BMJ Open

Cohort profile: cerebral palsy in the Norwegian and Danish birth cohorts (MOBAND-CP)

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ABSTRACT

Purpose: The purpose of *MO*thers and *BA*bies in *N*orway and *D*enmark cerebral palsy (MOBAND-CP) was to study CP aetiology in a prospective design.

Participants: MOBAND-CP is a cohort of more than 210 000 children, created as a collaboration between the world's two largest pregnancy cohorts—the Norwegian Mother and Child Cohort study (MoBa) and the Danish National Birth Cohort. MOBAND-CP includes maternal interview/questionnaire data collected during pregnancy and follow-up, plus linked information from national health registries.

Findings to date: Initial harmonisation of data from the 2 cohorts has created 140 variables for children and their mothers. In the MOBAND-CP cohort, 438 children with CP have been identified through record linkage with validated national registries, providing by far the largest such sample with prospectively collected detailed pregnancy data. Several studies investigating various hypotheses regarding CP aetiology are currently on-going.

Future plans: Additional data can be harmonised as necessary to meet requirements of new projects. Biological specimens collected during pregnancy and at delivery are potentially available for assay, as are results from assays conducted on these specimens for other projects. The study size allows consideration of CP subtypes, which is rare in aetiological studies of CP. In addition, MOBAND-CP provides a platform within the context of a merged birth cohort of exceptional size that could, after appropriate permissions have been sought, be used for cohort and case-cohort studies of other relatively rare health conditions of infants and children.

Strengths and limitations of this study

- The *MO*thers and *BA*bies in *N*orway and *D*enmark cerebral palsy cohort has data collected prospectively and repeatedly during pregnancy for more than 200 000 children, minimising recall bias.
- Children with cerebral palsy were identified through record linkage with validated national health registries.
- Participating mothers were older and more socioeconomically privileged than the general population, and data were collected mainly by telephone interview in Denmark and questionnaires in Norway, which may influence the results.

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INTRODUCTION

During the 1990s, researchers from Denmark and Norway collaborated in the planning of two large pregnancy cohort studies: the Danish National Birth cohort (DNBC)[1] and the Norwegian Mother and Child Cohort Study (MoBa).[2 3] Each cohort aimed to enrol 100 000 pregnancies using similar methods. The Danish cohort completed its enrolment in 2002 and the Norwegian cohort completed its enrolment in 2009. Both national birth cohorts include information on a range of exposures during pregnancy collected via maternal interviews/ questionnaires and biological samples, for example, information on maternal nutrition, medications and medical conditions during pregnancy and delivery. Except for within a few larger European cross-cohort collaborations,[4 5] and for nutrition data,[6] few efforts have been made to use the data combined.

In 2010, the US National Institute of Environmental Health Sciences (NIEHS) partnered with the DNBC and the Norwegian Institute of Public Health to form a collaborative project called MOBAND (for *MO*thers and *BA*bies in *N*orway and *D*enmark). The cerebral palsy (CP) study, described here as MOBAND-CP, includes a Steering Committee, a Scientific Advisory Board of CP experts and a network of collaborating investigators addressing specific aspects of CP. The purpose was to create from the two Scandinavian cohorts a single platform that could extend the possibilities

for studying prenatal risk factors associated with rare diseases in infants and children, specifically CP.

CP originates from non-progressive damage to the immature brain and is the most common cause of physical disability in children, affecting ~2 in 1000 live births.[7] It comprises several more-or-less distinct subtypes with a wide spectrum of severity of motor disability and is often accompanied by visual impairment, intellectual deficit or epilepsy.[8 9] Preterm delivery is one of the strongest risk factors identified, but also atypical intra-uterine growth, congenital malformations, placental pathology, intrauterine infection, multiple fetuses and perinatal stroke are recognised as risk factors in pregnancy and the perinatal period.[10–12] CP runs in families,[13] but current understanding of underlying genetics is limited. However, ongoing investigations making the use of techniques like high-throughput whole-genome sequencing may soon improve our understanding of the underlying heterogeneous and complex risk genetic factors for CP.[14 15]

Most previous studies of CP aetiology have had low statistical power or have been hampered by retrospective collection of pregnancy exposure data. The two combined pregnancy cohorts provide an excellent opportunity for the study of CP. While the origins of CP are thought to lie in fetal life, the condition is too rare to be studied in moderate-sized pregnancy cohorts. Meanwhile, conventional case–control studies of CP are limited by the fact that CP diagnosis is typically not final before the age of 4 years, at which time it can be

difficult to reconstruct the conditions and exposures of pregnancy. The combination of the Norwegian and Danish pregnancy cohorts addresses both of these study limitations by allowing case-cohort analyses within a cohort of unusual size.

COHORT DESCRIPTION
Participants and data collection in Denmark
In Denmark, 91 385 women were recruited to the DNBC at their first antenatal visit (around week 6–10 of pregnancy). Some women contributed more than one pregnancy, for a total of 100 417 pregnancies and 96 836 live-born children delivered during 1996–2003.[16] Pregnant women in the DNBC filled in a brief recruitment questionnaire at the time of enrolment, participated in a telephone interview approximately week 16, completed a food frequency questionnaire in week 25 and were interviewed again around week 31 and at about 6 and 18 months postpartum (table 1).

Maternal blood samples were collected in the first trimester and at midpregnancy, and cord blood was collected at delivery. Additional waves of postdelivery data collection have not yet been incorporated into the harmonised data.

Participants and data collection in Norway
In Norway, 95 093 women were recruited to MoBa at the time they received their invitation to a routine ultrasound examination (around week 13–17 of pregnancy).

Table 1 Cohorts and data used in the MOBAND-CP collaboration

	Denmark	Norway
Birth cohort	DNBC	MoBa
Recruitment		
Years	1995–2002	1999–2008
Time in pregnancy	Week 6–10	Week 13–17
Participating women (n)	91 385	95 093
Recruited pregnancies (n)	100 417	112 509
Pregnancies resulting in live birth (n)	94 747	111 618
Live births (singletons and multiples)	96 836	113 564
Stillbirths	329	281
Data used (from pregnancies resulting in live birth)		
1st questionnaire (approximately week 17)		101 181
1st interview (approximately week 16)	88 750	
3rd questionnaire (approximately week 30)		93 844
2nd interview (approximately week 31)	86 155	
Questionnaire 6 months postpartum		88 106
Interview 6 months postpartum	70 281	
Interview 18 months postpartum	66 705	
Verified CP cases (per 1000 live births)	191 (2.0)	247 (2.2)
Spastic unilateral (per 100 CP cases)	71 (37)	98 (40)
Spastic bilateral (per 100 CP cases)	97 (51)	107 (43)
Dyskinetic (per 100 CP cases)	17 (9)	21 (9)
Ataxic (per 100 CP cases)	3 (2)	14 (6)
Not classified (per 100 CP cases)	3 (2)	7 (3)

CP, cerebral palsy; DNBC, Danish National Birth Cohort; MoBa, Norwegian Mother and Child Cohort Study.

As in Denmark, MoBa many women contributed more than one pregnancy. In the data files used for the MOBAND-CP harmonisation, there were a total of 112 509 pregnancies and 113 564 live births during 1999–2009. Pregnant women in MoBa were invited to fill in a pregnancy questionnaire around week 13–17, a food frequency questionnaire around week 22 and a second pregnancy questionnaire around week 30. Additional questionnaires were distributed when children were 6 and 18 months old. Maternal blood and urine samples were collected at enrolment, plus cord blood and (eventually) deciduous teeth from the children. As with the Denmark cohort, further waves of Norwegian data collection are not yet included in the harmonised data.

Attrition

Approximately 60% of the Danish women invited to participate in DNBC agreed to participate.[17] Of the 94 747 enrolled pregnancies that resulted in a live birth, 94% of the mothers participated in the first pregnancy interview, 91% in the second pregnancy interview, 74% in the 6-month-postpartum interview and 70% in the 18-month-postpartum interview.

In Norway, 41% of invited women agreed to participate in MoBa.[18] Of the 111 618 pregnancies that resulted in a live birth, 91% of the mothers completed the first pregnancy questionnaire, 84% the third pregnancy questionnaire and 79% completed the 6-month-postpartum questionnaire (table 1).

Data harmonisation

The first task of the MOBAND-CP collaboration was to harmonise epidemiological variables from the two cohorts. A list of prioritised variables for CP research was created and refined through circulation among the collaborators. Initial harmonisation efforts have focused on variables considered essential for epidemiological research, in general, and for CP research, in particular. These include maternal and paternal characteristics, exposures during pregnancy, maternal medical conditions during pregnancy, delivery, birth characteristics and newborn conditions (see online supplementary table).

Data collections in the two cohorts were similar but by no means identical. A plan for harmonising each variable was developed through discussions and revisions involving Danish and Norwegian collaborators. The success of each harmonisation was judged as 'complete', 'partial' or 'impossible'. Once agreement on harmonisation was reached, code was written in Stata (V.12.1; Stata Corporation, College Station, Texas, USA). Code and documentation for each variable, including minutes from all meetings, have been posted on a secure DokuWiki website, accessible by username and password.

By 2016, data had been harmonised for 140 variables. Guidelines have been created for further harmonisation

of data, with the expectation that future investigators may contribute additional harmonised variables. Data (including the raw data underlying the harmonised variables) will be accessible through a secure server at the National Institute of Public Health, Norway and the central data server for the DNBC.

Linkage to national registries and identification of children with CP

Unique national identification numbers in both countries allowed cohort participants to be linked to additional data in the medical birth registries of the two countries,[19 20] as well as in the Danish National Patient Register,[21] the Norwegian Patient Register[22] and the Danish IVF Register.[23]

Children with CP in Denmark (191 in total) have been identified through record linkage with the Cerebral Palsy Registry of Denmark.[24] In Norway, 247 children with CP have been identified, nearly 90% through record linkage with the Cerebral Palsy Registry of Norway.[25] The remainder have come through record linkage with the Norwegian Patient Registry,[22] validated through medical record review by two paediatric neurologists.[26]

FINDINGS TO DATE

Data had been harmonised for 140 variables, and 438 children with CP identified through record linkage with national registries. Collaborating investigators have developed protocols for the analysis of exposures plausibly linked to the risk of CP. Results from these analyses will inform future studies that make use of biological specimens collected during pregnancy. The first papers from the MOBAND-CP project (now in preparation) explore specific hypotheses on maternal alcohol and caffeine consumption, pre-pregnancy body mass index, thyroid disorders and use of over-the-counter pain medication in relation to risk of CP.

STRENGTHS AND LIMITATIONS

Strengths of the study include prospectively collected exposure data, an exceptionally large sample size and the opportunity to follow all participants through linkages to national health registries. Denmark and Norway are similar in many respects, sharing culture, history, political systems and high standards of living and education levels. These cultural similarities support the practicality of harmonising variables across the two studies.

At the same time, there are important differences between the two studies and between the two countries. Data were collected primarily by telephone interview in Denmark and by questionnaire in Norway. How this may affect the harmonised data is difficult to evaluate. Also, varying differences between the two cohorts in the format of questions (or between the substance of the questions themselves) leads to loss of information in the harmonisation process. Nonetheless, harmonisation

for 42 of the 143 variables in our initial round were scored as 'complete' and 98 were scored as 'partial' with only three regarded as 'impossible'. Variables were considered impossible to harmonise if information was missing from one of the cohorts or format or content was considered too different to generate a meaningful common ground. All these judgments are of course subjective, and open to other interpretation by future investigators.

As usual in pregnancy cohort studies, participants are older and more socioeconomically privileged than the general population.[2 17] Self-selection affects the prevalence of exposures and outcomes, but estimates of known exposure-outcome associations in the DNBC and MoBa generally appear to be unbiased.[27 28] Norway and Denmark have fairly large immigrant populations, but few immigrants participated in either cohort study. The study is also limited by the data collected; for instance, information on placentas is limited to weight, and imaging data to what is recorded in the CP registries.

With regard to the current study of CP, the 438 cases provide by far the largest sample of children with CP with prospectively collected detailed pregnancy data. This study of more than 200 000 mother–child pairs permits the detection of a relative risk of 1.5 for CP for an exposure with a prevalence of 10%, assuming conventional levels for statistical significance (80% power and 5% α level).[29] The validation of the CP cases in the national registries using medical records is a definite strength. Furthermore, the large study size allows consideration of CP subtypes, which is rare in aetiological studies of CP.

COLLABORATION

The purpose and permissions of MOBAND-CP are to foster studies on CP. Investigators with an interest in hypotheses related to CP (and that meet the requirements of current approvals) are welcome to contact a member of the Steering Committee (Allen Wilcox, Camilla Stoltenberg or Anne-Marie Nybo Andersen). We anticipate future opportunities for the study of other infant and childhood outcomes based on the harmonisation efforts made for MOBAND-CP. Such studies would require regular application for data access from both cohorts (see more information on the individual cohorts' websites[30 31]), after which an application to the MOBAND steering committee to access the MOBAND DokuWiki website, with codes for data harmonisation and documentation, would be considered. The application should include a brief description of the project, which must include involvement of collaborators from Norway and Denmark.

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