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The Study to Explore Early Development (SEED): A Multisite Epidemiologic Study of Autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) Network

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Abstract

The Study to Explore Early Development (SEED), a multisite investigation addressing knowledge gaps in autism phenotype and etiology, aims to: (1) characterize the autism behavioral phenotype and associated developmental, medical, and behavioral conditions and (2) investigate genetic and environmental risks with emphasis on immunologic, hormonal, gastrointestinal, and sociodemographic characteristics. SEED uses a case–control design with population-based ascertainment of children aged 2–5 years with an autism spectrum disorder (ASD) and children in two control groups—one from the general population and one with non-ASD developmental problems. Data from parent-completed questionnaires, interviews, clinical evaluations, biospecimen sampling, and medical record abstraction focus on the prenatal and early postnatal periods. SEED is a valuable resource for testing hypotheses regarding ASD characteristics and causes.

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by qualitative impairments in social interaction and communication, and repetitive stereotyped behaviors and interests. Although previously reported to be rare (e.g., prevalence of 1–4 per 10,000 children), a number of systematic population surveys and routine monitoring systems in the United States and other countries since the 1990s have indicated the childhood prevalence to be from 0.7% to 1% (Fombonne 2009; CDC 2009). In comparison, the childhood prevalence of intellectual disability typically ranges from 1%–2% (Leonard and Wen 2002) and 13% of school-aged children in the United States have some type of developmental disability (Boulet et al. 2009). Changes in diagnostic criteria and development of improved clinical methods of autism screening and diagnosis have accompanied improvement in population-based monitoring of ASD prevalence. Yet, apart from the identification of some rare genetic conditions that commonly are associated with ASDs, causal mechanisms for this spectrum of disorders remain largely unknown.

The Study to Explore Early Development (SEED) was designed by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) Network to address

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gaps in understanding of the ASD phenotype and etiology. The CADDRE Network comprises study sites in six states (California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania), a data coordinating center (DCC) (in Michigan), and a central laboratory and biosample repository (CLBR) (in Maryland). SEED was conceived to be among the largest multisite epidemiologic investigations of multiple genetic and environmental (broadly defined as nongenetic) risk factors and causal pathways contributing to different ASD phenotypes. SEED's primary scientific aims were to: (1) characterize the ASD behavioral phenotype and associated developmental, medical, and behavioral conditions, with a special focus on identifying distinct symptom profiles to guide etiologic analysis, and (2) investigate genetic and environmental risk factors, with emphasis on immunologic, hormonal, gastrointestinal, and sociodemographic characteristics.

The purpose of this paper is to provide details about SEED's:

1. Scientific background, including its specific aims and the knowledge gaps it was designed to fill;
2. Study design and implementation, with a focus on methodological features that might be informative for the design of other ASD investigations; and
3. Strengths and expected contributions to the understanding of the ASD phenotype and associated risk factors.

SEED Scientific Background and Aims

ASD Behavioral Phenotype and Associated Conditions Addressed in SEED

Although the ASD behavioral phenotype is defined by deficits in three core behavioral domains, current diagnostic subtypes within the autism spectrum are distinguished by the number and level of impairments across the three domains. Adding to this diagnostic complexity are other developmental features that affect phenotypic diversity (such as cognitive ability and developmental trajectory), including the timing of achievement of behavioral milestones or appearance of a developmental plateau, or even the loss of acquired language or social skills, or both (McGovern and Sigman 2005; Rogers 2004; Turner et al. 2006). Further, other developmental (e.g., intellectual disability and inattention), medical (e.g., epilepsy and gastrointestinal, sensory, and sleep abnormalities), behavioral (e.g., aggression and hyperactivity), and psychiatric (e.g., attention-deficit/hyperactivity disorder, anxiety, and depression) conditions commonly co-occur with an ASD, thereby adding further complexity to the clinical phenotype (Gillot et al. 2001; Levy et al. 2010; Polimeni et al. 2005; Spence and Schneider 2009; Yeargin-Allsopp et al. 2003). Whether these conditions arise independently of ASDs as a consequence of the core ASD deficits or as an endophenotype that predisposes a child to have an ASD or can be attributed to the underlying neuropathologic abnormalities is not clear. Individuals with an ASD are more likely than the general population to have major congenital anomalies, especially those individuals with a co-occurring intellectual or other disability (Hultman et al 2002; Schendel et al 2009; Wier et al 2006). Children with autism who have dysmorphic features also are more likely to have a known genetic syndrome or a structurally abnormal brain, compared with children with autism who do not have dysmorphic features (Miles and Hillman 2000).

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A number of genetic, neurologic, and metabolic conditions have been identified as either causative for an ASD (in about 10% of cases) or related to ASD-like characteristics (Cohen et al. 2005; Fombonne 2003; Zecavati and Spence 2009). The pathogenetic mechanisms that link these conditions to expression of the ASD behavioral phenotype are not known. Key aims for SEED regarding the phenotypic profile are to derive quantitative and qualitative descriptions, investigate which aspects might be unique to ASDs, map the diversity of ASDs into consistent patterns of symptoms, and investigate the association of symptom profiles with underlying risk factors for ASDs.

ASD Risk Factors Addressed in SEED

The extreme heterogeneity of behavioral, developmental, and associated medical features across the autism spectrum suggests that multiple causal factors, perhaps producing separate but overlapping phenotypic profiles, contribute to ASDs. Evidence of a genetic component in ASDs was established from studies indicating higher pairwise concordance among monozygotic (36%–95%) than among dizygotic (0%–31%) twin pairs (Bailey et al. 1995; Folstein and Rutter 1977; Ronald et al. 2006; Rosenberg et al. 2009; Taniai et al. 2008; Hallmeyer et al. 2011) and a 2%–18% recurrence rate among siblings of children with an ASD (compared with a rate of 0.7%–1% among the general population) (Chakrabarti and Fombonne 2001; Icasiano et al. 2004; Lauritsen et al. 2005; Sumi et al. 2006; Ozonoff et al. 2011). Relatives of individuals with an ASD also might have qualitatively similar but less severe variations of the core features of ASDs, now referred to as the *broader autism phenotype* (Piven et al. 1997). Strong associations have been found between ASD and a variety of single-gene and chromosomal abnormalities such as tuberous sclerosis and fragile X, Rett, and Down syndromes (DiGuiseppi et al. 2010; Hall et al. 2008; Kielinen et al. 2004; Wulffaert et al 2009; Wassink et al. 2001; Wiznitzer 2004). Recent findings have implicated particular genes, as well as both inherited and *de novo* copy number variants (Freitag et al. 2010; Bremer et al. 2010). Yet, the fact that monozygotic twin concordance is less than 100% suggests that factors other than DNA sequence might play a causative role, thereby possibly contributing to the recent reports of increases in ASD prevalence.

Specific environmental factors that have been associated with ASDs include prenatal exposure to thalidomide and valproate (Moore et al. 2000; Rasalam et al. 2005; Stromland et al. 1994). Less specific markers of possible prenatal risk include associations with preterm birth, low birth weight or older parental age and obstetric conditions such as bleeding or general indices of a suboptimal perinatal situation (Gardener et al. 2009; Kolevzon et al. 2007; Moster et al. 2008; Schendel and Bhasin 2008; Stein et al. 2006; Durkin et al. 2008; King et al. 2009), although it is unknown if adverse fetal or obstetric characteristics are causal, or reflect epiphenomenon of autism or increased familial liability (Zweigenbaum et al. 2002). Various prenatal viral infections and elevated rates of postnatal childhood infection also have been associated with ASDs (Atladottir et al. 2010a, b; Chess et al. 1978; Deykin and MacMahon 1979; Ivarsson et al. 1990; Rosen et al. 2007; Sweeten et al. 2004). While available evidence does not support a causal link between ASDs and the ethyl mercury-based vaccine preservative thimerosal (DeStefano, 2007; Gerber and Offitt 2009; Price et al. 2010), there is growing evidence that exposure to chemicals in the environment

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might contribute to ASD risk (Kalkbrenner et al. 2010; Roberts et al. 2007; Volk et al. 2010; Windham et al. 2006), possibly mediated through immune or hormonal pathways, or both.

A variety of immune system abnormalities involving cytokines, immunoglobulins, inflammation, cellular activation, and autoimmunity have been reported in association with ASDs (Ashwood et al. 2006; Goines and Van de Water 2010; Pardo et al. 2005), suggesting that immune dysfunction might play an etiologic role. A possibly separate but related immune pathway is based on reported elevated rates of gastrointestinal symptoms and immunopathology among children with an ASD that might lead to a heightened systemic immune response and neuroinflammation and damage (Ashwood et al.2004; Ashwood et al. 2006; Jyonouchi et al. 2005). Hormonal influences also have been implicated in ASD etiology. A key indicator is the male sex bias associated with ASDs and accompanying hypotheses for a prenatal imbalance in sex hormones, especially testosterone levels (Baron-Cohen et al. 2005). A potential role for abnormal maternal reproductive hormone function is reflected in associations with older maternal age (Durkin et al. 2008; King et al. 2009) and, less consistently, with maternal assisted reproduction (Hvidtjørn et al. 2009; Hvidtjørn et al. 2011). Other potential hormonal candidates include abnormal maternal prenatal thyroid and stress hormone levels and exogenous exposures to pitocin or oxytocin for labor induction (Beversdorf et al. 2005; Colborn 2004; Gale et al. 2003; Li et al. 2009; Soldin et al. 2003; Wahl 2004).

Neural, immune, and endocrine functions are integrated closely, both chemically and structurally, and work synchronously in the regulation of central nervous system and peripheral organ development and function. The molecular constituents of these systems (e.g., neurotransmitters, cytokines, and hormones), which play important roles in normal development, have pleiotropic functions and, therefore, potentially have widespread effects on neuronal function, including behavioral effects. Perturbation in any one system during development—through intrinsic abnormalities or from external exposures—can initiate a cascade of events with adverse neurodevelopmental consequences. Further, many genetic candidate genes for ASDs include those involved in central nervous system development, function and regulation (e.g., reelin, serotonin transporter gene, and brain derived neurotrophic factor, and immune (e.g., complement C4B) and hormonal expression (e.g., oxytocin receptor) (Abrahams and Geschwind 2008; Ashwood et al. 2006).

Thus, the growing body of evidence suggesting an etiologic role for one or more neural, immune or infectious, or hormonal factors in ASDs is the foundation for selecting these areas as the primary risk factors of interest for SEED.

Finally, there are disparities in ASD prevalence across racial and ethnic groups. These include lower reported rates among Hispanic and non-Hispanic Black or African-American children compared with non-Hispanic White children (CDC 2009; Windham et al. 2011), higher reported rates among Somali children in the United States (Minnesota Department of Health 2009), higher rates among immigrant populations in Northern European countries (Hultman et al. 2002; Maimberg and Vaeth 2006), and variations in ASD prevalence by socioeconomic status (defined by household education and income) (Durkin et al. 2010). These observations suggest that sociodemographic factors might be important markers of

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risk for ASDs through unrecognized links to underlying etiologic factors. On the other hand, some of these disparities might reflect differences in ascertainment and diagnosis of affected people among different racial and ethnic groups.

SEED Study Design and Implementation Methodology

Study design

A case–control study design was adopted for SEED with multiple-source, population-based ascertainment of case and comparison groups. Case patients (ASD) were those children meeting study definitions for several ASDs (autistic disorder, pervasive developmental disorder-not otherwise specified, and Asperger syndrome). Two different control groups were defined for SEED: a group of children sampled from the general population (POP) and a group of children with developmental delays or disorders other than ASDs (DD). Comparisons between the ASD and POP groups were designed to identify risk factors in children with ASDs relative to children among the general population. Future comparisons between the ASD and DD groups might provide the opportunity to distinguish risk factors for ASDs independent of risks common to other developmental disorders. The DD group also might provide a means of controlling for recall bias that might be associated with having a child with developmental problems.

Study population and eligibility

The population characteristics of each SEED recruitment catchment area are described in Table 1. The use of multiple catchment areas across the United States has provided a study population characterized by diverse racial, ethnic, and socioeconomic distributions. [Place Table 1 about here]

Children were eligible for SEED if: (1) they were born in a study catchment area during the period from September 1, 2003, through August 31, 2006; (2) resided there at the time of first study contact; and (3) lived with a knowledgeable caregiver (family member or caregiver at least 18 years of age at enrollment who had resided with and consistently cared for the child since he or she was 6 months of age or younger) who was competent to communicate orally in English (or, at two sites, in English or Spanish) and gave consent. Enrolled children also had to be between 30–68 months of age at the completion of the in-person clinical developmental assessment to maintain the appropriate age range for validated study instruments. Children with circumstances (e.g., adoption) that prevented access to birth certificates or legal consent were not eligible to participate.

Ascertainment and Enrollment

Ascertainment of ASD and DD children—Both potential ASD and DD children were ascertained through multiple sources serving or evaluating children with developmental problems, including early intervention, special education, and related service programs for toddlers and young children; hospitals; clinics; and individual providers. Potential participants had to have received an ASD or related diagnosis (e.g., conduct disorder, intellectual disability, or significant developmental delay) from a clinical provider, or received early intervention or special education services for an ASD or related condition

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(e.g., intellectual disability or severe emotional disorder). This "broad diagnostic net" for ascertainment of potential ASD children ensured that both previously diagnosed and undiagnosed ASD children were identified (a full list of broad net diagnoses is available upon request). Parents who had a child with a documented ASD or ASD-related diagnosis also might have contacted the study directly and the child enrolled if eligible. [Place Figure 1 about here]

Ascertainment of POP children—POP children were identified by randomly sampling state vital records of children born in the specified birth date range to mothers resident in a study catchment area at delivery. The number of POP children sampled by site was based on very conservative estimates of the expected enrollment and completion rates of invited POP families with the aim of obtaining a final 1:1ratio of complete ASD and POP families. Thus, each site randomly selected an oversample of POP children that ranged from about 20- to 90-fold higher than the final target sample size and randomized this total oversample into smaller batches for study invitation. Birth records are linked to state death certificate files to remove deceased children from the contact list. [Place Figure 2 about here]

Invitation to potential participants and assessment of eligibility—Invitations to participate in SEED were issued first in the autumn 2007. An invitation packet, written in English (and Spanish at the Colorado and California sites), was mailed to the primary caregiver of all potentially eligible participants. The name Study to Explore Early Development was intentionally designed to avoid the use of the word "autism," in order to reduce participation bias by families with a particular interest in autism. The invitation described broad study objectives and provided an informational brochure, contact information, cash or a small toy of nominal value, and a prepaid response card to accept or decline further contact. Invitees who returned a positive response card received an invitation telephone call to assess their eligibility for the study (using previously cited criteria). Nonresponders received a second invitation letter in 2–6 weeks (at four sites) or a follow-up invitation telephone call (at two sites: nine attempts over different days of the week and times of day, leaving messages on most attempts). If the invitee expressed willingness to hear more about the study during an invitation call, the study staff proceeded to assess the invitee's eligibility. To date, among a total of 22,100 combined ASD and DD families and 24,646 POP families sampled for whom the invitation process has been finalized: 64% of combined ASD and DD families and 68% of POP families never responded to the written invitation or invitation call (in 76% of combined ASD and DD families and 80% of POP families who never responded, the accuracy of the contact information was unknown); a combined 9% of ASD and DD children and 12% of POP children exceeded the eligible age limit for the standardized study instruments before contact could be made; and 26% (N=5,678) of combined ASD and DD families and 21% (N=5,064) of POP families were contacted by telephone (either the invitation call to assess study eligibility following a positive response card or, at some sites, the study invitation call for nonresponders). Among invited families for whom telephone contact was made, 34% of combined ASD and DD families and 40% of POP families refused; 21% of combined ASD and DD families and 34% of POP families were determined to be ineligible; and 43% of combined ASD and DD families and 25% of POP families consented to participate.

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Screening for ASD—At the end of the study eligibility assessment call, the Social Communication Questionnaire (SCQ), a 5–10 minute interview, was administered to the primary caregiver of all eligible participants to identify children who required clinical diagnostic evaluation to determine final ASD status. Although the published SCQ was validated for children 4 years of age or older, several recent studies have found that a reduced cut-off score improves the sensitivity and specificity at younger ages, maximizing them at a cut-off score of 11 among children younger than 4 years of age (Lee et al 2007; Wiggins et al. 2007; Allen et al. 2006). For SEED, a positive screen was defined as an SCQ score ≥11. Regardless of ascertainment source (i.e., "broad diagnostic net" or vital records), any eligible children who had a positive screen or a previous ASD diagnosis or who were receiving special education services for an ASD were assigned to the ASD workflow which determined which instruments were administered and the type of diagnostic evaluation the child received during the data collection phase. DD and POP children with negative SCQ screens were assigned to the DD or POP workflow, respectively. If, during the clinical evaluation of a child in the DD or POP workflow, the clinician suspected an ASD, the child immediately was moved into the ASD workflow.

To date, 34% of children in the ASD workflow who had completed the clinical evaluation did not have a previous ASD diagnosis, but were assigned to the ASD workflow after a positive SCQ screen (32%) or clinical suspicion after a limited developmental evaluation (2%). Eighty-three percent of children in the ASD workflow without a previous ASD diagnosis were ascertained via the "broad diagnostic net" and 17% were ascertained via vital records (of whom 42% and 22%, respectively, received an ASD final classification; see final classification description below). It is expected that a larger proportion of children with a positive SCQ and consequent direction into the ASD workflow would be ascertained on the basis of a diagnosis of a developmental delay or disability (the "broad diagnostic net") than would be children ascertained from the general population (via vital records), although there are no published date on the yield of the SCQ screen comparable to these results because of differences in ascertainment methods and ages of participant children.

Data Collection

Extensive data were collected via multiple ways to address the SEED scientific aims. Table 2 lists each instrument and the version used, with references, and the mode of collection, target participant, primary purpose, and analytic domains addressed. Data collection was uniform across all study groups except that those in the ASD workflow completed additional instruments to assess specific ASD features (see Table 2). Participants in the DD or POP workflow completed the Vineland Adaptive Behavior Scales if they scored <1.5 standard deviations below the mean on the Mullen Scales of Early Learning (i.e., an Early Learning Composite score of 78 points or less). [Place Table 2 about here]

Due to the large number of items and the complexity of the data collection protocol, a number of strategies were incorporated to facilitate implementation and completion. Data collection was organized into multiple stages (Figure 3) to more evenly distribute the study burden over time, as well as to enhance the completion of data collection at one stage before proceeding to the next. The stages are made up of the mailed enrollment packet, three

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different packets of self-administered forms, a telephone-assisted caregiver interview, and one or two in-person visits (at a clinic or, by one site, offered at the family's home). Scheduling of the stages was determined with input from participants to enhance compliance. Support in completing self-administered forms was provided as needed to overcome literacy barriers. Periodic contacts by telephone, email, or biannual newsletter served as reminders for data item completion or scheduled data events.

Quality Control for Data Collection

The need for appropriate staff training and oversight, including systematic quality control (QC), was considered carefully for each contact with participants. QC steps included a variety of QC training exercises, initial "in-the-field" QC standards, and ongoing QC standards. For all instruments, high thresholds were set for "acceptable" QC, so that even slight variations from established protocols could be identified early and remediation strategies implemented (such as retraining and continued monitoring until acceptable standards were reached). QC details and results to date for each instrument or contact are presented in Table 3. [Place Table 3 about here]

Final Classification

To date, among families who consented to participate, 69% of children in the ASD workflow and 70% of children in the combined DD and POP workflow completed the clinical evaluation and were assigned a final study group classification. Final classifications were dependent on the child's ascertainment source (i.e., "broad diagnostic net" or birth certificate); workflow classification; and, for children in the ASD workflow, the results from both the Autism Diagnostic Observation Schedule (ADOS; using new scoring algorithms) (Gotham et al. 2007; Lord et al. 1999; Lord et al. 2000) and the Autism Diagnostic Interview–Revised (ADI-R) (Lord et al. 1994; Rutter et al. 2003). As shown in Figures 1 and 2, the SEED rubric placed children into one of four final classifications: (1) Final ASD, (2) Possible ASD, (3) Final DD, and (4) Final POP. Children with Final DD, Final POP or Possible ASD final classifications who went through the ASD workflow were further divided into several subclassifications to characterize children by degree of observed or reported, or both, ASD behavioral symptoms based on the ADOS or ADI-R. To date, among children who completed the clinical evaluation, 27% were classified as a Final ASD, 2% as a Possible ASD, 37% as a Final DD, and 34% as a Final POP. Among children who were classified as a Final ASD, 18% did not have a previous ASD diagnosis.

Target Sample Size and Study Power

During SEED planning, the proposed size of the study birth cohort, and therefore the anticipated number of potential ASD, DD, and POP participants, was determined partly by time and resource considerations. Few data were available to estimate anticipated effect sizes for particular exposure–outcome relationships of interest. Given these constraints, we calculated the minimum detectable relative risk estimates with the anticipated sample size, which was based on an estimated prevalence of 3.4 ASD cases per 1,000 children aged 3–10 years in metropolitan Atlanta in 1996 (Yeargin-Allsopp et al. 2003). Because we were focusing on preschool children, we chose a more conservative estimate of 3.2 cases per 1,000 children. Therefore, based on about 485,000 births among the SEED study population

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over a 24-month period (September 1, 2003–August 31, 2005), we anticipated that there would be about 1,550 potential ASD case children to be ascertained, including previously diagnosed and study-identified children. Based on estimated rates of invitation contact, eligibility, enrollment, and data collection completion, in part from another large study of ASDs using similar recruitment methods (Hertz-Picciotto et al. 2006), we expected about 42% of all potential case children, or 650 children (families) with an ASD, to be contacted, enroll, and provide complete data. Due to lower invitation contact, enrollment, and completion rates than anticipated, an additional birth cohort year was added (September 1, 2005–August 31, 2006), expanding the SEED study population to about 750,000 births, in order to obtain complete data on 650 ASD case children. Applying the same birth date, residence, and other eligibility criteria as those used to identify case children, we implemented the approach described previously to ascertain and enroll children in each of the two control groups, in a 1:1 ratio with case children.

A number of estimations were made to gauge the effects on minimum detectable odds ratios (MDORs) of different case group sizes—total ASD group or specific ASD phenotypic subgroups—and exposure prevalence rates. For all estimates, conventional alpha and beta error tolerances were applied (0.05 and 0.20, respectively). The MDORs ranged from 1.37 when using the total ASD group in an analysis of any infection during pregnancy (estimated exposure prevalence 50%) to 5.28 when using an ASD subgroup (nonverbal with regression, 30% of all cases) in an analysis of oral contraceptive use during pregnancy (1% prevalence). For all exposures with a prevalence of at least 5%, the MDOR using the total ASD group was less than 1.87. For the majority of ASD subgroups and likely exposure prevalences, the MDOR was estimated to be less than 2.0.

Minimum detectable risk estimates for interaction (e.g., a perinatal infection and mode of delivery) also were calculated for a range of prevalence estimates, from 0.025 to 0.5 for one exposure (Exposure 1), and 0.05 to 0.5 for the other (Exposure 2). For the minimum detectable interaction odds ratio (assuming no stratification), the values ranged from about 5.0 to 12.0 for the lowest prevalences of Exposure 1 combined with different Exposure 2 prevalences; they improved to about 2.0 to 3.5 for the highest prevalence for Exposure 1 combined with different Exposure 2 prevalences.

Management of Laboratory Specimens

SEED biospecimens were blood samples, dried blood spot cards, hair, and buccal (cheek cell) swabs. Blood sample collection tubes for children included EDTA (2 x 3 milliliters (mL)), CPT (2 x 4 mL]), SST (3.5mL), and Paxgene (2.5mL) and for parents include EDTA (6mL), CPT (8mL), and SST (5mL). All biologic specimens, other than buccal swabs, were collected by trained local staff, packaged, and shipped via overnight courier following standardized protocols to the CLBR in Maryland where they were received, processed, and stored. Samples were identified by laboratory-specific bar codes to enable tracking of receipt and inventory without direct links to other study information. All blood tubes were inspected visually upon receipt at the CLBR for tube integrity and volume, which were recorded in the laboratory database. Samples then were aliquoted into smaller portions (a variable number of aliquots depending on the type and volume of blood collection tube) for long-term storage

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to minimize thaws per aliquot. Blood spot cards were prepared both at the local recruitment sites and at the CLBR, using blood from one of the venipuncture tubes. All blood spot cards and hair samples were stored at room temperature. SEED buccal sample collection was self-administered (three brushes per person) and specimens were mailed directly to the CLBR by participants. DNA was extracted from buccal samples within 30 days. Recruitment sites were notified of samples with low DNA yield so that an additional buccal sample could be collected if needed; recollection was not prompted by familial inconsistencies which were detected later at genotyping and flagged for analysis. DNA from blood also was isolated as blood was received and stored in a standardized concentration in up to four aliquots. Integrated communication between the CLBR and the DCC allowed for inventory monitoring and for biosample requests to the CLBR to prepare specific participant samples for particular bioanalyses as needed.

Data Management and Protection

The primary functions of the SEED DCC in Michigan have been to develop, host, and support the CADDRE Information System (CIS), a web-based application developed exclusively for CADDRE. The CIS has provided the mechanisms for managing workflow and data processing. The CIS also has integrated with the Internet System for Assessing Autistic Children (ISAAC), a system built and maintained by Autism Speaks™ for entry of standardized clinical assessments, and the *Freezerworks* database of biologic specimens housed at the SEED CLBR. All participant data have been entered into the CIS by SEED staff and securely stored in a Health Insurance Portability and Accountability Act-class facility. Personally identifiable information has been encrypted with access governed by site-defined roles.

The DCC also provided a medical coding function for all text fields in SEED instruments, including medical diagnoses (International Classification of Diseases (ICD) codes) and procedures (Current Procedural Terminology (CPT) codes), medications (Slone Drug Dictionary™) (Slone Epidemiology Center 2009), and a variety of additional categories (such as ethnicity). The coding process, implemented in batches, used both a computer-based autocoding process followed by manual coding, with an updating of the autocoding electronic dictionaries following each completed batch. Each batch of coded fields was subjected to a quality assurance procedure involving review by a physician (ICD and CPT codes), research pharmacist (medications), or epidemiologist.

The DCC data cleaning management functions included a comprehensive system for internal validity checks to enable identification and correction of data discrepancies as new data were entered into CIS. A log of all data edits was maintained. The data cleaning functions were applied to newly entered data on a 24-hour cycle and the resulting cleaned data were presented in a series of de-identified tables organized by study instrument. The tables were frozen nightly to reflect the previous day's data entry and edits. Authorized users were granted access to the tables via a remote connection to a dedicated and secure DCC server for review and analysis.

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Community Involvement

Each SEED site made extensive efforts to involve health and education professionals, voluntary organizations, and parents in the development and implementation of the project. Site investigators participated in voluntary organizations such as Autism Society of America and Autism Speaks™, where they had the opportunity to communicate information about the project as it proceeded and receive feedback. Outreach activities focused on professionals serving children with developmental disabilities; parents of children who participated in early intervention or special education programs; and support groups, events, and conferences for parents of children with an ASD. Communication about the project also has taken place through SEED's biannual newsletter to participants, news articles, television profiles, and study websites.

SEED Scientific Contributions

Despite significant growth in ASD research funding in recent years, the number of large epidemiologic studies of ASD is still relatively small, due in part to their methodological complexity and expense. SEED was designed to provide unique insights into ASDs and other child development epidemiologic research at multiple levels: methodological, descriptive, and analytic (Table 4).

Implementation of the population-based SEED study protocol in multiple, U.S. settings was complex. Protocol implementation has yielded information that will inform the design and conduct of future epidemiologic studies and provide insights into both the practical feasibility and performance of a variety of data collection instruments and approaches in a large field study setting. Specific anticipated methodological contributions relate to recruitment strategies and associated participation rates; data collection strategies and associated completeness; comparisons of data retrieved via caregiver interview versus medical records; biospecimen collection; informatics, data management, and quality control; performance of both ASD- and non–ASD-specific instruments and data collection approaches in population-based field studies, including instruments for special types of data such as characterization of dysmorphic features (methods to be reported elsewhere); diet and stool patterns; and autism research among Hispanic populations, with a special focus on Spanish-speaking participants.

Another important contribution of SEED research will be descriptive in nature. Previous evaluations of developmental features and risk factors for ASD often have been based on smaller, clinic-based samples and often have lacked data from comparison groups. Given its size and population-based ascertainment, information from SEED will be able to fill many descriptive data gaps and provide more reliable estimates of the distributions of these factors among children with different developmental profiles. Specific contributions will include results from standardized developmental assessments; prevalences and distributions of developmental, behavioral, biologic, physical and morphologic and associated medical features and conditions; and prevalences and distributions of demographic characteristics and environmental and genetic risk factors.

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The primary goal of SEED was to test important hypotheses related to ASD phenotype and etiology. A key strength is that data have been collected to address multiple different but potentially interrelated hypotheses. Consequently, the type of data and targeted topics of information collection were diverse and will enhance SEED's analytic breadth and potential. The richness of detailed phenotype, environment, genetic, and biomarker data, coupled with the large, well-defined study sample, will permit the simultaneous investigation of numerous genetic factors, environmental factors and phenotypic features, and their interplay—an analytic strength addressing a limitation of many studies to date.

While SEED does have limitations, efforts have been made to reduce their effects on its analytic potential. First, although a population-based method to ascertain potential invitees was implemented, the actual proportion of invitees with contact for the study invitation and eligibility assessment telephone call was relatively low (as described previously, 28% of combined ASD and DD families and 19% of POP families). This might have limited the representativeness of the enrolled sample. Characteristics of the SEED participants relative to the base population will be assessed and remedial analytic steps devised as needed. For example, we may perform a sensitivity assessment by comparing results from an analysis based on participant data to an analysis based on a simulated augmented data set with an assumed distribution of the risk factor in question among those who chose not to participate (Molenberghs and Kenward 2007).

The results of the sensitivity assessment would guide analytic interpretation of SEED results. The low contact rates during the invitation process also might have increased the potential for biased measures of association if individuals in the case or comparison groups with certain exposures or sociodemographic characteristics responded disproportionately to the attempts to invite them, resulting in different enrollments. To reduce this possibility, study goals were described in broad terms to invitees so that parents with concerns about specific exposures would not have a heightened motivation to enroll.

A second study limitation was that much of the environmental risk factor data were collected retrospectively from parents via interview or questionnaire, long after critical prenatal or perinatal time periods; thus, the data were liable to recall error. The SEED target age range was a compromise between the need to gather risk factor information from parents as soon after pregnancy and infancy as possible, yet enroll families whose children were old enough for reliable developmental assessment. Further, the retrieval and extensive abstraction of medical records of mother and child, containing prospectively recorded data, were designed to complement and extend the array of information that parents provided and mitigate potential recall bias.

Finally, although minimum detectable interaction effect sizes are quite large when exposure prevalence is moderate to low, the power to detect causal effects also is influenced heavily by measurement error. Careful phenotyping of SEED participants reduced outcome misclassification and provided greater precision than less costly, but more error-prone, case confirmation protocols that afford collection of larger samples. Further, the detailed phenotyping in SEED will allow for the accurate identification of clinical subgroups with which it may be possible to detect interaction effects of sufficiently high magnitude. Last, to

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enhance SEED total sample size and analytic power, a second round of SEED enrollment and data collection will be initiated in 2012.

Conclusion

SEED was designed to collect a sufficient breadth and depth of data to make significant scientific contributions in several key research domains, while also filling important knowledge gaps in a variety of other areas. In addition to analytic hypothesis testing, SEED will contribute important methodological and descriptive information on many factors. Findings from the SEED study will inform the interpretation of results from previous studies, as well as the planning of the next generation of studies on ASDs and child development. Finally, SEED data, including the valuable biospecimen repository, will be a unique resource to test new hypotheses as they arise, reexamine old hypotheses from new perspectives, and contribute to future data pooling efforts for analyses requiring robust sample sizes beyond the reach of individual studies.

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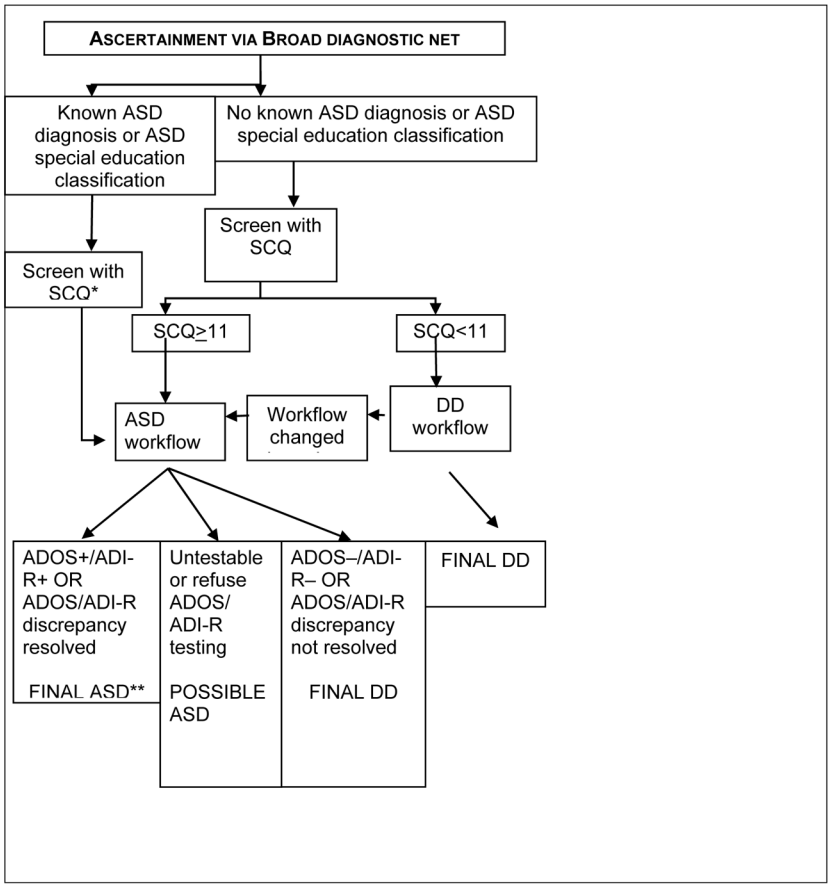

SEED: Study to Explore Early Development; SCQ: Social Communication Questionnaire; DD: Developmental Delay or Disorder; ASD: Autism Spectrum Disorder; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview – Revised

*All children in this pathway go on to ASD workflow regardless of SCQ screening results

** FINAL ASD meets either 1) ASD criteria on the new ADOS algorithms and autism criteria on the ADI-R or 2) ASD criteria on the new ADOS algorithms and one of three relaxed criteria on the ADI-R. Relaxed criteria for the ADI-R included: (a) met criteria on the social domain and was within 2 points on the communication domain, (b) met criteria on the communication domain and was within 2 points on the social domain, and (c) met criteria on the social domain and was within one point on the behavioral domain.

Figure 1.

SEED recruitment and final classification of ASD and DD participants

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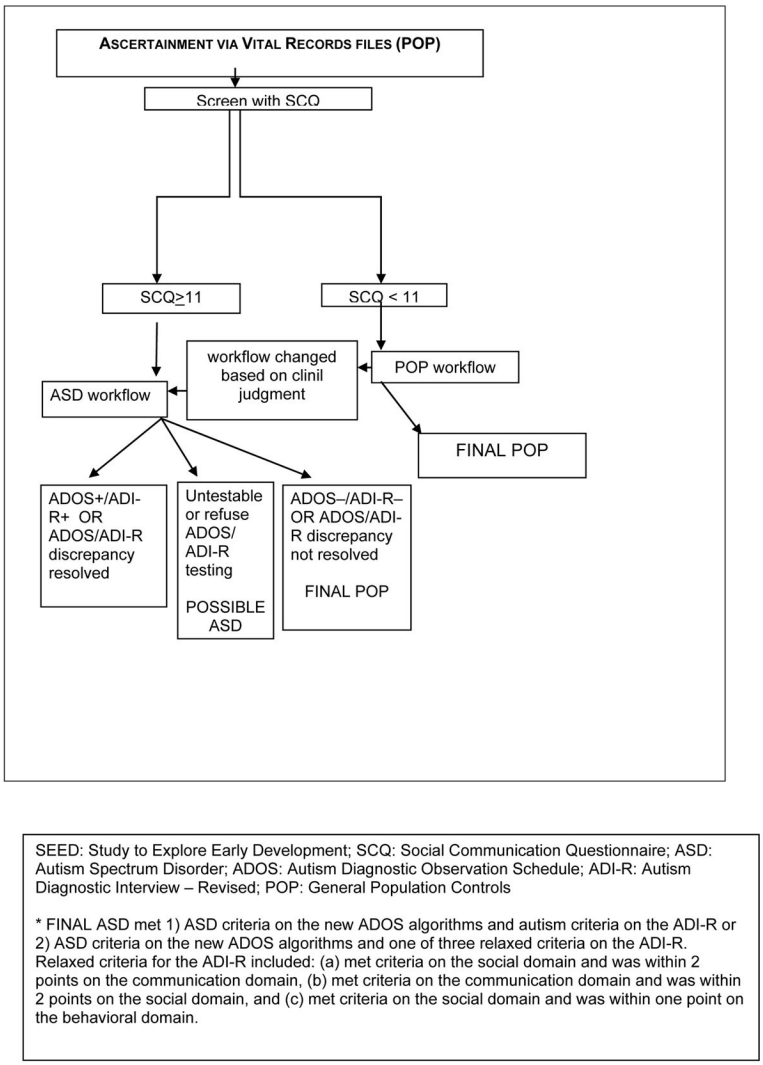

SEED: Study to Explore Early Development; SCQ: Social Communication Questionnaire; ASD: Autism Spectrum Disorder; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview – Revised; POP: General Population Controls

* FINAL ASD met 1) ASD criteria on the new ADOS algorithms and autism criteria on the ADI-R or 2) ASD criteria on the new ADOS algorithms and one of three relaxed criteria on the ADI-R. Relaxed criteria for the ADI-R included: (a) met criteria on the social domain and was within 2 points on the communication domain, (b) met criteria on the communication domain and was within 2 points on the social domain, and (c) met criteria on the social domain and was within one point on the behavioral domain.

Figure 2.

SEED recruitment and final classification of POP participants

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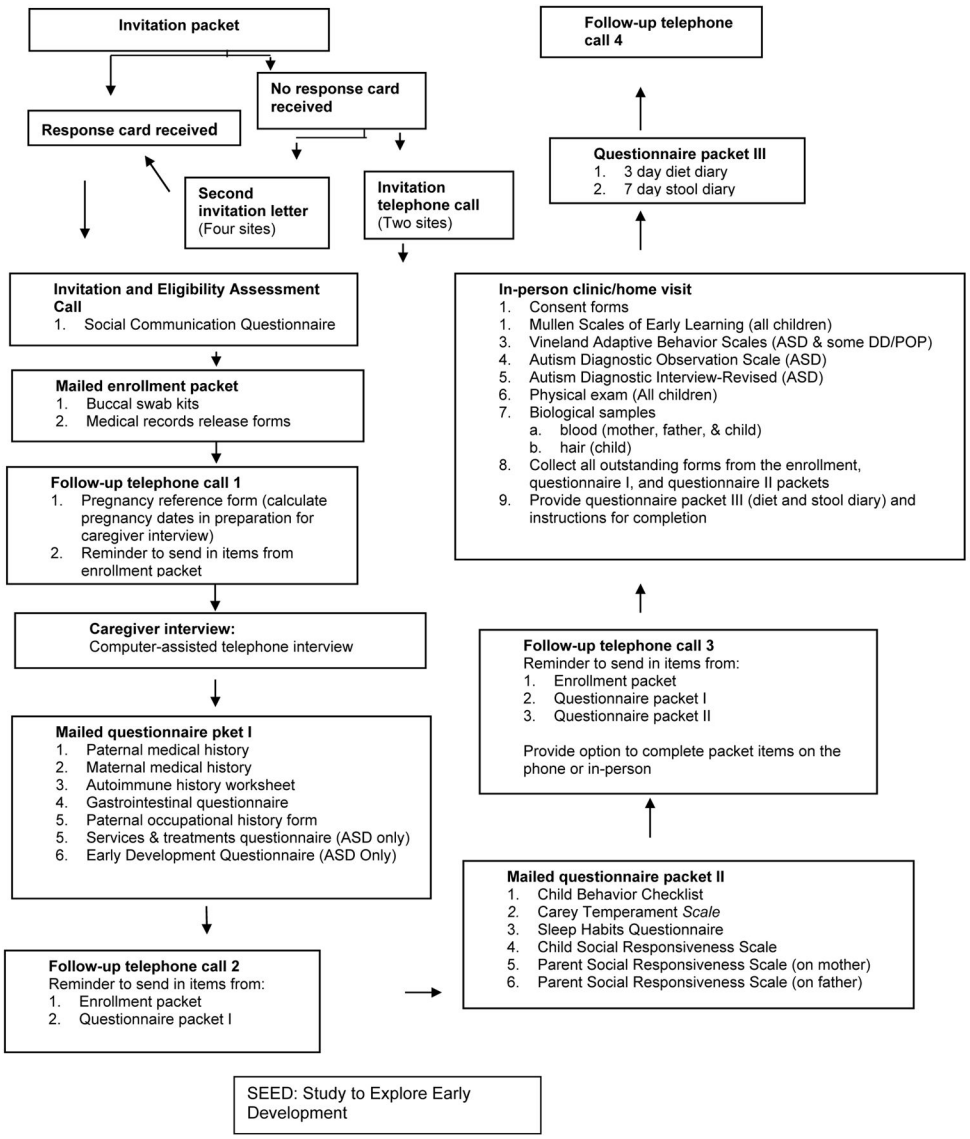

Figure 3.
SEED participant data collection steps

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Table 1

Population characteristics of the Study to Explore Early Development catchment areas

	California	Colorado	Georgia	Maryland	North Carolina	Pennsylvania
Catchment Area	**2 Counties, San Francisco Bay Area**	**7 Counties, Denver**	**5 Counties, metropolitan Atlanta**	**7Jurisdictions, northeast Maryland**	**10 Counties, central North Caroline**	**3 Counties, Philadelphia**
Live births/yr (N) (2005)	47,454	40,253	53,276	35,037	36,964	36,663
Maternal race/ethnicity (%)						
Black/African	6.7	5.9	38.2	35.7	23.2	32.3
American						
White	59.1	89.0	55.1	61.5	71.4	49.3
Non-Hispanic	25.6	55.5	32.3	56.2	53.6	46.1
Hispanic	33.5	33.5	22.7	5.3	17.8	2.9
Asian	16.6	4.5	6.2	5.1	4.7	6.3
Mixed/Other	14.5	0.6	0.1	0.0	0.7	9.3
Unknown	3.1	0.0	0.5	0.0	0.0	2.8
Non-Hispanic	65.8	65.9	70.5	94.3	82.0	85.6
Hispanic	34.2	34.1	22.7	5.7	18.0	12.9
Maternal education						
< 12 years	20.0	22.9	22.0	14.5	23.2	19.2
12 years	20.6	24.5	27.3	27.1	22.0	25.4
>12 and < 16 years	18.1	15.1	18.4	18.8	18.4	23.0
>= 16 years	41.3	34.9	32.3	38.6	36.1	31.2
Proportion of children under 18 years living in poverty (%)	12.2 (2005–07)	15.7 (2005)	17.6 (2005–07)	14.9 (2005)	20.1 (2005)	22.1 (2005–07)

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Table 2

Study to Explore Early Development data collection

Data collection	Reference; version	Collection mode (time to complete)	Participant[a]	Primary purpose for SEED	Analytic domains[b]
Autism-related assessments					
Social Communication Questionnaire (SCQ)	Rutter et al. 2003; 2003 WPS Current Version	Telephone (10 min)	C	Screen for autism spectrum disorders	B
Autism Diagnostic Observation Scale (ADOS)	Lord et al. 1999; Lord et al. 2000; Gotham et al, 2007; 2001 WPS Version	Clinic (40 min)	C (ASD)	Assess ASD symptoms; determine final ASD status	B
Autism Diagnostic Interview-Revised (ADI-R)	Lord et al. 1994; Rutter et al. 2003; 2003 WPS Version	Clinic (120 min)	C (ASD)	Assess ASD symptoms; determine final ASD status	B
Ohio State University (OSU) Autism Rating Scale (OARS)	OSU Research Unit, 2005; adapted for SEED	Staff review (n/a)	C (ASD)	Assess ASD symptoms and comprehensive clinical impression	B
Early Development Questionnaire (EDQ)	Ozonoff et al. 2005; Version 3	Filled out by parent (20 min)	C (ASD)	Assess regression of language and social skills, and functional behavior	B
Social Responsiveness Scale (SRS)	Constantino 2002; 2006 WPS Preschool Version & 2005 WPS Adult Version	Filled out by parent (15–30 min)	C, M, F	Assess social behavior	B
Other behavioral and developmental assessments					
Mullen Scales of Early Learning	Mullen, 1995; 1995 AGS/ Pearson Version	Clinic (45 min)	C	Assess cognitive function	B
Vineland Adaptive Behavior Scales	Sparrow et al. 1984; 2005 AGS/Pearson Version	Clinic (45 min)	C	Assess adaptive behavior	B
Child Behavior Checklist (CBCL)	Achenbach, 1992; 2000 ASBE Version	Filled out by parent (15 min)	C	Assess behavior problems and social competencies	B
Carey Temperament Scale	Carey and McDevitt, 1995; 1995 Behavioral / Developmental Initiatives Version,	Filled out by parent (10 min)	C	Assess temperament	B
Health and medical information					
Physical examination	CADDRE-derived	Clinic (15 min)	C	Anthropometry and dysmorphology exam	D
Services and treatments questionnaire	CADDRE-derived	Filled out by parent (5 min)	C (ASD)	Assess types and frequency of current services and treatments	B
Child Sleep Habits Questionnaire	Owens 2000	Filled out by parent (10 min)	C	Assess behaviors and medical disorders of sleep	B
Gastrointestinal questionnaire	CADDRE-derived	Filled out by parent (10 min)	C	Assess past and current gastrointestinal disturbances	GI

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Data collection	Reference; version	Collection mode (time to complete)	Participant[a]	Primary purpose for SEED	Analytic domains[b]
Paternal medical history form	CADDRE-derived	Self-administered (10 min)	F	Assess medical and psychiatric conditions	B
Maternal medical history form	CADDRE-derived	Self-administered (10 min)	M	Assess medical and psychiatric conditions	B, H, I
Autoimmune disease survey	CADDRE-derived	Self-administered (20 min)	Nuclear family	Assess history of autoimmune disease	I
Medical records for the preconception[c], prenatal, and labor/ delivery periods	CADDRE-derived	Staff review (n/a)	M	Prenatal, perinatal, and postnatal medical information related to risk factors of interest	S,H,I,GI,O
Medical records for the neonatal and pediatric[3] periods	CADDRE-derived	Staff review (n/a)	C	Prenatal, perinatal-, and postnatal medical information related to risk factors of interest	S,H,I,GI,O
7-day stool diary	Bristol Stool Form Scale (Lewis, 1997)	Filled out by parent (40 min)	C	Assess bowel movement and stool patterns	GI
3-day diet diary	CADDRE-derived	Filled out by parent (20 min)	C	Assess diet patterns during stool diary period	GI
Biologic specimens					
Buccal cells (cheek swab)		Kit mailed to family (15 min)	C, M, F	For analysis of genetic biomarkers	G
Blood		Clinic (15 min)	C, M, F	For analysis of genetic and non-genetic biomarkers	H,I,G,E
Hair		Clinic (1 min)	C	For analysis of environmental exposures	E
Guthrie card bloodspots		Clinic (4 min)	C	For analysis of genetic and non-genetic biomarkers	H,I,G,E
Other data					
Paternal occupational history form	CADDRE-derived	Self-administered (5 min)	F	Paternal occupational history during index pregnancy	E
Multidimensional					
Birth certificate		Data linkage	C		S
Caregiver interview	CADDRE-derived	Telephone (60 min)	M	Biologic mother as informant: biologic mother's full reproductive and pregnancy history and diagnosed developmental outcomes in all children; medical, therapeutic, obstetric and lifestyle characteristics of pregnancy (considered 3 months before conception through breastfeeding) with index child (including infertility treatments of either biological parent); maternal occupational history during index pregnancy	B,GI,H,I,O,E, S
				Biologic mother or other primary caregiver as informant: index child's postnatal developmental and medical history; parent/ caregiver demographics;	

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[a] C = Child M = Mother F = Father

[b] B = Behavioral Phenotype; D = Dysmorphology; GI = Gastrointestinal disorders; H = Hormonal; I = Infection and immune function; O = Obstetric; G = Genetic; E = Environmental; S = Sociodemographic

[c] Preconception records consist of specialists for infertility, immune, and psychiatric conditions in 3 years before conception; Pediatric records consist of pediatrician and specialists records in 3 years after birth (pediatric genetics clinic records consist of all evaluations prior to the date of the Study to Explore Early Development physical examination)

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Table 3

Study to Explore Early Development quality control procedures and results

Study contacts and instruments	Type of quality control assessment(s) and requirements	Specific quality control training requirements[a]	Ongoing quality control (frequency)	Results ongoing quality control[b]
Invitation telephone call, including eligibility screener and Social Communication Questionnaire	Semiqualitative call rating form—a priori criteria established for acceptable score.[c]	Acceptable scores on 4 role-playing (mock) calls and first 2 "live" calls.	5% per interviewer	88% acceptable rating scores overall, with improvements over time; >90% after first 6 months.
Follow-up call, including structured pregnancy dates questionnaire for caregiver interview	Semiqualitative call rating form—a priori criteria established for acceptable score.[c]	Acceptable scores on 3 role playing (mock) calls.	5% per interviewer	93% acceptable rating scores overall, with improvements over time; >90% after first 6 months and 100% after first 12 months.
Caregiver interview	**1** Semiqualitative call rating form—a priori criteria established for acceptable score.[c] **2** Quantitative inter-rater reliability assessment of selected interview items. Acceptable score is ≥95% concordance.	Acceptable scores for both assessments on 3 role-playing (mock) interviews and first 2 "live" calls.	5% per interviewer	99% acceptable call rating scores; 98% acceptable inter-rater reliability assessments throughout study.
Questionnaire packets I, II, and III (self-administered forms)[d]	No specific systematic QC requirements, but continual supervisor oversight and all forms reviewed for missing or illegible data or contradictory entries. Participants are recontacted as needed.	None. General training provided on forms and appropriate responses to participant queries.	NA	NA
Autism Diagnostic Observation Schedule (ADOS)	Intersite: Supervising clinicians establish reliability by scoring the same ADOS exam videotapes. Acceptable score is ≥80% concordance on algorithm items. Intrasite: All clinicians establish reliability with supervising clinician. Acceptable score is ≥80% concordance on algorithm items	Both intersite and intrasite reliability established in advance of study start.	Quarterly intersite and intrasite reliability exercises	Intersite: 99% acceptable scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass" Intrasite: 99% acceptable scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass".
Autism Diagnostic Interview-Revised (ADI-R)	Intersite: Supervising clinicians establish reliability by scoring the same ADI-R interview videotapes. Acceptable score is ≥90% concordance on algorithm items. Intrasite: All clinicians establish reliability with supervising clinician. Acceptable score is ≥90% concordance on algorithm items.	Both intersite and intrasite reliability established in advance of study start.	Quarterly intersite and intrasite reliability exercises.	Intersite: 99% acceptable scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass". Intrasite: 87% acceptable rating scores on "first pass" quarterly exercises and 100% acceptable scores on "second pass".
Mullen Scales of Early Learning	No specific systematic QC requirements, but continual supervisor oversight and all forms reviewed for missing or illegible data or contradictory entries.	5 clinicians monitor initial assessments until competency determined.	NA	NA
Vineland Adaptive Behavioral Scales	No specific systematic QC requirements, but continual supervisor oversight and all forms reviewed for missing or illegible data or contradictory entries.	None. Supervising site clinicians monitor initial assessments until competency determined.	NA	NA

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Study contacts and instruments	Type of quality control assessment(s) and requirements	Specific quality control training requirements[a]	Ongoing quality control (frequency)	Results ongoing quality control[b]
Dysmorphology physical examination: examination, photography, and anthropometric measurements.	Intersite: Examiners review common set of photos and compare measurements. Acceptable score is ≥80% concordance. Intrasite: Examiners certified as meeting acceptable levels of reliability (80% or higher depending on component) on performance standards in several areas.	Acceptable intrasite scores in all areas on 5 practice examinations and first 3 "live" examinations.	Intersite: 1 exercise / month Intrasite: 10% per examiner	Intersite: 100% acceptable scores on monthly exercises. Intrasite: 95% acceptable scores.
Biologic specimens: buccal swabs and blood specimens (child, mother, father) and hair specimen (child).	All: Central laboratory staff processes specimens upon receipt and performs preliminary QC (gross visual inspection). Sample of participants: Second blood specimen obtained for duplicate processing and analysis	None. Extensive staff training on study protocol for obtaining and processing biologic specimens	2% sample of duplicate blood specimens	Will assess analyte concordance (e.g., genotypes) among duplicates
Medical record abstraction (4 forms: prenatal, labor and delivery, neonatal, pediatric).	Intersite: Common reliability abstraction exercises, each focusing on different sections/ forms. Acceptable score is ≥90% concordance across sites. Intrasite: Quantitative inter-rater reliability assessment of selected items on each form. Acceptable score is ≥90% concordance.	Acceptable intrasite scores on first 2 "live" abstractions for each form type (8 total abstractions).	Intersite: Quarterly reliability exercises. Intrasite: 5% per abstractor (across form types)	Intersite: Exercises revealed minor inconsistencies in abstraction process; no major substantive differences noted. Intrasite: 91–100% acceptable rating scores across the 4 form types

[a]Training QC requirements consisted of requirement for staff to pass formal reliability or other QC assessment on mock exercises in advance of "live" field work and initial QC requirement on first instruments/examinations once in the field.

[b]For each instrument, if a study staff member did not meet criteria for acceptable score during ongoing QC, retraining and training QC requirements were instituted.

[c]Semiqualitative call rating forms for invitation, follow-up, and caregiver interview calls included items such as use of call script, coverage of essential points, ability to respond to participant questions, probing on unclear or neutral responses, professionalism, and delivery and response recording for applicable study instruments (Social Communications Questionnaire, pregnancy reference form, or caregiver interview). For each item, QC supervisor rated interviewer as "good", "fair", or "poor". Criteria for acceptable score consisted of: no item rated as "poor" and 20% or fewer rated as "fair"; and mandatory ratings of "good" for select items (dependent on type of call).

[d]Questionnaire packet I included maternal medical history form, paternal medical history form, family autoimmune disease history form, paternal occupational exposure questionnaire, child services and treatments questionnaire, child early development questionnaire, and child gastrointestinal function questionnaire. Questionnaire packet II included Child Behavior Checklist, Carey Temperament Scale, Child Sleep Habits questionnaire, Child Social Responsiveness Scale, and Parent Social Responsiveness Scale. Questionnaire packet III included child diet diary and child stool diary.

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Table 4

Study to Explore Early Development design-based research strengths

Feature	Advantage
Multisite	Multiple U.S. sites located in diverse communities improves generalizability of SEED findings to the broad U.S. population compared with studies performed in single areas.
Multisource ascertainment	Identification of potential ASD and DD participants from multiple facilities at each site improves representativeness of the full range of children with autism in each study area by diminishing biases that could arise from limiting study families to those who are seen only at single facilities.
Ascertainment of diagnosed and undiagnosed ASD children	Actively recruiting children who did not have a previous autism diagnosis but met SEED's rigorous autism case definition improves representativeness of ASD group in SEED's target preschool age range because not all affected children might have received an autism diagnosis from community providers by the time of SEED enrollment.
Two comparison groups	The DD (children affected with developmental problems other than autism) and POP (children drawn from the study population of births, most of whom have typical development) comparison groups are designed to control for potential recall bias among ASD parents and to more accurately distinguish features of autism from both typical development and other developmental problems.
Uniform study protocol across sites	Uniform eligibility criteria and data collection protocols, including final participant classification procedures, and robust quality control measures: • Ensure high intrasite and intersite data collection and developmental assessment reliability. • Enhance quality and precision of the multisite pooled data. • Enhance size of the multisite pooled analytic sample.
Large sample size	The final sample size will be among the largest of autism epidemiologic studies planned to date, resulting in: • Robust study power based on the total pooled analytic sample. • Good power for analyses based on key ASD subgroups and common (≥5 % prevalence) risk factors.
Data collection redundancy	Some data are being collected under different modalities (e.g., self-report and medical record abstraction). This will: • Better ensure certain classes of risk factor information are not missed. • Permit assessment of data retrieval and quality across different data collection modalities.
Enrollment of participants who speak only Spanish	Two sites are actively recruiting families who speak only Spanish to accommodate the large Hispanic population in their study areas. This will greatly inform the future development of appropriate autism study methods and improvement of autism instruments for Spanish-only speakers.
Use of both existing and novel CADDRE-derived instruments	Assess feasibility and performance in large, population-based research setting of both existing standardized instruments (performance of many instruments has not been assessed outside smaller clinical research applications), and CADDRE-derived novel instruments and approaches for special data types (e.g., stool, diet, and dysmorphology assessment)