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Pediatrics 2006;118;2173-2186
DOI: 10.1542/peds.2006-0360

SPECIAL ARTICLE

The National Children's Study: A 21-Year Prospective Study of 100 000 American Children

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Financial Disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

Prospective, multiyear epidemiologic studies have proven to be highly effective in discovering preventable risk factors for chronic disease. Investigations such as the Framingham Heart Study have produced blueprints for disease prevention and saved millions of lives and billions of dollars. To discover preventable environmental risk factors for disease in children, the US Congress directed the National Institute of Child Health and Human Development, through the Children's Health Act of 2000, to conduct the National Children's Study. The National Children's Study is hypothesis-driven and will seek information on environmental risks and individual susceptibility factors for asthma, birth defects, dyslexia, attention-deficit/hyperactivity disorder, autism, schizophrenia, and obesity, as well as for adverse birth outcomes. It will be conducted in a nationally representative, prospective cohort of 100 000 US-born children. Children will be followed from conception to 21 years of age. Environmental exposures (chemical, physical, biological, and psychosocial) will be assessed repeatedly during pregnancy and throughout childhood in children's homes, schools, and communities. Chemical assays will be performed by the Centers for Disease Control and Prevention, and banks of biological and environmental samples will be established for future analyses. Genetic material will be collected on each mother and child and banked to permit study of gene-environment interactions. Recruitment is scheduled to begin in 2007 at 7 Vanguard Sites and will extend to 105 sites across the United States. The National Children's Study will generate multiple satellite studies that explore methodologic issues, etiologic questions, and potential interventions. It will provide training for the next generation of researchers and practitioners in environmental pediatrics and will link to planned and ongoing prospective birth cohort studies in other nations. Data from the National Children's Study will guide development of a comprehensive blueprint for disease prevention in children.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-0360

doi:10.1542/peds.2006-0360

With the exception of Dr Berkowitz, the authors are investigators in the Queens, NY, Orange County, CA, and Salt Lake City, UT, Vanguard Centers of the National Children's Study. This project was funded in whole or in part with Federal funds from the National Institute of Child Health and Human Development, National Institutes of Health, under NICHD grant HHSN275200503411C/N01-HD-5-3411. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Key Words
National Children's Study, epidemiology, asthma, attention-deficit/ hyperactivity disorder, autism, schizophrenia, obesity

Abbreviations
CVD— cardiovascular disease
NICHD—National Institute of Child Health and Human Development
CDC—Centers for Disease Control and Prevention
NCS— National Children's Study
HPV— high production volume
NCPP—National Collaborative Perinatal Project
CHDS—Child Health Development Study
NIH—National Institutes of Health

Accepted for publication Jun 27, 2006

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ENVIRONMENTAL EXPOSURES IN early life can influence development, impair health, and increase risk of disease and dysfunction.[1–3] Chemical, physical, and psychosocial factors have all been shown to exert great influence. Among potentially harmful chemical and physical exposures are cigarette smoking during pregnancy,[4,5] thalidomide,[6,7] diethylstilbestrol,[8] lead,[9–15] ethyl alcohol,[16] ionizing radiation,[17,18] polychlorinated biphenyls and other organochlorine compounds,[19] methylmercury,[20–26] outdoor air pollutants,[27] benzene,[28] and certain pesticides.[29]

Evidence is mounting that prenatal factors and early childhood experiences may play a role in disease development in later life.[30] Altered fetal growth has been related to increased risk of cardiovascular disease (CVD), hypertension, and diabetes in adulthood,[31–34] and accelerated childhood growth is related to subsequent risk of breast cancer in women,[35] as well as to impaired glucose tolerance in adulthood.[36] There almost certainly exist additional etiologic associations between environmental exposures and disease in children that have not yet been discovered.

Progress in elucidating the role of the environment in causation of disease has for the most part been slow and incremental. Nearly all previous studies have examined relatively small populations of pregnant women and their offspring[37]; have considered only one chemical at a time[38]; have had little statistical power to examine interactions among chemical, social, and behavioral factors in the environment[39]; have had limited ability to examine gene–environment interactions[40]; and have suffered from brief duration of follow-up.[41] Almost nothing is known regarding the interrelationships between chemicals and other environmental hazards and between the chemical and physical environment and social environments.[42]

Large, prospective, multiyear epidemiologic studies can overcome the limitations of previous investigations. A great strength of the prospective study design is that it permits unbiased assessment of exposures as they occur, before the onset of disease or dysfunction. This is crucial for studies of fetal and infant exposures, because attempts to reconstruct past exposures months or years after their occurrence are inherently limited and subject to the vagaries of human memory, as well as of recall bias. These limitations constrain the ability of retrospective or case-control studies to obtain unbiased and precise data on the nature and timing of exposures in early life. Prospective studies have the additional advantage that they permit exploration of exposures within a multilevel framework, which considers exposures at the individual, family, neighborhood, and societal levels.[43,44] They are especially powerful when they incorporate biomarkers of exposure and of genetically mediated susceptibility.

To take advantage of new developments in study design, exposure assessment, and information technology, and to overcome the shortcomings of previous studies, the President's Task Force on Environmental Health and Safety Risks to Children recommended in 1998 that a large prospective, multiyear epidemiologic study of American children be undertaken.[45] In response to that recommendation, the US Congress, through the Children's Health Act of 2000, authorized the National Institute of Child Health and Human Development (NICHD) "to conduct a national longitudinal study of environmental influences (including physical, chemical, biological and psychosocial) on children's health and development."[46] The National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention (CDC), and the US Environmental Protection Agency have joined the NICHD in planning this study, now named the National Children's Study (NCS).

RATIONALE FOR THE NCS

Patterns of illness among children in the United States and in other industrially developed nations have changed substantially in the past 100 years.[47] Today the major illnesses confronting children are a group of chronic conditions termed the "new pediatric morbidity."[48] These include premature birth[49]; asthma[50]; childhood and young adult cancers, such as acute lymphocytic leukemias,[51] brain cancer,[52] and testicular cancer[53]; neurodevelopmental disorders such as learning disabilities, dyslexia, mental retardation, attention deficit/hyperactivity disorder, and autism[54–59]; obesity and type 2 diabetes[60–62]; and some birth defects, such as gastroschisis.[63–70]

The environment in which children live has also changed.[71,72] Today there are >80 000 synthetic chemicals, most of them developed since the 1950s.[73] These include plastics, pesticides, fuels, building materials, antibiotics, chemotherapeutic agents, flame retardants, and synthetic hormones. Children are at especially high risk of exposure to the 2800 synthetic chemicals that are produced in quantities of ≥1 million tons per year.[2] These high production volume (HPV) chemicals are the synthetic materials dispersed most widely in the environment in air, food, water, and consumer products in homes, schools, and communities.[74] In recent national surveys, quantifiable levels of a number of HPV chemicals have been detected in the bodies of most Americans, as well as in the milk of nursing mothers.[75]

A National Academy of Sciences committee on pesticides in the diets of infants and children identified 4 fundamental differences between children and adults that contribute to children's heightened susceptibility to toxic chemicals[76]:

- Children have disproportionately heavy exposures to environmental toxicants as a consequence of their

greater intake kilogram-for-kilogram of food, water, and air coupled with their unique behaviors, in particular their oral exploratory behavior.

- Children's metabolic pathways, especially in the first months after birth, are immature. In many instances, children are less able than adults to excrete and/or detoxify toxic compounds.
- Children are undergoing rapid growth and development. These developmental processes create windows of great vulnerability in which the course of development can be permanently disrupted by environmental toxins.
- Because children have more future years of life than most adults, they have more time to develop chronic diseases that may be initiated by early exposures.

Although much remains to be learned about associations between the environment and disease in children, evidence is accumulating that environmental factors make important contributions to disease causation. Numerous pollutants in the indoor environment have been shown to be triggers for childhood asthma, such as second-hand tobacco smoke, mold and mites, cockroach droppings, animal dander, and certain pesticides.[77,78] Reduction in children's exposures to these indoor pollutants was shown to reduce frequency of asthma.[79] Ambient air pollutants (fine particulates, ozone, oxides of nitrogen, and diesel exhaust) also were shown to increase incidence of asthma and to trigger asthmatic attacks.[26,80,81] Reduction in levels of ambient air pollution was associated with reduction in the number of hospitalizations resulting from asthma and other respiratory diseases.[82–84] Childhood cancer has long been linked to ionizing radiation. More recently, benzene, 1,3-butadiene, and pesticides were etiologically associated with childhood malignancies.[85,86] A recent National Academy of Sciences study suggests that ≥28% of developmental disabilities in children may be caused by environmental factors acting alone or in combination with genetic factors.[87]

A higher proportion of children in America today live in cities and suburbs than ever before, and the built environment has been shown to be capable of influencing children's health and risk of disease.[88–92] The adverse effects of the modern built environment are especially magnified in low-income, predominantly minority urban communities where crowded streets, lack of outdoor play-spaces, limited access to fresh and healthy food, and substandard housing all contribute to substantial and well-documented disparities in health care.[93–97] Recognition is increasing that characteristics of the built environment may influence diet and activity patterns and, as a result, increase the risk of obesity.[98,99]

PREVIOUS LONGITUDINAL STUDIES

Adult Longitudinal Studies

Previous major prospective epidemiologic studies of adults have yielded invaluable gains in knowledge of disease causation and have provided critical tools for prevention and treatment. A classic example is the Framingham Heart Study (Framingham, MA), established in 1948. At that time immediately after World War II, heart disease and stroke were epidemic in the United States. The causes were poorly understood. The goal of the Framingham Heart Study was to identify preventable risk factors for CVD. Data from Framingham identified cigarette smoking[100] and elevated cholesterol and hypertension as preventable causes of CVD[101,102]; later analyses elucidated the role of elevated triglycerides, sedentary lifestyle, and diabetes. This information provided the blueprint for highly successful programs of prevention that have reduced incidence of CVD in adult males in the United States by >50% over the past 4 decades (Fig 1).[103]

The Nurses' Health Study, established in 1976, and the Nurses' Health Study II, established in 1989, are 2 major prospective investigations in the United States into the risk factors for chronic disease in women. The initial goal was to study the health consequences of oral contraceptive use. Invitations were mailed to 170 000

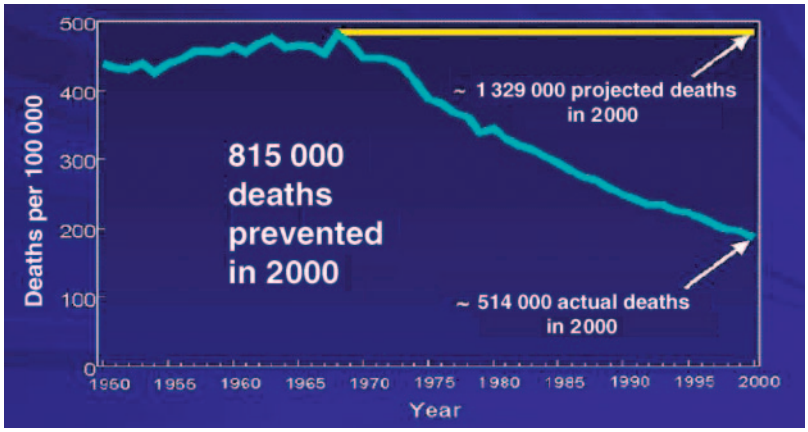

FIGURE 1
Incidence of coronary heart disease: United States, 1950–2000 (age-adjusted death rates, actual and expected). A striking reduction in incidence of heart disease and stroke was achieved over the past half century in US men and women. This decline resulted from discoveries made in prospective epidemiologic studies such as the Framingham Heart Study showing that elevated cholesterol, cigarette smoking, hypertension, obesity, diabetes, and sedentary lifestyle are powerful risk factors for CVD. (Reproduced with permission from a presentation by NIH director Elias Zerhouni, MD, at National Prevention Summit, Washington, DC, October 24–25, 2005. The full presentation is available at www.healthierus.gov/steps/summit/day1/Zerhouni-1030am.ppt.)

registered nurses in 11 states, and >120 000 enrolled. The Nurses Health Study II enrolled a younger cohort (25–42 years of age) of 116 686 women.[104] A third major study of women's health, the Women's Health Initiative sponsored by the National Heart, Lung, and Blood Institute has enrolled >161 000 women aged 50 to 79 years. Its goal is to study the risks and benefits of hormone replacement therapy in postmenopausal women, as well as the benefits of dietary supplementation to prevent osteoporosis, fractures, and breast and colorectal cancer.[105] These large population studies have also pioneered and tested a series of logistic and methodologic advances that provide the basis for future prospective studies.

PEDIATRIC LONGITUDINAL STUDIES

A number of prospective, longitudinal studies of children were previously conducted, and experience gained in these studies has helped to guide the NCS. A cohort study of 16 000 children in Bogalusa, Louisiana[106] showed that obese children frequently remain obese through adulthood[107] and identified a number of significant long-term consequences of childhood obesity for cardiovascular health.[108] Since 1970, 20 000 children have participated in the Muscatine (Iowa) study of childhood predictors of adult CVD,[109] which has identified genetic and environmental predictors of childhood obesity.[110]

Birth cohorts have also identified many of the important pharmaceutical, obstetric, socioeconomic, and genetic factors that are currently known to affect neurologic and behavioral development in utero and in childhood. The first such longitudinal study was the British National Survey of Health and Development, initiated in 1946, and based on a national sample of births in England during a 1-week period. The cohort has since been followed up 23 times, providing the most detailed data available anywhere on the evolution of health and disease over the life course. Later, British birth cohorts of 1958 and 1970 were constructed along similar lines.

In the 1950s, 2 very important studies were launched in the United States, the National Collaborative Perinatal Project (NCPP)[111] and the California Child Health and Development Study (CHDS).[112,113] These studies differed from the British studies in that they began follow-up before birth at the first prenatal visit, collected and archived biological specimens such as serum samples, and were of a much larger size. The NCPP was established by the National Institute of Neurologic Disorders and Blindness in the 1950s as a prospective epidemiologic study to investigate the relationships between pregnancy, labor, and delivery and subsequent neurodevelopmental outcomes in infants and children.[114] Fourteen medical centers within 12 universities collected data on >58 000 pregnancies and followed the health of surviving children through age 7 or 8. Similarly, the CHDS examined ~20 000 pregnancies, birth outcomes, and health in surviving children.[112] Additional pregnancy/birth cohorts were also established in Australia,[115] New Zealand,[116] Israel, and the Scandinavian countries. The NCPP still provides important knowledge about the causation of childhood disease decades later. Recent findings include the identification of in utero tobacco exposure as an important predictor of adolescent smoking behavior[117] and confirmation of the positive relationship between birth weight and childhood cognitive potential.[118]

More recently initiated pregnancy/birth cohorts provide an additional foundation of experience and knowledge for the NCS. The Avon Longitudinal Study of Pregnancy and Childhood in England[119] has collected genetic as well as detailed phenotypic information on ~15 000 children and their parents; the children are now in their teens. The Danish National Birth Cohort[120] and the Norwegian study of mothers, fathers, and infants[121] have collected data from the prenatal period to date on ~100 000 live births in each study. Examples of findings from the Avon study include identification of paternal depression as an important factor in a child's emotional and psychological development[122] and confirmation of the frequency and potential psychological basis for recurrent abdominal pain in children.[123] The Danish study has provided important insights into the health of the offspring of pregnancies begun through in vitro fertilization.[124]

Although follow-up of birth cohorts into adult life is always a challenge, especially among relatively mobile US populations, investigators at several sites have proven that long-term follow-up and cohort retention are feasible. For example, a subset of the Providence CPP cohort was recontacted at ages 18 to 27 years to examine the relationship between prenatal and delivery complications and psychiatric disorders in adult life.[113] The CHDS cohorts are currently being followed for nested case-control studies of prenatal determinants of schizophrenia, male reproduction, and neurodevelopment.[126–130]

These cohorts constitute national treasures, especially because of the availability through them of stored sera and carefully collected exposure and health outcome data. However, a shortcoming is that none of these previous longitudinal studies of children have obtained data on environmental exposures, nor did any of them incorporate newer technologies for the collection of biological and environmental samples or of genetic material. Pilot studies to explore the feasibility of obtaining environmental data in the context of prospective birth cohort studies have been conducted during the past 5 years within the initial network of federally funded Centers for Children's Environmental Health and Disease Prevention Research.

Smaller-scale prospective cohort studies were successfully launched by 3 of these federally funded centers

at Columbia University, Mount Sinai Medical School, and the University of California at Berkeley. These studies showed the feasibility of conducting epidemiologic studies in the United States that examine the health consequences of early environmental exposures.[29] They used a combination of exposure biomarkers and monitoring strategies to characterize in utero and postnatal exposures to environmental contaminants, and they incorporated molecular genetic assessments of individual susceptibility factors to examine the interplay between environmental exposures and the human genome. Although involving sample sizes of <1000 children, these studies yielded valuable data and experience that support and foreshadow the NCS initiative, and they provided practical lessons that can inform its conduct.

HYPOTHESES TO BE ADDRESSED BY THE NCS

The NCS is hypothesis-driven and will address a series of specified questions pertaining to the influence of the environment (chemical, biological, physical and psychosocial) on children's health, growth, development, and risk of disease. It will also seek to discover etiologically important gene-environment interactions, as well as the factors that modulate individual susceptibility to environmental exposures. Working groups convened by the NICHD and the NCS Advisory Committee developed the core hypotheses for the NCS, in consultation with hundreds of scientists, community groups, and professional organizations from across the United States and worldwide.

A current list of hypotheses with supporting scientific rationale that were accepted and refined by the Interagency Coordinating Committee (composed of senior scientists from the NICHD, National Institute of Environmental Health Sciences, CDC and US Environmental Protection Agency) is available at www.nationalchildrensstudy.gov.[131] As the NCS is implemented, new questions will emerge and be added, and some may become outdated. A key criterion for the selection of these hypotheses is that they cannot be reasonably studied with fewer children or a different study design.

A representative sample of the questions that NCS will address is provided below:

- What is the role of bioaerosols in the causation of asthma? Multiple studies have shown strong associations between exposures to bioaerosols and the exacerbation of asthma in children with preexisting disease. The NCS is perhaps the only opportunity to differentiate the complex interrelationships of allergens, endotoxins, mold, and indoor and outdoor air pollution in inducing asthma.[26]
- What is the role of the built environment in increasing risk for obesity and insulin resistance? Being overweight as a child is a risk factor for being overweight in adulthood[132] and is associated with increased risk of type 2 diabetes, hypertension, and coronary artery disease.[133] Overweight children have also been found to have a higher risk of developing diabetes at age 21 years.[134] Research in urban planning and public health finds that pedestrian-oriented environments are associated with increased walking,[135,136] and a small but growing literature is beginning to confirm that pedestrian-oriented environments are associated also with lower rates of obesity than car-dependent environments.[98,137] A study with the large sample size and prospective design of the NCS is needed if we are to carefully unravel the complex relationships among genetics, diet, physical activity, and risk for obesity and its comorbidities and develop effective prevention approaches to the obesity epidemic.
- What is the etiologic role of impaired glucose metabolism in birth defects? Women with type 1 or type 2 diabetes before pregnancy have an increased risk of congenital anomalies in offspring, and animal models confirm the teratogenicity of impaired glucose metabolism.[138–141] Limited data also suggest an association in women with gestational diabetes or those with lesser degrees of impaired glucose metabolism during pregnancy.[142,143] Because obesity and gestational diabetes are important risk factors for insulin resistance and have reached epidemic levels in the United States, evaluation of the impact of impaired glucose tolerance on certain birth defects becomes an important priority for efforts to reduce the burden of such conditions in the population.
- What is the role of psychosocial stressors in causing adverse neurobehavioral outcomes? Do these stressors act through altered gene expression? Efforts to find a cure for depression have been confounded by lack of a clear understanding of its complex etiology. One obstacle to understanding depression may be genetic variability in the influence of the environment on gene expression.[144] Research on nonhuman primates has also shown that genotype alone does not sufficiently predict aggression or antisocial behaviors.[145]
- Does increasing exposure to endocrine-disrupting chemicals such as phthalates explain the rise in hypospadias? Animal studies have suggested a pathway through which these synthetic chemicals may disrupt reproductive organogenesis,[146,147] but the relatively low rates of this particular birth defect make it difficult to detect an association without a cohort study of this size.
- How do factors in the chemical, psychosocial, and physical environment interact in the causation of disease and disability? Studies have documented variations in children's health outcomes across geographic areas, but they have not achieved the statistical power or interdisciplinary complexity necessary to estimate

impacts of community and neighborhood factors on children's health.[148]

- What are the interactions between environmental factors and individual, genetically determined susceptibility in the genesis of disease? The Human Genome Project is beginning to elucidate the complexity of the molecular genetic factors that influence individual susceptibility to environmental exposures. The NCS will apply the powerful findings of the Human Genome Project to definition of a wide array of gene–environment interactions that could not be delineated except through a large, prospective NCS that began at conception.[149] Previously, gene–environment interactions have been ascertained only in piecemeal fashion, mostly one at a time because of small sample sizes, but well-designed studies have confirmed the existence of such interactions and have reinforced the need for a large, prospective study like the NCS. One recent study found, for example, a fourfold increased risk of orofacial clefts among infants with the NAT1 and NAT2 genetic polymorphisms born to mothers who smoked.[150] Data from the Children's Environmental Health Center at Mount Sinai found an association between maternal exposure to the pesticide chlorpyrifos during pregnancy, low expression levels of the pesticide-metabolizing enzyme PON1, and increased risk of small head circumference at birth.[151]

DEVELOPMENT AND IMPLEMENTATION OF THE NCS

Since the legislation authorizing the NCS was enacted in 2000, working groups have been convened by the NICHD to develop hypotheses and propose research protocols to test them. For the past 4 years, these working groups convened and have been developing and delineating research protocols and planning logistics, such as specifying methods for collecting data to characterize environmental exposures that may cause or increase risk of asthma, CVDs, neurobehavioral disorders, diabetes, obesity, and osteoporosis, just to name a few.

The NCS will use a national probability sampling approach. The primary sampling units were based on counties in the United States, and 105 of 3400 US counties were selected to represent geography and population density. This sampling design uses a multistage clustered approach, with oversampling of certain subpopulations to ensure adequate numbers of participants in target groups and to allow valid inferences on exposure-outcome relations in these subpopulations. Women of childbearing age will comprise the population for enrollment, and household surveys of neighborhoods randomly selected within the 105 counties will be used to recruit a representative sample. Because the focus of the NCS is the assessment of the impact of exposures that occur early in pregnancy, pregnant women beyond the first trimester of pregnancy will not be enrolled. After recruitment, 3 subgroups of women and their partners will be followed according to the likelihood of pregnancy: pregnant women already in the first trimester, women planning pregnancy, and women of childbearing age but not planning a pregnancy. At enrollment, participants will be asked to provide written consent for participation in the study and will complete a short interview.

Families who are enrolled in the study will participate in a minimum of 15 in-person visits with research teams across stages of development (ie, before conception; 3 times during pregnancy; at birth; at 1, 6, 12, and 18 months of age in early childhood; at 3, 5, 7, 9, and 12 years of age in childhood; and at 16 and 20 years of age in adolescence). Seven of these visits will be in the participants' homes and 8 will be in clinical settings, including the infants' place of delivery. Data will be remotely collected via telephone, computer, or mail-in questionnaires every 3 months through the age of 5 and annually thereafter. Biological samples from the mother and child to measure body burdens of environmental chemicals and environmental samples such as air, water, dirt, and dust from the child's home environment will be collected over the course of the study. Individual parent, child, and family psychosocial domains to be assessed include family composition (including absentee parents and children not living at home and disruptions), family conflict (including domestic violence and abuse), mother and/or father's physical and mental health history, mother and/or father's current emotional and cognitive adjustment (eg, depressive symptoms, anxiety, cognitive functioning, literacy, coping style, parenting skills, and knowledge of child development), parent–child interaction, and quality of the caretaking environment.

The NCS has already awarded contracts to 7 academic institutions to establish Vanguard Centers for the study, sites where the NCS would start to recruit participants and test protocols to ensure that the study goes smoothly before it is brought to scale (recruiting and assessing 100 000 children from birth to age 21). The 7 Vanguard locations represent a broad array of rural and urban areas with a broad diversity of social, ethnic, and other demographic factors.[152] A map of study locations is provided in Fig 2, and a list of study sites is provided in the Appendix. Recruitment is scheduled to begin in 2007.

DISCUSSION

The NCS is the largest prospective study of American children ever to be undertaken. It is the first national cohort study of children in the United States since the Collaborative Perinatal Project of ~40 years ago. It is the first large birth cohort study in any nation to specifically examine the influence of environmental factors on birth outcomes, child health, and human development, and the first designed to systematically examine the influ-

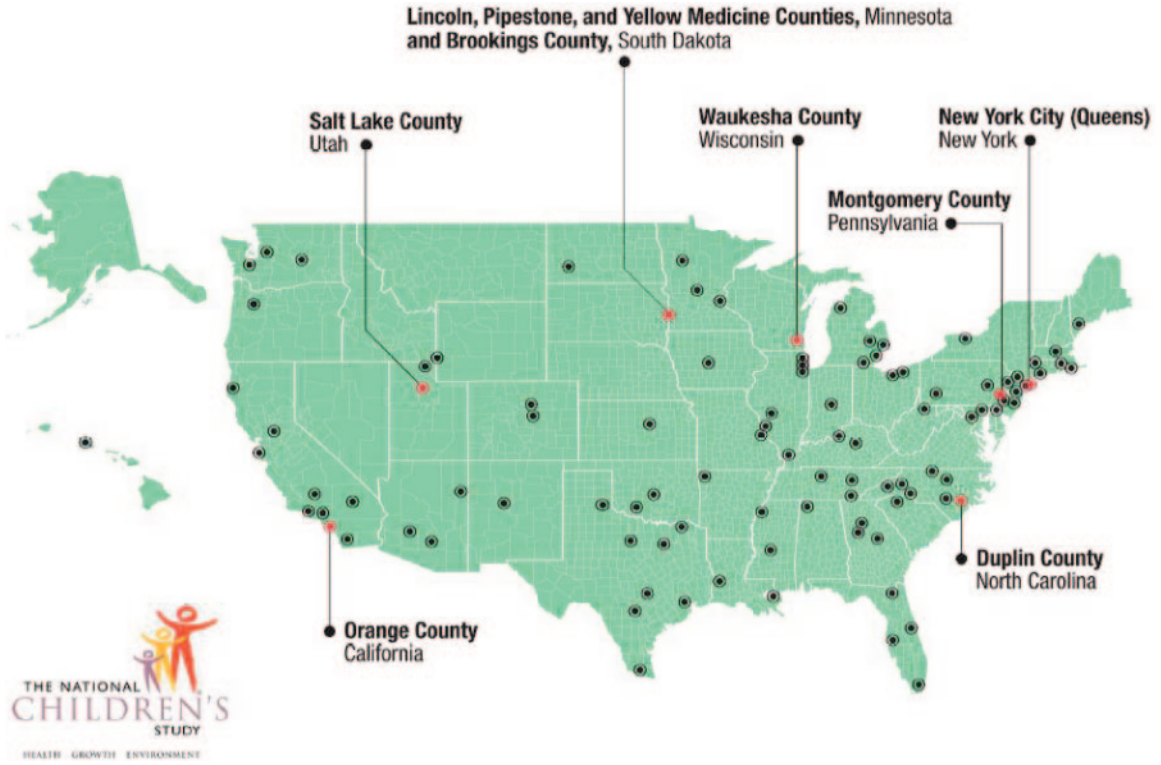

FIGURE 2
Map of study locations for the NCS (Vanguard sites named). (Adapted with permission from data at www.nationalchildrensstudy.gov.)

ence of gene-environment interactions on children's health.

We anticipate that the NCS will provide pediatricians and other child health providers with powerful information on preventable, environmental risk factors for disease in children. This information is available from no other source and will help practitioners to improve birth outcomes such as premature birth and to prevent such chronic diseases in children as asthma, certain birth defects, dyslexia, attention-deficit/hyperactivity disorder, autism and schizophrenia, and obesity. Just as data from the Bogalusa and Muscatine Heart Studies described the predictive power of childhood BMI with adult adiposity,[108,153] and as findings from the Framingham Heart Study provided critically important information on preventable risk factors for CVD in adults (information that has saved millions of lives), findings from the NCS promise to provide the evidentiary basis for a comprehensive blueprint for the prevention of chronic disease in America's children.

The NCS will also provide information on a wide range of other issues relevant to child health in the United States. The study will, for example, abstract medical records and unite these abstracts with data from other sources, such as hospital and school records, to create public access databases that will be available to properly qualified researchers for secondary analyses. Thus, health services researchers will be able to use the data from the NCS to conduct analyses of the impact of early treatment of childhood asthma with medications. Social psychologists could use these data to analyze the impacts of family structure and parental education on cognitive function. Pediatric emergency department physicians could use these data to assess the relationship of socioeconomic factors to use of emergency care and hospitalization and other adverse outcomes.

A major strength of the NCS is its prospective design. This design permits assessment of environmental exposures in real time as they actually occur, which is especially important for monitoring prenatal exposures where precise ascertainment of the nature, exact level, and timing of exposures is critical. The prospective design obviates the need to reconstruct past exposures from memory months or years after their occurrence, an inherently imperfect approach to exposure assessment. Although it is true that the level of detailed environmental sampling to be undertaken in the main cohort of the NCS is less than might be attained in smaller, more focused studies, nested, highly detailed environmental sampling will be undertaken in subsamples of the national cohort through the mechanism of satellite studies (eg, personal monitors will be used to measure air pollution at the level of the individual child's breathing zone, and robots will be used to assess exposures at floor level where young children play). Another strength of the NCS is that analyses of environmental samples will

be conducted at the laboratories of the CDC, the world's premier laboratory for the quantitative analysis of multiple exogenous chemicals in biological and environmental samples down to extremely low levels. Moreover, aliquots of environmental and biological samples will be archived under highly secure conditions and will be available for future analyses.

Some scientists have suggested that a large cohort study representing the age distribution of the current US population might provide a better design for the investigation of gene–environment interactions related to the major diseases of adult life. However, such an approach ignores the growing evidence that a number of important environmental contributions to disease in adult life have their origins early in development. Such early environmental exposures would be missed by a study that looked principally at adults. Only a longitudinal assessment of lifetime environmental exposures that follows individuals from conception onward can capture the consequences of early exposures and unravel the interactions between these exposures and individual susceptibility factors that underlie vulnerability to diseases of adulthood. It is now clear that vulnerability to a particular risk factor is often determined not only by the genome acquired at conception, but also by dynamic modifications to the genome over the life span. Therefore, to adequately assess gene–environment interactions, not only will the stable DNA sequence be essential but also epigenetic modifications to nuclear and mitochondrial DNA will have to be identified.

A multigenerational sample would represent another approach to the assessment of gene–environment interactions in the genesis of chronic disease. However, the cost to collect, store, process, and analyze material for genetic investigations across multiple generations would be enormous. Moreover, the opportunity exists within the prospective birth-cohort design of the NCS to acquire biological samples from family members across multiple generations, and the design of the study would provide the added benefit of linkage to environmental measures that will apply across the generations. As new genetic tests and methods are developed through efforts by many institutes, including the National Human Genome Research Institute, they can be applied immediately to environmental as well as genetic samples that will be stored in the NCS Data Repository, thus providing opportunities for rapid application of up-to-date knowledge initially on behalf of our nation's children.

Some have argued that a study of the magnitude of the NCS should be postponed until the most recent technologic advancements can be applied. Similar arguments were raised >50 years ago about large cohort studies such as the Framingham Heart Study, and to be sure none of those studies was perfect. But each of those studies was incredibly productive and has enormously benefited public health in the United States. Moreover, the methodologies used in each of those large study platforms have periodically been updated to take advantage of new developments in biomedical methodology; none have been methodologically static.

More than ever, pediatricians are yearning for guidance in the prevention and treatment of diseases of environmental origin in children.[154,155] Although the public is concerned about environmental threats to children's health[156] and patients frequently ask their physicians about the health effects of environmental exposures,[157] most pediatricians report that they have received little specific training in environmental pediatrics, and few report that they feel comfortable in diagnosing and managing disease of possible environmental origin.[158] As researchers better delineate the role of environmental exposures in childhood disease, findings from the study will inform pediatric practice. It may reasonably be anticipated that the study will provide the impetus for the training of a generation of pediatricians in environmental pediatrics, much as the Collaborative Perinatal Study provided the impetus for creation of the specialty of pediatric neurology.

Some scientists have argued the projected $2.7 billion cost of the 25-year NCS is too high and that the National Institutes of Health (NIH) should invest its funds in more focused research to investigate individual diseases. However, countering that argument is the expectation that the savings that will derive from the NCS will enable the study to pay for itself many times over. Six of the chronic diseases that the NCS plans to examine (obesity, injury, asthma, diabetes, schizophrenia, and autism) cost America $642 billion per year. Even if the NCS were to produce only a 1% reduction in the cost of these chronic diseases, it would yield savings of $6.4 billion per year, far more than the $2.7 billion that the study is projected to cost over 25 years.[38] Using conservative estimates of the impact of the NCS on 10 major adverse health outcomes, the Battelle Memorial Institute has projected that the NCS is poised to achieve an estimated 8-to-1 net benefit-to-cost ratio by 2020, 30-to-1 ratio by 2030, and 50-to-1 ratio by 2040 (Table 1) (Tim Pivetz, MS, and Warren Strauss, ScM, Battelle Memorial Institute, verbal communication, 2006).

Although some critics have also expressed concern that the NCS will threaten the viability of existing research projects funded by the NICHD and other institutes of the NIH, the effect is more likely to be the opposite. Findings from the NCS are likely to increase interest generally in prevention-oriented research that focuses on the diseases of children and to generate innumerable hypotheses for additional investigation. In previous large-scale projects, the bolus of findings triggered follow-up studies and provided investigators and trainees a framework to propose new studies. We expect the same effect from the use of data from the NCS.[159] Because the decoding of the human genome makes pos-

TABLE 1 **Potential Economic Savings From NCS: Median Estimated Reductions**

Health Outcome	Estimated Cost (2003), Billion $	Age at Diagnosis, y	Results Published	Projected Costs, Billion $ (2006)	Median Estimated Reductions, %	Cost Savings From NCS, Billion $ (2006)			
						2020	2025	2030	2040
Diabetes	136.6	10	2025	149.27	1.00	0.00	0.00	7.46	22.39
Asthma	14.5	3	2018	15.84	5.00	1.58	5.55	9.51	17.43
Obesity (excluding diabetes)	46.3	10	2025	50.59	3.00	0.00	0.00	7.59	22.77
Low birth weight	13.1	0	2015	14.31	5.50	3.94	7.87	11.81	19.68
Mental retardation	51.2	6	2021	55.95	3.50	0.00	7.83	17.62	37.21
Motor vehicle accidents	19	18	2033	20.76	0.25	0.00	0.00	0.00	0.36
Violence	24.3	18	2033	26.55	0.25	0.00	0.00	0.00	0.46
Mercury exposure	0.8	6	2021	0.87	0.12	0.00	0.00	0.01	0.02
Nonpersistent pesticide exposure	49	6	2021	53.54	0.50	0.00	1.07	2.68	5.35
Autism	40.6	3	2018	44.36	1.00	0.89	3.11	5.32	9.76
Total	395.4			432.06		6.41	25.43	62.00	135.44
Study implementation costs						1.24	1.60	1.92	2.0
Net cost savings (excluding medical cost of implementing findings)						5.17	23.83	60.09	133.41
Estimated cost of implementing prevention strategies (20% of net cost savings)						1.03	4.77	12.02	26.68
Net cost savings						4.14	19.06	48.07	106.73
Ratio of net cost savings from improved health outcomes to NCS implementation costs						3.3	11.9	25.1	52.6

Obtained from Tim Pivetz and Warren Strauss, Battelle Memorial Institute. Published with permission.

sible elucidation of the interplay between genetically determined individual differences in susceptibility to environmental exposures and risk of disease, a new generation of investigators armed with this knowledge should be able to make additional scientific advances well beyond those produced by earlier cohort studies.

We have described some of the weaknesses and criticisms of the NCS, and we recognize the proposed study is not perfect (no study is). Although the NCS will never be perfect, its time has come.

APPENDIX: LIST OF NCS SITES (ADAPTED FROM www.nationalchildrensstudy.gov)

Vanguard Locations (7 Total)

Orange County, California
Duplin County, North Carolina
New York City (Queens), New York
Montgomery County, Pennsylvania
Salt Lake County, Utah
Waukesha County, Wisconsin
Lincoln, Pipestone, and Yellow Medicine Counties, Minnesota, and Brookings County, South Dakota

Study Locations (98 Total)

Colbert County, Alabama
Benton County, Arkansas
Apache County, Arizona
Maricopa County, Arizona
Pinal County, Arizona
Humboldt County, California
Kern County, California
Los Angeles County, California
Sacramento County, California
San Bernardino County, California
San Diego County, California
San Mateo County, California
Ventura County, California
Denver, Colorado
Douglas County, Colorado
Litchfield County, Connecticut
New Haven County, Connecticut
New Castle County, Delaware
Baker County, Florida
Hillsborough County, Florida
Miami-Dade County, Florida
Orange County, Florida
Baldwin County, Georgia
DeKalb County, Georgia
Fayette County, Georgia
Honolulu County, Hawaii
Polk County, Iowa
Bear Lake County, Idaho and Lincoln and Uinta Counties, Wyoming
Cook County, Illinois
DuPage County, Illinois
Johnson, Union, and Williamson Counties, Illinois
Macoupin County, Illinois
Will County, Illinois

Marion County, Indiana
Saline County, Kansas
Jefferson County, Kentucky
Jessamine County, Kentucky
Beauregard and Vernon Parishes, Louisiana
New Orleans, Louisiana
Bristol County, Massachusetts
Worcester County, Massachusetts
Baltimore County, Maryland
Montgomery County, Maryland
Cumberland County, Michigan
Genesee County, Michigan
Grand Traverse County, Michigan
Lenawee County, Michigan
Macomb County, Michigan
Wayne County, Michigan
Becker, Clearwater, and Mahnomen Counties, Minnesota
Ramsey County, Minnesota
Stearns County, Minnesota
Jefferson County, Missouri
St Louis, Missouri
Coahoma County, Mississippi
Hinds County, Mississippi
Buncombe County, North Carolina
Burke County, North Carolina
Cumberland County, North Carolina
Durham County, North Carolina
Gaston County, North Carolina
Rockingham County, North Carolina
Stark County, North Dakota
Burlington County, New Jersey
Middlesex County, New Jersey
Passaic County, New Jersey
Warren County, New Jersey
Valencia County, New Mexico
Monroe County, New York
Nassau County, New York
New York City (Brooklyn), New York
New York City (Manhattan), New York
Cuyahoga County, Ohio
Lorain County, Ohio
Cleveland County, Oklahoma
Comanche County, Oklahoma
Marion County, Oregon
Philadelphia County, Pennsylvania
Schuylkill County, Pennsylvania
Westmoreland County, Pennsylvania
Providence County, Rhode Island
Spartanburg County, South Carolina
Bradley County, Tennessee
Cumberland and Morgan Counties, Tennessee
Davidson County, Tennessee
Bexar County, Texas
Childress, Collingsworth, Donley, and Hall Counties, Texas
Dallas County, Texas
Harris County, Texas
Hidalgo County, Texas
Lamar County, Texas
Stephens and Young Counties, Texas
Travis County, Texas
Cache County, Utah
Grant County, Washington
King County, Washington
Thurston County, Washington
Marion County, West Virginia

ACKNOWLEDGMENTS

We acknowledge the advice and input of Joseph Boscarino, Barbara Brenner, Paul Contino, Anne Golden, Jack Gorman, Jessica Moise, Larry Siever, Robert Southwick, and Ilene Wilets of Mount Sinai School of Medicine; Panos Georgopoulos and Cliff Weisel of the University of Medicine and Dentistry of New Jersey; and Howard Andrews, David Alge, Michaeline Bresnahan, Pam Factor-Litvak, William Fifer, Jeffrey Halperin, Steve Kahn, Eugene Mattes, Mary Mckay, Virginia Rauh, Deliang Tang, and Robin Whyatt of the Columbia University Mailman School of Public Health.

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Pediatrics 2006;118;2173-2186
DOI: 10.1542/peds.2006-0360