

The Copenhagen High-Risk Project, 1962-86

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Abstract

Since 1962 we have followed a sample of 207 children at high risk for schizophrenia as well as 104 control children. For these individuals, the following factors and their interaction are related to an increased risk for schizophrenic breakdown: (1) greater schizophrenia family backgrounds, (2) perinatal trauma, and (3) unstable parenting and public institutional child care. The perinatal difficulties are positively related to adult periventricular atrophy. Results of a subsequent study tentatively suggest that part of the neurological deviance in schizophrenia may be produced by disruption occurring in the second trimester of fetal development.

In the late 1950's and 1960's, we became acutely aware of the pitfalls involved in studying the etiology of schizophrenia by comparing schizophrenic patients with normal controls (Mednick and Higgins 1960). In such designs it is difficult to disentangle the consequences of schizophrenia from possible etiological agents. It became clear to us that it was necessary to study schizophrenics within a longitudinal, prospective framework, before the life-long concomitants of schizophrenia made it difficult to isolate and examine causal factors.

The high-risk prospective design is attractive for the following reasons: (1) The researchers and the relatives do not know whether the subject will become schizophrenic; the collected data are relatively unbiased. (2) The information gathered is mainly current and not biased by retrospective reporting. (3) The pre-morbid and followup data are uniformly and systematically obtained. Since all the subjects are diagnosed through interview independently of

their possible hospitalizations, a complete picture of psychopathological process and outcomes may be observed. (4) Study of high- and low-risk groups permits the examination of the effects of environmental stressors at two different levels of genetic vulnerability, encouraging the study of gene-environment interaction effects.

A prospective study of a large representative population would be ideal but would only yield 1 percent schizophrenics. Since many of the assessment techniques necessary to test our theories were expensive and time consuming, we increased the outcome yield of psychopathology by selecting children with severely schizophrenic mothers. The empirical risk for schizophrenia for such children is between 10 and 16 percent. A detailed statement of the rationale for "high-risk" research may be found in Mednick and McNeil (1968).

We decided to carry out this prospective study in Denmark for the following reasons: (1) The population is stable, and ethnically and racially homogeneous. (2) A national population address register exists, which makes it possible to locate all individuals living in Denmark, even many years after their identification. If an individual migrates, his address in the foreign region is usually also available. (For example, we have interviewed high-risk individuals who emigrated to Canada.) (3) Various central medical and social registers exist, such as the register of causes of death, criminal and psychiatric registers. The last of these contains information about all

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psychiatric hospital admissions since the beginning of the century.

In 1962, we identified and examined a group of 207 children with schizophrenic mothers and 104 controls. We have recently reviewed the hospital files of the schizophrenic mothers applying *DSM-III* diagnostic criteria (Jorgensen et al., in press). Of the 129 mothers, 108 met *DSM-III* criteria for schizophrenia; 10 met the criteria except for the age requirement. The remainder were diagnosed as follows: 3—schizophreniform disorder; 3—paranoid disorder; 3—schizoaffective disorder; 1—schizotypal personality disorder; 1—atypical personality disorder. We also examined 104 normal controls matched for sex, age, social class, education, children's home experience, and rural-urban residence. At the time of the initial assessment, the children ranged in age from 10 to 20 years (mean = 15.1 years). No children were included in the sample who were psychotic or seriously mentally disturbed when they were interviewed by a psychiatrist in 1962.

The entire sample was examined in 1962 with the procedures listed in table 1. The psychophysiological measures were included to test a theory of the development of schizophrenia (Mednick 1958). The theory suggested that the preschizophrenic inherits an "abnormally sensitive" autonomic nervous system. The thought disorder of schizophrenia is the product of a system of learned avoidant associations which serves to shield the individual from overly stressful environments. We predicted that the most autonomically sensitive children of schizophrenics would be at especially high risk.

Initial Assessment

High-Risk/Low-Risk Differences.

Table 1. List of experimental measures—1962 high-risk assessment

Psychophysiology
Conditioning-extinction-generalization
Response to mild & loud sounds
Wechsler Intelligence Scale for Children (Danish adaptation)
Personality inventory
Word association test
Continuous association test
30 words
1 minute of associating to each word
Adjective checklist used by examiners to describe subjects
Psychiatric interview
Interview with parent or rearing agent
School report from teacher
Midwife's report on subject's pregnancy & delivery

Initial comparisons of the high-risk (HR) and low-risk (LR) samples disclosed that the HR children as a group did not suffer significantly more perinatal complications than the LR children. The HR children were considerably more reactive on skin conductance measures—responding with greater amplitude, shorter latency, shorter recovery time, and poorer habituation. They displayed more disturbing behavior in school as well as more deviant performance on word association tasks (Mednick and Schulsinger 1965).

Five-Year Followup

In 1967, all of the children were interviewed by a social worker. At that point they averaged approximately 20 years of age. This structured interview obtained

information about the subject's social, familial, educational, and vocational adjustment. In addition, information was obtained on possible psychological disturbance and the sample was screened in the register for psychiatric hospitalization and treatment. On the basis of this followup, 20 HR children ("Sick" group) were identified who had suffered some form of psychiatric breakdown, not necessarily schizophrenia. This Sick group was matched on a variety of variables (including their level of adjustment in 1962) to 20 well-functioning HR subjects ("Well" group) and 20 LR "Controls." (Mednick and Schulsinger 1968). Table 2 summarizes the characteristics that significantly differentiated the Sick group from the Well and Control groups.

In examining the perinatal findings, we observed that those mothers of HR subjects who were functioning well (Well group) experienced an exceptionally easy preg-

Table 2. Characteristics distinguishing Sick from Well & Control groups: 1967 followup

Lost mother to psychiatric hospitalization relatively early in life
Teacher reports of disturbing, aggressive behavior in school
Evidence of associative drift
Psychophysiological anomalies (skin conductance)
Marked fast latency of response
Response latency evidenced no signs of habituation
Resistance to experimental extinction of conditioned skin conductance response
Remarkably fast rate of recovery following response peak
Sick group (70%) suffered serious pregnancy/birth complications

nancy and delivery, even easier than that of the LR control mothers. We interpreted these findings as suggesting the following hypothesis: Perinatal complications may interact with genetic predisposition as an etiological agent for psychiatric breakdown. The chances of an HR individual developing without serious mental illness are increased considerably by escaping perinatal stressors. This finding alerted us to the possibility that one of the precursors of schizophrenia may be perinatally induced brain damage in HR individuals (Mednick 1970).

Ten-Year Followup

In 1972, we contacted the sample for an intensive diagnostic interview and reassessment. Of the HR subjects, 94 percent (of those not deceased or emigrated) took part in the assessment. Of the LR subjects, 93 percent completed some part of the assessment. The assessment techniques used were similar to those of the 1962 followup. Of the HR subjects, 173 completed the entire as-

essment; of the LR subjects, 91 completed the entire assessment.

Three diagnoses resulted from the 3½-hour clinical interview of the subjects: CAPPS-DIAGNO (Endicott and Spitzer 1972), PSE-CATEGO (Wing et al. 1974), and ICD-8 (World Health Organization 1967) clinical diagnosis. A consensus diagnosis (table 3) was defined by agreement between two of these three diagnostic approaches (Schulsinger 1976). In all, 42 percent of the HR individuals received a schizophrenia spectrum diagnosis (SSD) (including schizophrenia, borderline schizophrenia, pseudoneurotic schizophrenia, pseudopsychopathic schizophrenia, paranoia, schizoidia). This result is comparable to the prevalence rates of Heston (1966) and Kety et al. (1978). The rate of schizophrenia observed was consistent with previous studies. A Danish study by Reisby (1967) found that the number of schizophrenics among offspring of schizophrenic mothers was 8 percent at age 25. These results are consonant with our number of consensus-diagnosed schizophrenics (15).

There were 55 HR individuals with *borderline state* diagnoses (table 3). This diagnosis includes pseudoneurotic, pseudopsychopathic, paranoid, and schizoid disorders. The high rate of these borderline state diagnoses as compared to Bleuler's (1972) reports of incidence of psychopathology in offspring of schizophrenic parents can be accounted for by the portions of the interview developed specifically to detect subschizophrenic symptomatology. Of the 55 borderline state individuals, 29 were clinically diagnosed as borderline schizophrenic (i.e., excluding paranoid and schizoid disorders).

The diagnosis of borderline schizophrenia corresponds closely to the current *DSM-III* category of schizotypal personality disorder (SPD). In fact, the development of the *DSM-III* diagnosis of SPD was based in part on studies performed at our Institute which used the borderline schizophrenia diagnosis (Spitzer and Endicott 1979). In the subsequent discussion we will use the term SPD instead of borderline schizophrenia.

Table 3. Diagnoses at 10-year followup

	Interviewer		CAPPS-DIAGNO II		CATEGO (PSE + SCL + AS)		"Consensus" diagnoses	
Schizophrenia ¹	13	(1)	30	(6)	10	(1)	15	(1)
Borderline states (including schizoid and paranoid personality disorders) ²	71	(5)	20	(1)	35	(3)	55	(4)
Psychopathy	5	(4)	2	(1)	4	(4)	5	(4)
Other personality disorders	26	(10)	3	(2)	22	(9)	22	(9)
Neuroses (symptoms & character)	34	(44)	31	(16)	43	(38)	30	(33)
Nonspecific conditions	0	(0)	43	(17)	24	(17)	13	(11)
No mental disorder	23	(27)	44	(47)	15	(17)	25	(27)
Other conditions (including affective & paranoid psychoses)	1	(0)	0	(1)	20	(2)	1	(0)
Disagreement among the 3 diagnoses							7	(2)
Total	173	(91)	173	(91)	173	(91)	173	(91)

¹ Two additional schizophrenics had died before the 1972-74 assessment, but hospital charts clearly indicated the presence of schizophrenia.

² These 71 individuals comprise 29 borderline schizophrenics (SPD), 29 schizoid personality disorders, and 13 paranoid personality disorders.

A diathesis-stress model formed the basis for our analysis of the data. We have been particularly inspired by the thinking of Paul Meehl, who has proposed that there is a group of individuals who share a genetic liability for schizophrenia. Such individuals are termed "schizotypal." Those who have this genetic liability and who suffer the experience of stressful environments may develop overt schizophrenia (Meehl 1962, 1972). Thus, it is our general hypothesis that deleterious environments will tend to produce schizophrenia in schizotypal individuals. Three hypotheses, derived from Meehl's theory, provided the structure of a series of data analyses: (1) We should find two groups among our HR subjects, the schizophrenics and the schizotypals. (2) These two groups should have comparable genetic backgrounds. (3) The life experiences of the schizotypals should be considerably more positive than those of the schizophrenics.

Results of 10-Year Followup

Genetic Risk Factors. At the 1972 assessment, 8.6 percent of the HR children and 1 percent of the LR children were diagnosed schizophrenic (ICD-8); 17 percent of the HR and 1 percent of the LR children were diagnosed SPD. The frequencies for HR psychopathology outcomes are dramatically worse than LR outcomes, suggesting possible familial transmission. In addition, the fact that schizophrenic mothers have offspring with high rates of both schizophrenia and SPD provides suggestive evidence for the second of our hypotheses—namely, the existence of a genetic relationship between schizophrenia and SPD. (This evidence is relatively weak support for the genetic hy-

pothesis; but there is better evidence. Adoption studies from our Institute indicate that SPD and schizophrenia are genetically related [Kendler et al. 1981].)

Another index of genetic background for schizophrenia is the age of onset of the disorder. It has been repeatedly shown (Kallmann 1978; Shields 1978; Tsuang et al. 1980; Kendler and Davis 1981) that early-onset schizophrenic probands have an excess of schizophrenic biological relatives. To examine hypothesis 2, we compared the age of onset for maternal schizophrenia for HR children with diagnoses of schizophrenia, SPD, and "No Mental Illness" (NMI). We found that age of onset of schizophrenia in the mother did not differ significantly between the schizophrenics and SPD; both of these groups had mothers with significantly younger maternal age of onset than did HR subjects diagnosed NMI. We interpret these results as indicating that schizophrenia and SPD have comparable genetic vulnerability, which is greater than the vulnerability of the other HR children (Talovic et al. 1980; Parnas et al. 1985).

We reasoned that this genetic comparability might be reflected in "schizotaxic" functioning in infancy in the schizophrenia and SPD groups. Our analyses revealed that in infancy the schizophrenics and SPDs were significantly more passive, and evidenced shorter attention spans than high-risk controls but did not differ significantly from each other. In adolescence, schizophrenics and SPDs evidenced comparable and significantly higher levels of formal thought disorder and defective emotional rapport than HR controls (Parnas et al. 1982a; Silvertown et al. 1985).

In summary, both schizophrenics and SPDs show comparable genetic

loading, and early signs of Meehl's "neurointegrative deficit." Interestingly enough, schizophrenics (especially the boys) evidence significantly poorer affective and impulse control than the SPDs (John et al. 1983). Perhaps the difference in impulse control in these two groups is a reflection of the poorer quality of environmental experience for schizophrenics (especially perinatal experience) referred to in Meehl's hypothesis.

Environmental Risk Factors. Hypothesis 3 states that some SPDs decompensate to schizophrenia because they suffer more severe environmental stress. To test this hypothesis, we compared the early life circumstances of the schizophrenics and SPDs with regard to the following factors: (1) Social stability of the parents; (2) parental separation and institutionalization experiences; (3) perinatal difficulties; and (4) computed tomographic (CT) evidence of ventricular enlargement.

Parent characteristics: Mothers. The mothers of the HR children were, of course, all schizophrenic. Despite this, we noted from examination of the clinical material that they varied quite widely in their ability to provide a stable home for their children. Some succeeded despite their handicap and some failed badly. We constructed a scale to reflect the level of social instability of the mother. The higher the score, the greater the social instability. The SPD children have mothers with a level of social instability that is about the same as the mothers of the children who were eventually diagnosed NMI. The mothers of those who became schizophrenic are significantly more socially unstable (Talovic 1984). HR children who later developed schizophrenia had a significantly less satisfactory rela-

tionship with their mothers (and fathers) than those eventually diagnosed SPD or NMI. (The latter two groups were almost identical in this regard [Burman et al., in press].) We have another bit of evidence here that the genetically loaded children who were spared from schizophrenia were reared in a relatively good environment.

Parent characteristics: Father.

From 1980 to 1982, Parnas administered a diagnostic interview to the mates of the schizophrenic women and controls. First we should note that he found a good deal of assortative mating. That is, the schizophrenic women tended to mate with men who were either themselves psychotic or suffered from psychosis-related personality disorder. The children who developed schizophrenia spectrum disorder had a high proportion of fathers who also evidenced schizophrenia spectrum disorder. This influence of the father was probably both genetic and environmental. The environmental influence of such a father is especially important in the HR children because of the severe disability of the schizophrenic mother. If the father is also severely ill, the child may be hard pressed to find a solid, supportive adult and is more likely to

end up in a public care institution (Talovic 1984; Parnas 1985).

Separation and institutionalization. Another early finding of this project was the negative outcomes in the HR children who experienced early separation from their parents (Mednick and Schulsinger 1968). The schizophrenics had less contact with their fathers and mothers than the SPD or NMI groups. Since we suspected that prolonged contact with a severely schizophrenic mother is unlikely to improve mental health, we reasoned that perhaps the bad outcomes related to early separation actually resulted from some influence associated with the parent's absence. For many of the HR children, separation from parents resulted in prolonged rearing in a public child care institution. The schizophrenics (especially the boys) suffered more institutionalization than the other HR children. The level of institutionalization for the SPDs was the same as for the NMI group. HR children who were fortunate enough to find foster placements had better outcomes (Walker et al. 1981). Again, we see evidence that a "genetically loaded" child must experience a kind environment if he is to escape decompensation to schizophrenia. It is important to

note that the effect of institutionalization is significant even with mother's age at onset and amount of parental separation statistically controlled (Parnas et al. 1985). In 1962 the LR controls were matched to the HR group for amount of institutional rearing. This means that there were a number of LR individuals who experienced extended periods of public institutional rearing. We were unable, however, to detect any psychopathogenic effect of institutionalization in the LR group. This is impressive support for the diathesis-stress model; this quality or level of stress is pathogenic only for genetically vulnerable individuals.

Perinatal factors. Quite early in the life of the project we noticed that those of the HR children who evidenced psychiatric disturbance had suffered a large number of birth difficulties (Mednick 1978). An important cause of this difference proved to be the fact that the children who eventually become schizophrenic had endured a more traumatic birth than any other diagnostic subgroup. Table 4 presents the pregnancy and birth complication (PBC) scores for the schizophrenic, SPD, and NMI groups. Note first that the schizophrenics indeed did suffer a more traumatic birth than the other sub-

Table 4. Pregnancy & birth complications (PBC) scores for schizophrenic, schizotypal personality disorders, and no mental illness groups

	Schizophrenia		Schizotypal personality disorder		No mental illness		Schizophrenia vs. schizotypal personality disorder
	Mean	SD	Mean	SD	Mean	SD	<i>p</i> value ¹
PBC frequency score	1.50	1.38	0.40	0.76	0.85	1.09	0.009
PBC severity score	1.08	0.90	0.40	0.71	0.72	0.83	0.019
PBC total score	3.17	2.82	0.76	1.67	1.92	2.85	0.008

¹Mann-Whitney *U* test.

jects; note also that the birth conditions of the SPDs were actually better than the births of the NMI subjects. Again, we interpret this to suggest that SPD individuals can escape schizophrenia if they do not suffer severe environmental trauma. It seemed likely to us that the birth complications resulted in damage to the brain and that this additional handicap loosened affective and impulse control, and increased the risk of a schizophrenic breakdown (Parnas et al. 1982b).

CT scan evidence. The evidence of birth difficulties suggested the possibility that the HR children who became schizophrenic were those who had suffered perinatal brain damage. A large number of studies have reported enlarged brain ventricles in schizophrenics (Weinberger 1984). In a pilot study we brought in a subgroup of 36 of our HR subjects for CT scans. The most widely used CT measure in schizophrenia is the ventricle/brain ratio (VBR). The higher the VBR, the less the brain area relative to ventricle area and the more the assumed atrophy.

We completed a pilot study to test our general hypotheses about the differences between the schizophrenic and SPD subjects. We had CT scans completed on 10 schizophrenics, 10 SPDs, and 16 of the HR

children with NMI (see table 5). The schizophrenics show a larger third ventricle and a larger VBR. The SPD subjects evidence the smallest third ventricle and the smallest VBR of all groups (Schulsinger et al. 1984).

We investigated the possibility that the enlarged ventricles of the schizophrenics might be a function of problematic prenatal experiences. The VBRs for the HR subjects were correlated significantly with level of birth complications. The correlation of birth weight and VBR was highly significant ($\rho = -.60$, $df = 26$, $p = .001$). Among the 14 subjects with birth weights at or below the median, all but two had VBRs above the median ($\chi^2 = 12.69$, $df = 1$, $p < .001$; Silvertown et al. 1985).

Perinatal-genetic interaction. The fact that perinatal stress is not related to schizophrenic outcome in the LR group suggests a perinatal-genetic vulnerability interaction influencing VBR. We determined to test for this interaction. We had only assessed VBRs within the HR group, all of whom have schizophrenic mothers. The major variation in genetic risk for schizophrenia in the HR subjects is due to the presence or absence of schizophrenia-spectrum disorder in their fathers. The subjects for this analysis were the 34 HR individuals for whom we had

both birth weight (an indicant of perinatal stress) and VBR measures. Paternal schizophrenia spectrum illness, birth weight, and an interaction term for these two factors were regressed on the VBR ratio. Birth weight contributed significantly to VBR. Although paternal spectrum illness did not itself significantly contribute to VBR, the interaction of paternal spectrum illness and birth weight was a very significant predictor of VBR (Silvertown et al., in press). We interpreted these findings as suggesting that a part of the genetic vulnerability to schizophrenia consists of a heightened sensitivity of the brain to perinatal insult.

Negative symptoms and VBR. Weinberger et al. (1983) have raised the issue of whether VBR-related, Type II schizophrenia is the end state of a changing (developing) symptom pattern or whether the *early* clinical picture of these Type II-large VBR patients also includes negative symptoms. We are able to contribute some modest information to this discussion. Clinical scale scores based on the 1972 assessment (Cudeck Scales; Cudeck et al. 1984) were correlated with the 1980 CT scan measures. These correlations reveal that 1972 psychopathological traits usually regarded as negative

Table 5. Computed tomographic group means (\pm SD) for schizophrenic (S), schizotypal personality disorder (SPD), and no mental illness (NMI) groups (1980 diagnoses)

	Schizophrenic ($n = 7$) ¹	Schizotypal personality disorder ($n = 11$)	No mental illness ($n = 13$) ¹	p^2
Third ventricle, mm	4.4 \pm 2.1	2.7 \pm 1.1	3.2 \pm 0.8	.028 (S/SPD)
Ventricle-brain ratio, %	11.4 \pm 6.7	5.5 \pm 1.9	6.8 \pm 1.9	.004 (S/SPD)
				.012 (S/NMI)
				.066 (SPD/NMI)

¹One schizophrenic and one individual in the NMI group refused to undergo computed tomographic scanning.

²Mann-Whitney *U* test (2-tailed probability). Values are for between-group comparisons: groups being compared are indicated in parentheses.

schizophrenic symptoms (e.g., anergia, retardation, personal neglect, decreased emotionality, flat affect, and anhedonia) are positively associated with (1980) cerebral atrophy. Although the strength of these results is again limited by the small sample size, they support research findings indicating a relationship between earlier negative schizophrenic symptoms and cerebral ventricular enlargement.

A preliminary analysis of correlations between 1980 ventricular measures and *concurrent* mental status description from the PSE (behavior, affect, and speech) revealed five significant or near-significant correlations: organic impairment with the width of the third ventricle (.35, $p = .052$); blunted affect with the width of the third ventricle (.45, $p = .021$); slow speech with the width of the third ventricle (.46, $p = .018$) and with the VBR (.43, $p = .018$). This analysis was performed only within the schizophrenia spectrum. These exploratory analyses support the hypothesis of an association between early negative schizophrenic symptoms and enlarged cerebral ventricles.

Negative symptoms, autonomic nervous system excitation, and the third ventricle. An important component of the negative symptom pattern is anhedonia. One might speculate that a part of the basis of anhedonia might involve damage to central brain structures controlling excitatory autonomic nervous system (ANS) functioning. Despite some disagreement in the literature, several reports have located central control of excitatory functioning of the ANS in the anterior hypothalamus. As early as 1937, Darrow pointed out "that this region may independently . . . mediate reflex galvanic and secretory responses to afferent stimuli after decerebration"

(p. 649). Winkler (1908) and Karplus and Kreidl (1909) found that stimulation of the anterior hypothalamus results in sweating of the footpads in cats. More recently, Wang (1964) presented evidence indicating that the anterior hypothalamus is an important sweat center and mediator of excitatory skin conductance responsiveness in the cat.

These reports are mentioned here since the anterior hypothalamus borders on the third ventricle (Barr 1979). Atrophy of tissue surrounding the third ventricle may involve damage to the anterior hypothalamus which may, in turn, result in deficiencies in excitatory ANS activity and one peripheral indicant of this activity, amplitude of skin conductance response. Cannon et al. (in preparation) hypothesized that there should be a negative relationship between degree of third ventricle atrophy and excitatory indices of skin conductance amplitude. Both skin conductance amplitude (from 1962) and third ventricle atrophy indices are available for the HR subjects assessed by CT scan in 1980. (Note that the two measures were separated by 18 years.) The skin conductance session in 1962 included responses to eight orienting stimuli (tones), nine unconditioned stimuli (loud noises), and five conditioned stimuli (tones which previously had been paired with the loud noises). The subjects were divided into those above (high atrophy) and below (low atrophy) the median for the third ventricle measure (in mm). On all trials, the high atrophy group evidenced lower skin conductance amplitude than the low atrophy group. The differences were significant only in the amplitude of responses to the five tests with the conditioned stimuli.

We plan to explore further the idea that these findings are conso-

nant with the hypothesis that periventricular atrophy in schizophrenia is associated with negative symptomatology in part because the atrophy involves key excitatory areas of the ANS located in the anterior hypothalamus.

As indicated above, an important part of the initial 1962 assessment included skin conductance measures. It was hypothesized that the children of schizophrenics with an exceptionally hyperresponsive ANS were at heightened risk for schizophrenia. While the 1962 skin conductance measure has yielded a number of interesting analyses, it does not predict to schizophrenia as assessed in 1972. We are currently engaged in a major reassessment of the Danish HR sample; we will examine the relationship of skin conductance to this final measure of clinical outcome.

Fetal Viral Infection and Schizophrenia. The apparent etiological importance of perinatal complications stimulated us to consider possible sources of these complications. Our attention was drawn to a perinatal study of an HR group in Helsinki in which pregnant schizophrenic women evidenced a considerable excess of illness in the second half of their pregnancy (Wrede et al. 1980). The descriptions of the illnesses were consistent with common symptoms of viral infection. We could not apply this information directly to the Copenhagen HR project since this set of data did not include information on viral infections during pregnancy. We did know, however, that viral infections are far more common in Denmark in the months of January, February, and March. We assumed that in these 3 months pregnant women would be more exposed to viral infection; this should be more true in crowded

Copenhagen than in more sparsely populated rural areas. The greater the crowding, the easier the transmission of infection. (This recalls the old finding that schizophrenia is more common in the lower classes only in larger cities [Clausen and Kohn 1959].) Consistent with the viral hypothesis, Machon et al. (1983) noted that the rate of schizophrenia was considerably higher (21.2 percent) for HR subjects born in the first 3 months of the year in Copenhagen than for other HR subjects (5.8 percent).

Another opportunity to test the viral hypothesis presented itself; from October 8 to November 14, 1957, Helsinki was swept by a serious Type A2 influenza virus epidemic. Mednick et al. (in press) traced the young adult (age 26.15 years) diagnoses of schizophrenia for the cohort of all live births in greater Helsinki exposed to this epidemic during their fetal development (i.e., those born November 15, 1957–August 14, 1958). Those of the cohort exposed to the epidemic during their second trimester of fetal development were found to be at increased risk of later admission to a psychiatric hospital with a diagnosis of schizophrenia (table 6). This was true in comparison to controls born in the Helsinki area in the corre-

sponding months of the previous 6 years and also in comparison to those exposed to the epidemic in their first or third trimester of fetal development. The second trimester effect was observed for both males and females, and independently in each of several of the psychiatric hospitals in the greater Helsinki area. The rate of schizophrenia (hospital diagnosis) per 1,000 Helsinki live births was also significantly elevated for those exposed to the epidemic in their second trimester of development.

Subdiagnoses of "second trimester" schizophrenics were different from subdiagnoses assigned to schizophrenic control subjects (either the controls born in the corresponding months in the previous 6 years or those exposed to the epidemic in their first or third trimesters of fetal development); the "second trimester exposed" schizophrenics attracted significantly higher numbers of ICD-8 diagnoses of Other (295.8) and Not Specified schizophrenia (295.9). These subdiagnoses suggest that the "second trimester exposed" schizophrenics may have evidenced negative symptoms.

Other research suggests that it may not be the *type* of trauma as much as the critical *timing* during fe-

tal neural development that may be decisive in increasing the risk of schizophrenia in those genetically vulnerable (Torrey et al. 1975; Huttenen and Niskanen 1978). During the second trimester (and especially in the fifth month of gestation), almost all neurons slated to compose the human cortex have been generated, but many have not yet migrated to their target structures, become positioned and synaptically connected (Rakic 1978). Therefore, the second trimester timing of a disturbance in fetal neural development might lead us to expect to observe aberrations in *cortical* structures in schizophrenics. Such aberrations have been reported by Ingvar and Franzen (1974), Weinberger et al. (1986), and Andreasen et al. (1986).

We have pointed to a number of early factors that relate to later schizophrenia or SPD in HR children. To assess the independent contributions of some of these predictors, we combined five indicants in two logistic regressions. These indicants were: (1) father-schizophrenia spectrum (father spectrum); (2) mother paranoid (as opposed to nonparanoid) (mother paranoid); (3) mother's age at first hospitalization (mother's age); (4) months HR child spent in institution in first 5 years (institutionalization); and (5) pregnancy and birth complications (PBCs).

In the first analysis we examined factors predictive of schizophrenia spectrum disorder *within* the HR group. Father spectrum and institutionalization were the high significant predictors. In the second logistic regression, we examined which of the five indicants differentiated the schizophrenic from the SPD HR children. PBCs and institutionalization were the significant predictors. (Parnas et al., in press).

Table 6. Percent of schizophrenia diagnoses for index and control groups by trimester of gestation during epidemic

	Trimester of gestation					
	Trimester 1		Trimester 2		Trimester 3	
	% Schizophrenia	<i>n</i>	% Schizophrenia	<i>n</i>	% Schizophrenia	<i>n</i>
Total sample						
Index	20.0	70	34.6	81	24.6	65
Controls	19.6	494	20.8	558	24.4	513
$\chi^2, df = 1$	NS		7.69 ¹		NS	

¹ $p < .01$.

Summary

1. A large proportion of children of schizophrenic mothers suffer an elevated predisposition to schizophrenia spectrum disorders.

2. This predisposition is transmitted to a greater extent by mothers whose schizophrenic illness begins at an early age and who have greater numbers of schizophrenic relatives. Because of assortative mating, many of the HR children have fathers with schizophrenia spectrum disorders. This adds to the genetic load of these children.

3. Our findings suggest that SPD is the basic genetically transmitted disorder. The Copenhagen HR subjects who later developed schizophrenia or SPD share a similar genetic family (maternal and paternal) background for schizophrenia. This genetic loading is greater than that of the other HR children. In early childhood they both evidence passivity and short attention span to a greater degree than the HR subjects with more benign outcomes. In adolescence, individuals with both clinical outcomes display elevated levels of thought disorder and inappropriate emotional rapport.

4. Despite their similarity in genetic and behavioral background characteristics, only some of these adolescents with SPD decompensate to schizophrenia. Why? Our results suggest that those who decompensate are marked by having suffered unfortunate early experiences. Among these early experiences, the most decisive for our Copenhagen HR subjects seem to have been perinatal trauma and unsatisfactory, unstable parenting.

5. In HR subjects, perinatal difficulties are positively related to adult measures of brain atrophy. In a separate study we examined exposure to a viral epidemic during fetal de-

velopment as a possible contributory factor in the relationship between perinatal trauma and schizophrenia. We found that exposure to the epidemic in the second trimester is strongly associated with increased risk for schizophrenia. This finding suggests focusing some of our attention on the disruption of cortical development in the second trimester of fetal life in our efforts to understand the etiology of schizophrenia.

6. Among the Copenhagen HR children, those who developed schizophrenia were distinguished by a heavy genetic load (also true of the SPDs), traumatic birth experiences associated with later brain atrophy, poor parental supervision, and public institutional care.

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Acknowledgments

This research is supported by USPHS grants MH-37692 and MH-41469. Dr. Mednick is supported by a Research Scientist Award MH-00619. The authors wish to acknowledge the aid of the Institute of Psychiatric Demography at the State Hospital in Risskov, Aarhus and the Social Science Research Institute, University of Southern California.

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