberg and Ellman 2013). Human studies have identified that elevations in specific inflammatory biomarkers, such as interleukin (IL)-8, during pregnancy are associated with increased risk for psychotic disorders, moderated by both timing of the elevation and fetal sex (Buka et al. 2001; Brown et al. 2004; Goldstein et al. 2014). A study from the New England Family Study (NEFS) examined the relationship between prenatal maternal cytokine levels and cognitive and academic outcomes across all offspring, finding that higher levels of tumor necrosis factor-alpha (TNF-α) in the second and third trimesters were associated with lower IQ at age 7 (Ghassabian et al. 2018). Higher maternal C-reactive protein has also been associated with poorer teacher-judged academic achievement in adolescence, a risk factor for psychosis, in a recent study of the Northern Finland Birth Cohort (Ramsay et al. 2021). No studies to date examine the relationship between prenatal inflammation and cognition in individuals with psychosis.

Methodological hurdles exist in examining immune markers and specific offspring outcomes. As such, animal models of maternal immune activation provide an opportunity to experimentally induce timing-specific changes in prenatal inflammation via bacterial (polyinosinic:polycytidylic acid) and viral (lipopolysaccharide; LPS) agents (Meyer 2014) to explore cognitive outcomes in offspring (Estes and McAllister 2016). For example, rodent models show that higher IL-10 and IL-6 at mid-gestation are associated with deficits in spatial exploration, associative learning, and prepulse and latent inhibition in adult offspring (Smith et al. 2007; Meyer et al. 2008). Furthermore, LPS-induction has been associated with changes in the hippocampus and alterations in learning and memory in rodents (Golan et al. 2005). These findings suggest that fetal exposure to maternal inflammation during pregnancy can result in cognitive changes similar to those observed in schizophrenia.

Overall, prenatal infection is associated with poorer general and verbal intellectual functioning in the premorbid period and in adults with psychotic disorders. There is also evidence that infection may impact verbal memory and executive functioning in adults with schizophrenia. These findings should be taken with caution given small sample sizes in nested case–control designs. Additional studies examining the link between proinflammatory markers and cognitive outcomes in individuals with psychosis are needed. Importantly, exposure to maternal prenatal infection has been linked to a greater incidence of infections in childhood, an additional risk factor for the onset of psychotic disorders (Blomström et al. 2016). Furthermore, serious early childhood infections have been linked with poorer cognitive performance (e.g., lower IQ) in individuals who develop a psychotic disorder, independent of genetic risk (Karlsson and Dalman 2020).

As such, prenatal infection is associated with poorer neurocognitive development in individuals prior to the onset of, and within the course of, psychotic disorders. Prenatal

adversity may also increase risk for additional “hits” later in development, conferring added risk to offspring. Because there is evidence that prenatal infection and inflammation, and childhood infection, are linked to a range of psychiatric outcomes, including autism and depression (Jiang et al. 2016; Murphy et al. 2017), the effects of prenatal infection on premorbid cognitive changes may be shared amongst psychological disorders. Although prenatal infection has been more extensively studied in the context of schizophrenia risk compared to other psychopathologies (Ellman et al. 2018), studies examining the link between prenatal infection and other diagnostic outcomes are growing (e.g., Simanek and Meier 2015). Preliminary findings from rodent and non-human primate models may provide insight into transdiagnostic premorbid neurological and cognitive outcomes following maternal immune activation that contribute to the course of neurodevelopmental disorders (Giovanoli et al. 2015; Vlasova et al. 2021).

2.2 Prenatal Maternal Stress

Prenatal maternal stress (PNMS) has been associated with risk for psychosis spectrum disorders, as well as several other adverse psychological (e.g., depression, attention deficit disorder, autism) and physical health outcomes (e.g., cardiovascular disease, obesity, asthma) in offspring (Van den Bergh et al. 2020). Ecologic (e.g., war, natural disaster) and individual level (e.g., traumatic life events, perceived stress) studies have linked PNMS to psychosis outcomes, in particular (Lipner et al. 2019). Operationalization of PNMS varies, sometimes including both objective and subjective measures of PMNS (Sutherland and Brunwasser 2018). Timing of PNMS and fetal sex are shown to impact vulnerability to the effects of PNMS on neurodevelopment (Lipner et al. 2019; Eyles 2021). Although the association between psychotic disorders and PNMS is well-replicated, to our knowledge, no study has examined the impact of PNMS on cognitive difficulties in the developmental course of psychotic disorders. As such, we can only hypothesize about how PNMS may impact cognitive development in individuals with psychotic disorders in both the premorbid period and in adulthood.

Studies from non-psychiatric, community samples provide insight into how PNMS may contribute to cognitive deficits in psychosis. PNMS is associated with several early cognitive outcomes typical of individuals who develop psychotic disorders (Beydoun and Saftlas 2008; Kingston et al. 2015; Lafortune et al. 2021). Researchers have demonstrated that 4.5-month-old infants exposed to high levels of PNMS had lower physical reasoning performance (e.g., ability to deduce physical causality; Merced-Nieves et al. 2020). As physical reasoning can be impaired in those with psychosis (Brunet et al. 2003), PNMS may contribute to this outcome. Cognitive delays associated with PNMS may become more pronounced with development, with one study documenting cognitive delays on both the mental and motor scales of the Bayley Scales of Infant Development upwards of three times greater in toddlers exposed to high levels of prenatal maternal anxiety than their non-affected counterparts (Brouwers et al. 2001). Several studies have documented an association between PNMS and decreased performance on cognitive tasks measuring: (1) regulating and shifting attention (Huizink et al. 2004), (2) language abilities (Laplante et al. 2008, 2018), (3) executive functioning (Buss et al. 2011), and (4) learning and memory (Gutteling et al. 2006). Each of these cognitive domains has been shown to be

impaired during the premorbid period for psychotic disorders (Mollon and Reichenberg 2018). Notably, there are mixed findings on the relationship between PNMS and child IQ (Grizenko et al. 2015; Cortes Hidalgo et al. 2020), a documented intermediate phenotype for multiple psychological disorders (Koenen et al. 2009; Kremen et al. 1998, 2010; Lewis 2004).

PNMS may also exacerbate risk for other OCs associated with poorer cognitive performance in psychotic disorders, including infection, fetal hypoxia, and low birth weight (Lipner et al. 2019). PNMS can also elevate maternal glucocorticoids and inflammatory levels, altering the fetal environment during pregnancy and consequentially the fetal HPA axis (Coussons-Read 2013). Higher maternal cortisol levels during pregnancy have been associated with low birth weight in males who developed schizophrenia (Ellman et al. 2019). Male fetuses appear to be particularly vulnerable to the deleterious effects of PNMS and may be more likely to suffer from cognitive difficulties following PNMS exposure (Sandman et al. 2013; Sutherland and Brunwasser 2018). From research using community samples, higher maternal cortisol in late gestation has been associated with lower childhood IQ (LeWinn et al. 2009), poorer mental functioning, and delayed psychomotor development (Zijlmans et al. 2015), which are also associated with risk for multiple psychological disorders. Further evidence from both rodent and human studies demonstrates that higher levels of glucocorticoids are linked to brain abnormalities associated with cognitive deficits found in psychotic disorders, including increases in dopamine D2-like receptors in the striatum of rodents (Vidal and Pacheco 2020), higher incidence of dermatoglyphic asymmetry (Newell-Morris et al. 1989), and overall structural and cerebral asymmetry (Weinstock 2001).

Exposure to PNMS can have long-term implications on brain development and adult cognition (Charil et al. 2010). High levels of PNMS have been linked to smaller accessory basal and cortical nuclei volumes in the amygdala as well as larger bilateral amygdala volumes to total brain volume ratios (Jones et al. 2019; Mareckova et al. 2021), similar to changes observed in schizophrenia patients (Rasetti et al. 2009). Similarly, PNMS is shown to alter prefrontal cortex (PFC) and hippocampal-dependent cognitive functions in humans, including consolidation of memory and passive avoidance, which may contribute to the pathogenesis of schizophrenia (Negrón-Oyarzo et al. 2016). Human studies examining the consequences of PNMS on cognitive outcomes beyond childhood/adolescence are scarce; instead, current PNMS longitudinal literature favors rodent models (Beydoun and Saftlas 2008; Paquin et al. 2021). Animal studies demonstrate that early cognitive delays pave the way for more profound cognitive deficits related to psychosis risk in adulthood. For example, adult male rodents exposed to PNMS exhibit deficits in memory, including novel object recognition memory, spatial memory, and working memory (Markham et al. 2010). Male vulnerability to these worse cognitive outcomes may contribute to heightened male vulnerability to psychosis risk. As such, additional longitudinal research in humans is needed to clarify the relationships between PNMS and cognitive outcomes in individuals on the psychosis spectrum, with particular attention to both premorbid and adult outcomes and how fetal sex may moderate these relationships.

2.3 Hypoxia-Associated Obstetric Complications

Hypoxia-associated OCs, OCs related to decreased oxygen to the fetus, are found in the histories of about 20–30% of cases of schizophrenia (Mittal et al. 2008). Hypoxia-related OCs are often categorized as chronic placental hypoxia, occurring during the prenatal period, and acute perinatal hypoxia, occurring around delivery. Often, studies examine *probable* hypoxia-ischemic exposures, given that they utilize medical records to identify OCs that may have hypoxic effects. Fewer studies utilize biomarkers of hypoxic events, such as erythropoietin from umbilical cord serum, to define hypoxia exposure (Fineberg et al. 2013).

Low birth weight is also often a consequence of OCs and has been associated with an increased risk of psychosis, although some findings suggest that these associations are more prevalent among male offspring (Cannon et al. 2002a; Eide et al. 2013; Ellman et al. 2019). It is important to consider that low birth weight itself may not be a causal factor that leads to the onset of psychosis, but rather an observable and reliably measurable proxy for other perinatal adversity like fetal hypoxia, preterm birth, or placental dysfunction (Brown 2011). A study examining the CPP cohort provided evidence to further clarify these relationships, utilizing serologic determination for both influenza and hypoxia (Fineberg et al. 2013). Individuals with schizophrenia or affective psychoses with exposure to fetal hypoxia and/or influenza had lower birth weight compared to controls and unexposed cases (Fineberg et al. 2013). These findings suggest that exposure to these OCs associated with psychosis outcomes is linked to lower birth weight, particularly in individuals with vulnerability for psychosis. OC type may also impact vulnerability to particular types of psychotic disorders. While fetal hypoxia was associated with lower birth weight among individuals with schizophrenia, influenza B exposure was associated with lower birth weight among individuals with affective psychoses (Fineberg et al. 2013). Recent evidence demonstrates that other early life environmental risk factors (e.g., physical abuse, bullying, sleep quality) are differentially associated with dimensionally-assessed psychotic experiences (Cosgrave et al. 2021); as such, future prenatal research may unveil if/how certain OCs may differentially contribute to specific psychosis diagnoses and symptoms, as well as shared phenotypes with other mental disorders.

Birth cohort and population-based studies have examined the relationship between hypoxia-related OCs and premorbid cognitive outcomes generally. Studies from the CPP examining the entire cohort identified an association between antenatal hypoxia-related OCs and poorer IQ, verbal-perceptual abilities, achievement, and perceptual-motor abilities at age 7 (Naeye and Peters 1987; Seidman et al. 2000). An additional study from the CPP identified sex differences in these relationships, showing that chronic placental hypoxia was associated with lower verbal IQ and increased inhibition in female offspring only, whereas acute perinatal hypoxia was associated with diminished cognitive outcomes across sexes (Anastario et al. 2012).

Relationships between fetal hypoxia and premorbid cognitive outcomes vary slightly when examining offspring who go on to develop a schizophrenia spectrum disorder. Particularly, genetic risk appears to interact with hypoxia-related OCs in the pathway to neurodevelopmental changes. High-risk studies, utilizing at least one parent with psychotic

disorder history as a marker of genetic risk, provide further insight into these pathways. An additional study of the CPP examined cases, siblings, and matched controls and IQ outcomes at ages 4 and 7 (measured by the Stanford-Binet Intelligence Scale and WISC, respectively; Cannon et al. 2000). Findings demonstrated that there was no significant relationship between hypoxia-related OCs or birth weight and IQ in individuals who went on to develop schizophrenia spectrum disorders. Given that there were also no differences between IQ outcomes between cases and their unaffected siblings, it is likely that genetic vulnerability drives this relationship. Relatedly, in a study of offspring of parents with schizophrenia spectrum disorders and controls also from the CPP, hypoxia exposure was not associated with lower IQ at age 7 in high-risk offspring (Goldstein et al. 2000). Although it is possible that these analyses were not sufficiently powered to identify significance in this subgroup, these data highlight the importance of examining gene-OC interactions in relationship to cognitive outcomes in offspring with diagnoses across the psychosis spectrum.

Mechanisms by which genetic risk may interact with OC exposure to result in cognitive outcomes have been explored. Firstly, evidence from high-risk studies demonstrate that genetic vulnerability-fetal hypoxia interactions may account for various neurological sequelae in individuals with schizophrenia also associated with cognitive differences, including smaller hippocampal volumes, reductions in gray matter, and periventricular damage (Cannon et al. 1989, 2002b; van Erp et al. 2002). Furthermore, a study of the CPP examined the expression of brain-derived neurotrophic factor (BDNF) in maternal cord blood in cases with psychotic disorders and controls exposed to hypoxia (Cannon et al. 2008). In cases with psychotic disorders, hypoxia exposure was associated with decreases in BDNF in cord serum, whereas in controls, BDNF increased after exposure. Finally, a recent study examined the interaction between OCs and expression of schizophrenia risk genes derived from genome-wide association studies (Ursini et al. 2018). Their findings corroborate and expand upon the aforementioned CPP studies, identifying that genetic risk moderates the relationship between OCs and schizophrenia outcomes, such that schizophrenia-related genes are upregulated in placental samples exposed to hypoxia-related OCs (pre-eclampsia and intrauterine growth restriction), particularly in male placentae. Furthermore, a follow-up study demonstrated schizophrenia risk genes were associated with smaller intracranial volumes in neonates, and poorer cognitive outcomes per the Mullen Scales of Early learning at ages 1 and 2, but these cognitive outcomes were only apparent in singleton pregnancies (Ursini et al. 2021). These associations were also stronger in males. Although these studies utilize a more sophisticated measurement of genetic risk, it is of note that these studies do measure OC severity via the McNeil–Sjöström Scale and assess OCs using a combination of maternal recall and medical records. As such, genetic vulnerability, perhaps differentially expressed in the placenta, and OC exposure may additively and/or interactively increase risk for cognitive outcomes in offspring who go on to develop psychosis, with increased vulnerability for males.

Moreover, individuals born with low birth weight or small for gestational age have been shown to have poorer cognitive outcomes in childhood and adolescence in the general population (Sacchi et al. 2020). A study from the CPP, examining all cohort members, demonstrated that the relationship between low birth weight and poorer performance across

all cognitive domains assessed (verbal-perceptual abilities, achievement, and perceptual-motor abilities) in children was strongest in effect size compared to other OC categories examined, including probable hypoxic-ischemic events and chronic hypoxia (Seidman et al. 2000). In individuals with psychosis, low birth weight has been associated with differences in intelligence and executive functioning. In the DIBS cohort, low birth weight was associated with impairments in performance on executive function tasks (WCST and Trails) as well as lower IQ as measured by the Wechsler Adult Intelligence Scale (WAIS) in adult cases with schizophrenia spectrum disorders and not controls (Freedman et al. 2013). A population-based study of schizophrenia cases and their unaffected siblings showed that both low birth weight and high birth weight were associated with poorer visuospatial reasoning, processing speed, set-shifting, and verbal and visual memory in adulthood, compared to cases born at normative birth weight (Torniainen et al. 2013). Of note, high birth weight has been identified as a protective factor against schizophrenia risk (Davies et al. 2020). Finally, changes in cognitive performance associated with low birth weight, particularly in individuals with psychosis, may not be reflected in studies examining neurological changes, as one study found that low birth weight was associated with reduced cortical surface area in adulthood across both cases and controls (Haukvik et al. 2014).

Additional studies have examined the relationship between various other OCs and cognitive deficits in adults with psychosis. A study of the Thematically Organized Psychosis cohort examined OC incidence broadly by examining records from the Norwegian birth registry and creating OC severity ratings using the McNeil-Sjöström Scale (Wortinger et al. 2020). Schizophrenia cases with exposure to severe OCs demonstrated lower premorbid and adult IQ, compared to unexposed cases. Another Norwegian study examined the impact of OCs on executive outcomes (measured by the WCST and D-KEFS Color Word Interference Test) in early onset schizophrenia cases and controls (Teigset et al. 2020). Exposure to various specific OCs (e.g., emergency cesarean, higher birth length, lower 5-min Apgar scores) was associated with executive dysfunction in schizophrenia cases. Shortened gestational length, not necessarily at threshold of preterm birth, was associated with poorer performance on the WCST only in adults with schizophrenia but no associations were identified between birth weight and executive functioning in this sample. It is of note that some OCs associated with executive dysfunction in schizophrenia patients in this study have not been reliably associated with psychosis risk in other studies (e.g., cesarean delivery), but may be associated with earlier age at onset (Verdoux et al. 1997).

A number of methodological limitations should be considered when assessing studies that examine OCs and psychosis outcomes. First, many studies examining OCs suffer from small sample sizes and, consequently, insufficient statistical power, to identify small effects (Cannon et al. 2002a). Second, given that OCs are a broad category of various pre- and perinatal adversities, there is substantial variability in the way these adversities are measured, operationalized, and analyzed. As previously mentioned, maternal recall of incidence and timing of OCs is likely biased (McIntosh et al. 2002), highlighting the importance of prospective designs. Additionally, many studies conflate OCs, examining them broadly as a combination of adversities or creating an overall severity rating, using scales like the McNeil–Sjöström Scale. Utilizing broad categories of OCs may be problematic, given that specific OCs may differentially impact fetal development and

because dimensions of OCs (e.g., severity, duration, timing) may moderate the relationship between OCs and offspring outcomes. As such, studies that prospectively assess prenatal adversity using medical record data and or serologic determination provide more specific accounts of these OCs.

2.4 Maternal Health Behaviors

Maternal health behaviors during pregnancy, including substance use and nutritional intake, can have direct and indirect impacts on fetal neurodevelopment. Maternal malnutrition has been associated with an increased risk for offspring psychotic disorders in ecologic studies of famine (Brown and Susser 2008). Lower levels of specific micronutrients (e.g., folic acid, iron, vitamin D) during pregnancy have also been associated with increased risk for schizophrenia among offspring (McGrath et al. 2011) A study of the DIBS cohort identified that, in adult offspring with schizophrenia, compared to controls, lower serum hemoglobin levels were associated with lower scores on the Information subtest of the WAIS-III and poorer neuromotor performance (Ellman et al. 2012). Higher levels of homocysteine, a reliable proxy used to measure folic acid levels in sera, are associated with an increased risk for psychosis among offspring (Brown et al. 2007). In a rodent model of schizophrenia, Canever et al. (2018) examined the impact of folic acid supplementation on cognition, in addition to other OCs related to cognitive dysregulation in psychosis patients, such as inflammation. Folic acid supplementation was associated with an anti-inflammatory effect in rodents and buffered against spatial memory deficits associated with a folic acid-deficient diet (Canever et al. 2018). Given that higher pre-pregnancy BMI also has been associated with increased risk for psychosis outcomes in offspring (Schaefer et al. 2000), inflammatory dysregulation may be one pathway by which nutritional deficits during pregnancy incur risk for neurocognitive changes in offspring who go on to develop psychotic disorders (Bordeleau et al. 2020).

Maternal smoking has also been linked to offspring outcomes of psychosis (Hunter et al. 2020). Although there is no research to date examining the relationship between prenatal nicotine use and cognitive outcomes in offspring with psychotic disorders, there is evidence that smoking during pregnancy is associated with other OCs linked to cognitive outcomes, such as low birth weight, prenatal hypoxia, and exposure to toxins like lead (Huizink and Mulder 2006; Ellman et al. 2007; Ko et al. 2014). PNMS (e.g., pregnancy-specific stress) may also increase engagement in adverse health behaviors like smoking (Lobel et al. 2008). Of note, a recent study utilizing sibling comparisons demonstrated that the link between smoking exposure and psychosis outcomes became insignificant when controlling for shared genetic and environmental factors (Quinn et al. 2017), highlighting the importance of examining gene–environment interactions in studies of OCs. Nonetheless, examinations of maternal health behaviors emphasize the transactional nature of possible insults to the fetus during the perinatal period and the utility of examining them in concert with one another.

2.5 Obstetric Complications and Cognition in Psychosis: Summary

There is preliminary evidence that demonstrates a relationship between prenatal infection, hypoxia-related OCs, and maternal nutrition on premorbid and adult cognitive outcomes in individuals with psychosis. Generally, these OCs are associated with declines in overall

IQ and in verbal IQ in the premorbid period, and difficulties in overall intelligence persist into adulthood, alongside poorer verbal memory and executive functioning (particularly, set shifting). Although there is evidence that PNMS is associated with alterations in cognition in population-based samples, and with intermediate phenotypes linked to poorer cognitive performance in individuals with psychosis (e.g., low birth weight), no study to date has examined the impact of PNMS on cognitive function in the course of psychosis. Given that many birth cohort studies employ nested case–control designs to examine differences in cognitive function based on OC exposure and diagnostic outcome (psychosis versus control), it is difficult to discern the specificity of these risk factors to cognitive outcomes in psychosis compared with other disorders. These comparisons are necessary, given that many of these OCs have been linked to a variety of mental health outcomes (Pugliese et al. 2019; Mathewson et al. 2017; Han et al. 2021). Nevertheless, all of these OCs likely confer risk for shared phenotypes between mental disorders, such as cognitive outcomes, which future studies will need to parse apart. A dimensional approach examining transdiagnostic symptom clusters (e.g., anhedonia), and/or examining multiple mental disorders simultaneously, may clarify the specificity of OCs to alterations in cognitive functioning in offspring with psychiatric symptoms and a range of mental disorders, more generally.

With the exception of research on prenatal infection, most studies examining OCs conflate exposures to various prenatal adversities in analyses, further stymieing our understanding of their unique effects on cognitive outcomes in psychosis. With greater specificity in the measurement of prenatal risk factors, we may also be able to more effectively examine the interactive influences of various OCs on cognitive outcomes (e.g., infection x fetal hypoxia). Existing literature examining the role of genetic risk in the relationship between hypoxia-related OCs and cognitive and psychosis outcomes (Ursini et al. 2021) emphasizes the need to examine how genetic vulnerability (and other early vulnerabilities) factor in concert with other OCs. Furthermore, our research on outcomes of depressive symptomatology in offspring demonstrates that second trimester daily life stress, only in the presence of infection, is associated with greater depressive symptoms in adolescent offspring (Murphy et al. 2017). Perhaps unique combinations of pre- and perinatal adversities contribute to earlier deficits in cognitive functioning in individuals who go on to develop psychotic disorders. Given high rates of comorbidity between mood disorders and psychosis, it is also possible that these unique combinations of pre- and perinatal risk factors may be related to cognitive outcomes evident across disorders or shared symptom clusters.

3 Early Life Stress and Cognition in Psychosis

Notably, not all fetuses exposed to OCs will go on to develop psychosis; therefore, it has been suggested that OCs may act as a “primer,” increasing susceptibility to the negative effects of other postnatal stressors (Estes and McAllister 2016). Furthermore, adversity occurring in childhood and early adolescence is, in itself, a significant contributing factor to the development of both psychosis and cognitive impairments found in those experiencing psychosis, as these are important periods for brain development (McCabe et al. 2012). In a sample of individuals with recent-onset psychosis, individuals who experienced childhood trauma had more severe symptoms and worse functional outcomes (Rosenthal

et al. 2020). The impact of early trauma on individuals' neurocognitive and psychosocial development highlights the importance of understanding links between early life stress, cognitive impairments, and psychosis.

Several forms of early adversity, including childhood trauma, peer victimization, and neighborhood-level stressors, likely contribute to the development of cognitive difficulties in schizophrenia by dysregulating the body's response to stress and increasing risk for neurobiological changes that impact cognition (Raymond et al. 2018). For example, chronic activation of the immune system in response to stress can lead to increased microglial activation, a key component of neuroinflammation, which may be associated with structural (e.g., impaired white matter integrity, volume loss; Müller et al. 2015; Poletti et al. 2015) and functional (e.g., changes to dopaminergic systems; Müller et al. 2015) changes that contribute to both cognitive difficulties and risk for psychosis (Nettis et al. 2020). Therefore, the relationship between early life stress and cognitive functioning among individuals with psychosis, and the mechanisms underlying these relationships, will be explored here.

3.1 Childhood Trauma

Childhood trauma is linked to cognitive difficulties in individuals across the psychosis spectrum. A meta-analysis of 23 studies found childhood trauma was associated with poorer overall neurocognitive function, measured as a single composite score averaged across multiple neuropsychological batteries, in individuals diagnosed with psychosis (Vargas et al. 2019). These findings contrast with earlier studies which reported no association (Sideli et al. 2014; van Os et al. 2017) or linked childhood trauma to better cognitive functioning in psychosis patients (Campbell et al. 2013). Among individuals at clinical high risk for psychosis (CHR), those with a history of childhood trauma show better overall cognitive functioning than those without childhood trauma (Velikonja et al. 2021). These discrepant findings may be because the link between childhood trauma and poorer cognition is stronger for non-psychiatric controls compared to patients (Vargas et al. 2019). It is also possible that specific cognitive domains are more likely to be affected by trauma in psychosis populations, or that these associations vary depending on the stage of the disorder examined (e.g., CHR versus chronic psychosis).

Childhood trauma may be particularly deleterious to higher order cognitive processes, such as executive functioning (Johnson et al. 2021). In the aforementioned meta-analysis, childhood trauma was associated with lower scores on a range of executive functioning tasks among individuals with psychosis, even prior to psychosis onset (Vargas et al. 2019; see review for specific tasks examined). In a study of individuals at CHR, childhood trauma was associated with worse performance on tasks involving cognitive control and executive functioning, such as the Stroop Test and WCST (Üçok et al. 2015). Among individuals with a family history of psychosis, those exposed to any childhood abuse or neglect (as identified by a clinician, rather than self-report) showed poorer performance in executive functions of initiation, as well as more combinations of cognitive deficits associated with lower overall functioning (Berthelot et al. 2015). However, in a large non-clinical sample, it was found that traumatic life events, but not psychotic-like experiences (PLEs; subclinical, attenuated forms of positive symptoms), contributed to attentional biases (demonstrated by

slower reaction time) on an emotional Stroop task (Gibson et al. 2019). Finally, in another non-clinical sample, childhood trauma fully explained the association between reduced inhibition on a Stroop task and higher levels of PLEs, suggesting that impairments in executive functions may constitute a causal mechanism through which childhood trauma leads to the later development of psychotic symptoms (Begemann et al. 2016). This may also explain why psychotic symptoms are directly related to poorer executive functioning later in the course of psychosis, but this relationship is accounted for by childhood trauma in earlier phases of the disorder. Evidence among non-clinical populations indicates that childhood trauma impacts executive functioning through dysregulation of the HPA-axis, which drives changes in cortisol levels that can affect the development of brain regions integral to executive functioning, such as the PFC (Feola et al. 2020); however, this has yet to be explored in individuals on the psychosis spectrum. Although childhood trauma has been associated with poorer executive functioning across the psychosis spectrum, future research is needed to determine if similar mechanisms (e.g., dysregulation of the HPA axis leading to structural changes in the PFC) are associated with these deficits across phases of illness.

Childhood trauma has also been associated with poorer working memory for individuals with psychosis. Of the domains examined by Vargas et al. (2019), working memory (including letter-number sequencing, digit span, N-back, and spatial working memory tasks) showed the largest negative association with childhood trauma. Childhood trauma also remains associated with scores on letter-number sequencing and digit span tests, even after controlling for premorbid IQ (Shannon et al. 2011; Campbell et al. 2013) and depressive symptoms (Shannon et al. 2011). Alternatively, some studies do not provide evidence of this relationship. One study of first-episode psychosis (FEP) patients and controls found no differences in performance on the MATRICS Consensus Cognitive Battery (MCCB) working memory subscale between the groups with comparable levels of childhood trauma (Kilian et al. 2018). Likewise, in a recent study of patients with schizophrenia and bipolar disorder (with and without psychotic features), verbal N-back scores did not mediate the relationship between early life stress and severity of psychotic symptoms (Corcoran et al. 2020). While it is possible this study was underpowered to detect a mediation effect, the findings are consistent with research reporting that the association between childhood trauma and cognition is stronger for non-clinical controls than for individuals with psychosis (Vargas et al. 2019). Therefore, it is possible discrepant findings may be due to a floor effect, in which individuals with psychosis already show poorer working memory performance compared to controls.

Poorer performance in additional cognitive domains has been associated with childhood trauma. Among individuals with psychosis, childhood trauma was associated with poor attentional functioning, measured by RBANS digit span and coding subtests (Kasznia et al. 2021) and MCCB attention domain (Schalinski et al. 2018). Furthermore, Ayesa-Arriola et al. (2020) reported that childhood trauma, particularly when combined with recent life stress, was associated with decreases in processing speed on the WAIS-III Digit-Symbol subtest. Similarly, for individuals at CHR, total childhood trauma exposure was associated with poorer performance on tasks involving attention and processing speed (Üçok et al. 2015; Velikonja et al. 2021). In a study of adult psychosis patients, childhood trauma

was associated with increased activation of the inferior frontal gyrus (IFG), a region involved in attentional processing, during a response-inhibition task (Go/No Go; Quidé et al. 2018). Decreased gray matter in the IFG has been associated with exposure to childhood trauma (Lim et al. 2014). Therefore, over-activation of the IFG may represent a possible compensatory mechanism in which individuals with childhood trauma require stronger salience signals from the IFG to maintain inhibitory control (Quidé et al. 2018). Regardless, childhood trauma appears to be associated with attentional functioning difficulties across the psychosis spectrum.

Childhood trauma is also associated with deficits in various memory processes for individuals with psychosis. For example, childhood trauma is associated with poorer scores on the Rey Auditory Verbal Learning Test, a test of verbal memory, in individuals in the early course of schizophrenia (Ayesa-Arriola et al. 2020). Similarly, in a study of FEP patients, lower cortisol awakening response, an indicator of blunted HPA-axis functioning, was also associated with deficits in verbal memory, measured by the Wechsler Memory Scale (Aas et al. 2011). Additionally, blunted HPA-axis functioning has been associated with early trauma in psychosis patients (Mondelli et al. 2010). Furthermore, for individuals with psychosis, childhood trauma was associated with poorer episodic narrative memory, measured by the WAIS-III logical memory test (Shannon et al. 2011), as well as lower scores on a visual facial memory task (Carrilho et al. 2019). Childhood trauma was also associated with lower scores on a range of tasks assessing delayed memory, such as list recall, list recognition, story memory, and figure recall among patients with psychosis (Kasznia et al. 2021). Among non-clinical individuals, childhood trauma is associated with deficits in short-term memory continuing throughout adulthood and these deficits are associated with severity of abuse (Bremner et al. 1995). Childhood trauma and subsequent HPA-axis dysregulation have been associated with reductions in hippocampal volume (Bremner et al. 1997, 2003; Stein et al. 1997), which are also evident in individuals with psychosis (Read et al. 2001), indicating a potential mechanistic pathway. Because memory impacts multiple cognitive domains, it is possible these deficits play a role in the dysfunction of higher-order cognitive processes among individuals with psychosis and a history of childhood trauma.

It is crucial to note that measurements of childhood trauma often rely on retrospective reporting. One such assessment, the Childhood Trauma Questionnaire, assesses frequency of five domains of childhood trauma, as well as if the individual may be minimizing their experiences (Bernstein et al. 1994). While measures like this one are well-validated, studies have shown that only 52% of individuals who reported traumatic events in prospective studies reported having experienced trauma when asked retrospectively (Baldwin et al. 2019). Retrospective reporting of trauma also fails to thoroughly capture the timing of such adversities. Timing and chronicity of childhood adversity, relative to developmental milestones, may be meaningful in understanding the impact on resulting cognitive deficits and its related functioning. Prospective reporting of childhood trauma may serve to improve the validity and timing-specificity of reporting.

Examining specific types of childhood trauma, such as abuse or neglect, may also shed light on the heterogeneity in cognitive difficulties observable in individuals with

psychosis. For example, in a study of patients with psychosis spectrum disorders, physical and emotional neglect significantly predicted poorer MCCB verbal learning and overall cognition composite score, whereas physical, sexual, and emotional abuse did not (Kilian et al. 2018). Similarly, neglect, but not abuse, was associated with poorer scores on a working memory composite for individuals with psychosis spectrum disorders (Mørkved et al. 2020) see paper for specific tasks). Consequently, while many studies report overall trauma exposure, evidence shows that trauma type differentially impacts individual outcomes (Dauvermann and Donohoe 2019). Findings in non-psychiatric controls also show differential outcomes following physical abuse versus neglect, such as atypical fear learning associated with abusive or threatening experiences and reduced executive function associated with neglect (McLaughlin and Sheridan 2016). Given the unique effect of different types of trauma and the fact that abuse and neglect typically co-occur, future studies should control for the effect of co-occurring traumas in statistical models to better understand the impact of trauma specificity on cognitive outcomes (Ered and Ellman 2019).

3.2 Neighborhood-Level Adversity

Neighborhood-level factors, such as urbanicity, have been identified as risk factors for the development of psychosis (Krabbendam and van Os 2005; Fett et al. 2011); however, it remains unclear which aspects of urban living (e.g., social/economic stress, environmental toxins/pollution, lack of green space) drive this relationship (Fett et al. 2011). For example, perception of the neighborhood's condition, including crime and physical or social disorder, was associated with longer duration of untreated psychosis, even after controlling for participant's socioeconomic status (SES; Ku et al. 2020). To our knowledge, only one study to date has examined the relationship between neighborhood-level factors and cognition in individuals on the psychosis spectrum. In a large prospective cohort of Swedish men at CHR or diagnosed with nonaffective psychosis, 23% of the association between neighborhood deprivation (measured by crime rates, unemployment, low income, and receipt of social benefits) and psychosis was accounted for by IQ (Lewis et al. 2020).

Notably, many adverse neighborhood-level factors disproportionately impact individuals from low SES. Individuals who develop psychosis may also be more susceptible to the negative effects of low SES (Yeo et al. 2014; Czepielewski et al. 2021). A study examining cognitive functioning in schizophrenia patients across five Latin American countries found patients performed worse on all MCCB domains compared to controls, and that SES was more strongly related to MCCB scores in patients than controls (Czepielewski et al. 2021). Similarly, a U.S. study reported an association between lower parental SES and poorer scores on tests of planning and inhibition in schizophrenia patients, but not non-psychiatric controls (Yeo et al. 2014). These findings also showed that lower parental SES was associated with reduced gray matter volume of the superior frontal gyrus in patients, but not controls, suggesting a potential mechanism through which SES can influence cognitive functioning in individuals with psychosis. However, further research is needed to elucidate which aspects of these environmental factors are driving the relationship between neighborhood-level adversity and cognitive difficulties, and why individuals with psychosis may be particularly susceptible.

Moreover, experiences of discrimination, particularly among racial/ethnic minority groups and individuals from low SES backgrounds, are associated with increased risk for psychosis (Oh et al. 2014; Anglin et al. 2021) and greater severity of psychotic symptoms (Anglin et al. 2014; Shaikh et al. 2016) While the relationship between discrimination and cognitive function in psychosis has yet to be examined, a recent longitudinal study reported that discriminatory experiences are associated with thinning of several cortical regions over time in CHR individuals (Collins et al. 2021). These findings were moderated by gender and race/ethnicity, indicating females and racial/ethnic minorities show steeper rates of cortical thinning associated with discrimination. Several of the cortical regions examined, such as the PFC, are integral to cognitive functioning. Therefore, future research should examine how experiences of discrimination, moderated by intersectional aspects of identity (e.g., gendered racism), may contribute to cognitive difficulties among individuals with psychosis.

3.3 Peer Victimization

Bullying and peer victimization have been linked to increased risk for both psychosis (Schreier et al. 2009; Varese et al. 2012) and impairments in cognitive flexibility, demonstrated by longer times on the Trail Making Test (Medeiros et al. 2016). Peer victimization may lead to cognitive impairments through dysfunction of the HPA-axis, as discussed previously (Lataster et al. 2006). This theory is supported by a study which found help-seeking youths who experienced high levels of bullying showed more intense negative affect and psychotic experiences in response to stress compared to non-help-seeking controls (Rauschenberg et al. 2021). These findings are consistent with the theory that stress reactivity, a key aspect of HPA-axis dysregulation, may constitute a marker of psychosis risk (Myin-Germeys et al. 2001), and a contributing factor to cognitive difficulties (Lataster et al. 2006).

Cognitive impairments associated with genetic and environmental (e.g., OCs) risk factors may precede experiences of victimization and precipitate increased risk of victimization (Danese et al. 2017). A large-scale longitudinal study reported that peer victimization mediated the relationship between developmental impairments (including OCs, low IQ, and motor impairments) and PLEs, suggesting that individuals with developmental impairments are more likely to be bullied, thereby increasing the risk for developing psychosis (Liu et al. 2020). Existing cognitive impairments may increase risk for peer victimization, further exacerbating the impairment; however, these transactional relationships require further investigation.

3.4 Early Life Stress and Cognition in Psychosis: Summary

Early life stress impacts a range of cognitive domains among individuals with psychosis, with pronounced effects on executive functions, including working memory, potentially underlying deficits in overall cognition (Vargas et al. 2019). Early life stress likely contributes to cognitive difficulties in psychosis by dysregulating the body’s response to stress (e.g., increased cortisol levels, chronic immune activation) which can negatively impact the neurodevelopment of regions involved in cognitive functioning, such as the PFC and hippocampus. Given that early life stress increases risk for a range of psychological sequelae, it is difficult to discern the extent to which early life stress impacts cognition in

psychotic disorders, specifically. Nonetheless, there is preliminary evidence that traumatic events are more strongly associated with PLEs, as well as PTSD and borderline personality disorder symptoms, than other symptom domains (Gibson et al. 2017). Importantly, when adjusting for these co-occurring symptoms, traumatic life events were no longer associated with depressive symptoms, anxiety, or substance use, which previously had been well-documented relationships (Green et al. 2010; van Nierop et al. 2015). Therefore, early life stress may be linked to specific symptom clusters, including psychotic symptoms, further exacerbating cognitive difficulties which are characteristic of psychotic disorders. Inconsistencies in findings may be due to variability in the methodologies used to measure trauma, lack of specificity of trauma type, timing, and chronicity, and failure to account for co-occurring symptoms.

4 Discussion

Overall, there is evidence that prenatal and early childhood environmental risk factors impact general intelligence, verbal intelligence, and executive functioning, often beginning in the premorbid period and continuing into adulthood, in individuals with psychosis. These risk factors align with the conceptualization of schizophrenia as a neurodevelopmental disorder in which cognitive deficits arise prior to illness onset and remain relatively stable (Reichenberg et al. 2010). However, it has been suggested that some individuals with psychosis exhibit average premorbid cognitive function which declines as the illness progresses (Weickert et al. 2000; Badcock et al. 2005). These cognitive subtypes, often referred to as “compromised” and “deteriorated,” respectively, show differing neurodevelopmental profiles (Woodward and Heckers 2015) and may account for variability in findings. The principle of multifinality (i.e., one risk factor may contribute to various outcomes) complicates our understanding of findings related to the pre-, perinatal, and childhood origins of psychosis risk. OCs and early childhood trauma have been associated with a number of psychopathological outcomes in offspring; as such, it is challenging to clarify the extent to which certain risk factors are *specific* to a particular diagnostic outcome (Huizink and de Rooij 2018). Few prenatal studies have attempted to answer questions of multifinality; however, investigations into early cognitive deficits may provide insight into potential mechanisms. Utilizing a developmental framework to understand issues of multifinality may be crucial to future analyses. For example, individuals who go on to develop schizophrenia, in particular, show lower premorbid cognitive performance (e.g., global IQ) compared to those that develop bipolar disorder (Bortolato et al. 2015). Prenatal and childhood stress are likely involved in the cascade of risk to neuropsychological deficits across disorders, but perhaps at different stages of neurodevelopment. Nonetheless, the high level of comorbidity of psychosis with other psychological disorders (e.g., affective disorders) adds to the challenge of identifying the specificity of early life risk factors to the emergence of psychosis and its related cognitive profile.

We have highlighted the myriad limitations of the existing research on these early life risk factors, including variability in measurement, issues with retrospective reporting, small sample sizes, and challenges in examining the specificity of various adversities on cognitive outcomes. Moreover, literature that integrates the impact of pre- and perinatal adversity and early life stress on cognitive outcomes in individuals with psychosis is scarce.

Figure 1 illustrates how environmental risk factors may work additively/interactively across development toward specific cognitive difficulties in psychotic disorders, underscoring the need for future studies integrating the impact of various pre- and postnatal adversities on cognitive outcomes in psychosis. It is likely that specific risk factors do not lead to cognitive difficulties in psychotic disorders, but that there may be myriad unique developmental cascades associated with such outcomes (Lipner et al. 2019; Ellman et al. 2018). As such, this underscores the importance of measuring the unique risk factors so more specific, longitudinal, and transactional analyses can be conducted.

Early intervention proximal to these perinatal and childhood risk factors may aid in preventing some of these cognitive difficulties from cascading into difficulties resulting in a psychotic disorder. As early as the prenatal period, there is preliminary evidence that micronutrient supplementation (e.g., folic acid, choline, and possibly Vitamin D) may buffer the effects of maternal nutritional deficiencies and other related OCs to decrease the risk for psychotic disorders (Freedman et al. 2021). Interestingly, there is evidence that fetal sex may moderate the relationship between Vitamin D supplementation and decreased risk for psychosis, such that this intervention was only associated with decreased risk for schizophrenia in male offspring in a Finnish study (McGrath et al. 2004). Physician monitoring of maternal mental well-being at prenatal visits may also allow for early identification of antenatal anxiety and depression, facilitating early intervention to decrease fetal exposure to PNMS (Bhat et al. 2017).

Postnatally, positive parenting may buffer the association between earlier adversities and cognitive difficulties. Previous work in a non-psychiatric sample demonstrated that sensitive parenting (defined as greater supportive scaffolding during play and challenging puzzle tasks), measured via clinician rating of maternal-child interactions, moderated the relationship between low birth weight and poorer executive functioning in children at ages 3 and 5 (Camerota et al. 2015). School-based interventions, such as adaptive training programs, have been shown to improve and sustain the enhancement of poor working memory in children (Holmes et al. 2009). An experimental early childhood intervention aimed to provide quality education to children from disadvantaged backgrounds was associated with significant improvements in both cognitive and non-cognitive skills, especially in children from the most disadvantaged backgrounds (Xie et al. 2020). Minimizing exposures to environmental contaminants (e.g., manganese, lead, plastics with BPAs, and air pollution) may also improve cognitive functioning across development (Clifford et al. 2016; Mhaouty-Kodja et al. 2018; Martin et al. 2021). Therefore, environmental stressors may have long-term effects on cognitive outcomes in psychotic disorders, but they are also identifiable and therefore treatable. Programs may aim to pay particular attention to the confluence of OCs and early life stressors as early cognitive complaints emerge and as an avenue for early intervention. Additional research on the utility of these various interventions on cognitive outcomes, specifically in those with psychotic disorders, is needed.

4.1 Considerations Pertaining to Intersectionality

Intersectional aspects of identity (e.g., sex/gender, race/ethnicity) likely also inform the developmental cascade to cognitive difficulties in the course of psychotic disorders. Firstly, males have demonstrated greater deficits in cognition and attention, specifically in verbal tasks, during the premorbid period (Goldstein et al. 1994) and sexual dimorphism persists into chronic schizophrenia (Goldstein et al. 1998). Pre- and perinatal risk factors likely set the stage for sex differences in cognitive performance, as studies have shown an increased risk for psychosis for male offspring after exposure to various OCs, including PNMS (Fineberg et al. 2016), and increased risk for intermediate phenotypes of psychosis, like low birth weight (Ellman et al. 2019). Increased psychosis risk for male offspring is likely regulated by the sex-moderated placenta (Bronson and Bale 2016), and recent findings demonstrate that males have higher placental expression of genetic risk factors for psychosis with stronger associations to poorer cognitive functioning in early life (Ursini et al. 2021). Sex differences in the inflammatory profile of the in-utero environment for male fetuses may also contribute to these differences, given that higher levels of proinflammatory cytokines are evident in males during the prenatal period, and male fetuses may be more sensitive to the impact of this inflammation (Kim-Fine et al. 2012; Hunter et al. 2021). Such findings support the theory that male and female fetuses are armed with different evolutionary strategies for survival, such that female fetuses are more equipped to adapt to environmental adversity whereas the male fetus more heavily invests resources in growth during adverse conditions (Sandman et al. 2013). These differences leave males at higher risk of prenatal environmental stressors and, consequentially, fetal neurodevelopmental deficits (Sutherland and Brunwasser 2018).

Sex differences also have been found in studies examining childhood trauma and cognitive deficits, such that females are more likely to be *protected* from the cognitive and neurological effects of childhood trauma, both for individuals with schizophrenia (Ruby et al. 2017) and in the general population (Samplin et al. 2013). Conversely, women with childhood trauma exhibit more positive and mood symptoms, as well as earlier age of onset of psychosis, compared to women without a history of childhood trauma, and this association is not present in men (Comacchio et al. 2019). As such, women may be protected from neurological effects (e.g., smaller hippocampi), but not the psychiatric effects, of childhood trauma exposure (Samplin et al. 2013). Examining sex differences in the trajectory from OCs to childhood trauma may serve to further clarify these trends in related cognitive difficulties.

Important to the discussion of the impact of environmental stressors on cognition is the disproportionate impact of these stressors on individuals of marginalized racial and ethnic groups due to systemic oppression. Mothers from marginalized racial groups in the US experience greater incidence of OCs overall, and perceived discrimination during pregnancy may account for increased risk for OCs, like low birth weight (Giscombé and Lobel 2005; Dominguez et al. 2008). In the postnatal period, individuals from marginalized racial groups are more likely to be exposed to childhood adversity such as physical abuse, sexual abuse, domestic violence, and low SES (Anglin et al. 2021). These stressors lead to HPA axis dysregulation and neural inflammation as early as the prenatal period (Glynn et al. 2007;

Gillespie et al. 2016) and may lead to damage in stress-sensitive brain regions including the PFC and hippocampus, resulting in cognitive difficulties (Howes and McCutcheon 2017). The disproportionate impact of these stressors on individuals from marginalized racial groups, as well as the differential exposure to stressors based on an individual's racial/ethnic group and gender identity (e.g., police victimization of Black males), must be considered in studies of early life adversity and cognition on the psychosis spectrum.

4.2 Gene × Environment Interactions

Examination of OCs and genetic vulnerability for psychosis together will facilitate a clearer understanding of their relative contributions to cognitive sequelae. Findings suggest that fetal hypoxia exposure on its own is unlikely to result in cognitive changes; however, it likely interacts with genetic risk factors associated with psychosis, particularly expressed in the placenta of male fetuses, to incur damage to the developing brain (Cannon et al. 2000; Ursini et al. 2021). It is likely that this gene x environment interaction exists with other types of OCs. For example, genetic vulnerability to the teratogenic effects of particular infections during pregnancy may be of importance. Multiple immune-related genetic polymorphisms (e.g., genes from the IL-1 complex) have been associated with brain changes found in schizophrenia and polymorphisms in both the IL-1 complex and TNF-α have been shown to heighten inflammatory response to infection (Fineberg and Ellman 2013). Consequentially, carriers of these polymorphisms may exhibit an exaggerated inflammatory response, with the potential to hinder brain development, increase risk for other OCs associated with psychosis risk, and/or render the fetus more vulnerable to the adverse effects of maternal infection (Ellman and Cannon 2008; Mittal et al. 2008; Fineberg and Ellman 2013). Additional research examining the interaction between various OCs and genetic vulnerability for psychosis on cognitive outcomes in these disorders is needed.

Polymorphisms linked to schizophrenia risk have also been shown to interact with childhood stress to impact cognitive performance. Catechol-O-methyltransferase (COMT) Val(158)Met polymorphism is a common genetic variant that has been shown to influence executive functioning, as well as prefrontal physiology and dopamine levels (Egan et al. 2001; Meyer-Lindenberg et al. 2006). Interestingly, a case–control study of participants from the Australian Schizophrenia Research Bank found that the COMT Val(158)Met polymorphism interacted with physical abuse to predict *better* executive functioning, despite a significant main effect of Val/Val homozygotes performing worse on tasks involving attention and immediate memory (Green et al. 2014). This suggests a pathway through which childhood trauma, namely physical abuse, downregulates Val/Val genotype expression and increases dopamine activity. Genetic variations implicated in stress response and glucocorticoid function (e.g., FKBP5, 5-HTTPLR) have also been shown to interact with childhood trauma to impart cognitive outcomes in patients with psychosis (Aas et al. 2012; Green et al. 2015). These findings highlight gene x environment interactions as potential mechanisms underlying the development of cognitive impairments associated with psychosis.

5 Conclusions and Recommendations

Further clarification of the role of early life adversity, beginning in the prenatal period, on cognition in disorders on the psychosis spectrum is needed. Methodological considerations for the future study of pre-, perinatal, and early childhood risk factors are outlined in Fig. 2. Comprehensive, prospective assessment of birth cohorts will serve to further our developmental understanding of individual and contextual factors that impact cognitive outcomes. Further understanding of these risk factors earlier in development provides earlier opportunities for intervention. Additionally, greater understanding of the specificity of these cognitive difficulties associated with perinatal and early childhood stress to schizophrenia spectrum disorders, versus other neurodevelopmental disorders like autism, may be of interest.

References

Aas M, Dazzan P, Fisher HL et al. (2011) Childhood trauma and cognitive function in first-episode affective and non-affective psychosis. Schizophr Res 129:12–19. 10.1016/j.schres.2011.03.017 [PubMed: 21601792]

Aas M, Djurovic S, Athanasiu L et al. (2012) Serotonin transporter gene polymorphism, childhood trauma, and cognition in patts with psychotic disorders. Schizophr Bull 38:15–22. 10.1093/schbul/sbr113 [PubMed: 21908796]

Anastario M, Salafia CM, Fitzmaurice G, Goldstein JM (2012) Impact of fetal versus perinatal hypoxia on sex differences in childhood outcomes: developmental timing matters. Soc Psychiatry Psychiatr Epidemiol 47:455–464. 10.1007/s00127-011-0353-0 [PubMed: 21327969]

Anglin DM, Lighty Q, Greenspoon M, Ellman LM (2014) Racial discrimination is associated with distressing subthreshold positive psychotic symptoms among US urban ethnic minority young adults. Soc Psychiatry Psychiatr Epidemiol 49:1545–1555. 10.1007/s00127-014-0870-8 [PubMed: 24695907]

Anglin DM, Ereshefsky S, Klaunig MJ et al. (2021) From womb to neighborhood: a racial analysis of social determinants of psychosis in the United States. Am J Psychiatry 178:599–610. 10.1176/appi.ajp.2020.20071091 [PubMed: 33934608]

Ayesa-Arriola R, Setién-Suero E, Marques-Feixa L et al. (2020) The synergetic effect of childhood trauma and recent stressful events in psychosis: associated neurocognitive dysfunction. Acta Psychiatr Scand 141:43–51. 10.1111/acps.13114 [PubMed: 31618440]

Badcock JC, Dragović M, Waters FAV, Jablensky A (2005) Dimensions of intelligence in schizophrenia: evidence from patients with preserved, deteriorated and compromised intellect. J Psychiatr Res 39(1):11–19. 10.1016/j.jpsychires.2004.05.002 [PubMed: 15504419]

Baldwin JR, Reuben A, Newbury JB, Danese A (2019) Agreement between prospective and retrospective measures of childhood maltreatment: a systematic review and meta-analysis. JAMA Psychiat 76:584–593. 10.1001/jamapsychiatry.2019.0097

Begemann MJH, Heringa SM, Sommer IEC (2016) Childhood trauma as a neglected factor in psychotic experiences and cognitive functioning. JAMA Psychiat 73:875. 10.1001/jamapsychiatry.2016.0924

Bernstein DP, Fink L, Handelsman L et al. (1994) Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 151:1132–1136. 10.1176/ajp.151.8.1132 [PubMed: 8037246]

Berthelot N, Paccalet T, Gilbert E et al. (2015) Childhood abuse and neglect may induce deficits in cognitive precursors of psychosis in high-risk children. J Psychiatry Neurosci 40:336–343. 10.1503/jpn.140211 [PubMed: 26035064]

Beydoun H, Saftlas AF (2008) Physical and mental health outcomes of prenatal maternal stress in human and animal studies: a review of recent evidence. Paediatr Perinat Epidemiol 22:438–466. 10.1111/j.1365-3016.2008.00951.x [PubMed: 18782252]

Bhat A, Reed SD, Unützer J (2017) The obstetrician-gynecologist's role in detecting, preventing, and treating depression. Obstet Gynecol 129:157–163. 10.1097/AOG.0000000000001809 [PubMed: 27926635]

Blomström Å, Karlsson H, Gardner R et al. (2016) Associations between maternal infection during pregnancy, childhood infections, and the risk of subsequent psychotic disorder--a Swedish cohort study of nearly 2 million individuals. Schizophr Bull 42:125–133. 10.1093/schbul/sbv112 [PubMed: 26303935]

Bordeleau M, Fernández de Cossío L, Chakravarty MM, Tremblay M-È (2020) From maternal diet to neurodevelopmental disorders: a story of neuroinflammation. Front Cell Neurosci 14:612705. 10.3389/fncel.2020.612705 [PubMed: 33536875]

Bortolato B, Miskowiak KW, Köhler CA et al. (2015) Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. Neuropsychiatr Dis Treat 11:3111–3125 [PubMed: 26719696]

Bremner JD, Randall P, Scott TM et al. (1995) Deficits in short-term memory in adult survivors of childhood abuse. Psychiatry Res 59:97–107. 10.1016/0165-1781(95)02800-5 [PubMed: 8771224]

Bremner JD, Randall P, Vermetten E et al. (1997) Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--a preliminary report. Biol Psychiatry 41:23–32. 10.1016/s0006-3223(96)00162-x [PubMed: 8988792]

Bremner JD, Vythilingam M, Vermetten E et al. (2003) MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry 160:924–932. 10.1176/appi.ajp.160.5.924 [PubMed: 12727697]

Bronson SL, Bale TL (2016) The placenta as a mediator of stress effects on neurodevelopmental reprogramming. Neuropsychopharmacology 41:207–218. 10.1038/npp.2015.231 [PubMed: 26250599]

Brouwers EPM, van Baar AL, Pop VJM (2001) Maternal anxiety during pregnancy and subsequent infant development. Infant Behav Dev 24:95–106. 10.1016/S0163-6383(01)00062-5

Brown AS (2011) The environment and susceptibility to schizophrenia. Prog Neurobiol 93:23–58. 10.1016/j.pneurobio.2010.09.003 [PubMed: 20955757]

Brown AS, Derkits EJ (2010) Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry 167:261–280. 10.1176/appi.ajp.2009.09030361 [PubMed: 20123911]

Brown AS, Susser ES (2008) Prenatal nutritional deficiency and risk of adult schizophrenia. Schizophr Bull 34:1054–1063. 10.1093/schbul/sbn096 [PubMed: 18682377]

Brown AS, Cohen P, Harkavy-Friedman J et al. (2001) A.E. Bennett research award. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biol Psychiatry 49:473–486. 10.1016/s0006-3223(01)01068-x [PubMed: 11257233]

Brown AS, Hooton J, Schaefer CA et al. (2004) Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am J Psychiatry 161:889–895. 10.1176/appi.ajp.161.5.889 [PubMed: 15121655]

Brown AS, Bottiglieri T, Schaefer CA et al. (2007) Elevated prenatal homocysteine levels as a risk factor for schizophrenia. Arch Gen Psychiatry 64:31–39. 10.1001/archpsyc.64.1.31 [PubMed: 17199052]

Brown AS, Vinogradov S, Kremen WS et al. (2009) Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. Am J Psychiatry 166:683–690. 10.1176/appi.ajp.2008.08010089 [PubMed: 19369317]

Brown AS, Vinogradov S, Kremen WS et al. (2011) Association of maternal genital and reproductive infections with verbal memory and motor deficits in adult schizophrenia. Psychiatry Res 188:179–186. 10.1016/j.psychres.2011.04.020 [PubMed: 21600665]

Brunet E, Sarfati Y, Hardy-Baylé M-C (2003) Reasoning about physical causality and other's intentions in schizophrenia. Cogn Neuropsychiatry 8:129–139. 10.1080/13546800244000256 [PubMed: 16571555]

Buka SL, Tsuang MT, Torrey EF et al. (2001) Maternal cytokine levels during pregnancy and adult psychosis. Brain Behav Immun 15:411–420. 10.1006/brbi.2001.0644 [PubMed: 11782107]

Buss C, Davis EP, Hobel CJ, Sandman CA (2011) Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. Stress 14:665–676. 10.3109/10253890.2011.623250 [PubMed: 21995526]

Camerota M, Willoughby MT, Cox M et al. (2015) Executive function in low birth weight preschoolers: the moderating effect of parenting. J Abnorm Child Psychol 43:1551–1562. 10.1007/s10802-015-0032-9 [PubMed: 25971883]

Campbell C, Barrett S, Shannon C et al. (2013) The relationship between childhood trauma and neuropsychological functioning in first episode psychosis. Psychosis 5:48–59. 10.1080/17522439.2012.660982

Canever L, Alves CSV, Mastella G et al. (2018) The evaluation of folic acid-deficient or folic acid-supplemented diet in the gestational phase of female rats and in their adult offspring subjected to an animal model of schizophrenia. Mol Neurobiol 55:2301–2319. 10.1007/s12035-017-0493-7 [PubMed: 28342013]

Cannon TD, Mednick SA, Parnas J (1989) Genetic and perinatal determinants of structural brain deficits in schizophrenia. Arch Gen Psychiatry 46:883–889. 10.1001/archpsyc.1989.01810100025005 [PubMed: 2802928]

Cannon TD, Bearden CE, Hollister JM et al. (2000) Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. Schizophr Bull 26:379–393. 10.1093/oxfordjournals.schbul.a033460 [PubMed: 10885638]

Cannon M, Jones PB, Murray RM (2002a) Obstetric complications and schizophrenia: historical and meta-analytic review. AJP 159:1080–1092. 10.1176/appi.ajp.159.7.1080

Cannon TD, van Erp TGM, Rosso IM et al. (2002b) Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry 59:35–41. 10.1001/archpsyc.59.1.35 [PubMed: 11779280]

Cannon TD, Yolken R, Buka S et al. (2008) Decreased neurotrophic response to birth hypoxia in the etiology of schizophrenia. Biol Psychiatry 64:797–802. 10.1016/j.biopsych.2008.04.012 [PubMed: 18486103]

Carrilho CG, Cougo SS, Bombassaro T et al. (2019) Early trauma and cognitive functions of patients with schizophrenia. Front Psych 10:261. 10.3389/fpsyt.2019.00261

Charil A, Laplante DP, Vaillancourt C, King S (2010) Prenatal stress and brain development. Brain Res Rev 65:56–79. 10.1016/j.brainresrev.2010.06.002 [PubMed: 20550950]

Clifford A, Lang L, Chen R et al. (2016) Exposure to air pollution and cognitive functioning across the life course – a systematic literature review. Environ Res 147:383–398. 10.1016/j.envres.2016.01.018 [PubMed: 26945620]

Collins MA, Chung Y, Addington J et al. (2021) Discriminatory experiences predict neuroanatomical changes and anxiety among healthy individuals and those at clinical high risk for psychosis. Neuroimage Clin 31:102757. 10.1016/j.nicl.2021.102757 [PubMed: 34273790]

Comacchio C, Lasalvia A, Ruggeri M (2019) Current evidence of childhood traumatic experiences in psychosis - focus on gender differences. Psychiatry Res 281:112507. 10.1016/j.psychres.2019.112507 [PubMed: 31465988]

Corcoran M, Hawkins EL, O'Hora D et al. (2020) Are working memory and glutamate concentrations involved in early-life stress and severity of psychosis? Brain Behav 10:e01616. 10.1002/brb3.1616 [PubMed: 32385970]

Cortes Hidalgo AP, Neumann A, Bakermans-Kranenburg MJ et al. (2020) Prenatal maternal stress and child IQ. Child Dev 91:347–365. 10.1111/cdev.13177 [PubMed: 30376186]

Cosgrave J, Purple RJ, Haines R et al. (2021) Do environmental risk factors for the development of psychosis distribute differently across dimensionally assessed psychotic experiences? Transl Psychiatry 11:1–13 [PubMed: 33414379]

Coussons-Read ME (2013) Effects of prenatal stress on pregnancy and human development: mechanisms and pathways. Obstet Med 6:52–57. 10.1177/1753495X12473751 [PubMed: 27757157]

Czepielewski LS, Alliende LM, Castañeda CP et al. (2021) Effects of socioeconomic status in cognition of people with schizophrenia: results from a Latin American collaboration network with 1175 subjects. Psychol Med. 10.1017/S0033291721002403

Danese A, Moffitt TE, Arseneault L et al. (2017) The origins of cognitive deficits in victimized children: implications for neuroscientists and clinicians. Am J Psychiatry 174:349–361. 10.1176/appi.ajp.2016.16030333 [PubMed: 27794691]

Dauvermann MR, Donohoe G (2019) The role of childhood trauma in cognitive performance in schizophrenia and bipolar disorder – a systematic review. Schizophr Res Cogn 16:1–11. 10.1016/j.scog.2018.11.001 [PubMed: 30581765]

Davies C, Segre G, Estradé A et al. (2020) Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. Lancet Psychiatry 7:399–410. 10.1016/S2215-0366(20)30057-2 [PubMed: 32220288]

Dominguez TP, Dunkel-Schetter C, Glynn LM et al. (2008) Racial differences in birth outcomes: the role of general, pregnancy, and racism stress. Health Psychol 27:194–203. 10.1037/0278-6133.27.2.194 [PubMed: 18377138]

Egan MF, Goldberg TE, Kolachana BS et al. (2001) Effect of COMT Val108/158 met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 98:6917–6922. 10.1073/pnas.111134598 [PubMed: 11381111]

Eide MG, Moster D, Irgens LM et al. (2013) Degree of fetal growth restriction associated with schizophrenia risk in a national cohort. Psychol Med 43:2057–2066. 10.1017/S003329171200267X [PubMed: 23298736]

Ellman LM, Cannon TD (2008) Environmental pre- and perinatal influences. In: Mueser KT, Jeste DV (eds) The clinical handbook of schizophrenia. Guilford Press, New York, pp 65–73

Ellman LM, Susser ES (2009) The promise of epidemiologic studies: neuroimmune mechanisms in the etiologies of brain disorders. Neuron 64:25–27. 10.1016/j.neuron.2009.09.024 [PubMed: 19840544]

Ellman LM, Huttunen M, Lönnqvist J, Cannon TD (2007) The effects of genetic liability for schizophrenia and maternal smoking during pregnancy on obstetric complications. Schizophr Res 93:229–236. 10.1016/j.schres.2007.03.004 [PubMed: 17475446]

Ellman LM, Yolken RH, Buka SL et al. (2009) Cognitive functioning prior to the onset of psychosis: the role of Fetal exposure to serologically determined influenza infection. Biol Psychiatry 65:1040–1047. 10.1016/j.biopsych.2008.12.015 [PubMed: 19195645]

Ellman LM, Vinogradov S, Kremen WS et al. (2012) Low maternal hemoglobin during pregnancy and diminished neuromotor and neurocognitive performance in offspring with schizophrenia. Schizophr Res 138:81–87. 10.1016/j.schres.2012.04.008 [PubMed: 22608109]

Ellman LM, Murphy SK, Maxwell SD (2018) Pre- and perinatal risk factors for serious mental disorders: ethical considerations in prevention and prediction efforts. J Ethics Mental Health 10:1–14

Ellman LM, Murphy SK, Maxwell SD et al. (2019) Maternal cortisol during pregnancy and offspring schizophrenia: influence of fetal sex and timing of exposure. Schizophr Res 213:15–22. 10.1016/j.schres.2019.07.002 [PubMed: 31345704]

Engman M-L, Adolfsson I, Lewensohn-Fuchs I et al. (2008) Neuropsychologic outcomes in children with neonatal herpes encephalitis. Pediatr Neurol 38:398–405. 10.1016/j.pediatrneurol.2008.02.005 [PubMed: 18486821]

Ered A, Ellman LM (2019) Specificity of childhood trauma type and attenuated positive symptoms in a non-clinical sample. J Clin Med 8:1537. 10.3390/jcm8101537 [PubMed: 31557792]

Estes ML, McAllister AK (2016) Maternal immune activation: implications for neuropsychiatric disorders. Science 353:772–777. 10.1126/science.aag3194 [PubMed: 27540164]

Eyles DW (2021) How do established developmental risk-factors for schizophrenia change the way the brain develops? Transl Psychiatry 11:1–15. 10.1038/s41398-021-01273-2 [PubMed: 33414379]

Feola B, Dougherty LR, Riggins T, Bolger DJ (2020) Prefrontal cortical thickness mediates the association between cortisol reactivity and executive function in childhood. Neuropsychologia 148:107636. 10.1016/j.neuropsychologia.2020.107636 [PubMed: 33045229]

Fett A-KJ, Viechtbauer W, Dominguez M-G et al. (2011) The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci Biobehav Rev 35:573–588. 10.1016/j.neubiorev.2010.07.001 [PubMed: 20620163]

Fineberg AM, Ellman LM (2013) Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. Biol Psychiatry 73:951–966. 10.1016/j.biopsych.2013.01.001 [PubMed: 23414821]

Fineberg AM, Ellman LM, Buka S et al. (2013) Decreased birth weight in psychosis: influence of prenatal exposure to serologically determined influenza and hypoxia. Schizophr Bull 39:1037–1044. 10.1093/schbul/sbs084 [PubMed: 22966148]

Fineberg AM, Ellman LM, Schaefer CA et al. (2016) Fetal exposure to maternal stress and risk for schizophrenia spectrum disorders among offspring: differential influences of fetal sex. Psychiatry Res 236:91–97. 10.1016/j.psychres.2015.12.026 [PubMed: 26753951]

Freedman D, Bao Y, Kremen WS et al. (2013) Birth weight and neurocognition in schizophrenia spectrum disorders. Schizophr Bull 39:592–600. 10.1093/schbul/sbs008 [PubMed: 22378899]

Freedman R, Hunter SK, Law AJ et al. (2021) Choline, folic acid, vitamin D, and fetal brain development in the psychosis spectrum. Schizophr Res S0920-9964(21):00128–00126. 10.1016/j.schres.2021.03.008

Ghassabian A, Albert PS, Hornig M et al. (2018) Gestational cytokine concentrations and neurocognitive development at 7 years. Transl Psychiatry 8:64. 10.1038/s41398-018-0112-z [PubMed: 29531226]

Gibson LE, Cooper S, Reeves LE et al. (2017) The association between traumatic life events and psychological symptoms from a conservative, transdiagnostic perspective. Psychiatry Res 252:70–74. 10.1016/j.psychres.2017.02.047 [PubMed: 28254578]

Gibson LE, Cooper S, Reeves LE et al. (2019) Attentional biases and trauma status: do psychotic-like experiences matter? Psychol Trauma 11:300–306. 10.1037/tra0000380 [PubMed: 30010376]

Gillespie SL, Porter K, Christian LM (2016) Adaptation of the inflammatory immune response across pregnancy and postpartum in black and White women. J Reprod Immunol 114:27–31. 10.1016/j.jri.2016.02.001 [PubMed: 26895093]

Giovanoli S, Notter T, Richetto J et al. (2015) Late prenatal immune activation causes hippocampal deficits in the absence of persistent inflammation across aging. J Neuroinflammation 12:221. 10.1186/s12974-015-0437-y [PubMed: 26602365]

Giscombé CL, Lobel M (2005) Explaining disproportionately high rates of adverse birth outcomes among African Americans: the impact of stress, racism, and related factors in pregnancy. Psychol Bull 131:662–683. 10.1037/0033-2909.131.5.662 [PubMed: 16187853]

Glynn LM, Schetter CD, Chicz-DeMet A et al. (2007) Ethnic differences in adrenocorticotropic hormone, cortisol and corticotropin-releasing hormone during pregnancy. Peptides 28:1155–1161. 10.1016/j.peptides.2007.04.005 [PubMed: 17537545]

Golan HM, Lev V, Hallak M et al. (2005) Specific neurodevelopmental damage in mice offspring following maternal inflammation during pregnancy. Neuropharmacology 48:903–917. 10.1016/j.neuropharm.2004.12.023 [PubMed: 15829260]

Goldstein JM, Seidman LJ, Santangelo S et al. (1994) Are schizophrenic men at higher risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions. J Psychiatr Res 28:483–498. 10.1016/0022-3956(94)90039-6 [PubMed: 7699608]

Goldstein G, Allen DN, Seaton BE (1998) A comparison of clustering solutions for cognitive heterogeneity in schizophrenia. J Int Neuropsychol Soc 4:353–362. 10.1017/S1355617798003531 [PubMed: 9656609]

Goldstein JM, Seidman LJ, Buka SL et al. (2000) Impact of genetic vulnerability and hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychoses. Schizophr Bull 26:323–334. 10.1093/oxfordjournals.schbul.a033456 [PubMed: 10885634]

Goldstein JM, Cherkerzian S, Seidman LJ et al. (2014) Prenatal maternal immune disruption and sex-dependent risk for psychoses. Psychol Med 44:3249–3261. 10.1017/S0033291714000683 [PubMed: 25065485]

Green JG, McLaughlin KA, Berglund PA et al. (2010) Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. Arch Gen Psychiatry 67:113–123. 10.1001/archgenpsychiatry.2009.186 [PubMed: 20124111]

Green MJ, Chia T-Y, Cairns MJ et al. (2014) Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. J Psychiatr Res 49:43–50. 10.1016/j.jpsychires.2013.10.018 [PubMed: 24252819]

Green MJ, Raudino A, Cairns MJ et al. (2015) Do common genotypes of FK506 binding protein 5 (FKBP5) moderate the effects of childhood maltreatment on cognition in schizophrenia and healthy controls? J Psychiatr Res 70:9–17. 10.1016/j.jpsychires.2015.07.019 [PubMed: 26424418]

Grizenko N, Fortier M-È, Gaudreau-Simard M et al. (2015) The effect of maternal stress during pregnancy on IQ and ADHD symptomatology. J Can Acad Child Adolesc Psychiatry 24:92–99 [PubMed: 26379720]

Gutteling BM, de Weerth C, Zandbelt N et al. (2006) Does maternal prenatal stress adversely affect the child's learning and memory at age six? J Abnorm Child Psychol 34:787–796. 10.1007/s10802-006-9054-7

Haager D, Vaughn S (1995) Parent, teacher, peer, and self-reports of the social competence of students with learning disabilities. J Learn Disabil 28:205–215, 231. 10.1177/002221949502800403 [PubMed: 7738433]

Han VX, Patel S, Jones HF et al. (2021) Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders. Transl Psychiatry 11. 10.1038/s41398-021-01198-w

Haukvik UK, Rimol LM, Roddey JC et al. (2014) Normal birth weight variation is related to cortical morphology across the psychosis spectrum. Schizophr Bull 40:410–419. 10.1093/schbul/sbt005 [PubMed: 23419977]

Holmes J, Gathercole SE, Dunning DL (2009) Adaptive training leads to sustained enhancement of poor working memory in children. Dev Sci 12:F9–F15. 10.1111/j.1467-7687.2009.00848.x [PubMed: 19635074]

Howes OD, McCutcheon R (2017) Inflammation and the neural diathesis-stress hypothesis of schizophrenia: a reconceptualization. Transl Psychiatry 7:e1024. 10.1038/tp.2016.278 [PubMed: 28170004]

Huizink AC, de Rooij SR (2018) Prenatal stress and models explaining risk for psychopathology revisited: generic vulnerability and divergent pathways. Dev Psychopathol 30:1041–1062. 10.1017/S0954579418000354 [PubMed: 30068410]

Huizink AC, Mulder EJH (2006) Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. Neurosci Biobehav Rev 30:24–41. 10.1016/j.neubiorev.2005.04.005 [PubMed: 16095697]

Huizink AC, Mulder EJH, Buitelaar JK (2004) Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility. Psychol Bull 130:115–142. 10.1037/0033-2909.130.1.115 [PubMed: 14717652]

Hunter A, Murray R, Asher L, Leonardi-Bee J (2020) The effects of tobacco smoking, and prenatal tobacco smoke exposure, on risk of schizophrenia: a systematic review and meta-analysis. Nicotine Tob Res 22:3–10. 10.1093/ntr/nty160 [PubMed: 30102383]

Hunter SK, Hoffman MC, D'Alessandro A et al. (2021) Male fetus susceptibility to maternal inflammation: c-reactive protein and brain development. Psychol Med 51:450–459. 10.1017/S0033291719003313 [PubMed: 31787129]

Jiang H, Xu L, Shao L et al. (2016) Maternal infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun 58:165–172. 10.1016/j.bbi.2016.06.005 [PubMed: 27287966]

Johnson D, Policelli J, Li M et al. (2021) Associations of early-life threat and deprivation with executive functioning in childhood and adolescence: a systematic review and meta-analysis. JAMA Pediatr 175:e212511. 10.1001/jamapediatrics.2021.2511 [PubMed: 34309651]

Jones SL, Dufoix R, Laplante DP et al. (2019) Larger amygdala volume mediates the association between prenatal maternal stress and higher levels of externalizing behaviors: sex specific effects in project ice storm. Front Hum Neurosci 13:144. 10.3389/fnhum.2019.00144 [PubMed: 31156408]

Karlsson H, Dalman C (2020) Epidemiological studies of prenatal and childhood infection and schizophrenia. Curr Top Behav Neurosci 44:35–47. 10.1007/7854_2018_87 [PubMed: 30852763]

Kasznia J, Pytel A, Stańczykiewicz B et al. (2021) Adverse childhood experiences and neurocognition in schizophrenia Spectrum disorders: age at first exposure and multiplicity matter. Front Psych 12:684099. 10.3389/fpsyt.2021.684099

Khandaker GM, Barnett JH, White IR, Jones PB (2011) A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. Schizophr Res 132:220–227. 10.1016/j.schres.2011.06.017 [PubMed: 21764562]

Kilian S, Asmal L, Chiliza B et al. (2018) Childhood adversity and cognitive function in schizophrenia spectrum disorders and healthy controls: evidence for an association between neglect and social cognition. Psychol Med 48:2186–2193. 10.1017/S0033291717003671 [PubMed: 29268811]

Kim-Fine S, Regnault TRH, Lee JS et al. (2012) Male gender promotes an increased inflammatory response to lipopolysaccharide in umbilical vein blood. J Matern Fetal Neonatal Med 25:2470–2474. 10.3109/14767058.2012.684165 [PubMed: 22506729]

Kingston D, McDonald S, Austin M-P, Tough S (2015) Association between prenatal and postnatal psychological distress and toddler cognitive development: a systematic review. PLoS One 10:e0126929. 10.1371/journal.pone.0126929 [PubMed: 25996151]

Ko T-J, Tsai L-Y, Chu L-C et al. (2014) Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. Pediatr Neonatol 55:20–27. 10.1016/j.pedneo.2013.05.005 [PubMed: 23850094]

Koenen KC, Moffitt TE, Roberts AL et al. (2009) Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. Am J Psychiatry 166:50–57. 10.1176/appi.ajp.2008.08030343 [PubMed: 19047325]

Krabbendam L, van Os J (2005) Schizophrenia and urbanicity: a major environmental influence—conditional on genetic risk. Schizophr Bull 31:795–799. 10.1093/schbul/sbi060 [PubMed: 16150958]

Kremen WS, Buka SL, Seidman LJ et al. (1998) IQ decline during childhood and adult psychotic symptoms in a community sample: a 19-year longitudinal study. AJP 155:672–677. 10.1176/ajp.155.5.672

Kremen WS, Vinogradov S, Poole JH et al. (2010) Cognitive decline in schizophrenia from childhood to midlife: a 33-year longitudinal birth cohort study. Schizophr Res 118:1–5. 10.1016/j.schres.2010.01.009 [PubMed: 20153140]

Ku BS, Pauselli L, Manseau M, Compton MT (2020) Neighborhood-level predictors of age at onset and duration of untreated psychosis in first-episode psychotic disorders. Schizophr Res 218:247–254. 10.1016/j.schres.2019.12.036 [PubMed: 31948900]

Lafortune S, Laplante DP, Elgbeili G et al. (2021) Effect of natural disaster-related prenatal maternal stress on child development and health: a meta-analytic review. Int J Environ Res Public Health 18:8332. 10.3390/ijerph18168332

Laplante DP, Brunet A, Schmitz N et al. (2008) Project ice storm: prenatal maternal stress affects cognitive and linguistic functioning in 5 1/2-year-old children. J Am Acad Child Adolesc Psychiatry 47:1063–1072. 10.1097/CHI.0b013e31817eec80 [PubMed: 18665002]

Laplante DP, Hart KJ, O'Hara MW et al. (2018) Prenatal maternal stress is associated with toddler cognitive functioning: the Iowa Flood Study. Early Hum Dev 116:84–92. 10.1016/j.earlhumdev.2017.11.012 [PubMed: 29253828]

Lataster T, van Os J, Drukker M et al. (2006) Childhood victimisation and developmental expression of non-clinical delusional ideation and hallucinatory experiences: victimisation and non-clinical psychotic experiences. Soc Psychiatry Psychiatr Epidemiol 41:423–428. 10.1007/s00127-006-0060-4 [PubMed: 16572272]

LeWinn KZ, Stroud LR, Molnar BE et al. (2009) Elevated maternal cortisol levels during pregnancy are associated with reduced childhood IQ. Int J Epidemiol 38:1700–1710. 10.1093/ije/dyp200 [PubMed: 19423658]

Lewis R (2004) Should cognitive deficit be a diagnostic criterion for schizophrenia? J Psychiatry Neurosci 29:102–113 [PubMed: 15069464]

Lewis G, Dykxhoorn J, Karlsson H et al. (2020) Assessment of the role of IQ in associations between population density and deprivation and nonaffective psychosis. JAMA Psychiat 77:729–736. 10.1001/jamapsychiatry.2020.0103

Lim L, Radua J, Rubia K (2014) Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. Am J Psychiatry 171:854–863. 10.1176/appi.ajp.2014.13101427 [PubMed: 24781447]

Lipner E, Murphy SK, Ellman LM (2019) Prenatal maternal stress and the cascade of risk to schizophrenia spectrum disorders in offspring. Curr Psychiatry Rep 21:99. 10.1007/s11920-019-1085-1 [PubMed: 31522269]

Liu Y, Mendonça M, Cannon M et al. (2020) Testing the independent and joint contribution of exposure to neurodevelopmental adversity and childhood trauma to risk of psychotic experiences in adulthood. Schizophr Bull 47:776–784. 10.1093/schbul/sbaa174

Lobel M, Cannella DL, Graham JE et al. (2008) Pregnancy-specific stress, prenatal health behaviors, and birth outcomes. Health Psychol 27:604–615. 10.1037/a0013242 [PubMed: 18823187]

Mareckova K, Marecek R, Andryskova L et al. (2021) Impact of prenatal stress on amygdala anatomy in young adulthood: timing and location matter. Biol Psychiatr Cogn Neurosci Neuroimaging. 10.1016/j.bpsc.2021.07.009

Markham JA, Taylor AR, Taylor SB et al. (2010) Characterization of the cognitive impairments induced by prenatal exposure to stress in the rat. Front Behav Neurosci 4:173. 10.3389/fnbeh.2010.00173 [PubMed: 21151368]

Martin KV, Sucharew H, Dietrich KN et al. (2021) Co-exposure to manganese and lead and pediatric neurocognition in East Liverpool, Ohio. Environ Res 202:111644. 10.1016/j.envres.2021.111644 [PubMed: 34246641]

Mathewson KJ, Chow CHT, Dobson KG et al. (2017) Mental health of extremely low birth weight survivors: a systematic review and meta-analysis. Psychol Bull 143:347–383. 10.1037/bul0000091 [PubMed: 28191983]

McCabe KL, Maloney EA, Stain HJ et al. (2012) Relationship between childhood adversity and clinical and cognitive features in schizophrenia. J Psychiatr Res 46:600–607. 10.1016/j.jpsychires.2012.01.023 [PubMed: 22329951]

McGrath J, Saari K, Hakko H et al. (2004) Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr Res 67:237–245. 10.1016/j.schres.2003.08.005 [PubMed: 14984883]

McGrath J, Brown A, St Clair D (2011) Prevention and schizophrenia--the role of dietary factors. Schizophr Bull 37:272–283. 10.1093/schbul/sbq121 [PubMed: 20974747]

McIntosh R, Vaughn S, Schumm JS et al. (1993) Observations of students with learning disabilities in general education classrooms. Except Child 60:249–261. 10.1177/001440299406000306

McIntosh AM, Holmes S, Gleeson S et al. (2002) Maternal recall bias, obstetric history and schizophrenia. Br J Psychiatry 181:520–525. 10.1192/bjp.181.6.520 [PubMed: 12456523]

McLaughlin KA, Sheridan MA (2016) Beyond cumulative risk: a dimensional approach to childhood adversity. Curr Dir Psychol Sci 25:239–245. 10.1177/0963721416655883 [PubMed: 27773969]

Medeiros W, Torro-Alves N, Malloy-Diniz LF, Minervino CM (2016) Executive functions in children who experience bullying situations. Front Psychol 7:1197. 10.3389/fpsyg.2016.01197 [PubMed: 27616998]

Mednick SA, Machon RA, Huttunen MO, Bonett D (1988) Adult schizophrenia following prenatal exposure to an influenza epidemic. Arch Gen Psychiatry 45:189–192. 10.1001/archpsyc.1988.01800260109013 [PubMed: 3337616]

Merced-Nieves FM, Aguiar A, Dzwilewski KLC et al. (2020) Association of prenatal maternal perceived stress with a sexually dimorphic measure of cognition in 4.5-month-old infants. Neurotoxicol Teratol 77:106850. 10.1016/j.ntt.2019.106850 [PubMed: 31812786]

Meyer U (2014) Prenatal poly(i:C) exposure and other developmental immune activation models in rodent systems. Biol Psychiatry 75:307–315. 10.1016/j.biopsych.2013.07.011 [PubMed: 23938317]

Meyer U, Engler A, Weber L et al. (2008) Preliminary evidence for a modulation of fetal dopaminergic development by maternal immune activation during pregnancy. Neuroscience 154:701–709. 10.1016/j.neuroscience.2008.04.031 [PubMed: 18495356]

Meyer-Lindenberg A, Nichols T, Callicott JH et al. (2006) Impact of complex genetic variation in COMT on human brain function. Mol Psychiatry 11:867–877. 10.1038/sj.mp.4001860 [PubMed: 16786032]

Mhaouty-Kodja S, Belzunces LP, Canivenc M-C et al. (2018) Impairment of learning and memory performances induced by BPA: evidences from the literature of a MoA mediated through an ED. Mol Cell Endocrinol 475:54–73. 10.1016/j.mce.2018.03.017 [PubMed: 29605460]

Mittal VA, Ellman LM, Cannon TD (2008) Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. Schizophr Bull 34:1083–1094. 10.1093/schbul/sbn080 [PubMed: 18635675]

Mollon J, Reichenberg A (2018) Cognitive development prior to onset of psychosis. Psychol Med 48:392–403. 10.1017/S0033291717001970 [PubMed: 28735586]

Mondelli V, Dazzan P, Hepgul N et al. (2010) Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: the role of stress and of antipsychotic treatment. Schizophr Res 116:234–242. 10.1016/j.schres.2009.08.013 [PubMed: 19751968]

Mørkved N, Johnsen E, Kroken RA et al. (2020) Does childhood trauma influence cognitive functioning in schizophrenia? The association of childhood trauma and cognition in schizophrenia spectrum disorders. Schizophr Res Cogn 21:100179. 10.1016/j.scog.2020.100179 [PubMed: 32461919]

Müller N, Weidinger E, Leitner B, Schwarz MJ (2015) The role of inflammation in schizophrenia. Front Neurosci 9:372. 10.3389/fnins.2015.00372 [PubMed: 26539073]

Murphy SK, Fineberg AM, Maxwell SD et al. (2017) Maternal infection and stress during pregnancy and depressive symptoms in adolescent offspring. Psychiatry Res 257:102–110. 10.1016/j.psychres.2017.07.025 [PubMed: 28750213]

Myin-Germeys I, van Os J, Schwartz JE et al. (2001) Emotional reactivity to daily life stress in psychosis. Arch Gen Psychiatry 58:1137–1144. 10.1001/archpsyc.58.12.1137 [PubMed: 11735842]

Naeye RL, Peters EC (1987) Antenatal hypoxia and low IQ values. Obstet Anesth Dig 7:98

Negrón-Oyarzo I, Lara-Vásquez A, Palacios-García I et al. (2016) Schizophrenia and reelin: a model based on prenatal stress to study epigenetics, brain development and behavior. Biol Res 49:16. 10.1186/s40659-016-0076-5 [PubMed: 26968981]

Neill E, Tan EJ, Toh WL et al. (2020) Examining which factors influence age of onset in males and females with schizophrenia. Schizophr Res 223:265–270. 10.1016/j.schres.2020.08.011 [PubMed: 32883558]

Nettis MA, Pariante CM, Mondelli V (2020) Early-life adversity, systemic inflammation and comorbid physical and psychiatric illnesses of adult life. In: Khandaker GM, Meyer U, Jones PB (eds) Neuroinflammation and schizophrenia. Springer International Publishing, Cham, pp 207–225

Newell-Morris LL, Fahrenbruch CE, Sackett GP (1989) Prenatal psychological stress, dermatoglyphic asymmetry and pregnancy outcome in the pigtailed macaque (Macaca nemestrina). NEO 56:61–75. 10.1159/000243104

Oh H, Yang LH, Anglin DM, DeVylder JE (2014) Perceived discrimination and psychotic experiences across multiple ethnic groups in the United States. Schizophr Res 157:259–265. 10.1016/j.schres.2014.04.036 [PubMed: 24856412]

Paquin V, Lapierre M, Veru F, King S (2021) Early environmental upheaval and the risk for schizophrenia. Annu Rev Clin Psychol 17:285–311. 10.1146/annurev-clinpsy-081219-103805 [PubMed: 33544627]

Poletti S, Mazza E, Bollettini I et al. (2015) Adverse childhood experiences influence white matter microstructure in patients with schizophrenia. Psychiatry Res Neuroimaging 234:35–43. 10.1016/j.pscychresns.2015.08.003

Pugliese V, Bruni A, Carbone EA et al. (2019) Maternal stress, prenatal medical illnesses and obstetric complications: Risk factors for schizophrenia spectrum disorder, bipolar disorder and major depressive disorder. Psychiatry Res 271:23–30. 10.1016/j.psychres.2018.11.023 [PubMed: 30458317]

Quidé Y, O'Reilly N, Watkeys OJ et al. (2018) Effects of childhood trauma on left inferior frontal gyrus function during response inhibition across psychotic disorders. Psychol Med 48:1454–1463. 10.1017/S0033291717002884 [PubMed: 28994360]

Quinn PD, Rickert ME, Weibull CE et al. (2017) Association between maternal smoking during pregnancy and severe mental illness in offspring. JAMA Psychiat 74:589–596. 10.1001/jamapsychiatry.2017.0456

Ramsay H, Surcel H-M, Björnholm L et al. (2021) Associations between maternal prenatal C-reactive protein and risk factors for psychosis in adolescent offspring: findings from the northern Finland birth cohort 1986. Schizophr Bull 47:766–775. 10.1093/schbul/sbaa152 [PubMed: 33202018]

Rasetti R, Mattay VS, Wiedholz LM et al. (2009) Evidence that altered amygdala activity in schizophrenia is related to clinical state and not genetic risk. Am J Psychiatry 166:216–225. 10.1176/appi.ajp.2008.08020261 [PubMed: 19074979]

Rauschenberg C, van Os J, Goedhart M et al. (2021) Bullying victimization and stress sensitivity in help-seeking youth: findings from an experience sampling study. Eur Child Adolesc Psychiatry 30:591–605. 10.1007/s00787-020-01540-5 [PubMed: 32405792]

Raymond C, Marin M-F, Majeur D, Lupien S (2018) Early child adversity and psychopathology in adulthood: HPA axis and cognitive dysregulations as potential mechanisms. Prog Neuro-Psychopharmacol Biol Psychiatry 85:152–160. 10.1016/j.pnpbp.2017.07.015

Read J, Perry BD, Moskowitz A, Connolly J (2001) The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. Psychiatry 64:319–345. 10.1521/psyc.64.4.319.18602 [PubMed: 11822210]

Reichenberg A, Caspi A, Harrington H et al. (2010) Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am J Psychiatry 167:160–169. 10.1176/appi.ajp.2009.09040574 [PubMed: 20048021]

Rosenthal A, Meyer MS, Mayo D et al. (2020) Contributions of childhood trauma and atypical development to increased clinical symptoms and poor functioning in recent onset psychosis. Early Interv Psychiatry 14:755–761. 10.1111/eip.12931 [PubMed: 32043308]

Ruby E, Rothman K, Corcoran C et al. (2017) Influence of early trauma on features of schizophrenia. Early Interv Psychiatry 11:322–333. 10.1111/eip.12239 [PubMed: 25808607]

Sacchi C, Marino C, Nosarti C et al. (2020) Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis. JAMA Pediatr 174:772–781. 10.1001/jamapediatrics.2020.1097 [PubMed: 32453414]

Samplin E, Ikuta T, Malhotra AK et al. (2013) Sex differences in resilience to childhood maltreatment: effects of trauma history on hippocampal volume, general cognition and subclinical psychosis in healthy adults. J Psychiatr Res 47:1174–1179. 10.1016/j.jpsychires.2013.05.008 [PubMed: 23726669]

Sandman CA, Glynn LM, Davis EP (2013) Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. J Psychosom Res 75:327–335. 10.1016/j.jpsychores.2013.07.009 [PubMed: 24119938]

Schaefer CA, Brown AS, Wyatt RJ et al. (2000) Maternal prepregnant body mass and risk of schizophrenia in adult offspring. Schizophr Bull 26:275–286. 10.1093/oxfordjournals.schbul.a033452 [PubMed: 10885630]

Schalinski I, Teicher MH, Carolus AM, Rockstroh B (2018) Defining the impact of childhood adversities on cognitive deficits in psychosis: an exploratory analysis. Schizophr Res 192:351–356. 10.1016/j.schres.2017.05.014 [PubMed: 28576548]

Schreier A, Wolke D, Thomas K et al. (2009) Prospective study of peer victimization in childhood and psychotic symptoms in a nonclinical population at age 12 years. Arch Gen Psychiatry 66:527–536. 10.1001/archgenpsychiatry.2009.23 [PubMed: 19414712]

Scott JG, Matuschka L, Niemelä S et al. (2018) Evidence of a causal relationship between smoking tobacco and schizophrenia spectrum disorders. Front Psych 9:607. 10.3389/fpsyt.2018.00607

Seidman LJ, Buka SL, Goldstein JM et al. (2000) The relationship of prenatal and perinatal complications to cognitive functioning at age 7 in the New England Cohorts of the National Collaborative Perinatal Project. Schizophr Bull 26:309–321. 10.1093/oxfordjournals.schbul.a033455 [PubMed: 10885633]

Shaikh M, Ellett L, Dutt A et al. (2016) Perceived ethnic discrimination and persecutory paranoia in individuals at ultra-high risk for psychosis. Psychiatry Res 241:309–314. 10.1016/j.psychres.2016.05.006 [PubMed: 27232552]

Shannon C, Douse K, McCusker C et al. (2011) The association between childhood trauma and memory functioning in schizophrenia. Schizophr Bull 37:531–537. 10.1093/schbul/sbp096 [PubMed: 19752010]

Sideli L, Fisher HL, Russo M et al. (2014) Failure to find association between childhood abuse and cognition in first-episode psychosis patients. Eur Psychiatry 29:32–35. 10.1016/j.eurpsy.2013.02.006 [PubMed: 23764407]

Simanek AM, Meier HC (2015) Association between prenatal exposure to maternal infection and offspring mood disorders: a review of the literature. Curr Probl Pediatr Adolesc Health Care 45:325–364. 10.1016/j.cppeds.2015.06.008 [PubMed: 26476880]

Smith SEP, Li J, Garbett K et al. (2007) Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 27:10695–10702. 10.1523/JNEUROSCI.2178-07.2007 [PubMed: 17913903]

Stein MB, Koverola C, Hanna C et al. (1997) Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med 27:951–959. 10.1017/s0033291797005242 [PubMed: 9234472]

Sutherland S, Brunwasser SM (2018) Sex differences in vulnerability to prenatal stress: a review of the recent literature. Curr Psychiatry Rep 20:102. 10.1007/s11920-018-0961-4 [PubMed: 30229468]

Teigset CM, Mohn C, Rund BR (2020) Perinatal complications and executive dysfunction in early-onset schizophrenia. BMC Psychiatry 20:103. 10.1186/s12888-020-02517-z [PubMed: 32131788]

Torniainen M, Wegelius A, Tuulio-Henriksson A et al. (2013) Both low birthweight and high birthweight are associated with cognitive impairment in persons with schizophrenia and their first-degree relatives. Psychol Med 43:2361–2367. 10.1017/S0033291713000032 [PubMed: 23360614]

Üçok A, Kaya H, Uğurpala C et al. (2015) History of childhood physical trauma is related to cognitive decline in individuals with ultra-high risk for psychosis. Schizophr Res 169:199–203. 10.1016/j.schres.2015.08.038 [PubMed: 26386899]

Ursini G, Punzi G, Chen Q et al. (2018) Convergence of placenta biology and genetic risk for schizophrenia. Nat Med 24:792–801. 10.1038/s41591-018-0021-y [PubMed: 29808008]

Ursini G, Punzi G, Langworthy BW et al. (2021) Placental genomic risk scores and early neurodevelopmental outcomes. Proc Natl Acad Sci U S A 118:e2019789118. 10.1073/pnas.2019789118 [PubMed: 33558239]

Van den Bergh BRH, van den Heuvel MI, Lahti M et al. (2020) Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. Neurosci Biobehav Rev 117:26–64. 10.1016/j.neubiorev.2017.07.003 [PubMed: 28757456]

van Erp TGM, Saleh PA, Rosso IM et al. (2002) Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. AJP 159:1514–1520. 10.1176/appi.ajp.159.9.1514

van Nierop M, Viechtbauer W, Gunther N et al. (2015) Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries. Psychol Med 45:1277–1288. 10.1017/S0033291714002372 [PubMed: 25273550]

van Os J, Marsman A, van Dam D et al. (2017) Evidence that the impact of childhood trauma on IQ is substantial in controls, moderate in siblings, and absent in patients with psychotic disorder. Schizophr Bull 43:316–324. 10.1093/schbul/sbw177 [PubMed: 28177077]

Varese F, Smeets F, Drukker M et al. (2012) Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull 38:661–671. 10.1093/schbul/sbs050 [PubMed: 22461484]

Vargas T, Lam PH, Azis M et al. (2019) Childhood trauma and neurocognition in adults with psychotic disorders: a systematic review and meta-analysis. Schizophr Bull 45:1195–1208. 10.1093/schbul/sby150 [PubMed: 30376115]

Velikonja T, Velthorst E, Zinberg J et al. (2021) Childhood trauma and cognitive functioning in individuals at clinical high risk (CHR) for psychosis. Dev Psychopathol 33:53–64. 10.1017/S095457941900155X [PubMed: 31959269]

Verdoux H, Geddes JR, Takei N et al. (1997) Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. AJP 154:1220–1227. 10.1176/ajp.154.9.1220

Vidal PM, Pacheco R (2020) The cross-talk between the dopaminergic and the immune system involved in schizophrenia. Front Pharmacol 11:394. 10.3389/fphar.2020.00394 [PubMed: 32296337]

Vlasova RM, Iosif AM, Ryan AM et al. (2021) Maternal immune activation during pregnancy alters postnatal brain growth and cognitive development in nonhuman primate offspring. J Neurosci 41:9971–9987. 10.1523/JNEUROSCI.0378-21.2021 [PubMed: 34607967]

Walker E, Mittal V, Tessner K (2008) Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annu Rev Clin Psychol 4:189–216. 10.1146/annurev.clinpsy.4.022007.141248 [PubMed: 18370616]

Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR (2000) Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch Gen Psychiatry 57(9):907–913. 10.1001/archpsyc.57.9.907 [PubMed: 10986554]

Weinstock M (2001) Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Prog Neurobiol 65:427–451. 10.1016/S0301-0082(01)00018-1 [PubMed: 11689280]

Woodward ND, Heckers S (2015) Brain structure in neuropsychologically defined subgroups of schizophrenia and psychotic bipolar disorder. Schizophr Bull 41(6):1349–1359. 10.1093/schbul/sbv048 [PubMed: 25904725]

Wortinger LA, Engen K, Barth C et al. (2020) Obstetric complications and intelligence in patients on the schizophrenia-bipolar spectrum and healthy participants. Psychol Med 50:1914–1922. 10.1017/S0033291719002046 [PubMed: 31456537]

Xie Y, Near C, Xu H, Song X (2020) Heterogeneous treatment effects on Children's cognitive/non-cognitive skills: a reevaluation of an influential early childhood intervention. Soc Sci Res 86:102389. 10.1016/j.ssresearch.2019.102389 [PubMed: 32056571]

Yeo RA, Martinez D, Pommy J et al. (2014) The impact of parent socio-economic status on executive functioning and cortical morphology in individuals with schizophrenia and healthy controls. Psychol Med 44:1257–1265. 10.1017/S0033291713001608 [PubMed: 23866983]

Zijlmans MAC, Riksen-Walraven JM, de Weerth C (2015) Associations between maternal prenatal cortisol concentrations and child outcomes: a systematic review. Neurosci Biobehav Rev 53:1–24. 10.1016/j.neubiorev.2015.02.015 [PubMed: 25795521]

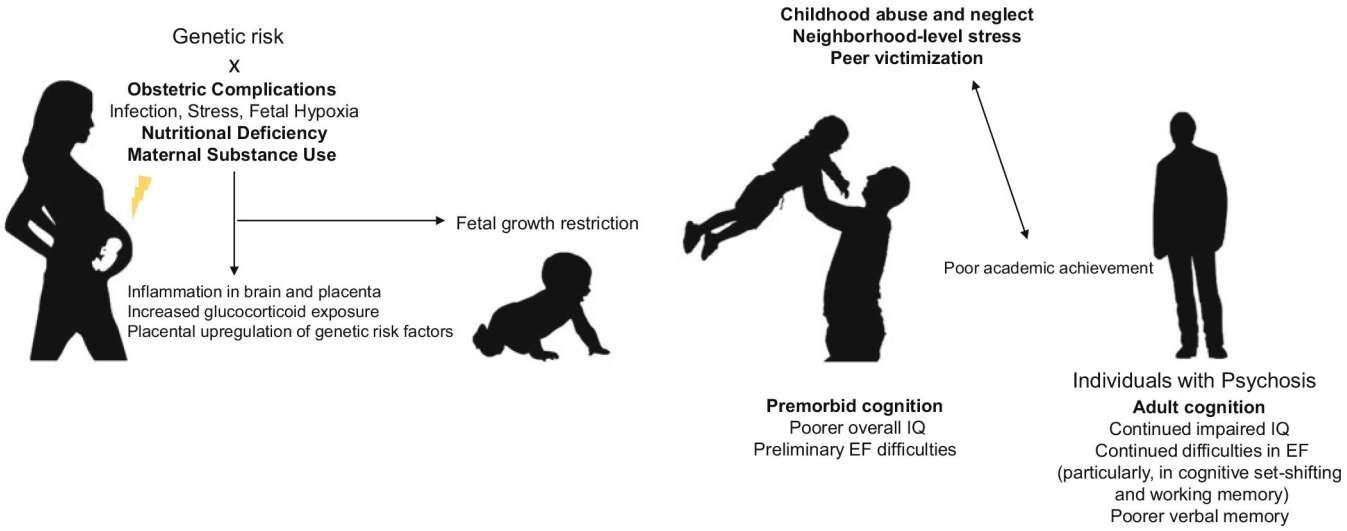

Fig. 1.

Proposed developmental trajectory for the onset of cognitive difficulties from pre-, perinatal, and early childhood environmental risk factors in individuals with psychotic disorders. OCs confer changes on the brain beginning in-utero, which can persist into the postnatal period. These changes are evidenced in cognitive changes apparent as early as infancy that may extend through adulthood. While many women experience OCs over the course of their pregnancy, most offspring do not go on to develop neurodevelopmental disorders like schizophrenia; therefore, understanding the additional risk factors that combine with OCs to portend risk for schizophrenia is needed (Ellman et al. 2018). For example, there is evidence OCs can impact one another. PNMS has been associated with greater risk of infection, increased engagement in adverse health behaviors, and increased risk for gestational complications (Lipner et al. 2019). Individuals with a history of OCs are also more likely to experience stressful events during childhood, such as peer victimization, which may subsequently increase the risk for psychotic experiences in adulthood (Liu et al. 2020). Poorer cognitive functioning also likely impacts the way that individuals are treated within their childhood environment by parents, peers, and teachers (McIntosh et al. 1993; Haager and Vaughn 1995). As we strive to understand early environmental and genetic risk factors for cognitive impairments, we must consider transactional ways in which early “hits” or “primers” can work synergistically or additively with postnatal environmental factors (Estes and McAllister 2016). Sequelae resulting from perinatal adversities may be compounded by environmental risk factors in the postnatal period, including chronic stress and trauma during childhood. Figure adapted from Lipner et al. (2019)

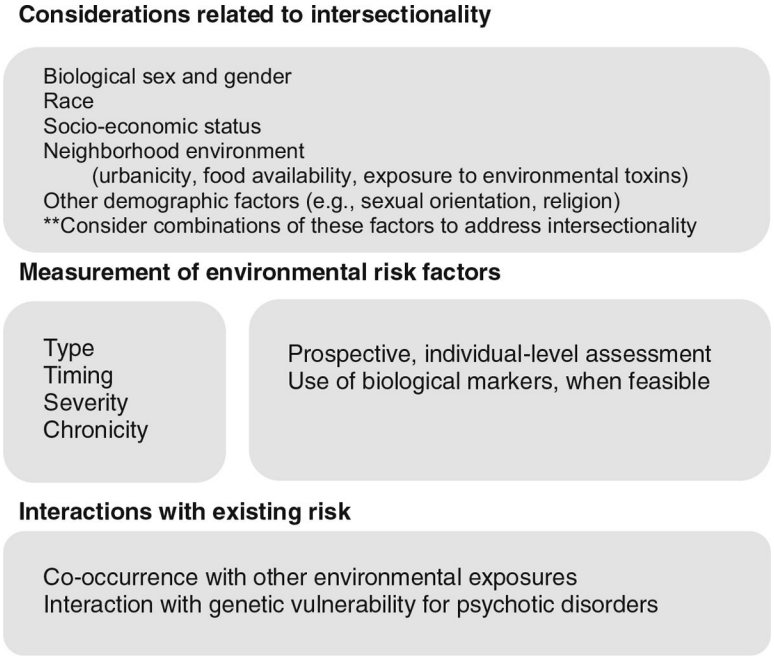

Fig. 2.

Methodological considerations for future studies examining early life environmental risk factors and cognitive outcomes in individuals on the psychosis spectrum