Psychiatric Assessments in Children from a Longitudinal Epidemiologic Perspective for the National Children's Study

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The National Children's Study (Study) proposes to follow a cohort of 100,000 individuals prenatally to age 21 years. Domains of interest include health, mental health, psychosocial functioning, and neurocognitive development, with a specific emphasis on three psychiatric disorders: autism, schizophrenia, and attention-deficit hyperactivity disorder (ADHD). This paper will outline procedures and assessments designed to characterize psychiatric functioning in this population.

Approximately 20 percent of youth are estimated to suffer from a significant mental health disorder (DHHS, 1999). Therefore, in the proposed cohort of 100,000 individuals, an estimated 20,000 may have a definable psychiatric illness. Furthermore, although currently available diagnostic screening tools demonstrate acceptable sensitivity and specificity ratings, population-wide screening for all forms of psychopathology would generate a large number of false positives and negatives identified as potential cases. Thus, the logistics of identifying all potential cases of psychopathology within this cohort are daunting. Moreover, the scientific merit of such an undertaking is not required for common disorders (those present in 2 percent or more of the population, including ADHD) since sufficient numbers can be studied in smaller cohorts. The proposed population of 100,000 individuals is necessary for adequately studying rare disorders, including autism and schizophrenia. Therefore, we will focus this proposal on three complimentary concurrent strategies:

- Assess the entire population using questionnaire measures to examine broad domains of psychopathology and related risk factors.
- Identify and follow all cases of the rarer, more complex psychiatric disorders of interest, autism, and schizophrenia.
- Randomly select a sample of 10,000 individuals from the larger population and follow them over the assessment period using more in-depth diagnostic protocols to examine the prevalence and trajectory of more commonplace conditions, including ADHD.

Although the logistical and cost issues will be significant, it is critically important for the Study to accurately and thoroughly assess the mental health status of this cohort. Psychiatric disorders are a major public health concern, affecting at least one out of five individuals, with enormous human and economic costs. Despite enormous gains in medical science, including the recent advances in genetics and molecular biology, the etiologic mechanisms underlying most psychiatric disorders have not yet been identified. Psychiatric disorders reflect the complexity of brain development and are presumed due to multifactorial processes involving the interplay between genetic, biological and/or environmental risk, and protective factors. The complexity is such that scientific inquiries regarding the cause, course, and associated features of psychiatric disorders require very large well-defined sample sizes, beyond the scope of most research efforts. The Study offers the means and methods to examine the developmental trajectories, psychosocial correlates, and biological underpinnings of psychiatric illnesses from infancy through adulthood.

In addition, the Study will be able to assess and potentially refine current diagnostic nosology. The validity of many psychiatric syndromes as discrete entities, especially childhood disorders, is not well established. As of yet, there are no biological markers, such as laboratory tests or radiographic findings, for psychiatric disorders. Diagnostic formulations are based on information and observations gathered from the child, parents, and other pertinent informants (such as teachers, relatives, and social service providers). Standardized diagnostic tools, including those proposed for this Study, have improved these processes. However, these practices are inherently vulnerable to variability and bias.

The resources and scope of the Study will allow comparison between the different diagnostic assessments, and a comprehensive array of pertinent domains and outcome measures, including family functioning, social-emotional functioning, academic performance, and neurocognitive development. These data provide an extensive nomological net to assess construct and predictive validity. Furthermore, the examination of genetic factors and exposure to environmental toxins may identify potential etiologic mechanisms underlying specific psychiatric disorders. This would greatly enhance the specificity of diagnostic assignment and be a significant advancement to the field.

Precedents for an undertaking of this magnitude do exist. Early examples of birth and pregnancy/ birth cohorts, primarily focusing on multiple neurodevelopmental and physical outcomes in childhood, include the 1946 British Birth Cohort—the first veritable birth cohort (N=5,362), the Jerusalem Perinatal Project (N=90,000), the Child Health and Development Study (N=20,000), and the National Collaborative Perinatal Project (N=55,000). More recently, large pregnancy/birth cohorts are being assembled in Norway—The Autism Birth Cohort/ Mother and Child Study (N=70,000, N=100,000) and Denmark (N=100,000). While each of the older projects has made valuable contributions to psychiatry research in identifying risk factors and early antecedents of psychiatric disorders (Buka et al., 2004; Jones et al., 1994; Schaefer et al., 2000), each is lacking in one or more key areas of exposure/outcome data collection important for these purposes (such as, prenatal data collection, biological samples, adequate sample size, direct assessment in childhood). For example, the ability to identify children with Autism Spectrum Disorders under any criteria is limited by the lack of screening and diagnostic schedules of known validity and reliability, and by smaller Ns in the older studies. Only the Norway Birth Cohort includes longitudinal outcome data collection on psychiatric symptoms and diagnoses beginning in early childhood and rigorous in-person diagnostic assessments on sample of sufficient size. We seek to both achieve comparability to this study, and to obtain information from this cohort that will facilitate “fine tuning” the Study’s instrumentation.

Specific Aims

The legislation outlining the goals of the Study emphasized three disorders of significant public health interest: autism, attention-deficit hyperactivity disorder, and schizophrenia. These disorders will be a primary focus, with measures designed for early identification, as well as the assessment of premorbid characteristics. Three strategies are proposed to accomplish the Study aims:

- The estimated prevalence rates for autism and schizophrenia within the proposed sample is less than 1 percent. Therefore, it is recommended that methods be used to identify every case. Screening protocols will be administered during the developmental periods of risk (infants and preschoolers for autism; early adolescence and older for schizophrenia). Hypothesized premorbid factors (early language and social deficits for autism; and social withdrawal, behavioral, and academic problems for schizophrenia) will also be assessed in the entire population. Potential cases will be evaluated using state-of-the-art diagnostic procedures to establish the diagnosis and comorbid conditions. Once identified, positive cases will be followed throughout the remainder of the Study.
- To address the prevalence and associated risk factors of more common disorders, including ADHD, consideration should be given towards selecting a random sample of 10,000 individuals that would be followed using comprehensive psychiatric batteries, with assessments every 2 years, beginning at age 36 months. The proposed assessment protocols should address the following areas:
  - Developmental Disorders (including PDD/Autism)
  - Mood Disorders (depression and mania)
  - Anxiety
  - Disruptive Behavioral Disorders (including ADHD)
  - Psychosis (including schizophrenia)
  - Substance Abuse
- Standardized psychopathology questionnaires will be administered to the entire sample over the longitudinal period, in conjunction with the screening questionnaires used to identify potential cases of autism and schizophrenia. This will provide population-based estimates of symptom and syndrome prevalence, and also will provide comparative data between dimensional and categorical diagnostic tools, when examined in comparison to the more extensive diagnostic assessments used with the random sample of 10,000 subjects.

The overarching goals of the psychiatric assessment protocols are to:

- Examine patterns of developmental psychopathology, studying the trajectory and evolution of psychiatric syndromes from infancy to young adulthood.
- Search for causes of psychiatric disorders. Using information obtained in this and other areas addressed in the Study (genetics; chemical, biological, social, and environmental exposures in the prenatal, perinatal, and postnatal periods), we aim to establish comprehensive etiologic research that includes genetic and environmental causes, and their interaction. Large sample sizes and rigorous and comprehensive assessments of continuous and categorical psychiatric outcomes will lay a strong foundation for this undertaking.
- Provide epidemiologic information regarding the prevalence of psychiatric disorders within this cohort. Information will also be obtained regarding the severity and functional impact of the disorders, associated diagnostic comorbidity, and service utilization.

In order to address these aims, the following parameters need to be met:

- Measures that address psychopathology and normative behavior/functioning for the developmental continuum over the followup period.

- Measures that provide some continuity across different periods of development so that the trajectory of symptoms/disorders can be assessed.
- Psychopathology assessments that include categorical and dimensional measures. Although DSM diagnostic constructs should be assessed, data regarding symptom specificity and severity independent of diagnostic status are needed to inform and refine the current diagnostic system.
- Information gathered from multiple informants to enhance diagnostic accuracy and allow the examination of how to best combine information from multiple sources within a diagnostic algorithm.
- Assessment protocols applicable to families and youth from different cultural backgrounds. Measures translated into different languages and validated in studies with diverse ethnic, cultural, and/or geographic populations are prioritized.

Finally, there are logistical and feasibility challenges in designing an assessment protocol for large populations. In order to logistically address the demands of the Study, the assessment protocol will focus on:

- Measures that can be scored easily, including scan forms and/or computerized versions
- Measures with standardized response sets (versus free text answers that require an individual to review and/or score).

Background

Psychiatric disturbances in children and adolescents are a major public health concern. Approximately 20 percent of juveniles in the general population suffer some form of serious emotional disturbance, with associated impairment in academic, social, and/or family functioning (Shaffer et al., 1996). Further research is needed to clarify the scope, presentation, and trajectories of psychiatric illnesses in youth. Moreover, etiologic mechanisms underlying these disorders, including genetic, biological, environmental, and/or interactional factors, are as of yet unknown.

There are several challenges inherent to the assessment of psychiatric disorders within a population of children and adolescents. The greatest challenges relate to the nature of the diagnoses themselves. Despite clear evidence that approximately 20 percent of youth have significant emotional disturbances, the validity of most childhood psychiatric disorders is not well established. Only a few disorders (such as autism, ADHD) have been extensively studied. Some disorders are diagnosed using the same criteria as for adults (such as depression), yet there is little research demonstrating how adult criteria should be extrapolated for youth, especially younger children.

The lack of a biological marker (such as a laboratory test) to define a disorder means that all psychiatric illnesses are defined by grouping reported and observed symptoms into agreed upon categories. While this model has clinical and administrative utility, it is also prone to subjectivity, with variability across clinicians, settings, and time. Comorbidity is a major challenge since many children with one psychiatric have two or more diagnosable conditions (Angold et al., 1999). Many childhood disorders are characterized by symptoms that are not

necessarily specific to any single disorder or even abnormal (for example, irritability, oppositional behavior, distractibility, sleep problems, and aggression). Diagnostic categories are generally a combination of symptoms that tend to cluster together, plus sufficient functional impairment, to warrant intervention. This raises questions as to whether all of the diagnostic categories truly represent a specific unique biological entity, versus a dimensional measure defined as much by severity as specificity of symptoms. Inasmuch, although children and adolescents with psychiatric disorders can be reliably differentiated from normal controls, the distinction between disorders is less clearly defined (Reeves et al., 1987).

Disorders of Interest

The National Children's Study legislation included an emphasis on three important public health disorders.

Attention-Deficit Hyperactivity Disorder (ADHD). ADHD is defined by problems with inattention and/or hyperactivity/impulsivity, with onset prior to age 7 years and resultant impairment in two or more settings. The population prevalence rate in the United States is generally held to be 3–7 percent of school age children (APA, 2000) although published estimates vary from 2–17 percent (Scahill and Schwab-Stone, 2002). ADHD is diagnosed much more often in boys (approximately 4:1). Although generally well accepted by the medical community, ADHD remains an area of public debate given concerns over the increased use of stimulant medications with children, including very young children (Coyle, 2000; Rappley et al., 2002; Zito et al., 2000) and also because of questions regarding how broadly the disorder should be defined. Attention span, impulse control, and motor activity are normal capacities that change developmentally, thus problems in these areas do not necessarily equate to a psychiatric disorder. Variations in diagnostic thresholds lead to the widely varied prevalence estimates across communities and subsequent discrepancies in treatment practices. This ultimately creates concerns and debate over mislabeling normal youthful behavior as psychopathology versus the risks of underrecognition (such as labeling the child as "bad" rather than having a mental illness) and thus denying appropriate treatment.

Research is needed to examine the long-term course, outcome, and impact of risk and moderating factors, including treatment interventions, on ADHD. Studies examining the prevalence, presentation, and course of ADHD in girls are particularly needed. Earlier longitudinal studies have noted an increased risk for the development of antisocial behavior and substance abuse, as well as ongoing ADHD symptoms, in boys with the syndrome (Mannuzza et al., 1998; Weiss et al., 1985). Subsequent studies of ADHD in children note high rates of comorbid mood and anxiety disorders (Costello et al., 2003). Research is needed to examine how these comorbid conditions evolve, and their relationship and continuity with adult mood disorders (especially bipolar disorder).

Autism. Autism Spectrum Disorders (ASDs), also known as Pervasive Developmental Disorders, encompass the diagnoses Autistic Disorder, PDD-NOS, and Asperger's Syndrome. Children with these disorders often have life-long difficulties with their ability to communicate and socially relate to others. These disorders vary in their severity, ranging from mild deficits to

profound impairments in functioning, and generally impact every area of a child's life. Autism is estimated to occur in approximately 10/10,000 individuals (Fombonne, 2003); the broader spectrum conditions, though less well studied, appear to be more common and taken together may occur in as many as 1 out of 250–500 youth. Boys are much more often affected than girls (approximately 4:1). At this time the cause or causes of ASDs are unknown. Family and twin studies both support that genetic mechanisms are important (Bespalova and Buxbaum, 2003). Current evidence suggests that the inheritance is complex, perhaps with as many as 10–100 genes involved. Several genes have been proposed to play a role in susceptibility to autism, although definitive links between specific mutations and the development of the illness have not yet been demonstrated for the majority of cases.

The prevalence of ASDs appears to be increasing. The interpretation of this historical trend remains unclear, and the extent to which it represents a true increase in prevalence, or an artifactual increase in prevalence, is unknown. A historical trend is potentially defined by three component effects—age, period, and generation effects. Age effects reflect changes in the relation between age and disease in the population; period effects change the disease rate of a population during a limited time period around the time of its occurrence; and generation effects reflect the impact of early exposures and cumulative life experience of a birth cohort. Disentangling these three effects may facilitate the interpretation of the rising prevalence. A change in diagnostic criteria is likely to manifest as a period effect. A change in recognition and ascertainment may manifest as both period and age effects. A change in a prenatal cause is likely to manifest as a generation effect, with each generation defined by a single year of birth. The identification of generation effects could provide valuable direction in the search for causes of real change in ASDs occurrence and have implications for prevention. Whether or not the rising number represents a true increase in the disorder, ASDs are a major public health concern with major implications for educational and human services now and in the future.

Longitudinal research beginning in the prenatal period will be an invaluable addition to autism research, contributing crucial information on the prenatal period and first years of life before the recognition of disorder, the developmental trajectory of symptoms, and the stability of diagnosis and prognosis of autism spectrum disorders. It will also provide a unique opportunity for much-needed research seeking to identify causes of these disorders and to determine whether there are potential ways to either prevent them, or at least lessen the impact upon the child's ability to learn and relate to others.

Schizophrenia. Schizophrenia is a severe psychiatric disease typically appearing in late adolescence or early adulthood. Hallmark symptoms of the disorder include delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and/or negative symptoms (for example, affective flattening, paucity of thought or speech). Schizophrenia is generally viewed as an adult disorder, with an overall prevalence of approximately 1 percent; onset prior to age 13 is rare, with an estimated prevalence of 1/10,000 (AACAP, 2001). Schizophrenia is associated with significant long-term morbidity and disability. Given the costs of this disease to individuals, families, and society, identifying preventable causes and means to avert development of schizophrenia remains a public health priority.

Converging evidence suggests that many cases of schizophrenia are neurodevelopmental in origin, and that genetic and environmental factors both play a role in the etiology of these cases. The theory that schizophrenia has its origins in prenatal brain development has been supported by evidence from several types of human and animal studies. Findings in patients with schizophrenia that suggest early origins include minor physical anomalies (Gourion et al., 2004; Ismail et al., 2000; McGrath et al., 2002), developmental disturbances in childhood (Bearden, 2000; Cannon et al, 1999; Crow et al., 1995; Jones et al., 1994), and structural anomalies on brain imaging (Lawrie and Abukmeil, 1998; Wright et al., 2000). By the time of onset, schizophrenia is associated with ventricular enlargement and decreased hippocampal volume, and these may possibly also have early origins; evidence from discordant monozygotic twins further suggest they may be partly of environmental origin.

Evidence for specific exposures during gestation increasing risk of later developing schizophrenia continues to accumulate. To varying degrees, specific maternal infections during gestation, prenatal malnutrition, and prenatal toxic exposures have been associated with risk of schizophrenia (Brown et al., 2004a, 2004b; Brown et al., 2000; Buka et al., 2001; Opler et al. 2004; Susser and Lin, 1996). Although the overall evidence is convincing, we still lack definitive evidence of a prenatal exposure that increases risk of schizophrenia, or a defined mechanisms linking a specific prenatal exposure to fetal neurodevelopment enhancing risk for schizophrenia. In addition, while prenatal exposures may play an important role in schizophrenia, this by no means precludes an important role for postnatal experience. The independent or risk moderating effects of postnatal risk factors (such as adolescent cannabis or urban residence during childhood) is also an area of research interest.

Working towards the goal of prevention necessitates a more secure understanding of the identity, timing, and mechanisms of prenatal exposures adversely influencing neurodevelopment and elevating the risk of schizophrenia, and the independent or moderating role of other postnatal risk factors. This requires more comprehensive and precise information on exposures across domains of interest (biological, chemical, social) beginning in prenatal period and extending through onset of disease, as well as more detailed understanding of the developmental and symptom trajectories of those who go on to develop disease. One challenge is that schizophrenia is relatively rare. Therefore, a population-based study would need to include a very large sample size to identify an adequate number of cases. This is true for autism as well. The power of the sample size in the Study allows these issues to be examined.

Assessment Issues

In order to improve the reliability (and by extension the validity) of the diagnostic process, a variety of assessment tools have been developed. Those most commonly used by clinicians and researchers are diagnostic interviews and questionnaires.

- Questionnaires are usually completed by patients, parents, or other significant individuals (such as teachers). The focus may be on broader domains of psychopathology, thus providing a dimensional profile of symptoms across a population, or more narrowly on specific illness states or symptoms.

- Diagnostic interviews are designed to elicit information from children and/or their parents about various aspects of functioning and mental health, including specific inquiries about symptom criteria for different psychiatric disorders. The interviews are usually administered by clinicians, researchers, and/or trained interviewers, and have primarily been used for psychiatric research, both in epidemiological surveys and in clinical studies (McClellan and Werry, 2000). The available diagnostic interviews are often described in terms of their degree of structure. In a highly structured interview (or respondent-based), the interviewer asks set questions using specified wording and records the response without interpretation. Semi-structured interviews (interviewer-based) allow interviewers to use their own probe questions and/or incorporate other sources of information in order to assess symptoms. Respondent-based interviews are typically used in epidemiological surveys, where trained lay interviewers, not clinicians, administer the measure. Interviewer-based interviews require some clinical decision-making on the part of the interviewer, and are often used in studies of clinical populations. These two methods are not necessarily mutually exclusive, and many interviews have elements of both.

All diagnostic tools have error, and even those with excellent ratings of sensitivity and specificity will misdiagnose cases. Moreover, what is a "case" remains a moving target. Modifications of diagnostic criteria may produce significant changes in prevalence estimates (Regier et al., 1998). For example, in the Methods for the Epidemiology of Child and Adolescent Disorders (MECA) study, the prevalence rates for having any disorder ranged from 50.4 percent when no impairment was necessary, to 5.4 percent if at least moderate impairment (as measured by the Global Assessment of Functioning Scale) was required (Shaffer et al., 1996).

Ultimately, the assignment of an accurate diagnosis is dependent on the validity of the diagnostic criteria and the subjective accuracy of the individual reporting the symptoms and the diagnostician interpreting them. One challenge is that children have a tendency to over-report rare or unusual phenomena, such as obsessive-compulsive, psychotic, or manic symptoms (Breslau, 1987). This is most likely because they either misinterpret the question, or are not familiar with the concept being described. In general, younger children have difficulties with the reporting of more abstract phenomena, including the duration of time symptoms have been present, which is a common perquisite for determining whether someone has an illness. Parents may also be biased in their reporting. For example, depressed mothers are more likely to perceive depression in their children, regardless of clinical status (McGee et al., 1983; Mick et al., 2000; Najman et al., 2000). Clinical judgment is generally needed to differentiate nonspecific experiences or problems from qualitatively specific psychiatric symptoms. This is a potential problem for nonclinician interviewers, although the "glossary-based" interviews (such as the CAPA, K-SADS) address this by developing clear definitions and training the interviewers to recognize the distinctions.

Another methodological issue is the potential for disagreement between diagnostic instruments. Different interviews, or different versions of the same measure, may vary significantly in estimates of prevalence rates, or in defining whether a specific individual is a "case" (Regier et al., 1998; Rutter, 1997). Boyle et al. (1997) compared a parent-completed questionnaire to a nonclinician administered structured interview in a sample of public school children. While the

overall reliability between the two measures was acceptable, substantial disagreement still occurred for specific diagnoses. There has not been adequate research comparing one structured diagnostic interview to another or examining whether different instruments are superior for certain diagnoses or clinical issues.

A third methodological problem is the overall poor agreement found between different informants (such as parent-child or parent-teacher) (Achenbach et al., 1987; Rutter, 1997). Poor agreement does not necessarily imply error. Some differences are expected, since children's behavior depends to some extent on the setting and situation (Achenbach et al., 1987). It is generally held that youth are better at describing their own internalizing states, whereas adults are better at describing acting-out behaviors in children.

Given all of the methodological issues noted above, it is generally recommended that multiple diagnostic tools, with repeated measures over time, be used in research studies to minimize error (Rutter, 1997). This allows the incorporation of multiple sources of information into the diagnostic process. It also allows exploration of different diagnostic models, such as comparing dimensional versus categorical classifications, or developing algorithms, to examine how to best combine reports from different informants (such as parent-child or parent-teacher). Furthermore, the multiple domains being assessed through the Study (for example: social-emotional functioning, cognitive development, family functioning) will allow exploration of the complex interactions between these domains and associated psychiatric illnesses. The predictive and/or construct validity of the different disorders can be examined using a strategy referred to as a nomological network (Cronbach and Meehl, 1955). For example, the results of a diagnostic interview are compared to several pertinent theoretically related attributes, such as patterns and stability of diagnoses, independent ratings of psychopathology, service utilization, and family psychiatric history. Thus, by a process akin to triangulation, researchers examine the validity of a measure by determining its proximity to that of other theoretically related measures or attributes.

Proposed Methods for Psychiatric Assessment

To address the aims of the Study, while also accounting for the logistical and methodological issues inherent to assessing psychopathology, we are proposing three complimentary strategies (see Table 1 for a schematic layout of Study procedures):

Questionnaire Assessments

Assess the entire cohort of 100,000 individuals with questionnaire assessments to broadly examine the longitudinal course and trajectory of broad domains of psychopathology and related risk factors. Developmentally appropriate measures will be administered to parents, teachers and/or subjects (dependent upon age) at 6, 18, and 36 months, then every 2 years thereafter through age 21 years. The proposed measures include:

- Broad domains of psychopathology:
  - Infant-Toddler Social-Emotional Assessment (ITSEA) (Carter and Briggs-Gowan, 2000). This is a parent-completed questionnaire with English, Spanish, French, Dutch, and Hebrew versions that takes approximately 30 minutes to complete. Four broad symptom

domains (externalizing, internalizing, dysregulation, competence) and three indices (maladaptive behaviors, atypical behaviors, social relatedness) are generated. The ITSEA is designed for ages 12–36 months. However, in discussion with the author (Alice Carter), some of the domains (dysregulation, social relatedness) appear valid in younger infants. Those items will be assessed in 6 month olds, with the entire ITSEA administered at ages 18 and 36 months.

  - Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997; Goodman et al., 1998). This is a widely researched 25-item rating scale for youth ages 3–17 years, addressing emotional symptoms, conduct problems, hyperactive/inattention, peer relationships, and prosocial behavior. The SDQ also includes functional impact questions to better discriminate clinical significance (Goodman, 1999). There are parent, teacher, and youth (ages 11–17 years) versions. Each takes approximately 15 minutes to complete. The SDQ will be administered at age ages 5, 7, 9, 11, 13, 15, and 17 years.
  - General Health Questionnaire (GHQ) (Goldberg, 1978). This is a widely used self-administered questionnaire designed to screen for mental health problems in adults. The GHQ has been translated into numerous languages and takes approximately 15 minutes to complete. The GHG-36 assesses domains related to anxiety, depression, somatic symptoms, and social dysfunction; it was found to be an effective screening tool in a Finnish epidemiological study (Holi et al., 2003). The GHQ will be completed when subjects are 19 and 21 years of age. The same measure(s) will also be used to assess symptoms of psychopathology in parents (see below).

- Risk and moderating factors:
  - Substance abuse, family functioning, peer relationships, school/occupational functioning are evaluated using the Drug Use Screening Inventory for Adolescents (DUSI-R) (Tarter et al., 1992, 1994). This self-report screening instrument takes approximately 20 minutes to complete. The measurement domains are: substance use, behavior problems, psychiatric disturbance, family dysfunction, peer relationships, school adjustment, work adjustment; social competence, health status, and leisure and recreation. Thus, this scale provides information on a number of important domains relevant to this Study. Information is obtained for the year prior to the assessment. The DUSI-R will be administered at the biennial evaluations, from age 11 through 21 years.
  - Sections from the Juvenile Wellness and Health Survey (JWHS-76) (Steiner et al., 1998) regarding sexual orientation and behavior (including high-risk behaviors) will be completed by subjects ages 13 years and older (approximately 5 minutes to complete).
  - The Risk Factors from Family Psychosocial Screening takes approximately 5–10 minutes to complete. Sections include: financial issues, history of childhood abuse, domestic violence, and parental mental illness concerns. For the parental psychopathology evaluation, parents will be asked to complete the General Health Questionnaire (GHQ) (Goldberg, 1978), the same measure used for subjects ages 18–21 years (see above).
- To provide population data, as well as identify potential cases of autism to be evaluated more intensively, we will use the following tools (approximately 15 minutes to complete) to screen for autism:
  - Modified Checklist for Autism in Toddlers (M-CHAT) (Robins et al., 2001). A 23-item parent completed measure widely recommended for autism screening. The M-CHAT will be completed at 18 and 36 months.

  - E-SAT (Dietz et al., submitted; Willemsen-Swinkels et al., submitted) The E-SAT is a 14-item screening instrument developed for identifying autism spectrum disorders during the second year of life. This instrument is currently being used to identify cases of autism in conjunction with the M-CHAT and Social Communication Questionnaire (Berument et al., 1999) in a large population-based longitudinal study in Norway, with a design similar to the Study. Using similar strategies will allow comparisons across these samples. The E-SAT will be administered at 18 and 36 months.
  - The Social Relatedness and Atypical Behavioral indices from the ITSEA will also be used as part of the autism/PDD screen.
- Screening for schizophrenia will include measures of schizotypal behavior to examine premorbid characteristics of the disorder.
  - Schizotypal Personality Questionnaire (SPQ-B) (Raine and Benishay, 1995). This self-reported 22-item instrument yields a total score, together with scores for each of the three main sub-factors (cognitive-perceptual, interpersonal, and disorganized). The SPQ-B will be administered to subjects ages 13 years and above and takes approximately 10 minutes to complete.
  - To identify potential cases, we will use two strategies. First, for youth less than age 15 years, parents will be surveyed as to whether their child has been diagnosed with schizophrenia or psychosis. A screening instrument will not be used to identify younger cases since there is not a validated tool available, the incidence is rare, and the likelihood that screening efforts will identify a large number of false positives. Second, screening for subjects 15 years and older will use the a short psychosis symptom inventory taken from a structured diagnostic instrument such as the DISC (lifetime); screen positives will be contacted to validate symptom reports as "clinically significant"; based on all information, possible cases will be identified based on adjusted symptom scores. These methods are consistent with the use of these psychosis scales in other epidemiological surveys (for example: Bijl et al., 1997; Cannon et al., 2002). Note that this method should also identify cases with earlier onset, since the very early onset forms appear to be continuous with later onset and the illness persists in most cases (AACAP, 2001).

Identify Subjects With Autism and Schizophrenia

It is feasible to identify and follow all subjects with autism and schizophrenia. This approach is recommended since these disorders are significant public health concerns, and a specific focus of the Study's legislation. The population-wide assessments described above will be used to identify potential cases, in addition to providing information regarding the premorbid course and clinical characteristics of the disorders in identified cases. Once potential cases are identified, more extensive diagnostic review will be undertaken.

- Autism. Subjects with positive screens per the E-SAT and M-CHAT should be assessed using the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994). The ADI-R and the ADOS are complementary diagnostic instruments used for research and clinical purposes. They are clinician-administered instruments and require specific training to use. They incorporate both DSM-IV and ICD-10 criteria to assess the three domains that define autism spectrum disorders: social reciprocity; communication and restricted, repetitive behaviors;

and interests. The ADI-R takes about 90 minutes to administer. The ADOS is a standardized observation of social behavior and uses different modules and tasks for children of different ages and language levels. The ADOS generates scores that fall within a range from autism to autism spectrum disorder, and takes about 30–45 minutes to administer. These instruments are widely used with good reliability.

- Schizophrenia. Positive screens should be assessed using either the KID-SCID (Hein et al., 1998) or the SCID (for subjects age 18 to 21 years) (First et al., 1996) administered by a clinically trained interviewer. The KID-SCID is a semi-structured diagnostic interview based on the Structured Interview for DSM-IV (SCID) (First et al., 1996), which is widely used in adult studies of schizophrenia. The KID-SCID allows the diagnostician to incorporate all available information into the assessment, and it includes the same psychotic disorders module that is found in the SCID. Both the KID-SCID and the SCID assess other relevant conditions, including substance abuse, mood, and anxiety disorders, with the KID-SCID also having a module on disruptive behavior disorders. Administration time is approximately 2 hours.

Random Sample Assessments

To obtain more extensive information regarding the prevalence, course, symptom presentation, and comorbidity of more commonplace psychiatric problems, including ADHD, we suggest that a random sample of 10,000 be identified and followed, using comprehensive assessments at 2-year intervals, beginning at age 36 months. The assessments would include diagnostic interviews, with information gathered from parents and youth (as developmentally appropriate). In addition, once cases of autism and schizophrenia are identified, they could also be followed using the same timelines to examine the course and outcome of those conditions. The diagnostic protocols for cases of autism and schizophrenia would need to be modified to address both the continuity of the core illness (such as autism or schizophrenia) plus examining for comorbid conditions and other pertinent factors (such as service utilization).

Given the number of issues involved, we will present some potential options for assessment tools. In general, diagnostic interviews may take an estimated 1–3 hours to administer, dependent in part on the instrument, and also the number of issues being assessed. For the 10,000 random sample, diagnostic assessments would need to meet several criteria: 1) applicable for a population-based study (administration by trained interviewers rather than clinicians); 2) continuity across the entire developmental period, including preschoolers; 3) demonstrated sensitivity and specificity in large epidemiological trials. There are at least three diagnostic systems that meet these criteria:

- Child and Adolescent Psychiatric Assessment (CAPA) (Angold and Costello, 2000). The CAPA uses trained interviewers and a glossary-based system of symptom definitions to assign diagnostic status. It has been widely researched, with good reliability ratings and validity estimates. Diagnoses addressed include mood, behavioral, anxiety, eating, elimination, tic, somatic disorders, schizophrenia, and PTSD, using DSM-III-R, DSM-IV or ICD-10 diagnostic systems. The basic interview covers 9–18 years of age. Advantages include the symptom glossary, which theoretically improves symptom assignment, and

therefore diagnostic validity. However, this interview also requires more extensive training and therefore is costlier. Related instruments include:

- Pre-school Age Psychiatric Assessments (PAPA) (Egger and Angold, 2004). This interview assesses for difficulties in youth ages 2–5 years. Diagnoses addressed include internalizing and externalizing disorders, regulatory problems, PTSD, and reactive attachment disorder. Preliminary studies suggest that the test-retest reliability is similar to results from interviews with older children (Egger et al., 2003).
- Young Adult Psychiatric Assessment (YAPA) (http://devepi.mc.duke.edu). The CAPA was modified for young adults, with a focus on diagnoses, living situation, relationships, and level of functioning.
- The Child and Adolescent Services Assessment (CASA) (Ascher et al., 1996). A self and parent report instrument designed to assess mental health service utilization in individuals ages 8–18 years.

- NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV) (Shaffer et al., 2000). The DISC is a highly structured diagnostic instrument that has been widely used, including in large scale epidemiological studies. Diagnoses addressed include mood, behavioral, anxiety, eating, elimination, tic, schizophrenia, and PTSD, using DSM-III-R, DSM-IV or ICD-10 diagnostic systems. Versions are available in Chinese (Cantonese/Mandarin), Dutch, English (US/UK), Finnish, French, German, Icelandic, Italian, Lithuanian, Spanish (Latin American/European), Vietnamese, and Xhosa. Only the English and Spanish versions have been approved by the DISC editorial board, the rest are under development (http://www.c-disc.com/t_versns.htm#translate). The DISC is in the public domain, therefore less costly than other measures. As a respondent-based, highly structured interview, it is designed for lay interviewers and is more easily administered to larger populations. Studies demonstrate good test-retest reliability and sensitivity. The DISC is prone to false positives, as probably is any instrument that is highly respondent-based. There are numerous versions available or under development, including a related child and parent interviews, young adult (ages 18–25 years), young child (ages 3–7 years) and a computerized version (the C-DISC).

In addition to diagnostic interviews, other relevant information would be collected at the assessments, including:

- Social Responsiveness Scale (SRS). A 65-item parent/teacher rating scale that measures the severity of autistic symptoms, social impairments, social awareness, social information processing, capacity for reciprocal social responses, social anxiety/avoidance, and autistic preoccupations and traits. This has been studied in youth ages 7–15 years and takes approximately 15 minutes to complete (Constantino et al., 2000, 2003)
- The Columbia Impairment Scale (CIS) (Bird et al., 1993, 1996) will be administered to children and caregivers to measure overall level of adaptive functioning. The CIS is a 13-item scale available in child and parent versions and covers ages 5–17 years.
- Suicidality: Self Harm Behavior Questionnaire (SHBQ) (Gutierrez et al., 2001). This is a self-report measure addressing past suicide attempts, self-harm, suicide threat, and suicide ideation. The advantage with this measure is that it will address self-harming behaviors that

occur commonly in adolescents, yet are not necessarily assessed with measures focused solely on suicidal ideation. We will give the SHBQ to youth ages 13 years and older.

Finally, in addition to the above-outlined strategies, there is also the potential to collect innovative sources of information regarding social, interactional, and language functioning. Specifically, it may be worthwhile to provide families with digital videocameras, and ask that that tape some specified series of birthday parties/celebrations. This type of information has been examined retrospectively to identify precursors of both autism (Maestro et al., 2002; Osterling and Dawson, 1994) and schizophrenia (Walker and Lweine, 1990). Methodologically, these could either be obtained on the entire sample, or in a more structured format on the random sample of 10,000 cases. Obtaining videosamples on the entire sample would be a very rich database, but costly and also much more difficult to establish any type of structure or standardization in regards to requested elements to be taped (such as asking the family to do certain tasks or activities on the tape to improve standardization of ratings). On the other hand, the studies to date, since they used previously made tapes, did not have any predefined activities, and were still able to examine patterns of social interactions and language.

Conclusions

The Study offers the potential to examine the prevalence, course, and outcome of mental health disorders from infancy through early adulthood. This information can also be linked with other information regarding health, genetics, environmental factors, and psychosocial functioning. Thus, this is a landmark Study that likely will influence diagnostic, clinical, and research practices for generations. The methods we propose will accomplish three major goals: 1) provide a backdrop of rates of psychopathology and mental health functioning in the entire population of 100,000 individuals; 2) identify and follow all cases of autism and schizophrenia; and 3) comprehensively assess and follow a random sample of 10,000 individuals within the larger cohort, thus providing detailed information regarding common disorders, including attention-deficit hyperactivity disorder. These three strategies will provide a very rich dataset to address the aims related to mental health, as well as those for the other domains being addressed within this project.

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Table 1: Outline of Measures

Age	Entire Sample of 100,000						Diagnostic Assessments for Positive Screens plus Random Sample		
	Parent			Teacher	Youth	Risk/ Moderating Factors	Autism (positive screens only)	Schizo-phrenia (positive screens only)	Random Sample of 10,000
	General Psycho-pathology	Autism Screening	Schizo-phrenia Screening						
Prenatal						GHQ FPS			
6 mos	ITSEA					GHQ FPS			
18 mos	ITSEA	E-SAT M-CHAT				GHQ FPS	ADOS ADI-R		Diagnostic Interviews
36 mos	SDQ	E-SAT M-CHAT				GHQ FPS	ADOS ADI-R		Diagnostic Interviews
5 years	SDQ			SDQ		GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS		Diagnostic Interviews CIS
7 years	SDQ		Screen	SDQ		GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS		Diagnostic Interviews CIS SRS
9 years	SDQ		Screen	SDQ		GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS SRS		Diagnostic Interviews CIS SRS
11 years	SDQ		Screen	SDQ	SDQ	GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS SRS		Diagnostic Interviews CIS SRS

Age	Entire Sample of 100,000						Diagnostic Assessments for Positive Screens plus Random Sample		
	Parent			Teacher	Youth	Risk/ Moderating Factors	Autism (positive screens only)	Schizo-phrenia (positive screens only)	Random Sample of 10,000
13 years	SDQ		Screen	SDQ	SDQ DUSI-R SPQ-B	GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS SRS SHBQ		Diagnostic Interviews CIS SRS SHBQ
15 years	SDQ		Screen	SDQ	SDQ DUSI-R SPQ-B	GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS SRS SHBQ	KIDSCID CIS SRS SHBQ	Diagnostic Interviews CIS SRS SHBQ
17 years	SDQ		Screen	SDQ	SDQ DUSI-R SPQ-B	GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS SRS SHBQ	KIDSCID CIS SRS SHBQ	Diagnostic Interviews CIS SRS SHBQ
19 years			Screen		GHQ DUSI-R SPQ-B	GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS SHBQ	SCID CIS SHBQ	Diagnostic Interviews SHBQ
21 years			Screen		GHQ DUSI-R SPQ-B	GHQ FPS	ADOS ADI-R Diagnostic Interviews CIS SHBQ	SCID SHBQ	Diagnostic Interviews SHBQ

ITSEA: Infant-Toddler Social-Emotional Assessment
SDQ: Strengths and Difficulties Scale (Parent, Teacher and Child Versions)

1. P3/4, P4–10, P11–17: Parent SDQ plus impact supplement for age groups 3–4 years, 4–10 years and 11–17 years.
2. T3/4, T4–10, T11–17: Teacher SDQ plus impact supplement for age groups 3–4 years, 4–10 years and 11–17 years.
3. S11–17: Youth completed SDQ plus impact supplement for age 11–17 years.

GHQ: General Health Inventory
SRS: Social Responsiveness Scale
SPQ-B: Schizotypal Personality Questionnaire
SHBQ: Self Harm Behavior Questionnaire
CIS: Columbia Impairment Scale
ADOS: Autism Diagnostic Observation Schedule
ADI-R: Autism Diagnostic Interview-Revised
M-Chat: Modified Checklist for Autism in Toddlers
ESAT: Screening Tool for Autistic Spectrum Disorders
FPS: Family Psychosocial Screen
JWS: Juvenile Wellness and Health Survey, sections on sexuality
SCID: Structured Clinical Interview for DSM-IV (KIDSCID is child and adolescent version)
Screen: For subjects less than 15 years of age, a parent questionnaire will be developed asking if the child has ever been diagnosed with a psychotic illness. For subjects 15 years and older, sections of a diagnostic instrument (e.g. DISC) assessing schizophrenia will be extracted to use as a screening questionnaire.