

THE AUTISM BIRTH COHORT STUDY

STUDY PROTOCOL SEPTEMBER 2018

1. Scientific aims

The Autism Birth Cohort (ABC) Study is a case-cohort study of autism spectrum disorder (ASD) nested within the Norwegian Mother and Child Cohort Study (MoBa).^{1,2} Investigations are based on MoBa questionnaire data and data collected specifically for the ABC Study. The scientific aims of the study are to:

- (1) Identify and characterize cases of ASD in MoBa.
- (2) Identify prenatal and perinatal risk factors for ASD, such as parental health and lifestyle, socio-economic characteristics, maternal diet during pregnancy, maternal medication use during pregnancy and complications of pregnancy and childbirth.
- (3) Describe the natural history of ASD, such as sex differences, autism symptom trajectories, other psychiatric symptoms, growth, language development, motor development, cognitive functioning and co-morbid medical and psychiatric disorders.
- (4) Describe health service use for children and young people with ASD, such as type and frequency of health service use, assigned diagnoses, medication use, treatment and interventions.
- (5) Describe service use and social outcomes for children and young people with ASD, such as daycare use, school participation, type of school, school results, respite care, assisted living, living status, work and benefits.

This study protocol describes the data collection of the ABC Study. The scientific aims relate to the research activity based on the ABC Study at the Norwegian Institute of Public Health (NIPH). Separate study protocols and ethics approvals are required for projects that share ABC-specific data with other institutions and projects that use ABC-specific data in combination with biological materials from MoBa.

2. Study organization

The ABC Study was initiated in 2003 in collaboration between NIPH and the Mailman School of Public Health at Columbia University in New York, NY, USA. Funding for data collection was obtained from the National Institute of Neurological Disorders and Stroke (NINDS) in the U.S. (grant no. NIH/NINDS U01 NS47537). The NINDS grant also provided funding to establish and maintain MoBa. The NINDS grant expired in 2016. The data collection of the ABC Study is now funded and managed by the Department of Child Health and Development at NIPH. The researcher responsible for the ethics approval is Pål Surén, pal.suren@fhi.no.

3. Ethics and regulatory approvals

MoBa has a license from the Norwegian Data Inspectorate. The ABC Study has approval from the Regional Committee of Medical and Health Research Ethics for South-East Norway. Participation in MoBa is based on written informed consent. The MoBa consent includes permission to perform linkages to health registries and collect data from medical records. The clinical assessments conducted by the ABC Study were based on a separate written informed consent.

4. Questionnaire-based screening

From 2005 to 2012, the ABC Study identified ASD cases through screening and clinical assessments of MoBa participants. The screening was based on the Social Communication Questionnaire, which was included in the MoBa 36-month questionnaire.³ Screen-positive children were invited to participate in a clinical assessment to determine whether they had ASD. A group of randomly selected controls was invited as a comparison group. Referrals

from parents and health professionals were accepted if the child was a MoBa participant and there was reason to suspect autism. Referrals were elicited through newsletters to MoBa participants and information on the NIPH website. If any invited child had a twin, the twin was also invited.

From 2009, MoBa participants with ASD diagnoses recorded in the Norwegian Patient Registry (NPR) were invited. From that year, children were also invited if the parents had reported that the child had autism or Asperger's syndrome in the MoBa questionnaires at ages 5 and 7 years. Screening and invitation procedures are described in detail in the 2010 study protocol (appendix 1).

5. Clinical assessments

Clinical assessments were conducted by Nic Waals Institute at Lovisenberg Hospital in Oslo. Before the clinical assessment, questionnaires were completed by the child's parents and daycare teacher (one for the parents and one for the teacher). The questionnaires included the following instruments:

Pre-assessment questionnaire for children aged 3-5 years:

- The Child Development Inventory (CDI)⁴
- The Early Childhood Inventory – Version 4 (ECI-4)^{5,6}
- The Behavior Rating of Executive Function – Preschool Version (BRIEF-P)⁷
- The Child Behavior Questionnaire (CBQ)^{8,9}
- The Preschool Play Behavior Scale (PPBS) (teachers only)¹⁰

Pre-assessment questionnaire for children aged 6 years and older:

- The Child Development Inventory (CDI)⁴
- The Child Symptom Inventory – Version 4 (CSI-4)¹¹
- The Behavior Rating of Executive Function (BRIEF)¹²
- The Child Behavior Questionnaire (CBQ)^{8,9}

The clinical assessment took one full day. At the end of the day, the clinician made a diagnostic conclusion and conveyed this to the parents.

Contents of the clinical assessment:

- The Autism Diagnostic Interview – Revised (ADI-R)¹³
- The Autism Diagnostic Observation Schedule (ADOS)¹⁴
- Children aged 3-5 years: The Stanford-Binet Intelligence Scales, 5th Edition (SB5)¹⁵
- Children aged 6 years and older: The Wechsler Abbreviated Scale of Intelligence (WASI)¹⁶
- Children who were too low-functioning for the SB5: The Mullen Scales of Early Learning (MSEL)¹⁷
- Vineland Adaptive Behavior Scales (VABS), communication domain¹⁸
- Gross motor and fine motor items from the MSEL¹⁷
- Physician history-taking and physical examination
- Anthropometric measures and photographic recordings
- Blood sampling
- Staff conference and diagnostic conclusion
- Feedback to the parents

The contents of the clinical assessments, and the procedures for training, quality control and data management are described in detail in the 2010 study protocol (appendix 1).

6. Diagnostic conclusions

The diagnostic conclusion was a best-estimate diagnosis based on all the available information. Diagnoses were assigned according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR).¹⁹

A total of 1032 children participated in the clinical assessments:

- 450 screen-positives
- 89 referrals
- 24 twins
- 368 controls
- 61 detected through NPR linkages
- 40 detected through the 5- and 7-year questionnaires

The diagnostic conclusions were distributed as follows:

- 195 had ASD
- 59 had autistic features, but insufficient to meet diagnostic criteria for ASD
- 330 had other developmental or psychiatric disorders
- 448 had no diagnosis

7. Record linkages and reviews of medical records

Since 2009, the ABC Study has conducted annual linkages between MoBa and the NPR to identify MoBa participants with ASD diagnoses. The NPR collects activity data from Norwegian specialist health services, beginning in 2008. Specialist health services include government-funded hospitals and outpatient clinics, and private practitioners receiving reimbursements from the government.

In 2015-2016, the ABC Study conducted reviews of medical records for children who had ASD diagnoses recorded in the NPR, but who had not previously been diagnosed with ASD by the ABC Study. The record reviews were based on NPR data from 2008 to 2014. The data set included 567 children who had not previously been diagnosed with ASD by the ABC Study. Of these, 477 (84%) had their ASD diagnoses confirmed.

Contents of the record review protocol:

- General information about the child and the clinic
- Referral and assessment information
- Test results from standardized instruments
- Diagnoses recorded in the multiaxial ICD-10 coding system
- Additional ICD-10 diagnoses recorded
- Review of ICD-10²⁰ and DSM-IV-TR¹⁹ criteria for ASD
- Reviewer's diagnostic conclusion based on DSM-IV-TR criteria

The record review protocol is included as appendix 2 (Norwegian version) and 3 (English version). The ABC Study will continue the annual linkages to the NPR and perform record reviews at regular intervals.

8. The ABC-specific data files

The ABC-specific data files include:

- Data from the ABC Study's clinical assessments
- NPR data for children diagnosed with ASD by specialist health services
- Data from the ABC Study's medical record reviews

The ABC Study's investigators have written an SPSS syntax for combining data from the different sources into common variables for ASD diagnoses. The document also shows how to derive variables for intellectual disability and language delay, which are the two most important specifiers for ASD diagnoses. The syntax document is included as appendix 4.

9. Protocol appendix

- (1) ABC Study Protocol, July 2010
- (2) ABC record review protocol, Norwegian version
- (3) ABC record review protocol, English version
- (4) ABC diagnostic syntax, September 2018

References

1. Stoltenberg C, Schjolberg S, Bresnahan M, et al. The Autism Birth Cohort: a paradigm for gene-environment-timing research. *Mol Psychiatry*. 2010;15(7):676-680.
2. Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2016;45(2):382-388.
3. Berument SK, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. *Br J Psychiatry*. 1999;175:444-451.
4. Ireton H. Child Development Inventory. Minneapolis, MN, USA: Behavior Science Systems Inc.; 1992.
5. Gadow KD, Sprafkin J. Early Childhood Inventory 4. Norms manual. Stony Brook, NY, USA: Checkmate Plus Ltd.; 1997.
6. Gadow KD, Sprafkin J. Early Childhood Inventory 4. Screening manual. Stony Brook, NY, USA: Checkmate Plus Ltd.; 2000.
7. Gioia GA, Espy KA, Isquith PK. Behavior Rating of Executive Function - Preschool Version. Lutz, FL, USA: Psychological Assessment Resources Inc.; 2003.
8. Rothbart MK, Ahadi SA, Hershey KL, Fisher P. Investigations of temperament at three to seven years: the Children's Behavior Questionnaire. *Child Dev*. 2001;72(5):1394-1408.
9. Putnam SP, Rothbart MK. Development of short and very short forms of the Children's Behavior Questionnaire. *J Pers Assess*. 2006;87(1):102-112.
10. Coplan RJ, Rubin KH. Exploring and assessing nonsocial play the preschool: the development and validation of the Preschool Play Behavior Scale. *Social Development*. 1998;7(1):72-91.
11. Gadow KD, Sprafkin J. Child Symptom Inventory 4. Screening norms and manual. Stony Brook, NY, USA: Checkmate Plus Ltd.; 2002.
12. Gioia GA, Espy KA, Isquith PK. Behavior Rating of Executive Function - Professional Manual. Lutz, FL, USA: Psychological Assessment Resources Inc.; 2000.
13. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24(5):659-685.
14. Lord C, Risi S, Lambrecht L, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord*. 2000;30(3):205-223.
15. Roid GH. Stanford-Binet Intelligence Scales, 5th Edition. Itasca, IL, USA: Riverside Publishing; 2003.
16. Wechsler Abbreviated Scale of Intelligence. Toronto, Canada: PsychCorp (Harcourt Assessment/Pearson Assessment); 1999.
17. Mullen EM. Mullen Scales of Early Learning, AGS Edition. Circle Pines, MN, USA 1995.
18. Sparrow SS, Cicchetti DV, Balla DA. Vineland Adaptive Behavior Scales. Livonia, MI, USA: Pearson Assessments; 2005.
19. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Arlington, VA, USA: American Psychiatric Association; 2000.
20. The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. Geneva, Switzerland: World Health Organization; 1993.