Perinatal Risks and Childhood Premorbid Indicators of Later Psychosis: Next Steps for Early Psychosocial Interventions

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Schizophrenia and affective psychoses are debilitating disorders that together affect 2%–3% of the adult population. Approximately 50%–70% of the offspring of parents with schizophrenia manifest a range of observable difficulties including socioemotional, cognitive, neuromotor, speech-language problems, and psychopathology, and roughly 10% will develop psychosis. Despite the voluminous work on premorbid vulnerabilities to psychosis, especially on schizophrenia, the work on premorbid intervention approaches is scarce. While later interventions during the clinical high-risk (CHR) phase of psychosis, characterized primarily by attenuated positive symptoms, are promising, the CHR period is a relatively late phase of developmental derailment. This article reviews and proposes potential targets for psychosocial interventions during the premorbid period, complementing biological interventions described by others in this Special Theme issue. Beginning with pregnancy, parents with psychoses may benefit from enhanced prenatal care, social support, parenting skills, reduction of symptoms, and programs that are family-centered. For children at risk, we propose preemptive early intervention and cognitive remediation. Empirical research is needed to evaluate these interventions for parents and determine whether interventions for parents and children positively influence the developmental course of the offspring.

Key words: psychosis/schizophrenia/early intervention/prevention/stress/psychological/parenting

Introduction

We briefly summarize an extensive literature on premorbid vulnerabilities of later psychosis,1 focusing on the period from pregnancy through the elementary school years. Our goal is to identify potential treatment targets for even earlier intervention than those currently emerging from the clinical high-risk (CHR) field,2 (also called “prodromal”, “ultra high-risk”, or “at risk mental state”) which typically address attenuated psychotic symptoms in teenagers and young adults. We also present a conceptual framework linking early psychosocial interventions with robustly identified developmental deficits. This article complements the 2 treatment articles in this Special Theme Issue that focus on potential biological preventive interventions.

Study Designs for Identifying Premorbid Risks

Given that we focus here on leveraging knowledge of premorbid deficits to develop a program of early psychosocial interventions, this article is not a comprehensive review. Indeed, literature on premorbid deficits has been reviewed from many angles previously.3,4 Our review incorporates a number of study designs including prospective cohort studies, which can provide potential population-level causal inferences regarding the exposure to environmental risks for those who later develop psychosis; follow-back designs, which examine childhood premorbid characteristics of adults with psychoses; and familial (“genetic”) high-risk (FHR) studies, which evaluate the offspring of parents with psychosis at different ages. The FHR approach enables researchers to study development deficits in individuals not necessarily identified for treatment, in contrast to youth at CHR, who are already suffering from attenuated positive psychotic symptoms and significant functional impairments, and are often seeking treatment.

The CHR field, focusing on the period just prior to the emergence of psychosis typically in adolescence, has rejuvenated the “early intervention” field in psychiatry.5 CHR research has focused on delaying the emergence of psychosis or reduction of liabilities, with promising
early findings. The idea of “staging” highlights the CHR period as a relatively late phase in the development of psychosis and provides a framework for even earlier intervention. Indeed, the relative success of early intervention has given support to the idea that transition to psychosis can be prevented in some CHR individuals.

The FHR approach provides opportunities for developmentally sensitive, earlier interventions. While the FHR paradigm allows the study of offspring, where approximately 10% go on to develop psychosis, it yields a much larger percentage (~50%) that have nonpsychotic problems. These problems could be targets for early intervention and could be addressed as a potential part of the trajectory to psychosis.

**Early Developmental Signs in Prepsychotic Individuals and Children at FHR**

Prepsychotic and FHR children show more neuromotor and minor physical anomalies (MPAs), speech and language, socioemotional, and cognitive abnormalities, in families with parental schizophrenia than preaffective psychosis (see table 1 for major studies).

**Neuromotor and Minor Physical Anomalies**

Neuromotor deviations may be the most common childhood abnormality for individuals that develop psychosis. Birth cohorts have documented developmental delays in sitting, standing, and walking alone at 2 years of age. Through a “follow-back” approach, archival-observational studies of home movies showed preschizophrenia children to have greater clumsiness or odd movements and slower reactions compared to their healthy siblings by age 2. Premorbid abnormalities such as unbalanced, involuntary, or unusual movements like heel-to-toe standing have been observed in development beyond toddlerhood. MPAs are a heterogeneous group of morphologic markers (eg, wider skull bases, shorter lower facial heights) potentially resulting from genetic or gestational insults that occur during craniofacial and brain development. MPAs are more prevalent in those with schizophrenia and those at high-risk neurodevelopmental disorders.

**Speech, Language, and Hearing**

Compared to controls, speech delays (ie, saying words other than calling parents) in toddlers, non-structural speech problems from toddlerhood to 16 years, and mispronunciation of words at ages 7 and 11 were more frequent among preschizophrenia children than comparsons. Unusual speech (eg, echolalia, meaningless laughter) at ages 4 and 7 significantly predicted children who later developed schizophrenia, and poorer speech performance at ages 5 and 14 was associated with later psychosis among males. Hearing impairments at age 4 have also been found to be associated with an increased risk for later nonaffective psychotic illness. Because speech, language, and hearing are central to social engagement and cognitive functioning, early deficits may derail trajectories in these functional domains.

**Cognition**

Cognitive impairments that typically characterize schizophrenia have been observed in milder forms before the onset of psychosis (see figure 1 and the accompanying article by Agnew-Blais et al). FHR and cohort studies evaluating children who later develop schizophrenia demonstrate persuasive evidence of impairments in children as early as 4 years of age. In crystallized verbal intelligence, development impairments were relatively stable, but increased developmental lag in fluid intelligence from ages 7 to 13 was observed in children with later schizophrenia. Although verbal, psychomotor, receptive language, attention, and memory deficits have been observed, the most robust evidence comes from IQ measures, which demonstrate greater impairments among preschizophrenia children compared to those developing affective psychoses.

The relatively stable verbal deficits of the preteenage years begin to lag increasingly behind that of healthy comparisons during the teen years among those who develop schizophrenia. The cohort studies do not identify whether these belong to a CHR subgroup; however, CHR studies clearly demonstrate greater impairment in those who go on to develop psychosis than those who do not.

In considering targeted interventions, a focus on individual rather than group differences is essential. Seidman and others proposed that substantial premorbid, neurocognitive heterogeneity is present in early childhood. In a cohort study, approximately 45% of preschizophrenia children were cognitively impaired at the age of 7. Thus, only a subgroup of individuals with schizophrenia may be appropriate for cognitive remediation.

**Socioemotional**

A review of 19 studies reported poor childhood social functioning as a sensitive predictor of later schizophrenia, but the effect was dependent on the specific developmental time point and aspect of social functioning. While social functioning within infancy or preschool was not predictive, antisocial-externalizing behavior was a sensitive and specific predictor for schizophrenia relative to other nonpsychotic disorders, as early as 5 years of age. Social–withdrawal internalizing behavior was a sensitive predictor for schizophrenia at the age of 11.

Using an archival-observational approach, one follow-back study evaluated the interpersonal experiences...
Table 1. Overview of Early Developmental Impairments in Prepsychotic and FHR Offspring up to Age 12

<table>
<thead>
<tr>
<th>Neuromotor and Minor Physical Anomalies</th>
<th>Speech/Language/Hearing</th>
<th>Socioemotional Behavior</th>
<th>Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Impairments predicting later psychosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn period &lt;3 months</td>
<td>Sitting, walking, and standing delays(^{11,13})</td>
<td>Delays in speech(^{11,13}), and in receptive language(^{13}) and hearing impairments(^{13})</td>
<td>Preference for solitary play(^{11}); fewer joy(^{16}); and more negative affect(^{17})</td>
</tr>
<tr>
<td>Infancy 3–12 months</td>
<td>Potty training delays(^{13,14})</td>
<td>Poor abnormal speech acquisition and quality(^{19,20}); abnormal language including echolalia, meaningless laughter(^{21})</td>
<td>More externalizing behaviors(^{20}); higher aggression, inattention,(^{19}) delinquency for males,(^{22}) social maladjustment and deviant behaviors(^{21}); more internalizing(^{30}); social anxiety,(^{15}) withdrawn(^{19}); depressed(^{19}); self-reported psychosis at 11 years(^{20}); positive psychosis screen at 14 years(^{9})</td>
</tr>
<tr>
<td>Toddler and preschool 1–4 years</td>
<td>Poor coordination and clumsiness, unusual movements (walking backward, heel-to-toe standing)(^{12,13,19})</td>
<td>Unusual language(^{15}); less communicative competence(^{16})</td>
<td>Low levels of stranger wariness(^{17}); lower reactivity in response to assessor(^{14}); less affection, hostility, and negative affect, higher activity levels,(^{36}) psychosocial delays, and irritability(^{20});</td>
</tr>
<tr>
<td>Elementary school 5–12 years</td>
<td>Neuromotor deviation: poor coordination,(^{39}) involuntary movements,(^{25,40,41}) balance(^{40,42,43}); autonomic hyperresponse(^{44})</td>
<td>Low verbal productivity, inadequate cohesion between ideas(^{46})</td>
<td>Less socially competent(^{46}); greater interpersonal problems,(^{39}) socially isolated(^{46,47}); distorted or aggressive behavior(^{33,44}); poor affective control; greater “schizoid” behaviors(^{48})</td>
</tr>
</tbody>
</table>

Note: Please refer to published reviews for detailed findings.\(^{3,8}\)

of the affective displays in 5–10-year-old schizophrenia and sibling controls, showing that those with schizophrenia had greater negative affect at 5–7 years.\(^{17}\) Lack of joy expressions throughout childhood was observed in another study comparing schizophrenia and nonpsychotic sibling controls, particularly for females.\(^{16}\)
Genetic Etiology and Biological Mechanisms

Schizophrenia is highly heritable; genetic factors may account for about 80% of the variation in risk. Many common genes of small effect and some rare mutations of larger effect may be associated with increased risk, such as genes involved in brain development, cell membrane functions, and immune mechanisms. Similar to disorders with many early impairments, genes underlying risk for schizophrenia cut across diagnostic boundaries, overlapping with those for bipolar disorder, autism, and attention deficit disorders.

Pathophysiological Mechanisms: Neurodevelopmental Abnormalities Underlying Risk for Schizophrenia. The longstanding theory that increased dopaminergic activity in the striatal and limbic systems is core to schizophrenia has not been examined directly in children at risk. Recent work points to an excess of presynaptic dopamine in the ventral striatum in CHR individuals. Other neurotransmitters, such as gamma-aminobutyric acid (GABA) and glutamate, have also been implicated in schizophrenia. Given the major role these neurotransmitter systems play in brain development and plasticity, it would be important to determine if such alterations are actually observed in early development since the adult brain is the outcome of gene by environment sculpting.

Timing of Pathophysiology. Previously reviewed studies suggest that the premorbid developmental abnormalities originate at or before birth. For example, the evidence of increased prevalence of MPAs in schizophrenia suggests abnormal intrauterine development. Neuropathological studies also suggest early developmental derails, such as a maldistribution of interstitial neurons in white matter regions, reflecting a failure of normal processes of neuronal migration. Imaging studies suggest abnormal cortical gyriﬁcation in schizophrenia. Gyriﬁcation—expansion of the surface area of the brain—begins early in development; thus, reduced gyriﬁcation could suggest early developmental origins. A recent review demonstrated structural abnormalities, especially in prefrontal cortex and hippocampus in FHR for schizophrenia children studied as young as 7 years of age.

Such alterations in early brain development may underlie the observed premorbid cognitive, social, and neuromotor difficulties seen in childhood but may not explain why psychotic symptoms do not usually begin until adolescence. Instead, early developmental abnormalities may interact with later developmental processes such as synaptic pruning and myelination or particular assessing the stressful experiences of parents and pregnant women in determining later risk for psychosis in their offspring.

Summary

Socioemotional abnormalities are predictive of who will develop psychosis. Uncovering abnormalities in early development is promising for interventions, given the sensitive period in which children’s regulatory systems may repair and resume a normally developing trajectory. However, the reliance on these signs for detecting psychosis is immensely challenging because many are not speciﬁc to psychosis. Rather, it would be advantageous if the earlier and speciﬁc roots of these developmental deﬁcits could be identiﬁed. For instance, a novel study by Gamma et al examining intermodal integration, the ability to relate perception across senses, found greater early impairments among the 8-month-old infants of parents with psychosis, especially in offspring of parents with schizophrenia. Comparing these early impairments in relation to those of other developmental disorders may provide greater insights into the developmental origins of psychosis.

Etiological Mechanisms in the Development of Psychosis Across Childhood

Identification of the biological origins of psychosis has been advanced by recent, large-scale genetic studies. Additionally, a large body of epidemiological research has contributed to our understanding of the prenatal and obstetric risks for later psychosis at a population level, along with more reﬁned laboratory studies
kinds of experience (eg, poor parenting, abuse), leading to the emergence of psychotic symptoms.\textsuperscript{34–36}

**Prenatal Environmental Risks and Mechanisms**

While knowledge of genetic susceptibility for psychotic disorders has become robust,\textsuperscript{34,97,98} the role of the earliest (eg, fetal) adverse environmental risks is also important. Environmental factors contribute to risks for neurodevelopmental disorders in offspring\textsuperscript{99} and an intervention within environmental factors may be more feasible than within genetic mechanisms.

**Prenatal Risks.** Maternally acquired infections that have been positively associated with schizophrenia\textsuperscript{100–106} are consistent with studies of exposures to viral pathogens via the maternal placenta,\textsuperscript{107} resulting in disruption of fetal brain development and abnormal neurodevelopmental outcomes. Researchers have identified several key nutrients, including vitamin D and folate, involved in DNA repair and methylation, and iron, where low levels may lead to dopaminergic dysfunction,\textsuperscript{108–115} with related structural and functional brain deficits characteristic of those with schizophrenia.\textsuperscript{113} Early socioeconomic factors, including housing in an urban environment, low-income status, or ethnic minority status, are also risks for the development of psychosis. Of additional concern is that lower socioeconomic status may be associated with increased health risk behaviors (eg, smoking, substance use),\textsuperscript{116} which may increase a child’s susceptibility to cognitive impairments and thus increase the risk for psychosis.\textsuperscript{117}

Another concern is that a mother’s stress response during pregnancy contributes to her offspring’s neurodevelopmental problems.\textsuperscript{118,119} For instance, children of mothers that experienced major life stress (ie, death or severe illness in family members, catastrophic events) during pregnancy were at higher risk for schizophrenia.\textsuperscript{120–123} These risks strongly indicate the need to prioritize the protection of women by ensuring that they have a stable and healthy lifestyle, preventing maternal infections during gestation or even preconception,\textsuperscript{124} and ensuring proper nutrition during pregnancy for optimal fetal brain development.

**Obstetric Complications.** Those at risk for schizophrenia tend to experience more obstetric complications (OCs),\textsuperscript{125} which can increase offspring risk for schizophrenia.\textsuperscript{125–130} This includes hypoxia,\textsuperscript{109,120} which is significantly associated with structural brain abnormalities.\textsuperscript{66} Children with low birth weight were also found to be more likely to develop schizophrenia.\textsuperscript{131–133} Other OCs such as pregnancy bleeding, preeclampsia, diabetes, delivery complications such as asphyxia or Cesarean section, or birth abnormalities including congenital malformations or small head circumference, have all been implicated as risk factors for schizophrenia.\textsuperscript{134,135} These complications can be reduced or mitigated through improved prenatal care.

**Postpartum and Childhood Environmental Risks and Mechanisms**

**Stress and Adversity.** Recent findings suggest that adverse life events may produce greater emotional reactivity to subsequent stressors, in turn contributing to the vulnerability for psychotic disorders.\textsuperscript{5,136} An association between childhood adversity and psychosis has been documented through prospective, case-control, and cross-sectional designs. In a meta-analysis, trauma (eg, sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying) was found to increase the risk of psychosis, regardless of the specific nature of the exposure.\textsuperscript{137}

Proposed biological mechanisms to explain the relationship between adversity on children’s neurodevelopment have suggested that persistent exposure to stressors and chronic heightened glucocorticoid activity in early development can produce permanent changes in the hypothalamic-pituitary-adrenal (HPA) axis, impairing the negative feedback system in dampening HPA activation.\textsuperscript{138} Early stress hypersensitivity may increase the risk for psychosis for those later developing schizophrenia.\textsuperscript{139,142} Furthermore, the pattern of socioemotional impairments among FHR children and those who later develop psychosis may reflect these HPA system alterations.

Stress exposure and childhood trauma may also affect dopaminergic transmission, which has been linked to psychosis.\textsuperscript{143} Chronic adverse exposures may produce sensitization and hyperreactivity of the dopaminergic system at high levels,\textsuperscript{144–146} even in moderate stress.\textsuperscript{147,148} Dopamine may be involved in the formation of particular psychotic experiences (eg, persecutory delusions that act as responses to threat-related stimuli).\textsuperscript{149} Altogether, these findings suggest that individual vulnerability in reactivity may be altered by prolonged or severe exposure to stress.

**Parents With Psychosis.** In addition to being at greater genetic risk for psychosis, children with parents that have psychosis are more likely than healthy peers to be exposed to stress, including financial and social challenges and stigma.\textsuperscript{150–152} Women with schizophrenia tend to have higher rates of unplanned pregnancy, exposure to violence during pregnancy, less partner support,\textsuperscript{153,154} and household instability, altogether posing risks to children’s socio-emotional and cognitive development.\textsuperscript{155–159} Indeed, household stability, social support, and high IQ have been shown to be protective for children with mothers with schizophrenia.\textsuperscript{160–162}

Problematic parenting and issues with the parent-child relationship among parents with schizophrenia may impede optimal development in their children.\textsuperscript{152,163–166}
Caretaking responsibilities may be affected by delusions or hallucinations, negative symptoms, or by dysregulated or unusual affect. Reduced parenting capacity may lead parents to be less responsive, sensitive or energetic, remote, intrusive, or overprotective with their child. Importantly, adoptees at FHR for schizophrenia spectrum disorder, when exposed to parental communication deviance of adoptive parents were more likely to show psychiatric disorders, including schizophrenia spectrum disorders. Altogether, this may explain the greater rates of insecure or disorganized attachment relationships associated with parental psychosis.

**Developmental Models Integrating Stress and Psychosis Risk.** The traumagenic-neurodevelopmental model posits that adversity or trauma in conditions where stress is prolonged, severe, or within crucial time points may contribute to the vulnerability for psychosis. Models that include familial risk may also explain how 11–14-year-old children who either showed multiple risks for schizophrenia (motor or speech abnormalities, socioemotional problems, and endorsement of psychotic-like symptoms) or had a family history of schizophrenia were more frequently exposed to negative life stress and daily stressors and were more distressed by these experiences, compared to typically developing children. Furthermore, other models that incorporate psychosocial experiences in early development and reflect the multicausality of psychosis should be considered. For instance, childhood bullying is a risk factor for psychosis among nonclinical and clinical samples. Of interest is the “attachment-developmental-cognitive” hypothesis, which proposes that specific disturbances in childhood attachment, perhaps emanating from trauma, lead to altered neural representation of the self and the formation of other psychosis symptoms. Additionally, the model of mutual regulation—although not specific to psychosis—argues that normal development is a process of effective reciprocal social emotional communication and that chronic reiterated daily stressors can lead to poor social-emotional functioning in both the child and the parent, ultimately spiraling in derailed development. Confirming these theories would provide evidence for early interventions involving the parent-child relationship.

**Epigenetic Mechanisms**

Given the broad array of environmental perinatal risks for psychosis, specific environmental risks at certain developmental time points may induce changes in gene expression—epigenetic effects—that influence the emergence of psychosis. Animal and human studies have shown the effect of postnatal factors on the gene regulation implicated in human psychosis. Of note is the role of environmental adversity, including lack of maternal care and chronic maternal separation, which approximates the childhood experiences of many children with parents suffering from psychosis. Early life maternal separation among mice have showed increased HPA-axis activity associated with phosphorylation of methyl CpG-binding protein 2 and hypomethylation of arginine vasopressin, which are genes involved in the expression of parvocellular division in hypothalamic paraventricular nucleus, an area implicated in psychosis.

Environmental factors, several of which may operate early during brain development, are likely to interact with risk genes to increase the liability of schizophrenia. Examples include interactions between fetal hypoxia and hypoxia-related genes on hippocampal structure and the effect of interactions between serotonin transporter and **COMT** gene polymorphisms and childhood trauma on cognitive functioning.

**Recommendations for “Earlier” Intervention Targets**

We argue that the knowledge of early developmental signs observed in prepsychotic and individuals at FHR for schizophrenia and the known etiological mechanisms in the development of psychosis across childhood is sufficient to identify plausible therapeutic targets for intervention. The conceptual model in figure 2 highlights promising and practical strategies that ameliorate stress and address early environmental risks and impairments across development.

Targeting FHR children and their families may be the most practical strategy for early intervention at this time. Parents with psychosis are an underserved population; the majority of mothers with psychosis serve as primary caretakers for their children who wish for a healthy family relationship. The implementation of enhanced care for parents is a public health strategy, because its effects would likely generalize to children. Conceivably, one could also target preteen children at CHR for treatment, and some investigators are studying such children. Of course, there may be some differences in the specific deficits between children at FHR versus CHR, with both types of risks exerting independent effects. Nevertheless, because our focus is conceptualized as a potential primary prevention of psychosis strategy, and because many of these children develop a wide range of nonpsychotic mental disorders and functional impairments, we chose to focus on a FHR population. Interventions may be better framed in terms that promote resilience and opportunities for improved development. We believe that such interventions could treat current difficulties and may prevent adverse outcomes including psychosis.
Early Psychosis Risks to Inform Intervention

**Parent-, Dyadic-, and Family- Oriented Targets**

1. **Elevate the importance of prenatal care.** Prenatal care may buffer the nutritional, obstetrical, and stress risks for psychosis. Adverse birth outcomes (prematurity, low birth weight) among offspring of women with psychosis may be attributable to inadequate prenatal care. Unfortunately, women with psychosis are less likely to receive adequate prenatal care than healthy women, even accounting for sociodemographic backgrounds. Treatment adherence may not be maintained during pregnancy, due either to parental or provider concerns regarding the potential medication effects on the fetus. Some studies show high rates of relapse during pregnancy for women with schizophrenia, which can adversely affect self-care and generate additional risks for the developing fetus. Lack of prenatal care is also associated with service utilization, including decreased pediatric care. A multidisciplinary team (eg, obstetricians, psychiatrists, adult- and infant-parent-trained psychologists, neonatologists, nutritionists, and social workers) could address problematic prenatal issues including nutritional deficiencies such as food or vitamins, lifestyle concerns such as the use of tobacco, alcohol or other drug substances, or life stresses including psychotic denial of pregnancy, unintended pregnancy, unstable housing or violence in the home.

2. **Increase social support.** Support may be one way to reduce stress among parents with psychosis, and in turn, increase their parenting capacities and buffer the risks on their children. Support groups, non-directive counseling, and home visits by nurses have demonstrated improvement in mother-infant interaction and maternal mood for depressed mothers. Family therapy may be effective in addressing family burdens.

3. **Enhance parenting skills.** Schizophrenia patients in recovery still experience parenting challenges. Parenting classes and coaching have been effective for mothers with schizophrenia. Interventions aimed at improving maternal sensitivity include observation and modeling through video-based feedback, although empirical evaluation of these approaches with this population is needed.

4. **Reduce cognitive deficits and symptoms in parents.** Parents with psychosis have cognitive problems that can affect the parent-child relationship including second-order Theory of Mind, speed of processing, cognitive flexibility, and motivation. Among the psychosocial interventions for psychosis (cognitive therapies, family therapy, life, and social skills training), cognitive behavioral therapy (CBT) seems best suited to address social cognitive deficits symptomatic of psychosis. Interventions to improve perspective-taking interventions, including video feedback or role play, may be useful. Cognitive remediation, which aims to improve processes such as memory, attention, and problem solving, has demonstrated improvements in emotion processing and social functioning, and may be a useful tool for parents, although little research has evaluated its effect on...
parents and children.\textsuperscript{172} Furthermore, research on the reduction of parental non-psychotic psychopathological symptoms and its effects on the child is mixed.\textsuperscript{227,228} Integrating cognitive remediation with treatment considering the context of caretaking and the parent-child relationship may help to enhance outcomes.

5. **Instituting family-centered care across development.** Although not an intervention per se, wrap-around care is crucial for healthy family functioning in families affected by psychosis. This includes services that support family health (prenatal, primary, psychiatric, or pediatric care) and practical needs (financial, legal, housing, transportation, vocational help, school) through counseling or coaching (spiritual, parenting), as well as crisis management.\textsuperscript{172,229,230} Moving the parents into recovery, keeping their children safe, and ensuring the health and stability of the family should help protect against later psychosis or impairments among children. Importantly, parent-child relationship-based interventions may be more effective within the context of other supports.\textsuperscript{217,231} Furthermore, such care is practical because it addresses everyday parenting challenges faced by parents with psychosis (eg, sharing about their illness, worrying about their children’s development, engaging in developmentally appropriate family activities such as sport activities or birthday parties). Psychoeducation for the child regarding coping with their parent’s mental illness at an appropriate age is important in raising the quality of life for all affected family members.\textsuperscript{232}

Additionally, the role of legal prevention is an unexplored yet possible buffer to risk for psychosis and related impairments. Families with psychosis may interact with the legal system (eg, custody loss, landlord-tenant disputes).\textsuperscript{233–235} Custody loss or even temporary separation (eg, hospitalization) from children is a major fear among parents with mental illness, and may explain their reluctance for service utilization.\textsuperscript{150,236} It is worrisome that chronic separation experiences could heighten the risks for psychosis and other impairments in children. One recommendation is that the care system includes a component by legal professionals who specialize in mental illness.

**Child-Oriented Targets**

6. **Regard early indicators of risk as treatment outcomes: A preemptive early intervention strategy.** With the exception of cognition, early intervention programs have not specifically targeted early developmental risks. Nonetheless, risk indicators yield a high rate of false positives for later psychosis risk and often overlap with other disorders.\textsuperscript{237,238} thus, understanding the combination of these risk indicators can improve the prediction of individuals who later develop psychosis and serve as targets for psychosocial intervention.

Evaluations and implementations of an intervention at earlier stages ['preemptive early interventions’ (PEI)] are now taking place. Uher has proposed an intervention beginning at 9 years of age among children at high and low familial risk.\textsuperscript{239} The “Skills for Wellness” program focuses on modifying early antecedents of psychosis (developmental delays or experiences of psychosis, anxiety, or affective lability) through cognitive-behavioral skills and parent training. Aside from being a feasible target for psychosis intervention, the amelioration of antecedents is also an important goal in and of itself, as impairments are often distressing to the child and family. It is a low-risk intervention relative to pharmacological treatments and probably less stigmatizing.

7. **Implement cognitive remediation in CHR children.** Thus far, there are no published studies of cognitive enhancement in children at risk for schizophrenia. Promising results have emerged from cognitive remediation techniques in patients with schizophrenia.\textsuperscript{240,241} and preliminary findings suggest that improvements may be obtained during the CHR phase.\textsuperscript{242} Nevertheless, while plasticity-based treatments have shown considerable promise and have few direct negative side effects, research is needed to determine their impact and durability on cognitive impairment in the premorbid period. Specification is needed for the primary targets (ie, executive functions, memory, attention, social cognition), the intervention approach and its duration.

Other interventions can be used to treat premorbid problems. A review of the literature on improving executive functions (EFs) in 4–12-year-olds suggests different ways to improve EFs, including “computerized training, noncomputerized games, aerobics, martial arts, yoga, mindfulness, and school curricula” (p. 959), with benefits going to those most impaired.\textsuperscript{243} Integrating social-emotional and physical training activities with cognitive enhancing ones may maximize EF improvement. Developing cognitive treatments that are effective in the premorbid risk period might prevent the growing adolescent achievement gaps affecting these children.\textsuperscript{67,74}

**How Treatment Milieus Support Both Early Prevention and Ongoing Early Intervention Efforts**

Given the developmental and intergenerational risks for psychosis, integrated care for both children and families is imperative. However, the US severely lacks such services. Parents with psychosis generally receive psychopharmacological and psychosocial treatments without any specialized features that support their caregiver role. Outpatient clinics or consultations within women’s health or perinatal psychiatry might provide care to parents with psychosis (mostly mothers), although these treatments may not incorporate parent skills training, promote activities toward improving child development,
or target the parent-child relationship. Without a comprehensive program, maintaining a healthy level of stability and family functioning will remain a struggle for most families, with variability in treatment engagement and adherence. Community-based supports in and out of the home that also integrate health and social services would help comprehensively address the various needs of parents affected by psychosis.

US parents with acute severe psychosis are often separated from their children following hospital admission, causing enormous stress on the family. Yet, models of comprehensive care for mothers and infants within inpatient and partial programs exist. Mother-Baby Units (MBUs), which began in the mid-1900s, exist in Europe, Australia, and New Zealand as inpatient and day treatment facilities with pharmacological and psychosocial interventions that accommodate mothers and infants. While this specific inpatient model has not been adopted in the US it could be adapted for a comprehensive outpatient program for mothers and their infants.

Conclusions

Clearly, the multidisciplinary understanding of developmental risks for schizophrenia has shaped a promising outlook for early intervention. Research to date supports the initiation of psychosocial interventions that target impairments and biological and psychosocial processes involved in the trajectory for psychosis. Reducing prenatal risk exposures, including family stress, is an important focus. Furthermore, the needs of families affected by psychosis warrant accommodations to treat both parents and infants through appropriate treatment settings that also equip parents with practical parenting skills and ways to improve the parent-child relationship. Because of the chronicity and severity of schizophrenia, substantial coordination to provide acute and long-term support is needed for parents and children. Additionally, systematic research is needed to examine the impact of such interventions on preventing psychopathology and functional disability, as well as its cost-effectiveness. The impact of the parent-child interactions and psychosocial adversity on brain development and plasticity in at-risk children needs to be understood to help identify therapeutic targets for early intervention. Early interventions may be more effective with reliable identification of parents and children at highest risk; ascertaining biomarkers of the early stages of psychotic disorders will be valuable. Such investments within early development, can improve the developmental risk trajectory and intergenerational transmission of risk of psychosis, and promote intact and healthy families.

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