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Childhood and adolescent predictors of schizophrenia in the Northern Finland 1966 Birth Cohort – a descriptive life-span model

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Abstract Subtle motor, emotional, cognitive and behavioral abnormalities are often present in apparently healthy children and adolescents who later develop schizophrenia. This suggests that some aspects of causation are established long before psychosis is manifest. We aim to develop a descriptive model of the factors contributing to the development of schizophrenia. Our main focus is on genetic factors, pregnancy and delivery complications, early development and scholastic performance. This is done by reviewing the Northern Finland 1966 Birth Cohort, its scientific activities (publications and work in progress) and selected literature.

Key words Schizophrenia · Development · Premorbid · Pregnancy · Model

Introduction

Schizophrenia is one of the major scientific mysteries. Since Kraepelin around the turn of the century, different efforts to formulate causal factors and developmental models of this entity have been made. Its etiology is still mostly unknown. Although we have many pieces of this complex puzzle, we cannot yet put them together in a satisfactory way. One wonders whether the most important pieces are still missing. The existence of diverse forms and manifestations of the syndrome suggests that many etiological causes may be important. This etiological and phenomenological uncertainty extends to precursors, which are not necessarily specific to schizophrenia, but also common to other psychotic disorders (Jones and Tarrant 1999).

Many somatic diseases in adulthood may have their origin in childhood (Barker 1994), even during pregnancy; why not mental disorders (Jones 1997, Cannon and Murray 1998)? Although its characteristic *symptoms* may emerge rapidly, there is increasing evidence that schizophrenia is not a *condition,* which manifests suddenly. There appear to be many developmental abnormalities in the premorbid and prodromal phases, which are distinct from the major psychotic symptomatology. These features present major challenges for comprehensive theories of causation, as well as practical problems for attempts at prediction, or estimation of risk in healthy individuals.

In this article, we aim to describe factors contributing to the development of schizophrenia. Our main focus is on pregnancy and delivery complications, and early development. This is done by reviewing articles (either published or those in progress) from the Northern Finland 1966 Birth Cohort (hereafter the Cohort) in the context of the necessarily selective literature. In this way we use the Finnish Birth Cohort as an entry point to the literature on risk factors for schizophrenia. We include a summary of the future research plans of the Cohort, which illustrate ongoing work. In addition, we propose theoretical explanations and present a descriptive model of factors contributing to the development of schizophrenia, particularly remote events: genetic factors, pregnancy and delivery complications, early developmental milestones, and scholastic performance.

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Historical account of the Cohort

Thirty-five years ago Professor Paula Rantakallio (1969) started the prospective Northern Finland 1966 Birth Cohort Study (12 058 live born children). The aim was to investigate biological, social and environmental factors concerning the mother, child and family, and mortality and morbidity of the child. In the early 1990s a major new line of research was commenced: the study of predictors and determinants of major mental disorders. In particular, we identified a remarkable opportunity to study risk factors for schizophrenia and other psychoses. We have prospectively collected extensive developmental data from pregnancy and birth, through childhood and adolescence and into early adulthood in a large sample of the general population. The cohort data are therefore rich in putative etiological variables for psychosis and other mental disorders, e. g., unwanted pregnancy, obstetric factors and virus exposure during childhood.

Cumulative incidence and age at onset of schizophrenia

In the Cohort, 100 cases of DSM-III-R schizophrenia arose by the end of the 31st year of age (cumulative incidence 0.91 %; 95 % CI 0.71, 1.06). Sixty-five of these schizophrenia cases were male (twofold increase in odds compared to women: Isohanni et al. 1997). The mean age at onset of schizophrenia up to the age of 28 years was 21.4 years in men and 21.2 years in women (Räsänen et al. 1999)

The cumulative incidence of schizophrenia is quite high, but in line with previous epidemiological studies in Finland (Lehtinen et al. 1990). Although in many first-episode cohort studies men are reported to develop schizophrenia 3–4 years earlier than women, in the Cohort no differences were found. This may be due to the nature of the birth cohort design. Only part of the period of lifetime risk for disorder has passed (so far). Future cases, which will be identified at subsequent follow-ups may be over-represented by women from older age groups. Then we may see the typical differences in mean age of onset.

Almost all studies have suggested that males exhibit more or different risk markers, more serious symptomatology, as well as poorer prognosis, than do females. We have reviewed this literature elsewhere (Räsänen et al. 2000). The greater number of males compared with females found in our study and many others suggests that negative results in females should be viewed with caution owing to the danger of type II statistical errors. However, the explanation of sex differences in risk and other factors remains an important task.

Early predictors of schizophrenia – the contribution of the Cohort

Social class at birth

One study in the Cohort (Mäkikyrö et al. 1997) has linked child's schizophrenia with higher social class. The cumulative incidence of schizophrenia until 23 years was 1.14 % among young persons from the highest social class I (determined according to father's occupation) and 0.47 % among children from lower social classes (a twofold increase in risk; $P < 0.05$). In addition to higher education, fathers had a great deal of serious psychopathology, especially alcoholism. This result is surprising and may be a related to rapid social change in Northern Finland. We note that similar findings have been reported by other birth cohort studies (Done et al. 1991; Jones et al. 1994a). Other cohort designs, e. g., first-episode studies, usually find that schizophrenia is linked with poor social status of parents (Jones et al. 1993), although it is also apparent in higher social classes.

Adverse events during pregnancy and delivery

In the Cohort, risk factors for schizophrenia identified during the pregnancy period or at birth (obstetric mishaps) were low birth weight and short gestation, as well as their combination, and prenatal brain damage (Jones et al. 1998). Few studies report the proportion of schizophrenia which might be attributable to potential risk factors. In the Cohort, low birth weight (< 2500 g) had a population attributable risk of 4.6 % (95 % CI 0.3–6.5), and 6.8 % (5.4 %–7.4 %) of the illness up to age 27 may be attributable to severe perinatal brain damage (Jones et al. 1998) if this is a causal relationship.

These results agree with a large body of previous literature which links abnormalities of pregnancy and complications of delivery with increased risk of adult schizophrenia. However, many previous studies will be compromised by recall and selection effects. Some cohort studies have failed to confirm this effect. Most studies state that obstetric complications are more prevalent in men destined to develop schizophrenia (Seeman and Lang 1990), although small numbers of women in many samples, including the Cohort, often hamper analysis.

Examples of specific factors that have been reported are delayed fetal growth, infections, poor nutrition, and hypoxic-ischemic damage. The meta-analysis reported by Geddes and Lawrie (1995) found a pooled odds ratio of 2.0 for an association between exposure to obstetric complications and development of schizophrenia. It did not take into account work from this Finnish Cohort nor, of course, other (cohort) studies that have been published subsequently (e. g., Rosso et al. 2000). It remains uncertain whether or not obstetric complications are the result of pre-existing fetal abnormalities. The most recent study, by McNeil and Cantor-Graae (1999) found no support for suggestions that

pre-existent fetal abnormality precedes obstetric complications in the histories of individuals with schizophrenia.

CNS viral infection during childhood

The Cohort was the first population-based study to confirm the association between childhood exposure to infections and the later development of schizophrenia (Rantakallio et al. 1997). Central nervous system viral infections during childhood carried an increased risk of adult onset schizophrenia and other psychoses (OR 4.8; 95 % CI 1.6–14), with a population attributable fraction of 4 % (95 % CI 1.9–4.8). These results concord with earlier studies which provided indirect evidence for an involvement of infections on the etiology of schizophrenia during the prenatal period and childhood (Westergaard et al. 1999).

Early motor milestones

In the Cohort, children who later developed schizophrenia were delayed in the attainment of motor milestones at age one. Among children who were late in learning to stand, walk or become potty-trained (defecation) the incidence of schizophrenia was higher (Isohanni et al. 1998a, Isohanni et al., submitted manuscript). There was some evidence of gender differences linking males with slow motor development, and females with delayed bowel and probably also with bladder control. This effect was also found in other functional psychoses but not in severe hospital-treated non-psychotic disorders.

These results partly replicate work in the British 1946 cohort where antecedents of schizophrenia (Jones et al. 1994a) and of affective disorder (van Os et al. 1997) differed more in terms of degree (magnitude of quantitative effects), than kind (which characteristics were identified as risk factors). Our findings provide evidence that the developmental effect inferred by Jones et al. (1994a) can be observed even earlier than that study indicated, perhaps in the first 12 months, as well as after two years. These findings extend to general population samples the results of the landmark study by Walker and Lewine (1990). They compared motor development in children who subsequently became schizophrenic, and healthy siblings by rating the parents' 'home-movies'. The pre-schizophrenics were more likely to show motor abnormalities such as clumsiness or odd movement; they reacted less and more slowly, and they had poor motor co-ordination. Clinic-based designs have also suggested that boys may have more premorbid motor abnormalities (Nicolson et al. 2000).

Early familial environment

In the Cohort, unwanted pregnancy (Myhrman et al. 1996) and depression during the antenatal period (Jones et al. 1998) were more common among mothers whose children later developed schizophrenia (although the latter effect may be questionable; compare Jones et al. 1998 with Veijola et al. 1998). There are comparatively few studies on the relationship between events during pregnancy and severe mental disorder in the offspring. Extreme maternal stress during pregnancy has been associated with the development of schizophrenia in the child (Huttunen and Niskanen 1978). These findings suggest that aspects of the early familial environment can have an adverse impact on later mental health. However, in the Cohort, living in a single-parent family did not predict schizophrenia (Mäkikyrö et al. 1998), nor did "grand multiparity" (being brought up in a family in which there were six or more children; Kemppainen et al. 2000).

The role of non-genetic familial factors is not clear. Much discussion, particularly from the earlier literature, (see, e. g., Alanen 1997 for review) has suggested that psychological, interactional and familial aspects are involved in the etiology, course and treatment of schizophrenia. Empirical testing of these hypotheses has been one major cause of dispute in the scientific community. Many possible psychosocial predisposing factors have been suggested, such as disturbances in parent (or mother)-child relationship (Jones et al. 1994a), communication deviance in the family (Goldstein 1987) and several social factors. In other words, a predisposition for schizophrenia is probably partly inborn and partly acquired. The direction of causality is, however, not clear. The relationship may be circular because the offspring, known to be deviant developmentally, may have elicited abnormal responses from adults.

Scholastic performance

In the Cohort, adolescents who were below their expected, normal grade (mainly due to low intelligence) were three times more likely to develop schizophrenia than those in their normal grade, but low school marks did not predict schizophrenia (Isohanni et al. 1998b). In another Finnish sample from Helsinki, pre-schizophrenic persons performed significantly worse than controls in non-academic skills (sports and handicrafts), contrary to our findings (Isohanni et al. 2000), but not on academic or behavioral factors (Cannon et al. 1999). A surprising finding from the Cohort was that 11 % of pre-schizophrenic boys had excellent school marks (on average) compared with 3 % in the normal population (OR 3.8; 95 % CI 1.6–9.3) (Isohanni et al. 1999).

Deterioration in school performance has been presented as a pre-morbid or prodromal sign in schizophrenia since Bleuler. The following categories or markers of these school predictors have been presented (Isohanni et al. 1998b): repeating a grade, difficulties in completing the final level of schooling, low childhood educational tests, low school marks, or social and behavioral difficulties. In the Copenhagen High Risk for schizophrenia project (Mednick et al. 1987, Olin et al. 1995) pre-schizophrenic schoolboys were lonely, rejected and emotionally strung, behaved inappropriately, had disciplinary problems and were more likely to have repeated a grade compared with

their controls. Girls were nervous and passive. These high-risk children were judged by their teachers to be vulnerable to future psychotic problems. These markers had considerable predictive power.

Linking adult schizophrenia with excellent pre-morbid performance is a new finding in a population sample and requires replication. If it is true, the result may be relevant both to the preservation of schizophrenia in the population, and to the mechanisms underlying the disorder.

How can we theoretically explain these results?

Early deviance in pre-morbid phase

Schizophrenia has been seen to stem from childhood psychological and behavioral markers, such as social awkwardness and withdrawal (Watt 1978), although the specificity of these abnormalities is low (Jones and Done 1997, Cannon et al. 1997). Our results regarding school performance may be partly explained by these antecedent psychological and behavioral symptoms.

An area that has not been emphasized so far in our reports from the Cohort but will be done in future are sex differences in personality and early behavioral deviance (Lewis 1992, Berenbaum and Fujita 1994, Räsänen et al. 2000). Girls have been shown to have more introspective symptoms; shyness and flat expression of emotion, and boys more behavioral problems and conflicts in the family home (Watt 1978, Seeman and Lang 1990, Walker et al. 1993, Done et al. 1994). The pre-morbid social functioning of schizophrenic males may be poorer than that of females (Childers and Harding 1990, Salokangas and Stengård 1990, Foerster et al. 1991). It has been argued that more male than female schizophrenics have a form of disease due to neurodevelopmental anomaly (Castle and Murray 1991, Castle et al. 1996), and that a neuro-developmental perspective has greater explanatory power for the gender differences in schizophrenia than, for example, the different social roles of men and women.

Schizophrenia as a neuro-developmental disorder

A gradually accumulating body of literature suggests that neuro-developmental dysfunction may precede the onset of the schizophrenic syndrome by many years (DeLisi 1997). A "neuro-developmental" subtype (Castle and Murray 1991, Castle et al. 1996) which is characterized by early onset, poor pre-morbid sociality, and male preponderance has been proposed. Others (Jones 1999) have put forward the view that developmental abnormalities may be more widespread, the majority being hidden within the wide range of normal variation in the population. Thus, a comprehensive model of schizophrenia must encompass these early manifestations of dysfunction as well as the immediate pre-morbid and post-morbid period, and gender. The antecedents we have found may be manifestations of a neuro-developmental abnormality that is already present. The challenge remains to identify other aspects of this causal constellation. We consider them as the building blocks of a longitudinal characterization of the psychotic phenotype, and simultaneously as manifestations of vulnerability. Investigations with genetic data may suggest how to distinguish these two emphases, and enable us to develop a more refined model.

Schizophrenia as a basic cognitive disturbance

For almost a century cognitive impairment has been hypothesized to be a mechanism responsible for the disintegration in individuals with schizophrenia, and there is an increasing trend to define schizophrenia based on cognitive disturbance rather than in terms of phenomenology alone (Andreasen 1999a). An interesting new finding suggests that an extensive cognitive test battery applied to asymptomatic adolescents might predict schizophrenia. Two studies of cognitive tests given to male conscripts (David et al. 1997, Davidson 1999) suggest that performance at this stage can predict future schizophrenia. The latter study had remarkable predictive power.

Cognitive disturbance may exist even in the early pre-morbid phase (Jones et al. 1993, 1994a and b, Isohanni et al. 1998a). In the Cohort, the excess of pre-schizophrenic adolescents who were found to be out of the normal educational trajectory may be explained by cognitive disturbances such as low IQ, be related to impaired attention, or even early thought disorder.

Intelligence

It is well recognized that patients with schizophrenia, as a group, have global intellectual impairments and that these pre-date the onset of psychotic symptoms by many years. In a review and meta-analysis Aylward et al. (1984) found that pre-schizophrenic children, adolescents, and young adults performed below matched controls on a variety of standardized measures of intelligence. Adult schizophrenics seen previously at the Maudsley Children's Department had low IQ as children (Jones et al. 1994b). The extensive study of 50 000 Swedish conscripts showed that the poorer the performance on the test covering IQ plus mechanical and general knowledge was, the greater the risk of schizophrenia (David et al. 1997). These results were replicated in a similar design using the Israeli Draft Board Registry (Davidson et al. 1999). These two studies replicated a population trend in risk first noted by Jones et al. (1994a).

The link between genius and madness is one of the most compelling and enduring myths in common thinking but it has been minimally studied in empirical psychiatric research. Ecological and case-control studies have been attempted, most notably by Karlsson (1983), who showed that psychotic patients were more likely than the remaining population of Iceland to graduate from college, or have a first-degree relative listed in *Who's Who*. The literature contains many reports of gifted and able persons who later developed schizophrenia. It is at least possible for highly

gifted people with creative talents or exceptional IQ to develop the syndrome (David 1999), as we confirmed in the Cohort (Isohanni et al. 1999). This association, if true, is theoretically interesting and relevant both to the preservation of schizophrenia in the population, and to mechanisms of developing schizophrenia. It is possible that deviation from the norm in either direction warrants further study as a risk factor for schizophrenia.

Impaired attention and thought disorder

Impaired attention measured for instance by the Continuous Performance Test (CPT) (Nuechterlein et al. 1986) and Span of Apprehension (SOA) (Asarnow et al. 1991) are the most commonly investigated signs of cognitive dysfunction in schizophrenic patients and their relatives. Attentional defects are more frequent in patients but also in their parents and siblings and in children of schizophrenic patients than in corresponding controls (Cornblatt and Keilp 1994). High-risk children (offspring of a schizophrenic parent) have been found to have poor performance on measures of attention. These characteristics predict poor global social adjustment (Erlenmeyer-Kimling et al. 1998) and also schizotypal personality disorder in adulthood (Squires-Wheeler et al. 1997). Importantly, these signs of impaired attention have been shown to be independent of the state of illness (Cornblatt et al. 1998, Wahlberg et al. 2000) suggesting that the defect may be considered a trait of personality, even in the pre-morbid phase. Such a perspective offers an alternative explanation for the problems at school reported in members of the Cohort.

This may also be the case regarding thought disorder, in itself a measurement of cognitive dysfunction (cf. the Thought Disorder Index, TDI; Holzman et al. 1986, Solovay et al. 1986). Thought disturbances have been found to correlate with attentional defects, which may mean that they have a similar biological basis. It is possible that the TDI may be sensitive to the hypothesized, underlying predisposition in persons who are at high genetic risk for schizophrenia and who may have sub-syndromal TDI signs (Nuechterlein et al. 1986). This hypothesis is supported by evidence that persons who are biological relatives of schizophrenics but who do not have a diagnosable schizophrenic illness tend to have higher total TDI scores than biological relatives of healthy individuals (Arboleda and Holzman 1985, Kinney et al. 1997).

Future research directions of the Cohort

Genetic factors

To date, we have not been able to examine the effect of genetic risk and its possible interactions with the risk factors mentioned above. In the Cohort and its 33-year follow-up between 1999–2001, we are assessing genetic risk using the structured family history method (FIGS or Family Interview for Genetic Studies) with relatives and information from hospital case notes. This offers a unique opportunity to link prospective, extensive developmental data from pregnancy, birth, childhood, and adolescence with genetic data. After this, genetic risk can be added to our analyses of perinatal risk and early developmental deviancies in psychoses. We will be able to test hypotheses such as whether or not genetic risk and the putative early causal factors, act independently or interactively, and whether particular risk factors are associated with particular clinical features. Most earlier studies, reviewed in the following, are not truly prospective.

Twin, adoption and family studies provide strong and consistent evidence that genetic factors play an important role in the familial aggregation of schizophrenia. The presumed neuro-developmental processes leading to the onset of schizophrenia are thought to be strongly determined by genetic factors. The risk decreases from close to more distant relatives (Gottesman 1994). The familial predisposition for schizophrenia is not only for the classic, psychotic disorder but also increases liability to "schizophrenia-like" personality disorders and probably for some other non-schizophrenic non-affective psychoses. Molecular genetics most likely has to search for susceptibility or risk factor gene(s) for schizophrenia, rather than genes for manifest disorder. Unfortunately, we are uncertain of the correct phenotypic boundaries for schizophrenia to use in linkage and association studies.

The pattern of inheritance is complex, and it is not clear whether the familial clustering in schizophrenia is due a single gene, to a few genes or to many genes. Indeed, it is perhaps more likely due to all three different mechanisms operating in different sub-populations of the conditions. Thus, it is very likely that additional factors are involved. It is plausible that multiple genes and multiple environmental factors interact. However, heredity is not a fate but, instead a kind of probability. Concordance between identical twins is approximately 40 %. A total of 89 % of schizophrenia patients have parents who are not schizophrenic, 81 % have no affected first degree relatives, and 63 % will show no family history of the disease whatsoever (Gottesman 1991). All this suggests that environmental factors are causally necessary in at least a proportion of cases (Tienari et al. 1994, 2000). Demonstrating familiarity does not necessarily imply that inherited genetic factors are alone causing the disorder, not even via gene-environment interaction, since families usually share common environment as well as common genes.

The morbidity risk of the relatives of female probands with schizophrenia may be higher for schizophrenia spectrum disorders than that of the relatives of male schizophrenics (Sham et al. 1994). Kringlen (1987) found that monozygotic women have a higher concordance rate of schizophrenia than men. These findings suggest that the causes of schizophrenia are more often hereditary in women than in men.

Interactions with genetic and obstetric complications have been studied. In high-risk designs it has been confirmed (Cannon et al. 1993) that particularly high-risk offspring have suffered obstetric complications. This hypothesis will be tested in the Cohort when genetic data have been gathered.

Brain morphology

As a part of the 33-year follow-up of the Cohort we aim to investigate to what extent, in an unselected population sample, schizophrenia and other psychosis are associated with structural brain abnormalities, and in which regions of the brain these patho-morphologies exist. This will be done using structural MRI scans which we are combining with an extensive cognitive test battery. We aim to identify predictive (gender, genetic risk, pregnancy and obstetric complications, delayed development, childhood CNS infections, low IQ) and associative (clinical features, cognitive disability) factors for these brain abnormalities. In addition to schizophrenia, we will also investigate these associations among other psychoses.

There is evidence of brain abnormalities in schizophrenia (Wright et al. 2000). Both genetic factors and early environmental hazards are thought to contribute to the structural brain abnormalities with ventricular enlargement, cortical atrophies in frontal and temporal lobe and loss of asymmetry being the most common findings (Lawrie and Abukmeil 1998). There are also studies with findings in subcortical structures, such as hippocampal region (Heckers 1997) and thalamus (Andreasen et al. 1994). The neuro-developmental hypothesis of schizophrenia suggests that the brain abnormalities are present early in life but do not manifest themselves as psychosis until late adolescence or early adulthood (Weinberger 1995). Schizophrenia may involve a defect in neuronal migration (Benes 1993), myelination (Weinberger and Lipska 1995) and cortico-cortical pruning (Friston 1998) causing the development of anomalous neural networks (Murray and Fearon 1999).

In many studies, men with schizophrenia have more central nervous system abnormalities than women (Jablensky 1993). Males exhibit more lateralization of cerebral function than do females (McGlone 1980), and the male brain may consequently be less able to "compensate" for those unilateral lesions considered important in the pathogenesis of schizophrenia.

There are no long-term follow-up studies on brain morphology from childhood into adult onset schizophrenia. There is evidence from early-onset schizophrenia that the brain abnormalities exist in early adolescence (Rapoport et al. 1999).

Building a descriptive life-span model

Among its many meanings, a model can be defined as an abstract representation of the relationship between empirical components of the system (Last 1995). An increasing trend in science is to link basic neurobiology, epidemiology and clinical research, as well as to formulate longitudinal pathways from asymptomatic, subthreshold and threshold stages to clinical disease over the life span (Wittchen 2000). Modeling schizophrenia – mostly after onset – is neither a new idea nor an easy task. There are hardly any causative factors that are specific to schizophrenia, although unitary models have been proposed (Andreasen 1999b). Other models, such as Ciompi's (1988), stress the importance of life-span aspects of schizophrenia and present more wide ranging descriptions of the premorbid, acute and chronic phases of psychosis. Cullberg's model (1993 a and b) proposes an integrated three-dimensional etiological view integrating genetic, brain-damage, and psychosocial elements. These elements (and drug abuse) are also emphasized by Murray and Fearon (1999). Alanen (1997) integrates biological, psychological and familial aspects to etiology and treatment, and Cornblatt et al. (1999) aims at the conceptualization of a recognition and prevention program by modeling the development of schizophrenia.

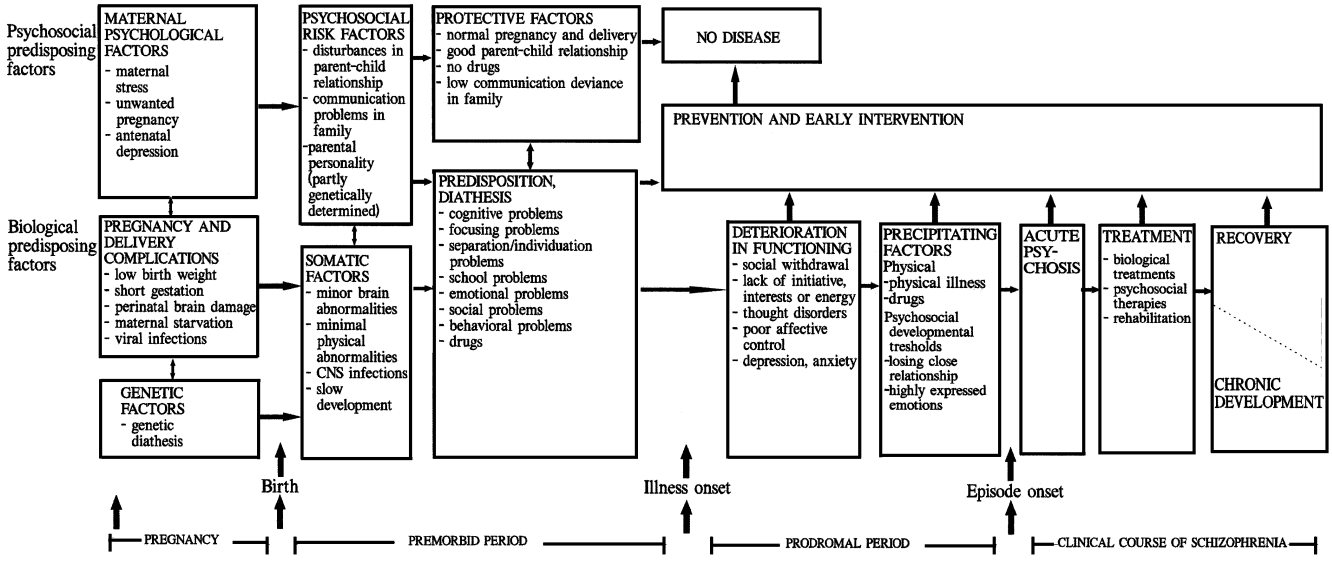

Fig. 1 Life-span developmental model of schizophrenia. Known etiological components are presented. Hypothetical ideas on protective factors are not necessarily evidence based.

We have tried to formulate a comprehensive model of the known etiological components and life-span course of schizophrenia. Our descriptive model of schizophrenia is presented in Fig. 1. Etiological factors during the pregnancy and early childhood are stressed, and the factors presented emphasize our own studies and therefore the availability of data in the Cohort. The model includes all the risk factors which we have summarized in this paper. In addition, we have added some hypothetical and speculative ideas on protective factors which are, as yet, not supported by evidence.

What is the value of this kind of model? The descriptive model we propose in Fig. 1 is not intended to be useful to clinical decision making. We are still far from a useful description of the childhood and adolescent characteristics that predict psychosis (Jones and Done 1997, Jones 1998). We believe that the variety of factors embraced by the Fig. 1 and the range of time periods identified argue for a serious treatment of the longitudinal dimensions to the syndrome that we call schizophrenia. The model may not be very heuristic for an experienced scientist – who may build a model of their own – but it may help young investigators to orient with the topic, with the findings of our Cohort, and with relevant literature. We propose it as heuristic for those who wish to localize their research interest, place their results within a framework, and communicate with other scientists. In the future, we hope to present a more sophisticated quantitative model which can link these diverse factors. We shall use single statistical indices from the study of individual risk factors for schizophrenia identified in the Cohort as building blocks for a larger structure, which is more explanatory in orientation, than purely descriptive.

It remains the case that no single premorbid sign or risk indicator has yet been identified that is specific for schizophrenia. No powerful risk or antecedent factor has been identified that is useful for prediction in the general population. The number needed to treat (NNT) for any of the risk factors identified in this review is high, as is the number needed to inconvenience unnecessarily (Jones and Croudace, in press). However, the immediate prospects may be much better in clinic samples who may already be experiencing features of the prodromal phase. These clinics are often active research facilities also advancing clinical practice. Other advances come from selected series which show strong genetic liability, e. g., where identical twin or both parents suffer schizophrenia (McGorry and Jackson 1999, Cornblatt 1999).

In summary, the findings from the Cohort and from elsewhere show that some young adults destined to develop schizophrenia show deficits in motor, cognitive, scholastic, and social performance long before they have psychotic symptoms; some abnormalities are present in very early life. Our future aims are to investigate whether a particular clinical syndrome and other social outcomes are associated with childhood abnormality and a longitudinal phenotype. We are investigating the roles of structural brain and cognitive abnormalities that may be the basis of a neuro-developmental lesion, together with genetic factors. In addition to the scientific pursuit of understanding, these investigations have the ultimate goal of prediction within the context of effective, ethical preventative interventions.

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