

National Children's Study

Improving Children's Environmental Health with High Quality Science Formulating Hypotheses and Study Design

The National Children's Study (Study) will study the complex relationship between health and the environment for approximately 100,000 U.S. children and their families. Enrollment will begin before birth and follow up will continue for at least 21 years. Planning for the Study began in 1999 as an activity of the President's Task Force on Environmental Health Risks and Safety Risks to Children. Title X of the Children's Health Act of 2000 subsequently authorized the National Institute of Child Health and Human Development, in collaboration with the Centers for Disease Control and Prevention, the U.S. Environmental Protection Agency, and other appropriate federal agencies, to "...plan, develop, and implement a prospective cohort study, from birth to adulthood, to... incorporate behavioral, emotional, educational, and contextual consequences to enable a complete assessment of the physical, chemical, biological, and psychosocial environmental influences on children's well-being..."

The authorizing legislation calls for a broad and deep investigation of the multitude of factors potentially associated with all aspects of child health and development. In addition to this broad mandate, the Study will be uniquely valuable in answering key children's environmental health questions that cannot be answered using existing data or new data from cross-sectional or smaller longitudinal studies. There is substantial public health concern about the impact of the quality of the environment on child health and development but surprising little research to help policy makers determine which environmental factors are harmful, harmless, or helpful.

Hundreds of scientists and representatives from community groups and professional organizations have contributed to the identification of key children's environmental health questions. No single research question is of sufficient breadth or import to fulfill the entire mission of the Study. The Study Design Working Group of the National Children's Study Advisory Committee (NCSAC) proposed the development of core hypotheses encompassing exposures and child health outcomes of great public health significance requiring long-term follow-up and which cannot be reasonably studied with fewer children or a different study design. The set of research questions forming the foundation of the Study must together provide: a rationale for a long-term, prospective study of approximately 100,000 children; the scientific framework to define the Study, including sample design, data collection, etc; as well as a "public identity" for the Study.

The Interagency Coordinating Committee (ICC) has used the findings from 20 Study Working Groups reported via the NCSAC, independent reviews of the children's environmental health literature, and comments from a broad-based Study Assembly to develop an initial set of these foundational, core hypotheses. These hypotheses are sufficient to support the determination of sample size and design for the Study and are essential to assure that specific research questions can be addressed by the Study. However, a manageable set of core hypotheses cannot alone convey the true breadth of the Study, nor do they, alone, assure the collection of data necessary to address the full range of topics to be covered by the Study. The priority outcomes and exposures outlined below go further to convey the full scope of the Study. Additional work is

necessary to complete a Study protocol that balances participant and family burden with data collection activities needed to address these important areas of children's environmental health.

PRIORITY OUTCOMES

Based on the above criteria, the following child health areas have been identified as priorities for the Study:

Pregnancy outcomes: Many pregnancy outcomes, including preterm delivery and birth defects, are plausibly related to environmental conditions and are understudied. These early life events can have profound impact on child health and development throughout life. These outcomes also provide a first set of results from the Study right from the start.

Neurodevelopment and behavior: Assessment of child development and behavior is key to the mandate of the Study. The Study can address multiple environmental factors that are potentially associated with severe health concerns such as autism and schizophrenia, as well as more commonly occurring childhood disorders such as depression and learning disabilities. The Study can also provide substantial data on variations in the course of normal child development and may provide insights into environmental factors related to aspects of development such as aggression, adjustment, achievement, and resilience.

Injury: A focus area of the President's Task Force, injury is a major cause of childhood morbidity and mortality. The Study expects to measure childhood injuries, particularly those that require hospitalization or other medical attention, and to evaluate a variety of environmental factors including aspects of the social and physical environment that may be associated with injury.

Asthma: While there is a substantial body of research into environmental factors that can trigger asthma attacks or exacerbate existing asthma, there is a need to understand more about contributions the environment and gene-environment interactions have on the development of asthma. Because asthma is relatively common among U.S. children, the Study will have enough statistical power to be able to examine various constellations of environmental and genetic factors that may be related to asthma incidence and exacerbation.

Obesity and physical development: The Study will likely have sufficient statistical power to examine disorders of physical development related to diabetes, obesity and altered puberty. The longitudinal nature of the data and the ability to examine the interaction of multiple environmental factors with an individual's genetic composition is expected to provide insight not only into growth-related disorders, but also to provide a strong study of variations in growth and physical and reproductive development that may be affected by the environment.

PRIORITY EXPOSURES

The priority exposures listed below are outlined in the Children's Health Act of 2000 and all have the potential to exert a pervasive influence (either beneficial or deleterious) on child health and development:

Physical environment: The Study will measure aspects of the physical environment, including housing quality and neighborhood and community conditions that may relate to child health and development. In addition, the influence of physical factors such as radiation (electromagnetic, ultrasound, microwave, x-irradiation), light, and noise may be studied.

Chemical exposures: Exposure to chemical environmental contaminants generally occurs through human contact with air, water, soil, dust, food, or industrial products. Pollutant exposures currently of concern in the Study include metals, PCBs and dioxins, phthalates, organic and inorganic pesticides, and herbicides. Exposure to many of these compounds, and their mixtures, at low background levels is ubiquitous. The Study can investigate the potential health effects associated with these complex low-level exposures. Additionally, the Study may select specific populations with unique exposure scenarios for special sub-studies of related health effects.

Biologic environment: The biologic environment includes exogenous factors (e.g., infectious agents, endotoxin, diet) and individual response to those factors (e.g., inflammatory response, glucose metabolism). *In utero* and early life exposures have potential implications for a wide range of health conditions including birth outcome, developmental outcomes, asthma, obesity, and cardiovascular disease. The Study will allow for elucidation of those associations as well as physiologic mechanisms underlying those relationships, including the influence of genetic composition on those interactions.

Genetics: The Study offers a unique opportunity to investigate the genetic component of many health outcomes. Although it is recognized that genetic factors play a role in many conditions, the mechanism behind the genetic contribution to specific diseases, such as autism, remains unknown. In addition, the quantitative contribution of genetics to more general conditions, such as obesity, is also unknown. A complete understanding of the effects of the environmental factors listed above requires elucidation of the interactions between these factors and genes, including the roles played by various polymorphisms in environmentally responsive genes and the effects of exposures on gene expression. The large sample size will allow for examination of the interaction between genetic make-up and chemical, biologic, and social exposures on many outcomes. The longitudinal and prospective nature of the Study offers the possibility of examining the potential development of somatic mutations in relation to specific exposures. The current state of the science likely does not allow for the genetic profiling of study participants but will, at least initially, require a focus on suspect candidate genes. This will change as the Study matures.

Psychosocial milieu: The Study expects to assess many potential aspects of the psychosocial environment including: families and households; socioeconomic status; social networks and social support; neighborhoods and communities; formal institutions; and public policy. These factors have the potential to influence a child's health either directly or indirectly, by affecting exposure to the chemical or physical environment. The Study will be able to examine those associations as well as shed light on the physiologic mechanisms underlying, for example, potential relationships between psychosocial stress and asthma or preterm birth. In addition to the putative influence on the health of an individual, social environmental factors may be an important area of consideration for investigation of health disparities.

INTEGRATING PRIORITY OUTCOMES AND EXPOSURES

Based on input from hundreds of experts, the ICC has proposed a set of core hypotheses to define a framework for study design. Though the current list of core hypotheses (attached - as of November, 2003) is still under debate, it is adequate to move forward with development of a sampling design. It is expected that, over the long course of the Study, new questions will emerge and be added to the study and some of the core hypotheses here may become outdated.

In addition, information related to other serious child health conditions that require medical attention but that are too rare to be well studied in the Study (e.g., cancer, autoimmune disease) will be collected. Such data may be used to generate hypotheses and to the extent possible, will be made available to support other more targeted studies of these conditions.

The Study is neither a general survey of the health of American children, nor a definitive in-depth examination of one specific research question. Development of a complete Study protocol requires the distillation of each priority outcome and exposure into specific measures suitable for a large scale rigorous epidemiologic study. The methodology necessary to collect valid data for specific Study areas, participant burden, and the availability of funding, will all factor into the decision-making process. The goal of the Study planning process is to develop a feasible and successful study that can answer multiple important public health questions, many of them currently unforeseen.

List of Priority Outcomes and Core Hypotheses for the National Children's Study November, 2003

I. Pregnancy Outcome

Hypothesis: Among women without diabetes before pregnancy, impaired glucose metabolism during pregnancy is proportional to risk of major congenital malformations of the heart, central nervous system, musculoskeletal system, and all birth defects combined.

Hypothesis: Intrauterine exposure to mediators of inflammation due to infection of either vaginal, cervical, uterine, or of more distal sites (e.g., periodontal disease), is associated with an increased risk of preterm birth.

II. Neurodevelopment and Behavior

Hypothesis: Repeated low-level exposure to nonpersistent pesticides *in utero* or postnatally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and later in childhood, especially, for certain agents, among those with genetically decreased paraoxonase activity.

Hypothesis: Prenatal infection and mediators of inflammation are risk factors for neurodevelopmental disabilities, such as cerebral palsy and autism.

Hypothesis: Infection and mediators of inflammation during pregnancy and the perinatal period are associated with increased risk of schizophrenia.

III. Injury

Hypothesis: Repeated head trauma has a cumulative adverse effect on neurocognitive development.

IV. Asthma

Hypothesis: Exposure to indoor and outdoor air pollution and bioaerosols (including allergens, endotoxin, and mold) is associated with increased risk of asthma.

Hypothesis: Respiratory viral infection early in life is associated with increased risk of asthma.

Hypothesis: Maternal stress during pregnancy is associated with increased risk of asthma.

Hypothesis: Antioxidant constituents of diet decrease risk of asthma.

Hypothesis: Early exposure to bacterial and microbial products decreases risk of asthma (hygiene hypothesis).

Hypothesis: Access to health care and management of asthma are strongly related to asthma hospitalization.

V. Obesity and Physical Development

Hypothesis: Impaired maternal glucose metabolism during pregnancy is directly related to risk of obesity and insulin resistance in offspring.

Hypothesis: Intrauterine growth restriction as determined by serial ultrasound examination is associated with subsequent risk of central obesity and insulin resistance in offspring, independent of subsequent body mass index.

Hypothesis: Breast milk feeding, compared with infant formula feeding, and breastfeeding duration are associated with lower rates of obesity and lower risk of insulin resistance.

Hypothesis: Dietary predictors of obesity and insulin resistance include reduced intake of fiber and whole grains, and high glycemic index.

Hypothesis: Environmental factors such as distance to parks, availability of walking routes in the neighborhood, and neighborhood safety are associated with risk of obesity and insulin resistance.

Hypothesis: Social, behavioral, and family factors that affect development of dietary preferences and physical activity patterns early in childhood determine risk of childhood obesity and insulin resistance.

Hypothesis: *In utero* and subsequent exposure to environmental agents that affect the endocrine system (bisphenol A, atrazine, and lead) results in altered age at puberty.