Setting up The Danish National Birth Cohort
Background, experiences and study example

Research – theory and practice
ESHRE Campus Symposium, Brussels

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National Institute of Public Health

The Danish National Birth Cohort

Background
National study on 100,000 pregnancies
Denmark 1996-2002

Aims:
To investigate short and longterm consequences of exposures early in life
(including the prenatal period)

Previously most birth cohorts have started at birth – this one and others
now start in early pregnancy so that prenatally collected data on
exposures can be studied

Why initiate new birth cohorts?

Short term:
• High mortality during perinatal period
• New health problems during pregnancy and adolescence are emerging
• Serious health outcomes

Long term:
• Early life determinants for adult morbidity
• ‘Life course approach’ to disease in adult life

The Danish National Birth Cohort

• New health problems during pregnancy and adolescence are emerging
• Serious health outcomes
The programming hypothesis

The ‘Barker early origins hypothesis’ (1986):
‘there are certain times in early life when the fetus or infant may be particularly susceptible to adverse influences which may produce lifelong effects on organ structure and function’

Fetal growth retardation is an important cause of some of the chronic diseases that we die from today. Both in rich and poor countries. Cardio-vascular diseases was the most frequent cause of death among middle-aged low risk men (i.e. lean, non-smoking, low cholesterol)
Using old midwife journals from a certain area in GB adult morbidity could be related to birth weight and placental weight
Subsequent studies confirm a relation between birth weight and adult chronic diseases

Mechanisms behind the hypothesis:
• Restricted intrauterine resources
• Organs are ‘primed’ for better survival
• Thrifty phenotype (‘economical’, ‘efficient’)

‘a smaller body size, a lowered metabolic rate and a reduced level of behavioural activity … adaptations to an environment that is chronically short of food’ (Bateson & Martin, 1999)

• More susceptable for e.g. type 2 diabetes, hypertension and cardio-vascular diseases in adulthood
• By adapting to restricted supply of nourishment, the fetus prioritize supply for vital organs (e.g. the brain) at the expense of an optimal development of other organs. These developmental adaptations may found the basis for a number of diseases later in life.

Public health implications

Barker recommendations today:
• Avoid excessive under- or overweight before pregnancy
• Ensure access to varying and well-balanced diet for girls and young women
• Avoid that children small at birth gain too much weight during childhood and become overweight early in life

However … better for all pregnant women can easily be confused with more diet (‘eat for two’)

Poverty     malnourished mothers     malnourished babies     low birth weight

This is a problem in countries that undergo a very quick change from shortage of food to better/more food
Data collection overview

1. Interview
2. Interview

Recruitment
Birth

Week 12-16
Week 30

½ year 1 ½ year

7 years 11 years

Follow up

Inclusion criteria

1) Living in Denmark
2) An intention to continue pregnancy (=not planning an induced abortion)
3) Speaking Danish well enough to participate in four telephone interviews

Design

Recruitment: First antenatal visit to GP
Prenatal exposures:
CATI (week 12 and 30)
Food frequency questionnaire (week 24)
CATI (6 and 18 months)
Blood samples from the mother (first trimester and week 25)
Blood samples from the child (cord sample at birth)

Exposures in early childhood: Bio bank:

Follow up: 7 years
11 years (or 12 or 13...)
Adolescence, adulthood, and old age
Self-reported data (exposures)

Prenatal interviews
- Health (before and during pregnancy)
- Reproductive history (gravidity, parity, TTP)
- Medicine use
- Work related exposures
- Socio-economic factors
- Lifestyle factors (tobacco, alcohol, drugs, diet, physical activity)

Postnatal interviews
- Diet
- Illnesses
- Cognitive development
- 'Milestones'

Register data (outcomes)

Danes are well-registered!

The National Register (residence – when and with whom)
Danish National Patient Register
The Medical Birth Register (e.g. miscarriages – clinically recognized – induced abortions, gestational age at birth, maternal diagnoses during pregnancy, perinatal/infant diagnoses)

'A big machine'

Pilot study (carrying out, documentation, evaluation, revisions)

Project group
Data bank (technology, documentation, code books, revised versions of interviews)
Bio bank (app. 1.2 mio samples)
Interviewer corps (adjudication/"ask for bids", on-going negotiations, quality vs. quantity, education, supervision)

Leading group (internal)
Steering group (external)
Administration of data
Collaboration with e.g. GPs and midwives
Key figures

- Enrolled pregnancies: 101,042
  - 1. interview: 92,892
  - 2. interview: 87,802
  - 3. interview: 70,296
  - 4. interview: 66,712
- 1. blood sample: 86,198
- 2. blood sample: 67,151
- 1. and 2. and cord sample: 45,742
- 7-year follow up: 53,211

54% of children aged of 18 months had a mother who had participated in all four interviews.

Use of data

- Public database for research within the aims of the study
- All projects need to be approved by external steering group
- Maximum use of interview data
- Restrictive use of biological samples
- All generated data should be returned to main database

Scientific results so far

- 17 PhD-theses
- 150 scientific publications on e.g.:
  - Alcohol consumption
  - Coffee consumption
  - Medicine use
  - Stress
  - Fertility
  - Health problems in pregnancy
  - Overweight
  - Weight gain
  - Diet
  - Work related factors
  - Breast feeding
  - Fetal death
  - Congenital malformations
  - Asthma/allergy
  - Infections in childhood
  - Cognitive/neurological disorders
  - Health problems in pregnancy
Examples on fertility

- Overweight → Longer TTP
- Longer TTP → Infant fever cramps and epilepsy
- Longer TTP, no treatment → Fewer dizygote twins

Another example, own research

Exercise and Preterm Birth

- < 37 completed gestational weeks
- Increased risk of perinatal death and also long term consequences
Exercise and Foetal Growth Measures

- Low birth weight (< 2500 g) – limited value
- Gestational age into account when possible
- Strong link between low birth weight at a given gestational age and perinatal death

Measurement of exposure

1) “Now that you are pregnant, do you engage in any kind of exercise?”
   In case of a positive answer, the following questions were posed:
2) “What kind of exercise do you engage in?”
3) “How many times per week do you engage in… (answer in question 2)?”
4) “How many minutes per time do you engage in… (answer in question 2)?”
5) “Do you engage in other types of exercise?”

Statistical analysis

- Descriptive statistics (numbers and percentages)
- Survival analysis, Cox regression analysis (hazard ratios)
- Linear regression analysis (mean differences – absolute, not relative)
- Logistic regression analysis (odds ratios)

SAS, Statistical Analysis Software, version 9.1
Results – Preterm birth

### Table 1: Preterm birth

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Data from pregnancy interview (n = 17,251)</th>
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<th>Data from pregnancy interview (n = 17,251)</th>
<th>Data from pregnancy interview (n = 17,251)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26-28%</td>
<td>29-31%</td>
<td>32-34%</td>
<td>35%</td>
</tr>
<tr>
<td>Any</td>
<td>55,236</td>
<td>55,236</td>
<td>55,236</td>
<td>55,236</td>
</tr>
<tr>
<td>No</td>
<td>55,236</td>
<td>55,236</td>
<td>55,236</td>
<td>55,236</td>
</tr>
<tr>
<td>Exercise</td>
<td>26-28%</td>
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<tr>
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<td>55,236</td>
<td>55,236</td>
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### Table 2: Preterm birth

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Crude HR</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>p for trend</th>
<th>p for interaction</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
<td>1</td>
<td>0.99</td>
<td>0.95-1.03</td>
<td>0.2461</td>
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<tr>
<td>Any</td>
<td>1.06</td>
<td>1.06</td>
<td>0.94</td>
<td>0.91-1.09</td>
<td>0.126</td>
</tr>
<tr>
<td>Hours/week</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.0002</td>
<td>0.2461</td>
</tr>
<tr>
<td>1-3</td>
<td>1.06</td>
<td>1.06</td>
<td>0.94</td>
<td>0.91-1.09</td>
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<tr>
<td>&gt;3</td>
<td>1.06</td>
<td>1.06</td>
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</tr>
<tr>
<td>Hours/week</td>
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<td></td>
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<td>0.126</td>
</tr>
<tr>
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<td>1.06</td>
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### Table 4: Preterm birth

<table>
<thead>
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<th>Crude HR</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>p for trend</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1</td>
<td>0.99</td>
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<tr>
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<td>0.126</td>
</tr>
<tr>
<td>Hours/week</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>0.126</td>
</tr>
<tr>
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<td>1.06</td>
<td>0.94</td>
<td>0.91-1.09</td>
<td>0.126</td>
</tr>
</tbody>
</table>
### Table 2

**Mean differences in foetal growth measures according to leisure time physical activity during pregnancy, The Danish National Birth Cohort, 1996-2002, n = 79,692**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Change in Foetal Growth</th>
<th>Adjusted*</th>
<th>95% CI</th>
<th>P-value</th>
<th>Change in Foetal Growth</th>
<th>Adjusted*</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth length (cm)</td>
<td>-0.06 (-0.09 to -0.03)</td>
<td>-0.07</td>
<td>-0.09 to -0.05</td>
<td>0.003</td>
<td>0.03 (-0.02 to 0.06)</td>
<td>-0.02</td>
<td>-0.04 to -0.00</td>
<td>0.123</td>
</tr>
<tr>
<td>Foetal weight (g)</td>
<td>-0.04 (-0.05 to -0.03)</td>
<td>-0.05</td>
<td>-0.06 to -0.04</td>
<td>0.000</td>
<td>0.02 (-0.01 to 0.05)</td>
<td>-0.01</td>
<td>-0.03 to -0.00</td>
<td>0.118</td>
</tr>
</tbody>
</table>

*An adjusted model includes maternal age, education, smoking, alcohol consumption, and Townsend score.*

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### Table 3

**Mean differences in birthweight difference among siblings according to exercise level in the 3 pregnancies, The Danish National Birth Cohort, 1996-2002, n = 324**

<table>
<thead>
<tr>
<th>Change in exercise level</th>
<th>Change in Foetal Growth</th>
<th>Adjusted*</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exercise</td>
<td>-0.02 (-0.05 to 0.02)</td>
<td>-0.08</td>
<td>-0.06 to -0.09</td>
<td>0.137</td>
</tr>
<tr>
<td>Light exercise</td>
<td>-0.01 (-0.04 to 0.02)</td>
<td>-0.09</td>
<td>-0.07 to -0.10</td>
<td>0.086</td>
</tr>
<tr>
<td>Moderate exercise</td>
<td>-0.00 (-0.03 to 0.03)</td>
<td>-0.08</td>
<td>-0.06 to -0.09</td>
<td>0.257</td>
</tr>
<tr>
<td>Heavy exercise</td>
<td>0.01 (0.00 to 0.01)</td>
<td>0.07</td>
<td>0.05 to 0.09</td>
<td>0.947</td>
</tr>
</tbody>
</table>

*An adjusted model includes maternal age, education, smoking, alcohol consumption, and Townsend score.*

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### Table 4

**Mean differences in birthweight difference among siblings according to exercise level in the 3 pregnancies, The Danish National Birth Cohort, 1996-2002, n = 324**

<table>
<thead>
<tr>
<th>Exercise Level</th>
<th>Change in Foetal Growth</th>
<th>Adjusted*</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exercise</td>
<td>-0.02 (-0.05 to 0.02)</td>
<td>-0.08</td>
<td>-0.06 to -0.09</td>
<td>0.137</td>
</tr>
<tr>
<td>Light exercise</td>
<td>-0.01 (-0.04 to 0.02)</td>
<td>-0.09</td>
<td>-0.07 to -0.10</td>
<td>0.086</td>
</tr>
<tr>
<td>Moderate exercise</td>
<td>-0.00 (-0.03 to 0.03)</td>
<td>-0.08</td>
<td>-0.06 to -0.09</td>
<td>0.257</td>
</tr>
<tr>
<td>Heavy exercise</td>
<td>0.01 (0.00 to 0.01)</td>
<td>0.07</td>
<td>0.05 to 0.09</td>
<td>0.947</td>
</tr>
</tbody>
</table>

*An adjusted model includes maternal age, education, smoking, alcohol consumption, and Townsend score.*

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Results - Foetal Growth Measures

<table>
<thead>
<tr>
<th>Exercise</th>
<th>&lt;br&gt;</th>
<th>P</th>
<th>95% CI</th>
<th>P</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>Gender</td>
<td>1.23</td>
<td>0.80-1.92</td>
<td>0.33</td>
<td>0.64-0.94</td>
<td>0.037</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>1</td>
<td>0.37</td>
<td>0.11-1.22</td>
<td>0.16</td>
<td>0.54-1.57</td>
<td>0.62</td>
</tr>
<tr>
<td>3-6</td>
<td>1.32</td>
<td>0.54-0.95</td>
<td>0.36</td>
<td>0.63-1.19</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>&gt; 6</td>
<td>1.06</td>
<td>0.82-1.44</td>
<td>0.52</td>
<td>0.54-1.42</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>1.31</td>
<td>0.75-2.13</td>
<td>0.38</td>
<td>0.70-1.14</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>&gt; 1</td>
<td>1.21</td>
<td>0.91-1.62</td>
<td>0.97</td>
<td>0.65-2.03</td>
<td>0.84</td>
<td></td>
</tr>
</tbody>
</table>

Adjustment Variables

- All analyses: Age, parity, occupational status, smoking
- Preterm birth: Gravidity, previous miscarriages, illnesses overall, abdominal diseases, subfertility, bleeding, coffee, alcohol, pre-pregnancy body mass index, working hours, working position, physically strenuous work, psycho-social job strain
- Foetal growth: Gestational age, pre-pregnancy body mass index, sex of the baby
- SGA: Pre-pregnancy body mass index

Conclusions on exercise during pregnancy

- Fewer preterm births among exercisers
- Perhaps fewer small-for-gestational-age babies
- No adverse effects of swimming
- Type of exercise was not important for the endpoints studied
- Reassuring results that support guidelines
Conclusions on today?

- An example of a large cohort study
- An example of own research

- What could be useful for you?
- What should we discuss now?

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Strenghts

- Sample size
- Prospectively collected exposure data

Limitations

- Weak exercise measure
- Only exercise not overall physical activity
- Selection into cohort

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Thank you
Selection bias

- Outcomes from registers (no loss to follow up)
- Selection at two levels (GP and individual)
- Selection into the cohort especially relevant in descriptive analysis (if DNBC-participants were healthier than others, then exercise prevalence is even lower in the general population)
- Associations were similar within DNBC and in the whole population (Nøhr 2006)
- No differential selection bias concerning the second interview (overall interview II participation was 92-93% no matter amount or type of exercise)
- Healthy exerciser effect (exercising women may be healthier and may also have a lower generic risk of e.g. PTB – exercise will turn out as preventive of PTB)
- Reverse causation (strongest protective effect of PTB in late pregnancy – the ones with symptoms or complications may have stopped. But excluding them did not change the results)

Information bias – misclassification of exposure

- Timing of exercise unclear (we did stratify by time of interview in survival analysis)
- Intensity of exercise (type as a proxy – pros and cons for using MET – we combined type and amount in one analysis)

Information bias – misclassification of outcome

- Substantial measurement error on GA (both errors in LMP and ULS – register data most often based on ULS. If exercise restricts foetal growth in early pregnancy, foetuses of exercising mothers will systematically be dated younger than those of non-exercisers)
- Substantial measurement error on baby size at birth (but unlikely to be differential according to exercise)
- SGA ne IUGR (the apparent contradictory results on mean BW and LGA may not be contradictory: Exercise may affect ‘normal’ growth but not pathological growth)
Confounding

• Underestimation of foetal growth impairment (under the assumption that exercise reduces foetal growth and that exercising women has a generic lower risk of FGI. Then we’d see less FGI among exercisers due to confounding from other factors, and thereby not get the whole growth-reducing effect of exercise)

• Reverse causation (if complications lead to restricted foetal growth they will bias the result towards showing reduced foetal growth among non-exercisers. But excluding them did not change the results)

• Confounders vs. intermediate factors (e.g. exercise leads to contractions that leads to PTB – one should not adjust. But excluding them did not change the results)

Paper III, AJOG – Table 3

<table>
<thead>
<tr>
<th>Exercise (wk)</th>
<th>Adjusted*</th>
<th>SE</th>
<th>% CI</th>
<th>Adjusted**</th>
<th>SE</th>
<th>% CI</th>
<th>Adjusted***</th>
<th>SE</th>
<th>% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ≤ 1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1 ≤ 2</td>
<td>5</td>
<td>25 (2)</td>
<td>35</td>
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<td>77</td>
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<td></td>
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<tr>
<td>1 ≤ 2</td>
<td>7</td>
<td>20 (2.7)</td>
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<td>15 (2.5)</td>
<td>20</td>
<td>15.49</td>
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<td>20 (10)</td>
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<td>15 (3)</td>
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<td>6.54</td>
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</table>

*Adjusted for: maternal age, parity, smoking, body mass index, social class, education, employment status

**Adjusted for: maternal age, parity, smoking, body mass index, social class, education, employment status, and birth weight

***Adjusted for: maternal age, parity, smoking, body mass index, social class, education, employment status, birth weight, and birth weight at delivery