Cohort profile: Cerebral Palsy in the Norwegian and Danish birth cohorts: MOBAND-CP

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<td>Tollånes, Mette; University of Bergen, Department of Global Public Health and Primary Care; Nasjonalt folkehelseinstitutt, Domain for Health Data and Digitalization Strandberg-Larsen, Katrine; University of Copenhagen, Department of Public Health Forthun, Ingeborg; University of Bergen, Department of Global Public Health and Primary Care; Nasjonalt folkehelseinstitutt, Domain for Health Data and Digitalization Knudsen, Tanja Majbrit; University of Copenhagen, Department of Public Health Moster, Dag; University of Bergen, Department of Global Public Health and Primary Care; Haukeland Universitetssjukehus, Department of Pediatrics Andersen, Anne-Marie; University of Copenhagen, Institute of Public Health Stoltenberg, Camilla; Nasjonalt folkehelseinstitutt, Director General; University of Bergen, Department of Global Public Health and Primary Care Olsen, Jørn; Aarhus University, Section for Epidemiology, Department of Public Health Wilcox, Allen; National Institute of Environmental Health Sciences</td>
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Cohort profile: Cerebral Palsy in the Norwegian and Danish birth cohorts: MOBAND-CP

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Keywords: cerebral palsy, rare disease, prospective study, Danish National Birth Cohort, Norwegian Mother and Child cohort study

Word count: 2201
ABSTRACT

Purpose

To study cerebral palsy 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 (DNBC). MOBAND-CP includes maternal interview/questionnaire data collected during pregnancy and follow-up, plus linked information from national health registries.

Findings to date

Initial harmonization of data from the two cohorts has created 140 variables for children and their mothers. In the MOBAND-CP cohort, 438 children with cerebral palsy 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 cerebral palsy aetiology are currently on-going.

Future plans

Additional data can be harmonized 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 cerebral palsy subtypes, an innovation in aetiological studies of cerebral palsy. 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 MOBAND-CP cohort has data collected prospectively and repeatedly during pregnancy for more than 200,000 children, minimizing recall bias.
- Children with CP 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.
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) and the Norwegian Mother and Child Cohort study (MoBa). Each cohort aimed to enrol 100,000 pregnancies using similar methods. The Danish cohort completed its enrolment in 2002, and the Norwegian cohort in 2009. Both national birth cohorts include information on a range of exposures during pregnancy collected via both maternal interviews/questionnaires and biological samples, e.g. information on maternal nutrition, medications, and medical conditions during pregnancy and delivery. Except for within a few larger European cross-cohort collaborations, and for nutrition data, few efforts have been made to use the data combined.

In 2010, the US National Institute of Environmental Health Sciences (NIEHS) partnered with the Danish National Birth Cohort and the Norwegian Institute of Public Health to form a collaborative project called MOBAND (for Mothers and Babies in Norway and Denmark). The cerebral palsy study, described here as MOBAND-CP, includes a Steering Committee, a Scientific Advisory Board of cerebral palsy experts, and a network of collaborating investigators addressing specific aspects of cerebral palsy. 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 cerebral palsy.

Cerebral palsy is the most common cause of physical disability in children, and comprises several more-or-less distinct subtypes having a wide spectrum of severity of motor disability. Motor disability is often accompanied by visual impairment, intellectual deficit, or epilepsy. Cerebral palsy originates from damage to the immature brain, the causes of which remain largely unknown, and there is no cure. Although cerebral palsy is by definition not a progressive disorder, problems secondary to cerebral palsy can become more severe with age. Birth injury and birth hypoxia were once regarded as primary causes,
but more careful studies suggest that birth complications may instead represent an early manifestation
of the cerebral palsy syndrome.\cite{7,8,9} Most previous studies of cerebral palsy 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 cerebral palsy.
While the origins of cerebral palsy are thought to lie in foetal life, the condition is too rare (2/1000 live
births\cite{10}) to be studied in moderate-sized pregnancy cohorts. Meanwhile, conventional case-control
studies of cerebral palsy are limited by the fact that cerebral palsy diagnosis is typically not final before
the age of four 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 and 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.\cite{11} 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 post-partum (Table).
Table. Cohorts and data used in the MOBAND-CP collaboration

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Denmark (DNBC)</th>
<th>Norway (MoBa)</th>
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<tbody>
<tr>
<td>Recruitment</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Years</strong></td>
<td>1995-2002</td>
<td>1999-2008</td>
</tr>
<tr>
<td><strong>Time in pregnancy</strong></td>
<td>Week 6-10</td>
<td>Week 13-17</td>
</tr>
<tr>
<td><strong>Participating women (n)</strong></td>
<td>91,385</td>
<td>95,093</td>
</tr>
<tr>
<td><strong>Recruited pregnancies (n)</strong></td>
<td>100,417</td>
<td>112,509</td>
</tr>
<tr>
<td><strong>Pregnancies resulting in live birth (n)</strong></td>
<td>94,747</td>
<td>111,618</td>
</tr>
<tr>
<td><strong>Live births (singletons and multiples)</strong></td>
<td>96,836</td>
<td>113,564</td>
</tr>
<tr>
<td><strong>Data used (from pregnancies resulting in live birth)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st questionnaire (approx. week 17)</td>
<td></td>
<td>101,181</td>
</tr>
<tr>
<td>1st interview (approx. week 16)</td>
<td>88,750</td>
<td></td>
</tr>
<tr>
<td>3rd questionnaire (approx. week 30)</td>
<td></td>
<td>93,844</td>
</tr>
<tr>
<td>2nd interview (approx. week 31)</td>
<td>86,155</td>
<td></td>
</tr>
<tr>
<td>Questionnaire six months post-partum</td>
<td></td>
<td>88,106</td>
</tr>
<tr>
<td>Interview six months post-partum</td>
<td>70,281</td>
<td></td>
</tr>
<tr>
<td>Interview 18 months post-partum</td>
<td>66,705</td>
<td></td>
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<tr>
<td><strong>Verified CP cases (per 1000 live births)</strong></td>
<td>191 (2.0)</td>
<td>247 (2.2)</td>
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DNBC, Danish National Birth Cohort; MoBa, Norwegian Mother and Child Cohort Study

Maternal blood samples were collected in the first trimester and at mid-pregnancy, and cord blood was collected at delivery. Additional waves of post-delivery data collection have not yet been incorporated into the harmonized data.

**Participants and data collection and 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). As in Denmark, MoBa many women contributed more than one pregnancy. In the data files used for the MOBAND-CP harmonization, 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 six 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 harmonized data.

Attrition

Approximately 60% of the Danish women invited to participate in DNBC agreed to participate. Of the 94,747 enrolled pregnancies that resulted in a live birth, 94% provided the first pregnancy interview, 91% the second pregnancy interview, 74% the six-month-post-partum interview, and 70% the 18-month-post-partum interview.

In Norway, 41% of invited women agreed to participate in MoBa. Of the 111,618 live births in MoBa, 91% completed the first pregnancy questionnaire, 84% provided data in the third pregnancy questionnaire and 79% completed the six-month-post-partum questionnaire (Table).

Data harmonization

The first task of the MOBAND-CP collaboration was to harmonize epidemiologic variables from the two cohorts. A list of prioritized variables for cerebral palsy research was created and refined through circulation among the collaborators. Initial harmonization efforts have focused on variables considered essential for epidemiologic research in general and for cerebral palsy research in particular. These include maternal characteristics (age, previous pregnancy history, body mass index (BMI), socioeconomic indicators, etc.), paternal characteristics (age, BMI), exposures during pregnancy...
(assisted reproductive technology, smoking, alcohol, caffeine, drug use, vitamins, etc.), maternal
conditions during pregnancy, delivery (presentation, complications), birth characteristics (plurality,
gestational age, birth weight), and newborn conditions (see Appendix for complete list).

Data collections in the two cohorts were similar but by no means identical. A plan for harmonizing each
variable was developed through discussions and revisions involving both Danish and Norwegian
collaborators. The success of each harmonization was judged as “complete,” “partial,” or “impossible.”
Once agreement on harmonization was reached, code was written in Stata (v.12.1; Stata Corporation,
College Station, Texas). 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 harmonized for 140 variables. Guidelines have been created for further
harmonization of data, with the expectation that future investigators may contribute additional
harmonized variables. Data (including the raw data underlying the harmonized variables) will be
accessible through a secure server at the National Institute of Public Health, Norway and the central
data server for the Danish National Birth Cohort.

Linkage to national registries and identification of children with cerebral palsy

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,14,15 as well as in the Danish National
Patient Register,16 the Norwegian Patient Register17 and the Danish IVF Register.18

Children with cerebral palsy in Denmark (191 in total) have been identified through record linkage with
the Cerebral Palsy Registry of Denmark.19 In Norway, 247 children with cerebral palsy have been
identified, nearly 90% through record linkage with the Cerebral Palsy Registry of Norway.20 The
remainder have come through record linkage with the Norwegian Patient Registry, validated through medical record review by two paediatric neurologists.

**FINDINGS TO DATE**

Data had been harmonized for 140 variables, and 438 children with cerebral palsy identified through record linkage with national registries. Collaborating investigators have developed protocols for the analysis of exposures plausibly linked to the risk of cerebral palsy. 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 consumption, body mass index, and mothers' consumption of caffeinated beverages during pregnancy as they may relate to risk of cerebral palsy. For example, caffeine treatment in preterm infants (to avoid apnoea) has previously been shown in a randomized clinical trial to increase the chance of survival without neurological disability.

**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 harmonizing 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 harmonized 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 harmonization process. Nonetheless, harmonization for 42 of the 143 variables in our initial round were scored as “complete” and 98 were “partial,” with only three regarded as “impossible.” Variables were considered impossible to harmonize 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 usually is the case with pregnancy cohort studies, participants are older and more socioeconomically privileged than the general population. Self-selection affects the prevalence of exposures and outcomes, but estimates of known exposure-outcome associations in both the DNBC and MoBa generally appear to be unbiased. Norway and Denmark have fairly large immigrant populations, but few immigrants participated in either cohort study.

With regard to the current study of cerebral palsy, the 438 cases provide by far the largest sample of children with cerebral palsy 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 cerebral palsy for an exposure with a prevalence of 10%, assuming conventional levels for statistical significance (80% power and 5% alpha level). The validation of the cerebral palsy cases in the national registries using medical records is a definite strength. Furthermore, the large study size allows consideration of cerebral palsy subtypes, an innovation in etiologic studies of cerebral palsy.
COLLABORATION

The purpose and permissions of MOBAND-CP are to foster studies on cerebral palsy. Investigators with an interest in hypotheses related to cerebral palsy (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 harmonized dataset prepared for MOBAND-CP. Such studies would require application for data access from both cohorts (see more information on the individual cohorts’ websites\textsuperscript{26,27}) and the involvement of collaborators from both Norway and Denmark.
Acknowledgements

We are grateful to all parents and children participating in the DNBC and MoBa cohort studies.

MOBAND-CP was initiated in 2011 by Allen Wilcox at the US National Institute of Environmental Health Sciences (NIEHS), and has been established in collaboration with the University of Copenhagen, Aarhus University, the Danish Cerebral Palsy Registry, the Norwegian Institute of Public Health (NIPH), the University of Bergen, and the Cerebral Palsy Registry of Norway. Data harmonization was led by Dag Moster and conducted by Ingeborg Forthun and Mette C. Tolllånes at the University of Bergen, and by Katrine Strandberg-Larsen and Tanja Knudsen at the University of Copenhagen. The MOBAND-CP collaboration has been supported by the Intramural Program of the National Institute for Environmental Health Sciences (NIEHS/NIH), University of Copenhagen, Aarhus University, the University of Bergen and the Norwegian Institute of Public Health.

Contributors

All authors contributed to conception and design of the study. MCT and IF performed the data analyses, and MCT drafted the manuscript. All authors critically revised the manuscript and have approved the final version to be published.

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Competing interests

None declared.
Ethics approval

Written informed consent was obtained from all participating mothers in DNBC and MoBa at time of enrolment. The Norwegian part of the study, including linkage with the National CP registry of Norway and the Norwegian Patient register was further approved by the Regional committee for Medical Research (2012/1738). The DNBC has been approved by the Danish Committee on Biomedical Research Ethics (case no. (KF) 01-471/94), and linkage to the Danish National CP Registry was approved by the Danish Data Protection Agency.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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27. What is the Norwegian Mother and Child cohort study? 
VARIABLES HARMONIZED AS OF MAY 2016

1. Maternal Characteristics
   Maternal age
   Parity (previous pregnancies, deliveries (live- and stillbirths), abortions, extra-uterine pregnancies)
   First time pregnant
   Menstrual cycle (usual length, regularity, etc)
   Pre pregnancy BMI
   Weight gain in pregnancy
   Socio-economic indicators (maternal and paternal occupational status, marital status)
   Planned pregnancy

2. Paternal Characteristics
   Paternal age
   Paternal BMI

3. Maternal Exposures during Pregnancy
   In vitro fertilization/assisted reproductive technology
   Maternal smoking (smoking, number of cigarettes, nicotine and passive smoking)
   Maternal alcohol intake (units per week and episodes of binge drinking)
   Caffeinated beverages
   Illicit drug use
   Folate/folic acid intake
   Multivitamin intake

4. Maternal Conditions during Pregnancy
   Nausea
   Hyperemesis
   Recurrent urinary tract infections
   Autoimmune disease (arthritis, inflammatory bowel)
   Thyroid disorders
   Ovarian cysts
   Epilepsy
   Diabetes, types I, II and gestational
   Thrombosis
   Vaginal bleeding
   Respiratory infection
   Fever
   Preeclampsia/eclampsia/HELLP syndrome
   Chorioamnionitis
   Sepsis
   Prolonged rupture of membranes

5. Delivery
   Presentation
   Mode of delivery
   Abruptio placentae
   Dystocia
   Fever in labor
6. **Birth Outcomes**
   - Birth year
   - Outcome
   - Sex
   - Plurality
   - Birth order (for plural births)
   - Apgar-score
   - Birth weight
   - Gestational age (LMP and “best estimate” ultrasound/LMP)
   - Birth defects

7. **Clinical Conditions of Newborn**
   - Transfer to NICU
   - Neonatal encephalopathy (irritability, depression, seizures)
   - Intracranial bleeding
   - Ventilator treatment, CPAP
   - Icterus
   - Neonatal seizures
   - Perinatal infections

8. **Cerebral Palsy**
   - CP with subtype
   - Degree of motor disability (gross motor function classification scale)
   - Age of CP diagnosis
   - Associated impairments (cognitive, vision, speech/communication, epilepsy)

9. **Questionnaire**
   - Response time

**Variables impossible to harmonize**
   - Birth month
   - Exposures to pesticides, chemicals, etc (work and home)
   - Thrombophilia
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8 National Institutes of Environmental Health Sciences, Durham, North Carolina, USA

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Cerebral palsy originates from non-progressive damage to the immature brain, and is the most common cause of physical disability in children, affecting approximately two in 1000 live births. 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. Preterm delivery is one of the strongest risk factors identified, but also atypical intrauterine growth, congenital malformations, placental pathology, intrauterine infection, multiple foetuses, and perinatal stroke are recognized as risk
factors in pregnancy and the perinatal period. Cerebral palsy runs in families, but current understanding of underlying genetics is limited. However, ongoing investigations making use of techniques like high-throughput whole-genome sequencing, may soon improve our understanding of the underlying heterogeneous and complex risk genetic factors for cerebral palsy.

Most previous studies of cerebral palsy 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 cerebral palsy. While the origins of cerebral palsy are thought to lie in foetal life, the condition is too rare to be studied in moderate-sized pregnancy cohorts.

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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. 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 post-partum (table).
Table. Cohorts and data used in the MOBAND-CP collaboration

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Denmark (DNBC)</th>
<th>Norway (MoBa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>1995-2002</td>
<td>1999-2008</td>
</tr>
<tr>
<td>Time in pregnancy</td>
<td>Week 6-10</td>
<td>Week 13-17</td>
</tr>
<tr>
<td>Participating women (n)</td>
<td>91 385</td>
<td>95 093</td>
</tr>
<tr>
<td>Recruited pregnancies (n)</td>
<td>100 417</td>
<td>112 509</td>
</tr>
<tr>
<td>Pregnancies resulting in live birth (n)</td>
<td>94 747</td>
<td>111 618</td>
</tr>
<tr>
<td>Live births (singleton and multiples)</td>
<td>96 836</td>
<td>113 564</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>329</td>
<td>281</td>
</tr>
</tbody>
</table>

Data used (from pregnancies resulting in live birth)

<table>
<thead>
<tr>
<th></th>
<th>Denmark</th>
<th>Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st questionnaire (approx. week 17)</td>
<td>88 750</td>
<td>101 181</td>
</tr>
<tr>
<td>2nd interview (approx. week 31)</td>
<td>86 155</td>
<td>93 844</td>
</tr>
<tr>
<td>Questionnaire six months post-partum</td>
<td>70 281</td>
<td>88 106</td>
</tr>
<tr>
<td>Interview six months post-partum</td>
<td>66 705</td>
<td></td>
</tr>
<tr>
<td>Verified CP cases (per 1000 live births)</td>
<td>191 (2.0)</td>
<td>247 (2.2)</td>
</tr>
<tr>
<td>Spastic unilateral (per 100 CP cases)</td>
<td>71 (37)</td>
<td>98 (40)</td>
</tr>
<tr>
<td>Spastic bilateral (per 100 CP cases)</td>
<td>97 (51)</td>
<td>107 (43)</td>
</tr>
<tr>
<td>Dyskinetic (per 100 CP cases)</td>
<td>17 (9)</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Ataxic (per 100 CP cases)</td>
<td>3 (2)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Not classified (per 100 CP cases)</td>
<td>3 (2)</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

DNBC, Danish National Birth Cohort; MoBa, Norwegian Mother and Child Cohort Study

Maternal blood samples were collected in the first trimester and at mid-pregnancy, and cord blood was collected at delivery. Additional waves of post-delivery data collection have not yet been incorporated into the harmonized 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). As in Denmark, MoBa many women contributed more than one pregnancy. In the data files used for the MOBAND-CP harmonization, 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 six 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 harmonized data.

Attrition

Approximately 60% of the Danish women invited to participate in DNBC agreed to participate. 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 six-month-post-partum interview, and 70% in the 18-month-post-partum interview.

In Norway, 41% of invited women agreed to participate in MoBa. 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 six-month-post-partum questionnaire (table).

Data harmonization

The first task of the MOBAND-CP collaboration was to harmonize epidemiologic variables from the two cohorts. A list of prioritized variables for cerebral palsy research was created and refined through
circulation among the collaborators. Initial harmonization efforts have focused on variables considered essential for epidemiologic research in general and for cerebral palsy research in particular. These include maternal and paternal characteristics, exposures during pregnancy, maternal medical conditions during pregnancy, delivery, birth characteristics, and newborn conditions (Supplementary table).

Data collections in the two cohorts were similar but by no means identical. A plan for harmonizing each variable was developed through discussions and revisions involving both Danish and Norwegian collaborators. The success of each harmonization was judged as “complete,” “partial,” or “impossible.” Once agreement on harmonization was reached, code was written in Stata (v.12.1; Stata Corporation, College Station, Texas). 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 harmonized for 140 variables. Guidelines have been created for further harmonization of data, with the expectation that future investigators may contribute additional harmonized variables. Data (including the raw data underlying the harmonized variables) will be accessible through a secure server at the National Institute of Public Health, Norway and the central data server for the Danish National Birth Cohort.

**Linkage to national registries and identification of children with cerebral palsy**

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 Register²² and the Danish IVF Register.²³

Children with cerebral palsy in Denmark (191 in total) have been identified through record linkage with the Cerebral Palsy Registry of Denmark.²⁴ In Norway, 247 children with cerebral palsy 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,\textsuperscript{22} validated through medical record review by two paediatric neurologists.\textsuperscript{26}

**FINDINGS TO DATE**

Data had been harmonized for 140 variables, and 438 children with cerebral palsy identified through record linkage with national registries. Collaborating investigators have developed protocols for the analysis of exposures plausibly linked to the risk of cerebral palsy. 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 cerebral palsy.

**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 harmonizing 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 harmonized 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 harmonization process. Nonetheless, harmonization for 42 of the 143 variables in our initial round were scored as “complete” and 98 were “partial,” with only three regarded as “impossible.” Variables were considered impossible to harmonize 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 usually in pregnancy cohort studies, participants are older and more socioeconomically privileged than the general population. Self-selection affects the prevalence of exposures and outcomes, but estimates of known exposure-outcome associations in both the DNBC and MoBa generally appear to be unbiased. 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 cerebral palsy registries.

With regard to the current study of cerebral palsy, the 438 cases provide by far the largest sample of children with cerebral palsy 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 cerebral palsy for an exposure with a prevalence of 10%, assuming conventional levels for statistical significance (80% power and 5% alpha level). The validation of the cerebral palsy cases in the national registries using medical records is a definite strength. Furthermore, the large study size allows consideration of cerebral palsy subtypes, which is rare in etiologic studies of cerebral palsy.
COLLABORATION

The purpose and permissions of MOBAND-CP are to foster studies on cerebral palsy. Investigators with an interest in hypotheses related to cerebral palsy (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 harmonization 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\textsuperscript{30,31}), after which an application to the MOBAND steering committee to access the MOBAND DokuWiki website, with codes for data harmonization and documentation, would be considered. The application should include a brief description of the project, which must include involvement of collaborators from both Norway and Denmark.
Acknowledgements

We are grateful to all parents and children participating in the DNBC and MoBa cohort studies.

MOBAND-CP was initiated in 2011 by Allen Wilcox at the US National Institute of Environmental Health Sciences (NIEHS), and has been established in collaboration with the University of Copenhagen, Aarhus University, the Danish Cerebral Palsy Registry, the Norwegian Institute of Public Health (NIPH), the University of Bergen, and the Cerebral Palsy Registry of Norway. Data harmonization was led by Dag Moster and conducted by Ingeborg Forthun and Mette C. Tollånes at the University of Bergen, and by Katrine Strandberg-Larsen and Tanja Knudsen at the University of Copenhagen. The MOBAND-CP collaboration has been supported by the Intramural Program of the National Institute for Environmental Health Sciences (NIEHS/NIH), University of Copenhagen, Aarhus University, the University of Bergen and the Norwegian Institute of Public Health.

Contributors

All authors contributed to conception and design of the study. MCT and IF performed the data analyses, and MCT drafted the manuscript. All authors critically revised the manuscript and have approved the final version to be published.

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Competing interests

None declared.
Ethics approval

Written informed consent was obtained from all participating mothers in DNBC and MoBa at time of enrolment. The Norwegian part of the study, including linkage with the National CP registry of Norway and the Norwegian Patient Register was further approved by the Regional Committee for Medical Research (2012/1738). The DNBC has been approved by the Danish Committee on Biomedical Research Ethics (case no. (KF) 01-471/94), and linkage to the Danish National CP Registry was approved by the Danish Data Protection Agency.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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References


### Supplementary Table. Variables harmonized as of May 2016

<table>
<thead>
<tr>
<th>Variables</th>
<th>Descriptions and details</th>
<th>Data source Denmark (missing, n (%))</th>
<th>Data source Norway (missing, n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>Age at birth</td>
<td>Key_DNBC (85 (0.0))</td>
<td>MBRN (0 (0.0))</td>
</tr>
<tr>
<td>Previous live births</td>
<td>01,2,3,4 or more</td>
<td>DNBC_all_reproductive_history (86 (0.1))</td>
<td>MBRN (5476 (4.8))</td>
</tr>
<tr>
<td>Previous stillbirths</td>
<td>Stillbirth after 28 weeks completed gestational age (0,1,2)</td>
<td>DNBC_all_reproductive_history</td>
<td>MBRN</td>
</tr>
<tr>
<td>Previous spontaneous abortions</td>
<td>Spontaneous abortions during pregnancy weeks 5-16 (range 0-10)</td>
<td>Int1 (768 (0.8))</td>
<td>Q1 (3431 (3.4))</td>
</tr>
<tr>
<td>Menstrual cycle, regularity</td>
<td>Regular menstrual cycle. No, yes.</td>
<td>Int1(415(0.5))</td>
<td>Q1 (416(0.5))</td>
</tr>
<tr>
<td>Menarche</td>
<td>Age (in years) at first menstrual period</td>
<td>Int1 (4066 (4.5))</td>
<td>Q1 (1324 (1.2))</td>
</tr>
<tr>
<td>Pre pregnancy body mass index</td>
<td>Calculated from pre-pregnancy weight and height</td>
<td>Int1 (1512 (1.7))</td>
<td>Q1 (2807 (2.7))</td>
</tr>
<tr>
<td>Weight gain in pregnancy</td>
<td>Reported directly in Denmark, calculated in Norway</td>
<td>Int3 (685 (1.0))</td>
<td>Q1 and Q4 (23 602 (23))</td>
</tr>
<tr>
<td>Maternal occupational status</td>
<td>Employed, unemployed, student, receiving pension/benefits</td>
<td>Int1 (40 (0.0))</td>
<td>Q1 (2101 (2.0))</td>
</tr>
<tr>
<td>Marital status</td>
<td>Spouse/partner,single</td>
<td>Int1 (65 (0.1))</td>
<td>Q1 (1561 (1.5))</td>
</tr>
<tr>
<td>Planned pregnancy</td>
<td>No, yes</td>
<td>Int1 (53 (0.1))</td>
<td>Q1 (1221 (1.2))</td>
</tr>
<tr>
<td><strong>Paternal characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal occupational status</td>
<td>Employed, unemployed, student, receiving pension/benefits</td>
<td>Int1 (1912 (2.1))</td>
<td>Q1 (2735 (2.7))</td>
</tr>
<tr>
<td>Paternal age</td>
<td>\leq 19,20-24,25-29,30-34,35-39,40-44,45-49,\geq 50</td>
<td>MBRD (1927 (1.9))</td>
<td>MBRN (552 (0.5))</td>
</tr>
<tr>
<td>Paternal BMI</td>
<td>Calculated from maternal report of father’s weight and height</td>
<td>Int3 (3142 (4.7))</td>
<td>Q1 (4708 (4.6))</td>
</tr>
<tr>
<td><strong>Exposures during pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro fertilization</td>
<td>No, yes</td>
<td>Danish IVF registry</td>
<td>MBRN and Q1</td>
</tr>
<tr>
<td>Maternal smoking up till Int1/Q1*</td>
<td>No, yes, stopped</td>
<td>Int1 (60 (0.1))</td>
<td>Q1 (653 (0.6))</td>
</tr>
<tr>
<td>Cigarettes daily at Int1/Q1*</td>
<td>Range 0-50</td>
<td>Int1 (137 (0.1))</td>
<td>Q1 (815 (0.8))</td>
</tr>
<tr>
<td>Maternal alcohol intake before pregnancy*</td>
<td>in units per week, range 0-65</td>
<td>Int1 (443 (0.4))</td>
<td>Q1 (2557 (2.5))</td>
</tr>
<tr>
<td>Binge drinking up till Int1/Q1*</td>
<td>Number of episodes of binge drinking (five or more drinks)</td>
<td>Int1 (371 (0.4))</td>
<td>Q1 (6298 (6.2))</td>
</tr>
<tr>
<td>Daily cups of coffee at Int1/Q1*</td>
<td>Range 0-69</td>
<td>Int1 (60 (0.0))</td>
<td>Q1 (4 (0.0))</td>
</tr>
<tr>
<td>Daily cups of tea at Int1/Q1*</td>
<td>Range 0-48</td>
<td>Int1 (59 (0.0))</td>
<td>Q1 (12 (0.0))</td>
</tr>
<tr>
<td>Daily intake of caffeinated soft drinks at Int1/Q1*</td>
<td>&lt;1 L, ≥1 L</td>
<td>Int1 (75 (0.1))</td>
<td>Q1 (10 (0.0))</td>
</tr>
<tr>
<td>Folate/folic acid intake weeks 0-30</td>
<td>No, yes.</td>
<td>Int1 and Int2 (9181 (9.5))</td>
<td>Q1 and Q3 (3204 (3.1))</td>
</tr>
<tr>
<td>Multivitamin intake up till Int1/Q1*</td>
<td>No, yes.</td>
<td>Int1 (2751 (3.0))</td>
<td>Q1 (3588 (3.5))</td>
</tr>
<tr>
<td>Physical activity up till Int1/Q1*</td>
<td>No exercise, once a week, twice a week, ≥3 times per week (aerobics, jogging, cycling, etc).</td>
<td>Int1 (57 (0.1))</td>
<td>Q1 (56 (0.1))</td>
</tr>
</tbody>
</table>

**Maternal medical conditions during pregnancy**

<p>| Nausea during pregnancy weeks 0-12* | No, nausea, vomiting. | Int2 (104 (0.1)) | Q1 (493 (0.5)) |
| Hyperemesis | Hospitalized for hyperemesis gravidarum. No, yes. | LPR (0 (0.0)) | Q3 (0 (0.0)) |
| Urinary tract infections up till Int1/Q1* | No, yes. | Int1 and Int2 (526 (6.6)) | Q1 and Q3 (0 (0.0)) |
| Rheumatoid arthritis | Diagnosed before birth. | LPR (0 (0.0)) | Q1 and Q3 (0 (0.0)) |
| Joint problems in pregnancy | No, yes. | Int1 and Int2 (194 (2.2)) | Q1 and Q3 (0 (0.0)) |
| Thyroid disorders | Hyper- or hypothyroidism. No, yes. | Int1 (183 (2.1)) | Q1 (0 (0.0)) |
| Ovarian cysts | Before or during pregnancy. No, yes. | Int1 (1835 (2.2)) | Q1 (0 (0.0)) |
| Epilepsy in pregnancy | No, yes. | Int2 (109 (1.1)) | Q1 (0 (0.0)) |
| Diabetes | Diagnosed before delivery. No, type I, type II, other/unspecified, gestational | LPR (0 (0.0)) | Q1 (0 (0.0)) |
| Thrombosis | Diagnosed during pregnancy. No, yes. | LPR (0 (0.0)) | Q1 (0 (0.0)) |
| Vaginal bleeding up till Int1/Q1* | No, yes. | Int1 and Int2 (110 (1.1)) | Q1 (869 (0.8)) |
| Respiratory infection during weeks 0-12* | No, yes. | Int1 (1502 (1.4)) | Q1 (1502 (1.4)) |
| Fever during weeks 0-12* | No, yes. | Int1 and Int2 (1800 (1.9)) | Q1 (2614 (2.5)) |
| Preeclampsia | No, light, serious, unspecified. | Int1 and Int2 (138 (0.1)) | Q1 (138 (0.1)) |
| Eclampsia | No, yes. | LPR (0 (0.0)) | Q1 (0 (0.0)) |
| HELLP syndrome | No, yes. | LPR (0 (0.0)) | Q1 (0 (0.0)) |
| Chorioamnionitis | No, yes. | LPR (0 (0.0)) | Q1 (0 (0.0)) |
| Sepsis during labor | No, yes. | LPR (0 (0.0)) | Q1 (0 (0.0)) |</p>
<table>
<thead>
<tr>
<th>Labour and delivery</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prolonged rupture of membranes</strong></td>
<td>Rupture of membranes ≥ 24 hours before delivery. No, yes.</td>
</tr>
<tr>
<td><strong>Fever in labor</strong></td>
<td>No, yes.</td>
</tr>
<tr>
<td><strong>Dystocia</strong></td>
<td>No, yes.</td>
</tr>
<tr>
<td><strong>Placental abruption</strong></td>
<td>No, yes.</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Cephalic, breech, transverse, unspecified.</td>
</tr>
<tr>
<td><strong>Caesarean section</strong></td>
<td>No, elective, emergency, unspecified.</td>
</tr>
<tr>
<td><strong>Forceps</strong></td>
<td>No, yes.</td>
</tr>
<tr>
<td><strong>Vacuum</strong></td>
<td>No, yes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td>The child’s condition at delivery. Live born, stillborn, spontaneous abortion, induced abortion, other.</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male, female.</td>
</tr>
<tr>
<td><strong>Plurality</strong></td>
<td>Number of fetuses in pregnancy. Range 0 (abortion) – 4.</td>
</tr>
<tr>
<td><strong>Birth order (for plural births)</strong></td>
<td>Range 0 (abortion) – 3.</td>
</tr>
<tr>
<td><strong>Apgar-score</strong></td>
<td>At five minutes.</td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td>In grams.</td>
</tr>
<tr>
<td><strong>Gestational age, last menstrual period</strong></td>
<td>In days.</td>
</tr>
<tr>
<td><strong>Gestational age, ultrasound (or last menstrual period)</strong></td>
<td>In days. Based on last menstrual period if ultrasound is missing.</td>
</tr>
<tr>
<td><strong>Birth defects, all</strong></td>
<td>Any birth defect. No, yes.</td>
</tr>
<tr>
<td><strong>Birth defects, serious</strong></td>
<td>Serious birth defect, as defined by the birth registries. No, yes.</td>
</tr>
<tr>
<td><strong>Specific birth defects</strong></td>
<td>According to ICD-10 (Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07, Q1, Q2, Q30-34, Q35-37, Q38-Q45, Q5, Q60-64, Q65-79, Q8, Q9). No, yes.</td>
</tr>
<tr>
<td><strong>Infant death</strong></td>
<td>Death during first year of life. No, yes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical condition of newborn</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transfer to NICU</strong></td>
<td>No, yes.</td>
</tr>
<tr>
<td><strong>Ventilator treatment</strong></td>
<td>CPAP or respirator treatment. No, yes.</td>
</tr>
<tr>
<td><strong>Neonatal encephalopathy</strong></td>
<td>No, cerebral irritability, cerebral depression, cerebral coma</td>
</tr>
<tr>
<td><strong>Intracranial bleeding</strong></td>
<td>No, yes.</td>
</tr>
<tr>
<td><strong>Icterus</strong></td>
<td>No, yes.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Neonatal seizures</th>
<th>No, yes.</th>
<th>LPR (0 (0.0))</th>
<th>MBRN (0 (0.0))</th>
</tr>
</thead>
</table>

**Cerebral palsy**

<table>
<thead>
<tr>
<th>CP</th>
<th>No, yes.</th>
<th>CPRD (0 (0.0))</th>
<th>CPRN (0 (0.0))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP subtype</td>
<td>No, spastic unilateral, spastic bilateral, dyskinetic, ataxic, not classified.</td>
<td>CPRD (0 (0.0))</td>
<td>CPRN (0 (0.0))</td>
</tr>
</tbody>
</table>

**Gross motor function**

<table>
<thead>
<tr>
<th>Gross motor function</th>
<th>Gross motor function classification scale level at age 5 years. Range I-V,</th>
<th>CPRD (1 (0.5))</th>
<th>CPRN (11 (4.5))</th>
</tr>
</thead>
</table>

**Age at CP diagnosis**

<table>
<thead>
<tr>
<th>Age at CP diagnosis</th>
<th>In completed months. Range 0-93.</th>
<th>CPRD (0 (0.0))</th>
<th>CPRN (0 (0.0))</th>
</tr>
</thead>
</table>

**CP with epilepsy**

<table>
<thead>
<tr>
<th>CP with epilepsy</th>
<th>No, yes, not CP.</th>
<th>CPRD (0 (0.0))</th>
<th>CPRN (0 (0.0))</th>
</tr>
</thead>
</table>

**CP with visual impairment**

<table>
<thead>
<tr>
<th>CP with visual impairment</th>
<th>No, yes, not CP.</th>
<th>CPRD (10 (5.2))</th>
<th>CPRN (57 (23))</th>
</tr>
</thead>
</table>

**CP with mental impairment**

<table>
<thead>
<tr>
<th>CP with mental impairment</th>
<th>No, yes, not CP.</th>
<th>CPRD (4 (2.1))</th>
<th>CPRN (86 (35))</th>
</tr>
</thead>
</table>

**General**

<table>
<thead>
<tr>
<th>Response time*</th>
<th>Gestational age in days when mother answered Int1/Q1.</th>
<th>Key_DNBC and Int1 MBRN and Q1</th>
</tr>
</thead>
</table>

Key_DNBC, data from the Medical Birth Registry of Denmark or the Danish Civil Registration System – cleaned by DNBC; DNBC_all_reproductive_history, data from the Medical Birth Registry of Denmark – cleaned by DNBC; LPR, The Danish Patient Registry; Int, DNBC Interview; Q, MoBa questionnaire; CPRD, CP Registry of Denmark; CPRN, CP registry of Norway; MBRD, Medical Birth Registry of Denmark; MBRN, Medical Birth Registry of Norway.

*similar variables also harmonized for later time points in pregnancy

For many variables, it was not possible to distinguish between missing and 0/no. Therefore, there are no missing values for many variables.