PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: Cerebral Palsy in the Norwegian and Danish birth cohorts (MOBAND-CP)
AUTHORS	Tollånes, Mette; Strandberg-Larsen, Katrine; Forthun, Ingeborg; Knudsen, Tanja Majbrit; Moster, Dag; Andersen, Anne-Marie; Stoltenberg, Camilla; Olsen, Jørn; Wilcox, Allen

VERSION 1 - REVIEW

REVIEWER	Karin B. Nelson NINDS/NIH scientist emeritus USA
REVIEW RETURNED	15-Jun-2016

GENERAL COMMENTS	This paper describes the background and preparation for future studies. The merging-- to the degree appropriate-- of two large prospective datasets will present good opportunities, within the limits of the variables the dataset includes. The paper states in the abstract and in the text that the consideration of CP subtypes will be an innovation in etiologic studies of CP. That just isn't so. Canadian, Australian and other studies of CP etiology have, wherever sample size permitted, explored the associations of risk factors with subtypes of CP. There is little awareness shown in general of the published literature on the etiology of CP. Unmentioned are a number of previous studies, some of which have been large and population-based or multicentered, and—for prenatal and neonatal variables—prospective. Some brief acknowledgement of the world literature on the topic would make the bibliography less narrowly ethnocentric. The variables available for investigation are limited. There is no mention of prenatal or neonatal imaging, no definition or systematic approach to identifying birth defects (although the Scandinavian registries for BDs should be a big help in the final analyses; see below), no effort described to assemble information on any placental investigations [not part of protocol. But surely some or many placentas will have been examined?] There is no mention of fetal growth restriction, shown to be an important risk factor for CP and partly accessible in this study thru information on gestational age and birth weight. Is placental weight systematically recorded? It is an important strength of this study that there can be future linkages with other Scandinavian registries, for birth defects, other developmental disabilities such as intellectual limitation and epilepsy, psychiatric diagnoses, cancer…. Given emerging understanding of the genetics of CP and the opportunity to explore the overlap in a large population and to intersect genetic with environmental data, seeking endophenotypes, future studies that explore the intersections of CP with these other outcomes and their risk factors may be really valuable. Just to explore the overlap of

	developmental and psychiatric outcomes, including related family studies, is likely to be informative. The collected biospecimens are of course of much interest. Care to provide any hints about what is contemplated for these? The absence of information on placentas and lack of systematic use of pre- and post-natal imaging should be mentioned among limitations. These merged datasets on CP will be a valuable resource.

REVIEWER	Jessica Miller Murdoch Childrens Research Institute, Australia
REVIEW RETURNED	18-Jun-2016

GENERAL COMMENTS	This is a well written paper describing the set up of an important combined birth cohort. I have a few minor comments: -It seems that the purpose of the paper in the abstract is not so much to study CP aetiology as it is to describe MOBAND-CP. -The titles under 'Cohort Description' should be changed to 'Participants and data collection in Denmark', rather than '...and in Denmark' and 'Participants and data collection in Norway'. -The paper does not mention when biological samples were collected for the DNBC. -Under 'Attrition' some of the questionnaires and/or interviews were described as "provided" while others were "completed". Is there a difference between the completion of the questionnaires/interviews at the different time points? -Also in the 'Attrition' section for Norway, the paper mentions that "111,618 live births in MoBA..." but according to the table this is the number for pregnancies resulting in live births, not the actual number of live births. This statement is not consistent with the similar statement for Denmark. -Can other pharmaceuticals be harmonized in the study rather than just illicit drugs?

REVIEWER	Ruth Gilbert University College London
REVIEW RETURNED	06-Jul-2016

GENERAL COMMENTS	In combination, the Norway and Danish cohorts offer an important resource for research. These very large cohorts combine self-reported exposures with exposures and outcomes captured in linked registry and administrative data. There is also the potential to use biological samples. The importance of this dataset should be viewed in the context of the withdrawal of funding for a very large birth cohort in the UK. Hence this resource report can help encourage maximise use of existing large cohorts. I think this paper is important to publish, but more detail is needed. Major comments 1. The list of harmonised variable is potentially very informative and useful. It should be referred to more clearly in the text and developed into a table that: a. Gives more information on the data source for Denmark and Norway (e.g. questionnaire/interview, registry, hospital data) b. More clarity about definitions (eg is maternal age – is this at delivery, Apgar score, transfer to NICU – does this include duration of stay?). In particular, more detail is needed about categories and

	sources, for example for socioeconomic status. c. Overall estimates of missingness 2. Users of these datasets might well want to analyse outcomes other than cerebral palsy. In particular, there would be interest with such a large cohort in analysing outcomes that are on the same causal pathway as CP, such as learning impairment, epilepsy, and stillbirth. More information about these related outcomes should be given in table 1. 3. An advantage of the dataset is the subtypes of cerebral palsy. These subtypes could be stated in table 1 and rates given. 4. Table 2 should include percentages along with the numbers. 5. There are some key variables that are not mentioned in the list of harmonised variables. These include maternal education, drug treatment during pregnancy and dates and outcomes of previous pregnancies (i.e. stillbirth, live birth, and neonatal mortality). Minor comments 6. More detail should be given on how to access the data and whether this is possible by from countries outside the host countries, and is it necessary to include a collaborator from the study teams? Also, are there application costs? 7. On page 9, postnatal caffeine use is mentioned in relation to caffeine use during pregnancy. The reasoning is hard to follow a postnatal use is as a respiratory stimulant but prenatal use will obviously work through different mechanisms. 8. More context would be helpful. What are the other birth cohorts that combine self report measures with administrative data?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Karin B. Nelson
Institution and Country: NINDS/NIH scientist emeritus, USA
Competing Interests: None declared.

This paper describes the background and preparation for future studies. The merging-- to the degree appropriate-- of two large prospective datasets will present good opportunities, within the limits of the variables the dataset includes.
The paper states in the abstract and in the text that the consideration of CP subtypes will be an innovation in etiologic studies of CP. That just isn't so. Canadian, Australian and other studies of CP etiology have, wherever sample size permitted, explored the associations of risk factors with subtypes of CP.

Response:
In the abstract and the text, this sentence has been modified and now reads:
“The study size allows consideration of cerebral palsy subtypes, which is rare in aetiological studies of cerebral palsy.”

There is little awareness shown in general of the published literature on the etiology of CP. Unmentioned are a number of previous studies, some of which have been large and population-based or multicentered, and—for prenatal and neonatal variables—prospective. Some brief acknowledgement of the world literature on the topic would make the bibliography less narrowly ethnocentric.

Response:
The third paragraph of the Introduction has been rewritten, and we have added references to

acknowledge previous literature.

The variables available for investigation are limited. There is no mention of prenatal or neonatal imaging, no definition or systematic approach to identifying birth defects (although the Scandinavian registries for BDs should be a big help in the final analyses; see below), no effort described to assemble information on any placental investigations [not part of protocol. But surely some or many placentas will have been examined?] There is no mention of fetal growth restriction, shown to be an important risk factor for CP and partly accessible in this study thru information on gestational age and birth weight. Is placental weight systematically recorded?

Response:
So far, thirteen proposed MOBAND studies have been approved by the steering committee. In one, the investigators aim to explore intrauterine growth and risk of cerebral palsy, as well as postnatal growth in cerebral palsy. Since investigators have not yet commenced data analyses, this study has not, along with several others, been described under the paragraph “Findings to date”.
Placental weight is recorded in the medical birth registries in both Denmark and Norway. No collaborating investigators have applied to use these data yet, but studying placental weight in relation to foetal growth and gestational age should surely be conducted within the MOBAND-CP collaboration. We thank you for making this point.

Response:
It is an important strength of this study that there can be future linkages with other Scandinavian registries, for birth defects, other developmental disabilities such as intellectual limitation and epilepsy, psychiatric diagnoses, cancer…. Given emerging understanding of the genetics of CP and the opportunity to explore the overlap in a large population and to intersect genetic with environmental data, seeking endophenotypes, future studies that explore the intersections of CP with these other outcomes and their risk factors may be really valuable. Just to explore the overlap of developmental and psychiatric outcomes, including related family studies, is likely to be informative. The collected biospecimens are of course of much interest. Care to provide any hints about what is contemplated for these?

Response:
As we write in the text, results from epidemiological analyses will inform future studies that make use of biological specimens collected during pregnancy. As of now, we believe it would be informative to perform analyses to assess thyroid function, maternal nutritional status and inflammatory markers, in addition to genetic analyses. However, the first attempt to obtain funding for biological analyses was unsuccessful. At this early stage, it seems somewhat premature to discuss any further details in the manuscript, though it is important to mention the opportunities are there.

The absence of information on placentas and lack of systematic use of pre- and post-natal imaging should be mentioned among limitations.

Response:
The following sentence was added under Strengths and limitations:
“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.”

These merged datasets on CP will be a valuable resource.

Response:
Thank you.

Reviewer: 2
Reviewer Name: Jessica Miller
Institution and Country: Murdoch Childrens Research Institute, Australia
Competing Interests: None declared

This is a well written paper describing the set up of an important combined birth cohort.
I have a few minor comments:
-It seems that the purpose of the paper in the abstract is not so much to study CP aetiology as it is to describe MOBAND-CP.

Response:
We have rephrased the Purpose of the Abstract to avoid confusion:
“The purpose of MOBAND-CP is to study cerebral palsy aetiology in a prospective design.”

-The titles under 'Cohort Description' should be changed to 'Participants and data collection in Denmark', rather than '...and in Denmark' and 'Participants and data collection in Norway'.

Response:
Thank you, the redundant word “and” has been removed in both these titles.

-The paper does not mention when biological samples were collected for the DNBC.

Response:
The following sentence can be found under “Participants and data collection in Denmark”, under the Table:
“Maternal blood samples were collected in the first trimester and at mid-pregnancy, and cord blood was collected at delivery.”

-Under 'Attrition' some of the questionnaires and/or interviews were described as "provided" while others were "completed". Is there a difference between the completion of the questionnaires/interviews at the different time points?

Response:
We meant essentially the same by “participated”, “provided data” or “completed”. We have replaced “provided” by “participated”, so that mothers are described as “participating” in interviews (in Denmark) and “completing” questionnaires (in Norway).

-Also in the 'Attrition' section for Norway, the paper mentions that "111,618 live births in MoBA..." but according to the table this is the number for pregnancies resulting in live births, not the actual number of live births. This statement is not consistent with the similar statement for Denmark.

Response:
Thank you, the words “…pregnancies that resulted in a…” was added to the sentence.

-Can other pharmaceuticals be harmonized in the study rather than just illicit drugs?

Response:
Yes, there is a lot of information on pharmaceuticals, and more information can be found on the websites of the respective cohorts. One of the ongoing MOBAND-CP studies is currently investigating use of over-the-counter pain medication and risk of CP in offspring, and this study has now been mentioned under “Findings to date”.

Reviewer: 3
Reviewer Name: Ruth Gilbert
Institution and Country: University College London, UK
Competing Interests: None declared

In combination, the Norway and Danish cohorts offer an important resource for research. These very large cohorts combine self-reported exposures with exposures and outcomes captured in linked registry and administrative data. There is also the potential to use biological samples. The importance of this dataset should be viewed in the context of the withdrawal of funding for a very large birth cohort in the UK. Hence this resource report can help encourage maximise use of existing large cohorts. I think this paper is important to publish, but more detail is needed.
Major comments
1. The list of harmonised variable is potentially very informative and useful. It should be referred to more clearly in the text and developed into a table that:
a. Gives more information on the data source for Denmark and Norway (e.g. questionnaire/interview, registry, hospital data)
b. More clarity about definitions (eg is maternal age – is this at delivery, Apgar score, transfer to NICU – does this include duration of stay?). In particular, more detail is needed about categories and sources, for example for socioeconomic status.
c. Overall estimates of missingness

Response:
The appendix has been replaced by a supplementary table, providing more details on definitions, data sources and missingness of the harmonized variables. The table was more than five pages long, and since the Instructions for authors state “Any table submitted that are longer/larger than 2 pages will be published online as supplementary material”, we have submitted it as a supplementary table.

2. Users of these datasets might well want to analyse outcomes other than cerebral palsy. In particular, there would be interest with such a large cohort in analysing outcomes that are on the same causal pathway as CP, such as learning impairment, epilepsy, and stillbirth. More information about these related outcomes should be given in table 1.

Response:
To capture children with other outcomes, like learning impairment and epilepsy, the cohorts would have to be linked again to national registries, with new ethical permissions sought. We therefore do not know these numbers. Stillbirths, however, have been added to table 1.

3. An advantage of the dataset is the subtypes of cerebral palsy. These subtypes could be stated in table 1 and rates given.

Response:
Subtypes have been added.

4. Table 2 should include percentages along with the numbers.

Response:
Which number should be the denominator when calculating a percentage depends on the study question, and the result may be misleading if the reader has a different study design in mind. We therefore suggest leaving the table as it is. We are, of course, willing to reconsider, in which case it would be helpful if the reviewer would state explicitly which calculations she has in mind.

5. There are some key variables that are not mentioned in the list of harmonised variables. These include maternal education, drug treatment during pregnancy and dates and outcomes of previous pregnancies (i.e. stillbirth, live birth, and neonatal mortality).

Response:
Unfortunately, we do not have information on DNBC participants' educational level. We have therefore harmonized information on socio-occupational status, which is reported in the supplementary table. Drug treatment during pregnancy is not mentioned because it was not harmonized during the first phase. One investigator is, however, harmonizing over-the-counter pain medication, which will be made available to collaborators in due course. Previous pregnancy outcomes are reported in the supplementary table.

Minor comments
6. More detail should be given on how to access the data and whether this is possible by from countries outside the host countries, and is it necessary to include a collaborator from the study teams? Also, are there application costs?

Response:
We have tried to clarify under "Collaboration". If the aim is to study CP, the process should be rather straight forward. If, however, the aim is to study other outcomes, the MOBAND-CP steering committee can only grant access to a website where code for harmonization is stored, but not to the harmonized data themselves. We have written explicitly that such investigators must apply for data from both cohorts separately (more information on the websites of the respective cohorts, also on costs for accessing data), after which they can apply for access to code they can use to create harmonized variables themselves:
"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 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."

7. On page 9, postnatal caffeine use is mentioned in relation to caffeine use during pregnancy. The reasoning is hard to follow a postnatal use is as a respiratory stimulant but prenatal use will obviously work through different mechanisms.

Response:
This sentence has been deleted, and the brief list describing the first papers from the MOBAND-CP collaboration has been updated.

8. More context would be helpful. What are the other birth cohorts that combine self report measures with are the other birth cohorts that combines self report measures with administrative data?

Response:
The aim of this paper is to present the MOBAND-CP collaboration, and the opportunities it may represent for researchers interested in CP or other rare childhood outcomes. Presenting other cohorts is beyond the scope of this paper.

VERSION 2 – REVIEW

REVIEWER	Karin B. Nelson NINDS/NIH (emeritus) USA
REVIEW RETURNED	30-Jul-2016

GENERAL COMMENTS	Happy to endorse it now.

REVIEWER	Jessica Miller Murdoch Childrens Research Institute, Australia
REVIEW RETURNED	05-Aug-2016

GENERAL COMMENTS	I have no further comments.