THE NATIONAL CHILDREN'S STUDY

RESEARCH PLAN

SEPTEMBER 17, 2007 – VERSION 1.3

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PREFACE

Growing up healthy is every child's right and every parent's dream for their children. As a nation, we have made significant advances in improving child health and development over the past century by identifying the causes of many diseases; by developing preventive measures, treatments, and cures; and by improving the overall health status of our children. Still, children today suffer high rates of conditions and chronic diseases that interfere with health and development: Asthma, developmental disorders, obesity, preventable injuries, and other problems. The progressive improvement of our children's health during the last century has reached a plateau and now threatens to move backward. In fact, our children are experiencing major increases in chronic health conditions, especially obesity, asthma, and learning disabilities. Many experts believe that fundamental changes in children's environments appear to be a common pathway for these increases.[1,2]

As many health and safety practices from past generations have been validated or dismissed based on new evidence, we have come to understand that the environments our children live in are profoundly important. From the air they breathe to the food they eat, from where they live to how they live, the environments in which our children grow affect their lifelong health and well-being. As described in the following research plan, multiple studies point to the association of various environmental exposures with problems in our children's health and development, such as air pollution and allergens with asthma, poor diet with obesity, and pesticides with impaired neurodevelopment. Today these problems stand among the most pressing public health concerns in the United States. Yet, with the prevalence of these conditions remaining stubbornly persistent or on the rise, few studies can confirm more definitive links that lead to prevention strategies. In addition, with threats of terrorism, violence, and other stress-inducing experiences becoming a daily exposure for many families, our children face unprecedented challenges to their well-being. Consequently, understanding and protecting our children's health and safety must be a national priority.

The National Children's Study reaffirms the federal government's commitment to the health and well-being of children by drawing together the nation's top experts on child health and the environment in an unprecedented collaboration. Multiple federal agencies, national non-profit groups, community health care providers, and more than 100,000 families stand poised to help child health move forward in the 21st century. The goals of the Study complement government efforts to challenge individuals, communities, and professionals to take action to ensure that good health and long life are enjoyed by all.

I am pleased to present this proposed Research Plan for The National Children's Study to inform scientific reviewers, professional colleagues, contributors, and all who are interested in this ground-breaking initiative that addresses these major challenges to our children's future. The Plan describes the Study's background, design, and measures, and the rationale for their selection, in sufficient detail so that readers can understand the basis of the Study and how it will be carried out. This plan was developed with input from scientists and other professionals across the country and from multiple federal agencies, especially the National Institute of Child Health and Human Development and the National Institute of Environmental Health Sciences at the National Institutes of Health, the Centers for Disease Control and Prevention, and the U.S. Environmental Protection Agency, with full awareness of competing

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[1] Van der Lee, J.H., Mokkink, L.B., Grootenhuis, M.S., Heymans, H.S., & Offringa, M. (2007). Definitions and measurement of chronic health conditions in childhood. *Journal of the American Medical Association, 297*, 2741-2751.

[2] Perrin, J.M., Bloom, S.R., & Gortmaker, S.L. (2007). The increase of childhood chronic conditions in the United States. *Journal of the American Medical Association, 297*, 2755-2759.

priorities, limitations of cost, and acceptable burden on participants. We welcome constructive comments and proposals for how The National Children's Study might address these pressing health concerns of our nation's children even more effectively. Comments and communication about the Research Plan may be submitted by e-mail to: ncsinfo@mail.nih.gov .

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PRÉCIS

Background

Our nation has made great strides in reducing or eliminating classic childhood illnesses such as measles, mumps, and chicken pox. Significant advances have been made to improve child health and development by identifying the causes of many diseases; by developing preventive measures, treatments and cures; and by providing resources to support health care for children. Trends in childhood illnesses have emerged such as increased rates of childhood asthma, alarming numbers of children diagnosed with autism, and an obesity epidemic. This new childhood morbidity threatens to undo the progress made in child health promotion and disease prevention and to add a significant new cost burden to the economy.

In the late 1990s, numerous experts called for new data to better understand child health and development. In 1999, the President's Task Force on Environmental Health and Safety Risks to Children recommended a large longitudinal study of children to fill knowledge gaps about environmental influences on child health and development. The Children's Health Act of 2000 authorized and directed a consortium of federal agencies, led by the National Institute of Child Health and Human Development (NICHD) in partnership with the Centers for Disease Control and Prevention (CDC), the United States Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences (NIEHS), to plan and to conduct the study.

The importance and timeliness of this study are based on factors that include the demonstrated and profound effects on child health of environmental exposures, such as lead in early childhood and alcohol during pregnancy; the special vulnerabilities of children to environmental exposures compared to adults; known ongoing exposures, such as prevalent levels of nonpersistent pesticides or hours of media exposure per day in young children; and evidence for environmental contributions to or causes of high-impact conditions, such as autism, developmental disabilities, asthma, and obesity. Science and technology have advanced to a point where it is possible to examine the individual and combined effects of genetic and environmental exposures, genetic variation, and multiple outcomes over life stages in the same individuals. The study design and data collected are determined by requirements necessary to test an integrated set of core hypotheses regarding the relations of environmental and genetic factors with priority outcomes in children, and later in adults.

Goal and aims

The goal of the National Children's Study (NCS) is to provide information that will ultimately lead to improvements in the health, development, and well-being of children. The primary aim of the NCS is to investigate the separate and combined effects of environmental exposures (chemical, biological, physical, and psychosocial) as well as gene-environment interactions on pregnancy outcomes, child health and development, and precursors of adult disease. In addition to this broad purpose, the Study has several specific goals:

(1) Determine the presence or absence of effects, both harmful and helpful, related to the timing, frequency, magnitude, and duration of specific chemical, physical, biological, and psychosocial exposures in children's environments from preconception to adulthood.

(2) Determine possible environmental contributions to, or causes of, specific diseases and conditions of children, including, but not limited to, prematurity and other outcomes

of pregnancy, neurological and developmental disorders, psychiatric and behavioral disorders, altered physical development and sexual maturation, obesity and insulin resistance, asthma, and injuries.

(3) Determine how genotypic variation and mechanisms, and the interaction of genes with environmental factors, influence disease risk and developmental trajectories in children.

(4) Serve as a national resource for future studies of child health and development by providing a rich database and repository of environmental and biological samples and information that can be used to address future questions and hypotheses.

Methods

This longitudinal cohort study will follow a representative sample of approximately 100,000 children born in the United States. Children will be followed from before birth until age 21.

Sampling and recruitment. The Study will employ a national probability sampling approach to select locations for conduct of the Study. The sampling design utilizes a multistage clustered approach. In the first stage, 105 locations (generally corresponding to single counties) were randomly selected from all U.S. counties. Seven of the locations will serve as the Vanguard Locations and will participate in the pilot phase of the Study. Because the focus of the Study includes assessment of the impact of exposures that occur early in pregnancy, both pregnant women and their partners and women of childbearing age comprise the initial target population for enrollment in the Study Locations. At the time of enrollment, participants will be asked to provide written informed consent for participation in the Study. Three distinct groups will be enrolled and followed: pregnant women and their partners; couples planning pregnancy; and women not currently planning pregnancy but with some probability of becoming pregnant during the four-year enrollment timeframe.

Follow-up. The initial follow-up of women enrolled in the study prior to pregnancy (the preconception cohort) will vary with each woman's probability of pregnancy. Women with a high probability of becoming pregnant (generally a subset of women trying to become pregnant) will receive an in-person visit and as many as three telephone contacts during the four months following enrollment. In contrast, women with the lowest probability of becoming pregnant will be contacted annually by phone. It is anticipated that during the enrollment period, a woman's probability of becoming pregnant will not be stagnant. Data collection schedules will be modified based on the most current information on each individual's probability of pregnancy.

Once women are pregnant, follow-up visit schedules will be identical for all women and children enrolled in the Study regardless of the initial probability of pregnancy. A minimum of six in-person visits are planned from the first trimester of pregnancy through age 3. Three of these visits are in the home, and three are in a clinical setting (one of which is the place of delivery of the infant). After age 3, in-person visits should occur every two to three years with an additional home visit after each change of permanent residence. Remote data collections (e.g., telephone, computer, or mail-in questionnaires) will occur between face-to-face contacts. The expected frequency of contact (face-to-face or remote) is approximately every three months through age 1, every six months through age 5, and annually thereafter. For a sample of children enrolled in the Study, visits will also be made to child care and school settings for collection of environmental samples and observational data.

The schedule of in-person contacts and phone interviews from pregnancy through age 21 are outlined in the table below:

Timing and Location of Study Contacts

Age of child	Location of visit
Preconception	As outlined above
1st trimester	Home
2nd trimester	Phone
3rd trimester	Clinic
Birth	Place of delivery
3 months	Phone
6 months	Home
9 months	Phone
12 months	Home
18 months	Phone
24 months	Phone
30 months	Phone
3 years	Clinic
5 years*	To be decided
7 years	To be decided
9 years	To be decided
12 years	To be decided
16 years	To be decided
21 years	To be decided

*Timing and location of visits from 5 years onward is provisional

Anticipated biologic specimens include blood, urine, hair, and nail clippings from mothers and children; blood, urine, and hair from fathers; cord blood, umbilical cord and placental tissues, and meconium collected at or around the time of delivery; vaginal swabs, and breast milk from mothers. Anticipated environmental samples include air, dust, soil, food, and water.

Expected contributions of the Study

The NCS is in a unique position to answer questions regarding the effects of environmental exposures on the long-term health of children. The focus on exposures prior to and early in pregnancy and the breadth of planned exposure and outcome measurements are unique features of the Study. As technology evolves, stored data specimens (biologic and environmental) will provide a valuable resource to answer questions for future generations.

The Study's prospective longitudinal design will permit an in-depth examination of the effects of environmental exposures as they unfold over the course of development. This will include an unprecedented, process-oriented understanding of how exposures at particular points in development lead to both immediate and long-term consequences for children, and what circumstances, characteristics, or genetic predispositions mediate or moderate the relation between exposure and outcome. The size and representative nature of the sample will permit both valid inferences about the U.S. population as a whole and exploration of subgroup-specific patterns of adaptation and maladaptation.

The data collected for the NCS will also provide a platform for future research. Data and biological and environmental samples will be available for future studies as science evolves and new questions arise. The NCS will serve as an exceptional resource both for science and for society.