

Attachment 1.
List of core hypotheses for the NCS, 11-6-02

The National Children’s Study (NCS) will be a cohort of U.S. children enrolled for study before birth, with 100,000 followed for at least 21 years. The effects of environmental factors on children will be investigated using a life-stage approach, to determine if those exposures are harmful, harmless, or helpful. A variety of environmental, medical, and social data will be collected to allow a broad investigation of the interactions of chemical, genetic, behavioral, and social factors that impact child health and development. The NCS, however, will be framed by a set of scientific hypotheses and will collect focused data to answer those questions. For all enrolled subjects, we will assess exposure to environmental agents known to adversely impact child health and development, such as exposure to lead and tobacco smoke, in order to control for those known risks while evaluating the effect of other factors. Biologic specimens will be collected to allow for assessment of exposure, subclinical health effects, and genetic studies. The data collection will be organized so as to allow evaluation of the reasons for health disparities among various groups. The table below shows five categories of priority outcomes; the core hypotheses listed below are grouped according to these categories. The categories serve as an organizing structure and do not imply, e.g., that all psychiatric outcomes are addressed by the core hypotheses. The categories also facilitate succinct conveyance of the essence of the NCS. We note also that while the core hypotheses will be given priority in deciding what will be within the scope of the study, that given the data and specimens to be collected many additional hypotheses will be easily addressed. In addition, to validate estimates of early pregnancy exposure in the cohort, a portion of the cohort will be enrolled prior to pregnancy. The background for development of the priority outcomes and core hypotheses is given on the last page of this document.

Table. The National Children’s Study priority outcomes

- I. Undesirable outcomes of pregnancy: birth defects and preterm birth
 - II. Altered neurobehavioral development, developmental disabilities, and psychiatric outcomes
 - III. Injury
 - IV. Asthma
 - V. Obesity and altered physical development
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(cont.)

I. Undesirable outcomes of pregnancy: birth defects and preterm birth

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. Altered neurobehavioral development, developmental disabilities, and psychiatric outcomes

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 CP and autism.

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

III. INJURY

Hypothesis: Exposures early in life that lead to neurotoxic effects are associated with increased risk of injury.

Hypothesis: Attributes of child care and relationship with caregivers influence risk of injury.

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

IV. ASTHMA

Implicit in the hypothesis statements below is the assumption that childhood asthma comprises three subtypes (early onset transient airway obstruction, early onset persistent asthma, and late onset asthma) and that risk factors need to be studied for each type separately. In addition, characterization of a large number of potential exposures and effect modifiers is needed to gain full understanding of disease etiology. We also recognize that the timing of exposures, as well as potential dose estimation, may be critical in studying asthma etiology.

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 and mortality.

V. Obesity and altered 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.

BACKGROUND FOR DEVELOPMENT OF THE PRIORITY OUTCOMES AND CORE HYPOTHESES

The criteria followed in developing the set of core priority outcomes and hypotheses included:

- Specific enough to guide the framework for the study population, sampling schemes, data collection, and follow-up schedule.
- Justification for the large sample size (currently stated to be approximately 100,000).
- Justification for prolonged follow-up (currently slated for at least 21 years).
- Compelling import for child health and development based on prevalence, severity, economic cost, and overall public health importance. These attributes relate to both exposures and outcomes.
- Topic area not already thoroughly studied.
- Amenability to rigorous scientific inquiry.

The individual core hypotheses do not have to satisfy each of the criteria specified above in toto, however, the final set of themes and core hypotheses must do so. Potential core hypotheses were generated from several sources, including the NCS Advisory Committee (NCSAC) and its Working Groups, the NCS Interagency Coordinating Committee (ICC), the NCS Program Office, as well as other sources.

This list of core hypotheses will serve as a document for the NCSAC and its Working Groups, the lead agencies, members of the Federal Consortium, and others to use in framing the general structure of the study, and to further deliberations on the focus and design of the study. Comments on the list will be received and considered by the ICC in the revision and further detailing of the study design.