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The Early Determinants of Adult Health Study

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Supplementary materials

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Abstract

This issue of the Journal features collaborative follow-up studies of two unique pregnancy cohorts recruited during 1959–1966 in the United States. Here we introduce the Early Determinants of Adult Health (EDAH) study. EDAH was designed to compare health outcomes in midlife (age 40s) for same-sex siblings discordant on birthweight for gestational age. A sufficient sample of discordant siblings could only be obtained by combining these two cohorts in a single follow-up study. All of the subsequent six papers are either based upon the EDAH sample or are related to it in various ways. For example, three papers report results from studies that significantly extended the 'core' EDAH sample to address specific questions.

We first present the overall design of and rationale for the EDAH study. Then we offer a synopsis of past work with the two cohorts to provide a context for both EDAH and the related studies. Next, we describe the recruitment and assessment procedures for the core EDAH sample. This includes the process of sampling and recruitment of potential participants; a comparison of those who were assessed and not assessed based on archived data; the methods used in the adult follow-up assessment; and the characteristics at follow-up of those who were assessed. We provide online supplementary tables with much further detail. Finally, we note further work in progress on EDAH and related studies, and draw attention to the broader implications of this endeavor.

Keywords

early determinants of adult health; EDAH; pregnancy cohorts; sibling pairs

Introduction

This issue of the Journal features collaborative studies that make use of the ongoing follow-ups of two unique pregnancy cohorts born during 1959–1966 in the United States. In New England, investigators have been following up the Boston and Providence cohorts of the Collaborative Perinatal Project (CPP) pregnancy study (now known as the New England Family Study – NEFS).^{1–3} In Oakland, investigators have been following up the large single site Child Health and Development Study (CHDS).⁴ The original designs and study protocols for these pregnancy cohorts were remarkable in many ways, for instance, the CPP and the CHDS were the first large prospective pregnancy cohorts in which prenatal maternal serum samples were collected and archived for later use. Now, in midlife, each of them offers an outstanding platform for studies of early determinants of adult health.^{5,6} The Early Determinants of Adult Health (EDAH) study combined the NEFS and the CHDS cohorts in

order to conduct a follow-up in midlife (age 40s) of same-sex siblings who were discordant on birthweight for gestational age.

This first paper introduces the ‘core’ EDAH study. The subsequent six papers are related to this ‘core’ EDAH study in various ways. The second paper introduces innovative statistical methods for analysis of growth trajectories, developed to meet the challenge of analyzing early childhood data in EDAH.⁷ The third paper analyzes anthropometric outcomes in the core EDAH sample.⁸ The next three papers are based upon studies that emanated from EDAH; these studies obtained separate funding to significantly extend the core sample – in terms of both number of subjects and data domains acquired – to address specific hypotheses about neuropsychiatric, neuropsychological and mammographic density outcomes.^{9–11} The final paper is based on a separate adult follow-up study that uses the CHDS sample exclusively¹² (it included pilot work across CHDS and CPP and used many comparable measures).

Rationale for the EDAH study

Many of the central questions about early determinants of adult health are best addressed by studies, which include in-depth prospective measures from pregnancy, thorough assessments of adult outcomes and rigorous control for confounding. The underlying rationale for the EDAH study was that by combining the NEFS and CHDS in a same-sex sibling study, we could meet these rigorous criteria. Fortunately, the NEFS and CHDS were sufficiently similar that a collaborative investigation, combining data from the two cohorts, was feasible. NEFS and CHDS both enrolled pregnant women over the same time period, followed their children into early childhood, used similar measures for many exposures and conditions and archived prenatal serum samples from pregnancy. The two cohorts were also of similar size (15–20,000 births). Thus, by making use of the in-depth prospective measures in these cohorts, adding assessments of adult health outcomes and combining data to yield a sufficient number of same-sex siblings discordant on prenatal exposure, we believed we would be in the best position to address a number of important questions about early determinants of adult health.

The comparison of same-sex siblings discordant for an exposure is a highly effective design for control of confounding, especially in studies that examine the relation of prenatal exposures or early growth to child or adult health outcomes.^{13,14} Although this was not so widely recognized at the time EDAH was conceived, numerous studies (including some by co-authors^{14–18}) have proved the power of this design for validating or refuting results based on population studies of unrelated individuals. In studies of prenatal exposures, in particular, family context and genetic predisposition are often the main potential confounders, and it is very difficult to measure them precisely. The comparison of same-sex full siblings ensures by design that the siblings share a similar family context and half their genes.

Family context comprises a vast array of experiences that are difficult to capture with measures used in epidemiologic studies. Familial interactions vary, such as the time spent talking with children and the vocabulary used, which influence the development of language. Familial resources vary, even among families with similar socioeconomic status

measured by education and occupation; some families access additional resources from kinship networks, while others deplete resources to share them with kinship networks. Because the family context represents the confluence of a multitude of factors, it is extremely difficult to capture even with in-depth assessments. Yet it can be a powerful confounder in research on developmental origins of health, because family context influences both early exposures and later health outcomes. The confounding usually (though not always) generates artifactual positive associations between an exposure and outcome. Siblings do, of course, differ in family environment according to birth order, but birth order can be controlled statistically. Siblings also differ as a result of random variability in individual experience,¹⁹ but this will rarely generate artifactual associations. For this and other reasons, various sibling designs have become increasingly central to epidemiological research in the past decade.¹⁴

Same-sex siblings discordant on prenatal exposure, however, are few in number. Studies that use this design often rely upon large population registries that have limited information about prenatal exposures, early growth and health outcomes. Though large, the NEFS and CHDS were not comparable in size to such registries. Therefore, it was important to design the follow-up study to include sufficient numbers of same-sex siblings who were discordant on a key variable of interest. This would not limit the use of the data to studies of that key variable, but would ensure that we could at a minimum address questions about the relation of that variable to adult health in the most rigorous way possible.

We chose discordance on birthweight for gestational age (bw/ga) among term babies as our key variable of interest. A large number of studies of unrelated individuals have reported associations between birthweight and various adult health outcomes.^{20–22} Low bw/ga is a better indicator than birthweight alone of suboptimal fetal growth (and can be further refined by the addition of other variables such as maternal height). Because bw/ga is a more valid measure of suboptimal fetal growth for term babies than for preterm babies,²³ we limited the study to term babies. This also made it possible to disentangle the effects of suboptimal fetal growth from the effects of preterm birth.

For two main reasons, we chose to measure adult health outcomes in multiple domains. First, as noted earlier, studies have reported associations of lower (or sometimes higher) birthweight with adult health outcomes in many domains. We sought to investigate whether these outcomes have common antecedents, reflected in their shared associations with birthweight. Second, we wanted to assess whether some early antecedents had beneficial effects in one domain but harmful effects in another domain.

As will be seen in the ensuing papers, the use of EDAH and the related studies is neither limited to studies of bw/ga, nor to studies based on discordance between siblings. The power of the design is most fully utilized in studies of bw/ga; however, the design is also useful for addressing a broad array of other questions. The extension of the core sample to larger studies of specific outcomes greatly increased the range of questions that could be addressed.

NEFS

The CPP was initiated more than 50 years ago to investigate prospectively the prenatal and familial antecedents of pediatric, neurological and psychological disorders of childhood. Nationwide, 12 university-affiliated medical centers participated, including two in New England (in Boston and Providence). More than 50,000 pregnancies were enrolled between January 2, 1959 and December 31, 1965^{1,2} (16,557 in the NEFS sites).³ The study followed up 88% of survivors at 1 year, 75% at 4 years and 79% at 7 years. Major findings from the CPP have been summarized in previous publications.^{2,24–26}

Data from examinations and interviews were recorded by trained staff at each site beginning at the time of registration for prenatal care, using standardized protocols, forms, manuals and codes. At the first prenatal visit, a complete reproductive and gynecological history, recent and past medical history, socioeconomic interview and family history were recorded. A socioeconomic index was assigned to each pregnancy, adapted from the Bureau of the Census and derived from education and occupation of the head of household along with household income.²⁷ Repeat prenatal assessments were conducted throughout pregnancy. Blood samples were collected for serology and for storage of frozen sera. After admission for delivery, trained observers recorded the events of labor and delivery, and the obstetrician completed labor and delivery protocols. The neonate was observed in the delivery room, examined by a pediatrician at 24-h intervals in the newborn nursery, and received a neurological examination at 2 days. Study offspring received five subsequent assessments: at ages 4, 8 and 12 months, and 4 and 7 years; pediatric-neurological examinations occurred at 4 and 12 months and 7 years; and psychological examinations at 8 months and 4 and 7 years. Family and social history information was obtained from the mother at intake and at 7 years. Diagnostic summaries were prepared by study physicians following the 12-month and 7-year assessments.

The NEFS (Boston and Providence CPP cohorts) comprised 16, 557 births. The final full assessment at age 7 years was completed by 80% of survivors. Archived sera are available for 98% of pregnancies (approximately three time points per pregnancy) and cord samples for 75% of pregnancies. Adult follow-up of these two New England CPP cohorts began in 1983 with the Providence sample. This work began through a collaboration between Ming Tsuang, who introduced the idea of investigating psychiatric outcomes within the cohort, Lewis Lipsitt who had directed the childhood assessments in Providence and Stephen Buka who co-designed and directed these initial follow-up efforts.²⁸ At the heart of these early investigations was the seminal work of Pasamanick *et al.*²⁹ who proposed ‘...a continuum of reproductive casualty extending from death [which] might descend in severity through cerebral palsy, epilepsy, mental deficiency, and perhaps even to behavior disorder’. The first major study selected approximately 500 infants born with moderate perinatal complications and 500 matched comparison subjects, and conducted standardized psychiatric diagnostic assessments at mean age 23.0 years.³⁰ Generally, the null results indicated no elevated risk for psychiatric disorder in relation to perinatal complications, with two exceptions. Infants born with conditions suggestive of chronic fetal hypoxia were at marginally elevated risk for both cognitive impairment and psychotic disorders, including schizophrenia. These initial findings led to a considerable body of subsequent work. The roles of perinatal

complications, infections during pregnancy and family history of psychosis have been investigated in multiple projects involving both the Providence and Boston sites.^{3,31–34} Investigations of schizophrenia now include over 1000 NEFS cohort members with and without psychotic disorders and incorporate detailed clinical diagnostic, neuropsychological, structural and functional imaging procedures and more;^{35,36} some based on collaborative efforts with the CHDS.^{37,38}

In 1999, we initiated a second major program of research, focused on nicotine dependence and related co-morbid psychiatric and physical disorders. This research initiated the follow-up and assessment of three-generation pedigrees in the NEFS, which is still ongoing (i.e. CPP mothers, their offspring who comprise the CPP cohort members and the offspring of the CPP cohort members). These projects all sought to integrate family designs with early life risk conditions, capitalizing upon the large number of cohort members with multiple offspring.^{39–41}

Recent work has moved from neuropsychiatric outcomes to physical conditions, with a particular emphasis on adult risks for cardiovascular disease,⁴² including investigation of comorbidity and common antecedents of depression and cardiovascular disease (see Goldstein *et al.*,¹¹ in this issue). Other major projects have included investigations of the stability and sequelae of childhood learning disorders,⁴³ social determinants of depression and other psychiatric disorders,⁴⁴ and potential mechanisms underlying the association between educational attainment and adult health status. Details are available at <http://www.bidmc.org/Research/Departments/Psychiatry/NewEnglandFamilyStudy.aspx>; <http://cnl-sd.bwh.harvard.edu>.

CHDS

The CHDS enrolled 98% of eligible pregnant women who were members of the Kaiser Foundation Health Plan in the Oakland, California area between 1959 and 1966. Its purpose was to investigate events of pregnancy, labor and delivery and subsequent childhood development.⁴ During the 7-year enrollment period, a total of 20,530 pregnancies were observed among the 15,528 women who were recruited into the study. At baseline, information was collected from a face-to-face interview with mothers. Prenatal measures, pregnancy complications, maternal morbidity and labor and delivery information were abstracted from the mothers' medical records. Gross placental exams were performed according to the Benirschke protocol⁴⁵ when funding was available, from 1960 to 1963 and 1965 to 1966. Serum samples in 3–4 cc aliquots were taken from fathers, and from mothers during pregnancy at each trimester and post delivery, and were frozen and archived. One to three samples of cord serum in 0.5 cc aliquots were also taken from a small sample of just over 3000 infants and were frozen and archived. Childhood serial growth measures and morbidity were abstracted from medical records for all CHDS children through age 5 years. Several special childhood follow-up studies targeting ages 5, 9–11 and 15–17 years were conducted among subsets of CHDS children. A description of CHDS data files can be found at <http://chdstudies.org>.

Because active follow-up ended in 1972, the cohort has been regularly monitored through passive surveillance by linkage to (1) the California Department of Motor Vehicles, for a history of location and timing of residence to identify the population at risk for morbidity and mortality,^{46,47} (2) the California Department of Vital Statistics, for identifying deaths and cause of death and (3) the California Cancer Registry, for identifying cancer diagnoses.^{48–50} All members of CHDS families and all names ever used by each family member are regularly matched to these sources. The accumulation of a name and address history for each cohort member protects against establishing false matches and failing to identify true matches. Surveillance efforts routinely identify one or more members of over 80% of CHDS families.

Record abstraction for cancer diagnoses to the California Cancer Registry is based primarily on pathology reports, and case identification is considered to be >99% complete after a 2-year lag. Life table analysis to estimate expected cases of testicular cancer through 2000 in CHDS sons⁵¹ and expected cases of breast cancer through 1998 in mothers showed high comparability with observed counts. The closeness between observed and expected numbers of cases for both parent and offspring in the CHDS cohort indicates that for cancer the surveillance is accurate, reliable and complete.

In 2000, the CHDS conducted a small pilot test of the completeness of the CHDS death match procedure. For this pilot, 1838 names for 1548 women (all known names were provided for each subject) were submitted for linkage to the National Death Index. Unconfirmed decedents through 2000 with limited information (e.g. no cause of death) were included in the pilot, as well as 50 women known to be alive and living in California through the pilot test period. A total of 195 deaths were identified by both sources combined. No death records were found in the National Death Index for the 50 women known to be alive in California. The National Death Index match identified 95.9% of all deaths; 11 of these were found only by the National Death Index. The CHDS identified 94.4% of all deaths; eight of these were found only by the CHDS match. These results provide confidence that the CHDS death surveillance methods, which include manual review, are relatively complete.

Earlier adult follow-up studies of CHDS offspring included studies of gendered behavior⁵² and time to pregnancy^{53,54} conducted in women aged 28–30 years who were also participants in the adolescent follow-up; a nested case control study of schizophrenia;^{55–57} and a pilot study to collect reproductive history and semen samples from CHDS sons.⁵⁸ From 2005 to 2008, a series of follow-up studies of the adult CHDS children who were in their 40s were initiated as part of an integrated effort to investigate the long-term impacts of fetal and childhood growth and development on adult health. This effort was broad-based, incorporating multiple adult health domains including neuropsychiatric function, breast development and male reproduction. These data are now being analyzed and are the source for papers in this special issue. Follow-up of the CHDS continues with a larger sample of CHDS daughters and their daughters in the 3 Generations Breast Cancer Study led by Barbara Cohn (see http://www.chdstudies.org/3gs/study_information/index.php).

Combining the two cohorts

Despite the similarities of the NEFS and CHDS noted above, the combination of the two cohorts in a single study posed multiple challenges. The studies were based in different health care delivery systems and enrolled populations with different demographic characteristics (see⁴ for an overview of the CHDS and^{1–3} for an overview of the NEFS cohorts). These differences are reflected in the NEFS and CHDS samples used in the EDAH study, as shown below.

The prenatal data collected in the original NEFS and CHDS studies were similar, but were not identical. Gestational length was recorded in weeks in the NEFS, and in days in the CHDS. Similar but not identical categories were used for education and occupation in the NEFS and the CHDS. The use of archived prenatal data from both studies requires the creation of identical variables. Although this is feasible for almost all variables of interest, it has to be done for each variable separately.

The studies diverged further in the timing and data collected on the offspring during childhood. For example, in the NEFS, data on height and weight were collected at multiple specified time points up to age 7 years; in the CHDS, height and weight were recorded at medical visits up to age 5 years, and for subsamples, up to later ages. Thus, the analysis of growth trajectories in the combined EDAH sample requires methods that allow for variation in the timing of measurements.

EDAH

Recruitment of the core EDAH sample

The total subject pool and the recruitment of study participants from this pool is displayed in Fig. 1a (NEFS) and 1b (CHDS). On the basis of archived data, we defined the total subject pool as all same-sex siblings who met the following criteria: (1) at least 38 weeks gestational age at birth; (2) serum samples collected and archived during the pregnancy; (3) growth data collected during early childhood follow-ups; (4) two or more siblings discordant on sex-specific bw/ga (as detailed below under the section ‘Sibling sets’). Using the ongoing surveillance of deaths in the CHDS described earlier, we applied a further criterion in the CHDS: the individual was not deceased. This resulted in a total subject pool of 515 in the NEFS and 651 in the CHDS.

We did not attempt to recruit all of the individuals in the total subject pool to the study. For ethical reasons, we did not attempt to recruit individuals who did not want to be contacted for follow-up. Individuals were sent a postcard so that they could communicate this before we attempted to contact them. Some had already done so in a prior study (mainly in the NEFS). For practical reasons, we only attempted to recruit individuals who were living within commuting distance of the study clinic. In the CHDS, for example, this excluded 148 individuals due to distance from the study clinic. As a result of these and other factors, the number of subjects targeted for recruitment was smaller than the total subject pool: 314 (61.0%) in the NEFS and 459 (70.5%) in the CHDS.

In the NEFS, 236 (75.2%) of the 314 targeted were located, and 149 (63.1%) of the 236 located were recruited and assessed at the time of these analyses. In the CHDS, 348 (75.8%) of the 459 targeted were located, and 243 (69.8%) of the 348 located were recruited and assessed. At both sites, the participation rate was somewhat higher for women than for men (see online Supplementary Table S1). These numbers reflect the data set that was created upon completion of the core EDAH study.

On the basis of funding from related studies, more individuals have subsequently been assessed (as shown in Fig. 1), and this process is still ongoing. As a result, the number of participants and the participation rates will be somewhat higher in analyses addressing specific questions in these related studies. Furthermore, analyses of archived prenatal sera and of newly collected blood samples are ongoing, also funded by related studies. When enough of these related studies are completed, we will be able to create a data set with a larger number of subjects and more variables.

Comparison of assessed with not assessed

Table 1 uses archived data to compare the participants in the total subject pool who were assessed and who were not assessed at each site. In the NEFS, but not the CHDS, the offspring of mothers and fathers with lower educational levels are underrepresented among the assessed. In the CHDS, the offspring of mothers who self-identified as black are overrepresented among the assessed. On all other variables, the assessed and not assessed are similar. The similarity is encouraging, as it limits the potential for selection bias. Online Supplementary Table S1 compares those assessed and not assessed by gender, as well as by site. Although a higher proportion of women than of men were assessed, the factors associated with being assessed were similar for women and men (with the exception of paternal education in the CHDS).

Sibling sets

In creating the total subject pool, we determined for each same-sex sibling his/her sex-specific percentile for bw/ga using the US 2000 gender-specific standards.⁵⁹ All same-sex sibships were then identified, in which at least one ‘proband’ sibling was in the lowest quintile of bw/ga and at least one ‘comparison’ sibling was in a higher quintile of bw/ga (and at least 10 percentiles higher in bw/ga than the proband sibling in the lowest quintile). In the NEFS, all 515 were selected in this way, and all of the participants were drawn from this pool. In the CHDS, this same procedure was used to select about one half of the total subject pool. Thus the full NEFS subject pool and about one half of the CHDS subject pool allowed us to examine whether lowest quintile bw/ga probands differed from their higher bw/ga siblings on adult health outcomes.

In the CHDS, where we studied a larger number of subjects, we used a second procedure to select the other half of the total subject pool. This second procedure was designed for comparison of siblings who differed in bw/ga to varying degrees, without requiring the proband sibling to be in the lowest quintile bw/ga. Thus we could also examine whether discordance in bw/ga had implications for later health, within the range of bw/ga in which the great majority of term babies are born. Such a comparison in the CHDS required a

spread of bw/ga discordance from high to low, with sufficient sibships in high as well as low bw/ga discordance categories. To achieve this spread, we prioritized siblings with the largest discordance between a low bw/ga proband and a higher bw/ga comparison sibling. For example, we gave higher priority to sibships in which the largest discordance between any two siblings on bw/ga was 50%, than to those in which the largest discordance was 40%. In the majority of sibships selected in this way, the largest discordance was at least 30 percentiles, but we also included a substantial number in which the largest discordance was 20–29 or 10–19 percentiles.

In practice, it was not always possible to assess more than one individual from a same-sex sibling set. In some instances, one sibling lived within commuting distance of the clinic but the other/s did not. In other instances, one sibling was willing to participate but the other/s were not. Thus, the majority but not all of the assessed sample comprised sibling sets at each site: 93 out of 149 (62.4%) in the NEFS and 163 out of 243 (67%) in the CHDS. The sibling sets assessed were almost all sibling pairs: 43 pairs in the NEFS and 80 pairs in the CHDS. In addition, there were three sibships with more than two siblings (total of 10 siblings).

As shown in Supplementary Table S2, the same-sex sibling pairs assessed were generally discordant on bw/ga as intended. In the NEFS, 4 of the 43 pairs were not discordant (i.e. we were able to assess two members of a sibship but not two siblings who met our bw/ga discordance criterion). In the CHDS, 4 of the 39 pairs with a proband in the lowest quintile also had a comparison sibling in the lowest quintile. In addition, 7 of the other 41 CHDS pairs were in the same bw/ga quintile, but this partly reflects the design, which allowed for less than a quintile difference in these other CHDS pairs as described earlier.

Because siblings are born at different times, they are not necessarily concordant with respect to the family-level confounders we wished to control. For example, mothers may increase their educational level or change their smoking habits across successive pregnancies, and maternal age will be higher for later born siblings. As shown in Supplementary Table S3, in this study all sibling pairs were perfectly concordant for maternal and paternal education and for maternal smoking during pregnancy as categorized in Table 1. With finer categories, some discordance is detectable, but it is small (data not shown).

Statistical power

There is an extensive literature on the computation of statistical power for studies with correlated observations.^{60,61} For illustration, consider bw/ga as a binary exposure, a sample of 120 discordant sibling pairs, a binary outcome with a frequency of 10% in the reference (unexposed) population and a logistic regression model with exchangeable correlation structure. With alpha set at 0.05, and correlation between siblings in the range 0.10–0.20 (power increases with intracluster correlation), the power is 65–70% for a relative risk of 2, and 91–94% for a relative risk of 2.5. The power will, of course, be much higher when the non-siblings are included in the sample. It will also be much higher for more common binary outcomes and for continuous outcomes. For an illustration of this increased power, see Lumey⁸ in this issue.

Assessments

The assessment procedures were approved by the Institutional Review Boards that oversee the ethics of human subjects research at Columbia University, other participating academic institutions and the clinic sites. The major outcome domains that were assessed are summarized in Table 2. With the exception of a Computer Assisted Telephone Interview (CATI) administered to women, all assessments were performed as part of a clinic visit, which took approximately 4–5 h. Study participants were asked to fast from midnight until the visit, and a fasting blood sample was taken when they arrived at the clinic. Following phlebotomy, blood pressure was taken three times using a Dinamap monitor and a full anthropometric assessment made. Participants were then given a light snack. Following the snack, men were administered a questionnaire to obtain data on social and demographic characteristics and health history of self and first-degree relatives (women had been administered a similar questionnaire via CATI as part of a related project⁹). A battery of neuropsychological tests was then administered, followed by a structured clinical psychiatric interview (the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental disorders-IV) and heart rate variability measurements. For women who signed a medical release form, mammograms done during the interval from 2 years before to 1 year after the interview were obtained (and returned after reading).

A careful process of training and quality assurance was used for the assessments. In Supplementary Table S4, we detail the procedures for key elements of the physical, psychiatric, neuropsychological and breast cancer risk assessments. The accompanying papers in this issue of the Journal further describe procedures for assessment, and detail procedures for quality assurance, in the domains relevant to their results.

Characteristics of the participants

Selected characteristics of the participants at follow-up by site and gender are shown in Table 3. One of the notable differences between the two sites is that there were more current and former cigarette smokers in the NEFS than in the CHDS sample. Not shown in Table 3, but evident from Table 1, a higher proportion of the CHDS than the NEFS sample were offspring of mothers who self-identified as black. Supplementary Tables S5 and S6 show a broader range of participant characteristics at follow-up than those included in Table 3, again by gender as well as by site.

Missing data

For the participants who completed the assessments, there were few missing data on the vast majority of variables. This is illustrated in Supplementary Table S7 where we show the percentage of participants with missing data for selected variables from the archived data and from the adult follow-up. Full details on missing data for variables used in the subsequent papers in this issue are included in those papers (as they will be in subsequent papers). We note that the same total n for the samples is retained in all the tables in this paper, but due to missing data, the number on whom the percentage is computed for a specific variable may be slightly less than the total n (e.g. % with different levels of education is based on individuals with data on level of education).

Future directions

The papers, which follow illustrate the enormous potential of the NEFS and the CHDS pregnancy cohorts for studying health across the life course. They also demonstrate that it is feasible to conduct collaborative studies across these cohorts. These initial papers from EDAH and related studies make significant contributions to our understanding of the relation between prenatal experience and midlife health (age 40s) and of the methods required for valid studies of these relationships. Subsequent papers will address a wider array of questions and draw on a rich array of other data, including early growth data, analyses of archived prenatal sera and analyses of blood samples collected in adult assessments.

We propose that we can substantially advance our knowledge of health and disease over the life course by following pregnancy cohorts into midlife and beyond. In the United States, the generation of such knowledge will depend upon the foresight of the National Institutes of Health. Thus, the intensive assessments of the NEFS and the CHDS cohorts were discontinued in early childhood; the cohorts had to be ‘reconstructed’ with much labor to provide the foundation for the follow-up studies now being done. Equally important, foresight is required to ensure that in future, pregnancy cohorts are supported to study the next generation (the offspring of the cohort members) prospectively from pregnancy onward, creating multigenerational studies that capture the critical period of fetal development and early childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Broman, SH. The collaborative perinatal project: an overview. In: Mednick, SA.; Harway, M.; Finello, KM., editors. Handbook of Longitudinal Research. Vol. Vol. 1. New York: Praeger Publishers; 1984. p. 166-179.
2. Broman, SH.; Bien, E.; Shaughnessy, P. Low Achieving Children: the First Seven Years. Hillsdale, NJ: L. Erlbaum Associates; 1985.
3. Buka S, Goldstein J, Seidman L, et al. Prenatal complications, genetic vulnerability and schizophrenia: the New England longitudinal studies of schizophrenia. *Psychiatr Ann.* 1999; 29:151–156.
4. van den Berg BJ, Christianson RE, Oechsli FW. The California child health and development studies of the School of Public Health, University of California at Berkeley. *Paed Peri Epidemiol.* 1988; 2:265–282.
5. Susser E, Terry MB, Matte T. The birth cohorts grow up: new opportunities for epidemiology. *Paed Peri Epidemiol.* 2000; 14:98–100.

6. Susser E, Terry MB. A conception-to-death cohort. *Lancet*. 2003; 361:797–798. [PubMed: 12642043]
7. McKeague IW, Lopez-Pintado S, Hallin M, Siman M. Analyzing growth trajectories. *J Dev Orig Health Dis*. 2011; 2:322–329. [PubMed: 22905314]
8. Lumey L. Maternal and pregnancy characteristics in relation to offspring size at birth and size at age 43 years; cohort and sibling analyses. *J Dev Orig Health Dis*. (In this issue).
9. Terry MB, Schaefer CA, Flom JD, et al. Prenatal smoke exposure and mammographic density in mid-life. *J Dev Orig Health Dis*. 2011; 2:340–352. [PubMed: 23378890]
10. Factor-Litvak P, Straka N, Cherkerzian S, et al. Associations between birth weight, preeclampsia and cognitive functions in middle-aged adults. *J Dev Orig Health Dis*. 2011; 2:365–374.
11. Goldstein JM, Cherkerzian S, Buka SL, et al. Sex-Specific impact of maternal–fetal risk factors on depression and cardiovascular risk 40 years later. *J Dev Orig Health Dis*. 2011; 2:353–364. [PubMed: 23378891]
12. Cirillo PM, Cohn BA, Krigbaum NY, et al. Effect of maternal coffee, smoking and drinking behavior on adult son's semen quality: prospective evidence from the Child Health and Development Studies. *J Dev Orig Health Dis*. 2011; 2:375–386.
13. Susser E, Eide MG, Begg M. The use of sibship studies to detect familial confounding. *Am J Epidemiol*. 2010; 172:537–539. [PubMed: 20631043]
14. Donovan S, Susser E. Commentary: advent of sibling designs. *Int J Epidemiol*. 2011; 40:345–349. [PubMed: 21450688]
15. Terry M, Wei Y, Esserman D, McKeague I, Susser E. Pre- and postnatal determinants of childhood body size. *J Dev Orig Health Dis*. 2011; 2:99–111.
16. Matte TD, Bresnahan M, Begg MD, Susser E. Influence of variation in birth weight within normal range and within sibships on IQ at age 7 years: cohort study. *BMJ*. 2001; 323:310–314. [PubMed: 11498487]
17. Lumey LH, Stein AD, Kahn HS, et al. Cohort profile: the Dutch Hunger Winter families study. *Int J Epidemiol*. 2007; 36:1196–1204. [PubMed: 17591638]
18. Gilman SE, Gardener H, Buka SL. Maternal smoking during pregnancy and children's cognitive and physical development: a causal risk factor? *Am J Epidemiol*. 2008; 168:522–531. [PubMed: 18653646]
19. Davey Smith G. Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in population health research and practice. *Int J Epidemiol*. 2011; 40:537–562. [PubMed: 21807641]
20. Kuh, D.; Ben-Shlomo, Y. *A Life Course Approach to Chronic Disease Epidemiology*. 2nd edn. New York: Oxford University Press; 2004.
21. Barker, DJP. *Fetal Origins of Cardiovascular and Lung Disease*. New York: M. Dekker; 2001.
22. Paneth N, Susser M. Early origin of coronary heart disease (the "Barker hypothesis"). *BMJ*. 1995; 310:411–412. [PubMed: 7873937]
23. Hutcheon JA, Platt RW. The missing data problem in birth weight percentiles and thresholds for "Small-for-Gestational-Age". *Am J Epidemiol*. 2008; 167:786–792. [PubMed: 18343882]
24. Niswander, KR.; Gordon, M. *The women and their pregnancies the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke*. Washington: National Institute of Health for sale by the Supt. of Docs., U.S. Govt. Print. Off.; 1972. National Institute of Neurological Diseases and Stroke.
25. Broman, SH.; Nichols, PL.; Kennedy, WA. *Preschool IQ: Prenatal and Early Developmental Correlates*. Hillsdale, NJ; New York: L. Erlbaum Associates; distributed by the Halsted Press Division of Wiley; 1975.
26. Nichols, PL.; Chen, T-C. *Minimal Brain Dysfunction: a Prospective Study*. Hillsdale NJ: Lawrence Erlbaum Associates; 1981.
27. Myrlandthopoulos NC, French KS. An application of the U.S. Bureau of the Census socioeconomic index to a large, diversified patient population. *Soc Sci Med* (1967). 1968; 2:283–299.
28. Buka SL, Lipsitt LP, Tsuang MT. Birth complications and psychological deviancy: a 25-year prospective inquiry. *Pediatr Int*. 1988; 30:537–546.

29. Pasamanick B, Rogers ME, Lilienfeld AM. Pregnancy experience and the development of behavior disorder in children. *Am J Psychiatry*. 1956; 112:613–618. [PubMed: 13292548]
30. Buka SL, Tsuang MT, Lipsitt LP. Pregnancy/delivery complications and psychiatric diagnosis: a prospective study. *Arch Gen Psychiatry*. 1993; 50:151–156. [PubMed: 8427556]
31. Goldstein JM, Seidman LJ, Buka SL, et al. Impact of genetic vulnerability and hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychoses. *Schiz Bull*. 2000; 26:323–334.
32. Seidman LJ, Buka SL, Goldstein JM, et al. The relationship of prenatal and perinatal complications to cognitive functioning at age 7 in the New England cohorts of the national collaborative perinatal project. *Schiz Bull*. 2000; 26:309–321.
33. Buka SL, Tsuang MT, Torrey EF, et al. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry*. 2001; 58:1032–1037. [PubMed: 11695949]
34. Buka SL, Tsuang MT, Torrey EF, et al. Maternal cytokine levels during pregnancy and adult psychosis. *Brain Beh Imm*. 2001; 15:411–420.
35. Thermenos HW, Goldstein JM, Buka SL, et al. The effect of working memory performance on functional MRI in schizophrenia. *Schiz Res*. 2005; 74:179–194.
36. Goldstein JM, Buka SL, Seidman LJ, Tsuang MT. Specificity of familial transmission of schizophrenia psychosis spectrum and affective psychoses in the New England family study's high-risk design. *Arch Gen Psychiatry*. 2010; 67:458–467. [PubMed: 20439827]
37. Susser E. Life course cohort studies of schizophrenia. *Psychiatr Ann*. 1999; 29:161–165.
38. Opler M, Buka S, Groeger J, et al. Prenatal exposure to lead, delta-aminolevulinic acid, and schizophrenia: further evidence. *Environ Health Perspect*. 2008; 116:1586–1590. [PubMed: 19057716]
39. Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry*. 2003; 160:1978–1984. [PubMed: 14594744]
40. Gilman SE, Martin LT, Abrams DB, et al. Educational attainment and cigarette smoking: a causal association? *Int J Epidemiol*. 2008; 37:615–624. [PubMed: 18180240]
41. Kahler CW, Strong DR, Papandonatos GD, et al. Cigarette smoking and the lifetime alcohol involvement continuum. *Drug Alc Dep*. 2008; 93:111–120.
42. Wen X, Triche EW, Hogan JW, Shenassa ED, Buka SL. Birth weight and adult hypercholesterolemia: subgroups of small-for-gestational-age based on maternal smoking status during pregnancy. *Epidemiology*. 2010; 21:786–790. [PubMed: 20798636]
43. Buka SL, Satz P, Seidman S. Defining learning disabilities: the role of longitudinal studies. *Thalamus*. *J Int Acad Res Lea Dis*. 1998; 16:14–29.
44. Gilman SE, Kawachi I, Fitzmaurice GM, Buka SL. Socioeconomic status in childhood and the lifetime risk of major depression. *Int J Epidemiol*. 2002; 31:359–367. [PubMed: 11980797]
45. Benirschke, K.; Driscoll, SG. *The Pathology of the Human Placenta*. New York: Springer-Verlag; 1967.
46. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension*. 2010; 56:166–171. [PubMed: 20516394]
47. Wang ET, Cirillo PM, Vittinghoff E, et al. Menstrual irregularity and cardiovascular mortality. *J Clin End Met*. 2011; 96:E114–E118.
48. Cohn BA, Cirillo PM, Christianson RE, van den Berg BJ, Siiteri PK. Placental characteristics and reduced risk of maternal breast cancer. *J Natl Cancer Inst*. 2001; 93:1133–1140. [PubMed: 11481384]
49. Cohn BA, Wolff MS, Cirillo PM, Sholtz RI. DDT and breast cancer in young women: new data on the significance of age at exposure. *Environ Health Perspect*. 2007; 115:1406–1414. [PubMed: 17938728]
50. Whittemore AS, Cirillo PM, Feldman D, Cohn BA. Prostate specific antigen levels in young adulthood predict prostate cancer risk: results from a cohort of Black and White Americans. *J Urol*. 2005; 174:872–876. discussion 876. [PubMed: 16093978]

51. Cohn BA, Cirillo PM, Christianson RE. Prenatal DDT exposure and testicular cancer: a nested case-control study. *Arch Environ Occup Health*. 2010; 65:127–134. [PubMed: 20705572]
52. Udry JR, Morris NM, Kovenock J. Androgen effects on women's gendered behaviour. *J Biosoc Sci*. 1995; 27:359–368. [PubMed: 7650053]
53. Cohn BA, Cirillo PM, Wolff MS, et al. DDT and DDE exposure in mothers and time to pregnancy in daughters. *Lancet*. 2003; 361:2205–2206. [PubMed: 12842376]
54. Cohn BA, Cirillo PM, Sholtz RI, et al. Polychlorinated biphenyl (PCB) exposure in mothers and time to pregnancy in daughters. *Reprod Tox*. 2011; 31:280–296.
55. Susser E, Schaefer C, Brown A, Begg M, Jed Wyatt R. The design of the prenatal determinants of schizophrenia study (PDS). *Schiz Bull*. 2000; 26:257–273.
56. Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence for prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004; 61:774–780. [PubMed: 15289276]
57. Bresnahan M, Schaefer CA, Brown AS, Susser E. Prenatal determinants of schizophrenia: what we have learned thus far? *Epidemiol Psychiatr Soc*. 2005; 14:194–197.
58. Cohn BA, Overstreet JW, Fogel RJ, et al. Epidemiologic studies of human semen quality: considerations for study design. *Am J Epidemiol*. 2002; 155:664–671. [PubMed: 11914194]
59. Oken E, Kleinman K, Rich-Edwards J, Gillman M. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003; 3:6. [PubMed: 12848901]
60. Liu G, Liang KY. Sample size calculations for studies with correlated observations. *Biometrics*. 1997; 53:937–947. [PubMed: 9290224]
61. Li Z, McKeague IW. Power and sample size calculations for generalized estimating equations via local asymptotics. *Statist Sin*. 2011 under revision.

Fig. 1.

(a) New England Family Study core sample: recruitment flowchart (*20 participants were later assessed but not included in the current dataset) and (b) Child Health and Development Study core sample: recruitment flowchart (*7 participants were later assessed but not included in the current dataset).

Table 1

Comparison of assessed and not assessed in total subject pool: by site

	NEFS (n = 515)		CHDS (n = 651)		P-value*
	Assessed (n = 149)	Not assessed (n = 366)	Assessed (n = 243)	Not assessed (n = 408)	
	n (%)	n (%)	n (%)	n (%)	P-value*
Maternal race					
White	138 (92.6)	325 (88.8)	148 (60.9)	303 (74.3)	
Black	11 (7.3)	41 (11.2)	55 (22.6)	57 (14.0)	
Other	0 (0)	0 (0)	40 (16.5)	48 (11.8)	0.00
Maternal marital status					
Married live with husband/common law	141 (94.6)	346 (94.8)	178 (99.4)	295 (99.3)	
Separated/divorced	6 (4.0)	12 (3.3)	0 (0)	1 (0.3)	
Single/ never married	2 (1.3)	7 (1.9)	1 (0.6)	1 (0.3)	0.69
Maternal age at birth (years)					
19	19 (12.8)	70 (19.1)	14 (5.8)	19 (4.7)	
20–24	67 (45.0)	147 (40.2)	86 (35.4)	155 (38.0)	
25–29	33 (22.2)	88 (24.0)	73 (30.0)	132 (32.4)	
30–34	23 (15.4)	46 (12.6)	45 (18.5)	69 (16.9)	
35–39	7 (4.7)	15 (4.1)	25 (10.3)	33 (8.1)	0.74
Maternal education at birth					
Less than high school	59 (40.1)	189 (52.7)	53 (21.8)	69 (16.9)	
High school	71 (48.3)	139 (38.7)	81 (33.3)	126 (30.9)	
More than high school	17 (11.6)	31 (8.6)	109 (44.9)	213 (52.2)	0.14
Paternal education at birth					
Less than high school	52 (38.5)	175 (52.9)	39 (16.6)	61 (15.5)	
High school	62 (45.9)	116 (35.1)	85 (36.2)	109 (27.7)	
More than high school	21 (15.6)	40 (12.1)	111 (47.2)	224 (56.9)	0.05
Maternal smoking during pregnancy					
No	72 (48.3)	145 (39.6)	148 (64.1)	256 (67.2)	
Yes	77 (51.7)	221 (60.4)	83 (35.9)	125 (32.8)	0.43

	NEFS (<i>n</i> = 515)				CHDS (<i>n</i> = 651)			
	Assessed (<i>n</i> = 149)		Not assessed (<i>n</i> = 366)		Assessed (<i>n</i> = 243)		Not assessed (<i>n</i> = 408)	
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>P</i> -value*
Maternal gravidity								
First pregnancy	35 (23.5)		75 (20.6)		43 (17.7)		98 (24.0)	
Second pregnancy	37 (24.8)		102 (28.0)		71 (29.2)		125 (30.6)	
Third–fourth pregnancy	46 (30.9)		127 (34.8)		88 (36.2)		126 (30.9)	
Fifth pregnancy	31 (20.8)		61 (16.7)		41 (16.8)		59 (14.5)	0.19
Birth weight (g)								
<2500	3 (2.0)		12 (3.3)		5 (2.1)		6 (1.5)	
2500–2999	43 (28.9)		97 (26.5)		52 (21.5)		79 (19.4)	
3000–3499	75 (50.3)		197 (53.8)		107 (44.2)		165 (40.4)	
3500–3999	27 (18.1)		55 (15.1)		66 (27.3)		124 (30.4)	
4000–4499	1 (0.7)		5 (1.4)		9 (3.7)		31 (7.6)	
4500	0 (0)		0 (0)		3 (1.2)		3 (0.7)	0.33
Length of gestation (completed weeks) from last menstrual period to birth								
38–42	147 (98.7)		358 (97.8)		234 (96.3)		395 (96.8)	
43 and more	2 (1.3)		8 (2.2)		9 (3.7)		13 (3.2)	0.72
Centile birth weight by gestational age								
<20	69 (46.3)		189 (51.6)		68 (28.0)		93 (22.8)	
20–39	33 (22.2)		90 (24.6)		58 (23.9)		102 (25.0)	
40–59	29 (19.5)		53 (14.5)		51 (21.0)		81 (19.9)	
60–79	12 (8.1)		27 (7.4)		39 (16.1)		72 (16.7)	
80	6 (4.0)		7 (1.9)		27 (11.1)		60 (14.7)	0.47

NEFS, New England Family Study; CHDS, Child Health and Development Study.

* *P*-value for the χ^2 test of distributions between the assessed v. not assessed samples.

** 1.1% of total sample were 40 years or older.

Table 2

Overview of adult assessments in EDAH

Demographic	Race/ethnicity
	Marital status
	Education
	Employment
	Household characteristics
General health and health history	Health history
	Self-health assessment
	Family health history
	Medications
	Conditions and procedures
Reproductive health	Reproductive health history
	Fertility
	Pregnancies and outcomes
	Conditions
	Leisure activities
Lifestyle	Physical activity
	Sleep
	Caffeine consumption
	Alcohol use
	Drug use
Physical assessment	Current smoking and smoking history
	Blood pressure
	Waist circumference
	Triceps and subscapular skinfolds
	Hand digit length
Psychiatric assessments	Height and weight
	HRV
	Fasting blood sample ^a
	Standardized clinical diagnostic interview
	Depressive disorders
Neuropsychological assessments	Anxiety disorders
	Symptom scales
	Neuropsychological battery
	General cognitive function
	Visual, spatial ability
Breast cancer risk	Attention, memory, handedness
	Analysis of mammographic density films

EDAH, Early Determinants of Adult Health; HRV, heart rate variability.

^aLaboratory analyses funded separately (thyroid function, sex hormones, lipid metabolism, stress hormones, fasting glucose, other).

Table 3

Selected outcomes at follow-up by site and gender

	NEHS (n = 149)			CHDS (n = 243)			Total (n = 392)		
	Females (n = 84)	Males (n = 65)	Total	Females (n = 125)	Males (n = 118)	Total	Females (n = 209)	Males (n = 183)	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age at examination (mean age in years and S.D.)	43.45 (2.00)	42.54 (2.31)	43.05 (2.18)	43.21 (1.96)	43.53 (1.96)	43.37 (1.96)	43.31 (1.97)	43.18 (2.14)	43.25 (2.05)
Educational attainment									
Less than high school graduate	4 (4.8)	5 (7.7)	9 (6.1)	3 (2.4)	2 (1.7)	5 (2.1)	7 (3.4)	7 (3.8)	14 (3.6)
High school graduate or GED	16 (19.3)	14 (21.5)	30 (20.1)	18 (14.5)	27 (22.9)	45 (18.6)	34 (16.4)	41 (22.4)	75 (19.2)
Some college/technical/associates/trade	36 (43.4)	27 (41.5)	63 (42.6)	50 (40.3)	48 (40.7)	98 (40.3)	86 (41.6)	75 (41.0)	161 (41.3)
Bachelors degree	23 (27.7)	11 (16.9)	34 (23.0)	36 (29.0)	28 (23.7)	64 (26.5)	59 (28.5)	39 (21.3)	98 (25.1)
Masters degree or above	4 (4.8)	8 (12.3)	12 (8.1)	17 (13.7)	13 (11.0)	30 (12.4)	21 (10.2)	21 (11.5)	42 (10.8)
Marital status									
Married/living with partner	52 (61.9)	38 (58.5)	90 (60.4)	80 (64.0)	73 (61.9)	153 (63.0)	132 (63.2)	111 (60.7)	243 (62.0)
Separated/divorced/widowed ^a	14 (16.7)	9 (13.9)	23 (15.4)	14 (11.2)	16 (13.6)	30 (12.4)	28 (13.4)	25 (13.7)	53 (13.5)
Single	18 (21.4)	18 (27.7)	36 (24.2)	31 (24.8)	29 (24.6)	60 (24.7)	49 (23.4)	47 (25.7)	96 (24.5)
Current employment									
Employed	61 (72.6)	58 (89.2)	119 (79.9)	103 (82.4)	104 (88.1)	207 (85.2)	164 (78.5)	162 (88.5)	326 (83.2)
Unemployed	7 (8.3)	0 (0)	7 (4.7)	6 (4.8)	9 (7.6)	15 (6.2)	13 (6.2)	9 (4.9)	22 (5.6)
Homemaker, not working outside home	11 (13.1)	0 (0)	11 (7.4)	10 (8.0)	0 (0)	10 (4.1)	21 (10.0)	0 (0)	21 (5.4)
Disability	5 (6.0)	6 (9.2)	11 (7.4)	4 (3.2)	3 (2.5)	7 (2.9)	9 (4.3)	9 (4.9)	18 (4.6)
Other	0 (0)	1 (1.5)	1 (0.7)	2 (1.6)	2 (1.7)	4 (1.6)	2 (1.0)	3 (1.6)	5 (1.3)
Smoking									
Never smoked daily for 1+ months	24 (28.9)	34 (53.1)	58 (39.5)	78 (63.4)	66 (55.9)	144 (59.8)	102 (49.5)	100 (55.0)	202 (52.1)
Smoked in the past (daily for 1+ months)	41 (49.4)	13 (20.3)	54 (36.7)	29 (23.6)	35 (29.7)	64 (26.6)	70 (34.0)	48 (26.4)	118 (30.4)
Current smokers	18 (21.7)	17 (26.6)	35 (23.8)	16 (13.0)	17 (14.4)	33 (13.7)	34 (16.5)	34 (18.7)	68 (17.5)
	Mean (S.D.)								
Body mass index (kg/m ²)	27.87 (6.35)	30.08 (5.72)	28.85 (6.16)	29.62 (8.81)	29.75 (6.17)	29.68 (7.61)	28.89 (7.91)	29.87 (6.00)	29.36 (7.08)
Wechsler Adult Intelligence Scale									

	NEFS (<i>n</i> = 149)			CHDS (<i>n</i> = 243)			Total (<i>n</i> = 392)		
	Females (<i>n</i> = 84)	Males (<i>n</i> = 65)	Total	Females (<i>n</i> = 125)	Males (<i>n</i> = 118)	Total	Females (<i>n</i> = 209)	Males (<i>n</i> = 183)	Total
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Digit Symbol score	10.86 (2.29)	9.22 (2.83)	10.14 (2.66)	11.77 (3.06)	10.13 (3.19)	10.99 (3.22)	11.39 (2.80)	9.78 (3.08)	10.65 (3.04)
Vocabulary score	10.42 (2.54)	10.66 (3.27)	10.52 (2.87)	10.61 (3.04)	10.61 (3.43)	10.53 (3.22)	10.53 (2.84)	10.52 (3.36)	10.53 (3.08)

NEFS, New England Family Study; CHDS, Child Health and Development Study; GED, General Educational Development.

^a 0.8% of total sample were widowed.