8. RATIONALE FOR OUTCOME MEASURES

The rationale for outcome measures is divided into subsections, one for each of the seven National Children's Study priority outcome areas. The measures outlined in these subsections will allow the NCS to address important hypotheses relevant to these outcome areas. The broad array of data to be collected by the NCS, however, will also enable the examination of countless additional health and developmental outcomes. Some of the outcomes comprise more or less definitive diagnoses, such as preterm birth or congenital anomalies. Others entail the initial assessments of quantitative trajectories that will be measured throughout the Study, such as cognitive development, behavior, or body composition.

8.1 Pregnancy Outcomes

8.1.1 Definition

Proximal outcomes of pregnancy will be the first measures of child health captured by the NCS. Preterm birth and structural congenital anomalies are of specific interest because of the immediate morbidity and mortality associated with those conditions and the potential persistence of associated morbidity and disability throughout life. In addition, growing evidence suggests that deviation from normal fetal growth trajectories, even if not associated with perinatal complications, may be related to cardiovascular or other chronic conditions later in life (Barker, 1994). Preterm birth is generally defined as birth prior to 37 completed weeks of gestation (calculated as the time from the start of the last menstrual period to the time of birth). A structural birth defect is generally defined as malformation of an organ or structure that is present at birth and adversely affects health and development. In addition to documenting major structural anomalies (e.g., neural tube defects, facial clefts, cardiac defects), the NCS also will attempt to measure subtle variations in morphogenesis that may be related to periconceptional chemical or metabolic exposures and later neurodevelopment.

8.1.2 Assessment of Gestational Age and Fetal Growth

While the majority of preterm births occur close to term and are at relatively low risk for severe morbidity, the relatively small proportion of births at the lower end of the viable gestational age range (down to approximately 24 weeks) are at greatly elevated risk for mortality and long-term morbidity. In addition, the quality of fetal growth assessment, either by growth parameters obtained in utero via ultrasound or by using birth weight and anthropometric measures obtained at birth, is dependent on accurate knowledge of gestational age. Thus accurate ascertainment of gestational age is important not only to identify degree of preterm birth, but also to collect accurate fetal growth measures that may be independent variables of interest for many child outcomes throughout the course of the NCS.

In a clinical setting, a fetus's gestational age is based on the date of the last menstrual period. An increasing proportion of women receive a first trimester ultrasound (generally between 8-12 weeks gestation) that also is used to estimate gestational age. These estimates are commonly based on crown-rump length (Hadlock, Shah, Kanon, & Lindsay, 1992), though algorithms using other measures, such as biparietal diameter, are also used.

Measures of gestational age

In the NCS, data for estimation of gestational age will come from a variety of sources. Among all women, questionnaire data will ascertain date of last menstrual period and whether a first trimester ultrasound was or will be obtained. If so, a report of that scan will be collected and used as a basis for gestational age. If a woman does not receive an early clinical scan, then she will be scheduled for one under the auspices of the NCS. Among women enrolled prior to pregnancy, the use of frequent pregnancy tests may provide an additional, potentially accurate, estimate of date of conception. For all women, date of birth should be directly available since collection of maternal and infant samples at birth is a focus of the NCS. In situations where the birth was missed by the NCS, retrospective interview data and review of the labor and delivery and neonatal charts will be used to ascertain birth date and other perinatal information.

Reconciliation of multiple, sometimes discordant, measures of duration of pregnancy is often neither simple nor straightforward. The various measures are based on three conceptually different constructs (Alexander & Allen, 1996): time (days from menstruation or ovulation to birth), size (sonography), or maturity (newborn examinations such as those of Ballard et al., 1991). Menstrual dating is the traditional gold standard, and all other measures were originally validated among women with well-characterized menstrual dates. Especially on the aggregate level, however, uncritical acceptance of menstrual dates leads to gestational age estimates that may be implausible, manifested particularly as a bimodal distribution of birth weight at early gestational ages and a biologically implausible number of pregnancies continuing considerably beyond the expected 280 days (David, 1980). When sonography was compared directly to menstrual dating, it was found that a menstrual age of less than 37 completed weeks was in agreement with sonography in only 78 percent of cases, and a menstrual age of greater than 42 weeks agreed with sonography in only 11 percent of cases.

Uncritical acceptance of sonography, however, could gloss over subtle differences in growth that may be of etiologic interest. The fundamental assumption underlying sonographic estimation of gestational age is that inter-individual differences in growth are nonexistent early in pregnancy. Recent research has suggested that this assumption is not tenable. For example, compared to menstrual dating, gestational age estimated from the fetal biparietal diameter consistently underestimated the gestational duration of girls compared to boys, and of fetuses of mothers who smoked compared to nonsmokers (Henrihsen, Wilcox, Hedegaard, & Jorgen Secher, 1995; Morin et al., 2005). This suggests that even in the first half of pregnancy, known influences on fetal growth are operative and can impact measurement of gestational age. This phenomenon has recently been reported in first-trimester sonography among pregnancies with a known date of conception (due to in-vitro fertilization). In that study (Bukowski et al., 2007) a fetus whose sonographic estimate of gestation was even one day greater than the known time of conception was less likely to be undergrown, or even preterm, at birth. This suggests that growth differences are present even in the first trimester, and may be of etiologic significance.

For these reasons, the NCS will not have a single "study gestational age." Data will be collected on menstrual history, sonography, and other clinical measures of duration of pregnancy, and individual researchers will be free to explore these intriguing differences further.

Measures of fetal growth

Assessments of fetal growth are based on relative size for a given gestational age. In the NCS, linear measures of growth including biparietal diameter, abdominal circumference, and femur length will be obtained via standardized ultrasounds at approximately 22-24 weeks and 28-30 weeks of gestation. These repeated measures, as well as others obtained from the newborn infant, will enable true

growth rates to be calculated and may enable the NCS to distinguish slow growth in the first half of pregnancy from slow growth occurring later. In addition, though not a routine clinical measure, mid-thigh lean and fat mass circumferences will be obtained. Although it would be ideal to acquire additional growth measures, cost and participant burden constraints will not allow additional study-related visits for standardized ultrasounds. However, if additional clinical scans are performed, relevant growth data from those scans will be collected. At birth, birth weight, length, head and abdominal circumferences, and triceps and subscapular skin folds will be measured on each infant. Birth weight may be compared to external size-for-gestational age standards, such as those of Alexander, Himes, Kaufman, Mor, and Kogan (1996), Zhang and Bowes (1995) or Kramer et al. (2001). Long-term impacts of size at birth may not, however, be limited merely to the smallest percentiles of size-for-dates, but rather may operate continuously across of broad spectrum of relative size (Innes et al., 2003), and therefore the complete continuum of size will be evaluated on the NCS.

8.1.3 Assessment of Congenital Anomalies

Clinical management of pregnancy offers the opportunity for congenital anomaly assessment of several types and at various stages, depending on maternal and familial risk factors. Women more than 35 years old or with a relevant genetic history will generally be offered chorionic villus sampling at 10-12 weeks gestation or, more commonly, amniocentesis around 16 weeks. Early ultrasounds primarily used for confirming gestational age can also be used to ascertain nuchal fold thickness, if performed between 10 and 14 weeks gestation; increased nuchal translucency is associated with increased risk of Down Syndrome, other chromosomal abnormalities, and some cardiac defects. Serum triple or quad screen is generally performed between 16-18 weeks of pregnancy to assess risk for neural tube defects or Down Syndrome. A fetus may also receive one or more anatomic surveys by ultrasound, depending on maternal risk factors and perceived fetal growth. Though commonly performed around the 20th week of pregnancy, anatomic scans are also obtained both earlier and later to assess for structural defects.

Case definition and ascertainment

The NCS will rely primarily on recording clinical diagnosis of major structural anomalies, rather than performing specific diagnostic tests as part of the Study protocol. NCS involvement in diagnosis of anomalies may be confusing to a pregnant woman, who is receiving principal medical care and advice from her clinician. In addition, the NCS is not in a position to provide the necessary counseling and follow-up if tests show positive or even equivocal results. Although the NCS ultrasounds are focused on measuring fetal growth, procedures for referral and follow-up, if abnormalities are noted, will be included in the manual of operations.

The prevalence of congenital anomalies depends heavily on the period of ascertainment, prenatal diagnosis, elective terminations, and the data sources reviewed. For example, the percentage of structural defects diagnosed by ultrasonography increases by the trimester of pregnancy (Withlow, Chatzipapas, Lazanakis, Kadir, & Economides, 1999). In addition, a pregnancy may be terminated before the time of viability because of a serious or lethal defect, and among spontaneous pregnancy losses and fetal deaths the prevalence of structural malformations declines as pregnancy progresses (Dimmick & Kalousek, 1992). Thus, although the NCS will rely primarily on existing clinical diagnosis, records from every spontaneous abortion, stillbirth, and elective termination will be obtained whenever possible to determine the presence of a structural defect in the fetus. Should a Study- or clinically-obtained sonogram detect an anomaly and the pregnancy not be terminated, birth records will be abstracted to determine the ultimate diagnosis; terminations because of defects detected sonographically will be confirmed by review of medical and/or pathology records whenever possible. Since the vast majority of pregnancies in the

NCS will have been ascertained in the first trimester, such complete surveillance will be technically feasible.

Review of the maternal and infant charts at birth, as well as maternal questionnaires during pregnancy, will be used to ascertain prenatal diagnosis of congenital anomalies. After birth, a standardized observational infant exam will record any major anomalies. Selected morphologic measurements, such as intercanthal distances and anogenital distance, also will be made at that exam. A standardized digital facial photograph will be taken at birth and stored for later analysis. Digital photographs of external anomalies will also be taken. Questionnaire data regarding medical diagnoses and information recorded in the child's health care visit log after birth will be used to identify birth defects not recorded at the birth visit. The accuracy of questionnaire reports of birth defects, however, has been called into question (Rasmussen, Mulinare, Khoury, & Maloney, 1990; Romitti, Burns, & Murray, 1997). Therefore, potentially major birth defects identified through questionnaire will be further investigated. To the extent possible, review of extant medical data, including physical examinations, operative notes, autopsy records, cytogenetic and metabolic studies, and/or imaging studies, will be used to identify and characterize major congenital anomalies accurately. Furthermore, a considerable fraction of all defects are not apparent at birth but only become known over time. This is particularly the case for defects of the internal organs, such as the heart and kidneys. Parents/guardians of all Study children will be interviewed on multiple occasions during the first 5 years of life and on each occasion will be asked about any diagnosis of birth defects as well as any operations or significant medical procedures. If these screenings suggest the presence of any defect, relevant records will be obtained for confirmation whenever possible, following procedures similar to those used by active birth defects surveillance programs (Correa et al., 2007).

Case classification

Researchers studying birth defects recognize that application of current knowledge of embryology and pathophysiology is essential when classifying these conditions. It is inappropriate simply to classify defects as any versus none, or even by organ system (e.g., all heart defects, all limb defects, etc.). Such classification ignores the etiologic heterogeneity present in these defects. Furthermore, researchers distinguish between infants with an isolated defect, a known malformation syndrome, a sequence (i.e., multiple defects that are the result of a single primary defect), or other complex sets of defects. Etiology can reflect malformations (i.e., a localized error in morphogenesis), deformations (alteration of an otherwise normally developing structure, usually by mechanical forces), disruptions (destruction of a normally formed structure, usually by vascular, mechanical, or infectious insults) or dysplasias (lack of normal organization of cells into tissues).

Distinguishing between these subtleties requires a thorough review of all available information on each child in order to classify defects in an etiologically homogeneous manner. As noted above, the information collected by the NCS will enable detailed, specific review of the information on each case by a group of experts in the relevant field, for example, a pediatric cardiologist, a clinical geneticist, etc. While such review may not necessarily be done in "real time," appropriate data will be collected to enable future research to make classifications based on the most current science.

8.1.4 Assessment of Other Pregnancy Outcomes

Information on the occurrence of miscarriage or stillbirth will be ascertained via maternal questionnaire. At each regular contact with an enrolled pregnant woman, the woman will be asked how the pregnancy is progressing. If the woman indicates she is no longer pregnant, she will be asked for

further information regarding when the loss occurred. When possible, additional diagnostic information, including evidence of chromosomal malformations or birth defects, will be obtained from medical or post-mortem records. A standardized procedure for examination of stillbirths similar to that used by the NICHD Stillbirth Collaborative Research Network may be possible in some Study sites, but will be difficult to implement universally due to the number and diversity of medical care systems involved in the NCS.

8.1.5 Assessment of Related Factors

Experiences during pregnancy, particularly maternal medical status, have been linked to adverse pregnancy outcomes. Suboptimal thyroid function in pregnancy is associated with risk for preterm birth. Impaired glucose metabolism during pregnancy is associated with a variety to congenital anomalies, including malformations of the heart, central nervous system, and musculoskeletal system. Maternal infection, and thus fetal exposure to mediators of inflammation due to maternal infection, has also been implicated in preterm birth. The NCS will assess maternal medical status and other maternal exposures repeatedly during pregnancy.

8.2 Neurodevelopment and Behavior

8.2.1 Definition

Children's achievement of age-normative levels of developmental functioning, and non-normative deviations from those developmental milestones, will be of great concern on the NCS. The domain of neurodevelopment and behavior, which includes neurocognitive and motor functioning, attentional abilities, social functioning, and behavior regulation, will be assessed at multiple time points. Identification of both symptoms of disorder, and of specific developmental, behavioral, or mental health disorders—conditions such as autism spectrum disorders, attention deficit-hyperactivity disorder, anxiety disorders, depression, or schizophrenia—will be identified using a number of modalities, as discussed below. Details about neurodevelopment and behavior measures appear in Appendix F.1.

8.2.2 Assessment of Developmental and Mental Health Problems and Disorders

Diagnoses of specific behavioral or mental health conditions in clinical research are generally based on a patient's history, patient-provider interaction, and the use of condition-specific diagnostic tools, such as the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview-Revised for autism. Actual diagnosis of specified conditions is currently defined by the International Classification of Diseases-Clinical Modification of the World Health Organization; the Diagnostic and Statistical Manual of Mental Disorders-IV of the American Psychiatric Association; or, the Diagnostic Classification of Mental Health and Development Disorders of Infancy and Early Childhood Zero-to-Three. Criteria for these diagnoses can be ascertained by any of the above methods. Additionally, targeted clinical studies can employ laboratory procedures such as functional imaging (e.g., positron emission tomography scans or functional magnetic resonance imaging), electroencephalograms, or other techniques to measure brain function. While potentially powerful, those imaging modalities are not appropriate for inclusion in the core protocol of a broad-based longitudinal study. Consequently, the NCS will rely on a combination of screening instruments and diagnostic information, including records of health care provider diagnoses, to identify developmental and mental health disorders.

Specific conditions of interest to the NCS include: learning, sensory, and motor disabilities; autism-spectrum disorders; attention and conduct problems (e.g., ADHD); depression and anxiety disorders; and schizophrenia. Importantly, the NCS will not only attempt to capture conditions meeting diagnostic criteria, but will also use instruments that capture relevant symptoms in order to identify subclinical manifestations operating below diagnostic thresholds. Early identification of symptoms will be dependent primarily upon reliable and valid parental report screening tools. Direct diagnostic assessment of the child will be used whenever possible. Between birth and age 1, the conditions of primary concern to the NCS are sensory and motor disabilities, as well as serious developmental delays. Early screening for autism and for early precursors of mood and behavioral disorders will be added to these domains between ages 1 and 2.

Diagnoses will also be confirmed, whenever possible, through the child's medical records of documented clinical diagnoses by the child's pediatrician or other health care providers. The American Academy of Pediatrics (AAP) issued a policy statement in 2006 instructing child health care providers to engage in a program of developmental surveillance, screening, and diagnosis (Council on Children with Disabilities et al., 2006). Specifically, the AAP recommended that surveillance take place throughout infancy and early childhood, and that regular developmental screening tests be administered at well-child visits at 9, 18, and 30 months. Positive screens should then be followed by full diagnostic evaluations and referrals to early intervention. By obtaining confirmation through the child's medical records when possible, the NCS should be able to track provider diagnoses of developmental and behavioral disorders. Using a combination of screening instruments for symptoms and diagnoses from health care providers, the NCS will track not only the onset of neurodevelopmental, behavioral, and mental health symptoms and disorders, but the course of the disorders across development. Through repeated assessments over time, the NCS will be able to examine trajectories of children with diagnoses, including precursors of disorder and responses to early intervention efforts. This will permit a better understanding of the stability and course of disorder as children develop and are exposed both to treatment and to new and different environmental influences.

Assessment of learning, sensory, and motor functioning and disabilities

Some sensory and motor difficulties are evident very early in the child's life, and such disorders are usually more severe than those identified later. Other sensory and motor disorders can often be identified by age 2, whereas learning disabilities are often not identified until children enter school. Routine infant hearing screening is recorded in the hospital chart at birth, which will be abstracted by the NCS. Screening for sensory and motor disabilities on the NCS will begin before the neonate has been discharged from the hospital. During a pre-discharge examination, the infant's neurological status will be assessed using the NICU Network Neurobehavioral Scale (NNNS)(Lester & Tronick, 2005), a direct examination of neuromotor and neurobehavioral functioning. The NNNS is an effective screen for problems in early neurobehavioral functioning and has been shown to be sensitive to in utero substance exposure (Lester et al., 2002).

The NCS will continue to track children's developmental status during infancy with regard to cognitive, motor, and language delays using multiple assessment strategies. At 12 months, the NCS will administer three of the Bayley III Scales of Development: Cognitive, Motor, and Language (Bayley, 2006) to all enrolled children to assess the achievement of developmental milestones within these domains. The Bayley is a widely used and extensively normed assessment of developmental functioning long recognized as a standard in the field of developmental assessment (Albers & Grieve, 2007; Sattler, 2001). Low scores can be interpreted as indicating developmental delay (Bayley, 2006).

In addition to the administration of the Bayley III, actual diagnosis of learning, sensory, and motor disabilities will be confirmed whenever possible through the child's medical records, including the diagnoses and treatment plans of their medical providers. The child's health care visits will be reviewed at every contact with the parents, including both in-person contacts at 6 and 12 months and phone contacts at 3, 9, 18, and 24 months, and will continue to be assessed regularly after that. Throughout childhood and adolescence, the child's developmental status with regard to cognitive, language, and motor functioning will continue to be assessed periodically through direct testing by the NCS, and diagnoses confirmed whenever possible through health care provider diagnoses.

Assessment of autism-spectrum disorders

Autism-spectrum disorders, including but not limited to autism, Asperger's syndrome, and other pervasive developmental disorders, are not generally diagnosed until the child's second year or later (Robins & DuMont-Mathieu, 2006). Autism is a developmental disorder of great concern because of increased prevalence and unknown etiology in most cases. Symptoms related to the autism spectrum include deficits in social behavior and communication, and repetitive and stereotyped behavior, and often extend to cognitive impairments or motor abnormalities (Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision, 2000). The NCS will begin screening for autism spectrum disorders when the child is 18 months old and continue to screen for symptoms periodically through the toddler and preschool period. The screening instrument the NCS will use is the Modified Checklist for Autism in Toddlers (M-CHAT)(Robins, Fein, Barton, & Green, 2001), a parental report instrument that has excellent psychometric properties. The M-CHAT, however, is a screen for risk of autism and does not yield a diagnosis of autism or autism spectrum disorders. For diagnostic information, the NCS will rely on diagnostic assessments conducted by the children's health care providers and abstracted from medical records whenever possible. This will include not only private pediatrician contacts, but also diagnoses received through specialty clinics for developmental disorders or through early intervention programs.

Assessment of depression, anxiety, and attention and conduct problems

Behavioral, attention, and mood disorders are rarely diagnosed in infants. Although infants display variability in their moods, conduct, and attentional abilities, configurations of individual differences in these domains are not usually sufficiently stable to warrant diagnoses at this age (Zeanah, Boris, & Scheeringa, 1997). Little is known, however, about precursors of adult mental illness, so during the infancy period the NCS will assess social and cognitive behaviors that may be precursor symptoms to later problems. At 12 months the parent will be asked to complete the Brief Infant-Toddler Social and Emotional Assessment (BITSEA)(Briggs-Gowan, Carter, Irwin, Wachtel, & Cicchetti, 2004) a validated screening instrument which assesses risk for mood problems, behavior problems, and self-regulatory deficits. The BITSEA, or an age-appropriate modification of the BITSEA, will be repeated through the toddler and preschool period to track risk for problems over time. As the children age, other similar screening instruments will be used, such as the well-validated and widely used Strengths and Difficulties Questionnaire (Bourdon, Goodman, Rae, Simpson, & Koretz, 2005; Goodman, 1997), which assesses conduct problems, emotional problems, hyperactivity and inattention problems, and relationship problems, and can be completed by parents, teachers, and in the teen years by the adolescents themselves.

Early diagnoses of disorders will be confirmed whenever possible through the children's health care providers' records. Later in childhood, measures and diagnostic interviews such as the Preschool Age Psychiatric Assessments (PAPA)(Egger & Angold, 2004) interview or the National Institute of Mental Health Diagnostic Interview Schedule for Children (NIMH-DISC-IV)(Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) may be used to supplement diagnostic information from the

health care providers and assure diagnostic information on children who do not visit health care providers regularly.

Assessment of schizophrenia

Schizophrenia, a psychotic disorder believed to have both genetic and environmental etiology (Walker, Kestler, Bollini, & Hochman, 2004), will also be of interest to the NCS. Schizophrenia, however, is rarely diagnosed before late adolescence or early adulthood (Hafner, Maurer, Loffler, & Riecher-Rossler, 1993). Because screening and diagnostic procedures for schizophrenia will likely continue to evolve before the NCS children reach that life stage, no specific screening or diagnostic tool will be identified at this point. Instead, the best tools available at the time will be evaluated for use on the NCS.

8.2.3 Assessment of Related Factors

There are many exposures that have the potential to exacerbate or buffer the aspects of children's neurodevelopmental and behavioral functioning that will be assessed on the NCS. This includes exposures such as prenatal infection and inflammation, child and parental exposure to organophosphate pesticides, social relationships, and child and family engagement with social institutions such as child care, schools, and religious organizations. Environmental and social exposures will also be investigated as they interact with genetic factors, such as genetic alleles for paraoxonase-1 or variations in the 5-HTT genetic alleles, to produce risk or protective factors for child neurodevelopment and behavior outcomes. See Section 9.5 for details.

8.3 Child Health and Development

8.3.1 Definition

Identification of neurodevelopmental, behavioral, and mental health disorders, as discussed in Section 8.2, is essential to the mission of the NCS. Nonetheless, the tracking of normative developmental trajectories—normal growth in functioning across domains that occurs with age—is equally important. Although there is overlap in the domains of functioning between the outcomes of neurodevelopment and behavior and child health and development, there are important conceptual and practical distinctions that warrant the separate consideration of these outcomes. Child health and development is concerned not with disorder or symptoms of disorder, but with individual differences in trajectories of normal, healthy adaptation over time. Age-appropriate development in social, cognitive, and behavioral and emotional health domains is usually defined either through age-normed benchmarks from standardized testing, or identification of patterns of adaptive functioning in a particular domain. For example, cognitive abilities, temperament, and social competence can be assessed along a continuum and tracked longitudinally among all children participating in the NCS. Details of child health and development measures appear in Appendix F.1.

8.3.2 Assessment of Developmental Trajectories

One challenge in assessing developmental trajectories is that behaviors indicative of normal development at one age—clinging to a caregiver who is trying to leave, for example—may be a marker of maladaptation later in development (Sroufe, 1979; Sroufe & Waters, 1977). At each phase of

development, decisions must be made regarding the most appropriate assessment tool to capture the construct of interest and close attention must be paid to interpreting the information in a developmentally appropriate fashion. A great deal of effort has been expended to find efficient, valid, and reliable assessments that will enable effective measurement of the same domains across developmental stages. The NCS will assess multiple domains of child development using standardized and frequently used instruments. One criterion for these assessments is their ability to connect to later developmental measures of the same constructs. Areas to be covered include cognitive processes, language, and social and emotional development.

Assessment of development and behavior in children is challenging, whether in clinical or research settings. For younger children, in particular, reports of child functioning are often dependent upon subjective parental or other third party reports, which can lead to reporting biases (Fiske, 1987). Determining the best assessment modality for child functioning requires careful planning and consideration. In addition, administration of direct assessments to a child requires attention to the child's comfort in the testing situation, whether at home or in a clinical setting, as variations in feelings of ease or distress can affect children's responsiveness to the examiner and cause dramatic variations in testing outcomes. All examiners who administer assessments to children on the NCS will be extensively trained in developing rapport with children.

Assessment of cognitive and language abilities

Trajectories of cognitive and language development are important indices of developmental progress and problems as the child's experiences and exposures can compromise healthy trajectories of cognitive and language development (Cicchetti, Rogosch, & Toth, 2000). The NCS will begin tracking these milestones during infancy and continue tracking them through adolescence. At 12 months, the NCS will administer the cognitive and language subtests of the Bayley III Scales of Development (Bayley, 2006), a direct child assessment of achievement of developmental milestones within these domains. The Bayley is a widely used and broadly normed "gold standard" assessment of developmental functioning (Albers & Grieve, 2007; Sattler, 2001). The cognitive subtest assesses sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, play, and other aspects of cognitive processing. The language subtest includes both expressive and receptive language ability. Also at 12 months the child's parent will be asked to complete the MacArthur-Bates Communicative Development Inventory Short Form (CDI)(Fenson et al., 2000). The CDI was developed to supplement direct assessment of child language by obtaining information about the parent's broad knowledge of the child's communication skills, thus incorporating information more representative of children's everyday language use than what can be obtained in a relatively short direct assessment. Both the vocabulary checklist and the actions and gestures communication subtests of the CDI will be administered.

During the preschool years and beyond, measures of cognitive and language abilities will reassess similar constructs, such as concept formation, memory, and expressive and receptive language ability. This may include repeating the Bayley III scales, or at older ages using developmentally appropriate standardized assessments of achievement and intelligence such as the Woodcock-Johnson Test of Achievement (McGrew & Woodcock, 2001) and the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 2004), both of which will also be used to assess parental abilities. This will permit an examination of the ways in which cognitive abilities and achievement can change over time, as the child responds to experiences and exposures in the environment. Other assessments will focus on additional developmentally relevant abilities such as executive function and attention, and will use a combination of parent and teacher report and direct testing of the child.

Assessment of social and emotional development

Social and emotional development covers several important domains of child functioning, both intrapersonal and interpersonal. Infants begin this trajectory with basic temperamental qualities and with the formation of their first relationships: parent-child relationships. They face subsequent challenges in learning to regulate their emotions and behavior and to navigate the increasingly complex reciprocity of relationship interactions. Social and emotional development in the first two years will be assessed on the NCS through a combination of parental report and direct observation.

Assessing temperament early in development is important, as temperamental qualities not only exert direct influence on children's adjustment but also influence parental reactions to the infant's signals and needs and thus affect subsequent development indirectly. When the infant is 6 months old, the NCS will collect maternal reports of child temperament using three subscales of the Rothbart Infant Behavior Questionnaire-Revised (IBQ-R)(Gartstein & Rothbart, 2003; Rothbart, 1981), including activity level, fearfulness, and positive anticipation of and approach to novelty. The IBQ-R asks the parent to report on specific, recent infant behaviors, a technique that minimizes parental bias in the report of child temperament (Rothbart & Goldsmith, 1985).

Also at 6 months, the NCS will conduct its first videotaped observation of mother-child interaction. This will entail videotaping the mother and infant for 15 minutes as they engage in a semistructured play session with a set of toys provided for them during the visit. This technique has been used on many studies, including the NICHD Study of Early Child Care and Youth Development, and the associated coding scheme taps elements of parent-child interaction such as parental sensitivity and cognitive stimulation (National Institute of Child Health and Human Development Early Child Care Research Network, 2003). Observation is considered the "gold standard" of assessment in the domain of parenting (Zaslow et al., 2006).

At 12 months the child's social and emotional development will be assessed using parental report on the BITSEA (Briggs-Gowan et al., 2004). The BITSEA, a well-established brief measure of infant and toddler problems and strengths, assesses effective behavioral, and emotional self-regulation as well as social competence skills, including compliance, attention, mastery motivation, imitation/play, empathy, and prosocial peer relations. At the 12-month visit, a parent-child interaction observation will be repeated, but this time with the child and the child's alternate caregiver (it is anticipated that this will most often be the child's father), giving an expanded view of the child's functioning within the social network.

During the toddler and preschool years, the same constructs will be assessed again, using the same procedures where appropriate, or assessments that are age-appropriate measures of these constructs such as the Strengths and Difficulties Questionnaire (Bourdon et al., 2005; Goodman, 1997), which assesses prosocial behavior and relationship skills.

As the child ages and begins to spend time in the broader social contexts of school and community, assessments of developmental trajectories in social and emotional competence will be tailored to include these normative changes. This will involve assessing family, peer, and eventually romantic relationship qualities in addition to child functioning and adaptation across multiple contexts, such as home and school. It is anticipated that although parents are the primary reporters on child behavior in infancy and early childhood, eventually both teachers and the children themselves will serve as respondents. It is also anticipated that direct observation of parent-child interaction will continue to be assessed periodically throughout development.

8.3.3 Assessment of Related Factors

Numerous factors may influence a child's developmental and behavioral health trajectories. Prenatal exposures, such as exposure to tobacco, alcohol and maternal infection, that potentially have broad health effects will be collected through a variety of mechanisms. Ascertainment of prenatal and postnatal exposure to environmental chemicals with potential impact on the child's developmental trajectories is also outlined in Section 9.1

Questionnaire data will be used to ascertain parental cognitive function and literacy (e.g., Kaufman Brief Intelligence Test; and Woodcock-Johnson III Letter-Word Identification and Passage Comprehension subscales), maternal depression during pregnancy and several times after delivery (Center for Epidemiological Studies Depression Scale), family history of psychiatric diagnoses, and measures of family process and parenting style. Information concerning child care environments and, later in life, school environments will also be collected through maternal questionnaire, direct observation in child care settings, or interview of providers. Information collected on prescription medication use and from the health diary may also be used as sources of conditions of interest in either the mother or the child.

8.4 Asthma

8.4.1 Definition

Asthma is a complex respiratory disease characterized by episodic, reversible, inflammation-mediated constriction of small and large airways. The resulting airway obstruction leads to air trapping and clinical manifestation of the disease: wheezing, dyspnea, and hypoxia. Severe untreated attacks can be fatal. Data from gene association studies indicate a complex inheritance pattern involving perhaps hundreds of genes governing the expression of varying asthma and atopy phenotypes (Ober & Hoffjan, 2006). Asthma phenotypes that emerge from the first through sixth year of life have been predictive of persistent asthma symptoms and long-lasting decrements in lung function in cohort studies (Stein & Martinez, 2004). Childhood "asthma" can be categorized into three phenotypes: (1) airway obstruction which begins in the first two years of life but does not persist to school age, often referred to as early onset transient airway obstruction; (2) early-onset airway obstruction that persists past school age, or early-onset persistent asthma; and (3) recurrent airway obstruction that begins after the first few years of life, or late-onset asthma (Martinez & Helms, 1998; Stein & Martinez, 2004). Prospective data are needed to examine risk factors for the development of these phenotypes and for persistence of early airway obstruction into later childhood and adulthood.

8.4.2 Assessment of Asthma

The NCS will be able to assess the effect of timing of exposures, particularly during critical windows of vulnerability (e.g., specific trimester of pregnancy, early vs. later postnatal periods, etc.), on the development of childhood asthma. This will include distinguishing the effects and interactions of biologics, air pollutants, and genetics with other potential causative factors (e.g., social and economic status, health care access, diet, stress). Accurate exposure and phenotypic data are needed to assess the significance of various asthma and allergy genotype-complex exposure interactions that result in several different asthma phenotypes (Bel, 2004; Taussig et al., 2003). Identification of children at risk for developing severe forms of asthma would have clear public health impact.

Diagnosis

There is no single test that provides an unequivocal diagnosis of asthma. In young children, the clinical diagnosis of asthma is based on relevant history and pulmonary auscultation. Chest x-ray and pulse oximetry are often used in the initial diagnosis and to monitor disease. When the child is old enough to cooperate, approximately 5 to 7 years old, spirometry or more detailed pulmonary function tests can be used for objective assessment of pulmonary status, though this is rarely necessary for clinical diagnosis. Spirometry or peak flow monitoring can be used to follow disease status and progression.

In population-based research, diagnosis of asthma generally is based on combinations of reported symptom history, reports of physician-diagnosed disease, and medical records. Clinical research studies use pulmonary function tests, often in combination with provocation tests such as methacholine or exercise challenges, to attempt to obtain objective measures of lung function. Recent advances in passive pulmonary function assessment have enabled those measures to be obtained in children as young as several days old; however, the equipment is expensive, results are operator dependant, and the procedures would most likely not meet the "minimal risk" criterion.

Assessment of asthma in the NCS

Information on symptoms, signs, and other factors related to asthma will be collected throughout the course of the NCS using multiple methodologies. Questionnaires will assess a child's history of asthma symptoms (using questions based on the International Study of Asthma and Allergies in Childhood) starting with the six-month visit and continuing through adolescence. Questions regarding recent or "ever" diagnosis of asthma in a medical setting will also be asked, and information on the use of asthma-related medications will be collected. Confirmation of physician diagnoses related to any office visits, emergency department visits, and hospitalizations will be obtained whenever possible. Attempts to measure lung function via spirometry will begin at the 36-month clinic visit, although the difficulty of obtaining consistent results at this age is recognized. These measures will be repeated at subsequent clinic visits. In addition, the NCS may ask for periodic peak flow measures to be taken at home and entered into the child's health care visit log beginning at approximately age 5. NCS field staff and medical professionals will assess allergic sensitization and allergic and nonallergic rhinitis and asthma. Immune system function can also be evaluated through such measures as lymphocytes, cytokines, IgE, and interlukins. This approach of multi-method, repeated measures of asthma over time will permit investigation of the ways in which symptoms are ameliorated or exacerbated as the child faces new environmental exposures and attempts new treatment strategies.

The NCS will collect biological samples that could be the source of DNA for traditional genetic analysis of candidate genes and for gene discovery based on genome-wide association scans. The anticipation of chip-based genotyping of all participants based on current technology, or complete sequencing of all individuals at some point in the future, will provide extraordinary detail about genetic variation of nuclear DNA. Along with the planned definition of cases based on asthma phenotypes, this provides an opportunity to use the efficient nested-case control design for subsets of the sample, or the proportional hazard design for the entire sample, to evaluate effects of genes, environments, and their interaction. In addition, the Study will collect biological samples at multiple points over time, which provides the opportunity to evaluate epigenetic changes proposed to be the molecular mechanisms of some gene-environment effects (Hanson & Gluckman, 2005). The epigenetic assays for environmental effects of methylation and chromatin status are rapidly evolving, and current methods are sure to improve rapidly as a result of extensive current work (Callinan & Feinberg, 2006) and anticipated future work.

Two overlapping study populations will be used to address asthma hypotheses. For questionnaire items and other data available for the entire cohort, we will analyze the full NCS sample data. For genetic data and other items that require laboratory processing, the study population will consist of a nested case-control study design with sampled cases such as those with wheezing/asthma symptoms and a matched cohort of controls. Matching factors might include date of birth, regional location of birth, race, gender, and socioeconomic status.

Assessment of upper and lower airway disorders

It should be noted that with disorders associated with the upper and lower airways, there exist numerous definitions that can be employed at different developmental stages depending on the availability of subjective (parental report) vs. objective (spirometry, sensitization) criteria. Below are potential outcomes that may be used in the NCS at different child ages depending upon data available at each interview or clinical exam.

- *IgE antibody quantification*: Total and allergen-specific IgE antibodies (RAST) can be measured from serum levels. One advantage of the RAST test is that it does not have to be performed in a physician/hospital office and can be done instead at the child's home. The disadvantage is that it requires a venipuncture and therefore may be less acceptable to children and their primary caregivers. Sensitization status can be ascertained by the measurement of specific IgE to mite, cat, dog, grasses, foods, etc., in serum levels of infants and children (Simpson et al., 2005).

- *Rhinitis:* Rhinitis presents with a constellation of symptoms, including: nasal congestion; sneezing; rhinorrhea; itchy nose, mouth, throat and/or ears; itchy, watery, and red eyes. Symptoms are present without a cold and last for a minimum of one month (American Academy of Allergy, Asthma, & Immunology, 2005).

- *Wheeze:* Diagnosis of wheeze symptoms consistent with the airway obstruction associated with asthma is dependent on a clinical history reported by a parent, and may not be predictive of current or future development of childhood asthma. Wheezing is likely to be the primary outcome until the child can be tested using objective measures such as pulmonary function testing. Wheezing can be defined as an episode of wheezing or whistling in the chest without a cold for a certain number of times over a specified time period. The presence of wheeze without a cold is a common definition used to identify potential asthma in young children. There are additional related questions for defining more serious wheezing in the young child, such as: total number of attacks; if the child's sleep is disturbed with wheezing; if the child sounds wheezy after exercising; and if the child has a dry cough apart from a cold. Inquiry into these symptoms will be standardized.

- *Asthma:* Diagnosing asthma in young children can be difficult, and under- or over-diagnosis is a problem. As the child ages, a diagnosis of asthma may be confirmed by pre- to post-bronchodilator forced expiratory volume in one second (FEV_1) in children who meet certain predetermined criteria such as: wheezing symptoms in the previous 12 months; physician treatment for "asthma" in the previous 12 months; or an increased exhaled nitrous oxide (eNO) of greater than 10 parts per billion. Confirmatory tests would allow for additional outcome definitions to be assessed, such as allergic asthma disease, nonallergic asthma disease, allergic asymptomatic airway reactivity (AR), and nonallergic asymptomatic AR.

- *Eczema:* Despite the fact that eczema is not an airway disease, the NCS may examine atopic dermatitis as an outcome since it is one of the earliest allergic diseases in childhood, and it is associated with asthma. The clinical criteria for childhood eczema can be determined by the parent questionnaire and/or a physical examination.

8.4.3 Assessment of Related Factors

In addition to measures related to ascertaining asthma in the child, relevant information regarding risk and exposures will be collected. For example, family history of asthma and atopy will be obtained via the T1 questionnaire. We will examine maternal psychosocial stress during pregnancy, including stress life events, social isolation, racism/discrimination, anxiety, depression, cortisol in saliva, urinary catecholamines, and low socioeconomic status. Other potential gestational factors are prematurity and the child's birth weight. History of early life infections will be collected through the child's health care visit log as well as by the six-month questionnaire. The relation between the risk of developing early onset transient airway obstruction and the diet during pregnancy and early childhood will be explored. The dietary variables include consumption level of antioxidant and other micronutrients, fresh fruits and vegetables, and vitamin intake. Other dietary factors of interest include breast feeding and its relation to the risk of early onset persistent wheezing, and obesity and its relation to the risk of late onset asthma. Indicators of socioeconomic status include household income, educational level, location of residence, household composition, housing characteristics, neighborhood and community characteristics (age, race/ethnic composition, population density, housing quality), neighborhood resources (community organizations, schools, recreational facilities, public services, commercial outlets, religious organizations), and neighborhood processes (neighborhood cohesiveness, crime levels, political activity, police activity, family's perceptions of neighborhood). These factors can be associated with exposure to social, physical, psychological, and environmental factors related to the risk of asthma. Exposure to allergens early in life will be measured through dust samples as well as specific questionnaire items (e.g., presence of pets). Air pollution data will be obtained by questionnaire or biomarker (e.g., tobacco), use of ambient air pollution monitors, and home-based air quality measurements at periodic home visits. Child care and school exposures will also be obtained by the NCS, either by direct measurement, when possible, or by other sources, as necessary.

8.5 Obesity, Body Composition, and Growth

8.5.1 Definition

The ongoing increase in childhood obesity and overweight in the United States gives rise to numerous questions regarding both the antecedents of overweight and adiposity and their long-term health effects (Flegal & Troiano, 2000; Ogden, Fryer, Carroll, & Flegal, 2004; Ogden et al., 2006). Obesity appears to remain consistent from childhood into adulthood (Serdula et al., 1993), and childhood obesity is directly related to the same adverse health outcomes generally associated with adult obesity (Freedman, Khan, Dietz, Srinivasan, & Berenson, 2001; Haji et al., 2006; Orio et al., 2007). Although the cause of overweight in an individual is ostensibly obvious—energy intake greater than expenditure—elucidation of reasons behind the population-level trends in obesity and overweight is necessary to enable appropriate interventions.

Most frequently, obesity is defined simply in terms of the relation of weight to height. For example, children who are ages 2 through 19 years are considered above the range of a healthy weight if their body mass index (BMI, an index of weight in relation to height) is above the 85th percentile compared to other children in their age and gender group (Centers for Disease Control, 2007). For adults, a BMI of greater than 25 is considered above the range of a healthy weight. BMI is correlated with overall

body fat and directly associated with adverse outcomes. However, it is neither a true measure of adiposity nor a measure of the relative distribution of central (visceral) and peripheral fat, characteristics that may be the true risk factors for adverse outcomes (Arner, 1998; Bergman et al., 2006). To the extent possible within the overall structure of the diverse Study protocol, the NCS will strive to obtain measures of obesity, body composition, and growth that go beyond simple relations between weight and height.

8.5.2 Assessment of Overweight and Obesity

Maternal and paternal measures

Assessment of maternal size and body composition will start with the first home visit, either before pregnancy or in the first trimester of pregnancy and continue throughout pregnancy until birth. Initial measurements will include height, weight, waist and hip circumferences, and triceps and subscapular skin folds. Segmental heights (e.g., knee height) will be obtained as there are established associations between those measures, prepubertal (and possibly intra-uterine) nutrition and growth, and later cardiovascular outcome (Gunnell et al., 2003). The subscapular-triceps skinfold ratio is among the commonly used estimates of fat distribution, often used in combination with the waist-to-hip ratio and BMI (Stein et al., 2007). Similar measures will be obtained from the father during the first trimester home visit.

Weight and skinfolds will be obtained from the mother at each subsequent pregnancy visit, because of potential associations between maternal weight gain and adiposity, in utero growth, and subsequent metabolic and cardiovascular outcomes (Barker, 1992). The assessment of maternal body composition by anthropometry during pregnancy is complicated by the attendant changes in body water, including skin and subcutaneous accumulation (Huston Presley, Wong, Roman, Amini, & Catalano, 2000; Stevens-Simon, Thureen, Barrett, & Stamm, 2001). Skinfold measures during pregnancy, however, are often used and remain a reasonable choice within the context of the NCS and the focus on subsequent child growth and health.

Child measures

In the NCS, assessment of the child's body habitus and composition will begin in utero with the second and third trimester ultrasounds. Along with routine linear measures of growth, measures of mid-thigh lean and fat mass area and abdominal wall thickness will be obtained (Bernstein & Catalano, 1991; Bernstein, Goran, Amini, & Catalano, 1997). Though not generally part of a routine fetal ultrasound, those measures are used in a growing number of studies, can be obtained with reasonable accuracy and precision, and will provide fetal analogues to the postnatal anthropometric estimates of peripheral and central fat distribution described below.

At birth, anthropometric measures will include weight, length, head circumference, body segment lengths, and triceps and subscapular skinfolds. These measures will be repeated at each home visit, until the three-year clinic visit. At that time, and at later clinic visits, DXA and BIA will be attempted, in concert with the ongoing anthropometric measurements. Depending on their availability during the Study period, other measures of body composition, such as air displacement plethysmography (Winsley et al., 2005) or MRI (Pietrobelli, Malavolti, Fuiano, & Faith, 2007) could be used on all or on a subset of the NCS population.

The correlation between the anthropometric and other body composition measures is variable and depends on the age of the participant, the measures used, the participant's body habitus, and

perhaps even gender (Semiz, Ozgoren, & Sabir, 2007; Winsley et al., 2005; Wright et al., 2007). However, there is evidence that, at least later in childhood, the anthropometric measures do correlate with metabolic measures of interest to the NCS, providing confidence in the use of those measures as a cornerstone of body composition assessment (Freedman, Serdula, Srinivasan, & Berenson, 1999).

Interpretation of measures of growth and body composition

An individual's growth can be quantified two ways. The first is by comparison with published references, such as the CDC BMI and BMI percentile curves (http://www.cdc.gov/nccdphp/dnpa/bmi/childrens_BMI/about_childrens_BMI.htm). However, population references do not exist for many of the measures the Study will use. In those instances, and even when external references do exist, internal NCS distributions can also be created and used. The probability-based sample of the NCS should provide a strong basis for quantification and, perhaps, serve as an external reference for future studies. Skin fold thicknesses can be analyzed as absolute measures, as ratios, or as terms in any of a number of equations that can be used to estimate percentage body fat. The NCS will report the absolute measurements, not the results of estimating equations, giving the analyst maximal flexibility in the definition of obesity or body composition.

8.5.3 Assessment of Related Factors

A child's energy expenditure early in life will be assessed primarily through parental report of activity and activity diary completion. In late childhood and in the assessment of parental activity, questions will be based on the International Physical Activity Questionnaire (IPAQ), both to enable comparison with other studies and to permit the estimated quantification of metabolic equivalence of task (MET) expenditure. Though the use of the IPAQ in adults is well validated (Craig et al., 2003), its performance among adolescents is less predictable and may vary depending on the study population (Arvidsson, Slinde, & Hulthen, 2005; Craig et al., 2003). As the NCS progresses, additional measures of physical activity, either questionnaire-based or activity-based (e.g., accelerometers), may be employed.

Fetal exposure to maternal glucose will be estimated by several HgbA1c measurements during pregnancy, as discussed in Section 9.4.3. Fasting blood samples to be analyzed for glucose, insulin, and lipids will be collected from at least some of the women during the third trimester clinic visit. Maternal diet will be assessed throughout pregnancy and after birth through a combination of food frequency questionnaires, food diaries, and recalls. Infant feeding practices, including breast and bottle feeding, and subsequent child diet will be collected via questionnaire. Family process, physical activity, and the child's exposure to television and other media will also be collected by questionnaire early in life. Neighborhood characteristics that may be conducive to physical activity, or lack thereof, will be assessed by parental report and by community-level observations and data. See Chapter 9 for details on these measures.

Potentially relevant laboratory analyses can include assessment of ghrelin, leptin, adiponectin, and other "adipocytokines" to determine if those compounds are causally related to increased weight and adiposity or are an intermediate phenotype. These can be measured in maternal blood as well as in the child from infancy onward. When the child is older, it may be possible to obtain fasting blood tests for assessment of glucose and insulin, although that will be determined at a later point in the study. Lipid profiles can be assessed starting with 12 month visit, though fasting samples are necessary for triglyceride assessment.

8.6 Injury

8.6.1 Definition

Injuries are a leading cause of childhood death and disability. After age 1, they are the single leading cause of death among children and adolescents in the United States. Injuries are generally classified by both the external cause (e.g., car crash, poisoning, fall) and the intent. Of the 23,636 injury deaths to U.S. children (ages 0-21 years) in 2004, 15,871 (67 percent) were unintentional ("accidents") (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control [CDC NCIPC], 2007). Intentional injuries (interpersonal violence, child maltreatment, and self-inflicted injuries) and injuries of undetermined intent accounted for the remaining 7,765 fatalities. The leading causes of injuries vary with the age of the child, with intentional injuries taking their greatest toll in adolescence (CDC NCIPC, 2007).

The World Health Organization injury surveillance guidelines (Holder et al., 2001) define injury according to the guidelines of Baker, O'Neill, Ginsburg, and Guohua (1992): "Injuries are caused by acute exposure to physical agents such as mechanical energy, heat, electricity, chemicals, and ionizing radiation interacting with the body in amounts or at rates that exceed the threshold of human tolerance…In some cases (for example, drowning and frostbite), injuries result from the sudden lack of essential agents such as oxygen or heat." (Baker et al., 1992, p.4). According to this definition, an injury from a motor vehicle crash would be due to exposure to mechanical energy, a scald burn due to exposure to thermal energy, and a poisoning due to exposure to a chemical agent.

It is expected that, of the 100,000 children enrolled in the NCS, more than 1,600 children will die from an injury and more than 8,000 will be hospitalized (Rivara & Villaveces, 2001) with many more seeking care from an emergency department or other health care provider. Virtually all children experience minor injuries (e.g., cuts and bruises). A challenge for the NCS is to use a definition that identifies the subset of injuries that are serious enough to potentially compromise health and future development. Although many studies include only those injuries for which medical care is sought, this definition is biased in a way that would preferentially identify injuries among those with greater access to health care. Thus, comparable to definitions used in the International Study of Health Behavior in School Children (Currie et al., 2004; Molcho et al., 2006; Pickett et al., 2005; Pickett et al., 2006), in the NCS an injury will be defined as physical damage to an individual that results in medical care or at least one day of limitations in activity.

8.6.2 Assessment of Injury

Beginning in early life and continuing through early childhood, ascertainment of injuries will be based on parental report. Later in childhood and adolescence parent or caregiver reports will be supplemented with self-reports from the child. Health visit logs will be provided to study participants for documentation of medical visits and will include a place for documentation of key data elements about injuries that result in medical care. Activity diaries may help identify injuries that result in limitations in activity, and specific activities associated with increased risk of injury.

Studies have shown that recall for injury events declines with time and severity of the injury (Cummings, Rivara, Thompson, & Reid, 2005; Harel et al., 1994). In one study, approximately 3 months following the event, parents were able to recall 88 percent of major injuries, 86 percent of minor injuries seen in an emergency department, 81 percent of minor injuries seen in an urgent care setting, and 58 percent of minor injuries seen in a clinic. At 6 months, recall of major injuries was 80 percent, but dropped to 56 percent by one year (Cummings et al., 2005). Throughout the Study, parents, caregivers,

and, when appropriate, children will be asked about injuries that have occurred during the interval period. Thus, from birth through age 1, information about injuries will be ascertained every 3 months and from 1 through 3 years every 6 months. Contact periods for later years have not yet been determined. For those reporting an injury, additional information will be sought about the external cause of the injury, the physical harm to the child (i.e. the nature of the injury), treatment received, and any lasting sequelae.

Traumatic brain injury is of particular interest to the Study both as a primary Study outcome and as a confounder with significant potential to impact trajectories of development and thus multiple other Study outcomes. Consequently, when a head injury is reported additional questions will be asked about changes in level of consciousness. Although even minor traumatic head injury can be identified through diffusion MRI or other advanced structural and functional imaging technologies (Suh, Davis, Hopkins, Fajman, & Mapstone, 2001), the expense and participant burden of such technologies are not appropriate for general use in the NCS population. At this time, biomarkers for measurement of head injury are not available for use in an epidemiologic study. However, it is recognized that this is an area of active research that may have implications for future protocol development or use of stored biospecimens (Berger et al., 2006; Berger & Kochanek, 2006).

Methods are being explored to supplement the self-reported data with data collection from medical records for the most severe injuries. This effort will likely be limited to those injuries that result in hospitalization or death. Like self-report data, data abstracted from medical records would include information about the external cause of the injury, the nature of the injury, treatment received, and any lasting sequelae.

8.6.3 Assessment of Related Factors

Numerous factors may be related to child behavior that increases subsequent risk of injury. Areas of interest include prenatal and early life exposures to neurotoxic chemicals, including metals and organic pesticides, family process and parenting behaviors, and home, child care, and school environments (see Chapter 9). Examination of the genetic contribution to aggressive behavior, and thus risk of injury, will be examined both for direct genetic influence on behavior, and for the interactive effects of specific environmental exposures (e.g., chemical, socio-emotional) and genotype on aggressive behavior.

Factors with potential direct relation to injury risk, in addition to temperament and activity, include the physical characteristics of a child's home and neighborhood environments. These will be assessed by questionnaire and by direct observation by Study personnel. Medication use by the child may provide additional information on either conditions associated with injuries (e.g., seizure disorder, ADHD) or medications that might have a direct influence on risk of injury (e.g., sedating antihistamines).

8.7 Reproductive Development

8.7.1 Definition

Development of the reproductive system begins early in gestation and continues through infancy, childhood, adolescence, and into adulthood. A number of adverse outcomes can occur as the result of interference with development of this complex system, which includes the reproductive organs, the endocrine system, and the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes that control their development and function. Early outcomes include birth defects such as hypospadias and cryptorchidism in boys (Pohl et al., 2007), as well as hormonal changes, such as hypothyroidism, in

boys and girls which interfere with optimal reproductive health. Later outcomes from the same exposures may include alterations in growth, timing, and progression of puberty (Herman-Giddens, 2006), and disease states such as polycystic ovary disease (PCOS) (Azziz et al., 2004) and endometriosis (Eskenazi et al., 2001) in females, and testicular dysgenesis syndrome in males (Skakkebaek et al., 2001).

Such changes in reproductive structure and development may be cumulative, that is, adverse outcomes at early ages may predispose an individual to be at greater risk for additional adverse effects, e.g., cryptorchidism and later changes in fertility (Lee, 2005) or early menarche and breast cancer (Vihko & Apter, 1986). In addition, recent studies in animal models suggest that certain exposures are associated with adverse reproductive development outcomes that are transgenerational, that is, effects that are carried into subsequent generations because of changes in DNA methylation patterns that are transmitted in the male germline to the next generation (Anway, Cupp, Uzumcu, & Skinner, 2005; Chang. Anway, Rekow, & Skinner , 2006).

8.7.2 Assessment of Reproductive Development

Evaluation of children at birth, at six month intervals during the first two years of life, and at regular intervals beyond that time, will allow assessment of birth defects and anthropometric measures. Health outcomes related to reproductive development can be assessed in relation to the timing of anthropometric measures and the physiologic development of reproductive organs and other regions of the body that respond to reproductive hormones. The NCS protocol will include physical examination for genital development and, where possible, will use medical record review for information on further diagnosis and/or surgical intervention. Following standard anthropometric measurement of weight, height/length, head circumference, and skin-fold thickness, a detailed observation of the body, particularly of the breasts and genitals, will be performed. Birth defects, such as hypospadias and cryptorchidism in boys or altered genital formation in girls, can be assessed at birth by direct observation by a medical professional or via medical record review when possible. Cryptorchidism (undescended testes) is determined by palpating for the testes in the scrotum. Surgical procedures may be required to fully diagnose and/or repair undescended testes. Hypospadias (abnormal opening of the urethal meatus along the ventral aspect of the penis) is diagnosed by direct observation. Location and severity of the urethral opening will be noted, and surgical repair may reveal more detailed diagnosis. Anogenital distance may also be measured at birth (Swan et al., 2005).

Measures of puberty onset (e.g., onset of breast development in girls, genital growth in boys, and pubic hair development in boys and girls), and stage of sexual maturation can be assessed used Tanner scales by self-assessment or examination by a medical professional (Marshall & Tanner, 1969; 1970). Validation of the best procedures to use for this assessment are likely to advance by the time children in the NCS reach age 6 or 7. Other key outcomes are age of menarche in females and spermarche in males. Menarche can be assessed through questionnaire or medical record abstraction, when possible, while spermarche can be determined through questionnaire and by examining for sperm in urine samples (Nielsen et al., 1986). In addition, hormone levels in both males and females obtained from blood samples throughout childhood will allow for the assessment of hormonal, thyroid, and pituitary gland status and function. It may also be possible to collect semen samples from participating male children when they reach age 18 to assess semen quality, sperm production, and morphology.

Serial assessment of reproductive outcomes at birth, in childhood, at puberty, and in adulthood, and collection of information from medical records, whenever possible, on disease states such as polycystic ovary disease (PCOS) and endometriosis in females and testicular dysgenesis syndrome in males, can be applied successfully to study reproductive development in the NCS. In addition, collection

of maternal breast milk and maternal and child blood and urine samples at multiple time points and serial questionnaires to assess pathways of exposure will provide the necessary data to evaluate both exposures and the links between exposures and reproductive development.

8.7.3 Assessment of Related Factors

Exposure to environmental agents that are hormonally active agents (HAAs; also called endocrine disruptors) has been shown to affect the reproductive system in a number of ways in both animals and humans. A variety of environmental chemicals have been cited in the literature as potential HAAs, including insecticides and herbicides (e.g., DDT, atrazine); pharmaceuticals (drug estrogens); chemicals associated with consumer goods/household products (e.g., bisphenol A, phthalates, nonylphenol, polybrominated diphenyl ethers [PBDEs], perfluorinated compounds [PFOA, PFOS]); industrial chemicals (e.g., polychlorinated biphenyls [PCBs], dioxins, polycyclic aromatic hydrocarbons [PAHs]); heavy metals (e.g., arsenic, lead, mercury, and cadmium); and natural hormones such as the phytoestrogens (Ashby, Tinwell, Stevens, Pastoor, & Breckenridge, 2002; Ceccatelli, Faass, Schlumpf, & Lichtensteiger, 2006; Eriksson, Fischer, & Fredriksson, 2006; Fenton, Hamm, Birnbaum, & Youngblood, 2002; Gray, Ostby, Cooper, & Kelce, 1999; Howdeshell, Hotchkiss, Thayer, Vandenbergh, & vom Saal, 1999; Kuriyama, Talsness, Grote & Chahoud, 2005; Lilienthal et al., 2006; McDonald, 2005; Rubin, et al., 2001; Schonfelder et al., 2002; Talsness et al., 2005; Wolf et al., 1999). Recent studies of environmental agents suggest that PCBs (Blanck et al., 2000) or organochlorine pesticides (Krstevska-Konstantinova et al., 2001) may accelerate pubertal development in girls while PAHs (Den Hond et al., 2002) or lead (Selevan et al., 2003; Wu et al., 2003) have been associated with delays in pubertal development. Data on the effects of HAAs on age at puberty in boys are fewer (Den Hond et al., 2002) but indicate an association between PCB and polychlorinated dibenzofuran (PCDF) exposures with delayed puberty and decreased penile length (Den Hond & Schoeters, 2006). These observations are concordant with laboratory data on the effects of HAAs. Because there are only limited data on specific critical windows for chemical exposures in relation to timing of puberty, the entire prepubertal period, including in utero growth and development and the peripubertal period, should be considered critical times for exposures. Environmental samples and biological specimens will be collected to allow measurements for a number of chemical exposures. These exposures will then be examined to look for associations with alterations in reproductive development.

Obesity, diet, and nutrition measures are important related factors for reproductive development. Higher percentage of body fat increases the risk of precocious puberty; later onset in underdeveloped nations is often attributed to poor nutrition (Anderson, Dallal, & Must, 2003). In addition, obesity and precocious puberty have been associated with conditions such as neurofibromatosis, hypothyroidism, PCOS, etc. (Cesario & Hughes, 2007). Delayed puberty has been associated with several conditions such as sickle cell disease, thalassaemia, Celiac disease, Gaucher disease type I, Cushing's disease, and other endocrine deficiencies. Anthropometric data, hormonal changes, and medical record abstraction, when possible, will be included in the NCS to examine these potential relations.

The prenatal and postnatal smoking status of parents may reduce the age of onset of puberty (Windham et al., 2004). Urine cotinine will be measured to examine active/passive smoking exposures.

Generally the mother's menstrual history is considered the biggest predictor of age of puberty, and some of this effect may be seen in ethnic differences (Blanck et al., 2000). There are genetic components for hypospadias, cryptorchidism, spermarche, and semen quality that may be related to the father's reproductive history (Pohl et al., 2007). In addition, genetic factors such as 5-alphareductase type 2 gene mutations (Silver & Russell, 1999) and androgen receptor mutations (Silver, 2000) are risk factors

for hypospadias. Maternal reproductive history and, when possible, paternal reproductive history will be collected using questionnaires and possibly medical records. Blood samples will be collected to determine genetic factors that may be involved.

There is some evidence that a younger gestational age at birth is associated with greater incidence of hypospadias and cryptorchidism (Pohl et al., 2007) and is a predictor of an earlier age at menarche; however, evidence points to small-for-gestational-age as the predictor of precocious puberty (Adair, 2001). Gestational age at birth and growth and development will be recorded in the NCS.

Maternal alcohol consumption may (Carbone et al., 2007) or may not (Blanck et al., 2000) be related to an increase in hypospadias and/or a delayed onset of puberty and can be monitored by measuring blood alcohol levels. In addition, the impact of stressful sociological factors may be related to precocious puberty (Cesario & Hughes, 2007). Questionnaire data on socioeconomic status and stress will be collected in the Study.