

2 Early Environmental Determinants of Schizophrenia

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Modern research conceptualizes schizophrenia as a disorder stemming from multiple sources of risk. Genetic vulnerability (having parents with schizophrenia) is the single strongest liability for schizophrenia. Researchers also identify early environmental determinants contributing to the later development of schizophrenia. Some of these early risk factors include maternal health during pregnancy, obstetrical complications through pregnancy, and later rearing circumstances through childhood. This chapter discusses each of these early environmental risk factors in turn.

To help explain the origins of schizophrenia, Mednick and colleagues propose a “two-hit model” (1). The theory suggests that two stressors, or “hits,” result in increased risk for schizophrenia. The *first hit* stems from a genetic liability for schizophrenia that may increase risk for disruptions of fetal neural development. In cases with low genetic risk, teratogens such as influenza, or maternal stress, during a critical period of gestation (e.g., second trimester), may cause disruptions of fetal neural development that contributes to later schizophrenia. According to the theory, the *second hit* is an environmental stressor; examples of second hits include high levels of family stress, unstable rearing circumstances, and possibly obstetrical complications. When the first and second hits occur, risk for schizophrenia increases.

THE FIRST HIT: SECOND-TRIMESTER DISRUPTION AND ADULT MENTAL HEALTH

In 1988, we reported an increase in the rate of schizophrenia among Helsinki residents exposed to the 1957 influenza virus. Individuals were at greater risk for

From: *Early Clinical Intervention and Prevention in Schizophrenia*
Edited by: W. S. Stone, S. V. Faraone, and M. T. Tsuang © Humana Press Inc., Totowa, NJ

schizophrenia if they were exposed to the virus during the second trimester (or more precisely, the sixth month) of fetal development (2). Since 1988, most research continues to support the hypothesis that a teratogen experienced during the second trimester increases risk for schizophrenia (3–6). There have been some failures to replicate (7). In a follow-up of our original 1988 report, we reported that 86.7% of schizophrenia patients whose second-trimester gestation overlapped the height of the epidemic had mothers who *actually contracted* influenza (not simply exposed) (8).

Sixth-Month Studies

Timing of exposure may impact later psychopathological outcome. Five prenatal influenza infection studies similar to our own suggest that the schizophrenia-relevant teratogen occurred during the sixth month of gestation (9–13).

In addition to schizophrenia, affective disorders, as well as violent offending, relate to maternal influenza infection (14,15). Results suggest increases in affective disorders among individuals exposed to the 1957 Helsinki influenza during the second trimester. The authors compared the precise timing of exposure of patients with schizophrenia to the exposure of patients with affective disorders. The majority of individuals with affective disorders experienced influenza exposure during the fifth month of gestation, whereas the majority of individuals with schizophrenia experienced influenza exposure during the sixth month of gestation (8).

Examining this same cohort also reveals a relation between violent offending and second-trimester exposure to the influenza epidemic. Mednick and Tehrani contend that late sixth-month and early seventh-month exposure to the influenza epidemic increases risk for violent criminal offending, but not property offending (16). These data suggest that specific behavioral deviance may differentially relate to specific brain systems. If the development of a specific brain system is compromised, then risk for a specific behavioral disorder may be increased. Which brain region is at risk may depend on which fetal brain area is experiencing rapid development at the time of the impact of the teratogen.

EFFECTS OF A FIRST HIT: SCHIZOTYPAL PERSONALITY DISORDER AND SECOND-TRIMESTER DISRUPTION

Schizotypal personality disorder (SPD) resembles schizophrenia in nature, but is lesser in terms of severity of symptoms. Researchers often consider SPD as a less severe condition on a continuum toward schizophrenia. SPD is more common and less debilitating than schizophrenia, therefore, studying individuals with SPD offers a more convenient population to derive information regarding the determinants of schizophrenia.

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As mentioned earlier, we have suggested that schizophrenia is a “two-hit” disorder. We posit that the first hit alone, without a second hit, may increase risk for neural disorganization leading to cognitive and perceptual distortions observed in people with SPD.

The Finnish Recruit Study

We predict that a severe influenza epidemic may constitute increased risk for a first hit and may correlate with an increase of births of individuals who later develop SPD. (Some of these individuals will suffer a second hit, which will increase risk for schizophrenia.) We determined to test the hypothesis that a second-trimester maternal influenza exposure would correlate with an elevation in the number of SPD individuals. We exploited the fact that almost all Finnish young men must serve in the military. All new recruits are given the Minnesota Multiphasic Personality Inventory (MMPI). We defined an MMPI scale score pattern that would relate to an SPD diagnosis. We hypothesized that recruits exposed to an influenza epidemic during their sixth month of gestation would more often evidence a pattern of MMPI scales scores reflecting a diagnosis of SPD than would nonexposed recruits.

All Finnish draftees are given a standardized battery of psychological tests, including the MMPI. In 1969, a pandemic of type A influenza struck Helsinki, Finland, between January 12 and January 26. We analyzed the adult MMPI results of individuals *in utero* during the pandemic ($N = 2339$). As a comparison group, we examined the adult MMPI results of a noninfluenza-exposed group born 2 years later ($N = 2151$). An individual's week of birth provided an estimate of the week of exposure to the pandemic. The influenza group had an average of 58 individuals born each week ($SD = 8.8$). (Note that the exposed and nonexposed subjects were tested with the MMPI at the same age.)

To provide a relative index of schizotypal personality disorder, we combined scales 7 (Pt, Psychasthenia) and 8 (Sc, Schizophrenia) of the MMPI to construct the SPD scale score (17). (The original formulation of the SPD composite included scale 2 [D, depression] in the index of SPD. The Army psychological evaluation of subjects in this study did not include the administration of scale 2 of the MMPI.) We hypothesized that individuals exposed to the influenza virus during the sixth month of gestation (weeks 21–24) would show elevated SPD scale scores as compared to control subjects born during the same week, 2 years later, in an epidemic-free year. Results suggest that fetuses exposed during the 23rd week of gestation have a significantly higher mean schizotypal scale score ($M = 9.2$, $SD = 3.9$) than control subjects born during the same week of the year, 2 years later ($M = 7.7$, $SD = .1$). Weeks 21, 22, and 24 show no differences between exposed and nonexposed. In exploratory analysis we find no other week evidencing an increase in the SPD scale score. The isolated effect of week 23 suggests the possibility of

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a narrow window for developmental disruptions impacting adult development of schizotypal traits.

BEHAVIORAL INDICANTS OF FIRST-HIT FETAL BRAIN DAMAGE

Research has uncovered various behavioral abnormalities more common among individuals who later develop schizophrenia. Preschizophrenia patients have been shown to evidence premorbid behavioral disturbances, as well as premorbid cognitive deficits. We suggest that some premorbid neuromotor and neurocognitive deficits reported in the literature may reflect second-trimester disruptions in fetal-neural development.

Childhood Neuromotor Deficits are Related to Adult Schizophrenia

In a study of childhood behavior and adult brain morphology in patients with schizophrenia, Walker and colleagues found that neuromotor deficits and negative affect during infancy linked with greater ventricular enlargement in adulthood (18). Also, parental ratings of the severity of “externalized” childhood behavior problems (likely associated with a difficult temperament) showed an inverse relation with adult cortical volume.

Infant Neuro-Behavioral Deficits are Related to Adult Schizophrenia

Researchers consistently find ventricular enlargement and decreased cortical volume in patients with schizophrenia (19). Prenatal and perinatal stressors have been linked to ventricular enlargement in humans (20), and to hippocampal structural and cellular abnormalities in rats (21). These brain abnormalities relate to schizophrenia later in life. Furthermore, Walker asserts that schizotypal adolescents with high rates of dysmorphic signs (reflecting prenatal stress), as well as heightened cortisol responses to stress, demonstrate more adjustment problems than controls (22).

Infants at high risk for neurological disorders, such as schizophrenia, have been found to evidence greater numbers of attentional and cognitive deficits as well. In addition, specific abnormalities in neuromotor functioning, as early as 6 months of age, seem to reflect the developmental neuropathology underlying these disorders (23).

One subtype of motor abnormality, excessive involuntary movements (clinical and subclinical hyperkinesias or dyskinesias), may uniquely link with schizophrenia and spectrum disorders (e.g., schizotypal personality disorder). Khot and Wyatt observed elevated rates of involuntary movements in treatment-naive and medicated schizophrenia patients (24). Similar to adult schizophrenia patients, children who subsequently manifest the disorder show heightened involuntary

movements (e.g., hand posturing and irregular, writhing movements of the hands) as observed in home movies of preschizophrenia children from birth to 2 years of age (25). Furthermore, the severity of premorbid dyskinesia predicts the severity of psychiatric symptoms in adulthood (26). Motor abnormalities such as these may result from early disruption of neural development that leaves the individual vulnerable to not only motor disturbances, but perceptual and cognitive deficits as well.

OBSTETRICAL COMPLICATIONS IN SCHIZOPHRENIA

Researchers have identified obstetrical complications (OCs) as an early risk factor for schizophrenia. McNeil and Cantor-Graae define OCs as deviations from a normal course of development during pregnancy, delivery, and the early neonatal period (27). Examples of OCs include deviations in gestational age; low birth-weight; deviation in size; small head circumference; oxygen deprivation during pregnancy, labor, or delivery; preeclampsia; placental abnormality; and instrumental interventions during labor.

A great deal of research supports a relation between early OCs and the later development of schizophrenia. One convincing study by Jones and colleagues examined a Finnish cohort of 11,017 subjects born in 1966 (28). The authors found schizophrenia patients six times more likely to be born prematurely and seven times more likely to have perinatal brain damage. Additionally, a recent study by Hultman and colleagues also lends support to the relation between OCs and later schizophrenia. The authors compared the rate of OCs of a large sample of schizophrenia patients to various control groups (29). Schizophrenia patients evidenced an increase in OCs compared to the controls.

Literature reviews of the OCs and schizophrenia also lend cogent support to role of OCs as an early determinant of schizophrenia. In a 1995 review, McNeil reported that seven of eight prospective studies found higher rates of OCs in schizophrenia patients than in normal comparison subjects (30). In a more recent meta-analysis, pooling data from 12 independent studies, Geddes and colleagues report a twofold increased risk for developing schizophrenia among subjects suffering from Ocs (31).

Specific OCs and Schizophrenia

OCs vary in terms of type and severity. Recently, researchers have attempted to identify particular OCs specific to later schizophrenia. In their meta-analysis, Geddes and colleagues identify premature rupture of membranes, prematurity, and use of an incubator or resuscitation as significant risk factors for the later development of schizophrenia (31). McNeil and Cantor-Graae cite other OCs typically related to schizophrenia, such as bleeding during pregnancy, prolonged labor,

umbilical cord complications, and asphyxia. These OCs often result in oxygen deprivation in the offspring, thus leading McNeil and Cantor-Graae to suggest that oxygen deprivation may underlie the relation between OCs and schizophrenia (27). In a large birth cohort study, Dalman and colleagues found preeclampsia to be the strongest risk factor for schizophrenia, but also noted the independent contributions of prematurity and hypoxia/ischemia factors (32). This suggests that a number of mechanisms, including abnormal fetal blood flow and oxygen deprivation, may act together to increase vulnerability to schizophrenia.

OCs and Brain Abnormalities

In addition to a relation between OCs and later schizophrenia, OCs also relate to brain abnormalities found in schizophrenia patients. In a study of monozygotic twins discordant for schizophrenia McNeil, Cantor-Graae, and Weinberger report that smaller hippocampi and larger ventricles found in the affected twin relate to OCs (specifically, labor–delivery complications) (33). Stefanis and colleagues report similar findings (34). In their study of 27 schizophrenia patients, they report that OCs significantly contribute to hippocampal abnormalities common in schizophrenia. Similar to McNeil and Cantor-Graae's assertion (27), Stefanis and colleagues conclude that OCs leading to oxygen deprivation may account for reduced hippocampal volume associated with schizophrenia.

Discrepant Findings in OC/Schizophrenia Research

Despite a majority of evidence supporting a link between OCs and later schizophrenia, several studies do not find this association. Using a prospective design, Done and colleagues failed to find an association between schizophrenia and OCs (35). Gunduz and colleagues also do not find an association between OCs and schizophrenia (36). Information regarding OCs in this study, however, was mostly obtained through retrospective maternal reports, considered less reliable than prospectively obtained hospital records.

Some researchers who accept the OC relation with schizophrenia, question the direction of effects between OCs and schizophrenia (37,38). In an alternative line of reasoning, some researchers suggest that OCs may be an epiphenomenal result of some other factors that relate more directly to schizophrenia. From this perspective, OCs may result from preexisting abnormalities in the fetus; these abnormalities also account for the later development of schizophrenia. McNeil and Cantor-Graae empirically address the hypothesis that preexisting abnormalities cause OCs in fetuses who later develop schizophrenia. They report that schizophrenia patients with signs of early abnormal fetal maldevelopment (e.g., minor physical anomalies, reduced head size) do not evidence more OCs than patients without early abnormal fetal development. They conclude that OCs do not result from preexisting fetal abnormalities (39).

OCs Among Vulnerable Children

As mentioned earlier, the interaction between a “first” and a “second hit(s)” leading to schizophrenia offers some promise toward understanding the etiology of schizophrenia. The role that OCs play in the “two-hit” model of schizophrenia remains unclear. Various research investigating OCs and schizophrenia among subjects at genetic risk for schizophrenia (generally considered “high risk” due to at least one parent with schizophrenia) suggests discrepant findings. In a study from our lab, we found that OC more closely correlated with increased ventricular volume as genetic risk increased. Those subjects with the highest genetic risk *and* with high OCs most often developed schizophrenia, thus suggesting that OCs serve as a “second hit” leading toward schizophrenia (20). To the contrary, DeLisi and associates found no differences in the hippocampi of high- and low-risk schizophrenia patients with and without OCs (40). Their sample, however, consisted of only seven subjects. The majority of studies described here do not specify the genetic liability of subjects; therefore, whether OCs are more likely “first” or “second” hits remains undetermined.

EARLY-REARING FACTORS IN SCHIZOPHRENIA

Researchers report mixed findings regarding the relationship between risk of developing schizophrenia and early-rearing factors such as family dysfunctioning and parental loss or separation. These relationships, however, seem clearer when research designs consider the vulnerability resulting from a first hit. It appears that when combined with the occurrence of a first hit, disruptive early-rearing circumstances contribute significantly to the later development of schizophrenia.

Family Disharmony and Schizophrenia: Low-Risk Studies

Early theories attempted to explain an apparent relation between family dysfunction and schizophrenia in offspring (41–43). Many of these theories have been psychoanalytic in nature and tended to focus attention on the ‘schizophrenogenic mother’ (44, 45). With a later acceptance of the strong role of genetics in the etiology of schizophrenia (46–48), the role of the family tended to be discredited (49). Early empirical reports were criticized for inadequate control groups, small sample sizes, inconsistent operationalization of “family dysfunctioning,” failure to include possible confounding factors, and retrospective bias.

Some recent work has lent renewed credence to family theories of schizophrenia. In a prospective design of troubled adolescents and their families, Goldstein found that parental disturbance in general, and communication deviance (CD) and negative affective style in particular, predict schizophrenia-spectrum outcome in at least one of the children (50). Rund found a similar pattern of CD and hostility in Norse families whose children later develop schizophrenia (51). Despite

these findings, the relation between family functioning and schizophrenia remains controversial. Other researchers point to negative findings (49,52), and the lack of close correspondence between the pattern of findings and a coherent theoretical model (53). In this light, many contemporary scholars are quick to echo Roff and Knight's suggestion that the etiological significance of family functioning to schizophrenia is unknown (54).

Parental Loss and Schizophrenia

Numerous studies examine parental loss and the development of general psychopathology, as well as schizophrenia specifically. Two reviews note mixed finding from investigations of parental absence and schizophrenia (55,56). Many of the included studies suffer from methodological limitations that may have influenced findings.

Whether parental loss serves as a general risk factor for later psychiatric problems or whether such an experience has a specific impact on outcomes of schizophrenia is another issue researchers attempt to address. Overall, the research does not provide clear results regarding the specific effects of separation and an outcome of schizophrenia (57–59).

Researchers also consider type of loss in relation to schizophrenia. The majority of parental loss studies only consider loss through death. Parental separation, through divorce, however, may have a unique effect on child development. The limited studies that do address this issue are inconclusive regarding the relation between type of loss and later schizophrenia (60–62).

Age of separation is another important factor that may moderate the relationship between schizophrenia and early parental absence. Children at different developmental stages may have different levels of vulnerability to stress associated with parental loss. Most studies generally consider early parental loss as including loss before the ages of 16 to 19. Consistent with other studies of parental loss and schizophrenia, studies of age of separation reveal mixed results (58,63).

The Impact of Rearing Environment on Genetically Vulnerable Children

The reviews presented here do not reveal a consistent pattern of findings regarding the relation between early negative rearing factors and schizophrenia in the general population. These findings remain unclear even when moderators such as type of loss and age of separation are taken into consideration. By contrast, investigations into the relationship between early-rearing stress and later schizophrenia *among genetically vulnerable individuals* find consistent significant effects. In most cases, studies define genetically vulnerable children as children with a parent with schizophrenia (“high risk” [HR]).

Family Discord and Schizophrenia: High-Risk Studies

A wide range of reports, utilizing diverse designs, point to family stress as a prominent risk factor within HR samples (64–68). In the Finnish adoption study, Tienari contrasts a group of HR children raised by their biological (i.e., schizophrenic) parents with a similar group of HR children raised by adoptive (and non-schizophrenic) parents (69,70). Across both groups, parental emotional disturbance is a powerful predictor of eventual decompensation in the children. In Marcus and colleagues' analysis of the 13-year diagnostic outcomes of the National Institute of Mental Health (NIMH) Israeli Kibbutz-City study, poor parenting appears to be a strong predictor of schizophrenia-spectrum outcome among HR children (65). Of the 19 HR children subject to poor parenting (defined as having at least one parent whose parenting combined at least two of three negative styles: over-involvement, inconsistency, and/or hostility), 9 (47%) developed a schizophrenia-spectrum disorder; none of the 31 HR children with relatively healthy parents did so. It is unknown if this finding is replicated with the most recent 23-year follow-up diagnoses, although a reduction in the number of lifetime schizophrenia-spectrum cases from nine to four (because of criteria changes) make this less likely (71,72).

The UCLA Family Study notes a high likelihood of schizophrenia-spectrum outcome in at least one child (71%) given a combination of both family history of severe mental illness and parental communication deviance (50). In his review of the family relations literature, Asarnow concludes that the evidence “points to the highest rates of schizophrenia spectrum disorders in individuals exposed to both disturbed rearing environments and genetic risk (73).

Our own findings support these general trends in the HR literature. The Copenhagen High-Risk Project, begun in 1962, assessed the rearing environments of 207 children of mothers with schizophrenia, as well as 104 children of parents without a psychiatric history. Rearing variables were drawn from both the retrospective accounts of the child (average age = 15) and their mother (or primary caregiver) and data from the mother's hospital records. These variables have shown consistent success in predicting both 10-year and 25-year outcomes. In an early study of the mother's hospital data, maternal social instability (a composite of items rating the mother's sexual promiscuity, substance abuse, unreliable employment, and premorbid antisocial tendencies) increased the risk for schizophrenia among the HR children (67).

A recent report from this same project suggests that those HR children who later manifested schizophrenia reported less satisfactory relationships with their parents than those who did not later manifest schizophrenia (68). The parent-child relationship scales contained items that relate to the children's attitudes toward their mothers and fathers, the nature of the relationship as perceived by

the parents, and current frequency of contact. Results tentatively suggest that getting along well with both parents may protect HR individuals from developing schizophrenia, whereas not getting along with both parents may increase the likelihood of schizophrenia. This report uses lifetime diagnosis (defined as the more severe of 10-year and 25-year diagnoses), and essentially replicates a finding by Burman and colleagues for 10-year outcome (64).

We began a second longitudinal study in 1971, assessing 72 children with a schizophrenic parent, 72 children with a mentally ill (but nonschizophrenic) parent, and 121 children of parents without a psychiatric condition at an average age of 11 (74). These children were selected from a birth cohort of 9125, consisting of all children born between September 1, 1959, and December 31, 1961, at Rigshospitalet in Copenhagen (75). Rearing variables were assessed through a social worker interview with the child and their parents. In a recent analysis of these data together with 20-year psychiatric outcome, a stressful rearing environment was found characteristic of the families of HR subjects who later decompensated to schizophrenia. In this study, rearing stress was indexed by father's negative attitude toward child, mother's negative attitude toward child, low social class, poor living conditions, and child's negative opinion of family health (76).

High-Risk Studies of Parental Loss and Schizophrenia

Accounting for genetic liability for schizophrenia may also help clarify the previously reported equivocal relationships between schizophrenia and parental absence (77,78). An early report from the Copenhagen High-Risk Project finds that genetically vulnerable children experiencing maternal and paternal separation in the form of child institutionalization (but not supportive foster homes) during the first 3 years of life more often developed schizophrenia at 10-year follow-up than those who were not institutionalized (78). This finding was recently confirmed using 25-year diagnostic outcomes (79). Using a different model, Cannon, Mednick, and Parnas found that a family instability variable (combining separation from one or both parents, institutionalization, and changes in the family constellation in the first 5 years) specifically predicted positive-symptom schizophrenia among children at genetic risk (80).

In the Danish birth cohort of 9125 children described earlier, parental separations were recorded through the first year of life. Separation from parents (resulting from death, hospitalization, and/or children's institutionalization) during the first year was found to predict schizophrenia, but only for children with a family history of schizophrenia (81). Because data were not available on parental separation after the first year, it is uncertain whether this effect is specific to losses in infancy, or whether early separations predict a pattern of losses throughout childhood (death, illness, divorce) that exert a cumulative effect.

Comparison of Rearing Factors Within a High-Risk Design

In our work with the Copenhagen High-Risk Project and the Danish Perinatal Project, we have found that both family discord and parental absence variables increase the risk for genetically predisposed individuals. Building on this, we can consider the relationship among different rearing variables in the prediction of schizophrenia. Which is more predictive: parental absence or family discord? What type of parental absence most affects the vulnerable child: is it inconsistency in who their parents are, or is it periods of isolation from parents in an impersonal rearing environment? Is it the misbehavior and hostility of the mother or the father that affects the child more? Conversely, are the measures we have of the rearing environment perhaps not so much independent variables, as indicators of a global stress factor?

In an attempt to resolve these issues, we recently used the Copenhagen High-Risk Project data to create five variables measuring different aspects of the rearing environment (82). Number of upheavals in the parental dyad was composed of instances of parental death and divorce, as well as changes in single parents' domestic partners. Length of time spent in a children's institution was measured in months. Negative personality and parenting qualities of the mother were brought together in a maternal conflict scale; a similar paternal conflict scale pertained to the father (or father figure). We also included a measure of the peer environment, tapping the number and closeness of the child's peer contacts, owing to literature that suggests that a positive peer network is a possible buffer to negative family dynamics (83).

Within the HR sample, institutionalization was the single variable most predictive of lifetime schizophrenia diagnosis (contrasted with no mental illness; $[1, 100] = 6.89, p = .010$), followed by paternal conflict ($f = 5.16, p = .025$) and upheavals in the parental dyad ($f = 4.96, p = .028$). Maternal conflict showed a trend toward predicting schizophrenia ($f = 2.03, p = .16$), and the peer environment appeared to have no impact ($f = 0.67, p = .41$). These findings suggest that changes in the family unit, whether because of death, divorce, or dating, appear to increase the risk of schizophrenia in a vulnerable child. Also, father's negative behavior appears to have a greater impact than mother's negative parenting (alternately, the behavior of the mothers with schizophrenia was already poor, whereas the variation in the father's behavior was greater). Furthermore, it seems that children's institutions are a far less favorable place to grow up than the schizophrenic family environment. These three aspects appear to predict relatively independently because when each is entered in a hierarchical regression equation, the others remain significant (with the exception that paternal conflict is no longer significant when institutionalization is considered first).

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The greatest predictive efficacy, however, is achieved if the relationship between genetic risk and global rearing stress is modeled as a true multiplicative interaction. Within the HR group, multiplying the number of schizophrenia-spectrum parents (e.g., one or two) by the equally weighted sum of the five rearing variables results in an interaction term that strongly predicts schizophrenia vs no mental illness outcome ($f = 19.85, p < .05$). If this model is applied to the entire sample (with low-risk individuals assigned an interaction score of 0), the interaction term accounts for 26% of the variance ($f[1,159] = 56.09, p < .00005$); almost twice as much as genetic risk alone (16%) and two-and-a-half times as much as any single rearing variable (upheavals in parental dyad—11%).

This may indicate that a global, diffuse ‘rearing stress’ variable, although criticized at times for being too vague (84), may be the specific variable of interest. This is consistent with the general robustness of the rearing findings despite the use of different methods of assessment. For example, within the Copenhagen High-Risk sample alone, the following variables have *all* been noted to predict schizophrenia: institutionalization before age 3 (78), institutionalization before age 10 (79, 85); an index combining parental absence, constellation changes, and institutionalization (80); number of upheavals in parental dyad; mother’s social instability (67); perceived relationship with parents (68), and maternal and paternal conflict (85).

It may be that our search for the most specifically deleterious rearing event for HR youth is a case of missing the forest for the trees. Although it is true that individuals differ in their ability to process stress (84, 86), this does not prohibit us from drawing general conclusions regarding the ill effects of rearing stress on a predisposition for schizophrenia, as individual differences will tend to cancel each other out with increased numbers and diversity of samples.

Rival Interpretations

The research reviewed here supports an interactive relationship between rearing stressors and HR status impacting later schizophrenia. Another interpretation of these results suggests that mothers and fathers with greater genetic liability for schizophrenia tend to have poorer relationships with their children; thus the observed relationship between poor parenting and schizophrenic outcome in the offspring may be only an artifact of the underlying genetic transmission. Although our design does not control for severity of parental illness, it remains unlikely that parents’ genetic loading would have such a direct impact on the parental absence and institutionalization variables, which also predict later schizophrenia. In addition, the Finnish Adoption Study separates rearing from genetic parenting, and finds that emotional disturbance in the rearing parents, whether biological or adoptive, increases the risk of schizophrenia-spectrum breakdown (69).

Another interpretation identifies family discord and parental absence as markers of a more general predisposing factor: low socioeconomic status (SES). This reading is grounded in evidence of increased schizophrenia associated with poorer neighborhoods, urban residence, and more crowded living quarters (87, 88). The schizophrenogenic effects of low SES may operate through either the general stress of chronic poverty or an increased frequency of adverse events such as obstetrical complications and viral infections. However, at least within the Copenhagen High-Risk sample, the data dispute this interpretation, as rearing variables remain predictive even after the effect of SES is accounted for.

A third hypothesis holds that the direction of implied causality between rearing stress and later schizophrenia should be reversed: that a disturbed child, already on a trajectory toward schizophrenia, negatively impacts the family (49). Thus, we are asked to believe that all (or most) rearing disruptions that occur in pre-schizophrenic childhoods are external effects of an insidious disease process, and that the rearing environment itself exerts little influence. That this seems unlikely is bolstered by evidence that premorbid behavior disturbances are typically noted in only a subset of schizophrenia cases, and tend to be subtle before adolescence (89). Also, parents are not noted to be especially accurate in predicting which of their children will eventually develop schizophrenia. Finally, this ‘disturbed child’ hypothesis is not supported by the Copenhagen data: even when personality in adolescence is factored in as a precursor of schizophrenia, rearing environment exerts a significant effect.

In summary, the literature and data from HR designs is most consistent with a multiplicative interaction between the level of genetic vulnerability and the cumulative effect of stress and disruptions in the rearing milieu. In other words, the impact of traumas and other painful events experienced during childhood will be magnified in the vulnerable individual and contribute to eventual development of schizophrenia.

THE TWO-HIT THEORY

The findings presented here suggest that the likelihood of developing schizophrenia is increased by an interaction between prenatal disruptions of fetal neural development and early environmental stress. We have proposed a “two-hit model” to help explain this interaction (1). As mentioned earlier, the two-hit model suggests that two events, or “hits”, are associated with increased risk for schizophrenia. The first hit can stem from a genetic liability for schizophrenia. It is hypothesized that this genetic liability may be transmitted from a parent with schizophrenia, and may result in a preprogrammed disruption of fetal neural development. The disruption of fetal neural development may interfere with

neural migration, connections, or cell death, and correlate with later cognitive and perceptual disturbances. These disturbances may later increase risk for schizophrenia. Events during gestation may also cause neural developmental disruption. These prenatal events (potential first hits) might include maternal influenza or maternal stress during a critical period of gestation (e.g., second trimester). Examinations of this model, however, generally focus on having a parent with schizophrenia as the indication of a first hit.

The second hit is modeled as an environmental stressor. Possible second hits include separation from parents, institutional rearing, and high levels of family stress. Although still undetermined, our investigation of OCs and schizophrenia among HR individuals suggests that OCs may also serve as a second hit (19). According to the theory, a second hit in the absence of a first hit does not increase the risk for schizophrenia. In conjunction with a first hit, however, a second hit increases the likelihood of later schizophrenia (90).

As a whole, the two-hit model accounts for several consistent findings, but is far from verified. In its support, it seems evident that rearing trauma acts as a second hit when genetic risk is present. Although unreplicated, results from our lab suggest that OCs may also interact with genetic predisposition in a manner consistent with the model. Additionally, the weight of evidence points to a consistent elevation of risk among the general population when exposed to prenatal teratogens (e.g., maternal influenza) or perinatal stressors (e.g., hypoxia).

The question remains as to whether the etiological mechanisms of genetic transmission and prenatal insult are interchangeable (as ‘first hits’), or even similar. In our most recent results, we find that we can account for one-quarter of the total variance in eventual outcome of schizophrenia using the two-hit model in a HR setting; however, the proportion of variance explained by the pre- and perinatal events proposed as first and/or second hits in the general population is typically much smaller (probably only 0–5%). To our knowledge, no studies have yet explicitly addressed the extent to which second hits may increase the risk of those exposed to an *environmental* first hit. It is unknown whether certain disruptions in the fetal environment mimic the neurological changes wrought by schizophrenic genes; or whether pre- and perinatal irregularities may either reflect or enhance an underlying genetic process. We noted that the timing of in utero insults plays a role in determining what disorder develops, but the specificity and predictive efficacy of particular gestational ‘windows’ awaits further research. In any case, the vast majority of the population exposed to early environmental stressors does *not* develop a schizophrenia-spectrum disorder. For the many cases of schizophrenia that appear to be without genetic precedent, then, we are left with a puzzle as to what chain of events or combination of factors abrupt normal development in favor of schizophrenogenesis.

REFERENCES

1. Mednick SA, Watson JB, Huttunen M, et al. A two-hit working model of the etiology of schizophrenia. In: Lenzenweger M, Dworkin RH, eds. *Origins and Development of Schizophrenia: Advances in Experimental Psychopathology*. Washington DC: American Psychological Association, 1998.
2. Mednick SA, Machon RA, Huttunen MO, Bonnet D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1988; 45:189–192.
3. Adams W, Kendell RE, Hare HH, Munk-Jorgensen P. Epidemiological evidence that maternal influenza contributes to the aetiology of schizophrenia: an analysis of Scottish, English, and Danish data. *Brit J Psychiatry* 1993; 163:522–534.
4. Fahy TA, Jones PB, Sham PC, Takei N, Murray RM. Schizophrenia in Afro-Caribbeans in the UK following prenatal exposure to the 1957 A2 influenza pandemic. *Schizophr Res* 1993; 9: 132.
5. Machón RA, Mednick SA. Adult schizophrenia and early neurodevelopmental disturbances. In: *Confrontations psychiatriques: Epidemiologie et psychiatrie*. No. 35. Specia Rhone-Poulenc Rore, 1994.
6. Waddington JL. The declining incidence of schizophrenia controversy: a new approach in rural Irish Population. Paper presented at the annual meeting of the Royal College of Psychiatrists, July 24–27, 1992, Dublin, Ireland.
7. Brown AS. Prenatal infection and adult schizophrenia: a review and synthesis. *Int J Ment Health* 2001; 29:22–37.
8. Machón RA, Mednick SA, Huttunen MO. Fetal viral infection and adult schizophrenia: empirical findings and interpretation. In: Mednick SA, Hollister JM, eds. *Neural Development and Schizophrenia*. New York: Plenum Press, 1995.
9. Barr C, Mednick SA, Munk-Jorgensen P. Exposure to influenza epidemics during gestation and adult schizophrenia. *Arch Gen Psychiatry* 1990; 47:869–874.
10. Kendell RE, Kemp IW. Maternal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry* 1989; 46:878–882.
11. Kunugi H, Nankos S, Takei N. Influenza and schizophrenia in Japan. *Brit J Psychiatry* 1992; 160:274–275.
12. O’Callaghan E, Sham P, Takei N, Glover G, Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet* 1991; 337:1248–1250.
13. Sham PC, O’Callaghan E, Takei N, Murray GK, Hare H, Murray RM. Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960. *Brit J Psychiatry* 1992; 160:461–466.
14. Machón RA, Mednick SA, Huttunen MO. Adult major affective disorder following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1997; 54:322–328.
15. Tehrani JA, Brennan PA, Hodgins S, Mednick SA. Mental illness and criminal violence. *Soc Psychiatry Psychiatr Epidemiol* 1998; 33:S81–S85.
16. Mednick SA, Tehrani JA. Prenatal disturbances and criminal violence. In: Gottesman R, ed. *Encyclopedia of Violence in the United States*. New York: Charles Scribner’s Sons, 1999.
17. Meyer RG. *The Clinician’s Handbook: Integrated Diagnostics, Assessment, and Intervention in Adult and Adolescent Psychopathology*, 3rd ed. Needham Heights, MA: Allyn and Bacon, 1993.
18. Walker EF, Lewine FJ, Neumann C. Childhood behavioral characteristics and adult brain morphology in schizophrenia. *Schizophr Res* 1996; 22:93–101.

AU: ref.
page range

19. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 1999; 122:593–624.
20. Cannon TD, Mednick SA, Parnas J, Schulsinger F, Praestholm J, Vestergaard A. Developmental brain abnormalities in the offspring of schizophrenic mothers. I. Contributions of genetic and perinatal factors. *Arch Gen Psychiatry* 1993; 50:551–564.
21. Hayashi A, Nagaoka M, Yamada K, Ichitani Y, Miake Y, Okado, N. Maternal stress induces synaptic loss and developmental disabilities of offspring. *Int J Dev Neurosci Special* 1998; 16:209–216.
22. Brennan PA, Walker EF. Vulnerability to schizophrenia: risk factors in childhood and adolescence. In: Ingram RE, Price JM, ed. *Vulnerability to Psychopathology: Risk Across the Lifespan*. New York: Guilford, 2001.
23. Hollister MJ, Mednick SA, Brennan PA. Impaired autonomic nervous system habituation in those at genetic risk for schizophrenia. *Arch Gen Psychiatry* 1994; 51:552–558.
24. Khot V, Wyatt R J. Not all that moves is tardive dyskinesia. *Am J Psychiatry* 1991; 148: 661–666.
25. Walker EF, Savoie T, Davis D. Neuromotor precursors of schizophrenia. *Schizophr Bull* 1994; 20:441–451.
26. Neumann CS, Walker EF. Childhood neuromotor soft signs, behavior problems, and adult psychopathology. In: Ollendick T, Prinz R, eds. *Advances in Clinical Child Psychology*, Vol. 18. New York: Plenum, 1996.
27. McNeil TF, Cantor-Graae E. Obstetric complications as risk factors for schizophrenia. *Int J Ment Health* 2000; 29:73–83.
28. Jones P, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P. Schizophrenia as a long term outcome of pregnancy and delivery complications: a 28-year follow-up of the 1966 North Finland general population birth cohort. *Am J Psychiatry* 1998; 155:355–364.
29. Hultman CM, Soren P, Takei N, Murray R, Chattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis. *BMJ* 1999; 310:421–425.
30. McNeil TF. Perinatal risk factors and schizophrenia: selective review and methodological concerns. *Epidemiol Rev* 1995; 17:107–112.
31. Geddes JR, Verdoux H, Takei N, et al. Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. *Schizophr Bull* 1999; 25:413–423.
32. Dalman C, Allebeck P, Cullberg J, Grunewald C, Koster M. Obstetrical complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. *Arch Gen Psychiatry* 1999; 56:234–240.
33. McNeil TF, Cantor-Graae E, Weinberger DR. Relationship of obstetric complications and differences in size of brain structures in monozygotic twin pairs discordant for schizophrenia. *Am J Psychiatry* 2000; 157:203–212.
34. Stefanis N, Frangou S, Yakeley J, et al. Hippocampal volume reduction in schizophrenia: effects of genetic risk and pregnancy and birth complications. *Biol Psychiatry* 1999; 46:697–702.
35. Done DJ, Johnstone EC, Frith CD, Golding J, Shepherd PM, Crow TJ. Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample. *BMJ* 1991; 302:1576–1580.
36. Gunduz H, Woerner MG, Alvir JM, Degreef G, Lieberman JA. Obstetrical complications in schizophrenia, schizoaffective disorder and normal comparison subjects. *Schizophr Res* 1999; 40:237–243.
- 27 Goodman R. Obstetric complications and schizophrenia. *Brit J Psychiatry* 1988; 153:850.
- 27 Owen M, McGuffin P. Obstetric complications and schizophrenia. *Lancet* 1990; 336:122.

AU: refs.
37 & 38:
page range



Uncorrected Proof Copy

- AU: ref. 44, page range
- AU: refs. 53–61, page range
39. McNeil TF, Cantor-Graae E. Does preexisting abnormality cause labor-delivery complications in fetuses who will later develop schizophrenia? *Schizophr Bull* 1999; 25:425–435.
 40. DeLisi LE, Dauphinais ID, Gershon ES. Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. *Schizophr Bull* 1988; 14:185–191.
 41. Lidz T, Cornelison A, Terry D, Fleck S. The intrafamilial environment of schizophrenic patients: II. Marital schism and marital skew. *Am J Psychiatry* 1957; 114:241–248.
 42. Wynne LC, Ryckoff I, Day J, Hirsch S. Pseudomutuality in the family relations of schizophrenics. *Psychiatry Res* 1958; 21:205–220.
 43. Wynne LC. Family transactions and schizophrenia: II. Conceptual considerations for a research strategy. In: Romano J, ed. *The Origin of Schizophrenia*. Amsterdam: Excerpta Medica, 1967.
 44. Lukoff D, Snyder K, Ventura J, Neuchterlein KH. Life events, familial stress, and coping in the developmental course of schizophrenia. *Schizophr Bull* 1984; 10:258.
 45. Mahler M. On child psychosis and schizophrenia. *Psychoanal Study Child* 1952; 7:286–305.
 46. Shields J, Slater E. Heredity and psychological abnormality. In: Eysenck HJ, ed. *Handbook of abnormal psychology*. New York: Basic Books, 1961.
 47. Gottesman II, Shields J. Schizophrenia and genetics: a twin study vantage point. New York: Academic, 1972.
 48. Gottesman II, Shields J. *Schizophrenia: the Epigenetic Puzzle*. New York: Cambridge University Press, 1982.
 49. Wender PH, Rosenthal D, Rainer JD, Greenhill L, Sarlin B. Schizophrenics' adopting parents: psychiatric status. *Arch Gen Psychiatry* 1977; 34:777–784.
 50. Goldstein MJ. The UCLA High-Risk Project. *Schizophr Bull* 1987; 13:505–514.
 51. Rund BR. The relationship between psychosocial and cognitive functioning in schizophrenic patients and expressed emotion and communication deviance in their parents. *Acta Psychiatr Scand* 1994; 90:133–140.
 52. Moldin SO, Gottesman II. At issue: genes, experience, and chance in schizophrenia—positioning for the 21st century. *Schizophr Bull* 1997; 23:547–561.
 53. Byrne CP, Velamoor VR, Cernovsky ZZ, Cortese L, Loszтын S. A comparison of borderline and schizophrenic patients for childhood events and parent-child relationships. *Can J Psychiatry* 1990; 35:590.
 54. Roff JD, Knight R. Family characteristics, childhood symptoms, and adult outcome in schizophrenia. *J Abnorm Psychol* 1981; 90:510.
 55. Granat G, Grossman K. Early bereavement and schizophrenia. *Brit J Psychiatry* 1966; 112:1027.
 56. Ragan PV, McGlashan TH. Childhood parental death and adult psychopathology. *Am J Psychiatry* 1986; 143:153.
 57. Gay M, Tonry P. The late effects of loss of parents in childhood. *Brit J Psychiatry* 1967; 113:753.
 58. Hilgard J, Newman M. Parental loss by death in childhood as an aetiological factor among schizophrenic and alcoholic patients compared with a non-patient community sample. *J Nerv Ment Dis* 1963; 137:14.
 59. Munro A, Griffiths A. Psychiatric non-sequelae of childhood bereavement. *Brit J Psychiatry* 1969; 115:305.
 60. Brill N, E. Parental loss in adults with emotional disorders. *Arch Gen Psychiatry* 1966; 14:307.
 61. Furukawa T, Mizukawa R, Hirai T, Fujihara S, Kitamura T, Takahashi K. Childhood parental loss and schizophrenia: evidence against pathogenic but for some pathoplastic effects. *Psychiatry Res* 1998; 81:353.

Uncorrected Proof Copy

- AU:
ref 62:
page range
62. Maekikyroe T, Sauvola A, Moring J, et al. Hospital-treated psychiatric disorders in adults with a single-parent and two-parent family background: a 27-year follow-up of the 1966 Northern Finland Birth Cohort. *Fam Process* 1998; 37:335.
63. Watt NF, Nicholi A. Early death of a parent as an etiological factor in schizophrenia. *Am J Orthopsychiatry* 1979; 49:465–473.
64. Burman B, Mednick SA, Machon RA, Parnas J, Schulsinger F. Children at high risk for schizophrenia: parent and offspring perceptions of family relationships. *J Abnorm Psychol* 1987; 96:364–366.
- AU:
ref. 65:
provide city,
publisher
and page
range
65. Marcus J, Hans S, Nagler S, Auerbach J, Mirsky A, Aubrey A. Review of the NIMH Israeli Kibbutz-City Study and Jerusalem Infant Development study. In: [redacted] S, ed. *Annual Progress in Child Psychiatry and Child Development*. 1987; 13:425.
66. Singer MT, Wynne LC, Toohey ML. Communication disorders and the families of schizophrenics. In: Wynne LC, Cromwell RL, Matthysse S, eds. *The Nature of Schizophrenia: New Approaches to Research and Treatment*. New York: Wiley, 1978.
67. Talovic A. High-risk for schizophrenia: Father's contribution to child outcome. Unpublished doctoral dissertation, University of Southern California, 1984.
68. Schiffman J, LaBrie J, Carter J, et al. Perception of parent-child relationships in high-risk families, and adult schizophrenia outcome of offspring. *J Psychiatry Res* 2002; 36:41–47.
69. Tienari P. Interaction between genetic vulnerability and family environment: the Finnish adoptive family study of schizophrenia. *Acta Psychiatr Scand* 1991; 84:460–465.
70. Tienari P, Lahti I, Sorri A, Naarala M, Moring J, Wahlberg KE. The Finnish adoptive family study of schizophrenia: possible joint effects of genetic vulnerability and family environment. *Brit J Psychiatry* 1989; 155:29–32.
71. Mirsky AF, Kugelmass S, Ingraham LJ, Frenkel E, Nathan M. Overview and summary: twenty-five-year followup of high risk children. *Schizophr Bull* 1995; 21:227–239.
72. Nathan M, Frenkel E, Kugelmass S. From adolescence to adulthood: development of psychopathology in kibbutz and town subjects. *J Youth and Adolescence* 1993; 22:605–621.
73. Asarnow JR. Children at risk for schizophrenia: converging lines of evidence. *Schizophr Bull* 1988; 14:613–631.
74. Mednick S, Mura E, Schulsinger F, Mednick B. Perinatal conditions and infant development in children with schizophrenic parents. *Soc Biol* 1971; 18:5103–5113.
75. Zachau-Chistiansen B, Ross EM. *Babies: Human Development During the First Year*. New York: Wiley, 1975.
76. Schiffman J, LaBrie J, Mednick S, Cannon T, Parnas J, Schulsinger F. The two-hit model: a prospective investigation. Unpublished manuscript, University of Southern California, 1999.
77. Parnas J, Teasdale T, Schulsinger H. Institutional rearing and diagnostic outcome in children of schizophrenic mothers. *Arch Gen Psychiatry* 1995; 42:762–769.
78. Walker EF, Cudek R, Mednick SA, Schulsinger F. The effects of parental absence and institutionalization on the development of clinical symptoms in high-risk children. *Acta Psychiatr Scand* 1981; 63:95–109.
- AU:
ref. 79:
update?
79. Gutkind D, Mednick B, Cannon T, Parnas J, Schulsinger F, Mednick SA. Parental absence and schizophrenia—a 27-year follow-up of the Copenhagen High-Risk Cohort. University of Southern California, 1996, submitted.
80. Cannon TD, Mednick SA, Parnas J. Antecedents of predominantly negative- and predominantly positive-symptom schizophrenia in a high-risk population. *Arch Gen Psychiatry* 1990; 47:622–632.
81. Schiffman J, Barr CE, Mednick SA, et al. Very early parental separation: a risk factor for schizophrenia and other psychiatric disorders. Unpublished manuscript, 1999.

Uncorrected Proof Copy

AU:
ref. 82:
update?

82. Carter JW, Schulsinger F, Parnas S, Cannon T, Mednick SA. A multivariate prediction model of schizophrenia, submitted.
83. Price JM. Friendships of maltreated children and adolescents: contexts for expressing and modifying relationship history. In: Bukowski WM, Newcomb AF, Hartup WW, eds. *The Company They Keep: Friendship in Childhood and Adolescence*. New York: Cambridge University Press, 1996.
84. Strauss JS, Hafez H, Lieberman P, Harding CM. The course of psychiatric disorders: III. Longitudinal principles. *Am J Psychiatry* 1985; 142:289–296.
85. Carter JW, Mednick SA. Premorbid intervention: identification of those at risk. In: Miller T, Mednick SA, McGlashan T, eds. *Early Intervention in Psychiatric Disorders*. Dordrecht, Netherlands: Kluwer Academic, 2001.
86. Weintraub S. Risk factors in schizophrenia: the Stony Brook High-Risk Project. *Schizophr Bull* 1987; 13:439–450.
87. Torrey EF, Yolken RH. Is household crowding a risk factor for schizophrenia? Paper presented at the Ninth Biennial Winter Workshop on Schizophrenia, Davos, Switzerland, 1998.
88. Harrison G, Glazebrook C, Page K, Brewin J. Social deprivation at birth and increased risk of psychosis: evidence from a first episode study. Paper presented at the Ninth Biennial Winter Workshop on Schizophrenia, Davos, Switzerland, 1998.
89. Watt NF. Longitudinal changes in the social behavior of children hospitalized for schizophrenia as adults. *J Nerv Ment Dis* 1972; 155:42–54.
90. Walker E F, Diforio D. Schizophrenia: a neural diathesis-stress model. *Psychol Rev* 1997; 104:667–685.

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