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Postnatal Risk Factors in the Etiology of Schizophrenia: Association with Good Premorbid Adjustment

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Abstract

Research shows distinct premorbid subtypes in schizophrenia. While family history of schizophrenia and obstetric complications are associated with poor premorbid adjustment, risk factors associated with good premorbid adjustment, characterizing most patients, remain unidentified. Both childhood trauma and premorbid substance use appear to increase vulnerability to schizophrenia. The goals of this study were to determine the association among family history, obstetric complications, childhood trauma, and premorbid substance use; and secondly, to assess whether trauma and premorbid substance use are associated with good premorbid schizophrenia. Trauma and substance use were assessed in 26 schizophrenia patients whose mothers were asked about family history of schizophrenia and obstetric complications. Results suggest that childhood trauma may co-occur with a family history of schizophrenia; high premorbid cannabis consumption was significantly associated with an absence of family history. Childhood trauma and premorbid substance use, however, did not consistently predict a good premorbid adjustment profile.

Abrégé

La littérature scientifique en schizophrénie démontre l'existence de sous groupes de personnes souffrant de ce trouble, se différenciant par leur fonctionnement prémorbide. Quoique les antécédents familiaux et les complications obstétriques soient souvent liés à un fonctionnement prémorbide considéré "faible," les facteurs de risques prédisposant les individus présentant un "bon" fonctionnement prémorbide (soit la plupart des cas recensés) demeurent inconnus. Par ailleurs, les traumatismes infantiles et la consommation prémorbide de drogues illicites semblent accroître la vulnérabilité au développement de la schizophrénie. Le but de cette recherche était à la fois de déterminer quels liens unissent les antécédents familiaux, les complications obstétriques, le trauma infantile et l'abus de drogue ainsi que de vérifier si l'abus de drogues et le trauma étaient liées à un "bon" fonctionnement prémorbide. Les informations concernant la consommation de drogues et la présence de traumatismes infantiles furent relevées auprès de 26 personnes souffrant de schizophrénie et, leurs mères furent interviewées au sujet des antécédents familiaux et des complications obstétriques. Les résultats suggèrent la présence conjointe d'antécédents familiaux et de trauma, alors qu'une forte consommation prémorbide de cannabis fut présente auprès des individus n'ayant pas d'antécédents familiaux. Le trauma infantile ainsi que la consommation prémorbide de drogues apparaissent irrégulièrement liées au "bon" fonctionnement prémorbide.

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Introduction

During the past century, there has been remarkable research interest in the heterogeneous nature of schizophrenia. The heterogeneity of the illness is, simultaneously, a burden to researchers attempting to understand its etiology, and a potential clue to its origins. Variability in symptomatology, course, and outcome have led many researchers to suspect, and posit, the presence of distinct subgroups within the schizophrenia disorder. Ultimately, the goal of delineating subtypes is identification of etiologically distinct categories of illness that can be effectively treated or, perhaps even, prevented.

Historically, there have been two general approaches for delineating illness subtypes: The clinical description design and the biological markers approach. The latter attempts to identify underlying genetic markers for the illness, whereas the former focuses on measures of personal functioning (Goldstein & Tsuang, 1988), such as premorbid adjustment. Research suggests that there are significant differences in the timing, nature, and severity of premorbid dysfunction in pre-schizophrenic children (Neumann, Grimes, Walker, & Baum, 1995). Since the beginning of the1930's, research findings demonstrate two separate patterns of childhood development in pre-schizophrenic patients: One of early, severe, and progressive developmental deviation (termed "poor premorbid adjustment") which occurs in 27% to 50% of patients, and one of no observable developmental problems (termed "good premorbid adjustment"), found in the remaining 50% to 73% of subjects (Kasanin & Veo, 1932; Neumann et al., 1995; Pollack et al., 1966; Torrey, Bowler, Taylor, & Gottesman, 1994; Watt & Lubensky, 1976).

The poor premorbid adjustment subtype has been found to be associated with the presence of a family history of schizophrenia (Cannon, Mednick, & Parnas,1990; Rosenbaum-Asarnow, Asarnow, Hornstein, & Russell, 1991) and obstetric complications (Walker, Neumann, Baum, Davis, DiForio, & Bergman, 1996). To date, however, good premorbid adjustment schizophrenia, the subtype characterizing the majority of patients, has only been linked to the *absence* of a family history of schizophrenia and obstetric complications. Our efforts to clarify the risk factors for schizophrenia involved in the

good premorbid adjustment subtype has led to a re-conceptualization of the notion of neurodevelopment.

The term "neurodevelopment" generally denotes pre- and perinatal central nervous system maturation (Pilowsky, Kerwin, & Murray, 1993; Woods, 1998). This classic definition of neurodevelopment suggests that schizophrenia results from damage occurring at a very early stage of brain development, possibly as a result of obstetric insults. However, the term "progressive neurodevelopment" refers to elaborate neurobiological mechanisms which control the process of development throughout the life-span (Walker & Neumann, 1996). In this case, schizophrenia is conceptualized as arising from postnatal damage to a maturing central nervous system. It is well documented that postnatal environmental factors can deleteriously affect normative neurodevelopment (Agarwal et al., 1989; Kiessling, Marcotte, & Culpepper, 1993). Non-genetic, environmental stressors, such as childhood trauma and premorbid substance use, have been associated with later development of schizophrenia and may, theoretically, behave as postnatal neurodevelopmental insults to the developing organism.

Despite research findings that link poor premorbid adjustment to a family history of schizophrenia or to the exposure of obstetric complications, risk factors for schizophrenia associated with the predominant subtype remain to be elucidated. Until the causes involved in good premorbid adjustment schizophrenia are understood, our understanding of the illness itself is rather limited. As such, the objectives of this study are to determine the patterns of association among childhood trauma, premorbid substance use, genetic and obstetric risk factors in a sample of schizophrenia patients and, secondly, to determine whether childhood trauma and premorbid substance use are associated with good premorbid adjustment schizophrenia.

Review of the Literature

Heterogeneity of the Schizophrenia Presentation

Heterogeneity is evident in the schizophrenia symptom profile. Variability in symptomatology has led many researchers to delineate more homogeneous subgroups based on illness presentation. Exploitation of the positive and negative symptom

distinction has been particularly promising as a subtyping strategy in schizophrenia (Andreasen & Olsen, 1982; Crow, 1980). Negative symptoms, defined as those symptoms that reflect an absence of normal functioning, including loss of affect, anhedonia, alogia, and avolition, have been associated with a worse prognostic profile in patients than patients who display predominantly positive symptomatology (Andreasen & Olsen, 1982; Kelley, Gilbertson, Mouton, & van Kammen,1992; Mukherjee, Reddy, & Schnur,1991). The positive symptoms of schizophrenia refer to an excess of abnormal behaviors and experiences, such as hallucinations, delusions, and formal thought disorder.

Another useful subtyping strategy based on illness presentation is the paranoid and non-paranoid contrast (Kendler, Gruenberg, & Tsuang, 1984). Paranoid schizophrenia denotes a clinical dominance of persecutory, grandiose, or jealous delusions or hallucinations (Goldstein & Tsuang, 1988). Studies have shown that the paranoid subtype is associated with better clinical outcomes than non-paranoid schizophrenia (Stephans, 1978; Strauss & Carpenter, 1978; Tsuang & Winokur, 1974).

Longitudinal investigations have also revealed heterogeneity in the course of illness in schizophrenia. Studies have found that the majority of schizophrenia patients have an undulating long-term course of illness, indicating a level of social functioning which fluctuated with respect to time. Long-term course of illness in the remainder of patients was described as simple-progressive, indicating a level of social functioning which stabilized over time; Ciompi, 1980a; Ciompi, 1980b; Harding, Brooks, Ashikaga, Strauss, & Breier, 1987a; Harding et al., 1987b). Studies have shown that, of schizophrenia patients with an undulating course of illness, 35% to 45% of patients had a favorable outcome (defined as recovered or mildly dysfunctional), whereas 17% to 31% of subjects showed moderate or severe impairments (Ciompi, 1980a; Ciompi, 1980b; Harding et al., 1987a; Harding et al., 1987b). The simple-progressive course type in schizophrenia was associated with a favorable outcome in 15% to 17% of patients, whereas 7% to 32% showed significant impairments (Ciompi, 1980a; Ciompi, 1980b; Harding et al., 1987a; Harding et al.,1987b).

Although research is needed to explain the complex link between course and

outcome in schizophrenia, studies indicate that the best predictor of outcome is type of premorbid adjustment.

Heterogeneity of Premorbid Adjustment

The premorbid phase in schizophrenia refers to the time period prior to emergence of the prodrome. The prodrome marks the beginning of illness onset which coincides with subtle pathological deviations in thought, affect, and behavior, prior to the onset of overt psychosis. During the prodrome, deviations are typically subclinical forms of negative symptoms, thought disorganization, and psychosis. Typically, anhedonia and withdrawal are noted, although various unusual, non-delusional beliefs may be expressed at this time: Speech may become digressive, vague, overly abstract or concrete; behavior may be bizarre (Bustillo, Buchanan, & Carpenter, Jr., 1995). The duration of the schizophrenic prodrome is notoriously variable, ranging from a complete absence of a prodrome to 20 years duration. In one Canadian study of schizophrenia patients, the median prodrome length was 52.7 weeks (Beiser, Erickson, Fleming, & Iacono, 1993). The prodrome ends with the onset of psychotic symptoms, frequently visual or auditory hallucinations and paranoid or grandiose delusions.

Premorbid adjustment refers to the pattern of intra-personal, interpersonal, and occupational development and functioning during the premorbid phase of development. Since the premorbid period can only be defined after onset of the prodrome, the concept is necessarily retrospective in nature. Research suggests that good premorbid adjustment in schizophrenia predicts a favorable prognosis, whereas poor premorbid adjustment is associated with a poor outcome (Ciompi, 1980a; Ciompi, 1980b).

There are at least two ways of conceptualizing premorbid adjustment in schizophrenia research. Some studies, more notably the earlier ones, describe poor versus good premorbid adjustment in terms of a greater, or lesser, than average number of behavioral problems, respectively, during childhood. Other, more recent, studies describe two distinct premorbid subgroups, or "clusters," of schizophrenia patients (discussed in greater detail shortly). In the latter studies, poor premorbid adjustment is characterized by a positive linear trend, indicative of increasing behavioral problems over time,

irregardless of the actual number of problems, whereas good premorbid adjustment is exemplified by an absence of severe behavioral problems over time, and as such, the linear trend tends to have a flat slope (i.e., a horizontal line). The former conceptualization of premorbid adjustment is reflected in the two premorbid adjustment scales that will be described here as historical examples, whereas the latter conceptualization of premorbid adjustment is illustrated in the third premorbid adjustment scale, the approach adopted in the current study.

The Premorbid Asocial Adjustment Scale (PAAS; Gittleman-Klein & Klein, 1969) was devised to assess premorbid asocial adjustment, a behavior pattern thought to be a crucial aspect of poor premorbid functioning in schizophrenia. PAAS measures shut-in, withdrawn, and asocial personalities during two stages of development: Pre-adolescence and adolescence. The measurement of functioning at two separate age levels was an important advance over previous scales in delineating longitudinal aspects of premorbid development (Kokes, Strauss, & Klorman,1977). PAAS ratings are based on information derived from three sources: A psychiatric case history, a social case history, and reports from previous treatment sources. PAAS items are scored only if items are specifically addressed in the case histories. Although inferential judgments are strictly avoided in scoring appropriate items, clinical "impressions" are often obtainable from the data (Kokes et al.,1977), thus facilitating scoring.

The three subscales contained in the PAAS are isolation, peer relationships, and interests. Each subscale is rated for the two life periods on a 7-point Likert scale (0-6). Overall scores are computed by averaging all scored items. A high PAAS score is indicative of poor premorbid adjustment.

The Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982) was developed in part because PAAS and other scales were outdated with respect to cultural norms (Kokes et al., 1977). The PAS assesses premorbid "competence," operationalized as the attainment of certain age- and sex-appropriate milestones believed necessary for normative development. PAS evaluates level of functioning in four interpersonal domains: Social accessibility-isolation, peer relationships, ability to

function outside the nuclear family, and capacity to form intimate socio-sexual ties (Kokes et al., 1977). The scale measures functioning during four life periods: Childhood (birth-11 years), early adolescence (12-15 years), late adolescence (16-18 years), and adulthood (19 years and beyond). The inclusion of infant premorbid adjustment in PAS was an important advance for identification of an early deviating subgroup in schizophrenia.

According to PAS, premorbid adjustment is defined as "the period ending 6 months prior to either onset of psychotic symptomatology or first psychiatric contact," whichever came first (Cannon-Spoor et al., 1982). Herein lies the major limitation of the scale: PAS arbitrarily defines the premorbid phase as ending 6 months prior to psychosis or treatment without taking into account individual variability for length of prodrome.

PAS ratings are based on histories obtained from personal interviews with the patient and relatives, and hospital records. The overall score for the scale is calculated by averaging scores for the four rated subscales. A high score on PAS is indicative of poor premorbid adjustment.

Research findings derived from PAAS and PAS have been correlational in nature. Findings from PAAS suggest that the premorbid adjustment of schizophrenia patients has a bimodal distribution, indicating two distinct subtypes of the illness with distinct prognostic profiles: Good and poor premorbid adjustment were significantly associated with good and poor clinical prognosis, respectively (Gittleman-Klein & Klein, 1969). Furthermore, PAS findings have established that poor premorbid adjustment significantly predicted an insidious onset, longer length of hospitalization, and worse illness outcome than good premorbid adjustment (Cannon-Spoor et al., 1982).

Findings of two distinct premorbid subtypes provided confirmation of earlier observational findings for heterogeneous premorbid trajectories in schizophrenia. In 1932, Kasanin and Veo found the incidence of unusual personality traits to be 30% in the pre-schizophrenic group and 5% in the control group, suggesting the salience of poor premorbid adjustment in mental illness. In 1946, Bellack and Parcell found that 50% of schizophrenia subjects were noticeably disturbed as children, as characterized by odd,

peculiar, shy, or seclusive personality types, while the remainder of patients were well adjusted, once again, suggesting distinct premorbid subtypes in schizophrenia. Subsequent correlational studies demonstrated that poor premorbid adjustment was significantly associated with lower IQ, increased incidence of scholastic difficulty, poor peer-group adjustment, and earlier age at first clinical contact (Belmont et al., 1964; Pollack et al., 1966; Pollack, Levenstein, & Klein, 1968).

Poor premorbid adjustment schizophrenia has been consistently linked to an earlier age at onset for the disorder (Belmont et al.,1964; Offord & Cross, 1969; Pollack et al., 1966; Wittman, 1948) and a predominance of negative symptomatology (Andreasen & Olsen, 1982; Kelley et al., 1992; Mukherjee, Reddy, & Schnur, 1991), whereas good premorbid adjustment predicts a significantly later age at onset of schizophrenia and predominantly positive symptoms (Andreasen, 1985; Andreasen & Olsen, 1982; Pogue-Geile & Harrow, 1984). Finally, patients with poor premorbid adjustment have a more chronic course of schizophrenia (Cannon-Spoor et al.,1982) and poorer clinical outcomes than subjects with good premorbid adjustment (Andreasen & Olsen, 1982; Cannon-Spoor et al., 1982; Gittleman-Klein & Klein, 1969; Opler , Kay, Rosado, & Lindenmayer, 1984; Strauss & Carpenter, 1974).

The third measurement reviewed here, a more recent premorbid adjustment scale, is the modified Child Behavior Checklist (CBCL; Achenbach, 1991). The CBCL is based on the assessment of behavioral problems in the general population, and its versions comprise a parent and teacher format. The scale was developed to measure a broad range of childhood and adolescent developmental dimensions contained in 8 subscales: Social, thought and attentional problems, withdrawal, somatic complaints, anxiety/depression, delinquency, and aggression, which are assessed at two age periods (2-3 years and 4-18 years). The subscales are, then, combined to produce the internalizing and externalizing scales.

Ratings of the 104 items range from a score of 0 (not true) to 2 (very true). Composite scores for each CBCL behavior dimensions are determined by summing items in that particular subscale.

In 1995, a modification to the CBCL by Elaine Walker's group at Emory University made it especially effective as an assessment of premorbid adjustment: Parents are asked to rate each of the items within four equally-spaced age periods (birth to 3 years, 4-7 years, 8-11 years, and 12-16 years; Neumann et al., 1995).The addition of an infant assessment and the refinement of the subsequent age categories allows researchers to trace and date subtle developmental deviations with greater precision than would be possible with the PAAS and PAS. In fact, it might be argued that the modified CBCL would be the most comprehensive approach for assessing behavioral problems since it covers the infant, childhood, and adolescent periods. Furthermore, as recent evidence indicates, assessment of the infant stage of premorbid development is essential in identifying the presence of an early deviating subgroup (i.e., prior to 4 years of age) in schizophrenia (Neumann et al., 1995). As a result, the CBCL was the method of choice for premorbid adjustment assessment in the current study.

Premorbid Subtypes of Schizophrenia

Recently, Neumann et al. (1995) have established two empirical subtypes of schizophrenia using the modified CBCL. Employing the non-correlational technique of cluster analysis, a statistical algorithm that exploits differences to determine separate groupings within the data, two patterns of premorbid adjustment emerged: Thirty percent of their schizophrenia sample demonstrated poor premorbid adjustment (termed "Cluster I"), whereas the remaining 70% of subjects demonstrated good adjustment (termed "Cluster II"). These empirically-derived results confirm earlier correlational findings of two distinct developmental subtypes of schizophrenia (Kasanin & Veo, 1932; Neumann et al., 1995; Pollack et al., 1966; Torrey et al., 1994; Watt & Lubensky, 1976).

In addition, using a modeling growth analysis on the same sample, a type of analysis which uses indices of linear and non-linear trends to examine group differences in the rate of behavior change over time, Neumann et al. (1995) visually describe the two premorbid clusters. Some of the behavior dimension profiles for Clusters I and II are presented in Figures 1 to 4 found after the results section. Results indicated that, not only were the Cluster I and Cluster II profiles strikingly distinct with respect to the slope of

behavior problems across the age periods, but clusters differed significantly with respect to the mean severity of behavioral problems. With respect to attention problems, Cluster I subjects exhibited significantly more attention problems than Cluster II subjects beginning in the first age period (0 to 4 years; see Figure 1). With respect to social problems, the clusters differed significantly from each other by the second age period (4 to 8 years; see Figure 2). With respect to withdrawn problems, the clusters differed significantly from each other by the third age period (8 to 12 years; see Figure 3). Finally, with respect to thought problems, the clusters differed significantly from each other by the fourth age period (12 to 16 years; see Figure 4). It is interesting to note that, although Cluster II pre-schizophrenic subjects exceeded the sibling comparison group on all behavior problem dimensions, differences between Cluster II subjects and siblings controls were not statistically significant.

These findings suggest that poor premorbid adjustment is evident as early as 4 years of age in some pre-schizophrenic children, and that patients with good premorbid adjustment showed very little dysfunction from childhood through adolescence, even when compared to their siblings. This conclusion is consistent with another research finding indicating that 27% of monozygotic twins discordant for schizophrenia diverged from each other in their pattern of childhood development within the first five years of life, while the remaining twins did not differ from each other developmentally until adolescence (Torrey et al., 1994). As a result of this early developmental divergence for poor premorbid adjustment schizophrenia, it is not surprising that patients with poor premorbid profiles had significantly more physical anomalies than subjects with good premorbid profiles (Lewine, 1991), suggesting prenatal neurodevelopmental trauma in the poorly adjusted group.

Static View of Neurodevelopment in Schizophrenia

Despite numerous findings indicating two distinct premorbid subtypes of schizophrenia, most research efforts have concentrated on elucidating etiologic factors for a more heterogeneously-defined illness. Many risk factors have been independently cited to increase risk for schizophrenia, such as a family history for the illness, obstetric

complications, season of birth, and maternal influenza, although no one risk factor can explain etiology in all cases of the illness. Two of the most consistently cited risk factors for the illness are genetics and obstetric complications.

Degree of genetic relatedness for biological relatives of schizophrenia patients is reflected in risk estimates for development of the illness. Estimated risk for schizophrenia in siblings of patients is10%, followed by half-siblings at 4.5%, and first cousins, 2.5% (Gottesman & Shields, 1982; Slater, 1972; Zerbin-Rudin, 1967). While schizophrenia affects1% of the general population, offspring with one or two schizophrenic parents have a 17% and 46% chance of developing the illness, respectively. Furthermore, concordance rates for schizophrenia among monozygotic and dizygotic twins yield estimates of 46% and 14%, respectively (Gottesman & Shields, 1982). Although schizophrenia does not follow a Mendelian mode of transmission, it is evident that genes contribute significantly to the illness (Gottesman & Shields, 1982; McGuffin et al., 1987).

Obstetric complications have also been widely investigated as an early etiological factor for schizophrenia. Studies have found that subjects exposed to obstetric complications were at least twice as likely to develop schizophrenia than subjects who were not exposed to such complications (Geddes & Laurie, 1995; Verdoux & Bourgeois, 1993). In fact, the rate of obstetric complications was found to be significantly higher in schizophrenia patients than in healthy siblings (Eagles et al., 1990; Heun & Maier, 1993; Kinney, Yurgelun-Todd, Waternaux, & Matthysse, 1994), bipolar patients, and normal controls (Verdoux & Bourgeois, 1993). Furthermore, individuals with a genetic predisposition to schizophrenia who were exposed to obstetric complications were significantly more likely to develop the illness than high-risk subjects who did not have obstetric difficulties (Cannon et al., 1989), suggesting an additive effect of early developmental insults.

Evidence for obstetric complications in schizophrenia is an example of a static, as compared to progressive (discussed in a later section), neurodevelopmental insult. Static insults denote active pathogenic damage occurring during the pre- and perinatal stages of development (Pilowsky et al., 1993; Woods, 1998). The research literature contains much

evidence of static neurodevelopmental insults in schizophrenia, in addition to obstetric complications. Two well-research examples are season of birth and maternal influenza.

Studies have found a 5% to 15% increase in risk for schizophrenia among those born during the winter months (i.e., January to March; Mortensen et al., 1999; Pulver, Stewart, Carpenter Jr., Childs, 1983), suggesting a seasonal increase in exposure to environmental factors in utero, such as infection or maternal influenza (Eagles, Hunter, & Geddes, 1995). Maternal influenza, particularly in the 5th and 6th month of pregnancy, has also been associated with a higher incidence for schizophrenia in the offspring (Huttunen, Machon, & Mednick, 1994), again, suggesting that the illness results from a pathogen introduced during a specific prenatal stage of development.

While season of birth and maternal exposure to influenza have not been examined as risk factors for schizophrenia in the context of premorbid subtypes for the illness, obstetric complications have been linked to the poor premorbid subtype. Neumann et al. (1995) have established that patients with poor premorbid adjustment (i.e., Cluster I) had a significantly higher rate of prenatal and delivery complications than good premorbid subjects (i.e., Cluster II). In a study of monozygotic twins discordant for schizophrenia, obstetric complications, again, predicted a poor premorbid adjustment in the ill twin (Stabenau & Pollin, 1967). Poor premorbid adjustment in schizophrenia has also been associated with the presence of a family history for the illness (Friedlander, 1945; Frazee, 1953; Morris, Escoll, & Wexler, 1956; Nameche, Waring, & Ricks, 1964; Robins, 1966), indicating that genes, like obstetric complications, may also exert very early effects in pre-schizophrenic children.

While evidence suggests that poor premorbid adjustment in schizophrenia is associated with early static damage to the developing central nervous system, good premorbid adjustment is not, suggesting that the quality and timing of the insult may play an important role in the type of premorbid adjustment expressed. Research indicates that good premorbid schizophrenia may be related to a different type of etiologic factor than those involved in poor premorbid adjustment (Walker et al., 1996). As a result, the failure to identify the risk factors suspected to be involved in the good premorbid subtype may

require a reconsideration of the definition of neurodevelopment.

Progressive View of Neurodevelopment

In contrast to the static view, which restricts the possibility of neurodevelopmental damage to the pre-and perinatal time-frame, the progressive view refers to elaborate neurodevelopmental mechanisms, several of which normally extend into adult life (Woods, 1998;Yakovlev & Lecours, 1967), and many of which may be disrupted by insults occurring during the postnatal period. Myelination and synaptic pruning are two examples of processes that may be disrupted by postnatal insults. Myelination refers to the enveloping of central nervous system axons with the insulating substance myelin, a protein produced by oligodendroglia during various stages of postnatal brain development (Weickert & Weinberger, 1998). The process of myelination is influenced by a variety of endogenous factors that can induce, or suppress, production of myelin basic protein, a major component of myelin (Cameron & Rakic, 1991; Goldman, 1992), suggesting the potential for the postnatal disruption of the process.

The hypothesis that myelin is somehow disrupted in schizophrenia is supported by evidence that schizophrenia-like psychoses are a frequent manifestation of the dysmyelination disorder, metachromatic leukodystrophy (Hyde, Ziegler, & Weinberger, 1992). Although, as yet, there is no evidence of abnormal myelination in the schizophrenic brain (Weikert & Weinberger, 1998), the theoretical possibility remains that postnatal injury to the myelinating brain may disrupt its normative development.

Progressive neurodevelopment, particularly during the periods of late childhood and adolescence, is also associated with the pruning of redundant, juvenile synapses. Synaptic pruning refers to the stabilization of developing neuro-circuitry that is achieved by overproduction of neural connections, followed by elimination of neurons or synapses that were "outcompeted" by more functional neighbors (Keshavan, Anderson, & Pettegrew, 1994). The process of synaptic pruning stabilizes during adulthood (Huttenlocher, 1979).

Very recent research has found that synaptic pruning occurs at a significantly faster rate in the dopamine D_2 receptors of adult schizophrenia patients than in healthy

adult subjects (Seeman, 1999). The significant decrease in the density of dopamine receptors in schizophrenic brains may explain one aspect of the pathophysiology of the illness: The increase and decrease of dopamine function in the mesolimbic and mesocortical brain regions, respectively (Weinberger hypothesis; Weinberger, 1987).

According to the progressive view of neurodevelopment, postnatal insults may disrupt the elaborate neurobiological mechanisms, such as myelination or synaptic pruning, thus exerting deleterious effects on the developing organism. Evidence exists demonstrating that postnatal exogenous and endogenous factors disrupt postnatal neurodevelopment: Nutritional deficiency and infectious agents have been shown to produce cognitive function abnormalities (Agarwal et al., 1989), and excessive glutamate release can cause neuropathology in an immature central nervous system (Olney, 1993). In addition, environmental stressors may behave as exogenous insults to neurodevelopment if they occur during critical maturational periods in vulnerable individuals.

Childhood Trauma and Premorbid Substance Use as Risk Factors in Schizophrenia

There are many potential sources of environmental insults. Stressful life events, including childhood trauma, have been hypothesized to moderate an increasing vulnerability to schizophrenia (Goodman, Rosenberg, Mueser, & Drake, 1997). Research has associated childhood trauma with major mental illness, including schizophrenia. One study found as many as 50% of female schizophrenia patients reported a history of childhood sexual trauma (Craine, Colliver,& MacLean, 1988). In addition, exposure to childhood physical or sexual trauma or neglect is a significant predictor of psychotic symptoms in mental illness (Beck & van der Kolk, 1987; Ellason & Ross, 1997; Muenzenmaier, Meyer, Struening,& Ferber, 1993). Schizophrenia patients with a reported history of childhood physical or sexual trauma were also significantly more likely to endorse the positive symptoms of the illness, including ideas of reference, voices commenting, thought insertion, mind reading, paranoid ideation, and visual hallucinations compared to patients with no reported trauma history (Ross, Anderson, & Clark, 1994).

Although childhood trauma and neglect seem to be associated with schizophrenia

and its defining symptoms, it is not known whether childhood trauma is related to a particular subtype of premorbid adjustment in schizophrenia. It might be hypothesized, however, that childhood trauma is linked to good premorbid adjustment, since both are associated with the presence of predominantly positive symptomatology. Moreover, it remains to be elucidated whether childhood trauma is associated with schizophrenia independently, or in combination with other risk factors, such as obstetric complications or family history of schizophrenia.

Illicit substance use is another postnatal, environmental factor hypothesized to moderate an increasing vulnerability to schizophrenia. The research literature is replete with tentative findings suggesting that premorbid substance use is associated with later development of schizophrenia (Andreasson, Allebeck, Engstrom, & Rydbeck, 1987; Andreasson, Allebeck, & Rydbeck, 1989; Allebeck, Adamsson, & Engstrom, 1993; Boutros, Bonnet, & Mak, 1996; Breakey, Goodell, Lorenz, & McHugh, 1974; Glass & Bowers, 1970; Linszen, Dingemans, & Lenior, 1994). In one study of 45,570 Swedish male conscripts, the relative risk for schizophrenia among high consumers of cannabis (i.e., defined by use on more than 50 occasions) was 6.0 compared to non-cannabis users (see Table 1; Andreasson et al., 1987). The association between an elevated level of cannabis use and schizophrenia at 15 year follow-up was not attributable to a family history of the disorder, other narcotic substance use, or social background (Andreasson et al., 1987; Andreasson et al., 1989), suggesting the salience of cannabis use as an independent risk factor for schizophrenia (Andreasson et al., 1987).

The hypothesis that substance use may trigger onset of schizophrenia is further supported by evidence that, when given a single large dose of a dopaminergic agent, such as cocaine or amphetamine, healthy subjects exhibit a brief schizophreniform psychosis (Weller, Ang, Latimer-Sayer, & Zachary, 1988). The mechanism, however, by which substance use may trigger onset of schizophrenia in vulnerable individuals remains ambiguous. Preclinical studies examining the effects of psychotogenic drugs reveal a preferential increase of dopamine metabolite concentration in the mesolimbic pathway (Bowers, 1987), which would, in turn, produce a reduction of dopamine metabolite

concentration in the mesocortical pathway, brain pathways implicated in the pathophysiology of schizophrenia (Bannon, Reinhardt, Bunney, & Roth, 1982). Although unsubstantiated, it has been suggested that repeated substance misuse may alter the dopamine system in such a way that makes it supersensitive to neurotransmitter release (Mueser et al., 1992).

Research suggests that the association between substance use and schizophrenia may be more salient in the absence of a genetic loading for the illness (Boutros et al., 1996), such that schizophrenia patients who had used substances premorbidly were significantly less likely to have had a family history of schizophrenia than patients who had not had premorbid substance use (Bowers, 1987). Furthermore, when hallucinogenic substance use was examined in a sample of schizophrenia inpatients with a low genetic predisposition to the illness, 81% of patients had used hallucinogens about 4 years prior to illness onset (Breakey et al., 1974), suggesting that substance use was probably premorbid and unrelated to a genetic predisposition for schizophrenia.

Substance use in schizophrenia has been linked to a good premorbid adjustment subtype. Studies have found that schizophrenia patients who had misused substances prior to illness onset had had better premorbid adjustment profiles than patients who had not had premorbid substance use (Andreasson et al.,1989; Breakey et al., 1974; Glass & Bowers, 1970). In addition, schizophrenia patients who used hallucinogens were less likely to have a family history for the disorder, and had more positive symptomatology and better clinical outcomes compared to subjects who did not have premorbid substance use (Bowers, 1987), suggesting a similarity in etiology, clinical presentation, and prognosis between patients with premorbid substance use and those with a good premorbid adjustment.

Despite research findings suggesting that substance use may precipitate schizophrenia, conventional wisdom in the medical community is such that substance use is believed to result from an attempt to alleviate onset of the distressful prodromal symptoms (self-medication hypothesis; Schneider & Siris, 1987), suggesting that substance use occurs *after*, and not *prior to*, schizophrenia prodrome onset.

It should be noted that, despite the vast literature associating substance use and later development of schizophrenia, most studies fail to precisely date the onset of the misuse with respect to the premorbid and prodromal periods. Simply suggesting that substance use occurred a number of years prior to illness onset does not necessarily make the drug use "premorbid," nor does it take in account individual variability for length of prodrome. In order to determine whether substance use precedes, or is simultaneous with, illness onset, age at first substance use must be temporally related to the timing of the prodrome onset. If substance use precedes prodrome onset, then substance use may be causally related to the illness; If misuse is concurrent with prodrome onset, then it may represent an attempt to self-medicate (Turner & Tsuang, 1990). Only with stringent methodology can research attempt to resolve this issue.

Not only is premorbid substance use related to schizophrenia, but it is also associated to a history of childhood trauma. Twenty-five to forty percent of substance abuse patients report trauma in childhood (Brown & Wolfe, 1994; Triffleman, Marmar, Delucci, & Ronfeldt, 1995), suggesting that trauma may predispose an individual to later substance misuse. Elucidating the independent, or combined, influences of substance use and childhood trauma in schizophrenia may serve to provide a more comprehensive understanding of the etiologies involved in the illness.

The following section provides the historical roots behind the conception of the current research project.

Historical Roots of the Current Study

The current study was undertaken in the laboratory of Dr. Suzanne King at the Douglas Hospital Research Center and builds upon data collected in the context of earlier studies. The purpose of the initial studies of EE94 (A Psychophysical Construct Validation of Expressed Emotion:1994-1998) and SIBS96 (Personality and Expressed Emotion in the Parents of Schizophrenic Young Adults:1996-1998), involving schizophrenia outpatients living with their families, was to better understand the extent to which familial expressed emotion (EE) status is a stressor on patients and/or a reflection of parental personality. Results from these studies led Dr. King to hypothesize distinct

etiological subtypes among her subjects.

From 1997 to 1999, mothers from these studies were recruited to participate in the "Envirogen Project," a project conceived with the purpose of examining two types of etiological factors in schizophrenia: genetics and obstetric complications. Preliminary analyses of these data suggest that a family history of schizophrenia and obstetric complications were each associated with a worse premorbid adjustment in schizophrenia patients (see Figures 5 and 6; Cunningham, Champagne, & King, 1998, Toronto). The resulting illustrations of the number of premorbid CBCL social problems for patients with or without a family history of schizophrenia and with or without obstetric complications are highly reminiscent of Neumann et al.'s (1995) distinct premorbid profiles described in the literature review. However, despite the ability to differentiate type of premorbid adjustment based on genetics and obstetric complications, genetic and obstetric insults could not account for all cases of schizophrenia in these patients; Twenty-one percent of subjects actually had no identified genetic or obstetric risk factor for the illness. In addition, neither a family history of schizophrenia, nor obstetric complications, could account for the development of schizophrenia in patients with a good premorbid profile. As such, the search for postnatal risk factors involved schizophrenia was proposed, leading to the conception of the current study.

Research Problems and Objectives

Since genetic and obstetric risk factors cannot account for all cases of schizophrenia, the possibility exists that postnatal risk factors are involved in the illness process, particularly in the good premorbid profile. Given that this subtype characterizes the majority of schizophrenia patients, understanding its etiology would be an important advance in the understanding of the etiology of schizophrenia in general. As such, there are two main objectives for the current study. First, we would like to determine the patterns of association among childhood trauma, premorbid substance use and genetic and obstetric risk factors in schizophrenia patients. Secondly, we would like to determine whether childhood trauma and premorbid substance use are associated with good premorbid adjustment schizophrenia.

Research Questions

1. Do childhood trauma and premorbid substance use occur more often in patients who are family history negative for schizophrenia and who have had no obstetric complications, regardless of type of premorbid adjustment?
2. Are childhood trauma and premorbid substance use associated with good premorbid adjustment schizophrenia independently, or in combination with other risk factors, such as obstetric complications or family history of schizophrenia?

Hypotheses

1a. Despite the paucity of research indicating the direction of association between childhood trauma and schizophrenia, it is hypothesized that childhood trauma will occur significantly more often in patients without a family history of schizophrenia and without obstetric complications.

1b. Based on the research literature that substance use may be more salient in the absence of a family history of schizophrenia, it is hypothesized that premorbid substance use will occur significantly more often in patients who are family history negative for the disorder and who have had no obstetric complications.

2. Based on the similarity of the clinical presentation between subjects with reported childhood trauma and premorbid substance use and the good premorbid subtype, it is hypothesized that both childhood trauma and premorbid substance use will be independently associated with good premorbid adjustment, even after controlling for family history of schizophrenia and obstetric complications.

Methodology

Subjects

Twenty-one schizophrenia patients and their mothers and, whenever, possible, fathers were recruited from two completed Expressed Emotion studies (EE94 and SIBS96) and five mother-patient dyads were recruited from the recent study of First Episode Schizophrenia. First Episode Schizophrenia is a two-hospital pilot study which was established in 1998 to determine the feasibility of launching a full-scale study of first episode psychosis (First Episode; King, Lesage, & Lalonde). Since the First Episode

study included patient assessments (i.e., SCID, PANSS, MiniMental Status Exam, Trails A&B, Verbal Fluency, AIMS) and parent interview (i.e., FIGS and CBCL), it seemed to provide an excellent opportunity for further examination of prenatal (i.e., obstetric complications) and postnatal (i.e., trauma and substance use) risk factors in schizophrenia. As such, these subjects were recruited to participate in the current study.

All 26 patients in the present study had a DSM-III-R and, in the case of recruitment from the First Episode study, DSM-IV SCID diagnosis of schizophrenia, were considered stabilized by their treating psychiatrists, and were living with their families at the time of the interview.

Eligibility requirements for the patients included not having a diagnosis of organic psychosis, being at least 18 years of age, and residing within the Greater Montreal region. Patients ranged in age from 19 to 48 years.

Eligibility requirements for the mothers included being the biological mother of the patient, the ability to speak conversational English or French, being less than 80 years of age, and residing within the Greater Montreal area. Mothers ranged in age from 39 to 78 years.

Instruments: Maternal Interview

Family Interview for Genetic Studies (FIGS): Family history of psychopathology was assessed using the FIGS (Maxwell, 1992). There are three parts to this interview. First, the informant is asked to provide a family tree consisting of all first (e.g., parents, siblings), second (e.g., half siblings, nephews, nieces, uncles, aunts, grandparents), and third (e.g., first cousins) degree relatives. Then, the General Screening Questionnaire, which contains specific questions regarding a wide range of mental illness, is administered to help identify potential psychiatric problems in family members. If, during the General Screening Questionnaire, a relative is identified, then a symptom checklist from the Diagnostic Interview for Genetic Studies (DIGS: Nurnberger et al., 1994) which most closely resembles the description of the psychopathology is completed. The DIGS contains five checklists for mental illness: Depression, mania, psychosis, personality disorders (paranoid, schizoid, schizotypal), and alcohol and substance abuse (see

Appendix A for a copy of the General Screening Questionnaire and psychosis checklist).

Ratings of potential psychopathology in family members took place during consensus meetings which included trained interviewers who had conducted the interview and at least one trained interviewer who had not attended the interview. During each rating session, relatives from at least two different families were rated in a randomized manner and, in order to prevent bias, the identity of the families was not revealed. Each relative for whom a checklist had been completed was classified as either having "no diagnosis" or a "diagnosed," "probable," or "reported" mental illness. Potential diagnoses of mental illness included schizophrenia, mania, depression, paranoid, schizoid, or schizotypal personality disorders, alcohol or substance abuse. The classification of the status of mental illness for each relative was based on the quality and quantity of information provided by the informant. For a relative to have received a "diagnosed" rating of psychopathology, the informant must have been aware of a professional diagnosis or treatment for the mental illness. A rating of "probable" psychopathology would refer to any relative appearing to meet DSM-IV criteria for the disorder, but for whom the informant was unaware of professional diagnosis or treatment for the mental illness. Finally, a "reported" rating of psychopathology was assigned when information provided by the informant may not have met full DSM-IV criteria for the mental illness, but for whom the informant reported the relative as having the disorder, although was unaware of professional diagnosis or treatment for the illness.

For the purposes of this research project, the family history variable was dichotomized. Any patient with a first, second, or third degree relative with a diagnosed or probable diagnosis of schizophrenia was considered to be family history positive for the disorder.

Kinney Medical and Obstetric History Questionnaire: The nature and severity of pregnancy and birth complications in the patients was assessed using the Kinney Medical and Obstetric History Questionnaire (Kinney et al., 1994). Mothers were asked about 62 potential pregnancy (e.g., anemia, diabetes) labor and delivery (e.g., forceps delivery, general anesthesia) and neonatal complications (e.g., meningitis, hyperactivity), and

maternal alcohol and cigarette consumption (see Appendix B for a copy of the questionnaire). In addition, maternal and infant medical charts were consulted to validate and corroborate maternal obstetric information.

The severity of obstetric complication information was rated using the McNeil-Sjöström Scale (McNeil &Sjöström, 1995) which is used to rate a broad range of complications during the pregnancy, birth, neonatal, and early childhood periods. Severity is rated on a scale of 1 to 6. A rating of 1 is defined as "not harmful or relevant," and includes, for example, first trimester nausea. A severity rating of 4 is defined as "potentially or clearly harmful or relevant," and includes maternal pelvic disproportionality. Finally, a rating of 6 is defined as "very great harm or cause deviation in offspring," and includes maternal shock prior to delivery. Severity ratings of 4 to 6 on the scale constitute a significant obstetric complication.

The McNeil-Sjöström Scale is the most sensitive instrument for obstetric complication assessment (McNeil &Sjöström, 1995) and is especially effective in discriminating obstetric complication histories between schizophrenia patients and control subjects (McNeil, Cantor-Graae, & Sjöström , 1994).

For the purpose of the current study, the obstetric complication variable was dichotomized. Patients with at least one obstetric complication with a severity rating of 4 or above on the McNeil-Sjöström Scale were considered to have been exposed to obstetric complications.

Child Behavior Checklist (CBCL): Premorbid adjustment in patients was assessed using the modified retrospective version of the CBCL (Achenbach, 1991; Neumann et al., 1995; Walker et al., 1996). Modifications included changing items to past tense and the addition of a fifth age range (i.e., 16-18 years). This version of the CBCL consists of 124 items covering potential behavioral problems in 8 subscales: Social, thought and attentional problems, withdrawal, somatic complaints, anxiety/depression, delinquency, and aggression (see Appendix C for a copy of the checklist). Several of the subscales are, then, combined to produce the internalizing and externalizing scales. The internalizing scale encompasses the withdrawn, somatic problems, and anxious/depressed dimensions.

It includes items, such as being secretive, often feeling overtired, and feeling/complaining no one loved him/her. The externalizing scale includes the delinquency and aggression subscales. It includes items, such as not feeling guilty after misbehaving, using alcohol or drugs, and physically attacking others. The social, attention, and thought problem subscales are not included in either the internalizing or externalizing scales. The social problem subscale includes items, such as not being liked by other children, and problems with gross and fine motor coordination. The attention problem subscale includes items, such as difficulty with concentration, hyperactivity, and doing poorly in school. Finally, the thought problem subscale includes items, such as obsessions and compulsions, hearing sounds and seeing things that were not actually there, and having strange ideas. All items are rated on a scale of 0 (not true), 1 (sometimes true), and 2 (very true).

For the purposes of the analyses, the internalizing and externalizing scales, and the social problem and attention problem subscales of the CBCL were examined, chosen on the basis of previous findings in pre-schizophrenic subjects (Frazee, 1953; Friedlander, 1945; Walker et al., 1996). Inclusion of the CBCL internalization and externalization scales, as well as the social and attention problem subscales, in our examination allowed for the simultaneous assessment of all relevant dimensions. Thus, the only CBCL subscale not directly, or indirectly, examined in this study is that of thought problems, a dimension which may be more closely associated with prodromal, rather than premorbid, problems.

The purpose of the current research required the computation of both a continuous and dichotomous variable for premorbid adjustment. Using Neumann et al.'s (1995) algorithm (see Appendix D), a continuous variable for premorbid adjustment was obtained: Linear slopes (growth curves) were calculated for each subject for the internalizing, externalizing, social problem, and attention problem dimensions. The algorithm is designed to produce a linear composite, or slope, of behavioral change. Essentially, the algorithm computes a straight line using the weighted time variables and then calculates how well the behavioral variables map onto the line (Neumann, 1999, personal communication).

It should be noted that, unlike Neumann et al.'s (1995) conceptualization of premorbid adjustment which did not take into account the age at prodrome onset, the current study conceptualizes premorbid adjustment as the pattern of behavioral functioning *prior* to prodrome onset. Therefore, for all analyses involving the assessment of premorbid adjustment, only those data points from each subject that were estimated to occur in the premorbid period were included in the analyses. Data points occurring during, or after, the estimated age at prodrome onset were subsequently dropped from the analyses. As a result, data points entered into analyses for subjects whose estimated age at prodrome onset occurred during the third age period (8 to 11 years; The third age period is the first age period at which some of our subjects had a prodrome onset) included data obtained from first two age periods (0 to 3 years and 4 to 7 years) for all CBCL dimensions examined. Similarly, data points entered into analyses for subjects whose estimated age at prodrome onset occurred during the fourth age period (12 to 15 years) included data obtained from the first three age periods (0 to 3 years, 4 to 7 years, and 8 to 11 years). Data points entered into analyses for subjects whose estimated age at prodrome onset occurred during the fifth age period (16 to 18 years) included data obtained from the first four age periods, and analyses for subjects whose prodrome occurred after the fifth age period (19 years and up) included data points from all five age periods. As a result of only including data points from the premorbid period, only true premorbid behaviors were examined in the current study.

The dichotomous premorbid adjustment variable categorized subjects as Cluster I (i.e., poor premorbid adjustment) and Cluster II (i.e., good premorbid adjustment) based on their calculated linear slopes for the behavior dimensions. For each dimension, any subject who exhibited a slope of zero (indicative of no behavioral deviation over time) or a negative slope (indicative of behavioral improvement over time) was categorized as Cluster II for that behavioral dimension. Subjects who displayed a positive slope (indicative of increasing severity of behavioral problems over time) for a dimension was considered to be Cluster I for that dimension. As a result of this method of classification, it was possible for a subject to be considered Cluster I for one CBCL dimension and

Cluster II for another. It should be noted that in Neumann et al.'s (1995) study, the cluster designation assigned to each subject, based on a cluster analysis using the computed linear slopes and intercept variables for each subject for all dimensions, remained constant across all dimensions examined. As a result, a subject who was designated to be Cluster I for attention problems was also Cluster I for all other dimensions.

Instruments: Patient Interview

Childhood Trauma Questionnaire and Childhood Trauma Interview (CTQ, Bernstein & Fink, 1994; *CTI,* Fink, 1994)*:* History of childhood trauma was determined using the CTQ (Bernstein & Fink, 1994), a self-report measure of five types of trauma: emotional, sexual, and physical abuse, and emotional and physical neglect. Emotional abuse refers to verbal assaults on the child's sense of worth or well-being. It includes humiliating, demeaning, or threatening behavior directed toward the child by an older person. Sexual abuse refers to sexual contact or conduct between a child and an older person and may include explicit coercion. Physical abuse refers to bodily assaults on a child by an older person that pose a risk of, or result in, injury. Emotional neglect refers to the failure of caretakers to provide for a child's basic psychological and emotional needs, such as love, encouragement, belonging, and support. Finally, physical neglect refers to the failure of caregivers to provide for a child's basic physical needs, including food, shelter, safety, supervision, and health (Bernstein & Fink, 1998).

The CTQ incorporates a number of features which may enhance the accurate reporting of traumatic events. Items on the CTQ describe childhood events in objective, non-evaluative terms, such as "When I was growing up, people in my family hit me so hard that I had to see a doctor or go to the hospital," and potentially pejorative terms, such as *abuse* and *perpetrator*, are kept to a minimum (Fink et al., 1995). Furthermore, the self-report format may increase the likelihood of disclosure of sensitive information (Bernstein & Fink, 1998). The multiple items used to inquire about each type of trauma, not only facilitate recall (Peters, Wyatt, & Finkelhor, 1986), but also enhance reliability of the trauma scales (Nunnally, 1967). Finally, a three-item minimization/denial scale of the CTQ can help identify subjects with a tendency to give socially desirable responses, or

those who are likely to deny trauma.

The CTQ comprises 28 objective statements about childhood events, which are endorsed on a 5-point Likert-type scale according to their frequency of occurrence (i.e., never true, rarely true, sometimes true, often true, and very often true). Item scores are, then, summed to produce scores for the five trauma scales, each with a possible value ranging from 5 to 25. Each scale score value is, then, reclassified as "none," "low levels," "moderate levels," or "severe levels" of abuse by comparing the observed value to cutoff values in the CTQ manual. Higher severity ratings are the result of a greater quantity and/or a greater frequency of relevant trauma items.

The CTQ is a reliable and valid measure of childhood interpersonal trauma (Fink, Bernstein, Handelsman, Foote, & Lovejoy, 1995). Internal consistency reliability coefficients for the five CTQ scales range from the highest for sexual abuse (median =.92) to the lowest for physical neglect (median= .66). Test-retest reliability, assessed with the sample of adult substance abusers after a test interval ranging from 1.6 to 5.6 months (mean= 3.6 months, SD= 1.0), ranged from r = .81 for sexual abuse and emotional neglect to r =.79 for physical neglect (Bernstein & Fink, 1998).

The concurrent validity of the CTQ is also impressive. All five types of maltreatment were significantly associated with psychological disturbance on measures of depression, post-traumatic stress disorder, dissociation, and alexithymia for the sample of adult substance abuse patients (Bernstein & Fink, 1998). With respect to construct validity, confirmatory factor analyses performed with CTQ data from the adult substance abuse population, adolescent psychiatric inpatient sample, and female HMO members suggests that the constructs of emotional, physical, and sexual abuse, and emotional and physical neglect retained their precision (i.e., held essentially the same meaning) across the three diverse samples (Bernstein & Fink, 1998).

The CTQ does not contain an exhaustive index of childhood and adolescent traumatic events. Therefore, other types of traumatic events were compiled from the Childhood Trauma Interview (CTI; Fink, 1993; same author as the CTQ) into a self-report format. Specifically, questions borrowed from the CTI were related to the

witnessing of domestic violence, the sixth type of childhood trauma assessed in this study (see Appendix E for a copy of the CTQ/CTI self-report). The witnessing of domestic violence refers to acts of domestic violence, as well as, violence involving victims and/or perpetrators who were well-known to the child at the time of the violence. This type of trauma was rated on a scale of 1 (low) to 6 (extreme) during consensus meetings using detailed examples provided by the CTI manual. Based on the CTI manual, a rating of 1 included seeing a parent spank a sibling through clothing with an open hand, but not for extended periods of time and not with extreme force. A rating of 3 included seeing a stepfather punch the child's mother in the stomach. A rating of 5 included seeing an aunt try to suffocate cousin with a pillow.

Positive trauma responses for all six types of childhood trauma were followed-up with probes borrowed from the CTI to provide a synopsis of what transpired, age at trauma onset, length of trauma, number of perpetrators, and relationship to perpetrator.

During the group consensus meetings for the rating of witnessing domestic violence, it was noticed that some subjects who would deny a specific type of trauma on the CTQ would, inadvertently, disclose details about the trauma during the course of the interview. In all cases in which this occurred, the score for minimization/denial was elevated (i.e., indicative of the minimization of childhood trauma). Therefore, it was decided that if the subject had provided enough detailed information about the trauma, relevant items in the CTQ would be re-scored to more accurately reflect the severity of trauma exposure. A conservative approach was taken when adjusting trauma items. Items were only adjusted if the subject had *specifically* addressed those items during the course of the interview.

For the purpose of this study, all childhood trauma variables (i.e., physical, sexual, and emotional abuse, physical and emotional neglect, and witnessing of domestic violence) entered into the analyses were continuous.

Prodromal Interview: The prodromal interview was conceived to establish the temporal evolution of the schizophrenic illness by dating the most common prodromal (e.g., depressed mood, anergia, concentration difficulties) and early psychotic (e.g.,

paranoia, thought broadcasting) symptoms of schizophrenia (Birchwood et al., 1989; Birchwood, MacMillian, & Smith, 1992a; Birchwood et al., 1992b; Hertz & Melville, 1980; Hirsch & Jolley, 1989; Malla & Norman, 1994; Yung & McGorry, 1996) prior to first medical contact for the illness, in an attempt to attain a precise estimate of the age and month/year at prodrome and psychotic onsets (see Appendix F for a copy of the interview). The semi-structured interview comprises 17 questions adapted from validated diagnostic instruments, namely, the Structural Clinical Interview for DSM-III-R (SCID), DSM-IV, Composite International and Diagnostic Interview (CIDI), and the Interview for Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Häfner et al., 1992).

Since, the inherent nature of the retrospective assessment of age at prodrome onset is complicated, particularly since individual length of prodrome varies dramatically from a few weeks to many years (Beiser et al., 1993), the ages of onset for the prodrome and psychosis were determined during group consensus meetings using information derived from the prodromal interview conducted with the patient and from the CBCL conducted with the mothers, and in the case of subjects recruited from the Envirogen project, also from psychiatric medical charts, and past maternal and paternal Camberwell Family Interviews. The age at onset variables consisted of the best estimates of the age at prodrome and psychotic onset for each subject.

Modified Composite International Diagnostic Interview (CIDI): Substance use was assessed using questions adapted from the CIDI. Subjects were asked to consider a list of medications and drugs and to identify any non-prescribed or illicit drugs used at least once during their lifetime. The list included potentially misused substances such as valium, codeine, sedatives, marijuana, hashish, mescaline, LSD, cocaine, PCP, mushrooms, and glue. Subjects where then asked if they had ever used any other, unidentified substances at least once in their lives. Substance identity, frequency, amount, and timing of misuse were recorded in order to delineate a continuous history of abuse for each substance used (see Appendix G for a copy of the interview).

Quantity and quality of premorbid substance use could only be identified after the age for prodrome onset had been established for each subject. If substance use occurred

prior to the estimated age for prodrome onset, substance use was considered to be premorbid. If use occurred after this age, but prior to estimated age for onset of psychosis, substance use was considered to be prodromal and would be suggestive of an attempt to self-medicate the onset of prodromal symptoms.

In light of Andreasson et al.'s (1987) finding of the accelerated risk for schizophrenia among high consumers of cannabis (i.e., defined by use on more than 50 occasions), two dichotomous premorbid substance use variables were introduced. First, premorbid substance use was dichotomized on the basis of its presence and absence. Secondly, the premorbid cannabis variable was dichotomized relative to level of cannabis consumption (i.e., use on more than 50 occasions and use on less than 50 occasions). Continuous variables for premorbid, prodromal, and psychotic substance use were also included for descriptive purposes.

Procedure

Research Ethics Board Approval

Prior to conducting the pilot testing of the patient protocol, Research Ethics Board approval was granted from the Douglas, Montreal General, Royal Victoria, Jewish General, and Louis H. Lafontaine hospitals (see Appendix H for REB approvals and consent forms).

Pilot Testing of the Patient Protocol

To ensure that the patient interview was easily comprehensible for a psychotic population and could be completed within the allotted two hours, the interview was pre-tested on one inpatient and one outpatient recruited from the Douglas Hospital. Subjects were informed that the interview was a pre-test to ensure a clarity of questioning and that the interview was administrable within the time constraint. Subjects were told that they could refuse to answer any questions and could terminate the interview at any time. Subjects were aware that their participation was voluntary, and they were not compensated for their time.

The pilot testing of the patient protocol resulted in the modification of the length of the prodromal interview. Originally, the interview contained 35 questions and was

estimated to take about a half hour to complete. However, when the interview was pre-tested in a psychotic population, it took almost two hours to complete. As a result, only questions concerning the most common prodromal and psychotic symptoms were retained, and the interview was reduced to 17 questions.

Patient Recruitment

The recruitment of patients for the current study consisted of several different stages. Initially, a member of the research team contacted each patient's psychiatrist or principal therapist. Once approval was obtained concerning the ability of the patient to provide informed consent for the present study, patients were contacted by a research team member. In the event that the psychiatrist was not certain of the patient's ability to give informed consent, the patient was not recruited.

Patients were contacted and informed about the nature of the current research. They were told that we were interested in recruiting them, and their mothers, for a new study. Patients were informed that we would ask them questions about stressful childhood events and potential illicit drug use. Patients were also told that we would like to talk to their mothers about their family history of mental illness, presence of obstetric complications, and their childhood development. All consenting subjects agreed that the data collected in the context of earlier studies could be merged with the data obtained in the new study.

If patients accepted to participate, they were met in person and provided with a detailed consent form to read over carefully. If patients demonstrated an understanding of what the study entailed, their consent was accepted, the interview initiated, and their mothers contacted for their participation.

Patient protocol consisted of three stages. First, information about timing and symptoms at illness onset was collected in the prodromal interview. Then, patients were asked about substance use using the modified CIDI interview. Finally, childhood trauma was assessed with the CTQ and CTI self-report questionnaire.

The patient interview took about 2 hours to complete. Patients were provided with breaks between stages and at their request. Subjects were compensated $40 for their time.

Maternal Recruitment

Mothers were informed regarding the nature of the research study. They were told that we would ask them questions about their family history of mental illness, obstetric complications during the pregnancy and birth of the subject, and the subject's childhood development. At the time of the interview, mothers were provided with a detailed consent form.

The maternal interview also consisted of three stages. First, family history of mental illness was assessed with the FIGS. Then, obstetric complication information was collected in the Kinney Medical and Obstetric History Questionnaire. Finally, patient premorbid adjustment was assessed using the CBCL. In the case that mothers were recruited from the First Episode study, only the obstetric complication information needed to be collected.

The maternal interview took about 3 hours to complete (1 hour for First Episode mothers). Mothers were provided with breaks between stages and at their request. They were compensated $50, or $25 in the case of First Episode mothers, for their time.

Involvement of Present Candidate

Of the thirty mothers recruited from the Envirogen project, the present candidate was involved in the interviewing of twenty of them. The present candidate interviewed all five mothers recruited from the First Episode study. All twenty-six patient interviews were also conducted by the present candidate. Finally, the conception and co-ordination of the present study was managed by the present candidate.

Statistical Analyses

In an effort to address the main objectives of the current study, the first set of proposed analyses were designed to thoroughly explore the associations among the risk factors. The following set of analyses, designed to address the second main objective of this study, attempt to discover how the risk factors are associated with the different premorbid clusters.

Research Question #1: Do childhood trauma and premorbid substance use occur more often in patients who are family history negative for schizophrenia and who have

had no obstetric complications, regardless of the type of premorbid adjustment?

The first research question is concerned with determining whether childhood trauma reported and premorbid substance use are significantly associated with each other, and whether childhood trauma reported and premorbid substance use occur significantly more often in patients who are family history negative for the disorder and who not been exposed to obstetric complications.

Substance Use and Childhood Trauma. First, t-test analyses were conducted in order to determine whether the mean severity for the six types of childhood trauma reported is significantly higher in patients with, compared to without, premorbid substance use.

Childhood Trauma and Family History of Schizophrenia. In an effort to determine whether the mean severity of the six types of childhood trauma reported is significantly higher in patients who are family history negative for schizophrenia, t-test analyses were conducted between the mean severity of childhood trauma reported for family history positive and negative patients.

Childhood Trauma and Obstetric Complications. In order to ascertain whether the mean severity of the six types of childhood trauma reported is significantly higher in patients who did not have obstetric complications, t-test analyses were conducted between the mean severity of childhood trauma reported for patients with and without obstetric complications.

Premorbid Substance Use and Family History of Schizophrenia. In order to determine whether patients who did not have a family history of schizophrenia were significantly more likely to have had premorbid substance use, Chi square analyses were conducted between the dichotomous family history and premorbid substance use variables.

In an attempt to determine whether patients who did not have a family history of schizophrenia were significantly more likely to have been high premorbid consumers of cannabis (i.e., used cannabis on more than 50 occasions), Chi square analyses were conducted between the number of family history positive and negative patients who were

high premorbid cannabis users.

Premorbid Substance Use and Obstetric Complications. To determine whether patients with an absence of obstetric complications were significantly more likely to have had premorbid substance use, Chi square analyses were conducted between the dichotomous premorbid substance use and obstetric complication variables.

Finally, in an attempt to ascertain whether patients with an absence of obstetric complications were significantly more likely to have been high premorbid cannabis consumers, Chi square analyses were conducted between the number of high premorbid cannabis-consuming patients with, and without, obstetric complications.

Research Question #2: Are childhood trauma and premorbid substance use associated with good premorbid adjustment schizophrenia independently, or in combination with other risk factors, such as obstetric complications or family history of schizophrenia?

The second research question is concerned with determining whether childhood trauma reported and premorbid substance use are significantly associated with the good premorbid profile in schizophrenia.

In order to determine whether the Cluster II premorbid profiles had a significantly higher mean severity of childhood trauma, t-test analyses were conducted between the mean severity for the six types of childhood trauma reported for Cluster I and Cluster II subjects.

Chi square analyses were conducted in an attempt to ascertain whether the Cluster II premorbid profiles differed significantly from the Cluster I profiles, with respect to family history of schizophrenia, obstetric complications, and premorbid substance use for the internalizing, social and attention problem dimensions. For the externalization dimension, Chi square analyses were conducted to determine whether the Cluster II premorbid profiles differed significantly from the Cluster I profiles, with respect to family history of schizophrenia and obstetric complications. Premorbid substance use was omitted from these analyses, since, by definition, externalizing problems include substance use.

Prior to conducting the logistic regression analyses, the presence of multicollinearity among the childhood trauma variables was assessed. Then, in order to determine the best linear combination of risk factors that predict the premorbid clusters, four hierarchical, stepwise, logistic regression analyses were conducted. In order to control for the influence of family history of schizophrenia and obstetric complications, both variables were allowed to enter in Block 1. In Block 2, the emotional, physical, and sexual abuse; emotional and physical neglect; witnessing of domestic violence, and premorbid substance use variables were allowed to enter. The only exception, however, concerned the externalizing behavior dimension: Premorbid substance use was not allowed to enter for externalizing problems. As a result of the exploratory nature of the analyses, the minimum significance level required for a variable to enter into the logistic regression equation was set at .20 and the maximum significance level for a variable to remain in the equation before being removed was set at .40. The a priori alpha level was set at .10. Bonferroni correction was used.

Results

In order to screen CBCL scores for outliers, mean scores and standard deviations were calculated for each dimension. Any score value greater than 3 standard deviations from the mean was replaced by the next highest score value (Kirk, 1982). Four outliers were found, one in each of the four CBCL dimensions examined, and were the result of high scores across several items incorporated within each subscale (see Appendix I for details).

Demographic characteristics for the mothers and patients who participated in the current study and those who did not are presented in Table 2. Of the 38 families contacted for the current study, nine patients and 3 mothers refused to participate, resulting in a total sample size for this project of 26 mother and offspring dyads. All patient refusals were attributable to a lack of interest in the study; mothers complained of a shortage of free time.

Independent samples t-test analyses, conducted to determine whether significant differences existed between mothers and patients who participated in the study and those

who refused, revealed that there were no significant differences in maternal and patient age and level of completed education; patient age at first psychiatric contact; and positive, negative, and total PANSS scores between the two groups ($p > .10$). A Chi square analysis revealed that biological sex did not differ significantly between patients who accepted participation and those who refused ($p = .685$).

Demographic and etiological characteristics of the 21 subjects recruited from the Envirogen project and the 5 subjects recruited from the First Episode study are presented in Tables 3 and 4, respectively. Independent samples t-test analyses, conducted to determine whether significant differences existed between patients recruited from the two studies, revealed that differences in age at prodrome onset, level of completed education, and mean severity scores for the six types of childhood trauma reported were not significant between the two groups ($p > .10$). However, as a result of the highly specialized selection criteria associated with the First Episode study (i.e., the first episode of psychosis), it is not surprising that significant differences were found between subjects recruited from the First Episode study and those recruited from the Envirogen project, a project representing a more chronic group of schizophrenia patients. First Episode patients were significantly younger at first psychiatric contact ($p = .014$) and at study recruitment ($p = .001$). First Episode patients tended to have higher positive ($p = .184$), and significantly higher negative ($p = .015$) and total PANSS scores ($p = .006$) compared to subjects recruited from the Envirogen project. First Episode patients also had significantly higher mean slopes for the internalizing ($p = .009$) and attention ($p = .024$) problem dimensions as based on maternal ratings of premorbid adjustment.

Chi square analyses also indicated that First Episode subjects were significantly more likely to be female ($p = .003$) and tended to have more premorbid substance use ($p = .091$) than patients recruited from the Envirogen project. Family history of schizophrenia and obstetric complications did not differ significantly between the two groups of subjects ($p > .10$).

Patterns of Risk. In an effort to describe the sample characteristics of the current study, the patterns of association among the examined risk factors are presented in Table

5. Of the 26 subjects who participated in the current study, 10 had at least one other first, second, or third degree relative with a diagnosis of schizophrenia. Of the 16 subjects who had no family history of schizophrenia, 9 had obstetric complications. Seven subjects had neither a family history for the illness, nor obstetric complications. Of these subjects, five had reported childhood trauma or premorbid substance use. Potential risk factors for two subjects remained unidentified.

Rates of Childhood Trauma. The frequency of each type of childhood trauma (i.e., scores of "low levels" or higher) examined in this study are presented in Figure 7. The most commonly reported type of childhood trauma was emotional neglect occurring in 81% of the sample, followed by sexual abuse in 46%, and emotional abuse and physical neglect in 42% of patients. Witnessing domestic violence and physical abuse were the least commonly reported childhood traumas, occurring in 27% and 19% of the sample, respectively.

The frequency of four severity levels (none, low, moderate, and severe) of each type of childhood trauma reported for the sample are presented in Figure 8. Childhood emotional abuse was reported at a severe level in 8% of the sample, at a moderate level in 15%, and at a low level in 19%. Childhood physical abuse was reported at a severe level in 4% of patients (n=1), at a moderate level in 4%, and at a low level in 12%. Sexual abuse in childhood was reported at a severe level in 4% of subjects, at a moderate level in 23%, and at a low level in 19%. Childhood emotional neglect was reported at a severe level in 12% of the sample, at a moderate level in 19%, and at a low level in 50%. Physical neglect in childhood was reported at a severe level in 12% of subjects, at a moderate level in 15%, and at a low level in 15%. The witnessing of domestic violence in childhood was reported at a severe level in 15% of the sample, at a moderate level in 4%, and at a low level in 8%.

Rates of Substance Use. The pattern of substance use relative to the evolution of the schizophrenia illness is presented in Figure 9. Most substances used in the sample occurred during the premorbid period. During this period, cannabis was the most commonly misused substance, abused by 46% of patients, followed by LSD in 31%,

mushrooms in 23%, and mescaline in 19%. During the prodromal period, rates of use for all five common premorbid drugs were much lower. In addition, after prodrome onset, new types of substances were introduced for the first time, such as quaaludes, opium, and ecstasy (presented in the figure as "other" category).

Levels of misuse for the four most common premorbid substances are presented in Figure 10. Twenty-seven percent of the sample were high cannabis consumers, 12% were moderate cannabis consumers, and 8% were minor cannabis consumers. With respect to premorbid LSD use, 4% of patients (n=1) were moderate or high LSD consumers, whereas 23% were minor LSD consumers. High and minor premorbid mushroom consumption occurred in 4% and 23% of the sample, respectively. High and minor premorbid mescaline use was reported in 4% and 15% of patients, respectively.

Premorbid Clusters. For each premorbid dimension, subjects were assigned to Cluster I (poor premorbid adjustment) or Cluster II (good premorbid adjustment) depending on their calculated slope of premorbid behavioral problems. In order to visualize the actual pattern of premorbid problems for each cluster, the mean severity of behavior problem scores were plotted for the four scales examined in the current study. Figures 11 to 14 present the patterns of behavioral problems for the two premorbid clusters. T-test analyses were conducted to determine the age periods at which the premorbid clusters differed significantly, in terms of mean severity of behavioral problems. Results are presented in Tables 6 to 9. The following sets of results are reported using bonferroni correction (α= .02).

Starting at the second age period, Cluster I subjects tended to exhibit more severe internalizing problems (p= .087), but showed significantly more internalizing problems than Cluster II subjects at the third (p= .006), fourth (p= .002), and fifth (p= .008) age periods. Cluster I subjects tended to have more externalizing problems at the second (p= .033), third (p= .025), and fourth (p= .032) age periods, but had significantly more externalizing problems than Cluster II subjects at the fifth (p= .012) age period. Cluster I subjects tended to have more social problems than Cluster II subjects in the third (p= .064), fourth (p= .040), and fifth (p= .133) age periods. At the second, third, and fifth age

periods, Cluster I subjects had significantly more attention problems than Cluster II subjects ($p < .020$) and tended to have more attention problems at the fourth age period ($p = .029$).

In order to determine whether there is a greater likelihood of retaining cluster status for multiple dimensions, Chi square analyses were conducted between each possible pair of the four problem dimensions. Results are presented in Table 10. The following sets of results are reported using bonferroni correction ($\alpha = .025$). Subjects were not significantly more likely to share the same cluster status between the internalizing and externalizing ($p = .249$), and internalizing and attention problem dimensions ($p = 1.000$). However, subjects who were Cluster II for social problems tended to be Cluster II for internalizing problems ($p = .099$) and externalizing problems ($p = .099$). Subjects who were Cluster II for externalizing problems were significantly more likely to be Cluster II for attention problems ($p = .018$).

The following sets of analyses were conducted in order to determine the associations among genetics, obstetric complications, childhood trauma reported and premorbid substance use.

Premorbid Substance Use and Childhood Trauma. Six t-test analyses were conducted to determine whether the mean severity of childhood trauma reported differed significantly in patients with and without premorbid substance use. Results are presented in Table 11. Bonferroni correction was set at $\alpha = .017$. No significant differences were found.

Childhood Trauma and Family History of Schizophrenia. In order to determine whether the mean severity of the six types of childhood trauma reported differed significantly between patients with and without a family history of schizophrenia, six t-test analyses were conducted. Results are presented in Table 12. Bonferroni correction was set at $\alpha = .017$. No significant differences were found.

Childhood Trauma and Obstetric Complications. In order to determine whether the mean severity for the six types of childhood trauma reported differed significantly between patients with and without obstetric complications, six t-test analyses were

conducted. Results are presented in Table 13. Bonferroni correction was set at $\alpha = .017$. No significant differences were found.

Premorbid Substance Use and Family History of Schizophrenia. Six Chi square analyses were conducted in order to determine whether premorbid substance use occurred significantly more often in patients without a family history of schizophrenia compared to those with a family history. Results are presented in Table 14. Bonferroni correction was set at $\alpha = .017$. High premorbid cannabis consumers were significantly more likely to have been family history negative. Every patient who used cannabis on more than fifty occasions was family history negative for the disorder ($p = .014$); No patient with a family history of schizophrenia had used cannabis on more than fifty occasions prior to illness onset.

Premorbid Substance Use and Obstetric Complications. Six Chi square analyses were conducted in order to determine whether premorbid substance use occurred significantly more often in patients with an absence of obstetric complications. Results are presented in Table 15. Bonferroni correction was set at $\alpha = .017$. No significant differences were found.

Postnatal Factors in Good Premorbid Adjustment. The following sets of analyses were conducted in order to determine whether childhood trauma reported and premorbid substance use are significantly associated with good premorbid schizophrenia. Six t-test analyses were conducted to determine whether the mean severity for the six types of childhood trauma reported differed significantly between the premorbid clusters for each of the four premorbid dimensions. Results are presented in Tables 16 to 19. Bonferroni correction was set at $\alpha = .017$. No significant differences were found.

Chi square analyses were conducted to determine whether the premorbid clusters differed significantly, in terms of family history of schizophrenia, obstetric complications, and premorbid substance use. Results are presented in Tables 20 to 23. Bonferroni correction was set at $\alpha = .025$ except for externalizing problems for which it was set at $\alpha = .05$. No significant cluster differences were found for any of the CBCL dimensions.

Prior to conducting logistic regression analyses, the risk of multicollinearity was

assessed among the childhood trauma reported variables. Correlations among the variables are presented in Table 24. Physical abuse correlated significantly with emotional abuse, sexual abuse, and physical neglect. Physical neglect correlated significantly with emotional neglect.

Stepwise, hierarchical, logistic regression analyses were conducted in order to determine the best linear combination of risk factors that predict the premorbid clusters. The presence of multicollinearity, however, did not affect the results, as presented in Tables 25 to 28.

The equation yielding the best linear combination of independent variables for predicting internalizing problems included family history of schizophrenia as a control variable, and emotional abuse and emotional neglect from the possible postnatal variables. This model was a significant predictor of internalizing problems (χ^2= 10.8, R^2= .46, $p < .05$). Comparing the standardized regression coefficients, the results suggest that family history of schizophrenia was the strongest predictor, with an absence of family history being associated with a good premorbid adjustment. The second strongest predictor was emotional neglect, with a higher severity being associated with good premorbid adjustment. The third strongest predictor was emotional abuse, with a higher severity being associated with good premorbid adjustment.

The equation yielding the best linear combination of independent variables for predicting externalizing problems included emotional abuse and sexual abuse from the possible postnatal variables; neither family history or obstetric insults entered the equation. This model was a significant predictor of externalizing problems (χ^2= 5.8, R^2= .27, $p < .10$). Comparing the standardized regression coefficients, the results suggest that emotional abuse was the strongest predictor, with a higher severity being associated with a good premorbid adjustment. The second strongest predictor was sexual abuse, with a lower severity being associated with good premorbid adjustment.

The equation yielding the best linear combination of independent variables for predicting social problems included family history of schizophrenia as a control variable and witnessing domestic violence from the possible postnatal variables. Although this

model explained approximately 24% of the variance in social problems, it was not strong enough to be considered statistically significant (χ^2= 4.5, p< .20). Comparing the standardized regression coefficients, the results suggest that family history of schizophrenia was the strongest predictor, with an absence being associated with a good premorbid adjustment. The second strongest predictor was witnessing domestic violence, with a lower severity being associated with good premorbid adjustment.

The equation yielding the best linear combination of independent variables for predicting attention problems included obstetric complications as a control variable, and sexual abuse from the possible postnatal variables. This model was a significant predictor of attention problems (χ^2= 4.7, R^2= .22, p< .10). Comparing the standardized regression coefficients, the results suggest that obstetric complications was the strongest predictor, with an absence being associated with a good premorbid adjustment. The second strongest predictor was sexual abuse, with a lower severity being associated with good premorbid adjustment.

Table 1

Cannabis Consumption and Relative Risk for Schizophrenia

	Reported Cannabis Consumption (number of occasions) n= 45 570			
	0	1-10	11-50	>50
Number of subjects	41 280	2836	702	752
Cases of Schizophrenia	197	18	10	21
Relative Risk	1.0	1.3	3.0	6.0
95% CI	-	0.8-2.2	1.6-5.5	4.0-8.9

Note. From "Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts," by S. Andreasson, P. Allebeck, A. Engstrom, and U. Rydbeck, 1987, Lancet, December 26, p.1484.

Table 2

Demographic Characteristics of Participants and Non-Participants

	Accepted (n=26)		Refused (n=12)			
Demographics	Mean	SD	Mean	SD	t	p
Patient Age	30.3	8.15	29.2	7.66	-.395	.695
Age at Psychiatric Contact	21.1	5.22	21.9	2.57	.502	.619
Patient Education (Yrs)	11.0	2.59	11.6	2.87	.616	.542
Positive Symptoms[a]	15.9	7.91	13.1	5.00	-1.11	.273
Negative Symptoms[a]	13.2	5.71	14.8	5.98	.770	.446
Total Symptoms[a]	58.8	20.4	57.7	19.9	-1.16	.877
Maternal Age (Yrs)	56.7	10.7	59.8	9.56	.763	.451
Maternal Education (Yrs)	10.1	3.58	10.9	3.56	.534	.597

		Number of Patients			χ^2	p
Sex	male	19	male	8	.164	.685
	female	7	female	4		
Hollingshead Rating	upper class	2	upper class	0		
	middle upper	2	middle upper	1		
	middle	1	middle	3		
	lower middle	9	lower middle	1		
	lower	12	lower	8		

[a] If the PANSS contained more than one score, the average was calculated

Table 3

Demographic Characteristics of Envirogen and First Episode Patients

Demographics	Envirogen (n=21) Mean	SD	First Episode (n=5) Mean	SD	t	p
Patient Age (Yrs)	32.9	6.81	19.4	0.55	8.94	.001
Age at Prodrome Onset (Yrs)	17.2	5.45	14.6	6.58	.921	.366
Age at Psychiatric Contact	21.8	5.63	18.4	0.55	1.31	.201
Patient Education (Yrs)	11.4	2.70	9.80	1.79	1.21	.239
Positive Symptoms[a]	14.4	6.54	22.2	1.76	-2.11	.045
Negative Symptoms[a]	11.9	4.71	18.6	6.91	-2.62	.015
Total Symptoms[a]	53.6	16.1	80.4	24.0	-3.05	.006
Internalizing Behaviors	1.65	1.97	4.76	3.05	-2.86	.009
Externalizing Behaviors	1.83	2.45	2.69	3.08	-.674	.506
Social Problems	0.81	1.74	1.64	2.46	-.889	.383
Attention Problems	1.55	2.44	4.78	3.69	-2.42	.024

	Number of Patients				χ^2	p
Sex	male	18	male	1	8.86	.003
	female	3	female	4		

[a] If the PANSS contained more than one score, the average was calculated

Table 4

Etiological Characteristics of Envirogen and First Episode Patients

Characteristics	Envirogen (n=21) Mean	SD	First Episode (n=5) Mean	SD	t	p
Severity of						
Emotional Abuse	1.81	1.08	1.40	0.55	.816	.423
Physical Abuse	1.33	0.80	1.20	0.45	.358	.724
Sexual Abuse	1.81	0.98	1.80	0.84	.020	.984
Emotional Neglect	2.14	0.96	2.20	1.10	-.116	.908
Physical Neglect	1.76	1.09	2.00	1.22	-.429	.672
Witnessing Viol.	1.14	1.96	0.40	0.89	1.27	.224

	Number of Patients				χ^2	p
Family History[a]	present	8	present	2	.006	.937
	absent	13	absent	3		
Obstetric Complications	present	12	present	4	.891	.345
	absent	9	absent	1		
Premorbid Substance Use	present	8	present	4	2.85	.091
	absent	13	absent	1		

[a]Family history of schizophrenia

Table 5

The Distribution of Possible Risk Factors for Schizophrenia in the Sample

Family History+ n=10								Family History- n=16							
OC+ n=7				OC- n=3				OC+ n=9				OC- n=7			
Trauma+ n=6		Trauma- n=1		Trauma+ n=3		Trauma- n=0		Trauma+ n=5		Trauma- n=4		Trauma+ n=4		Trauma- n=3	
drug+ n=2	drug- n=4	drug+ n=1	drug- n=0	drug+ n=0	drug- n=3	drug+ n=0	drug- n=0	drug+ n=2	drug- n=3	drug+ n=4	drug- n=0	drug+ n=2	drug- n=2	drug+ n=1	drug- n=2

Table 6

Mean Severity of Internalizing Problems for the Clusters at Each Age Range

	Mean	SD	n	t	p
0 to 3 yrs					
Cluster I	3.357	5.813	14	-1.098	0.283
Cluster II	1.412	2.021	12		
4 to 7 yrs					
Cluster I	4.571	5.653	12	-1.783	0.087†
Cluster II	1.500	2.023	14		
8 to 11 yrs					
Cluster I	8.917	8.240	12	-3.374	0.006*
Cluster II	0.800	1.135	10		
12 to 15 yrs					
Cluster I	12.111	7.976	9	-4.329	0.002*
Cluster II	0.556	0.727	9		
16 to 18 yrs					
Cluster I	7.600	3.209	5	-4.390	0.002*
Cluster II	1.000	1.000	5		

† $p < .10$ * $p < .02$

Table 7

Mean Severity of Externalizing Problems for the Clusters at Each Age Range

	Mean	SD	n	t	p
0 to 3 yrs					
Cluster I	3.793	5.561	14	-1.035	0.314
Cluster II	2.083	2.503	12		
4 to 7 yrs					
Cluster I	7.150	8.333	12	-2.343	0.033†
Cluster II	1.667	2.499	14		
8 to 11 yrs					
Cluster I	9.347	10.021	12	-2.531	0.025†
Cluster II	1.700	2.751	10		
12 to 15 yrs					
Cluster I	12.916	13.193	10	-2.487	0.032†
Cluster II	2.250	2.816	8		
16 to 18 yrs					
Cluster I	10.333	5.086	6	-3.273	0.012*
Cluster II	2.500	2.381	4		

† $p < .05$ * $p < .02$

Table 8

Mean Severity of Social Problems for the Clusters at Each Age Range

	Mean	SD	n	t	p
0 to 3 yrs					
Cluster I	1.333	1.633	6	-0.367	0.717
Cluster II	1.000	2.026	20		
4 to 7 yrs					
Cluster I	2.833	1.722	6	-1.012	0.322
Cluster II	1.650	2.681	20		
8 to 11 yrs					
Cluster I	3.750	1.708	4	-1.964	0.064†
Cluster II	1.167	2.479	18		
12 to 15 yrs					
Cluster I	5.000	1.414	2	-2.239	0.040†
Cluster II	1.188	2.316	16		
16 to 18 yrs					
Cluster I	2.000	-	1	-1.673	0.133†
Cluster II	0.444	0.882	9		

† $p < .15$

Table 9

Mean Severity of Attention Problems for the Clusters at Each Age Range

	Mean	SD	n	t	p
0 to 3 yrs					
Cluster I	2.077	2.690	13	-1.000	0.327
Cluster II	1.077	2.397	13		
4 to 7 yrs					
Cluster I	4.769	3.492	13	-2.934	0.007*
Cluster II	1.308	2.429	13		
8 to 11 yrs					
Cluster I	5.556	4.773	9	-2.895	0.009*
Cluster II	1.154	2.304	13		
12 to 15 yrs					
Cluster I	6.714	5.376	7	-2.817	0.029†
Cluster II	0.9091	1.136	11		
16 to 18 yrs					
Cluster I	7.000	3.000	3	-4.839	0.001*
Cluster II	1.286	0.951			

† $p < .05$ * $p < .02$

Table 10

Likelihood of Retaining Cluster Status for the CBCL Problem Dimensions

	Cluster I n (column %)	Cluster II n (column %)	χ^2	p
Internalization				
Externalization				
Cluster I	9 (64.3)	5 (41.7)	1.330	.249
Cluster II	5 (35.7)	7 (58.3)		
Social Problems				
Cluster I	5 (35.7)	1 (8.3)	2.729	.099†
Cluster II	9 (64.3)	11 (91.7)		
Attention Problems				
Cluster I	7 (50.0)	6 (50.0)	.001	1.000
Cluster II	7 (50.0)	6 (50.0)		
Externalization				
Social Problems				
Cluster I	5 (35.7)	1 (8.3)	2.729	.099†
Cluster II	9 (64.3)	11 (91.7)		
Attention Problems				
Cluster I	10 (71.4)	3 (25.0)	5.571	.018*
Cluster II	4 (28.6)	9 (75.0)		
Social Problems				
Attention Problems				
Cluster I	4 (66.7)	9 (45.0)	.867	.352
Cluster II	2 (33.3)	11 (55.0)		

† $p < .10$ * $p < 0$

Table 11

Mean Severity of Reported Childhood Trauma and Premorbid Substance Use

	Mean	SD	t	p
Emotional Abuse				
No Drug Use	1.93	1.14	1.091	0.286
Drug Use	1.50	0.80		
Physical Abuse				
No Drug Use	1.29	0.61	-0.161	0.873
Drug Use	1.33	0.89		
Sexual Abuse				
No Drug Use	2.07	1.07	1.650	0.113
Drug Use	1.50	0.67		
Emotional Neglect				
No Drug Use	2.07	0.92	-0.462	0.648
Drug Use	2.25	1.06		
Physical Neglect				
No Drug Use	1.93	1.07	0.600	0.554
Drug Use	1.67	1.15		
Witnessing Violence				
No Drug Use	1.07	1.90	0.213	0.833
Drug Use	0.92	1.78		

Note. Trauma scores: 1= none, 2= low level , 3= moderate level, 4= severe level

Table 12

Mean Severity of Reported Childhood Trauma and Family History of Schizophrenia

	Mean	SD	t	p
Emotional Abuse				
No FH	1.75	0.86	0.121	0.904
FH	1.70	1.25		
Physical Abuse				
No FH	1.38	0.89	0.582	0.566
FH	1.20	0.42		
Sexual Abuse				
No FH	1.63	0.81	-1.270	0.216
FH	2.10	1.10		
Emotional Neglect				
No FH	1.88	0.89	-1.963	0.061†
FH	2.60	0.97		
Physical Neglect				
No FH	1.63	1.09	-1.078	0.292
FH	2.10	1.10		
Witnessing Violence				
No FH	1.06	1.81	0.218	0.829
FH	0.90	1.91		

Note. FH: Family history of schizophrenia

Trauma scores: 1= none, 2= low level , 3= moderate level, 4= severe level

† $p < .10$

Table 13

Mean Severity of Reported Childhood Trauma and Obstetric Complications

	Mean	SD	t	p
Emotional Abuse				
No OCs	1.80	1.03	0.273	0.787
OCs	1.69	1.01		
Physical Abuse				
No OCs	1.10	0.32	-1.381	0.182
OCs	1.44	0.89		
Sexual Abuse				
No OCs	1.70	0.82	-0.455	0.653
OCs	1.88	1.02		
Emotional Neglect				
No OCs	2.10	0.88	-0.220	0.828
OCs	2.19	1.05		
Physical Neglect				
No OCs	1.60	0.84	-0.757	0.456
OCs	1.94	1.24		
Witnessing Violence				
No OCs	0.90	1.66	-0.218	0.829
OCs	1.06	1.95		

Note. OC: Obstetric Complications

Trauma scores: 1= none, 2= low level , 3= moderate level, 4= severe level

Table 14

Premorbid Substance Use and Family History of Schizophrenia

	Premorbid Use			
	No Use n (row %)	Use n (row %)	χ^2	p
Total Substances				
No FH	7 (43.8)	9 (56.3)	1.706	0.191
FH	7 (70.0)	3 (30.0)		
Cannabis				
No FH	7 (43.8)	9 (56.3)	1.706	0.191
FH	7 (70.0)	3 (30.0)		
Cannabis 50+[a]				
No FH	9 (47.4)	7 (52.6)	5.987	0.014*
FH	7 (100.0)	0		
LSD				
No FH	9 (56.3)	7 (43.8)	3.291	0.070†
FH	9 (90.0)	1 (10.0)		
Mushrooms				
No FH	10 (62.5)	6 (37.5)	2.365	0.124
FH	9 (90.0)	1 (10.0)		
Mescaline				
No FH	11 (68.8)	5 (31.3)	1.565	0.211
FH	9 (90.0)	1 (10.0)		

[a]Reported cannabis use on over 50 occasions

Note. FH: Family history of schizophrenia

† $p < .10$ * $p < .017$

Table 15

Premorbid Substance Use and Obstetric Complications

	Premorbid Use			
	No Use	Use	χ^2	p
	n (row %)	n (row %)		
Total Substances				
No OCs	7 (70.0)	3 (30.0)	1.706	0.191
OCs	7 (43.8)	9 (56.3)		
Cannabis				
No OCs	7 (70.0)	3 (30.0)	1.706	0.191
OCs	7 (43.8)	9 (56.3)		
Cannabis 50+[a]				
No OCs	8 (42.1)	11 (57.9)	0.396	0.529
OCs	2 (28.6)	5 (71.4)		
LSD				
No OCs	7 (70.0)	3 (30.0)	0.005	0.946
OCs	11 (68.8)	5 (31.3)		
Mushrooms				
No OCs	8 (80.0)	2 (20.0)	0.396	0.529
OCs	11 (68.8)	5 (31.3)		
Mescaline				
No OCs	8 (80.0)	2 (20.0)	0.087	0.768
OCs	12 (75.0)	4 (25.0)		

[a]Reported cannabis use on over 50 occasions

Note. OC: Obstetric Complications

Table 16

Internalizing Clusters and Mean Severity of Reported Childhood Trauma

	Mean	SD	t	p
Emotional Abuse				
Cluster I	1.50	0.94	1.284	0.211
Cluster II	2.00	1.04		
Physical Abuse				
Cluster I	1.21	0.43	0.692	0.496
Cluster II	1.42	1.00		
Sexual Abuse				
Cluster I	1.93	1.07	-0.702	0.490
Cluster II	1.67	0.78		
Emotional Neglect				
Cluster I	1.86	0.86	1.759	0.091[†]
Cluster II	2.50	1.00		
Physical Neglect				
Cluster I	1.50	0.76	1.529	0.145
Cluster II	2.17	1.34		
Witnessing Violence				
Cluster I	1.14	1.99	-0.427	0.673
Cluster II	0.83	1.64		

Note. Trauma scores: 1= none, 2= low level , 3= moderate level, 4= severe level

[†] $p < .10$

Table 17

Externalizing Clusters and Mean Severity of Reported Childhood Trauma

	Mean	SD	t	p
Emotional Abuse				
Cluster I	1.43	.076	1.725	0.097†
Cluster II	2.08	1.16		
Physical Abuse				
Cluster I	1.36	0.84	-0.364	0.719
Cluster II	1.25	0.62		
Sexual Abuse				
Cluster I	2.00	1.04	-1.135	0.268
Cluster II	1.58	0.79		
Emotional Neglect				
Cluster I	2.21	0.80	-0.338	0.738
Cluster II	2.08	1.16		
Physical Neglect				
Cluster I	1.71	0.99	0.462	0.648
Cluster II	1.92	1.24		
Witnessing Violence				
Cluster I	0.93	1.69	0.213	0.833
Cluster II	1.08	2.02		

Note. Trauma scores: 1= none, 2= low level , 3= moderate level, 4= severe level

† $p < .10$

Table 18

Social Problem Clusters and Mean Severity of Reported Childhood Trauma

	Mean	SD	t	p
Emotional Abuse				
Cluster I	1.67	0.82	0.175	0.862
Cluster II	1.75	1.07		
Physical Abuse				
Cluster I	1.33	0.52	-0.095	0.925
Cluster II	1.30	0.80		
Sexual Abuse				
Cluster I	1.83	1.33	-0.075	0.941
Cluster II	1.80	0.83		
Emotional Neglect				
Cluster I	2.50	0.84	-1.000	0.327
Cluster II	2.05	1.00		
Physical Neglect				
Cluster I	2.17	0.75	-0.912	0.371
Cluster II	1.70	1.17		
Witnessing Violence				
Cluster I	1.83	2.23	-1.303	0.205
Cluster II	0.75	1.65		

Note. Trauma scores: 1= none, 2= low level , 3= moderate level, 4= severe level

Table 19

Attention Problem Clusters and Mean Severity of Reported Childhood Trauma

	Mean	SD	t	p
Emotional Abuse				
Cluster I	1.85	1.07	-0.579	0.568
Cluster II	1.62	0.96		
Physical Abuse				
Cluster I	1.54	0.97	-1.654	0.121
Cluster II	1.08	0.28		
Sexual Abuse				
Cluster I	2.08	1.12	-1.498	0.150
Cluster II	1.54	0.66		
Emotional Neglect				
Cluster I	2.15	0.69	0.001	1.000
Cluster II	2.15	1.21		
Physical Neglect				
Cluster I	1.77	1.17	0.175	0.862
Cluster II	1.85	1.07		
Witnessing Violence				
Cluster I	0.92	1.61	0.212	0.834
Cluster II	1.08	2.06		

Note. Trauma scores: 1= none, 2= low level , 3= moderate level, 4= severe level

Table 20

Internalizing Clusters and Family History of Schizophrenia, Obstetric Complications, and Premorbid Substance Use

	Cluster I n (column %)	Cluster II n (column %)	χ^2	p
Family History				
Positive	8 (57.1)	3 (25.0)	2.735	0.098[†]
Negative	6 (42.9)	9 (75.0)		
Obstetric Complications				
Positive	9 (64.3)	7 (58.3)	0.097	0.756
Negative	5 (35.7)	5 (41.7)		
Premorbid Substance Use				
Positive	6 (42.9)	6 (50.0)	0.133	0.716
Negative	8 (57.1)	6 (50.0)		
Premorbid Cannabis 50+[a]				
Positive	3 (21.4)	4 (33.3)	0.465	0.495
Negative	11 (78.6)	8 (66.7)		

[a]Reported premorbid cannabis use on over 50 occasions

[†] $p < .10$

Table 21

Externalizing Clusters and Family History of Schizophrenia and Obstetric Complications

	Cluster I	Cluster II	χ^2	p
	n (column %)	n (column %)		
Family History				
Positive	6 (42.9)	5 (41.7)	0.004	0.951
Negative	8 (57.1)	7 (58.3)		
Obstetric Complications				
Positive	10 (71.4)	6 (50.0)	1.254	0.263
Negative	4 (28.6)	6 (50.0)		

† $p < .05$

Table 22

Social Problem Clusters and Family History of Schizophrenia, Obstetric Complications, and Premorbid Substance Use

	Cluster I n (column %)	Cluster II n (column %)	χ^2	p
Family History				
Positive	4 (66.7)	7 (35.0)	1.896	0.169
Negative	2 (33.3)	13 (65.0)		
Obstetric Complications				
Positive	4 (66.7)	12 (60.0)	0.087	0.768
Negative	2 (33.3)	8 (40.0)		
Premorbid Substance Use				
Positive	2 (33.3)	10 (50.0)	0.516	0.473
Negative	4 (66.7)	10 (50.0)		
Premorbid Cannabis 50+[a]				
Positive	0	7 (35.0)	2.874	0.090[†]
Negative	6 (100.0)	13 (65.0)		

[a]Reported premorbid cannabis use on over 50 occasions

[†] $p < .10$

Table 23

Attention Problem Clusters and Family History of Schizophrenia, Obstetric Complications, and Premorbid Substance Use

	Cluster I n (column %)	Cluster II n (column %)	χ^2	p
Family History				
Positive	6 (46.2)	5 (38.5)	0.158	0.691
Negative	7 (53.8)	8 (61.5)		
Obstetric Complications				
Positive	10 (76.9)	6 (46.2)	2.600	0.107
Negative	3 (23.1)	7 (53.8)		
Premorbid Substance Use				
Positive	6 (46.2)	6 (46.2)	0.000	1.000
Negative	7 (53.8)	7 (53.8)		
Premorbid Cannabis 50+[a]				
Positive	4 (30.8)	3 (23.1)	0.343	0.558
Negative	9 (69.2)	10 (76.9)		

[a]Reported premorbid cannabis use on over 50 occasions

Table 24

Correlational Matrix For Trauma reported Variables: Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, Physical Neglect, and Witnessing Violence

	E.A.	P.A.	S.A.	E.N.	P.N.	W.V.
E.A.	1.000	.442*	.198	-.038	.351	-.022
P.A.		1.000	.436*	.156	.523*	.250
S.A.			1.000	.166	.274	-.024
E.N.				1.000	.444*	.091
P.N.					1.000	.383
W.V.						1.000

* Correlation is significant at the 0.05 level (2-tailed)

Note. E.A.: Emotional Abuse; P.A.: Physical Abuse, S.A.: Sexual Abuse; E.N.: Emotional Neglect; P.N.: Physical Neglect; W.V.: Witnessing Violence

Table 25

Logistic Regression for Internalizing Clusters

	Model 0	Model 1	Model 2	Model 3
Independent		b	b	b
Variables		(se)[a]	(se)	(se)
Block 1				
Family History		1.10 †	2.7**	2.7**
		(.85)	(1.3)	(1.4)
Block 2				
Emotional Neglect		-	-1.5**	-1.6**
		-	(.69)	(.68)
Emotional Abuse			-	-.72†
			-	(.53)
Summary Statistics				
Chi square: Model		1.7†	8.8**	10.8**
Chi square: Block		-	7.0**	9.1**
-2 Log Likelihood		34.1	27.1	25.1
Percent Classified		61.5	69.2	73.1
Nagelkerke R^2		.09	.38	.46

Note. Cluster I coded "1" and Cluster II coded "0"

[a]Standard error of metric regression coefficients in parentheses

[b]Variables allowed to enter in block 1: family history, obstetric complications

[c]Variables allowed to enter in block 2: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, witnessing violence, premorbid substance use

† $p < .20$ $^{*}p < .10$ $^{**}p < .05$

Table 26

Logistic Regression for Externalizing Clusters

	Model 0	Model 1	Model 2	Model 3
Independent		b	b	b
Variables		(se)[a]	(se)	(se)
Block 1				
Block 2				
Emotional Abuse		-	-.74[†]	-.99[•]
			(.46)	(.53)
Sexual Abuse		-	-	.88[†]
				(.58)
Summary Statistics				
Chi square: Model			3.0[•]	5.8[•]
Chi square: Block			-	5.8[•]
-2 Log Likelihood			32.9	30.1
Percent Classified			65.4	65.4
Nagelkerke R^2			.14	.27

Note. Cluster I coded "1" and Cluster II coded "0"

[a]Standard error of metric regression coefficients in parentheses

[b]Variables allowed to enter in block 1: family history, obstetric complications

[c]Variables allowed to enter in block 2: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, witnessing violence

[†] $p < .20$ [•] $p < .10$ [••] $p < .05$

Table 27

Logistic Regression for Social Problems Clusters

	Model 0	Model 1	Model 2	Model 3
Independent		b	b	b
Variables		(se)[a]	(se)	(se)
Block 1				
Family History		1.5 †	2.7†	
		(.99)	(1.3)	
Block 2				
Witnessing Violence		-	.37†	
			(.27)	
Summary Statistics				
Chi square: Model		2.6†	4.5†	
Chi square: Block		-	2.0†	
-2 Log Likelihood		25.5	23.6	
Percent Classified		76.9	84.6	
Nagelkerke R^2		.14	.24	

Note. Cluster I coded "1" and Cluster II coded "0"

[a]Standard error of metric regression coefficients in parentheses

[b]Variables allowed to enter in block 1: family history, obstetric complications

[c]Variables allowed to enter in block 2: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, witnessing violence, premorbid substance use

† $p < .20$ * $p < .10$ ** $p < .05$

Table 28

Logistic Regression for Attention Problems Clusters

	Model 0	Model 1	Model 2	Model 3
Independent		b	b	b
Variables		(se)[a]	(se)	(se)
Block 1				
Obstetric Complications		1.4 †	1.4†	
		(.86)	(.90)	
Block 2				
Sexual Abuse		-	.69†	
			(.50)	
Summary Statistics				
Chi square: Model		2.7†	4.7*	
Chi square: Block		-	2.1†	
-2 Log Likelihood		33.4	31.3	
Percent Classified		65.4	57.7	
Nagelkerke R^2		.13	.22	

Note. Cluster I coded "1" and Cluster II coded "0"

[a]Standard error of metric regression coefficients in parentheses

[b]Variables allowed to enter in block 1: family history, obstetric complications

[c]Variables allowed to enter in block 2: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, witnessing violence, premorbid substance use

† $p < .20$ * $p < .10$ ** $p < .05$

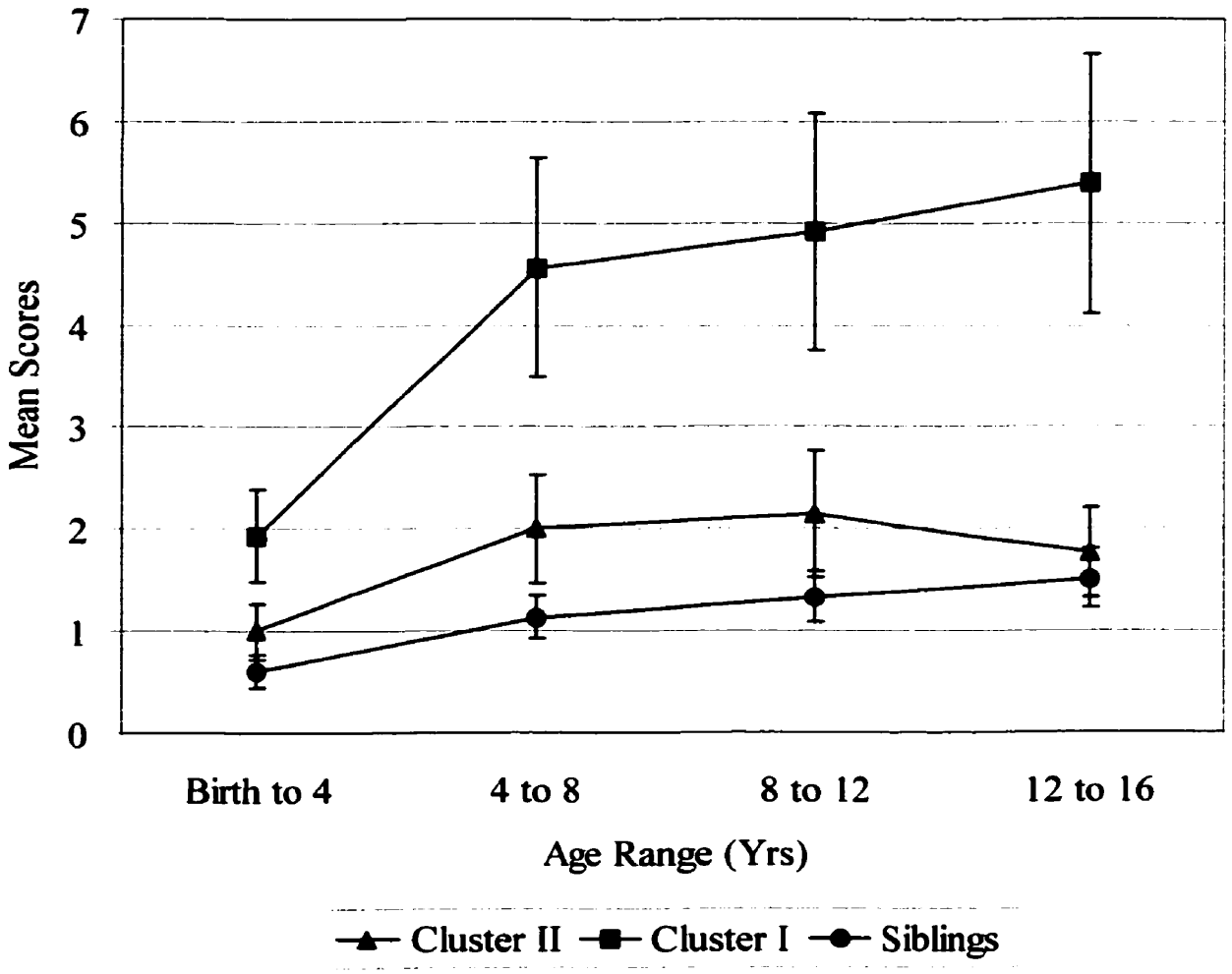

Figure 1. Mean severity of CBCL attention problems for Cluster I and II subjects.

Note. From "Developmental Pathways to Schizophrenia: Behavioral Subtypes," by C.S. Neumann, K. Grimes, E.F. Walker, and K. Baum, 1995, Journal of Abnormal Psychology, 4, p.563.

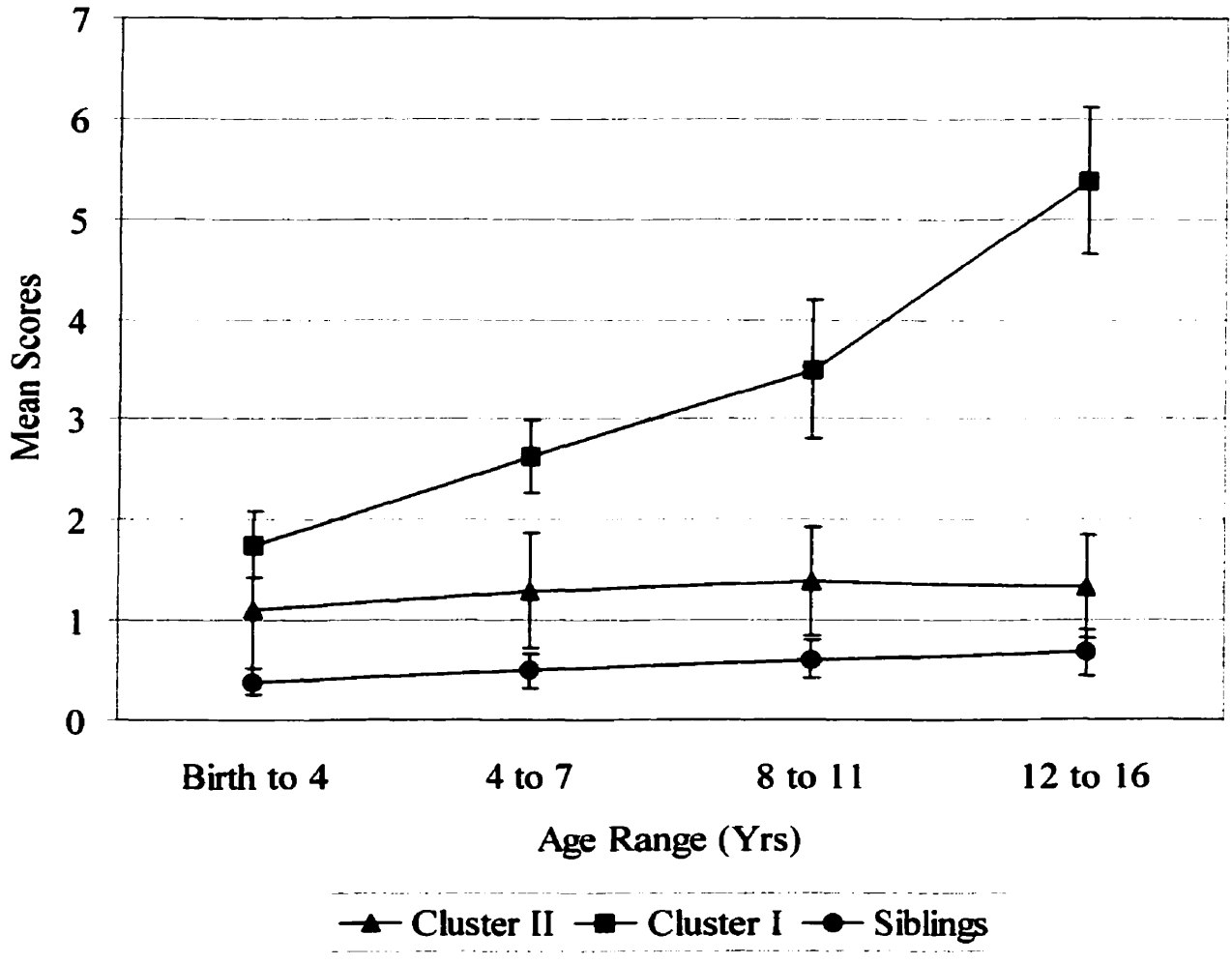

Figure 2. Mean severity of CBCL social problems for Cluster I and II subjects.

Note. From "Developmental Pathways to Schizophrenia: Behavioral Subtypes," by C.S. Neumann, K. Grimes, E.F. Walker, and K. Baum, 1995, Journal of Abnormal Psychology, 4, p.563.

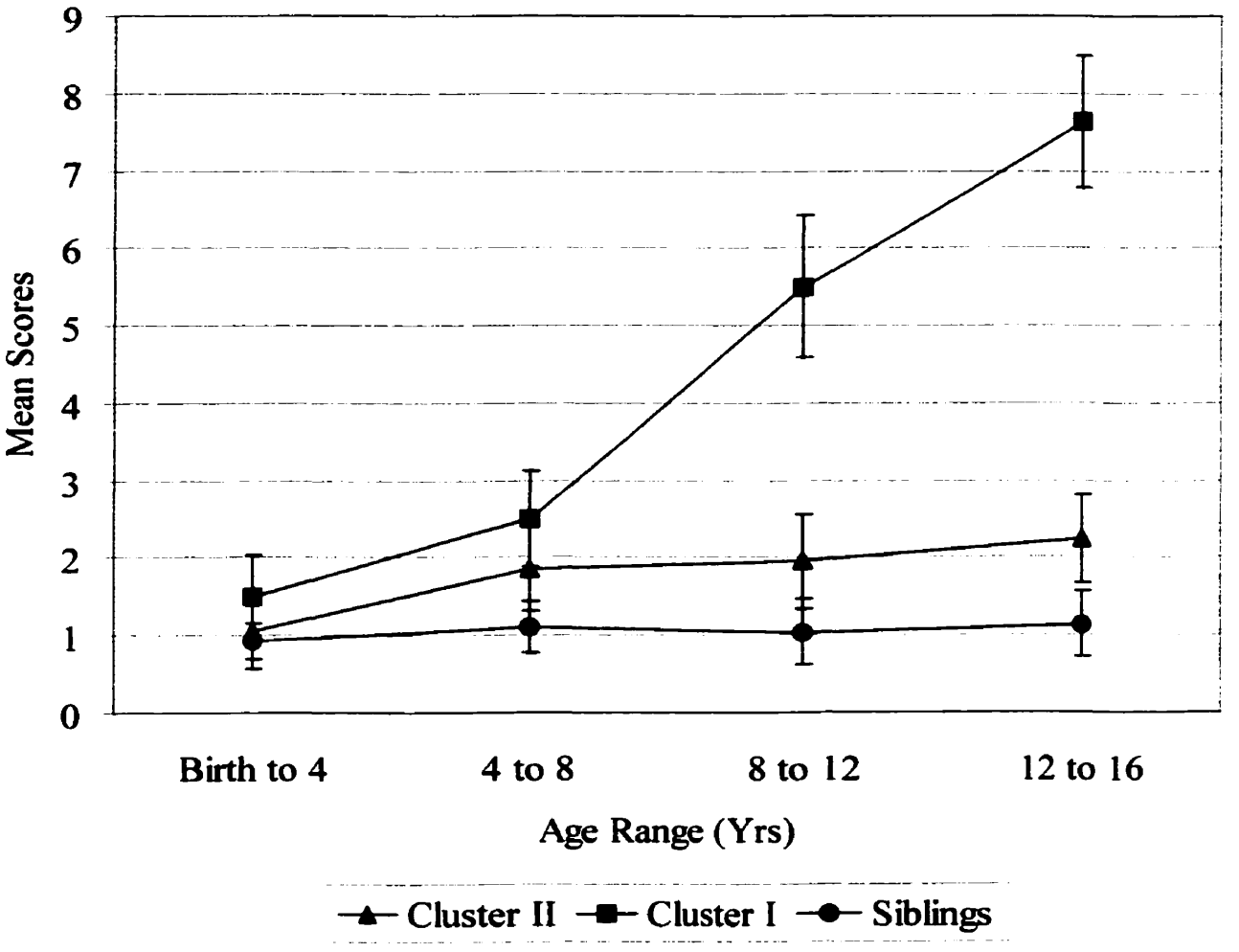

Figure 3. Mean severity of CBCL withdrawn problems for Cluster I and II subjects.

Note. From "Developmental Pathways to Schizophrenia: Behavioral Subtypes," by C.S. Neumann, K. Grimes, E.F. Walker, and K. Baum, 1995, Journal of Abnormal Psychology, 4, p.563.

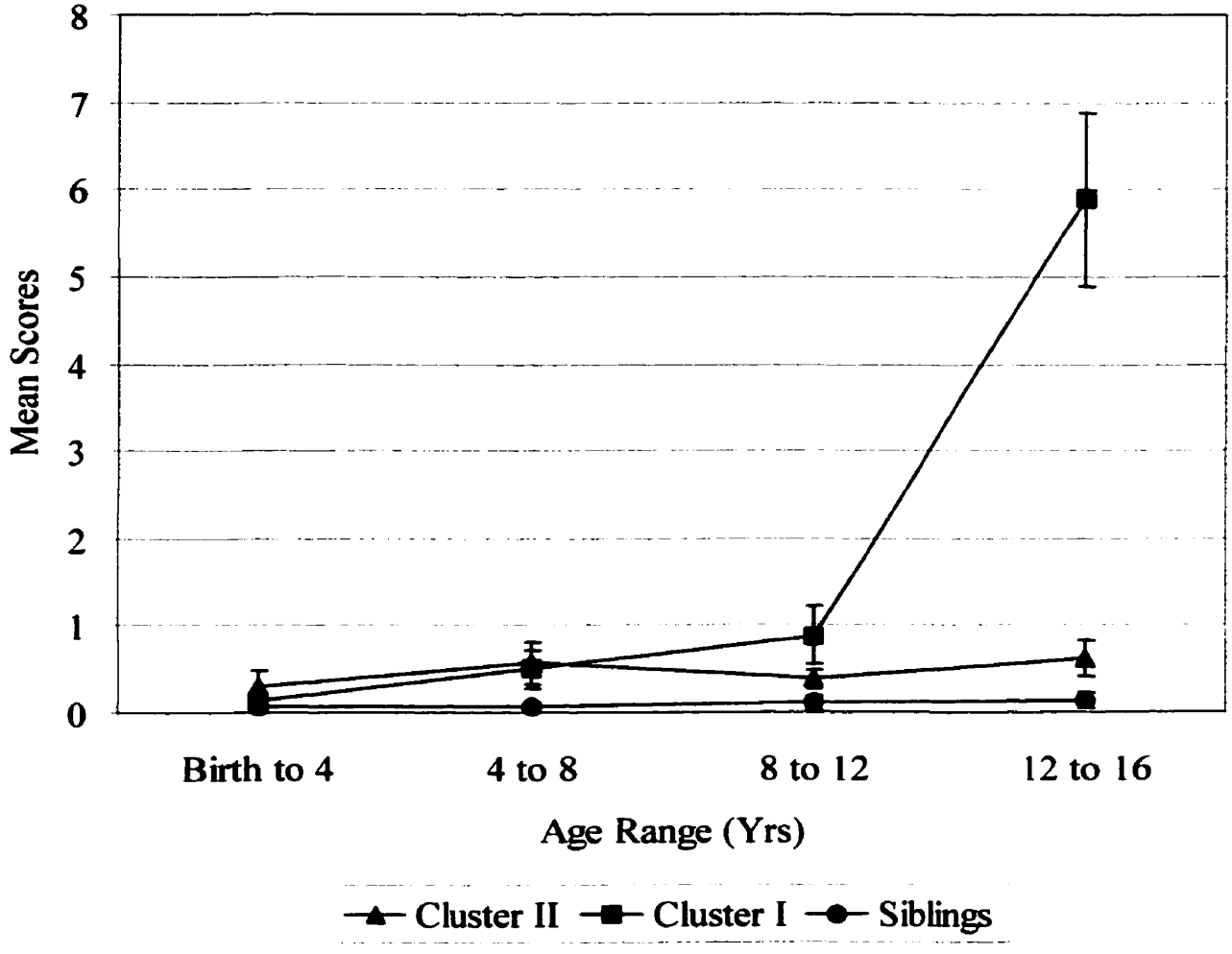

Figure 4. Mean severity of CBCL thought problems for Cluster I and II subjects.

Note. From "Developmental Pathways to Schizophrenia: Behavioral Subtypes," by C.S. Neumann, K. Grimes, E.F. Walker, and K. Baum, 1995, Journal of Abnormal Psychology, 4, p.563.

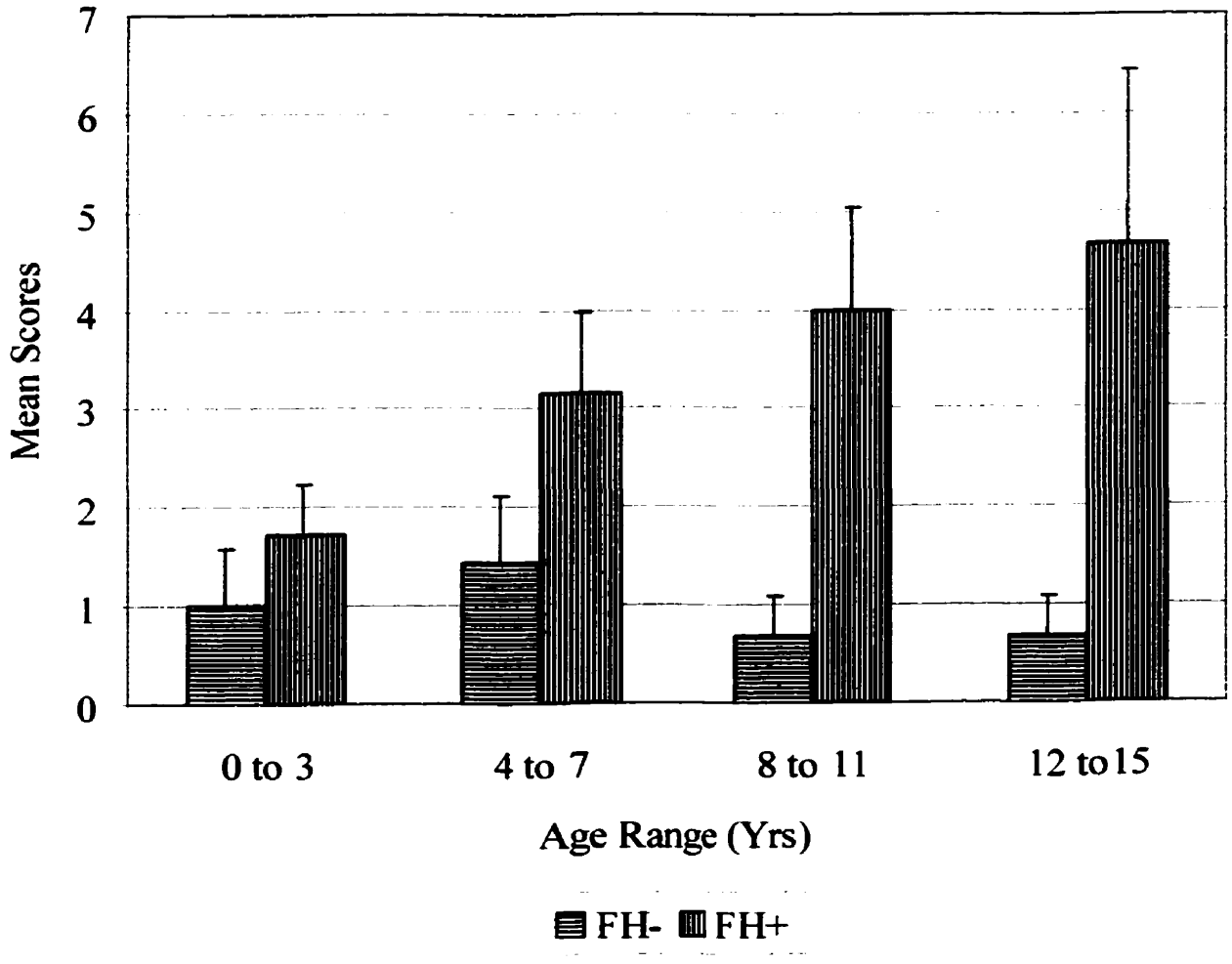

Figure 5. Mean severity of social problems in schizophrenia patients with and without a family history for schizophrenia.

Note. From Cunningham, H., Champagne, F., & King, S. (1998). Genetic and environmental factors in the etiology of schizophrenia: Relation to premorbid adjustment. Presented at Schizophrenia Research, 1998, Toronto, Ontario.

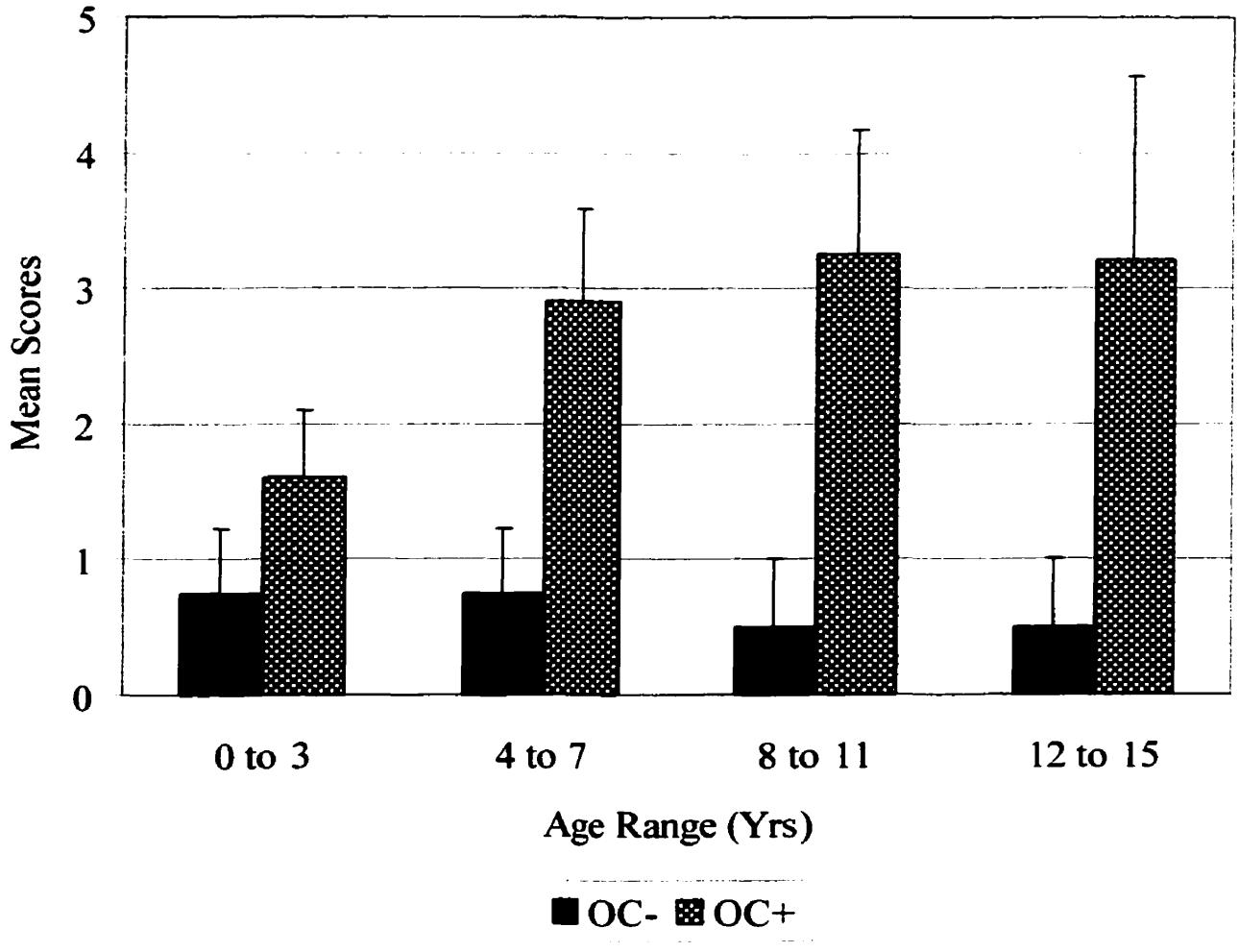

Figure 6. Mean severity of social problems in patients with and without obstetric complications.

Note. From Cunningham, H., Champagne, F., & King, S. (1998). Genetic and environmental factors in the etiology of schizophrenia: Relation to premorbid adjustment. Presented at Schizophrenia Research, 1998, Toronto, Ontario.

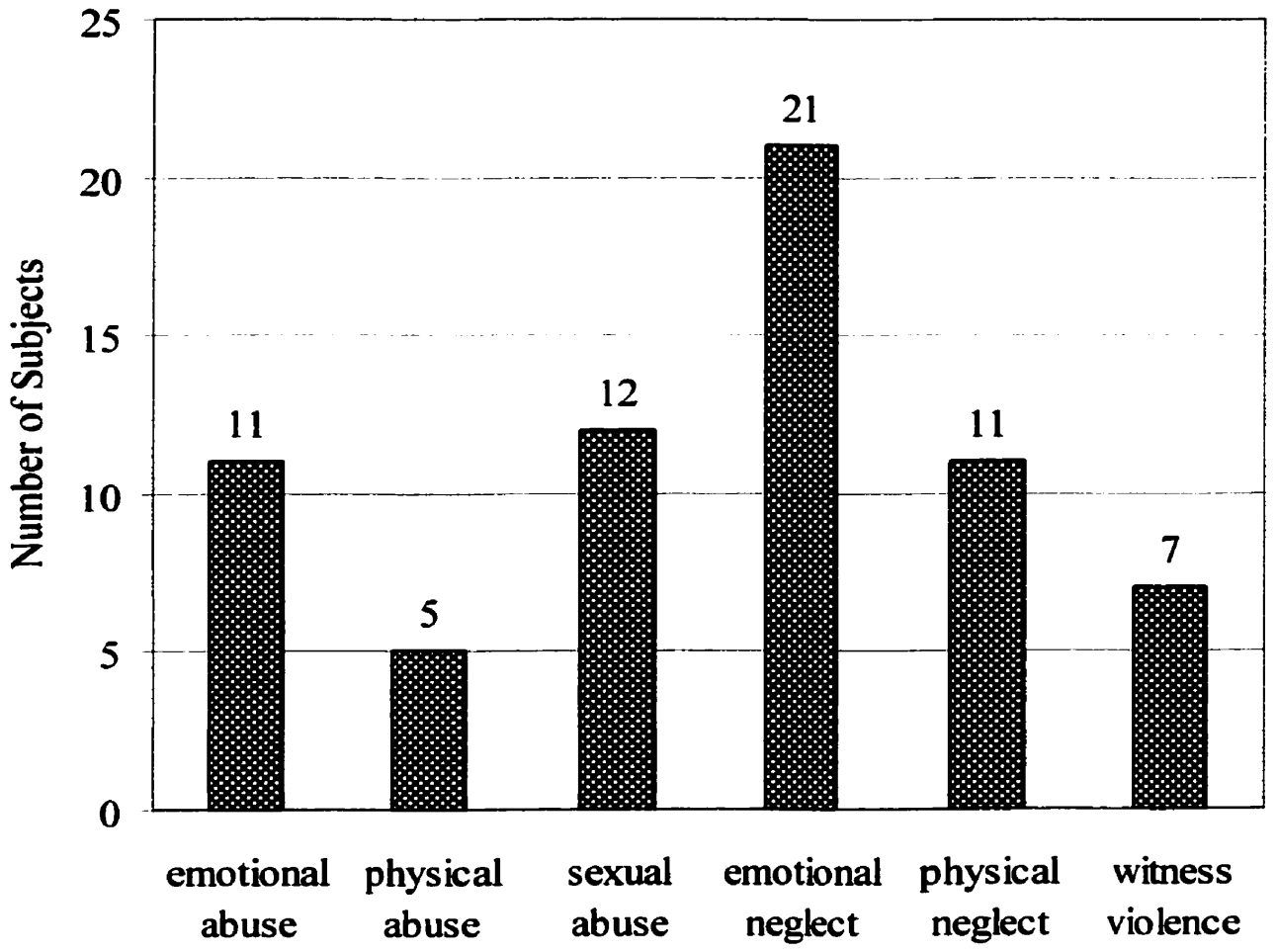

Figure 7. The frequency of reported childhood traumas in the sample.

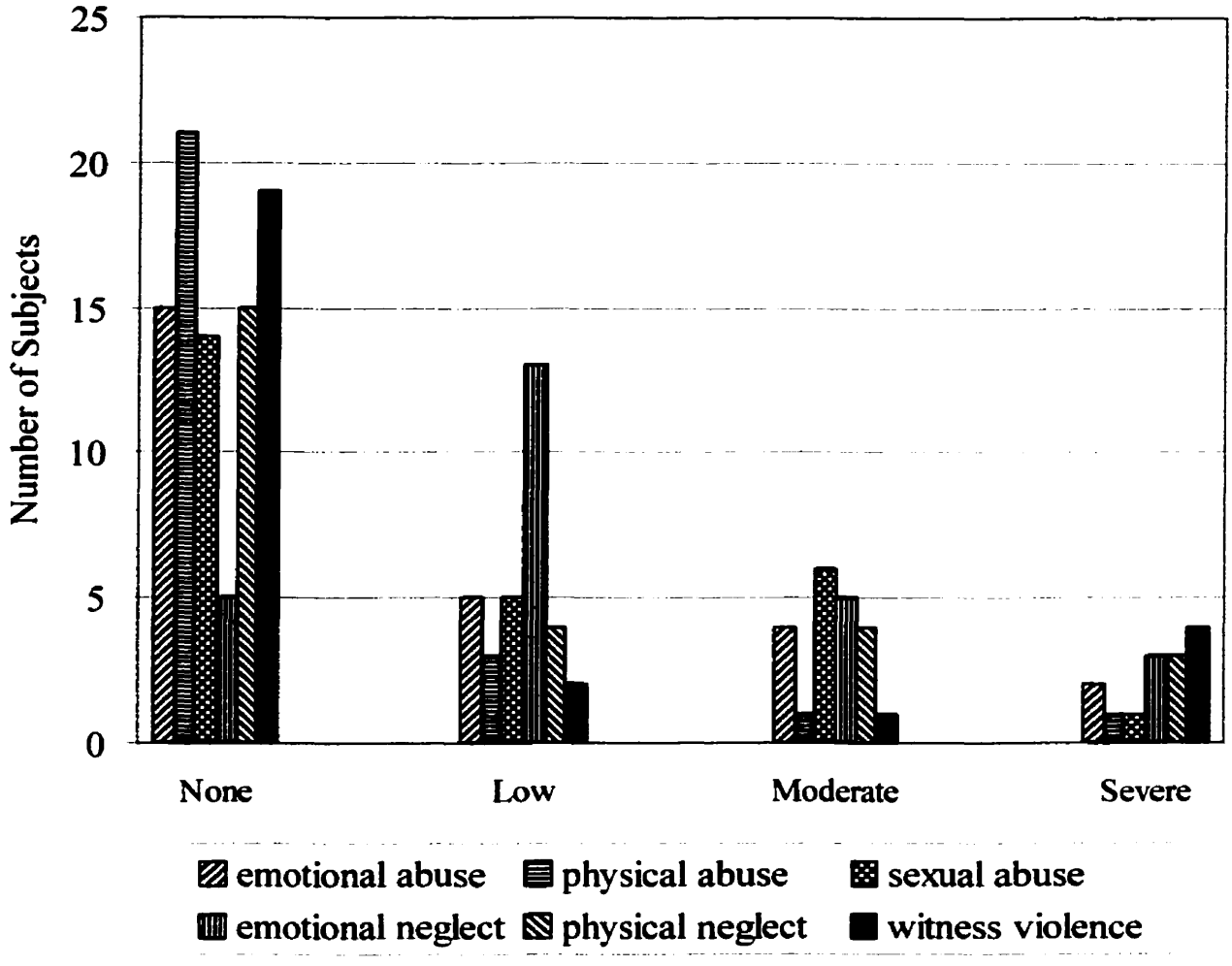

Figure 8. Reported severity levels for each of the childhood traumas examined in the sample.

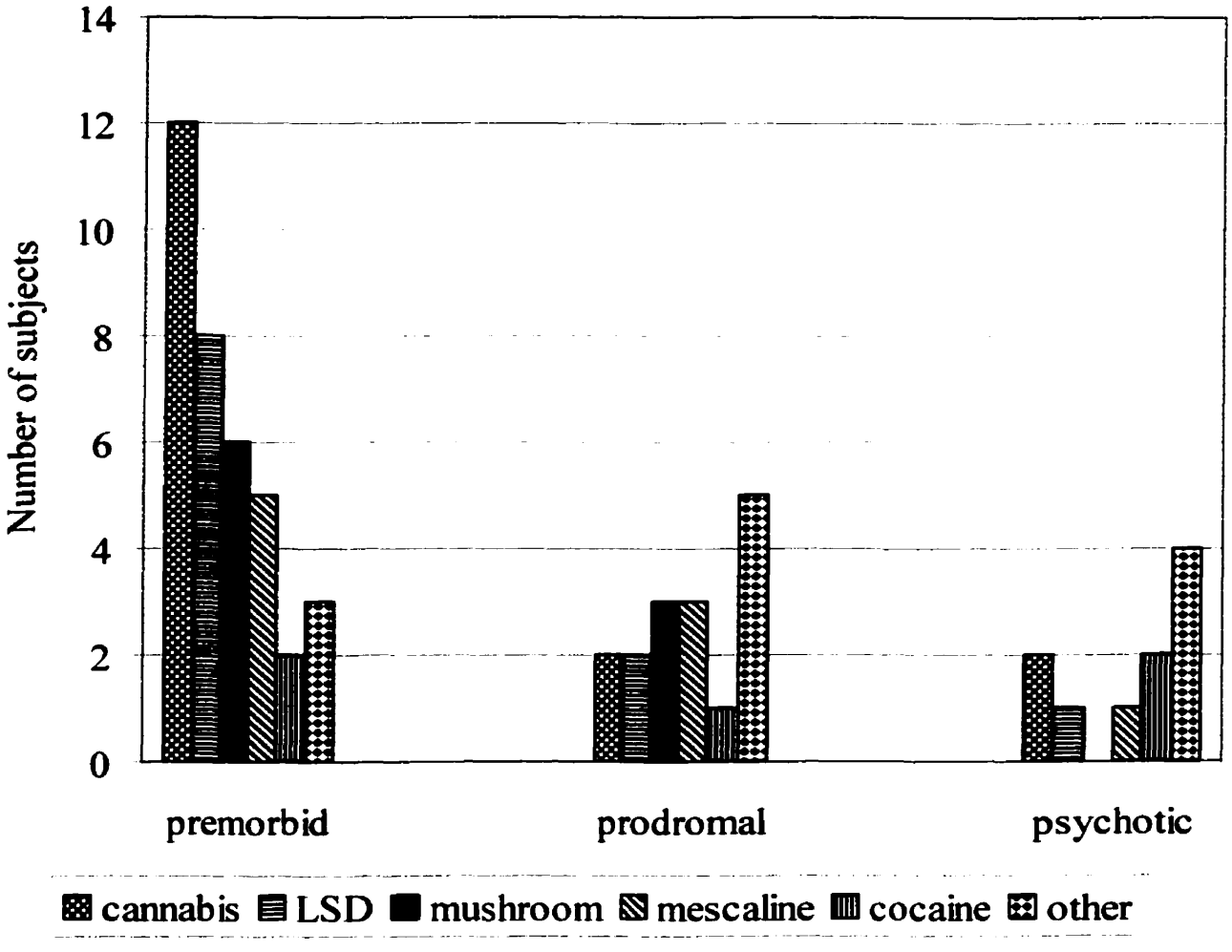

Figure 9. Pattern of substance use relative to evolution of schizophrenia illness.

Note. If prodrome onset and onset of psychosis occurred within a few months of each other (n=4), substances used for the first time during this period were considered only in the psychotic phase.

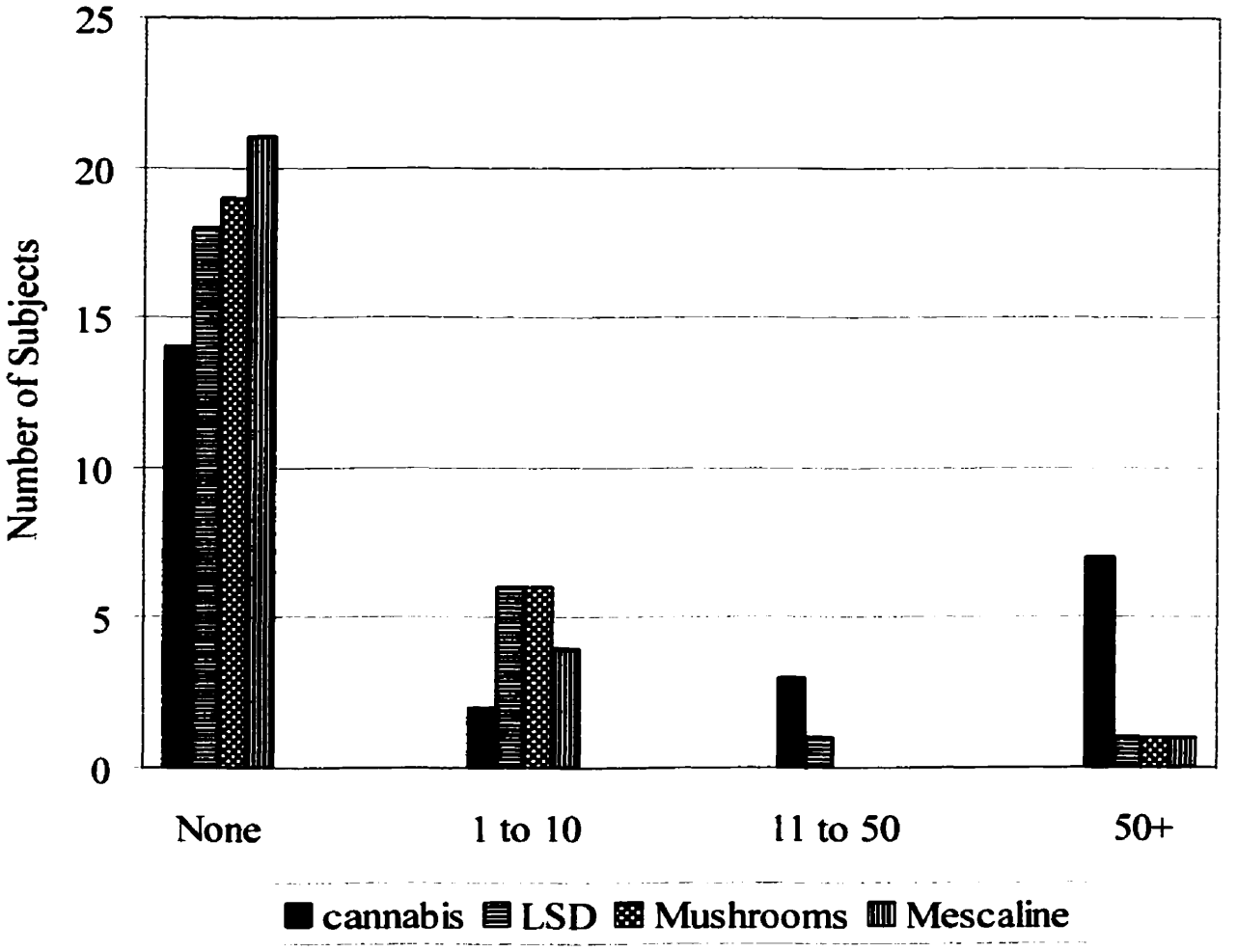

Figure 10. Reported number of occasions for premorbid substances used in the sample.

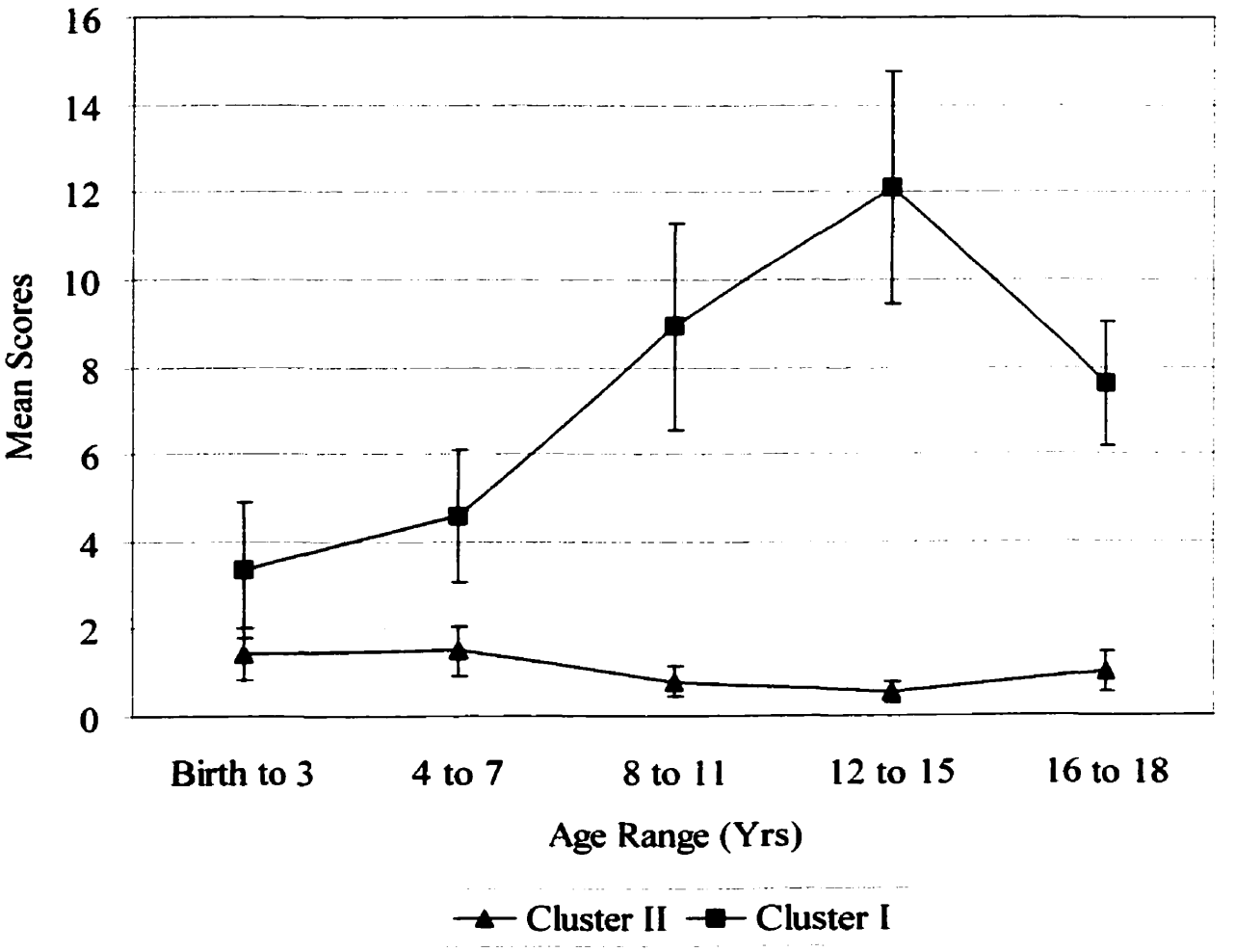

Figure 11. Mean severity of CBCL internalizing problems for Cluster I and II subjects.

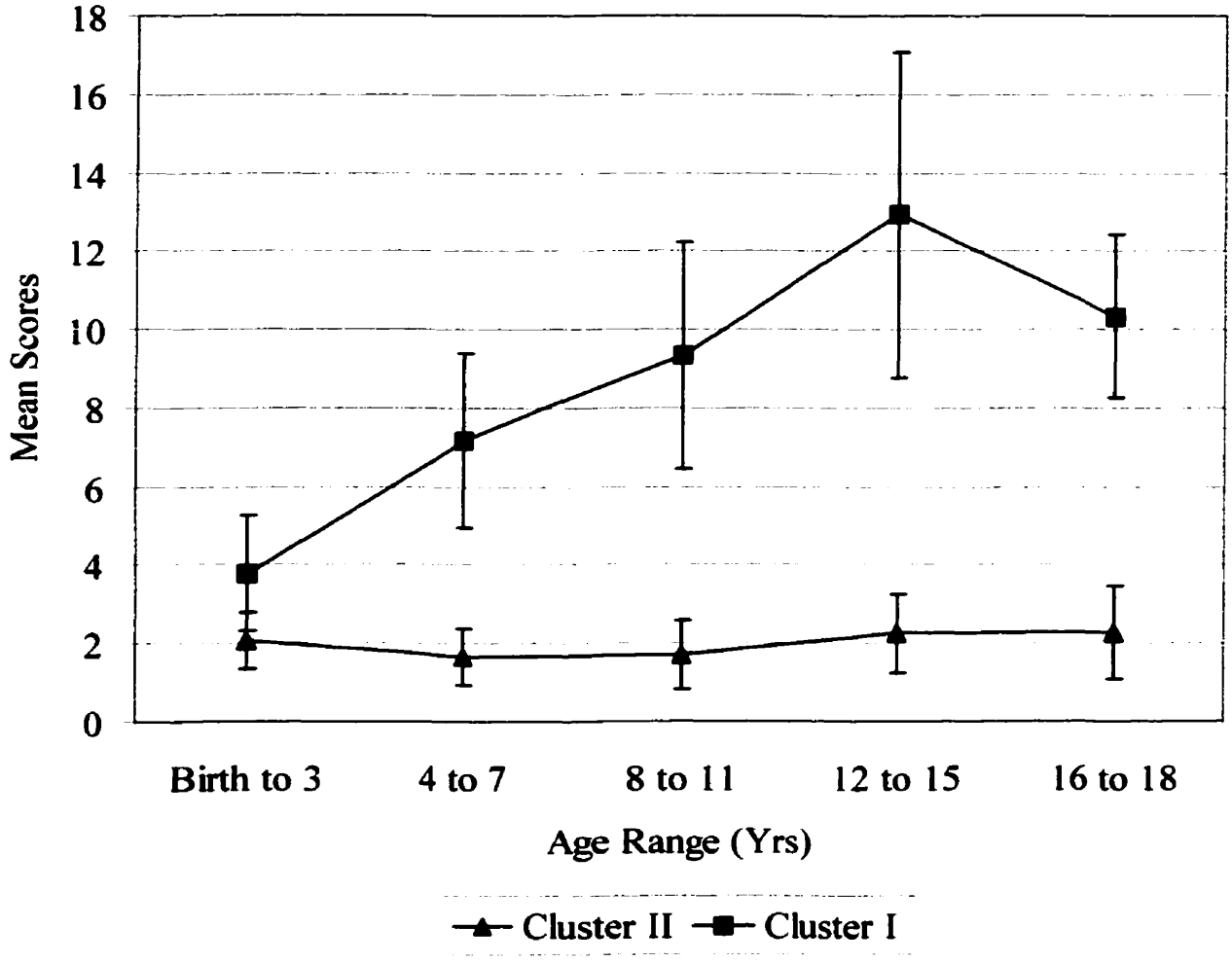

Figure 12. Mean severity of CBCL externalizing problems for Cluster I and II subjects.

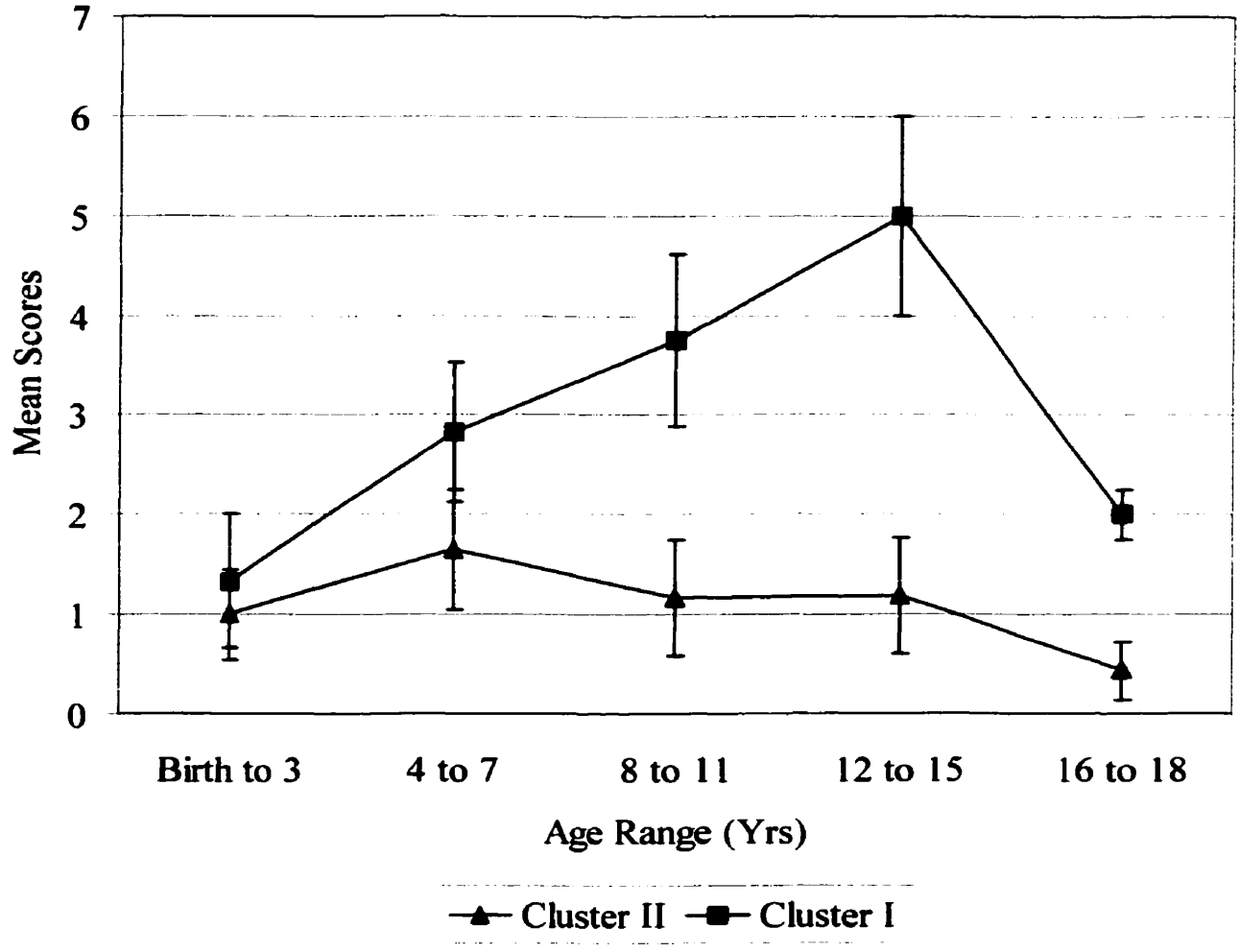

Figure 13. Mean severity of CBCL social problems for Cluster I and II subjects.

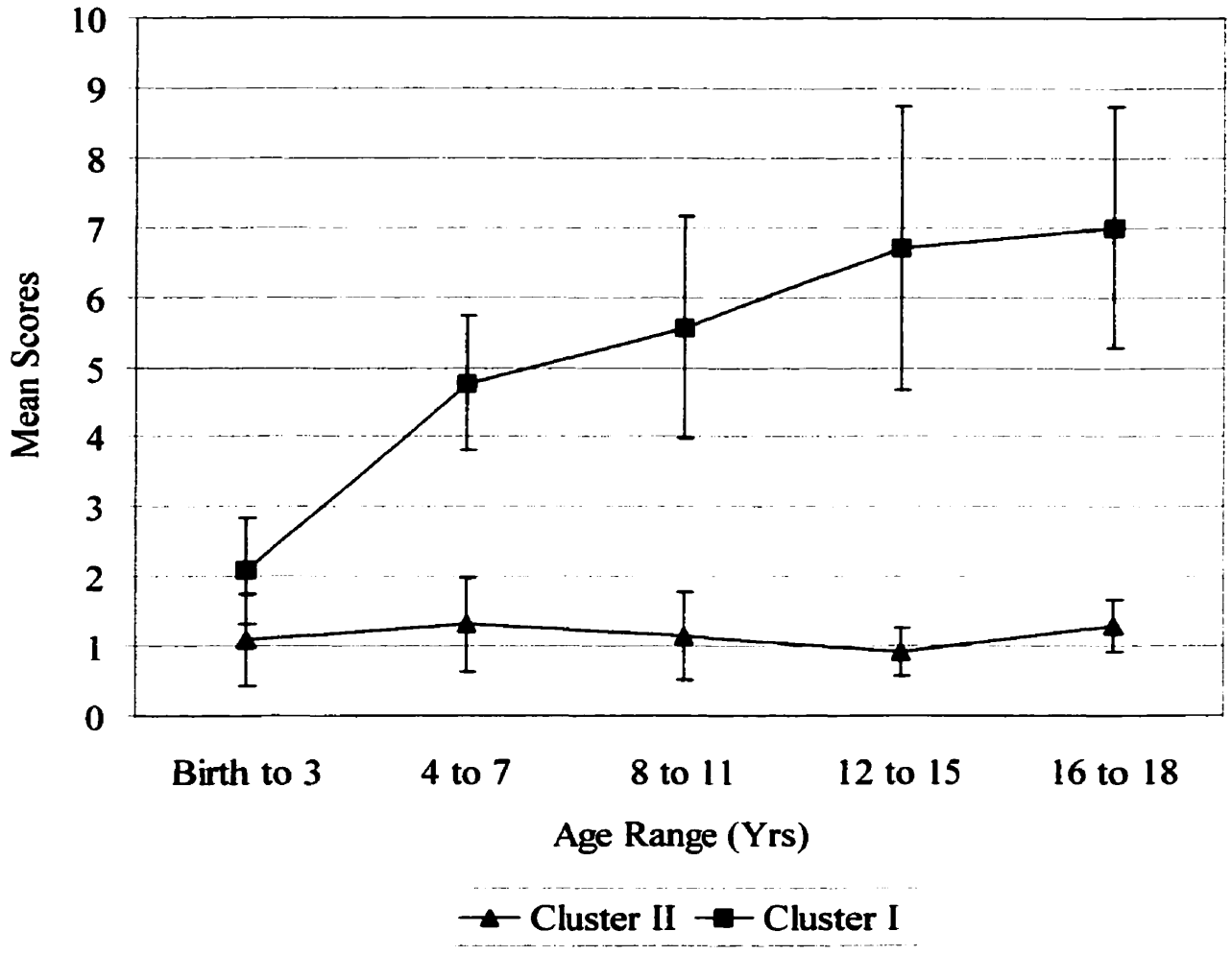

Figure 14. Mean severity of CBCL attention problems for Cluster I and II subjects.

Discussion

Study Objectives.

The present study has attempted to assess the contribution of childhood trauma reported and premorbid substance use to the heterogeneity of schizophrenia, with a specific interest in the good premorbid subtype, the subtype representing the majority of schizophrenia patients. While research has linked poor premorbid adjustment in schizophrenia to a family history for the disorder and obstetric complications, risk factors for schizophrenia associated with the good premorbid subtype remained unidentified. As such, the main objectives of the current study were to determine the patterns of association among reported childhood trauma, premorbid substance use, family history of schizophrenia, and obstetric complications in schizophrenia patients, and, secondly, to assess whether childhood trauma reported and premorbid substance use occur at a significantly higher rate in the good premorbid subtype.

Patterns of Association.

Both reported childhood trauma and premorbid substance use were not found to be significantly associated with each other, suggesting that they act independently of one another. Furthermore, neither a reported history of childhood trauma nor premorbid substance was significantly associated with obstetric insults, suggesting that such independent effects are not mediated by obstetric complications. Reported childhood trauma and premorbid substance use were, however, differentially associated with the family history variable. Reported childhood emotional neglect tended to be associated with a positive family history of schizophrenia. By contrast, premorbid LSD tended to be, and high premorbid cannabis use was significantly, more likely to occur in the absence of a family history of schizophrenia.

Verification of the Postnatal Hypothesis.

Results also provided partial support for our hypothesis that good premorbid adjustment would be associated with the presence of postnatal, rather than family history or obstetric, risk factors. With respect to the internalizing problem dimension, good premorbid adjustment was predicted by an absence of a family history of schizophrenia

and the presence of emotional abuse and neglect. With respect to externalizing problems, good premorbid adjustment was predicted by the presence of emotional abuse and an *absence* of sexual abuse. Good premorbid adjustment for social problem dimension was predicted by the *absence* of both a family history of schizophrenia and having witnessed domestic violence in childhood. Finally, good premorbid adjustment for the attention problem dimension was predicted by the *absence* of both obstetric complications and sexual abuse.

Saliency of Internalizing Behavior Dimension.

It is worthwhile to mention that, of the four CBCL behavior dimensions examined, our hypothesis stating that the presence of reported childhood trauma would predict a good premorbid profile, independent of a family history of schizophrenia and obstetric complications, was thoroughly supported for the internalizing problem dimension. The low number of internalizing problems in our good premorbid adjustment schizophrenia patients was associated with an absence of a family history of schizophrenia and the presence of emotional abuse and emotional neglect, whereas the greater number of internalizing problems among the Cluster I subjects was associated with a family history of schizophrenia in the absence of childhood trauma reported.

The internalizing problems scale was the behavior dimension for which we had the largest Chi square value (χ^2= 10.8, p= .01), explaining 46% of the variance (compared to between 22% and 27% of variance explained for the other dimensions). Thus, contrary to what we expected, the presence of reported childhood trauma does not always predict the good premorbid subtype, suggesting that a reported trauma history plays a complex relationship in premorbid adjustment. However, interestingly, it should be noted that the presence of reported emotional abuse and the absence of sexual abuse figure relatively prominently in the good premorbid subtype.

Assessment of Premorbid Behaviors.

Confidence in the assessment of premorbid behaviors, including those of reported childhood trauma and premorbid substance use, lay in its multiple measures for carefully estimating age at prodrome onset. The age at onset variables consisted of the "best

estimates" of the age at prodrome and psychotic onset for each subject using information derived from the prodromal interview conducted with the patient and from the CBCL conducted with the mothers, and in the case of subjects recruited from the Envirogen project, also from psychiatric medical charts, and past maternal and paternal Camberwell Family Interviews. In deriving premorbid behavioral scores, analyses were conducted which only included those data points prior to the estimated age for prodrome onset. For example, behavioral information that was collected during either the maternal or patient interviews which referred to an age period that coincided with the patient's estimated age at prodrome onset were not entered into any analyses. Therefore, since the earliest estimated age at prodrome onset occurred during the third age period, all data points for the 26 subjects for the first two age ranges were entered into analyses. Data points for the third, fourth, and fifth age ranges coincided with 4, 8, and 16 patients' estimated age at prodrome onset, respectively, and, consequently, were omitted from the analyses.

In contrast to Neumann et al.'s (1995) conceptualization of premorbid adjustment which did not take into account age at prodrome onset, our efforts to include only those data points occurring prior to the estimated age at prodrome onset resulted in the examination of purely premorbid behaviors. The isolation of truly premorbid behavior is an important topic that has been relatively neglected, especially in the substance use and schizophrenia research literature. Unless the prodrome has been precisely dated, there is no consistent method of determining which behaviors were definitively premorbid. Estimation of age at prodrome onset is particularly important when investigating the legitimacy of a risk factor for an illness. If a risk factor is present prior to prodrome onset, then the possibility exists that the factor is causally related to the illness. If, by contrast, the "risk" factor is only present *after* illness onset, then there is no possibility of a causal association.

Saliency of Premorbid Behavior Dimensions.

Despite the difference in methodology between Neumann et al.'s investigation and the present study, the findings of an early, severe and progressive developmental deviation in about half of schizophrenia patients and an absence of observable

developmental problems in the remaining patients attest to the saliency of premorbid behavioral patterns in pre-schizophrenic children.

The power of our model to predict premorbid adjustment for the internalizing dimension does not appear to be a chance finding, but is consistent with much of the earlier clinical and research literature on premorbid adjustment. Internalizing problems consist of behaviors, such as being withdrawn, suspicious, and depressed, and complaining of loneliness. Other studies have shown that these behaviors are prominent during the childhoods of many, but not all, schizophrenic subjects (Bower, Shellhamer, Daily, 1960; Kasanin & Veo, 1932; Warnken & Siess, 1965). This internalizing, asocial pattern of behavior was so often associated with later development of schizophrenia, that premorbid adjustment scales, including the PAAS and PAS, emphasize the assessment of these behavioral patterns. What is novel about the results of the current study is that a single model has succeeded in finding the putative etiological factors involved in both the subtype of schizophrenia patients with many premorbid internalizing problems--they appear to be cases of familial schizophrenia, and in the remaining cases, who, without an apparent genetic loading, were subjected to emotional abuse and neglect as children. In short, our results suggest that the internalizing dimension of premorbid adjustment may be the dimension with the greatest relevance to etiological subtypes.

Prevalence of Premorbid Behavior: High Premorbid Cannabis Use.

Premorbid substance use occurred in 46% (n=12) of our sample. Every patient with premorbid substance use had used cannabis at least once. Of the seven patients (27%) who used cannabis on more than 50 occasions, one patient reported using cannabis 80 times. one admitted to using it about 700 times; two reported its use on 1000 occasions; two, over 1500 times; and one reportedly used it 5000 times. Cannabis was, unmistakably, the most misused substance in our sample, confirming previous reports of the prevalence of its use (Segal & Stewart, 1995).

High Premorbid Cannabis Use: An Independent Risk Factor?

It cannot be denied that premorbid substance use may represent an underlying vulnerability to the illness that was so subtle that it could not be picked up by the

assessment of other premorbid behaviors–a theory known in the literature as the self-medication hypothesis stating that substance use in schizophrenia is the result of an attempt to self-medicate the onset of prodromal symptoms (Schneider & Siris, 1987). However, although our data are purely correlational, when taken together, many of our findings do not support the self-medication hypothesis, but indicate that some patients who are diagnosed with schizophrenia may actually have a non-genetic, drug-induced form of psychosis. First, our findings indicate that most substance use occurs for the first time during the premorbid period, before the onset of the measurable prodromal changes in thought, affect, and behavior. Secondly, the most commonly misused substances in the sample, notably cannabis, LSD, mushrooms, and mescaline, are psychotogenic drugs, drugs which are, in and of themselves, capable of inducing a temporary schizophreniform psychosis and which mimic the classical negative symptoms of schizophrenia, such as anhedonia and anergia, when chronically abused (Glass & Bowers, 1969), suggesting a clinical and physiological similarity between chronic psychotogenic substance use and the schizophrenic illness. Finally, the finding that all seven patients who reportedly used cannabis on more than 50 occasions prior to prodrome onset were actually family history negative for schizophrenia suggests that the development of schizophrenia in these patients was probably not attributable to a genetic predisposition for the illness. These findings, coupled with Andreasson et al.'s (1987) finding of a 6-fold increase in the relative risk for schizophrenia in individuals who consumed cannabis on over 50 occasions prior to illness onset, suggests the viability of premorbid cannabis use as an independent risk factor for schizophrenia psychosis. Furthermore, the cutoff of cannabis use on over 50 occasions seems to suggest a threshold effect for the risk of schizophrenia in vulnerable, non-genetically predisposed individuals.

Reported Childhood Trauma: Emotional Neglect & Physical Neglect.

In comparison to the relatively high rates of premorbid substance use in our schizophrenia sample, our patients also seemed to report relatively high rates of significant childhood trauma, defined as trauma reported at a moderate or severe level. Thirty-one percent (n=8) of patients reported moderate or severe levels of emotional

neglect and 27% (n=7) reported significant physical neglect. Our findings suggest a trend for a higher severity of emotional neglect in family history positive patients. While this result may suggest that the schizophrenia illness may be the product of both genetic and postnatal risk factors, it might be more plausible to conceive of trauma as an underlying factor of psychopathology, or perhaps an indicator of a latent etiological factor. In analyses not presented here, we found a significant association between paternal alcoholism and childhood physical abuse, physical neglect, and sexual abuse. Since there is evidence to suggest that alcoholism is related to development of schizophrenia in the offspring (Sham et al., 1994), the resulting schizophrenic illness in these patients may simply be related to a higher genetic loading for schizophrenia in these families. As a result, childhood trauma reported would not have any independent predictive value in schizophrenia but would be epiphenomenal to having a dysfunctional father. Further research is needed to clarify the role of reported childhood trauma in patients with a family history of schizophrenia.

Reported Sexual Abuse.

Twenty-seven percent (n=7) of our sample reported significant levels of sexual abuse. Contrary to the research literature which finds that reported childhood trauma is a predisposing factor to substance use (Brown & Wolfe, 1994; Triffleman et al., 1995), we did not find any significant association between reported sexual abuse and premorbid substance use. We did, however, find that patients who used substances premorbidly tended to have a *lower* severity of sexual abuse in childhood. This discrepancy might be attributable to a difference in the study populations: investigations into trauma-substance use relationships typically are conducted with severe clinical substance abuse populations, whereas our study consisted of a much less severe substance abuse sample, suggesting that it may be an artifact of the choice of sample population.

Reported Witnessing of Domestic Violence.

Nineteen percent (n=5) of our sample reported having witnessed moderate or severe levels of domestic violence. The saliency of the witnessing of domestic violence, although not perceived in the research literature as a traditional childhood trauma, was

noted in this study by patients themselves, who, in their own words, expressed its significance in their life. One high functioning female patient in our sample, who also had a significant obstetric insult, genuinely believed that the daily domestic disputes she witnessed between her mother and father, ranging from seeing her father try to throw her mother down a flight of stairs to seeing her father try to strangle her mother with a phone cord, caused the onset of her illness.

The severity of the witnessing of domestic violence variable was rated by objectively comparing details of the actual event to detailed examples of hypothetical events included in the CTI manual. An example of a low severity rating for witnessing domestic violence came from a male patient in our sample when he described how, on occasion, he would see his father hit his mother with his hand and how his mother would cry after the incidents. Another example, one with a severe rating, came from a male patient who, almost everyday of his childhood, would see his father beat his mother, brother, and sister with a belt. He noted that his mother was always very bruised, and he was fearful for his, and the family's, safety.

Domestic Violence During Pregnancy?

There is a growing body of literature associating significant trauma during pregnancy, especially during the third trimester of gestation, with an increased incidence of schizophrenia in the offspring (Huttunen,& Niskanen, 1978). The fact that some patients reported witnessing violence directed against their mother during childhood presents the possibility that this violence also existed during their mother's pregnancy with the patient, suggesting that domestic violence may operate as a prenatal and postnatal insult, further complicating efforts to disentangle potential prenatal and postnatal risk factors.

Veracity of Patient Reports.

The reports of childhood trauma by our subjects had a non-delusional quality. Patients approached questions with incredible lucidity, offering details of events whenever relevant. It was evident that, sometimes, patients just did not want to discuss very specific details, stating that it is best to leave the past behind them. Frequently,

distress in patients was noted after having discussed the childhood trauma, suggesting that the events had affected them profoundly. Furthermore, evidence suggests that false-negative reports (i.e., subject does not admit to trauma when it was present) are much more common than false-positive reports (i.e., subject admits to trauma when it was not present; Briere, 1992).

Reported Physical Abuse.

We found a relatively low rate of significant physical abuse in our sample. While studies indicate that between 34% and 53% of patients with severe mental illness report childhood physical trauma (Craine et al., 1988; Mueser et al.,1998), the prevalence rate for significant physical abuse in our sample was 8%. One US study cites the prevalence of childhood physical abuse at 11% in a community sample (Goodman et al., 1997), a percentage that seems to be, oddly enough, more representative of the prevalence of physical abuse in our schizophrenic sample.

Measuring Childhood Trauma.

It is important to note that the way childhood trauma is measured has a direct impact on the reported prevalence rates. Research indicates that the number and types of childhood trauma, which would be reflected in higher severity scores, has been found to be predictive of more severe symptomatology in psychiatric populations (Ellason & Ross, 1997; Mueser et al., 1998), suggesting the saliency of severe traumatic events in psychiatric patients. The distinction between a low and severe score of childhood trauma should be made, not only for descriptive purposes, but in order to assess the psychological impact of the event on the individual. One male patient in our sample who received a low severity rating for sexual abuse in childhood, who, incidentally, also had heavy premorbid drug use which may have been the main precipitating factor in his illness, reported that, when he was ten years old, his father would, on occasion, force him to look at Playboy magazines. Another male subject from our sample, one who received a severe rating for sexual abuse, and who also had a family history of schizophrenia, in addition to obstetric complications, reported that he was the victim of monthly incest over several years beginning at the age of five. The two examples denote two very different types of sexual

trauma and reflect two very different subjective perceptions of the event. While the first subject now reflects on the humor inherent in the Playboy incidents, the second subject has personally noted that the incident has, and continues to, taint his life completely, and he attributes the onset of his illness to the trauma of these incestuous events with his alcoholic grandfather. The latter subject is also an example of multiple prenatal and postnatal insults. Not surprisingly, he exhibited a Cluster I premorbid profile for all four CBCL dimensions examined.

The Premorbid Clusters.

Similar to prevalence rates for good premorbid adjustment schizophrenia in other studies (Kasanin & Veo, 1932; Neumann et al., 1995; Pollack et al., 1966; Torrey et al., 1994; Watt & Lubensky, 1976), we also found that about half of patients had a good premorbid adjustment profile. We found that patients with good and poor premorbid profiles also differed significantly with respect to severity of behavioral problems at a very early age (Kasanin & Veo, 1932; Neumann et al., 1995; Pollack et al., 1966; Torrey et al., 1994; Walker et al., 1996; Watt & Lubensky, 1976). For three out of the four CBCL scales examined in the current study, Cluster I and II subjects diverged from each other in their pattern of development at about 4 years of age, providing evidence for the findings for the presence of very early insults, such as obstetric complications or family history for the illness, in Cluster I patients.

In contrast to Neumann et al.'s (1995) study, where a subject's cluster designation was derived using cluster analysis and thus, any given subject retained the same cluster status across all behavior dimensions, the present study analyzed behavior status with respect to each behavior dimension and, as a result, cluster status was not necessarily constant across all dimensions. Since it is potentially more informative to know that a subject had a Cluster II premorbid profile for attention problems but a Cluster I profile for externalizing problems, than it is to know that a subject seemed to fit a Cluster I premorbid profile overall, analyzing cluster status separately for each behavior dimension may better reflect the individual pattern of premorbid behavioral problems. In addition, we found that subjects tended not retain the same cluster status between the internalizing

and externalizing, and internalizing and attention problem dimensions, suggesting salient differences among behavioral problems.

The importance of analyzing premorbid adjustment by behavioral dimension is illustrated by our findings suggesting that different risk factors for schizophrenia are associated with different types of premorbid adjustment. As confirmed in the research literature (Cannon et al., 1990; Neumann et al., 1995; Rosenbaum-Asarnow, 1991; Walker et al., 1996), we also found that a family history of schizophrenia and obstetric complications are associated with the Cluster I premorbid profile. Patients with a family history of schizophrenia were 4 times and 3.7 times more likely to have a Cluster I premorbid profile for internalizing and social problems, respectively, compared to patients with no family history for the disorder. With respect to externalizing and attention problems, patients with obstetric complications were 2.5 and 3.9 times, respectively, more likely to have a Cluster I profile than subjects with no obstetric complications. Of additional interest is the finding that, although a genetic loading for schizophrenia and obstetric complications both contribute significantly to a poor premorbid adjustment, only one risk factor tends to be associated with the Cluster I subtype at a time. In analyses not presented here, we found that a positive family history of schizophrenia was not associated with the presence of obstetric complications, suggesting that patients might have one risk factor or the other, but tend not to have both.

Since evidence suggests that poor premorbid adjustment is associated with early static neurodevelopmental insults, we hypothesized that good premorbid adjustment would be associated with a different quality and timing of insults, suggesting the possibility of progressive neurodevelopmental trauma, such as childhood trauma and premorbid substance use, in good premorbid schizophrenia. Despite suggestions that reported childhood trauma and premorbid substance use may be involved in schizophrenia, these postnatal risk factors did not consistently predict a good premorbid profile. Although premorbid substance use was inversely associated with a family history of schizophrenia, it was not associated with good premorbid schizophrenia for any of the behavior dimensions examined. Furthermore, the presence of reported childhood trauma

did not reliably predict a good premorbid profile for the CBCL dimensions, indicating a more complex relationship between reported trauma and premorbid adjustment in schizophrenia than expected. Inherent differences between the "soft" and "hard" childhood traumas and the saliency of sexual abuse in severe behavioral problems may explain why both emotional abuse and emotional neglect were associated with good premorbid adjustment, whereas sexual abuse and the witnessing of domestic violence were related to the poor premorbid subtype.

Social Problems.

The present study was unable to account for postnatal risk factors involved in good premorbid adjustment schizophrenia for the social problem and attention problem dimensions. The vast majority of our subjects had a good premorbid profile for social problems. This may be an artifact of the study sample, since those patients who had more social problems would have declined consent to participate. Despite this shortcoming, we found that poor premorbid adjustment for social problems was associated with a family history of schizophrenia and the witnessing of domestic violence, suggesting that a genetic insult combined with exposure to violent and socially inappropriate behavior may result in a child who has difficulty initiating and maintaining normal relationships.

Attention Problems.

Attention problems in childhood are particularly striking in schizophrenia--50% in our sample had poor premorbid adjustment for attention problems--and present an early (i.e., 4 years of age), severe and progressive developmental deviation. While this study was unable to posit the risk factors involved in the good premorbid subtype, we found that attention problems in the poor premorbid subtype was associated with the presence of both obstetric complications and childhood sexual abuse. Perhaps, the obstetric insult is the primary risk factor in attention problems, producing the very early and severe deviation, after which, childhood sexual abuse further intensifies the problem.

Postnatal Risk Factors?

Our findings suggest that reported childhood trauma and premorbid substance use may moderate an increasing vulnerability to schizophrenia, independent of genetic and

obstetric insults. Seven subjects (27% of the sample) did not have either a family history of schizophrenia or obstetric complications. Of these subjects, five had reported significant childhood trauma or premorbid substance use: one subject, a female patient with no identified family history of schizophrenia or obstetric complications, had suffered severe sexual abuse at the hands of an adult boyfriend when she was a minor; a male subject reported severe emotional neglect in childhood; a female patient reported significant emotional abuse; finally, two male subjects reported large amounts of premorbid substance use, including a high level of premorbid cannabis use.

Two subjects, however, remained unidentified with respect to the risk factors examined in the current study. Etiology in these patients, however, may be explained in terms of risk factors for schizophrenia which were not assessed here. One of these subjects is suspected of having a schizotypal first degree relative (i.e., had a genetic loading for the illness that was not identified with our methodology), while the other subject has a winter season of birth, suggestive of a static neurodevelopmental insult.

Limitations

Unidentified Etiology.

The possibility of unidentified etiology occurs for at least three reasons. First, error in measurement is always a possibility. Recollecting obstetric complication information may be difficult, particularly when two or three decades have since elapsed. Identifying mental illness in distant relatives may also be rather challenging, especially when one might have seen them only a few times in their life. A second possible reason for the inability to identify risk factors in all subjects may lie in our rather crude measurement of genetic vulnerability to schizophrenia. While there is evidence for familial psychiatric morbidity in schizophrenia, research also suggests that depression and alcoholism figure prominently in families of schizophrenia patients (Sham et al., 1994). By restricting our assessment of genetic vulnerability to a dichotomous measure of family history of schizophrenia, much important genetic information may have been omitted. Finally, all known risk factors for schizophrenia could not be assessed in our analyses which may have resulted in the omission of relevant etiological factors in certain subjects.

Other Methodological Concerns.

Our ability to fully comprehend the role of reported childhood trauma and premorbid substance use was severely restricted by the study's small sample size, which limited statistical power and contributed to an inability to thoroughly examine the co-occurrence and interaction effects among the genetic, prenatal, and postnatal environmental risk factors. However, despite the sample size problem, the primary purpose of this study was to serve as pilot research from which to launch a larger, more comprehensive project.

The current study was based on a convenience sample of young, stabilized schizophrenia outpatients living with their families, which might be argued to be over-representative of patients in the high-functioning spectrum. In spite of the convenience sampling, which would potentially limit generalizability of findings, the rates for reported childhood trauma and the premorbid adjustment subtypes were comparable to findings published from more representative samples. It should be mentioned, however, that while our rates of reported childhood trauma resemble those published in the research literature, our study did not contain a control group, and, as such, it is difficult to determine whether our schizophrenia patients were exposed to more severe childhood trauma and substance use than matched controls in the general population.

One potentially significant methodological issue is the fact that the study relied heavily on maternal and patient recall as the primary source of information. Memory is fallible, especially for events that happened many years in the past, and is always a concern. A number of measures were incorporated into the study in order to counter this potential limitation. Regarding recall for obstetric data, only information about relatively severe obstetric complications was collected. Confidence in maternal recall of obstetric information is partly based on the saliency of the severity of pregnancy and birth complications and the on consultation of medical birth records, whenever possible.

With respect to maternal recall of patients' premorbid development, it was felt that if there was any bias for the memories of childhood development concerning a child

who has since become schizophrenic, the bias should be relatively consistent throughout the sample reports, since all children had since developed the illness. In addition, mothers who invested time in the study consistently reported doing so, not for monetary compensation, but out of genuine interest to better understand what happened to their child. As a result, it is felt that biases were kept to a minimum.

Finally, patients were asked about the timing and frequency of substance use. In an attempt to facilitate recall, tables with the names of potentially abused substances were used. However, in most cases, it was felt that patients were genuinely interested in talking about their substance use and seemed to remember which substances were abused, when they were abused, and the frequency of abuse without confusion.

Implications

It has long been speculated that schizophrenia comprises many different illness subtypes. Although a single patho-physiologic process, or even a two-factor model (Kinney, Levy, Yurgelun-Todd, Tramer, & Holtzman, 1998), may be posited to account for the variability associated with the illness (Carpenter & Buchanan, 1994), it is more plausible to suspect that schizophrenia comprises several distinct etiological processes, each with its own clinical presentations that might be manifest in early childhood, years before illness onset. Although the genetic component in schizophrenia is indisputable, heredity cannot account for all cases of the illness. Non-genetic, environmental insults have been posited to explain the remaining cases of schizophrenia. The present study highlights the importance of examining both genetic and environmental factors, in particular postnatal risk factors, within the same sample of schizophrenia patients.

Ultimately, the goal in elucidating the risk factors involved in schizophrenia is the identification of etiologically distinct categories of illness that can be effectively treated. Post-traumatic stress disorder (PTSD), which is likely to occur after severe childhood trauma, can accompany schizophrenia (Putten & Emory, 1973), or, even, masquerade as the illness (Butler, Mueser, Sprock, & Braff, 1996), presenting at least two heterogeneous subgroups within the schizophrenia illness itself. Waldfogel and Mueser (1988) describe the case study of a 31 year old veteran who presented with paranoid delusions and

auditory hallucinations. Although the subject met the DSM-III-R criteria for schizophrenia, he was unresponsive to neuroleptics. After a period of 12 years, it became clear that a sexual assault precipitated his first psychotic episode, a diagnosis of PTSD was made, a psychotherapeutic intervention was initiated, and, after three days of imaginal exposure, he was discharged without medication. At 16-month follow-up, he remained free of psychotic and PTSD symptomatology, suggesting that the subject's "true" diagnosis was PTSD and not schizophrenia. This case has important clinical implications for the differential diagnosis in schizophrenia and the etiological heterogeneity involved in the illness, particularly in light of research indicating that 20% to 40% of schizophrenia patients prove resistant to antipsychotic medication (Schultz & Buckley, 1995), many of them from the earliest stages of illness (Johnstone, McMillian, Frith, Benn, & Crow, 1990), suggesting the possibility of myriad etiologically distinct subgroups contained under this one classification alone. Our findings reflect on the question of how schizophrenia could still be the same illness with respect to whether it was precipitated by substance use or a traumatic event.

Despite the complex relationships between family history and obstetric insults, and reported childhood trauma and premorbid substance use in premorbid adjustment, our findings emphasize the saliency of postnatal risk factors in the schizophrenia illness and highlight the importance of examining both the early, static and the postnatal, dynamic influences in the development of the illness.

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Appendix A: FIGS Screening Questionnaire & DIGS Psychosis Checklist

French versions available upon request from Dr. Suzanne King

FIGS: GENERAL SCREENING QUESTIONS

INTERVIEW DATE (dd/mm/yy): _____ INTERVIEWER'S NAME: _____

ID: _____ Subject's Name: _____

Informant Name: _____ EE94/SIBS96: R1 R2

Note all positive responses to screening questions on the pedigree.

Was anyone adopted?

Was anyone mentally retarded?

Did anyone:

Have problems with their nerves or emotions? Take medicine or see a doctor for it? Take lithium?

Feel very low for a couple of weeks or more, or have a diagnosis of depression?

Attempt or complete suicide?

Seem overexcited (or manic) day and night, or have a diagnosis of mania?

Have visions, hear voices, or have beliefs that seem strange or unreal?

Have unusual or bizarre behaviour, or have a diagnosis of schizophrenia?

Have trouble with the police, with completing school, or with keeping a job?

Have alcohol or drug use that caused problems (with health, family, job, or police)? Go to AA or NA, or have treatment for this?

(Was anyone) hospitalized for psychiatric problems, or for drug or alcohol problems?

Have inherited medical diseases such as Huntington's disease or seizure disorder or any other disorders of the brain or nervous system?

<u>For Schizophrenia Centres only</u>:

(Did anyone) have few friends, or seem to be a loner?

(Did anyone) seem odd or eccentric in behaviour or appearance?

(Was anyone) extremely jealous, or suspicious, or believe in magic, or see special meaning in things that no one else saw?

FIGS CHECKLIST "C"

Interview Date (dd/mm/yy): _____ Interviewer's Name: _____
ID: _____
Subject's Name: _____ Informant's Name: _____

Person Being Described: _____
Relationship to Subject: _____

1. What were his/her unusual beliefs or experiences? (Describe)

Did he/she ever . . .

1.a) believe people were following him/her, or that someone was trying to hurt or poison him/her?

1.b) believe someone was reading his/her mind?

1.c) believe he/she was under the control of some outside person or power or force?

1.d) believe his/her thoughts were broadcast, or that an outside force took away his/her thoughts or put thoughts into his/her head?

1.e) have any other strange or unusual beliefs?
(If YES, describe:)

1.f) see things that were not really there?

1.g) hear voices or other sounds that were not real?
(If YES, describe:)

1.g.1) (Code YES if: voice with content having no relation to depression or elation, or voice keeping up running commentary on subject's behavior or thoughts, or two or more voices conversing.)

1.h) speak in a way that was difficult to make sense of?
(If YES, describe:)

1.i) seem to be physically stuck in one position, or move around excitedly without any purpose?

1.j) appear to have no emotions, or inappropriate emotions?

2. How long did the <u>longest</u> of these experiences last? (weeks)

INTERVIEWER: If less than 1 week (unless successfully treated), STOP HERE. Otherwise continue, if informant is knowledgeable about this person.

FIGS CHECKLIST "C" - PAGE 2

INTERVIEWER: If subject did NOT have any episode of Major Depression or Mania (by FIGS checklists from this informant), skip to question 6.

3 When any (SX above) happened, did he/she also have the mood disturbance we discussed before, at the same time? (If answer is "NO" skip to question 6)

INTERVIEWER: For the rest of this checklist, "illness duration" refers to total time of illness, including active and prodromal and/or residual symptoms and/or treatment.

4. (Probe and code YES if mania and/or depression lasted at least 30% of total duration of illness described above, or medication for it.)

5. (Probe and code YES if illness described above, or medication for it, was ever present for as long as one week, without depression and/or mania.)

5.a) (Code YES if the above was true for as long as two weeks.)

6. Describe professional treatment (Circle all that apply):

0 = None
1 = Inpatient
2 = Outpatient
3 = ECT
4 = Medication
U = Unknown

(Describe details and/or other treatment): _____

7. Age of onset: _____

8. Number of episodes (01 if chronic symptoms and/or treatment since onset): _____

9. Total illness duration (all episodes, includes active (weeks) and prodromal and/or residual symptoms and/or treatment). _____

10. Rata Impairment or Incapacitation (Circle one):

0 = None
1 = Impaired
2 = Incapacitated
U = Unknown

11. Interviewer judgment on reliability of this information:
1 = Good 2 = Fair 3 = Poor

INTERVIEWER: If informant apparently does not know subject well enough to give information on Prodromal/Residual symptoms. STOP HERE

BIPOLAR CENTRES ONLY: If duration criterion for DSM III-2 Schizophrenia, Chronic Type, already met (Item 9, Total illness duration > 2 years), STOP HERE.

Appendix B: Kinney Medical and Obstetric History Questionnaire

French version available upon request from Dr. Suzanne King

ID: _____ **Name of Respondent:** _____ **Date:** _____ **Interviewer:** _____

EE94/SIBS96 : **R1** **R2**

MEDICAL AND OBSTETRICAL HISTORY QUESTIONNAIRE

Please describe the history for <u>each</u> child. Your responses will be treated confidentially. Thank you very much for your help!

PART A - PREGNANCY, BIRTH, AND GYNECOLOGIC HISTORY

1. Please give information for each child, as best you can recall, starting with your first-born:

Birth date	Child's first name	Birth weight	Length of Labor	Full term?	If early or late, by how many weeks?

2. Please indicate which of the following conditions or complications you had during any of your pregnancies or deliveries; please give name of child or children in whose pregnancy the condition or complication occurred and note which months of pregnancy were affected and details, as best you can recall.

PREGNANCY CONDITIONS	YES	NO	WHICH CHILD (REN)'S PREGNANCY	WHICH MONTHS	EXPLANATION/ DETAILS
Nausea or vomiting?	__	__	_____	_____	_____
Weight loss or unusual gain?	__	__	_____	_____	_____
Diet pills?	__	__	_____	_____	_____
Anemia?	__	__	_____	_____	_____
Diabetes?	__	__	_____	_____	_____
Flu?	__	__	_____	_____	_____
Rubella?	__	__	_____	_____	_____
Other infections?	__	__	_____	_____	_____
(Please describe) _____					
High fever?	__	__	_____	_____	_____
Vaginal bleeding or spotting?	__	__	_____	_____	_____
High blood pressure?	__	__	_____	_____	_____
Asthma attack?	__	__	_____	_____	_____
Swelling of hands or feet?	__	__	_____	_____	_____
Toxemia or pre-eclampsia?	__	__	_____	_____	_____

PREGNANCY CONDITIONS	YES	NO	WHICH CHILD (REN)'S PREGNANCY	WHICH MONTHS	EXPLANATION/ DETAILS
Convulsions or seizures?	__	__	_____	_____	_____
Rh problems?	__	__	_____	_____	_____
Cigarette smoking?	__	__	_____	_____	_____
Alcohol consumption?	__	__	_____	_____	_____
Hospitalized for any reason?	__	__	_____	_____	_____
Other illnesses or problems in Pregnancy? (Please describe):	__	__	_____	_____	_____

LABOR AND DELIVERY CONDITIONS

	YES	NO	WHICH CHILD (REN)'S PREGNANCY	EXPLANATION/ DETAILS
Low forceps delivery?	__	__	_____	_____
Mid or high forceps?	__	__	_____	_____
Vacuum extraction?	__	__	_____	_____
Ceasarian section (emergency?)	__	__	_____	_____
General anesthesia (were you unconscious for any part of labor or delivery?)	__	__	_____	_____
Epidural?	__	__	_____	_____
Breech delivery?	__	__	_____	_____
Were medications used to stimulate labor?	__	__	_____	_____
Was labor held back (e.g., because doctor was late)?	__	__	_____	_____
Tearing of birth canal (other than episiotomy)?	__	__	_____	_____
Rupture of membranes/bag of waters before labor began? (If so, how long before?) _____	__	__	_____	_____
Amniotic fluid NOT clear when water broke?	__	__	_____	_____
Bleeding while still in labor?	__	__	_____	_____
Hemorrhage/unusual blood loss after delivery?	__	__	_____	_____
Complications of cord (e.g., knotted, prolapsed, or wrapped around neck)?	__	__	_____	_____

LABOR AND DELIVERY CONDITIONS

	YES	NO	WHICH CHILD (REN)'S PREGNANCY	EXPLANATION/ DETAILS
Placenta previa?	___	___	_____	_____
Other placental complications?	___	___	_____	_____
Abnormal infant heartbeat during labor?	___	___	_____	_____
Breathing problems for baby?	___	___	_____	_____
Other problems with labor or delivery?	___	___	_____	_____

Please describe:_____

3. Please describe and give year of any reproductive system illness or problems (e.g., miscarriages, operations, or infections involving ovaries, Fallopian tubes, or uterus).

4. Studies indicate that most women take severl types of prescription or non-prescription ("over-the-counter") medications or drugs while pregnant. Please list any medications or drugs you took while pregnant, even non-prescription ones or those not considered a "medicine" (such as aspirin, hay-fever medicine, or pills for appetite-control, nausea or infection, or vitamins). If you do not recall a drug's name, give the reason you took it.

Drug or Medication	Which pregnancy? (Name of child)	When it was taken (for example, "1st mo." or "6-9 mo.")

PART B. EVENTS DURING PREGNANCY, BIRTH AND INFANCY OF EACH CHILD

1. Please describe any situations or events that were emotionally upsetting or psychologically stressful for you during any pregnancy (for example, spouse's serious illness; financial worries; or interpersonal conflicts with a relative, co-worker, or neighbor, etc.): (Only other children, SLEDS will cover with subject).

Event or situation	Pregnancy (child's name)?	Months of that pregnancy

2. Please describe any situations or events that were stressful or upsetting for you during labor, delivery, or during the child's first year.(all children)

Event or situation	Which labor or delivery? (Name of child)

Event or situation	Infancy of which child?

PART C. CHILDREN'S HEALTH AND DEVELOPMENT HISTORY

Please indicate which of the following conditions have occurred in any of your children at any time since birth. For each condition that has occurred, please give the first name of each child affected and the child's ages at the time affected with a particular condition.

NEWBORN/CHILD CONDITIONS	YES	NO	CHILD(REN) AFFECTED	WHAT AGE(S) (please state if age is in weeks, months, or years)	DETAILS
Did baby require incubator or intensive care in nursery?	___	___	_____	_____	_____
Newborn had trouble breathing?	___	___	_____	_____	_____
Newborn had infection or fever?	___	___	_____	_____	_____
Newborn had jaundice?	___	___	_____	_____	_____
Newborn had forceps marks?	___	___	_____	_____	_____
Newborn had birth defects?	___	___	_____	_____	_____
Please describe: _____					
At any time since birth:					
Concussion or head injury?	___	___	_____	_____	_____
Any loss of consciousnes?____					
If so, for how long? _____					
Brain infections, encephalitis or meningitis?	___	___	_____	_____	_____
Toxic effects of drugs or poison?	___	___	_____	_____	_____
Seizures, convulsions, or other neurological problems?	___	___	_____	_____	_____
High fever with delirium or coma?	___	___	_____	_____	_____
Did any of your babies stay in the	___	___	_____	_____	_____

hospital after they were born and you had gone home?					
Any other hospitalizations for any of your children?	___	___	_____	_____	_____
Were any of your children:					
Delayed in walking or talking?	___	___	_____	_____	_____
Thought to be hyperactive by you or other people?	___	___	_____	_____	_____
On medications for a behavior problem before age 15?	___	___	_____	_____	_____
In special classes or repeated grade in elementary school?	___	___	_____	_____	_____

Appendix C: Childhood Behavior Checklist

French version available upon request from Dr. Suzanne King

CHILD BEHAVIOR CHECKLIST

ID: _____ Name of Respondent: _____

Date of Interview (dd/mm/yy): _____ Name of Interviewer: _____

Subject Name: _____ EE94/SIBS96: R1 R2

This childhood behavior checklist is to be completed regarding only _____ (subject name) and not regarding any of his/her siblings that are also participants in the study. For each question please place an "X" in the row (0, 1 or 2) that best applies for each age period.

Example: ***Child A usually slept less than other children until he/she was 3 years old. For the 4-7 age period, Child A slept less than other children for part of this age period, but this sleep pattern was not present during the entire 4-7 age period. From the age of 8 onwards, Child A did not sleep less than other children.***

	Age in Years				
	0 - 3	4 - 7	8 - 11	12 - 15	16 - 18
Slept less than other children					
0 - Not True (as far as you know)			X	X	X
1 - Somewhat or Sometimes True		X			
2 - Very True or Often True	X				

If you have any questions, feel free to call Helen Cunningham or Frances Champagne at (514)761-6131 ext.24349. Thank you very much for your help!

For each age period, place an "X" in the row with the description that best applies to _____.

	Age in Years				
	0 - 3	4 - 7	8 - 11	12 - 15	16 - 18
1. Problems with nursing, feeding, or appetite					
0 - Not True (as far as you know)					
1 - Somewhat or Sometimes True					
2 - Very True or Often True					
2. Resistant to affection					
0 - Not True (as far as you know)					
1 - Somewhat or Sometimes True					
2 - Very True or Often True					
3. Slept more than other children during the day and/or night					
0 - Not True (as far as you know)					
1 - Somewhat or Sometimes True					
2 - Very True or Often True					
4. Slept less than other children					
0 - Not True (as far as you know)					
1 - Somewhat or Sometimes True					
2 - Very True or Often True					
5. Talked or Walked in Sleep					
0 - Not True (as far as you know)					
1 - Somewhat or Sometimes True					
2 - Very True or Often True					

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

6. Nightmares
   - 0 - Not True (as far as you know) _____
   - 1 - Somewhat or Sometimes True _____
   - 2 - Very True or Often True _____

7. Headbanging
   - 0 - Not True (as far as you know) _____
   - 1 - Somewhat or Sometimes True _____
   - 2 - Very True or Often True _____

8. Felt Dizzy
   - 0 - Not True (as far as you know) _____
   - 1 - Somewhat or Sometimes True _____
   - 2 - Very True or Often True _____

9. Cried more than others
   - 0 - Not True (as far as you know) _____
   - 1 - Somewhat or Sometimes True _____
   - 2 - Very True or Often True _____

10. Cried less than others
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

11. Poorer physical coordination than others
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

12. Better physical coordination than others
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

13. Speech abnormalities (e.g., made up own words, had difficulty pronouncing words, stuttered)
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

14. Activity level higher than others
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

15. Activity level lower than others
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

16. Feared certain animals, situations, or places (other than school)
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

17. Feared going to school
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

18. Acted too young for his/her age
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

19. Suspicious of or feared other people
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

20. Sensitive to loud noises
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

21. Imagination better than others
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

22. Imagination poorer than others
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

23. Unusual fascination with object or toy
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

24. Rocked, or had other repetitious body movements
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

25. Nervous movements; twitching
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

Age in Years

0 - 3 | 4 - 7 | 8 - 11 | 12 - 15 | 16 - 18

26. Self-injurious behaviours (e.g., pulling hair out, scratching self)
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

27. Suicidal attempts
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

28. Difficulties with concentration/attention
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

29. Temper tantrums or hot-tempered
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

30. Wet self during the day
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

31. Wet the bed at night (Enuresis)
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

32. Constipated; did not move bowels
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

33. Had bowel movements outside toilet
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

34. Had aches or pains (not headaches) without known medical cause
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

35. Had headaches without known medical cause
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

36. Had nausea without known medical cause
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

37. Had problems with eyes without known medical cause
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
      (Describe _____)
    - 2 - Very True or Often True _____
      (Describe _____)

38. Had rashes or other skin problems without known medical cause
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

39. Had stomach aches or cramps without known medical cause
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

40. Vomited without known medical cause
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

41. Bragged/boasted
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

42. Showed-off/clowned
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

43. Could not get his/her mind off certain thoughts; obsessions
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
      (Describe _____)
    - 2 - Very True or Often True _____
      (Describe _____)

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

44. Repeated certain acts over and over; compulsions
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
      (Describe _____)
    - 2 - Very True or Often True _____
      (Describe _____)

45. Could not sit still; restless; hyperactive
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

46. Dependent (e.g., clinged to adults; liked to have things done for him/her; little autonomy)
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

47. Complained of loneliness
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

48. Not liked by other children
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

49. Shy/timid
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

50. Liked to be alone
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

51. Preferred playing with younger children
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

52. Preferred playing with older children
    - 0 - Not True (as far as you know) _____
    - 1 - Somewhat or Sometimes True _____
    - 2 - Very True or Often True _____

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

53. Had friends who got into trouble
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

54. Confused; seemed to be in a fog
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

55. Daydreamed; got lost in his/her thoughts
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

56. Heard sounds or voices that were not there
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    (Describe _____)
    2 - Very True or Often True _____
    (Describe _____)

57. Saw things that were not there
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    (Describe _____)
    2 - Very True or Often True _____
    (Describe _____)

58. Strange ideas
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    (Describe _____)
    2 - Very True or Often True _____
    (Describe _____)

59. Strange behaviors
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    (Describe _____)
    2 - Very True or Often True _____
    (Describe _____)

60. Cruel to animals
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

61. Cruel, bullied, or mean to others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

62. Got into fights
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

63. Physically attacked others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

64. Did not seem guilty after misbehaving
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

65. Jealous of others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

66. Irritable
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

67. Sudden changes in mood or feelings
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

68. Destroyed his/her own things
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

69. Destroyed things that belonged to the family or other children
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

Lied or cheated
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

Age in Years

0 - 3 | 4 - 7 | 8 - 11 | 12 - 15 | 16 - 18

71. Set fires
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

72. Disobedient at home
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

73. Disobedient at school
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

74. Felt that he/she had to be perfect
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

75. Felt worthless or inferior
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

76. Accident-prone
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

77. Impulsive; acted without thinking
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

78. Self-conscious; easily embarrassed
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

79. Stubborn, sullen, or irritable
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

80. Stole at home
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

81. Stole outside the home
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

82. Underactive, slow moving, or lacked energy
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

83. Unusually loud
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

84. Felt or complained that no one loved him/her
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

85. Got teased a lot
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

86. Was nervous, high strung, or tense
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

87. Worried a lot
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

88. Ran away from home
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

89. Secretive; kept things to self
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

90. Teased others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

Age in Years

0 - 3 | 4 - 7 | 8 - 11 | 12 - 15 | 16 - 18

91. Truant; skipped school
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

92. Unhappy, sad, or depressed
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

93. Used alcohol and/or drugs for nonmedical purposes
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

94. Vandalism
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

95. Participated in more school-related activities than others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

96. Participated in fewer school-related activities than others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

97. Had more peer relationships than others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

98. Had fewer peer relationships than others
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

99. Argued a lot
    0 - Not True (as far as you know) _____
    1 - Somewhat or Sometimes True _____
    2 - Very True or Often True _____

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

100. Demanded a lot of attention
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

101. Did not get along with other children
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

102. Feared he/she might think or do something wrong
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

103. Felt others were out to get him/her
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

104. Was too fearful or anxious
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

105. Felt too guilty
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

106. Often overtired
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

107. Overweight
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

108. Did poorly in school
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

Age in Years

0 - 3 | 4 - 7 | 8 - 11 | 12 - 15 | 16 - 18

109. Refused to talk
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

110. Screamed a lot
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

111. Smeared or played with bowel movements
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

112. Stared blankly
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

113. Sulked a lot
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

114. Swore or used obscene language
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

115. Talked too much
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

116. Threatened people
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

117. Sucked his/her thumb
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

118. Overly concerned with neatness or cleanliness
0 - Not True (as far as you know) _____
1 - Somewhat or Sometimes True _____
2 - Very True or Often True _____

Age in Years

0 - 3 4 - 7 8 - 11 12 - 15 16 - 18

119. Whined a lot
   0 - Not True (as far as you know) _____
   1 - Somewhat or Sometimes True _____
   2 - Very True or Often True _____

120. Withdrawn, did not get involved with others
   0 - Not True (as far as you know) _____
   1 - Somewhat or Sometimes True _____
   2 - Very True or Often True _____

121. Showed problems with gross motor coordination (e.g. walking, running, throwing, jumping)
   0 - Not True (as far as you know) _____
   1 - Somewhat or Sometimes True _____
   2 - Very True or Often True _____

122. Showed problems with fine motor coordination (ie. doing things with hands)
   0 - Not True (as far as you know) _____
   1 - Somewhat or Sometimes True _____
   2 - Very True or Often True _____

123. Showed unusual postures or unintentional movement of hands
   0 - Not True (as far as you know) _____
   1 - Somewhat or Sometimes True _____
   2 - Very True or Often True _____

124. Seemed to have below average muscle tone
   0 - Not True (as far as you know) _____
   1 - Somewhat or Sometimes True _____
   2 - Very True or Often True _____

For the child who is the subject, at what age was s/he when you first noticed behaviour that concerned you and what were these behaviors?

Do you have reason to believe your child experimented with illegal drugs? _____

If so, at what age do you think this first occurred and what substance was abused? _____

COMMENTS:

Appendix D: CBCL Algorithm

CBCL Algorithm: SPSS Commands for the Internalization Dimension

Compute T1= .25

Compute T2= .75

ComputeT3= 1.25

Compute T4= 1.75

Compute T5= 2.25

Compute T5 mean = mean (T1, T2, T3, T4, T5)

Compute suma = int_1 + int_2 + int_3 + int_4 + int_5

Compute sumb = T1 + T2 + T3 + T4 + T5

Compute sumba = (T1*int_1) + (T2*int_2) + (T3*int_3) + (T4*int_4) + (T5*int_5)

Compute sumbsq = ((T1*T1) + (T2*T2) + (T3*T3) + (T4*T4) + (T5*T5))

Compute numb = 5

Compute xterm = (sumb*suma) / numb

Compute yterm = (sumb*sumb) / numb

Compute int_mean = mean(int_1, int_2, int_3, int_4, int_5)

Compute int_slope = (sumba- (xterm) / (sumbsq- yterm)).

Appendix E: Modified CTQ/CTI Self Report

French version available upon request from Dr. Suzanne King

WHEN I WAS GROWING UP...	Never True	Rarely True	Some-times True	Often True	Very Often True
PA9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	•	•	•	•	•
PA11. People in my family hit me so hard that it left me with bruises or marks.	•	•	•	•	•
PA12. I was punished with a belt, a board, a cord, or some other hard object.	•	•	•	•	•
PA15. I believe that I was physically abused.	•	•	•	•	•
PA17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.	•	•	•	•	•
SA20. Someone tried to touch me in a sexual way or tried to make me touch them.	•	•	•	•	•
SA21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	•	•	•	•	•
SA23. Someone tried to make me do sexual things or watch sexual things.	•	•	•	•	•
SA24. Someone molested me.	•	•	•	•	•
SA27. I believe that I was sexually abused.	•	•	•	•	•
EA3. People in my family called me things like "stupid," "lazy," or "ugly."	•	•	•	•	•
EA8. I thought that my parents wished I had never been born.	•	•	•	•	•

WHEN I WAS GROWING UP...	Never True	Rarely True	Some-times True	Often True	Very Often True
EA14. People in my family said hurtful or insulting things to me.	•	•	•	•	•
EA18. I felt that someone in my family hated me.	•	•	•	•	•
EA25. I believe that I was emotionally abused.	•	•	•	•	•
PN1. I didn't have enough to eat.	•	•	•	•	•
PN4. My parents were too drunk or high to take care of the family.	•	•	•	•	•
PN6. I had to wear dirty clothes.	•	•	•	•	•
WV33. I saw people in my family get hit or beaten	•	•	•	•	•
FP43. I had serious money problems.	•	•	•	•	•
FP44. My family had serious money problems.	•	•	•	•	•
H45. I was living on the streets by the time I was a teenager or younger.	•	•	•	•	•
EPA48. People in my family argued or fought with each other.	•	•	•	•	•
EPA49. I had to protect myself from someone in my family by fighting, hiding, or running away.	•	•	•	•	•
PA51. The punishments I received seemed cruel.	•	•	•	•	•

WHEN I WAS GROWING UP...	Never True	Rarely True	Some-times True	Often True	Very Often True
PN2. I knew that there was someone to take care of me and protect me.	•	•	•	•	•
PN26. There was someone to take me to the doctor if I needed it.	•	•	•	•	•
EN5. There was someone in my family who helped me feel that I was important or special.	•	•	•	•	•
EN7. I felt loved.	•	•	•	•	•
EN13. People in my family looked out for each other.	•	•	•	•	•
EN19. People in my family felt close to each other.	•	•	•	•	•
EN28. My family was a source of strength and support.	•	•	•	•	•
MD10. There was nothing I wanted to change about my family.	•	•	•	•	•
MD16. I had a perfect childhood.	•	•	•	•	•
MD22. I had the best family in the world.	•	•	•	•	•
SS46. There was someone outside the family (e.g. teacher or neighbor) who was like a parent to me.	•	•	•	•	•
SS47. There was someone in my family whom I could talk to about my problems.	•	•	•	•	•
PA50. The punishments I received seemed fair.	•	•	•	•	•

WHEN I WAS GROWING UP...	Never True	True
SA52. I had sex with an adult or with someone who was at least 5 years older than me.	•	•
PN53. People in my family had secrets that I wasn't supposed to share with anyone.	•	•
V34. I was robbed or mugged or attacked.	•	•
WV35. I saw someone get robbed or mugged or attacked.	•	•
WV36. I saw someone get hurt or killed.	•	•
LS29. My parents separated or divorced.	•	•
LS30. I lived in a group home or foster home or with a relative.	•	•
LS31. My parent or relative died suddenly /committed suicide	•	•
LS32. A close friend died suddenly/committed suicide.	•	•
ND37. I was in a serious natural disaster (earthquake, hurricane, fire, flood).	•	•
AC38. I was in a serious accident (in a car, at work or somewhere else).	•	•
AC39. A close family member was in a serious accident (in a car, at work, or somewhere else).	•	•
AC40. I saw a serious accident (e.g. car accident, work accident).	•	•
J41. One of my parents spent time in jail.	•	•

WHEN I WAS GROWING UP...	Never True	True
J42. I spent time in jail.	•	•
C54. I had an abortion of miscarriage (lost my baby).	•	•
C55. I was separated from my child against my will.	•	•

HAVE YOU EXPERIENCED ANY OTHER STRESSFUL SITUATION?
[IF YES], WHAT WAS IT ?:_____

_____

OF ALL THE STRESSFUL EVENTS EXPERIENCED, WHICH ONES HAD THE GREATEST IMPACT ON YOU?

WORST EVENT:_____

SECOND WORST
EVENT:_____

THIRD WORST EVENT:_____

Appendix F: Prodromal Interview

French version available upon request from Dr. Suzanne King

Section 1: Establishing First Contact

1. What is your date of birth?

2. When was the very first time that you went to the hospital or saw a psychiatrist for this illness?

3. Do you know what your diagnosis is?

4. How far did you get in school?

5. How old were you when you stopped going to school?

6. Did you have a job after you stopped going to school?

    6a. What was it?

    6b. How old were you when you started/ ended it?

Section 2: Establishing the Prodromal Time-frame

"I would now like to ask you about things that happened before you were (age at prodrome)."

1. "What were you like as a child/teenager?"

2. "How old were you when you think it changed?"

Section 3: Prodromal Symptoms

Probe to pinpoint date of occurrence(s) <u>if prior to age at prodrome</u> and determine type of behavior.

"Before _____ (age at prodrome), did you ever...

3. feel depressed for some period of time or attempt suicide?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

4. lose your appetite for some period of time?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)
(describe)

5. feel anxious or nervous for some period of time?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)
(describe)

6. lack in energy or feel very tired?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)
(describe)

7. have problems sleeping?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)
(describe)

8. have problems concentrating or were unable to think clearly?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)
(describe)

9. find yourself not wanting to go to school/work?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)
(describe)

"Before _____ (age at prodrome), did you ever...

10. **did you find that you enjoyed things less than usual?"**

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

11. **find yourself wanting to be alone or seeing less of your friends or family?"**

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

Section 4: Psychotic Symptoms

Probe to pinpoint date of occurrence(s) if <u>event occurred for the first time prior to age at prodrome</u> and determine type of behavior.

"Before _____ age at prodrome), did you ever...

12. **find that people were talking about you, laughed at you, or wanted to hurt you?"**

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

13. **find that you were receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?"**

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

14. feel that someone or something outside yourself was controlling you?"

[if YES,]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

15. feel that other people could actually hear what you were thinking OR that voices spoke your thoughts aloud?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

16. hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

17. see things that other people couldn't see?"

[if YES]: (indicate month(s)/year(s) OR season/year, if month(s) unknown)

(describe)

Appendix G: Substance Use Interview

French version available upon request from Dr. Suzanne King

A: MEDICINES

Sleeping pills	Quaaludes	Percodan
Stimulants	Sedatives	Amphetamines
Tranquilizers	Barbiturates	Demerol
Valium	Seconal	Morphine
Librium	Codeine	Methadone
Xanax	Darvon	Dilaudid

B: DRUGS		
Marijuana	Gasoline	Cocaine
Hashish	Tolulene	Crack
Heroin	Peyote	DMT
Betel nut	Mescaline	PCP
Speed	LSD	Glue
Inhalants	Psilocybin	Mushrooms
Coca leaves	Opium	Ecstasy

1. Did you ever use any of the medicines in Part A at least once when they were **not** prescribed for you to get high?

Which ones? Any others?

2. Have you ever taken any of the drugs in Part B at least once to get high?

Which ones? Any others?

3. Have you ever taken any drugs not on the list at least once to get high?

Which ones? Any others?

4. Have you ever used alcohol in large amounts?

1. How old were you when you first used (DRUG CATEGORY)?

1a. How often did you use (DRUG CATEGORY) at this point?
(how many times [for drug category] or drinks[for alcohol] per week/month?)

2. How old were you when first used (DRUG CATEGORY) the most frequently?

2a. How frequently did you use (DRUG CATEGORY) at this point?

3. How frequently did you use (DRUG CATEGORY) between these ages?

4. How frequently were you using (DRUG CATEGORY) at (THREE MONTHS PRIOR TO PRODROME)?

5. How frequently did you use (DRUG CATEGORY) between these ages?

Appendix H: REB Approval and Consent Forms

EXTRACT FROM THE MINUTES
OF THE RESEARCH ETHICS BOARD
OF DOUGLAS HOSPITAL

of November 10, 1998 at 12:00 noon
in Room B-2151, Dobell Pavilion

5.5 **Protocol 98/32** *Childhood and Adolescent Experiences in the Etiology of Schizophrenia: An Addendum to the Genetic and Environmental Factors in the Etiology of Schizophrenia: Relation to Course and Outcome*
Addendum to Protocol 97/19
Principal Investigator: Dr. Suzanne King

The REB raised two issues about the patient's consent form.

1. The second paragraph mentions that there will be questions relating to drug and medication use. The REB felt that this sentence should specify that questions will be asked about illegal drug use.

2. In the third paragraph it is mentioned that the results of the study are confidential. Given that the questionnaires may reveal illegal drug taking activity, and that courts can subpoena research records, the REB requires that statements on the confidentiality of the data collected be qualified by the clause "unless otherwise specified by law".

The REB agreed that when the corrected version of this protocol is received it does not need to be considered by the whole REB, but can be passed by the chairperson if it is changed satisfactorily.

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CENTRE DE COLLABORATION OMS DE MONTRÉAL
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MONTREAL WHO COLLABORATING CENTRE
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MENTAL HEALTH

Experiences in Childhood and Adolescence

(Addendum to the "Envirogen" Project)

Suzanne King, Ph.D (Douglas Hospital Research Center) Telephone: 762-3048
Alain Gratton, Ph.D (Douglas Hospital Research Center)
Howard Steiger, Ph.D (Douglas Hospital Research Center)
Coordinator: Monica Pukall, B.A.H. (Douglas Hospital Research Center)

Consent Form

We would like to thank you for the permission you gave us to interview your mother and siblings to find out what events and influences could have caused the types of experiences that you have been having. We would now like to gain a better understanding of the other types of events which may explain the experiences and problems that you have had. Studies have found that certain stressful events may explain these types of experiences. Other studies have also found that drug use could explain certain similar problems to the ones that you have had.

The interview will take about two hours. It will consist of questions on when you began having certain experiences, such as feeling depressed or nervous, trouble concentrating, hearing things. Then, there will be questions relating to illegal drug and medication use: when was an illegal drug or medication taken, how much was taken, what type of substance was taken. Next, you will be given a questionnaire about how many times you have had certain experiences in daily life, such as not recognizing friends or family. Finally, you will be given a questionnaire on events that might have happened to you that very stressful.

You will be given $40 for participation after the interview is completed, or in the case

that it is not completed, you will be paid $20 for each completed hour. Although there is no direct benefit for participating in this study, you understand that the information that you provide is important in better understanding the problems that you have had. You understand that there are no risks associated with the study, except for discomfort that may be associated with certain questions. You know that your decision to participate or not participate in this project, or to withdraw from the study at any time, will have no consequence on the clinical services that you, or your family, may receive. This project is confidential which means that only the persons associated with the project will have access to your information, unless otherwise specified by law, and all information will be kept in a drawer of a locked filing cabinet. Finally, you understand that any publications of the study will not identify any particular individual, but will only contain reports on groups of individuals.

Participant's consent

I have read and understood the description of my involvement in this project and have had opportunities to ask questions.

I give permission to the researchers of this project to interview me about the types of events that may have happened in the past that could explain the kinds of problems that I have experienced. I understand that the questions that I will be asked may be sensitive in nature, but I can refuse to answer any questions or end the interview at any time.

I have received a copy of this form. I understand that if I have any questions, I can contact the researchers identified on the first page at 762-3048. I may also contact the Douglas Hospital Ombudsman if I have any questions about my rights as a patient or a research subject at 762-3010.

Name (please print)_____

Signature_____ Date_____

Witness_____

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DOUGLAS HOSPITAL
RESEARCH CENTRE

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MENTAL HEALTH

Les Expériences de l'Enfance et de l'Adolescence: Relation avec l'Evolution des Problèmes Prémorbides (Suivi de l'Etude "Envirogen")

Suzanne King, Ph.D Université McGill (514) 762-3048
Pierre Lalonde, M.D., Hôpital Louis-H. Lafontaine
Monica Pukall, B.A.H. Coordinatrice (514) 762-3048

Formulaire de Consentement

Plusieurs études ont révéle que certains événements stressants peuvent expliquer l'expériences des troubles importants de santé mentale. D'autres études ont montré que l'usage de drogues illicites peut aussi leur être associé. La présente recherche nous permettra d'identifier et de mieux comprendre les événements qui peuvent avoir un impact sur les personnes vivant des expériences similaires aux vôtre. Nous voulons aussi examiner d'autres types d'événements qui pourraient être également reliés à ces expériences.

L'entrevue dure environ deux heures et comporte plusieurs questionnaires. Ces questionnaires portent sur le début et la fréquence de vos expériences de dépression, d'anxiété, de troubles de concentration ou de sommeil. Ils s'intéressent aussi à l'usage possible de médicaments et de drogues illicites et aux événements stressants qui ont pu survenir dans votre vie.

A la fin de l'entrevue, en guise de dédommagement une somme de $40 vous sera remise. Mais si l'entrevue n'est pas complétée, il vous sera remis $20 pour chaque heure d'entrevue complétée. Le seul risque, minime, associé à cette entrevue est que vous puissiez vous sentir

troublé(e) ou perturbé(e) en parlant des moments difficiles que vous aviez vécu. Votre décision de participer ou non ou de vous retirer de l'étude n'aura aucune conséquence sur les services cliniques que vous ou votre famille pouvez recevoir. De plus, sauf si spécifié par la loi, seuls les membres de l'étude auront accès aux données qui seront gardées sous clef. Les publications issues de cette recherche ne révéleront pas les noms des personnes qui y ont participé, elles ne s'intéresseront qu'aux groupes de personnes.

Nous vous remercions pour votre participation et d'avoir déjà donné votre permission de contacter certains membres de votre famille. Nous vous invitons à signer le formulaire de consentement ci-joint, qui indique votre accord à participer à cette étude. Vous pouvez parler aux chercheurs identifiés ci-haut au 762-3048 ou à l'adresse ci-dessous. Vous pouvez également appeler l'ombudsman de l'hôpital Louis-H Lafontaine au 251-4000 post 2920 si vous avez des questions sur vos droits en tant que sujet de recherche.

Consentement du patient

J'ai lu et j'ai compris les conditions de ma participation à cette recherche.
Je donne ma permission aux chercheurs de me poser des questions ayant trait à cette étude.
J'ai reçu une copie de ce formulaire.

Nom (en lettres moulées s.v.p)_____

Signature_____ Date_____

Témoin _____

CENTRE DE RECHERCHE
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ENVIROGEN RESEARCH PROJECT: PATIENT CONSENT FORM
(PATIENT CONSENT TO CONTACT PARENTS/SIBLINGS)

Principal Investigator: Suzanne King, PhD (Douglas Hospital Research Centre)
Co-Investigators: Frances Champagne, BAH & Helen Cunningham, BA (DHRC)
Dr. Pierre Lalonde (Hôpital Louis-H-Lafontaine, Clinique Jeunes Adultes)

Name (please print): _____

You and your family have already participated in a study to better understand how families get along. We thank you for your previous participation.

We are now trying to answer a new question. We are hoping to gain a better understanding of what types of events and influences may explain the experiences and problems you have had. Numerous studies have found that people who share similar experiences and problems as you, have often also had family members with these types of experiences.

Some studies are also finding that certain events that occurred before birth may be related to present experiences. To find out more about this, we would like your permission to contact your parents. We would like to ask them some questions about when you were born, and your experiences while growing up.

When we ask your mother questions about when she was pregnant with you and about your birth, we understand that she may not be able to remember everything about that time. We are therefore asking her permission to look at her medical records concerning her pregnancy with you. These records do not include information about you at birth. For this reason, we would like your permission to look at your medical birth records from the time of your birthdate until you were six months old.

Other studies are also finding that sometimes other family members have similar ways of processing information, although they do not share your exact kinds of experiences. We would like to examine how your siblings process information. We would therefore like your permission to contact your brothers and sisters for this study.

The information that we get from your parents and siblings is most useful if we can

combine it with the information you have given us before. Therefore, we would like your permission to combine the new information from your relatives with the old information you gave us before.

CONSENT FORM

I give the investigators in this project permission to contact my parents and my siblings for this study. This new project does not involve any interviews with me.

I give the investigators authorization to have access to my medical records from the period of my birthdate until six months of age.

I also give permission for the investigators to use the information I gave during the study entitled "_____" for the purpose of answering these new questions.

I know that my decision to authorize or not authorize the contacting of my parents and siblings, and their decision to participate or not, or to withdraw at any time from the study, will have no effect on any clinical services that I or members of my family may receive. This project is confidential, which means that only the staff of this project will have access to the information provided by your parents and siblings, should they agree to participate. Finally, I understand that publications which are the product of this study will contain reports about groups of people, and that no one person will be identifiable.

I have received a copy of this form. I understand that if I have any further questions, I may contact any of the local investigators named above at 762-3048 or at the address below. My relatives and I may also contact the Douglas Hospital ombudsman (762-3010) if we have questions about my rights as a research subject.

Signature:_____ Witness: _____

Date (mm-dd-yy): _____

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FACTEURS GÉNÉTIQUES ET ENVIRONNEMENTAUX DANS L'ÉTIOLOGIE DE LA SCHIZOPHRÉNIE: RELATION AVEC LE DÉROULEMENT ET L'ISSUE

(FORMULAIRE DE CONSENTEMENT DU PATIENT POUR CONTACTER LES PARENTS/FRÈRES/SOEURS)

Chercheure Principale : Suzanne King, PhD (Centre de Recherche de l'Hôpital Douglas)
Co-Cheucheures: Frances Champagne, BAH (CRHD) & Helen Cunningham, BA (CRHD)
Dr. Pierre Lalonde (Hôpital Louis-H-Lafontaine, Clinique Jeunes Adultes)

Nom (en lettres moulées s.v.p.): _____

Votre famille et vous avez déjà participé à une étude pour mieux comprendre comment fonctionnent les familles. Nous vous remercions pour votre participation passée.

Nous tentons maintenant de répondre à une nouvelle question. Nous espérons gagner une meilleure compréhension des types d'événements et d'influences qui peuvent expliquer les expériences et problèmes que vous avez eus. Plusieurs études ont trouvé que les gens qui partagent des expériences et problèmes similaires aux vôtres ont souvent également des membres de leur famille qui ont ces types d'expériences.

Quelques études trouvent aussi que certains événements qui se produisent avant la naissance peuvent être reliés à des expériences présentes. Pour en savoir plus à ce sujet nous aimerions avoir votre permission afin de contacter vos parents. Nous voudrions leur demander quelques questions à propos de votre naissance et de vos expériences en grandissant.

Quand nous posons des questions à votre mère concernant la période où elle était enceinte de vous ou au sujet de votre naissance, nous comprenons qu'il est fort possible qu'elle puisse ne pas se rappeler d'une grande partie de ce qui s'est passé à ce moment là. Nous demandons donc sa permission afin d'avoir accès à son dossier médical se rapportant à cette grossesse. Cependant, ces renseignements médicaux n'incluent pas les informations sur vous-même à votre naissance. Pour cette raison, nous aimerions également obtenir votre permission pour consulter votre dossier médical à partir de la date de votre naissance jusqu'à l'âge de six mois.

ENVIROGEN: nctestfr Created on 97-12-08 11:03

D'autres études ont également trouvé que quelquefois d'autres membres de la famille ont des façons similaires de traiter l'information même s'ils ne partagent pas vos sortes d'expériences exactement. Nous aimerions examiner comment vos frères/ soeurs traitent l'information. Nous aimerions en conséquence votre permission pour contacter vos frères et soeurs pour cette étude.

L'information que nous obtiendrons de vos parents et frères/soeurs est le plus utile si nous pouvons la combiner à l'information que vous nous avez donné auparavant. Nous aimerions donc votre permission afin de combiner la nouvelle information obtenue de votre parenté à l'ancienne information que vous nous avez donné dans le passé.

FORMULAIRE DE CONSENTEMENT

Je donne la permission aux chercheurs de ce projet de contacter mes parents et mes frères/soeurs pour cette étude. Ce nouveau projet ne comprend pas d'entrevue avec moi.

Je donne aussi la permission aux chercheurs d'utiliser l'information que j'ai fournie lors de l'étude intitulée « _____ _____ » afin de répondre à ces nouvelles questions.

Je sais que ma décision d'autoriser ou de ne pas autoriser le contact de mes parents et frères/soeurs, et que leur décision de participer ou non, ou de se retirer de l'étude en tout temps n'aura aucune conséquence sur les services cliniques que je ou les membres de ma famille peuvent recevoir. Ce projet est confidentiel, ce qui signifie que seuls les membres du personnel de ce projet auront accès à l'information obtenue de mes parents et frères/ soeurs s'ils acceptent de participer. Finalement, je comprends que les publications qui seront le produit de cette étude ne contiendront que des rapports sur des groupes d'individus et qu'aucune personne en particulier ne sera identifiée.

J'ai reçu une copie de ce formulaire. Je comprends que si j'ai des questions je peux contacter les chercheurs identifiés ci-haut au 762-3048 ou à l'adresse ci-dessous. Ma parenté et moi pouvont également contacter l'ombudsman de l'Hôpital Douglas (762-3010) si nous avons des questions à propos de nos droits en tant que sujet de recherche.

Signature:_____Témoin:_____Date (mm-jj-aa): _____

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ENVIROGEN RESEARCH PROJECT
CONSENT FORM (MOTHER)

Principal Investigator: Suzanne King, PhD (Douglas Hospital Research Centre)
Co-Investigators: Frances Champagne, BAH & Helen Cunningham, BA (DHRC)

Name (please print):_____ Mother of _____

I have been asked to participate in this study of recipients of mental health services. The purpose of this study is to understand what influences may be important in the development and course of mental illness. The potential influences that we will be investigating are of two types. First, we hope to learn more of the different ways to determine how influential genetics are in the nature of the illness. Secondly, we hope to learn more about how environmental prenatal events and experiences of the mother may influence the development and course of severe mental disorders.

I understand that my involvement will consist of one meeting with a member of the project staff. The first part of this meeting will involve an interview about the history of mental illness in our family; this first part will take about 1 hour and 30 minutes to 2 hours. Following a break, the next 30-45 minutes will involve an tape recorded interview about events that occurred in the year before my son or daughter (subject name: _____) was born. After a break, I will be interviewed about any pregnancy and birth complications I may have encountered with my son(s) and/or daughter(s). This portion of the meeting will last from 1 hour and 30 minutes to 2 hours, and it will be tape recorded. The final portion of the meeting will consist of my answering a questionnaire about the childhood behaviour of my son or daughter (subject name: _____); this final part will take about 45 minutes. The meeting will last a total of about 4 ½ hours to 5 hours.

I authorize the researchers to have access to my medical chart for the period of the time encompassing the pregnancies of my son(s) and/or daughter(s) (those that are discussed in the interview).

I understand that I will receive $50 at the completion of the meeting, plus reimbursement for any travel expenses. While there are no direct benefits to me, I understand that information gathered during this study may provide important information to researchers who are trying to understand the development of severe mental illness. As well, I understand that there are no dangers involved in this study, and that the only reasonable risk is discomfort in talking about somewhat personal aspects of my life. However, I may withdraw from the study at any time, or refuse to answer questions I prefer not to answer. Should I withdraw from the study during the interview, I understand that I will be paid $10 for each hour of participation, plus any travel expenses.

I give the researchers permission to ask my son(s) and/or daughter(s) to be part of this study with me (name(s):_____). I know that my decision to participate or not in this research project, or to withdraw from the study at any time, will have no effect on any clinical services that I or members of my family may receive. This project is confidential, which means that only the staff of this project will have access to the information I provide, and that all information will be kept in a locked file drawer. Finally, I understand that publications which are the product of this study will contain reports about groups of people, and that no one person will be identifiable.

I have received a copy of this form. I understand that if I have any further questions, I may contact any of the local investigators named above at 762-3048 or at the address below. I may also contact the Douglas Hospital ombudsman (762-3010) if I have questions about my rights as a research subject.

Signature: _____Witness: _____Date (mm-dd-yr):_____

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FACTEURS GÉNÉTIQUES ET ENVIRONNEMENTAUX DANS L'ÉTIOLOGIE DE LA SCHIZOPHRÉNIE: RELATION AVEC LE DÉROULEMENT ET L'ISSUE

FORMULAIRE DE CONSENTEMENT (MÈRE)

Chercheure Principale : Suzanne King, PhD (Centre de Recherche de l'Hôpital Douglas)
Co-Cheucheures: Frances Champagne, BAH (CRHD) & Helen Cunningham, BA (CRHD)
Dr. Pierre Lalonde (Hôpital Louis-H-Lafontaine, Clinique Jeunes Adultes)

Nom (en lettres moulées s.v.p.): _____Mère de _____

On m'a demandé de participer à cette étude des bénéficiaires de services en santé mentale. Le but de cette étude est de comprendre quelles influences peuvent être importantes dans le développement et le déroulement d'une maladie mentale. Les influences potentielles que nous examinerons sont de deux types. Premièrement, nous espérons apprendre plus des différentes façons qui déterminent à quel point la génétique est influentielle dans la nature de la maladie. Deuxièmement, nous espérons en apprendre plus sur la façon dont les événements environnementaux prénataux et les expériences de la mère peuvent influencer le développement et le dénouement des désordres mentaux sévères.

Je comprend que ma participation consistera en une rencontre avec un membre du personnel du projet. La première partie de cette rencontre comprendra une entrevue à propos de l'histoire familiale de maladie mentale ; cette première rencontre durera de 1 heure et demie à 2 heures environ. Suite à une pause, les prochains 30 à 45 minutes seront alloués à une entrevue enregistrée sur audio-cassette à propos des événements qui se sont produits dans l'année précédent la naissance de mon fils ou ma fille (nom du sujet : _____). Après une pause, je participerai à une entrevue à propos de toutes complications au cours de la grossesse et de la naissance de mon (mes) fils et/ou fille(s). Cette portion de la rencontre durera de 1 heure et demie à 2 heures et sera enregistrée sur audio-cassette. La portion finale de cette rencontre sera utilisée pour que je complète un questionnaire à propos des comportements de mon fils ou ma fille (nom du sujet : _____) au cours de son enfance ; cette portion finale durera environ 45 minutes. La rencontre sera d'une durée totale d'environ 4 ½ à 5 heures.

J'autorise les chercheurs à avoir accès à mes dossiers médicaux pour la période de temps qui englobe la (les) grossesse(s) de mon (mes) fils et ou fille(s) (ceux qui sont discutés dans l'entrevue).

6875 BOUL. LASALLE, VERDUN (QUÉBEC) CANADA H4H 1R3 • FAX: (514) 762-3049 • TÉL.: (514) 762-3048

Je comprends que je recevrai 50$ à la fin de la rencontre, plus un remboursement pour n'importe quel frais de déplacements. Bien qu'il n'y ait aucun bénéfice direct pour moi, je comprends que l'information obtenue au cours de cette étude peut fournir de l'information importante aux chercheurs qui tentent de comprendre le développement des maladies mentales sévères. De plus, je comprends qu'il n'y a aucun danger d'impliqué dans cette étude et que le seul risque raisonnable est l'inconfort de parler de certains aspects quelques peu personnels de ma vie. Toutefois, je peux me retirer de cette étude en tout temps ou refuser de répondre aux questions auxquelles je préfère ne pas répondre. Si je me retire de l'étude au cours de l'entrevue, je comprends que je serai payée 10$ pour chaque heure de participation, plus n'importe quel frais de déplacement.

Je donne la permission aux chercheurs de demander à mon (mes) fils et/ou fille(s) de participer à l'étude avec moi (nom(s) :_____). Je sais que ma décision de participer ou non à ce projet de recherche, ou de me retirer de l'étude en tout temps n'aura aucune conséquence sur les services cliniques que je ou les membres de ma famille peuvent recevoir. Ce projet est confidentiel, ce qui signifie que seuls les membres du personnel de ce projet auront accès à l'information que je donne et que toutes ces informations seront gardées dans un tiroir d'un classeur barré. Finalement, je comprends que les publications qui seront le produit de cette étude ne contiendront que des rapports sur des groupes d'individus et qu'aucune personne en particulier ne sera identifiée.

J'ai reçu une copie de ce formulaire. Je comprends que si j'ai des questions je peux contacter les chercheurs identifiés ci-haut au 762-3048 ou à l'adresse ci-dessous. Je peux également contacter l'ombudsman de l'Hôpital Douglas (762-3010) si j'ai des questions à propos de mes droits en tant que sujet de recherche.

Signature:_____Témoin:_____Date (mm-jj-aa): _____

Appendix I: CBCL Outliers

Winsorization of Outliers in the Slope Data

Internalizing	Externalizing	Social Probs	Attention Probs
mean= 2.55	mean= 2.39	mean= 1.28	mean= 2.40
SD= 3.45	SD= 3.95	SD= 3.30	SD= 3.71
Score (Winsorized Score)			
.00	.00	.00	4.00
1.00	2.00	2.00	4.00
4.00	.00	.00	.00
.00	.60	.00	.00
4.60	2.80	.00	1.40
.00	8.00	14.00 (6.0)	4.00
5.20	4.80	4.20	.40
4.00	.00	4.00	.00
2.80	.60	.00	.00
.00	7.80	.80	3.60
4.40	.60	.00	.30
.00	3.20	.00	.20
.00	.00	.00	1.20
.00	1.0	.00	1.00
3.80	3.80	.00	.60
.00	.20	.00	.00
.00	1.20	.00	1.80
2.80	1.20	.00	.00
.00	.00	.00	.00
.00	.60	.00	.00
2.00	.00	.00	16.00 (10.0)
4.00	2.00	6.00	10.00
7.40	2.04	.60	4.40
.00	.00	.00	.00
15.40 (7.4)	18.40 (8.0)	.60	6.20
5.00	1.40	1.00	3.30