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THE AUTISM BIRTH COHORT (ABC): A PARADIGM FOR GENE-ENVIRONMENT-TIMING RESEARCH

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Abstract

The reported prevalence of autism spectrum disorders (ASD) has increased 5–10× over the past 20 years. Whether ASD are truly more frequent is controversial; nonetheless, the burden is profound in human and economic terms. Although autism is among the most heritable of mental disorders, its pathogenesis remains obscure. Environmental factors are proposed; however, none is implicated. Furthermore, there are no biomarkers to screen for ASD or risk of ASD. The Autism Birth Cohort (ABC) was initiated to investigate *gene × environment × timing* interactions and enable early diagnosis. It employs a large, unselected birth cohort wherein cases are prospectively ascertained through population screening. Samples collected serially through pregnancy and childhood include parental blood, maternal urine, cord blood, milk teeth and rectal swabs. More than 107 000 children are continuously screened via questionnaires, referral and a national registry. Cases are compared with a control group from the same cohort in a “nested case-control” design. Early screening, diagnostic assessments and re-assessments are designed to provide a rich view of longitudinal trajectory. Genetic, proteomic, immunologic, metagenomic and microbiological tools will be used to exploit unique biological samples. The ABC is a paradigm for investigating the role of genetic and environmental factors in complex disorders.

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Keywords

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Introduction

For millennia, philosophers have debated the role of nature (genetics) and nurture (environment) in health and disease. This debate has intensified with advances in human genomics. Indeed, recent emphasis on metagenomics, epigenetics and systems biology reflects increasing appreciation for an integrated approach to medicine and biology. This is particularly true in developmental neuroscience where an awareness of the vulnerability of the fetus and the child to environmental factors already influences public health investments, ranging from folate supplementation during pregnancy to preschool environmental enrichment programs. Studies linking drugs like thalidomide and divalproate to fetal defects, and animal models wherein gestational exposure to infectious agents results in anatomical and behavioral deficits, clearly demonstrate the importance of investigating gene-environment interactions within their temporal context.^{1, 2, 3} An opportunity to do this at the population level has arisen with the advent of large prospective pregnancy and birth cohorts.⁴

Autism is a neurodevelopmental disorder, defined by the presence of: (i) deficits in social interactions, ii) deficits in communication, and iii) restricted, repetitive and stereotyped patterns of behavior, interests and activities.⁵ The observation that these features may vary in severity and time of onset led to the concept of 'autistic spectrum disorders' (ASD), comprised primarily of autistic disorder (childhood autism), Asperger syndrome, and pervasive developmental disorder-not otherwise specified ('PDD-NOS').

The reported prevalence of autism spectrum disorders (ASD) in continental Europe, the UK and the US has increased 5–10 fold over the past 20 years.⁶ The extent to which the increase in reported prevalence represents a *bona fide* increase or is due to enhanced and earlier case detection, and/or modification of diagnostic criteria, is not known. Nonetheless, there is consensus that the burden in economic as well as social and individual terms is profound. In the United States alone, given a birth rate of 4 million and a prevalence of 1/150, almost 27 000 children at risk for ASD are born annually.⁷ Autism is amongst the most heritable of mental disorders; however, the genetic basis and pathogenesis of most cases remains obscure.⁸ Environmental factors are proposed; however, none has been established as causal.⁹ Furthermore, although these disorders may begin in prenatal life there are no known biomarkers at birth that can be used for diagnosis.

The Autism Birth Cohort (ABC)

The Autism Birth Cohort (ABC) was established to address the natural history of ASD, explore genetic and pre- or perinatal environmental factors in causation, as well as the interplay between genes and environment, and to facilitate discovery of biomarkers with potential to enable early recognition and treatment. Although not restricted to the following

candidate environmental factors, the ABC was designed to focus on prenatal or postnatal infection, obstetric risk factors, and dietary and/or environmental exposure to potential toxins during pregnancy and postnatal life. ABC resources include a serial collection of detailed questionnaires and biological samples for genetic, transcriptomic, proteomic, microbiologic and toxicologic analyses.

The Norwegian Mother and Child Cohort (MoBa)

The ASD cases in the ABC study are identified from Norwegian Mother and Child Cohort (MoBa) participants. The MoBa is a nation-wide population-based pregnancy cohort initiated in 1999.^{10, 11} At termination of recruitment in December 2008, 90 700 mothers, 72 100 fathers, and 108 500 children were enrolled. The last child to be included was born in 2009.

Information is obtained from questionnaires, biological materials, sub-studies and linkage to registries. Mothers complete questionnaires during pregnancy and at intervals after birth. Fathers complete one questionnaire during pregnancy. The questionnaires query health, dietary intake, socio-economic status, child development and behavior, and psychosocial and emotional status of the mother, father, and child. Blood samples are obtained from both parents during pregnancy and from mothers at birth. A urine sample is also taken from the mother during pregnancy. From the child, a blood sample is taken from the umbilical cord directly after birth. Plasma, RNA, and DNA are collected from blood. Pilot analyses of aliquots of blood samples retrieved from the MoBa biobank using oligonucleotide microarrays, quantitative real time PCR, Luminex technology and MALDI TOF MS/MS, indicate the viability of these materials for genetic and expression profiling, proteomics, microbiology and toxicology (unpublished).

The MoBa 18-month questionnaire includes the Early Screening of Autistic Traits (ESAT) and the Modified Checklist for Autism in Toddlers (M-CHAT).^{12, 13} The 36-month questionnaire includes the Social Communication Questionnaire (SCQ) and selected M-CHAT items.^{14, 15, 16} Information on both cases and controls with respect to signs and symptoms of ASD provides the basis for describing the natural history of ASD and defining endophenotypes that may provide insights into the pathogenesis of ASD.

Identification of children with ASD and selection of controls

Potential ASD cases within the MoBa cohort are identified via four mechanisms (Figure 1): (1) screening at 36 months; (2) professional referrals by the healthcare system; (3) self-referrals from parents; and (4) linkage with the Autism Database, which is coordinated by the NIPH and funded by the Research Council of Norway. The Autism Database includes MoBa children diagnosed with ASD in the Norwegian healthcare system (hospitals and outpatient clinics). To enhance capture of potential cases that elude identification by screening at the age of three years, new MoBa questionnaires have been designed for 5- and 7-year-old children that include specific questions about autism, autistic traits and Asperger's disorder. We will also identify cases via referral and a national patient registry. ABC controls are selected randomly among MoBa participants, matched to potential cases by birth date (± 14 days).

Screening criteria

The ABC screening mechanism includes the Social Communication Questionnaire (SCQ) in addition to other selected items.^{14, 15, 16} All 40 SCQ items are included in the 36-month questionnaire, but only those 33 items that do not require language to be present (SCQ-33) are used in the ABC screening algorithm. The screening criteria are outlined in Table 1.

Clinical assessments

Screen-positive children are assessed clinically at 36–42 months of age to collect detailed neurobehavioral and developmental information, and to generate a diagnosis of ASD or associated disorders, using standardized and validated diagnostic instruments (Table 2). Core diagnostic instruments are the Autism Diagnostic Interview–Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS).^{17, 18} The ASD subgroups included are (with or without concurrent mental retardation): Autistic Disorder, (DSM-IV 299.00), Asperger's Disorder (DSM-IV 299.80) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS, DSM-IV 299.80).

Expected number of cases

Based on an evaluation of recent reports, we assume a prevalence of ASD of 6 per 1 000 in the MoBa cohort; thus the ABC has the potential to identify approximately 600 ASD cases.^{19, 20, 21, 22} All screen-positive potential cases are invited to participate in clinical assessments. We anticipate assessing a minimum of 2 000 children. Blood and stool samples are taken at the time of assessment to enable molecular, serological and microbiological analyses.

Follow-up

MoBa records provide information from early pregnancy onwards, through questionnaires and registry linkages. The MoBa database is linked to the Medical Birth Registry of Norway (MBRN) (www.fhi.no) and other national health registries. Linkage can also be established with socioeconomic and demographic data from Statistics Norway (www.ssb.no).

Several other MoBa sub-studies intersect with the ABC. At present, these include sub-studies of attention deficit/hyperactivity disorder (AD/HD), language delay, preterm birth, *de novo* mutations and epigenetic events, and one-carbon metabolism and related single-nucleotide polymorphisms. All data emerging from MoBa sub-studies are collected into the central MoBa database to enable recognition of common themes and outcomes.

Attrition and characteristics of participants

Subject attrition is a substantial concern in longitudinal studies. The participation rate of invited mothers in MoBa is about 40%. Fathers are invited only if the mother participates. Father participation rate is approximately 83%. Among participants, response rates are about 95% for the early questionnaires, and then decline. The 36-month questionnaire, which is the basis for the autism screening, has a 61% response rate. Approximately 50% of potential cases and controls invited to the ABC clinical assessments accept the invitation.

Comparisons of the MoBa cohort to the general Norwegian population indicate that the participants on average have a higher socio-economic status, with a higher proportion of parents having completed higher education, a lower proportion of single mothers and a lower proportion of smoking mothers compared to the population at large.²³ Similar selection biases are found when responders to the 36-month questionnaire are compared to non-responders.

Advantages of MoBa and the ABC

The MoBa includes more than 100 000 children and their parents, and is the only comprehensive population-based prospective cohort with the data required to investigate gene-environment-timing and follow the trajectories of neurodevelopmental disorders such as ASD. Information and samples are collected from all children and both of their parents prior to, and independent of, diagnosis and severity of disease. Biological samples are optimized for genetic, transcriptomic, proteomic, microbiological and toxicological analyses. Thus, a wide range of exposures and outcomes can be studied in the cohort as a whole and in each participant. Sib-ships and twins, represent an added value to studies of the contributions of genes and gene-environment interactions in disease development. Linkage of the cohort to nationwide health registries enables extensive longitudinal follow-up of the cohort at low costs.

As with any longitudinal population-based cohort, challenges include retaining participants, and the continuous investment required to establish and maintain the program until results can be achieved. However, the ABC has advantages that enhance the probability of success. Emigration is less common in Norway than in some other industrialized nations. Socialized medicine and national registries facilitate follow up and case capture. Lastly, there is national recognition of the cohort as an important contribution to science and public health.

We view the ABC as an international scientific resource. We welcome input into models and platforms that can be used to extract information from data and sample sets. Please post comments and inquiries to Columbia University (abc@columbia.edu) or NIPH (abc.coordinator@fhi.no).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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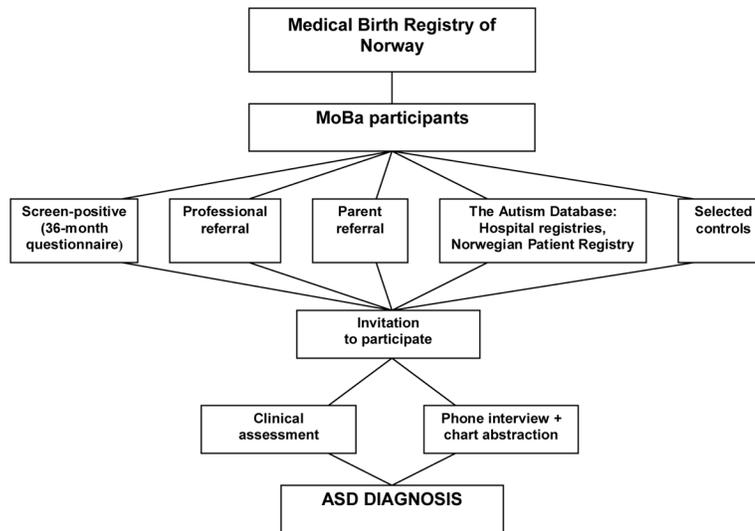


Figure 1. Strategy for identifying children with autism spectrum disorder (ASD) in the Autism Birth Cohort (ABC). The ABC is nested within the Norwegian Mother and Child Cohort Study (MoBa)

Table 1

The Autism Birth Cohort (ABC) Study: Screening criteria at age 36 months

Screening criteria based on the Social Communication Questionnaire (SCQ) and other selected items in the MoBa ¹ questionnaire at 36 months ²	
1	SCQ-33 score ≥ 12
2	Repetitive behavior sub-domain score on SCQ-33 = 9
3	Parent reports language delay AND child has been referred to a specialist for it
4	Parent reports autism/autistic trait AND/OR reports that child has been referred to a specialist for it
5	Parent reports worry that child shows little interest in playing with other children
6	Parent reports that others (family, day-care staff, well-baby nurse) have expressed concern for the child's development

Children are defined as screen-positive when:	
	Meeting one or more of criteria 1, 2, 3 or 5 AND meeting criterion 6
	Meeting criterion 4

Note: All 40 SCQ items are included in the 36-month questionnaire, but only those 33 items that do not require language to be present (SCQ-33) are scored.

¹ MoBa10: The Norwegian Mother and Child Cohort Study (MoBa)

² Screening was implemented for MoBa children born on or after 1 Feb 2002; thus, the oldest 6 500 MoBa participants were not screened for ASD.

Table 2

Clinical assessments in the Autism Birth Cohort (ABC) Study

Clinical exam components	
	ADOS (video-taped) ¹
	Psychometric testing (video-taped): Stanford-Binet Intelligence Scales 5 th edition ² , Mullen Scales of Early Learning ³
	Physical examination (video-taped)
	Anthropometric measurements, photo

Maternal/parental interview	
	ADI-R (video-/audio-taped) ⁴
	PAPA (video-/audio-taped) ⁵
	Vineland Adaptive Behavior Scales ⁶ (video-/audio-taped)
	Child and family psychiatric and medical history

ABC-specific biological samples	
	At the clinical assessment, a new blood sample (plasma, full blood, DNA, RNA) is collected from the child
	If blood from mother and/or father is lacking in the MoBa biobank, blood is also collected from the parent(s)

only.

¹ **ADOS18**: Autism Diagnostic Observation Schedule.

² **Stanford-Binet24**: From 2005 through 2008: Full version. From 2009 onwards: Shortened version, 5 out of 10 subscales.

³ **Mullen25**: From 2005 through 2008: Fine motor and gross motor subscales for all. Full version of Mullen if child too low-functioning for SB5. From 2009 onwards: Selected items only from gross motor subscale, otherwise unchanged.

⁴ **ADI-R17**: Autism Diagnostic Interview - Revised.

⁵ **PAPA26**: Preschool Age Psychiatric Assessment: Used on 500 children, 2005 through 2008. Omitted from 2009 onwards.

⁶ **Vineland27**: From 2005 through 2008: Full version. From 2009 onwards: Communication sub-domain