The early origins of schizophrenia

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Large population-based studies indicate that children who will as adults develop the clinical syndrome of schizophrenia are different from their peers in terms of the acquisition of a range of neurological, cognitive and behavioural characteristics. These studies are also identifying possible causal factors which might operate early in life and so be responsible for a longitudinal aspect of the disorder. Studies of the brain yield results consistent with the multi-system nature of the clinical syndrome of schizophrenia in adult life, and with the notion of a longitudinal or developmental phenotype, of which the adult syndrome is but one aspect. Work in these areas is reviewed with special reference to national birth cohorts from Britain and Finland.

The idea that schizophrenia has its origins in early life is as old as the first descriptions of the disorder. Kraepelin\(^1\) and Bleuler\(^2\), who bear considerable responsibility for our current concepts of schizophrenia, both described abnormalities in the personalities of children who would later suffer from it. The idea is also popular; an article\(^3\) in a recent edition of Readers’ Digest used the notion that peculiarities of fetal brain development may lead to schizophrenia as an illustration of the ‘miracles of the brain’. However, despite being both old and popular, the idea is not necessarily correct and its validity and underlying mechanisms are topical issues in schizophrenia research. They represent much of psychiatry’s current contribution to the wider epidemiological debate which forms the subject of this issue.

In this article, early origins will be discussed in terms of characteristics of children who, as adults, will develop schizophrenia, and in terms of possible causal factors which may precede these characteristics. Preference is given to evidence from population-based, longitudinal studies, a number of which have yielded important clues recently. The plausibility of the ideas presented is discussed in terms of relevant evidence from biological psychiatry research.
What is a case of schizophrenia?

A brief description of what is meant by schizophrenia may be helpful for the non-psychiatrist. For much of this century, schizophrenia research has been dogged by loose and unreliable definitions. The demonstration in the early 1970s of unacceptable discrepancies in definitions used by English and American psychiatrists precipitated the development and widespread use of operational diagnostic criteria, now available across the spectrum of psychiatric conditions. The trap of mistaking reliability for validity in these definitions is well recognised, but they have made research evidence at least comparable between studies.

All operational systems rely on a cross-sectional definition of schizophrenia as a clinical syndrome. Core features include certain types of auditory hallucinations, particularly voices heard talking in the third-person, changes in thought construction and form and, finally, bizarre delusions often involving a person's ego boundary such that thoughts may be available to others or a person is influenced by outside forces. These positive, psychotic phenomena comprising the core diagnostic features, usually occur together with changes in an individual's behaviour or social functioning. There may also be, so called, negative features, such as restriction of the range of emotions, and decreased ability to initiate thoughts and ideas. These are thought of heuristically as cognitive analogues of some motor features of the Parkinsonian syndrome.

None of the core features is pathognomonic, although the presence of at least one, in the absence of an obvious organic precipitant such as drug misuse, is essential for the diagnosis. Thus, several psychological systems can be affected, including perceptions in various modalities, the generation, construction of and inference from thoughts, emotions and volition; any neurobiological explanation must involve more than one brain area.

Adult onset schizophrenia as a developmental disorder

There is a characteristic association between age and the emergence of this clinical syndrome, regardless of the detailed differences between classification systems and exactly how onset is defined. Figure 1, taken from work by Häfner and colleagues, shows the frequency distribution of ages at onset. Much is made of the slight but reliable difference between men and women but, for both sexes, the association between age and incidence is striking and suggests a prime facie case for schizophrenia being related to the life course and being, in some sense, a developmental disorder. The clinical formulation of this as a developmental, rather than a degenerative, process depends largely upon
whether there are abnormalities or differences demonstrable before the onset of the schizophrenia syndrome.

Are there abnormalities before the onset of the syndrome of schizophrenia?

There is now firm epidemiological evidence that there are such abnormalities. However, they appear to be quite different from the characteristic features of the syndrome of schizophrenia, and their identification and description beg a number of questions. Do they represent vulnerability to a separate disorder or are they manifestations of that same disorder which change over time? Does their identification in some individuals but not others indicate heterogeneity of the clinical syndrome of schizophrenia, or in terms of its aetiology? A thorough description of any abnormalities and their prevalence is the starting point to answer these questions.

Studying the early origins of schizophrenia

The problems that apply to research in this area are not unique to schizophrenia but, set within the range of developmental epidemiology covered in this issue, the task is probably towards the more problematic end of the scale. Information bias arising from retrospective recall, with
its systematic distortions and general lack of detail, is added to selection bias; cases and controls with particular characteristics tend to be recruited in case control studies or retained in follow-up samples. The time scale between early childhood, or even fetal life, and the onset of schizophrenia spans several decades (Fig. 1), adding to the risk of these biases and to the difficulty of designing studies. A particular constraint for schizophrenia arises from it being relatively rare.

For analytic epidemiology, large cohort studies, or case-control studies nested within clearly identified cohorts exploiting prospective data are the cornerstone of research. Thus, studies are usually opportunistic, using data collected originally for other purposes. In this article, attention is focused on three general population cohorts, with reference to work from other representative samples. From Britain, two national birth cohorts from 1946 (the Medical Research Council National Survey of Health and Development; NSHD) and 1958 (the National Child Development Study; NCDS) have now been followed into the age at risk for schizophrenia and have examined early antecedents. The third sample considered in detail here is the North Finland 1966 cohort. This was assembled from pregnant mothers so that follow-up of the cohort members began during their own gestation.

The NSHD, described most recently by Wadsworth, has its origins in a survey of all births in England, Scotland and Wales during the week 3–9 March 1946 from which a stratified sample of 5362 children has been followed regularly and a large amount of data collected over the ensuing decades. Data on childhood analysed in the studies of schizophrenia come from the 11 contacts with the survey members prior to age 16 years during which data were collected by health visitors, school nurses and doctors, teachers, mothers and the children themselves.

The NCDS began with the British Perinatal Mortality Survey of 1958. This included some 98% of all births in England, Scotland and Wales during the week 3–9 March 1958, the same birth week as the NSHD. Four subsequent attempts (ages 7, 9, 16 and 23 years) to trace members of the cohort to monitor physical, educational and social development became known as the National Child Development Study (NCDS 1–4). The numbers of subjects followed up at each stage were 15,398, 15,303, 14,761, and 12,537. This account is of work by Done and colleagues.

Follow-up of individuals who developed mental illness has been undertaken both in the NSHD and in the NCDS. Methods of identifying individuals who developed schizophrenia used similar methods in both cohorts, although the precise definition of schizophrenia differed. The methods, together with the main results, have been compared by Jones and Done.

Of 4746 individuals in the NSHD alive in the UK at age 16, 30 (20 male) met DSM-IIIIR criteria for schizophrenia or schizo-affective
disorder (for details, see Jones et al\textsuperscript{12}). In the work on schizophrenia, these were compared with the 4716 individuals remaining in the risk set. In the NCDS, there were 29 individuals with a PSE/CATEGO diagnosis of 'narrow schizophrenia' who had data collected during at least two of the three childhood interviews. In the schizophrenia studies, these were compared with a random, 10\% sample of NCDS subjects never admitted to hospital for psychiatric treatment, who had been traced at least once in any NCDS sweep.

Rantakallio's North Finland 1966 birth cohort consists of 12,058 unselected live births in Northern Finland (Oulu and Lapland provinces) whose expected date of delivery fell in 1966, representing 96\% of all such births\textsuperscript{8}. Detailed data are available from mid-pregnancy and the post-natal period, with delivery data for a stratified sample. The subjects have been studied further at ages 1 and 14 years, with further information available through the remarkable opportunities for record linkage in Finland. From a risk set of 11,017 cohort members alive in Finland at age 16 years, 76 cases of DSM-III-R schizophrenia were identified up until age 28 years (see Isohanni et al\textsuperscript{16} for details).

What are the pre-psychotic abnormalities in schizophrenia and when do they begin?

The two British birth cohorts have provided considerable insights into the characteristics of children who, as adults, develop schizophrenia. Early developmental milestones, behaviour and educational achievement or IQ are considered here.

There is considerable evidence from a variety of study designs that these characteristics are in some way deviant prior to psychosis. Aylward et al\textsuperscript{17} reviewed the literature up to the early 1980s regarding IQ; few studies were population based and many used out-dated concepts of schizophrenia. However, there was consistent evidence of a premorbid deficit in IQ. Convincing evidence of early neurological differences has come from studies of children at high risk of schizophrenia by virtue of having an affected parent; these studies are considered later. A novel approach yielding impressive results was taken by Walker and Lewine\textsuperscript{18} who collected old cine films of families where one child was later to develop schizophrenia. During the first 2 years of life, objective assessments of motor behaviour distinguished the pre-psychotic child from their siblings. Effects involving posturing and choreo-athetoid movements were subtle and tended not to be apparent at later ages. Would similar, direct evidence of differences in motor and cognitive development be demonstrable in unselected population-based samples?
Jones and Done\textsuperscript{15} reviewed recent work from the two British cohorts\textsuperscript{12-14} and attempted a synthesis of results. The aim was to answer the question posed above and to test the specific hypothesis that any abnormality in development of psychomotor skills and cognitive functioning in children destined to develop schizophrenia as adults would be best described, not as excessively 'abnormal', but as a continuous risk (or protective) factor for the illness.

**Early milestones and motor function**

In the NSHD an interview was conducted by health visitors when the survey members were 24–26 months old. Mothers were asked to recall the age at which sitting/standing/walking alone, beginning to talk and cutting of first tooth were reached\textsuperscript{12}. The mean ages at which speech and gross motor milestones were reached were consistently later for children who later developed schizophrenia than for controls, independent of the major confounders of sex and social class. This was particularly so for the age at walking independently (cases 1.2 months later). Although of statistical and theoretical significance, this direct evidence of developmental differences in the cases of schizophrenia was subtle and would have been of little significance to the parents; all the children were walking by 2 years.

At the health visitor interview at age 2 years, pre-schizophrenic cases were almost 5 times less likely to have reached all their milestones; speech, the latest of these milestones in the general population, was the one not attained. Later in childhood, school doctors were more likely to note non-structural speech defects in the pre-schizophrenic children than in their peers and, throughout childhood, health professionals were 3 times more likely to note any speech problem in the pre-schizophrenia group. Although speech seemed particularly affected, the pre-schizophrenic children showed a small delay on all milestones but, as Walker and Lewine\textsuperscript{18} noted, they seemed to 'catch-up', indicating that they may be delayed in terms of some latent developmental factor.

In the NCDS, there were several early measures and indicators of motor function (e.g. balancing on one leg) and neurological soft-signs (e.g. tics, twitches, epileptic attacks) collected by school doctors when the survey members were age 7 and 11 years\textsuperscript{13,15}. At 7 years, those who developed schizophrenia were more abnormal than controls on coordination and clumsiness factors, and regarding incontinence. At age 11, those who later developed schizophrenia were significantly more abnormal on hand preference/relative hand skill due to reduced laterality.
of hand skill, co-ordination, CNS impairment and regarding a group of miscellaneous deficits, predominantly incontinence and articulation.

The evidence from each British cohort was consistent with the other. Those from the 1946 cohort indicated that motor and speech development during the first 2 years of life were slightly delayed prior to schizophrenia. Through childhood, school doctors noted abnormalities in speech not due to structural problems. Data from the 1958 cohort confirm that these differences were not merely reflections of developmental timing; at ages 7 and 11, speech and other aspects of CNS function were rated as being qualitatively abnormal prior to schizophrenia.

Educational achievement in the British cohorts: tests of IQ

In the NSHD results of a range of cognitive tests were available from four time points, ages 8, 11 and 15 years. Children destined to develop schizophrenia scored consistently lower than the controls at all three ages across all sub-scores. Mean values of a composite ‘IQ’ score, expressed as standard deviations (15) from the mean (100), were lower in the cases than controls by 30% of a standard deviate at age 8, 20% at age 11, and 50% of a standard deviate lower at 15 years, each result achieving statistical significance.

The general ability tests used in the NCDS were similar to those used in the NSHD. At the ages of 7 and 11 years, children who later developed schizophrenia performed more poorly than the population controls on a wide range of tasks which included general ‘IQ’, oral ability and quality of speech. Not only was there a consistent deficit across many of the varied tests but, as in the NSHD, this deficit was found consistently at three different ages. Social disadvantage, lack of family interest and obstetric complications (see Done et al.) did not account for the effects.

These deficits are in line with those reported by Aylward et al. and, in both studies, the cognitive deficit appeared to be broadly based. Pragmatic or crystallised aspects of intelligence were as deficient as mechanical or fluid aspects, and the decrement was apparent when the tests were first administered in mid-childhood.

Jones and Done combined IQ scores from the pre-cases in both birth cohort samples in order to examine whether the mean deficits were due to a subgroup of very abnormal individuals. Although there were many caveats, the availability of over 50 comparable, standardised IQ scores on 11 year old children who were to develop schizophrenia as adults, together with population controls represented a valuable opportunity. Were the decrements in scores due to a subgroup of very deviant
individuals, perhaps having a developmental sub-type of schizophrenia, or was there evidence of a population shift? Both sets of IQ scores had been ‘normalised’ to give a population mean of 100 and standard deviation of 15, and comparison was made with a sample of 300 controls from the NSHD.

The frequency distribution of IQ scores is shown in Figure 2. Examined simply by eye, there appears no evidence of bimodality, either between cases and controls, or within the case group, alone. Scores for the majority of cases were within two standard deviations of the mean value for the controls, although scores above the mean were less common than scores below it. There was insufficient statistical power to attempt a formal, confirmatory admixture analysis but there was little doubt that cases were rarer from the population with scores above the mean value (i.e. a score of zero in Fig. 2) than they were from those with scores below it.
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The parsimonious explanation is that the lower the IQ at 11, the greater the risk of schizophrenia; the majority, or even all of the children destined to become cases of schizophrenia, clever or dull, showed a slight decrement in observed IQ, thereby shifting the entire distribution and resulting in a lower group mean. The downward shift shown by the combined case population (40% standard deviation) may have been due to an effect on each individual. A more formal statistical approach taken in the NSHD alone supported a similar conclusion. Whether this may be a deleterious effect lowering IQ or some manifestation of a protective effect associated with higher IQ is as yet unclear. What is clear is that there is a deficit in IQ associated with schizophrenia which exists before the onset of the clinical syndrome of psychosis.

These findings may not be specific to schizophrenia amongst serious mental illness. In the NSHD, the developmental differences have also been demonstrated to a lesser degree in those who developed chronic affective (depressive) illness. It is of interest that, in contrast to schizophrenia, these individuals were predominantly women. The consequences of early vulnerability must be attenuated by many factors—not all those at increased risk develop a disorder—and it is likely that sex may play a major role in determining outcome in such a model.

**Behaviour**

Both the NSHD and NCDS showed differences in behaviour between children who later developed schizophrenia and their peers. As early as age 4, children in the NSHD who would develop schizophrenia preferred to play alone, rather than with other children. This tendency for a solitary, 'schizoid' habit continued throughout childhood and was demonstrable in ratings by teachers, and even the children themselves. This was similar to the social awkwardness and withdrawal demonstrated elsewhere in the school records of adults with schizophrenia.

In the NCDS, behavioural ratings also showed premorbid differences, although the tests and the effects demonstrated were somewhat different. Boys in particular showed an excess of 'naughty' behaviours which were not apparent in the earlier cohort, perhaps due to the different sample or to differences between the instruments used. However, differences between cases and controls were clear and provided further evidence for expression of abnormality during development before the appearance of the schizophrenia syndrome. It seems reasonable to link these behavioural differences to the more direct evidence of neurological involvement arising from the studies of IQ and early milestones.
What about the brain?

Nowadays, the symptoms of schizophrenia are to be considered as products of disordered neural systems and, as discussed above, their diversity suggests that many such systems may be affected. Similarly, the developmental syndrome appears to involve maturation of motor and speech systems, and those involved with cognitive abilities and behaviour. Is there evidence of brain changes in schizophrenia compatible with a multiple systems disorder and changing manifestations with age? Is the notion of a vulnerable brain now more useful than a vulnerable personality?

Differences in various aspects of brain structure have been demonstrated throughout this century and they are compatible with a developmental model\textsuperscript{24,25}. The advent of computerized X-ray tomography saw the seminal study of Johnstone and colleagues\textsuperscript{26} which showed that a group of elderly subjects with chronic schizophrenia had larger lateral cerebral ventricles than controls. Structural neuroimaging research now uses magnetic resonance imaging routinely. The sampling methods may have lagged behind the technology\textsuperscript{27}, but appropriate selection of cases and controls, and the control of confounding factors, is now routine, certainly in structural neuroimaging where the finding of cerebral ventricle dilatation is robust, albeit rather more limited than suggested by the early studies\textsuperscript{28,29}.

Schizophrenia is not, though, a disorder of the cerebral ventricles. The enlargement of these is interpreted as a marker of cerebral pathology which neuroimaging and neuropathological studies indicate may be diffuse\textsuperscript{25}; the thalamus\textsuperscript{30}, cerebral cortex and white matter\textsuperscript{31} have all been shown to be the site of abnormality or difference. It may be that changes in some of these areas give rise to the motor and speech effects and general decrement in intellectual functioning in schizophrenia seen early in life, whereas pathology in other systems is responsible for the positive symptoms and signs of psychosis which make up the adult syndrome; the temporal lobe and circuits of the hippocampus being likely, but not sole, candidates\textsuperscript{32,33}.

Evidence that this brain pathology may already exist during early life comes from diverse sources. Firstly, people with schizophrenia are more likely than controls to have, so called, minor physical abnormalities\textsuperscript{34}. These are developmental abnormalities such as furrowed tongue, low set ears, curved fingers which may represent fossilised evidence of damage \textit{in utero} to ectodermal structures, one of which is the brain. Some of the neuroimaging findings, particularly large cerebral ventricles, have been demonstrated at onset of the psychosis\textsuperscript{35} before drug treatment has begun\textsuperscript{36,37} and appear not to be progressive\textsuperscript{38-41}. These findings are
compatible with a developmental lesion and incompatible with a progressive, degenerative process.

Recent neuropathological findings provide much more direct evidence of a developmental explanation for brain changes seen in adults with schizophrenia. One of the most replicable findings in this area has been a conspicuous lack of gliosis, the neural scarring which follows lesions other than those which occur during early development. Furthermore, disturbances in the strict laminar architecture of the cerebral cortex, with cells characteristic of the superficial cortical layers misplaced deeper than they ought to be, are explicable only in terms of perturbations of the usual ‘inside out’ development of the cortex. Such cortical damage might result in widespread dysfunction, either directly or secondary to attenuated cortical circuitry, and gives rise to the possibility that a problem in a single process may give rise to widespread structural and functional consequences, just as are found in schizophrenia. Is such a model compatible with the fact that the most characteristic of those manifestations, the symptoms and signs of psychosis, are silent until early adult life? Again, multiple sources of evidence suggests that it is.

In monkeys, prenatal lesions of the dorsolateral prefrontal cortex can remain undetectable until sexual maturity when there is a catastrophic development of deficits in neuropsychological tests which were performed adequately before, perhaps by other cortical regions. Similarly, Lipska and colleagues have shown that prenatal lesions in the hippocampi of rats remain apparently silent until adult life when there is an abnormally dramatic response to stress and challenge with amphetamine. In humans, Benes has demonstrated that the development (myelination) of circuitry to and from the hippocampus is complete only in adolescence, providing a mechanism whereby a lesion affecting this area may not be apparent until these pathways are mature. It is unclear whether this represents an inevitable route to schizophrenia, determined as soon as the early lesion appears, or whether this is a vulnerability to psychosis with which later factors interact.

Is this vulnerability of the brain restricted to a sub-group of schizophrenia? Two lines of evidence from the neuroimaging literature suggest that it may not be. Like many continuous biological variables identified as risk factors for disease (e.g. blood pressure for stroke), there is considerable overlap between values of the sizes of cerebral structures for those unaffected and affected by schizophrenia, even though there are clear differences in group means. Attempts to identify a subgroup of cases with particularly large cerebral ventricles have failed; the distribution of values is always best described by a single curve with no evidence of bimodality, although the whole population of schizophrenics may be shifted relative to controls. Jones et al demonstrated a similar effect by using the distribution of ventricle
volume in the normal control population as a reference, thus avoiding an arbitrary definition of abnormality. There was a clear linear relationship between ventricle volume and risk of schizophrenia: the larger the volume the greater the risk. This finding was compatible with the notion that the majority, not a minority, of cases had ventricles rather bigger than they should have been.

The second line of evidence comes from studies of discordant monozygotic twins and sibling pairs. In these studies, affected cases do not represent a homogeneous subgroup of brain structural abnormality, but are each predictably different from their twin or sibling; all cases were affected to some degree. These conclusions regarding cerebral abnormality are reminiscent of those for childhood IQ from the two British birth cohorts (Fig. 2). There is no affected sub-group of cases; group differences may be due to effects on the majority of cases, to a greater or lesser extent perhaps resulting in greater or lesser vulnerability.

**Causes and mechanisms of a developmental syndrome prior to schizophrenia**

Early manifestations of schizophrenia necessitate early causes, at least in terms of establishing predisposition. The true cluster of necessary causes of the schizophrenia syndrome for many individuals may well include later, precipitating factors such as adverse life events or acute febrile illness, but these are not discussed here. Simple classification of remote causes into genetic and environmental is useful, albeit an obvious over-simplification.

**Genes**

The differences between brains of discordant monozygotic twins discussed above suggests environmental factors are involved, whereas twin, family and adoption studies suggest a large genetic component to vulnerability to schizophrenia. The latter cannot be a sufficient cause of the schizophrenia syndrome as monozygotic twins can remain discordant throughout the period of risk for the disorder, with both unaffected and affected individuals passing-on an increased risk to their children.

If genetic factors were responsible for the early origins of schizophrenia then those who have these genes may be particularly likely to show signs of the developmental syndrome. The ‘high-risk’ study design involves
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following-up children of mothers with schizophrenia, ideally until they themselves have passed through the period of risk for the disorder. The most influential of these studies which have measurements in childhood are the New York high-risk project\textsuperscript{59}, the Jerusalem infant development study\textsuperscript{60} and the high-risk study of Barbara Fish\textsuperscript{61,62}. The subjects are still in their teens and twenties, and full information on outcome in the cohorts will not be available for another 10 years or so. However, data on infant and early childhood development among the high-risk children are available, with a high degree of consistency between studies.

Developmental abnormalities were found in 25–56\% of high-risk children during different stages of childhood. In the neonatal period, hypoactivity, extreme variation in alertness, hypotonia and poor ‘cuddliness’ were noted. Developmental milestones were delayed in infancy and Fish noted a disordered pattern of acquisition of these milestones which she has termed ‘pandysmaturation’\textsuperscript{62}. In early childhood, soft neurologic signs, in particular poor motor co-ordination have been noted, and in later childhood deficits in information processing and in attention occur, particularly in the New York sample.

The question which remains to be answered is whether the children who have displayed these neurodevelopmental abnormalities throughout childhood will develop schizophrenia or a schizophrenia-spectrum disorder in adulthood. However, the results are strikingly similar to those from the British birth cohorts discussed above, and it seems highly likely that the different designs are studying the same phenomena, with the high-risk samples able to gather more detailed data. Genes may be part of the cause of the developmental syndrome\textsuperscript{63} and it is feasible that they may be involved in the genesis of brain abnormalities. As for what the genes are, molecular genetics appears to be making progress in schizophrenia now after one or two false starts\textsuperscript{64}, but whether genes associated with schizophrenia can be shown to be active during development remains to be seen.

Early environment

There are consistent associations between a number of events before or around the time of birth and later schizophrenia, reviewed recently by Murray\textsuperscript{65}. There is no consensus as to either a critical time during development, or the nature of the risk factors, themselves. Analogy with childhood epilepsy and cerebral palsy may be useful; like schizophrenia, these disorders have a similar incidence throughout the world. For all conditions the direction of causality is unclear for some associations
regarding abnormal events at and around birth where already abnormal babies may, themselves, instigate abnormal parturition\textsuperscript{66,67}.

People who develop schizophrenia are born in winter and spring months slightly more frequently than the general population\textsuperscript{68}, suggesting they may have been exposed to environmental events, such as infections, which are more prevalent at those times. Similar effects are demonstrable for other conditions ranging from cerebral palsy to diabetes\textsuperscript{69} with the common thread that prenatal infection may be causal. Regarding schizophrenia, influenza has been implicated by ecological studies showing association between birth dates in adults with schizophrenia and the timing of the great influenza epidemics\textsuperscript{70,71}, particularly that for 1957/8\textsuperscript{72,73}, where mid-gestation seemed to be the crucial time. There is yet to be a convincing demonstration of this effect in individuals known to both have been exposed to influenza and to have developed schizophrenia. The NCDS was ideally placed to investigate this as its survey members were \textit{in utero} during the 1957 epidemic. No effect was demonstrated but statistical power was low for what is likely to be a small effect and the exposure defined loosely\textsuperscript{74}; the jury is still out on this one and evidence is still accruing.

Prenatal famine during early gestation appears to increase risk for men and women in a dose dependent way\textsuperscript{75,76} as does rhesus incompatibility with the mother, at least in men\textsuperscript{77}. Abnormal events around birth, so called obstetric complications, have been repeatedly demonstrated as being more common in the histories of people with schizophrenia. Geddes and Lawrie\textsuperscript{78} performed a meta-analysis of studies. They showed that there may be considerable publication bias in this literature and that prospective, population based studies tended to be largely negative. These latter studies included the NCDS\textsuperscript{13} although neither this, nor the National Collaborative Perinatal Study\textsuperscript{79} gave a completely clean bill of health to the babies who developed psychosis, or to their mothers\textsuperscript{80}.

The third birth cohort considered in detail in this review, the 1966 North Finland cohort based at the University of Oulu, has recently reported findings which extend both the range of abnormal pregnancy events which may raise the risk of schizophrenia and extend the length of the vulnerable period. The strength of the evidence comes from the population base of the data, collection of which began in pregnancy, record linkage in order to identify adult outcomes, and the existence of a wide literature from which to draw hypotheses. Pregnancy and postnatal events did predict schizophrenia. There was evidence that the vulnerable period during which time possible CNS insult increases the risk of schizophrenia extended into childhood\textsuperscript{81,82}.

In the North Finland cohort, the demographic characteristics and previous obstetric histories were similar for the mothers of children who developed schizophrenia as for the mothers of those who did not\textsuperscript{83}. The
mothers of the former group were almost twice as likely to be noted as more depressed than usual during pregnancy but the standard recording of other information and the similarity in obstetric risk of the mothers makes it unlikely that any further differences were the result of information bias, as was suggested by Sacker et al. This may represent, though, some genetic liability to mental illness.

Fetal growth appeared to have been attenuated; the prevalence of low birth weight was more than doubled in the schizophrenia group but so was short gestation. The combination of these events was more than 3 times as common in the case group. That children who would develop schizophrenia were more likely to be born early, but appropriately grown (in terms of weight) was reflected in relative risk of unity for being below the 10th centile of birth weight adjusted for gestational age. Why were children who would develop schizophrenia so likely to be born early?

At birth, a random sample of mothers was assessed on the basis of their antenatal clinic records as to whether or not they had suffered a significant fever (> 38°C) during the third trimester. This was an indirect opportunity to test in individuals the hypothesis linking pre-natal viral illness and schizophrenia, although in our present state of knowledge it may be fever and not infection that is the primary event. Mothers of children who later suffered schizophrenia were nearly 4 times as likely to have suffered a fever. This was significant with 90% confidence and, given the prior hypothesis, was unlikely to be a chance finding.

There was evidence of early brain damage. As the study was originally set-up in order to examine the causes of childhood epilepsy and mental retardation, a group of children had been identified as having suffered from perinatal brain damage, defined as detention in or re-admission to a children's hospital, neonatal convulsions, low Apgar scores (0 at 1 min or < 5 at 15 min) or a diagnosis of asphyxia (based on arterial blood gas analysis and need for assisted ventilation), intraventricular haemorrhage (based on CSF analysis) or brain injury in the new-born period (clinical diagnosis plus abnormal neurological signs at discharge from paediatric unit). Almost 5% of babies who survived such severe perinatal brain damage later developed schizophrenia. If this were causal, almost 7% of schizophrenia in the cohort up to age 28 may have been attributable to such damage. These findings regarding hypoxia and other serious neonatal events are supported by evidence from a study of routine records in a Scottish population.

Taking the infection and brain damage theme further in terms of time and the agents involved, Rantakallio and her colleagues examined the risk of schizophrenia following documented infections of the central nervous system (CNS) during childhood; just as for perinatal brain damage, these had been identified independently within the cohort.
Risk of schizophrenia following a CNS infection in childhood was raised approximately 4-fold, even higher for viral infections. Once again, assuming causality, the data suggested a population attributable fraction of around 4%. Given that the infections identified were likely to be the most severe ones, it is possible that the true attributable risk is higher if less severe infections can also increase the risk.

These pieces of independent evidence regarding early risk factors are of particular interest in that they are compatible with damage, rather than being merely markers of existing attenuated development as might be caused by a purely genetic event. The sizes of these effects is considerable when compared with other putative aetiological variables, including genetic associations and on this basis one might conclude that they may be causal or at least closely associated with true causes. However, it is premature to conclude that either might be a sufficient cause, and a study which would be able to test the hypothesis of an interaction between genetic risk and such damage prospectively has not been reported.

Is it all biological?

There are some pieces of the aetiological jigsaw which, despite fitting in terms of timing, are less easy to accommodate into a purely biological perspective of the early origins of schizophrenia and await a synthesis of social and neurobiological theories. Death of the father during pregnancy, interpreted (understandably) as a cause of maternal stress, has been shown to be associated with increased risk of the child developing schizophrenia as an adult, and there is evidence that abnormal social interactions in a family where one child is adopted from a parent with schizophrenia may be associated with later schizophrenia in that child, although the direction of causality is quite unclear. Similarly, health visitors in the NSHD were asked to assess the mother’s understanding and management of the child at age 4 years as average, below average or above average. The mothers of children who later developed schizophrenia were almost 5 times as likely to be rated as having below average mothering skills as were the mothers of controls. Like the finding of Tienari and colleagues, the direction of causality could go either way; we know that the children were already different in a variety of ways and they could just as easily have been eliciting abnormal responses from their mothers, as have been affected by them.

Perhaps the most curious finding regarding early psycho-social risk factors has come from the North Finnish cohort. At the initial interview in the antenatal clinics during mid-gestation, mothers were asked if the
pregnancy was wanted, was mis-timed but wanted nonetheless, or was unwanted\textsuperscript{88}. Previous work in this cohort\textsuperscript{89} and elsewhere\textsuperscript{90} had shown that unwantedness of a pregnancy was associated with a range of later social and educational disadvantages in the child. Myhrman and colleagues examined the risk of subsequent schizophrenia in wanted or mis-timed children versus those who were unwanted. The risk in the latter group was raised almost 3-fold, even after adjustment for confounding by sociodemographic, pregnancy and perinatal variables\textsuperscript{91}. It was not known exactly why these babies were unwanted but it would be premature to conclude that early risk factors mediate their effects through entirely physical mechanisms, or that any future interventions might be restricted to such mechanisms.

**Conclusions**

There is growing evidence from population based studies indicating that young children who will later develop the clinical syndrome of schizophrenia are different from their peers in terms of development in several domains. Predictive power on the basis of available measures is low but the effects might be widespread both for those who will develop schizophrenia and possibly for children who will develop other mental illnesses, too.

Studies of the brain yield results consistent with the multi-system nature of the clinical syndrome of schizophrenia in adult life, and with the notion of a longitudinal or developmental phenotype, of which the adult syndrome is but one aspect. There is evidence for a range of possible ‘causal factors’ which might operate early in life and so be responsible for this longitudinal aspect to the disorder. These include the consequences of genes, of environmental factors or, most likely, interactions between these. To date, no population based studies have examined such interactions, and direct measures of brain structure and function would best be incorporated into this next generation of work. However, parsimony suggests that the same systems, causes and mechanisms are involved in the developmental and the psychotic syndromes, that schizophrenia is a multi-systems disorder with a longitudinal phenotype, and that we recognize but one stage of its possible evolution as the schizophrenia syndrome.
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References

17. Aylward E,. Walker E, Bettes B. Intelligence in schizophrenia: meta-analysis of the research *Schizophr Bull* 1984, 10: 430–59
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20 Pidgeon DA Details of the fifteen year tests. In Douglas JWB, Ross JM, Simpson HR (Eds) All Our Futures.* London: Peter Davies, 1968; 194–7


22 van Os J, Jones PB, Lewis GH, Murray RM. Evidence for similar developmental precursors of chronic affective illness and schizophrenia in a general population birth cohort. Arch Gen Psychiatry 1997; In press

23 Watt NF Patterns of childhood social development in adult schizophrenics. Arch Gen Psychiatry 1978; 35: 160–5

24 Weinberger D. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987; 44: 660–9

25 Weinberger DR. From neuropathology to neurodevelopment. Lancet 1995; 346: 552–7


27 Jones PB, Harvey I, Lewis SW et al. Cerebral ventricle dimensions as risk factors for schizophrenia and affective psychosis. An epidemiological approach to analysis. Psychol Med 1994; 24: 995–1011

28 van Horn JD, McManus IC. Ventricular enlargement in schizophrenia— a meta analysis of studies of the ventricle:brain ratio (VBR). Br J Psychiatry 1992; 160: 687–97

29 Lewis SW. X-Ray CT in schizophrenia: 15 years on Br J Psychiatry 1990; 157 (Suppl 9: 16–24

30 Andreasen NC, Flashman L, Fiaum M et al. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA 1994, 272: 1763–9

31 Harvey I, Ron M, Du Boulay G et al. Diffuse reduction of cortical volume in schizophrenia on magnetic resonance imaging. Psychol Med 1993; 23: 591–604


34 Green MF, Satz P, Christenson C. Minor physical abnormalities in schizophrenia patients, bipolar patients and their siblings. Schizophr Bull 1994; 20: 433–40


37 Degreef G, Ashtan M, Bogerts B et al. Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. Arch Gen Psychiatry 1992; 49: 531–7

38 Nasrallah HA, Olsen SC, McCaIley-Whitters M, Chapman S, Jacoby EC. Cerebral ventricular enlargement in schizophrenia a preliminary follow-up study. Arch Gen Psychiatry 1986; 43: 157–9

39 Reveley AM, Reveley MA, Clifford CA, Murray RM. Cerebral ventricular size in twins discordant for schizophrenia. Lancet 1982; ii: 540–1


42 Arnold SE, Hyman BT, Van Hoesen GW, Damasio AR. Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. Arch Gen Psychiatry 1991; 48 625–32

Fetal and early childhood environment: long-term health implications


45 Pilowsky L, Murray RM. Why don’t preschizophrenic children have delusions and hallucinations? Behav Brain Sci 1991; 14: 41–2


51 Daniels DG, Goldberg TE, Gibbons RD, Weinberger DR. Lack of a bimodal distribution of ventricular size in schizophrenia: a Gaussian mixture analysis of 1056 cases and controls. Biol Psychiatry 1991; 30: 887–903


57 Menninger KA. Influenza and schizophrenia. An analysis of post-influenzal ‘dementia praecox’, as of 1918, and five years later. Further studies of the psychiatric aspects of influenza. Am J Psychiatry 1926; 4, 469–529

58 Gottesman II, Bertelsen A. Confirming unexpressed genotypes for schizophrenia. Risks in the offspring of Fischer’s Danish identical and fraternal twins. Arch Gen Psychiatry 1989; 46: 867–72


61 Fish B. Neurobiologic antecedents of schizophrenia in childhood. Arch Gen Psychiatry 1977; 34: 1297–313


63 Jones PB, Murray RM. The genetics of schizophrenia is the genetics of neurodevelopment. Br J Psychiatry 1991; 158: 615–23


The early origins of schizophrenia


70 Barr CE, Mednick SA, Munk-Jorgensen P. Exposure to influenza epidemics during gestation and adult schizophrenia. *Arch Gen Psychiatry* 1990; 47: 869–74


72 Mednick SA, Machon RA, Huttenen MO et al. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1988; 45: 189–92


76 Mednick SA, Machon RA, Huttenen MO et al. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1988; 45: 189–92

77 Holister JM, Laing P, Mednick SA. Rhesus incompatibility as a risk factor for schizophrenia in male adults. *Arch Gen Psychiatry* 1996; 53: 19–24


80 Rantakallio P, Jones PB, Moring J, von Wendt L. Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses. A 28 year follow-up. *Int J Epidemiol* 1997; In press


