Cohort Profile: The Nordic Perinatal Bereavement Cohort

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How did the study come about?

Fetal and early postnatal life is an important and vulnerable time period in human development.1–3 Subtle adverse exposures in this period may potentially lead to functional deficits and increase disease risk later in life, such as reproductive dysfunctions, cardiopulmonary diseases, diabetes, obesity, hypertension, cancers, neuropsychiatric conditions, immune deficits and autoimmune diseases.4 Influences on gene expression and the resulting epigenetic changes may constitute an important mechanism for programming effects.2,3,5 This hypothesis of developmental origins of health and diseases has gathered mounting support, but much remains to be explored.4 So far evidence has mostly come from animal studies, and long-term follow-up studies in humans are needed because some exposures may produce health effects decades later.

A cohort study based on data from national registers in Nordic countries will provide an opportunity to study developmental origins of diseases in a large population. It is well recognized that use of nationwide register data in epidemiological studies is important and such research has, in recent decades, substantially contributed to our knowledge of disease patterns, aetiology and frontline science.6,7 All Nordic countries provide both primary and secondary health care within a public health-care system that report to national registers. The unique feature is that data from all registers can be linked by using the personal identification number, which has been given to each citizen since the 1960s or earlier.5–8 Within this system, it is possible for researchers to track any particular person over decades and link data on demographic, vital, social and economic, medical history, medication usage to the study. In this sense, each Nordic country serves as a cohort in itself.6,7

It is well recognized that the impact of stress on health has increased in modern society9 and stress has been hypothesized as one of the key factors in the developmental origins of health and disease.10–13 Mounting evidence from animal studies indicates that severe stress during fetal life may permanently change organ function and have long-term health effects on the offspring, via programming effects of glucocorticoids.10–13 However, observational studies on stress are often hampered by small exposure contrasts between the compared groups, or recall bias, which impede interpretation and comparison of results.14–17 To use bereavement as an indicator of stress has a number of advantages in epidemiological research.18 It has been shown that bereavement in one's adult life has great impact on health,19–28 followed by significant physiological changes in neurological and immune–endocrine body systems.29,30 Its potential effects are likely to be even more important if it occurs during fetal life. If stress during fetal life is important for human health,31 one would expect that children born to mothers bereaved by death of a close relative during the pregnancy would be affected. On the other hand, there has been limited research on the long-term health consequences in children who experienced bereavement during early years of life.

The Nordic Perinatal Bereavement Cohort resulted from long-term collaborations among researchers in Denmark, Finland and Sweden and from the findings in our earlier studies on bereavement during adult life. Those studies showed that bereavement by death of a child has long-term adverse health
This cohort was initiated by a research call of 'Joint Nordic Use of Research Infrastructure' in late 2007 from NordForsk, the Nordic Research Board with responsibility for cooperation on research and researcher training in the Nordic region. Further funding is received from Nordic Cancer Union, and the Danish Medical Research Council. The described study aims to examine the health consequences following two types of bereavement, namely, maternal bereavement by death of a close relative (a child, husband, sibling, parent) during one's fetal life and bereavement by death of a close relative (a parent, sibling, grandparent) during one's early years of life.

Who is in the study sample?
Overall, the study is comprised of 7,022,718 subjects from Denmark, Sweden and Finland. We included all children born in Denmark from 1970 to 2004 (N = 2,359,539) and in Sweden from 1973 to 2006 (N = 3,391,096). In Finland, we were allowed to include only a 90% random sample of persons born from 1987 to 2007 (N = 1,272,083), since Statistics Finland does not allow register studies with complete population data due to their strict interpretation of the National Statistics Act. The baseline characteristics of the study population are presented in Table 1.

Table 1 Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Denmark</th>
<th>Sweden</th>
<th>Finland</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>849,201 (51)</td>
<td>1,742,575 (51)</td>
<td>650,147 (51)</td>
<td>3,241,923 (51)</td>
</tr>
<tr>
<td>Girls</td>
<td>805,437 (49)</td>
<td>1,648,520 (49)</td>
<td>621,865 (49)</td>
<td>3,075,822 (49)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>1</td>
<td>71</td>
<td>75 (&lt;1)</td>
</tr>
<tr>
<td><strong>Apgar score at 5 min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–6</td>
<td>11,580 (1)</td>
<td>38,498 (1)</td>
<td>–</td>
<td>50,078 (1)</td>
</tr>
<tr>
<td>7–10</td>
<td>1,515,283 (91)</td>
<td>3,352,598 (92)</td>
<td>–</td>
<td>4,632,690 (92)</td>
</tr>
<tr>
<td>Unknown</td>
<td>127,778 (8)</td>
<td>235,181 (7)</td>
<td>–</td>
<td>362,969 (7)</td>
</tr>
<tr>
<td><strong>Apgar score at 1 min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–6</td>
<td>–</td>
<td>148,231 (4)</td>
<td>53,141 (4)</td>
<td>201,372 (4)</td>
</tr>
<tr>
<td>7–10</td>
<td>–</td>
<td>320,621 (94)</td>
<td>1,205,625 (95)</td>
<td>4,411,838 (94)</td>
</tr>
<tr>
<td>Unknown</td>
<td>–</td>
<td>36,552 (1)</td>
<td>13,317 (1)</td>
<td>49,969 (1)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>474,688 (29)</td>
<td>1,429,188 (42)</td>
<td>396,605 (31)</td>
<td>2,300,481 (36)</td>
</tr>
<tr>
<td>2</td>
<td>37,008 (33)</td>
<td>1,230,394 (36)</td>
<td>385,263 (30)</td>
<td>1,985,764 (31)</td>
</tr>
<tr>
<td>≥2</td>
<td>175,816 (11)</td>
<td>731,514 (22)</td>
<td>483,854 (38)</td>
<td>1,391,184 (22)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6,344,048 (38)</td>
<td>0</td>
<td>6,361 (&lt;1)</td>
<td>640,409 (10)</td>
</tr>
<tr>
<td><strong>Gestational age, weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37</td>
<td>86,790 (5)</td>
<td>198,199 (6)</td>
<td>73,348 (6)</td>
<td>358,337 (6)</td>
</tr>
<tr>
<td>≥37</td>
<td>1,430,089 (86)</td>
<td>3,184,604 (94)</td>
<td>1,189,762 (94)</td>
<td>5,804,455 (92)</td>
</tr>
<tr>
<td>Unknown</td>
<td>137,762 (8)</td>
<td>8293 (&lt;1)</td>
<td>8973 (1)</td>
<td>155,028 (2)</td>
</tr>
<tr>
<td><strong>Birth weight, g</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500</td>
<td>80,296 (5)</td>
<td>143,846 (4)</td>
<td>53,725 (4)</td>
<td>277,867 (4)</td>
</tr>
<tr>
<td>≥2500</td>
<td>1,457,608 (88)</td>
<td>3,237,083 (95)</td>
<td>1,212,571 (95)</td>
<td>5,907,262 (94)</td>
</tr>
<tr>
<td>Unknown</td>
<td>116,737 (7)</td>
<td>10,167 (&lt;1)</td>
<td>5787 (&lt;1)</td>
<td>132,691 (2)</td>
</tr>
<tr>
<td><strong>Maternal age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–26</td>
<td>558,096 (34)</td>
<td>1,318,416 (39)</td>
<td>370,530 (29)</td>
<td>2,247,042 (36)</td>
</tr>
<tr>
<td>27–30</td>
<td>514,852 (31)</td>
<td>976,813 (29)</td>
<td>366,575 (29)</td>
<td>1,858,240 (29)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>575,859 (35)</td>
<td>1,095,591 (32)</td>
<td>534,899 (42)</td>
<td>2,206,349 (35)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5834 (&lt;1)</td>
<td>276 (&lt;1)</td>
<td>48 (&lt;1)</td>
<td>6189 (&lt;1)</td>
</tr>
</tbody>
</table>

What does it cover?

The first overall aim of the study is to estimate the effects of bereavement on health during the first decades of life. The second overall aim is to establish a large database for observational research on developmental origins of health and illnesses based on Nordic collaboration. By using this historical register-based cohort, we are planning a series of studies with specific aims. The exposure has two sub-categories: prenatal exposure [maternal bereavement by death of a close relative (a child, husband, parent or sibling) during pregnancy (the child’s fetal life)] and postnatal exposure [bereavement by death of a close relative of the child (a parent, sibling or grandparent) during early years of life]. Throughout follow-up, we will investigate the associations between exposure and a number of health outcomes, such as:

(i) Overall mortality and morbidity during first decades of life.
(ii) Adverse birth outcomes, such as preterm birth, Apgar scores at birth, low birth weight, intra-uterine growth retardation and congenital malformations.
(iii) Outcomes related to diseases defined by hospitalization (inpatients and outpatients).
   (a) Metabolic disorders, such as diabetes and overweight.
   (b) Cardiovascular diseases.
   (c) Cancer, such as cancers related to hormonal exposure like breast cancer or testis cancer.
   (d) Immune/autoimmune disorders, such as asthma, infection and rheumatoid arthritis.
   (e) Neurological disorders, such as epilepsy, cerebral palsy and cognitive skills.
   (f) Psychiatric disorders, such as depression, schizophrenia, autism and attention deficit hyperactivity disorder (ADHD).
(iv) Prescribed medication defined by Anatomical Therapeutic Chemical (ATC) Classification System.
(v) Visits to general practitioner.

We will first analyse the data for each country and then provide a common estimate when the results are comparable.

What has been measured/what information has been collected?

The cohort was approved by the following authorities and institutions: Danish National Board of Health and Statistics Denmark, Denmark; THL (National Institute for Health and Welfare) and Statistics Finland, Finland; Karolinska Institutet, the Swedish National Board of Health and Welfare, and Statistics Sweden, Sweden. Data were abstracted from seven national registers in Denmark, five national registers in Finland and five national registers in Sweden, respectively. Each resident was assigned a unique 10- or 11-digit identification number at birth or at immigration, and this number is identical in all national registers. By using this personal number as identifier, all 7022718 children could be linked to their relatives (parents, siblings and grandparents) in the Danish Civil Registry System, the Swedish Multigeneration Register and Statics Finland Registry/Population register, respectively. Moreover, children could be further linked to their mother’s siblings through the linkage to their grandparents. Data on demographic variables, vital statistics, health outcomes (hospitalization, medication, visit to general practitioner, etc.) and socio-economic variables were collected by different registers. Table 2 summarizes the data sources and main contents of the national registers in the three countries. We (researchers) would receive only the encrypted data, which can not be used to identify any particular person. The combined data will be stored at Statistics Denmark and the project group will access the data via the secure server at Statistics Denmark.

How often have they been followed up?

The data have been stored in the national register system, in which all the information is updated at least annually for administrative purposes. Data on immigration, deaths, births, hospitalization and medication are updated every week, or every month, or at least once a year. This applies to each individual, including the children and all their relatives.

What was the attrition like?

By the end of 2006, 1.6% of the 62,443 children born in 1980 in Denmark were dead, 5.9% of them had emigrated and 0.08% were for unknown reasons lost to follow-up. As expected, these rates decreased for the children born later. For example, after 14 years of follow-up, 0.67% of the 74,503 born in 1994 were dead, 3.61% had emigrated and 0.02% were for unknown reasons lost to follow-up. For all 1,654,641 children born in Denmark from 1980 to 2004 (longest time of follow-up was 26 years), 0.89% of them were dead, 3.23% had emigrated and 0.03% were for unknown reasons lost to follow-up. In Sweden, by the end of 2008 (longest time of follow-up was 35 years), 2.1% of the 107,501 children born in 1973 were dead, and 9.2% of them had emigrated. Of 109,885 born in Sweden during 1994, 0.56% were dead, and 3.57% had emigrated during time of follow-up. For all children born in Sweden during the study period,
0.98% were dead, and 4.46% emigrated. Such estimates for Finnish data are not yet ready but we believe the estimates will be similar. These findings are in line with some previous reports based on data from separate registers.\(^{36}\)

Overall, the loss to follow-up is very low and similar in the Nordic countries. Based on these studies, we estimate a virtually no loss-to-follow-up related to disappearance from the registers. This makes the study the most comprehensive longitudinal databases in the world.

**What has the study found?**

We identified 165,294 children born to mothers who lost a close relative (a child, a parent or a sibling) during pregnancy, and those children are categorized...
as exposed children due to bereavement during fetal life. Maternal bereavement during pregnancy was associated with an increased risk of several adverse birth outcomes, such as low birth weight [odds ratio (OR) 1.120, 95% confidence interval (CI), 1.120–1.121], preterm birth [OR 1.087 (95% CI 1.065–1.110)], low Apgar score at 1 min (OR 1.038, 95% CI 1.012–1.065) and low Apgar score at 5 min (OR 1.088, 95% CI 1.031–1.148) (Table 3), after adjusting for maternal age, parity and country.

What are the main strengths?
The unique strengths of this cohort based on Nordic register-based data include a large sample size, decades of almost complete follow-up, and detailed documentation on social and health status. These data sources have only recently been open to researchers. Experience has demonstrated that this research can be carried out without risks to the participants because the study is based upon secondary data. No individuals will be approached as a result of the study, nor will we get access to any other data from the participants. Only data without personal identification numbers will be available for research. Using state of the art computer technologies make it simple to maintain data confidentiality throughout the analyses.

Large cohorts with decades of follow-up are important for examining the associations between rare exposures (such as death of child during pregnancy) and rare outcomes (such as childhood cancer). The Nordic countries are the only place in the world where such a cohort can be established at present.

What are the main weaknesses and limitations?
The main limitation is that we are not allowed to identify people to check validity of disease codes or to collect additional primary data as in other cohorts. Combining data from different countries is also a challenge because health systems and health information systems vary between countries. Procedures for data collection and documentation for the wide range of social and health data is complicated due to differences in register systems and their governing agencies, although many similarities exist between the countries.

The validity of linking mothers to relatives is different between countries. In Sweden and Finland, the mothers have almost complete linkage to all their relatives. And in Denmark, the mothers have complete linkage to their children but not complete linkage to their parents in earlier years. Furthermore, bereavement of close relatives living outside of the country of study cannot be identified.

The aetiology of most diseases involves both genetic and environmental factors. Our study, however, has limited data on lifestyle factors and no data on biomarkers of stress responses and genetic susceptibility. The cohort can be linked to other existing databases with such information, such as the Danish National Birth Cohort, which will provide the possibility to include biological measurements of stress hormones and to further adjust for confounders in a subset of the cohort.

Can I get hold of the data? (Where can I find out more and potential for collaboration?)
The data are stored and maintained electronically in Statistics Denmark. We encourage interested parties to make contact with the leader and chief investigator of the study, Prof. Jørn Olsen, at jo@ucla.edu, or the study coordinator, Dr Jiong Li, at jl@soci.au.dk.

A dedicated website is under construction to highlight the cohort profile, progress, main findings and questions related to data documentation, etc. The website will provide the links to all study reports.

Table 3 Odds ratios (ORs) of being born preterm, low birth weight, a low Apgar score between exposed and unexposed children: logistic regression

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preterm birth (&lt;37 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>10 267</td>
<td>1.099 (1.087–1.110)</td>
<td>1.087 (1.120–1.121)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>348 070</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td><strong>Low birth weight (&lt;2500 g)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>8122</td>
<td>1.116 (1.087–1.121)</td>
<td>1.120 (1.120–1.121)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>269 745</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td><strong>Low Apgar score (&lt;7) at 1 min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>5174</td>
<td>1.105 (1.012–1.065)</td>
<td>1.038 (1.012–1.065)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>196 198</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td><strong>Low Apgar score (&lt;7) at 5 min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>1395</td>
<td>1.054 (1.031–1.148)</td>
<td>1.088 (1.031–1.148)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>48 683</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
</tbody>
</table>

*Adjusted for country, gender, parity and maternal age. 95% CI = 95% confidence interval.
conference presentations and as well as an online en-
quiry form that generates an email to the study team,
for questions or notification of change of contact
details.

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Conflict of interest: None declared.

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