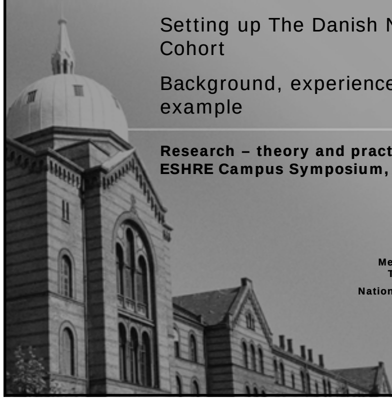


Setting up The Danish National Birth Cohort

Background, experiences and study example

Research – theory and practice
ESHRE Campus Symposium, Brussels

4-5 March 2010
Mette Juhl, Midwife, MPH, PhD
The Child Health Programme
National Institute of Public Health

National Institute of Public Health

UNIVERSITY OF SOUTHERN DENMARK

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 desease in adult life

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 deseases that we die from today. Both in rich and poor countries.

Cardio-vascular diseases was the most frequnt 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 deseases

The programming hypothesis

Mechanisms behind the hypothesis:

- Restricted intrauterine ressources
- 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 susceptiple for e.g. type 2 diabetes, hypertension and carido-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

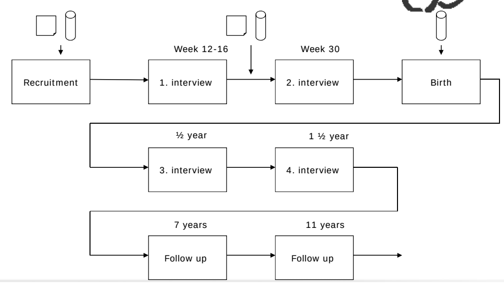
However … *better* for all pregnant women can easily be confused with *more* diet ('eat for two')

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

The Danish National Birth Cohort

Data collection overview



The Danish National Birth Cohort

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

The Danish National Birth Cohort

Design

Recruitment:	First antenatal visit to GP
Prenatal exposures:	CATI (week 12 and 30)
	Food frequency questionnaire (week 24)
Exposures in early childhood:	CATI (6 and 18 months)
Bio bank:	Blod samples from the mother (første trimester and week 25)
	Blood samples from the child (cord sample at birth)
Follow up	7 years
	11 years (or 12 or 13…)
	Adolescence, adulthood, and old age

The Danish National Birth Cohort

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'

NOT IN REGISTERS

The Danish National Birth Cohort

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)

The Danish National Birth Cohort

'A big machine'

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

Project group
Data bank (technology, documentation, code books, revised versions of interviews)
Bio bank (appr. 1,2 mio samples)
Interviewer corps (adjudication/'ask for bids', on-going negociations, quality vs. quantity, education, supervision)

Leading group (internal)
Stearing 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% af children aged of 18 months had a mother who had participated in all four interviews

Use of data

- Puplic database for research within the aims of the study
- All projects need to be approved by external stearing group
- Maximum use of interview data
- Restrivtive 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

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 gestional 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. Distribution (%) of physical exercise according to gestational age at birth, Danish National Birth Cohort, 1996–2002

Exercise	Data from pregnancy interview 1* (n = 87,232)					Data from pregnancy interview 2† (n = 81,001)		
	No. of pregnancies	Completed weeks of gestation at birth				No. of pregnancies	Completed weeks of gestation at birth	
		22–27 (n = 333)	28–31 (n = 435)	32–36 (n = 3,511)	≥37 (n = 82,953)		22–36 (n = 2,949)	≥37 (n = 78,052)
Hours per week								
0	55,226	66	64	65	63	56,366	73	70
>0–≤1	11,616	12	12	13	13	11,801	13	15
>1–≤2	8,749	10	9	9	10	6,534	7	8
>2–≤3	4,762	5	6	6	5	2,704	3	3
>3–≤5	4,312	5	6	5	5	2,251	3	3
>5	2,373	2	2	3	3	1,194	1	1
Preferred type								
None	55,226	66	64	65	63	56,366	73	70
Swimming	6,901	9	8	7	8	8,517	10	11
Low-impact activities‡	9,857	9	11	11	11	8,501	9	11
High-impact activities§	2,459	2	2	2	3	244	0	0
Working out/fitness training	1,473	1	2	1	2	556	1	1
Bicycling	8,001	10	9	9	9	4,299	5	5
Horseback riding	988	1	1	1	1	224	0	0
Other	2,133	2	3	2	2	2,143	2	3

* There were 194 missing values for exercise variables in the first interview.
† There were 151 missing values for exercise variables in the second interview.
‡ Low-impact activities were defined as activities in which at least one foot is always on the ground (included were: aerobics/gymnastics for pregnant women, aerobics/gymnastics, dancing, walking/hiking, yoga).
§ In high-impact activities, there are moments at which both feet leave the ground simultaneously (included were: jogging, ball games, racket sports).

Results – Preterm birth

TABLE 3. Crude and adjusted hazard ratios for preterm birth according to amount of physical exercise during pregnancy (n = 87,232), Danish National Birth Cohort, 1996–2002

Exercise	Crude HR*	Adjusted HR†	95% CI*	p for trend	p for trend‡
None	1	1			
Any	0.86	0.82	0.76, 0.88		
Hours/week					
0	1	1		0.0002	0.2461
>0–≤1	0.82	0.80	0.72, 0.87		
>1–≤2	0.86	0.81	0.72, 0.92		
>2–≤3	0.93	0.89	0.76, 1.05		
>3–≤5	0.94	0.89	0.75, 1.06		
>5	0.87	0.81	0.64, 1.04		

* HR, hazard ratio; CI, confidence interval.
† Adjusted for age, gravidity, parity, previous spontaneous abortions, uterine fibroids/malformations/cone biopsy, subfecundity, coffee consumption, alcohol consumption, smoking, body mass index, job status, working hours, working position, and job strain.
‡ When zero exposure was separated from the dose-response.

Results – Preterm birth

TABLE 5. Crude and adjusted hazard ratios for preterm birth according to possible changes in physical activity level during pregnancy (n = 67,861), Danish National Birth Cohort, 1996–2002

Exercise (yes/no) (+/−)		No. of pregnancies	Crude HR*	Adjusted HR†	95% CI*
<22 weeks‡	≥22 weeks§				
−	−	34,767	1	1	
+	−	12,233	1.08	1.06	0.96, 1.18
−	+	8,128	0.89	0.83	0.73, 0.95
+	+	12,733	0.86	0.81	0.72, 0.91

* HR, hazard ratio; CI, confidence interval.
† Adjusted for age, gravidity, parity, previous spontaneous abortions, uterine fibroids/malformations/cone biopsy, subfecundity, coffee consumption, alcohol consumption, smoking, body mass index, job status, working hours, working position, and job strain.
‡ Data from the first pregnancy interview, carried out before 22 completed weeks of gestation.
§ Data from the second pregnancy interview, carried out between 22 and 36 completed weeks of gestation, inclusive.

Results - Foetal Growth Measures

Public Health

TABLE 2

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

	Birthweight, g (mean = 3575)				Birth length, cm (mean = 52.2)				Ponderal index, g*100/cm^3 (mean = 2.53)			
Exercise (h/wk)	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend
0	0	0	–	0.1276	0	0	–	0.1968	0	0	–	
>0–≤1	−6	1	−8 to 10		0.03	0.01	−0.03 to 0.06		−0.01	−0.009	−0.007 to 0.06	0.7429
>1–≤2	−6	5	−6 to 15		0.03	0.02	−0.03 to 0.07		−0.04	−0.04	−0.1 to 0.04	
>2–≤3	−14	0	−14 to 13		−0.007	−0.009	−0.07 to 0.06		−0.04	−0.03	−0.1 to 0.06	
>3–≤4	−30	−8	−26 to 9		−0.04	−0.01	−0.09 to 0.07		−0.05	−0.04	−0.2 to 0.08	
>4–≤5	−24	−6	−27 to 16		−0.01	−0.01	−0.1 to 0.1		−0.05	−0.05	−0.2 to 0.1	
>5	−46	−11	−30 to 7		−0.14	−0.07	−0.2 to 0.02		−0.05	−0.03	−0.2 to 0.1	

Juhl. Physical exercise during pregnancy and fetal growth measures. Am J Obstet Gynecol 2009.

Results - Foetal Growth Measures

Public Health

TABLE 2

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

	Abdominal circumference, cm (mean = 33.5)				Head circumference (cm) (mean = 35.3)				Placental weight (g) (mean = 661)			
Exercise (h/wk)	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend	Crude[a]	Adjusted[b]	95% CI	P value for trend
0	0	0	–		0	0	–	< .0001	0	0	–	0.0604
>0–≤1	−0.02	0.02	−0.02 to 0.07	0.0460	−0.02	−0.004	−0.04 to 0.03		−7	−3	−6 to 0	
>1–≤2	−0.04	0.02	−0.03 to 0.07		−0.04	−0.02	−0.06 to 0.02		−4	1	−3 to 4	
>2–≤3	−0.11	−0.03	−0.09 to 0.04		−0.08	−0.05	−0.1 to −0.003		−7	0	−5 to 4	
>3–≤4	−0.18	−0.07	−0.2 to 0.02		−0.11	−0.06	−0.1 to 0.0005		−14	−6	−12 to 0	
>4–≤5	−0.19	−0.1	−0.2 to 0.01		−0.12	−0.08	−0.2 to −0.002		−13	−6	−13 to 2	
>5	−0.21	−0.1	−0.1 to 0.04		−0.21	−0.1	−0.2 to −0.06		−13	−4	−10 to 2	

Juhl. Physical exercise during pregnancy and fetal growth measures. Am J Obstet Gynecol 2009.

Results - Foetal Growth Measures

Public Health

TABLE 4

Mean differences in birthweight difference among siblings according to exercise level in the 2 pregnancies, The Danish National Birth Cohort, 1996-2002, n = 5521

		Change in birthweight, g (mean [illegible])			
Change in exercise between the 2 pregnancies	N	Crude[a]	Adjusted[b]	95% CI	P value
From much exercise[c] to nothing	[illegible]	[illegible]	30	−4 to 64	[illegible]
From much to little exercise or from little to nothing	859	57	44	11–77	
No change[d]	[illegible]	0	0	–	
From nothing to little or from little to much	[illegible]	21	[illegible]	[illegible]	
From nothing to much	[illegible]	[illegible]	[illegible]	[illegible]	

Results - Foetal Growth Measures

TABLE 6
HRs of SGA and LGA according to leisure time physical activity, The Danish National Birth Cohort, 1996–2002, n = 79,692

	SGA[a]			LGA[b]		
Exercise	HR[c]	95% CI	P value for trend	HR[c]	95% CI	P value for trend
No exercise	1			1		
Exercise	0.88	0.83–0.93		0.90	0.86–0.96	
h/wk						
0	1	–	0.1168	1	–	0.0057
>0–≤1	0.87	0.81–0.93		0.98	0.89–1.05	
>1–≤2	0.83	0.76–0.91		0.90	0.83–0.98	
>2–≤3	1.00	0.89–1.14		0.85	0.74–0.98	
>3–≤5	0.83	0.73–0.95		0.89	0.77–1.04	
>5	1.04	0.87–1.23		0.72	0.57–0.91	

[illegible]

Adjustment Variables

All analyses: Age, parity, occupational status, smoking

Preterm birth: Gravidity, previous miscarriages, illnesses overall, abdominal diseases, subfecundity, bleeding, coffee, alcohol, pre-pregnancy body mass index, working hours, working position, physically strenuous work, psycho-social jobstrain

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?

Thank you

Conclusions

Strenghts

- Sample size
- Prospectively collected exposure data

Limitations

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

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 3

Adjusted mean differences in birthweight (g) according to leisure time physical activity and smoking during pregnancy, The Danish National Birth Cohort, 1996-2002, n = 79,692

	Smoking in early/midpregnancy, cig/d					
	0 (n = 58,425)		1 – < 10 (n = 11,627)		10+ (n = 9418)	
Exercise (h/wk)	Adjusted*	95% CI	Adjusted*	95% CI	Adjusted*	95% CI
0	0	–	0	–	0	–
>0–≤1	−11	−22 to −1	34	9–59	51	19–82
>1–≤2	9	21 to 2	33	5–60	79	43–115
>2–≤3	−14	−30 to 1	[illegible]	−21 to 51	92	[illegible]
>3–≤4	−29	−54 to −3	[illegible]	[illegible]	[illegible]	[illegible]
>4–≤5	−18	−43 to 7	36	−27 to 99	26	−62 to 111
>5	−33	−64 to −1	6	−41 to 54	45	−17 to 107

[illegible]

CI, confidence interval.

* Adjusted for gestational age, sex, maternal age, prepregnant body mass index, occupational status, parity, and smoking.

[illegible]