

IMPACT OF MATERNAL NUTRITION ON CHILDREN'S HEALTH AND DEVELOPMENT

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Talk to be given at The JECS Symposium at the 21st World Congress of Epidemiology in Japan

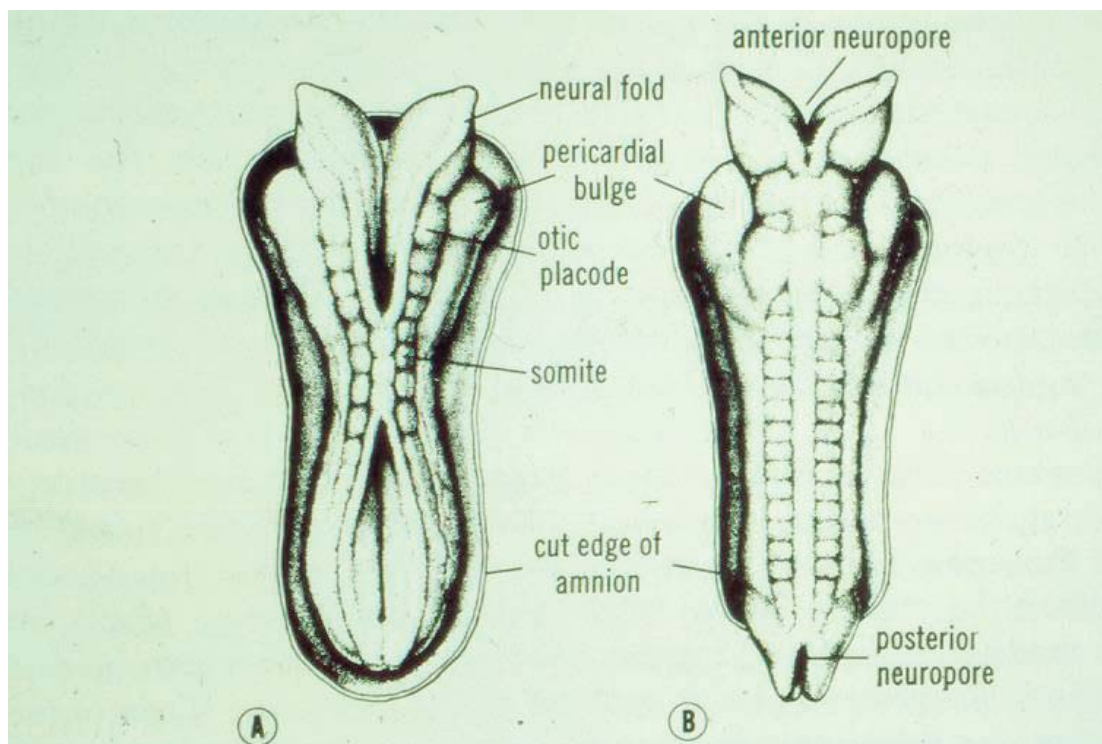
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IMPACT OF MATERNAL NUTRITION ON MATERNAL AND CHILD HEALTH – OVERVIEW OF TALK

- ❖ Examples of 'substantiated relationships' – *five examples*
- ❖ Examples of 'hypothetical relationships'
- ❖ Research opportunities in Denmark

FOLIC ACID AND NEURAL TUBE DEFECTS

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Very strong evidence, deriving mainly from three trials

Two trials with randomization

- ❖ MRC Vitamin trial. Lancet 1991; 388: 131
 - 4 mg folic acid / day reduces risk of recurrence of neural tube defects (from 3.5% to 1.0%)
- ❖ Czeizel & Dudas. NEJM 1992; 327: 1832
 - 0.8 mg folic acid per day (+ other vitamins and minerals) reduces risk among 'all' pregnant women

One trial without randomization

- ❖ Berry et al. NEJM 1999; 341: 1485
 - China-U.S. Collaborative Project for Neural Tube Defect Prevention with >200,000 newly married women in China encouraged to take folic acid
 - 0.4 mg folic acid per day, without other vitamins, is sufficient to reduce the risk

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FOLIC ACID AND NEURAL TUBE DEFECTS

General recommendation to take 0.4 mg folic acid in the periconceptual period

Mandatory fortification of staple foods with folic acid has been initiated in many countries – outside Europe – **Debatable!**

Denmark example:

Should we expose 5 mil. people to folic acid to prevent 30-50 cases per year of NTDs?

Olsen & Knudsen. *Folic acid for the prevention of neural tube defects: The Danish experience.* **Food and Nutrition Bulletin**, vol. 29, 2008: S205-9

Olsen & Enni. *Should Danish foods be fortified with folic acid?*

Ugeskrift for Læger 2015

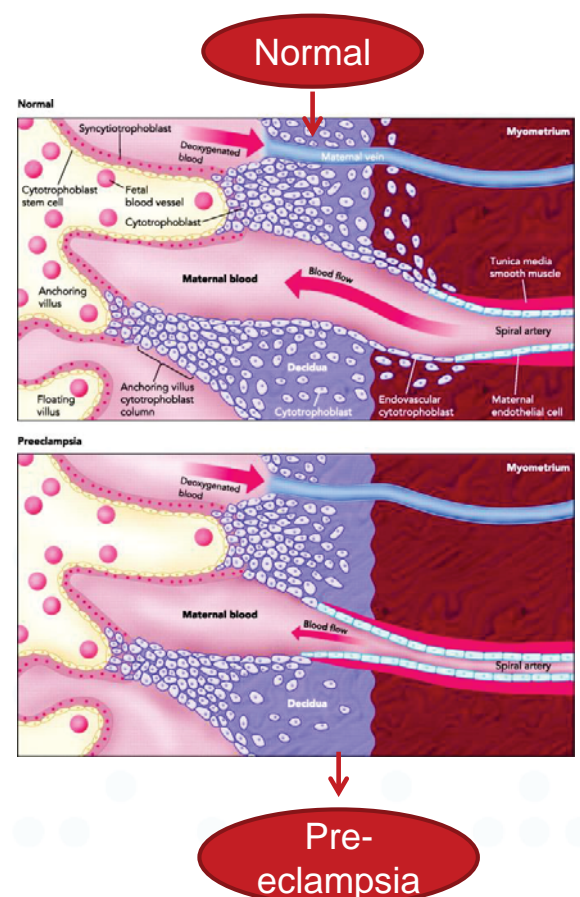
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CALCIUM AND PREECLAMPSIA

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PREECLAMPSIA - PATHOGENESIS

- ❖ Preeclampsia is a pregnancy specific syndrome characterized by new onset **hypertension and proteinuria**
- ❖ An initiating event is reduced placental perfusion
- ❖ This is followed by widespread dysfunction of the maternal vascular endothelium and hypertension by mechanisms that remain to be defined



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Important public health problem

- ❖ Affects 2-10 % of all pregnancies
- ❖ May develop in to eclampsia or HELLP syndrome
- ❖ Major cause of maternal mortality
- ❖ Contributes greatly to fetal and neonatal mortality

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PREECLAMPSIA – CALCIUM

Idea came from a population comparison

- ❖ Villar and Belizan AJOG 1980

Mayan Indians in Guatemala, who traditionally soak their corn in lime water ($\text{Ca}(\text{OH})_2$) before cooking, had a high calcium intake and a low incidence of preeclampsia and eclampsia.



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Systematic review based on 14 trials

- Hofmeyr et al. Cochrane Review 2014
 - 15,730 women were randomized
 - Calcium supplementation (≥ 1 g/day) reduces risk of preeclampsia - but substantial heterogeneity between studies

Critical consideration:

Calcium may ameliorate a symptom (the hypertension) of pre-eclampsia but may not repair the underlying pathology of pre-eclampsia and prevent its associated (rarer) serious complications (e.g. HELLP syndrome)

– **requires very large trials**

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IODINE DEFICIENCY AND CRETINISM

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Cretinism

- ❖ A congenital disease characterized by physical deformity, dwarfism, and mental retardation
- ❖ Maternal iodine deficiency → Fetal hypothyroidism → Cretinism



FIGURE 1. Typical neurological cretin (on right), from western China.

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IODINE DEFICIENCY AND CRETINISM

- ❖ Papua New Guinea - The Jimi River Valley
- ❖ Highland area with endemic goitre and cretinism
- ❖ Randomized trial conducted in 1966



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West Highland District of Papua New Guinea

- Pharoah POD, Buttfield LH, Hetzel BS. **Lancet** 1971; i: 308-310.
- Trial hypothesis: preventing maternal iodine deficiency prevents cretinism
- 27 villages, population of 16,500 in 1966
- **'Controlled trial' in connection with 1966 census:**
 - Every second family: all members injected with **iodinated oil**
 - Every second family: all members injected with **saline**
- **Visits again in 1967, 1969, and 1970**
- 1047 births, 883 still alive, 832 examined
 - **Iodinated oil: 7 cretins among 498 children (1.4%)**
 - **Untreated: 26 cretins among 534 children (4.9%)**

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FISH OIL AND ASTHMA IN THE CHILD

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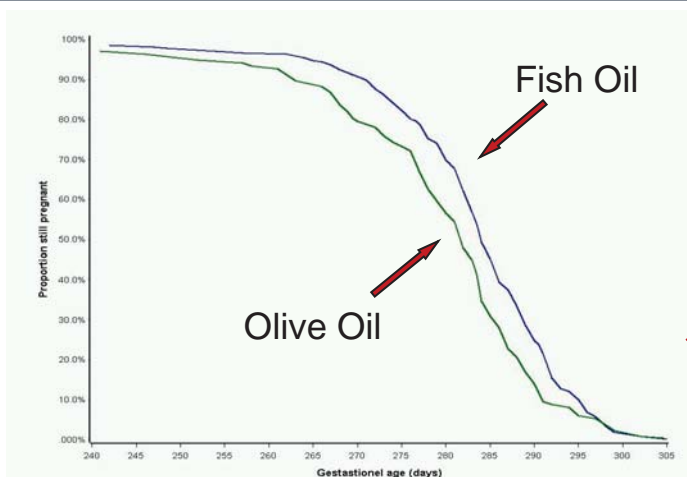
Trial with fish oil to pregnancy women, 1990

• Olsen SF et al. Lancet 1992

- 533 uncomplicated pregnancies in Denmark
- Randomized in gestation week 30 to fish oil

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FISH OIL IN PREGNANCY AND ASTHMA IN THE CHILD



Trial results v. results from population comparison

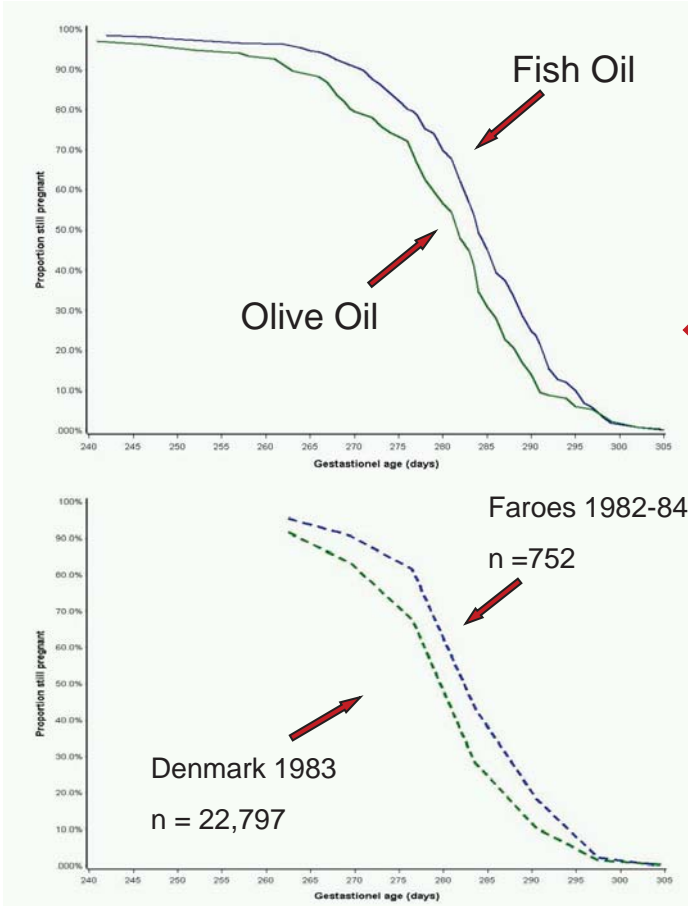
Pregnancy duration visualized with 'survival curves'

← **Result from trial (Danish women)**
Olsen SF et al. Lancet 1992

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Trial results v. results from population comparison

Pregnancy duration visualized with 'survival curves'



← **Result from trial (Danish women)**
Olsen SF et al. Lancet 1992



Faroese
Population with high fish intake

Denmark

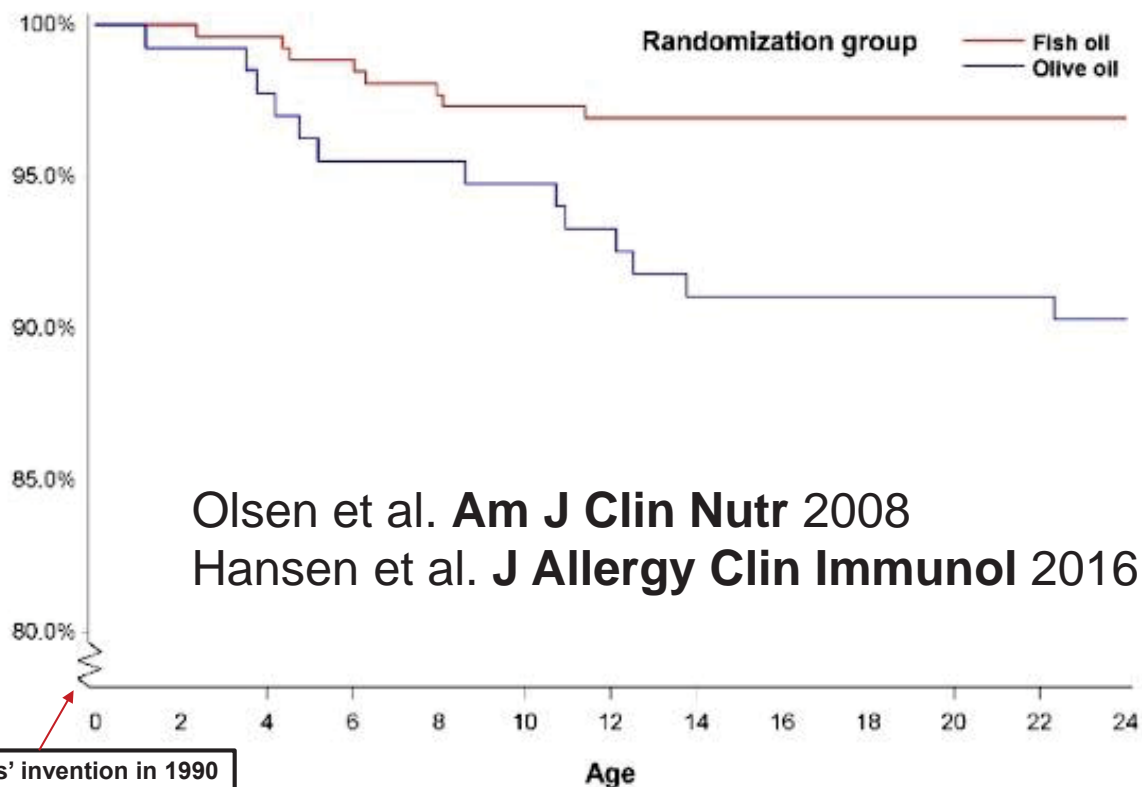
← **Population comparison (Faroese v. Danish women)**
Olsen SF et al. Lancet 1986

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A

Asthma hospitalization

RCT with fish oil to pregnant women conducted in 1990: 24y follow up



Olsen et al. **Am J Clin Nutr** 2008
Hansen et al. **J Allergy Clin Immunol** 2016

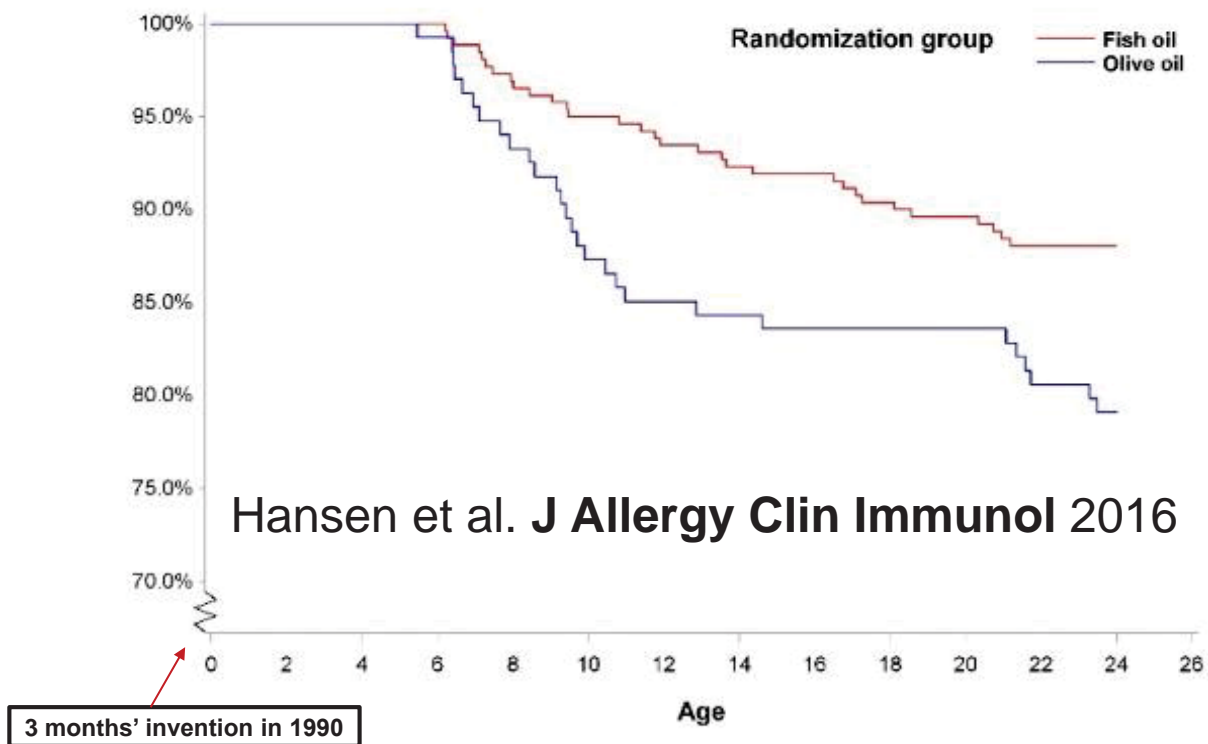
3 months' invention in 1990

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B

Asthma medication

RCT with fish oil to pregnant women conducted in 1990: 25y follow up



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FAMINE IN FETAL LIFE AND TYPE 2 DIABETES

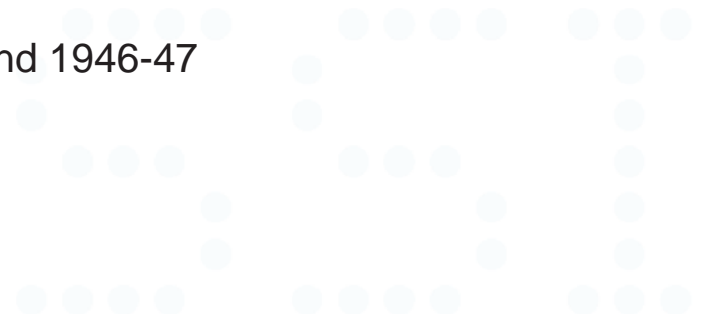


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FAMINE IN FETAL LIFE AND TYPE 2 DIABETES

“Experiments of Nature” *studies of man made famines*

- ❖ Siege of Leningrad (St Petersburg): 1941-44
- ❖ Dutch Hunger Winter: 1944-45
- ❖ Great Chinese Famine: 1959-1961
- ❖ Austrian famines: 1918-19, 1938 and 1946-47
- ❖ Great Ukrainian Famine: 1933



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“Experiments of Nature” *studies of man made famines*

- ✚ Siege of Leningrad (St Petersburg): 1941-44
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- ✚ Great Chinese Famine: 1959-1961
- ✚ **Austrian famines: 1918-19, 1938 and 1946-47**
- ✚ **Great Ukrainian Famine: 1933**

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Three Austrian famines Turner et al. PNAS 2013

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Three Austrian famines (Turner et al. PNAS 2013)

✿ 1918-19

Collapse of Austro-Hungarian Empire, severing Austria from the areas upon which it relied for the majority of agricultural products; exacerbated by “starvation embargo”, i.e. no food transport into the country

✿ 1938

Global and local crises due to Great Depression, civil war, and decline in international trade and staple crop yields; food availability recovered rapidly at German annexation

✿ 1946-47

Allied occupation, extensive war damage lead to severe food shortage; relieved at Marshall Plan in 1948

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PROPORTION OF POPULATION UNDER PHARMACEUTICAL TREATMENT FOR DIABETES DURING 2006-7, ACCORDING TO YEAR OF BIRTH

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Great Ukrainian Famine 1933



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Great Ukrainian Famine 1933

- Result of the Soviet Union government's forced collectivization of agriculture
- 1-10 million excess deaths in 1933
- Examine prevalence of type 2 diabetes 70 years later

(Figure has been deleted due to copyright)



Great Ukrainian Famine 1933: prevalence of type 2 diabetes 2000-8

(Figure has been deleted due to copyright)

Lumey, Khalangot, Vaiserman. Lancet Diabetes Endocrinol 2015, Fig. 2

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Great Ukrainian Famine 1933: prevalence of type 2 diabetes 2000-8

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Lumey, Khalangot, Vaiserman. Lancet Diabetes Endocrinol 2015, Fig. 3

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Conclusion from famine studies

- ❖ Famine studies support that early life factors can increase risk of developing type 2 diabetes in adult life
 - Famine per se, i.e. diet?
 - Distress?

Mechanisms

Fetal 'programming'? epigenetic 'memory'?

Recommended literature

- ❖ Lumey LH, Vaiserman AM, eds. **Early life nutrition and adult health and development**. Lessons for changing dietary patterns, famines and experimental studies. New York, NY: Nova Science. 2013
- ❖ Rooij SR et al. Famines in the last 100 years: Implications for diabetes. **Curr Diab Rep** 2014; 14: 536
- ❖ Lumey LH et al. Association between type 2 diabetes and prenatal exposure to the Ukraine famine of 1932–33: a retrospective cohort study. **Lancet Diab & Endocr** 2015 Oct 787-794.

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EXAMPLES OF 'SUBSTANTIATED RELATIONSHIPS' -- ACCORDING TO MY SUBJECTIVE JUDGEMENT

- ❖ **Folic acid and neural tube defects**
- ❖ **Calcium and preeclampsia / hypertension in pregnancy**
- ❖ **Maternal iodine deficiency and Cretinism**
- ❖ **Fish oil in pregnancy and asthma in the child**
- ❖ **Famine in fetal life and type 2 diabetes**

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- ⌘ Examples of ‘substantiated relationships’
- ⌘ **Examples of ‘hypothetical relationships’**
- ⌘ Research opportunities in Denmark

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EXAMPLES OF ‘HYPOTHETICAL RELATIONSHIPS’

Diet in pregnancy and maternal and child health – ‘hypothetical relationships’

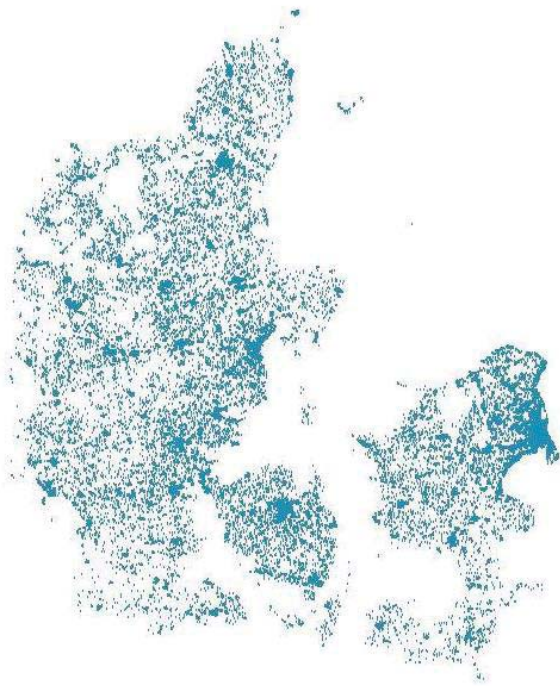
- ⌘ **Adverse outcomes appearing during pregnancy, or shortly after**
 - Malformations – *retinol in excessive amounts is teratogenic, but also in relatively low amounts?*
 - Preeclampsia – *some antioxidants may be preventive (but it seems that vitamins C and E are not!)*
 - Gestational diabetes – *red meat may increase, and fruit & vegetables may reduce risk*
 - Impaired fetal growth – *cow milk may increase growth*
- ⌘ **Adverse outcomes appearing during childhood – *very uncertain***
 - Cognitive development – *is DHA essential to secure normal fetal brain development?*
 - Bone development – *is low vitamin D status a risk factor for impaired bone development?*
 - Childhood cancer – *is cured meat a risk factors for brain tumors? are fruit & vegetables protective to ALL?*
 - Type 1 diabetes – *do omega-3 fatty acids reduce risk? does low vitamin D increase risk?*
- ⌘ **Adverse outcomes appearing during adulthood – *highly uncertain***
 - Cardio-metabolic diseases – *role of protein in pregnancy?*
 - Breast cancer – *phytoestrogens? omega-6 fatty acids in pregnancy?*

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- Examples of ‘substantiated relationships’
- Examples of ‘hypothetical relationships’
- **Research opportunities in Denmark**

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COHORTS WITH INFO ON MATERNAL DIETARY EXPOSURES



A nationwide birth cohort...

- ❖ 101,042 women recruited while in their early pregnancies for long term follow of themselves and their offspring
- ❖ Recruited during 1996-2003
- ❖ Around 96,000 liveborn children, who are followed through questionnaires and registry linkages

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DANISH NATIONAL BIRTH COHORT

Data sources

- ❖ Enrolment form (gw10)
- ❖ 4 telephone interviews (gw12, gw30, 6m, 18m)
- ❖ 3 blood samples (gw9-10, gw25-26, umbilical cord)
- ❖ Questionnaire on diet in pregnancy (gw25)
- ❖ Questionnaire to mother when child is 7y
- ❖ Questionnaire to mother and child when child is 11y
- ❖ Food Frequency Questionnaire when child is 14y

Linkages to **national registries** by means of a unique ID-number for every citizen

Jørn Olsen et al. Scand J Soc Medicine 2001

DNBC Scientific and Management Group

- ❖ Mads Melbye
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- ❖ Katrine Strandberg-Larsen
- ❖ Ellen Aagaard-Nøhr

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Method to assess pregnancy diet Questionnaire in gestation week 25

Food frequency questions:

- ❖ 19 A4 pages long
- ❖ Around 300 food items
- ❖ One month back in time (from gw25)
- ❖ Fixed time categories
- ❖ Fixed food item names

Also questions on food supplements

SF Olsen et al. Perinatal Pediatric Epidemiology 2007

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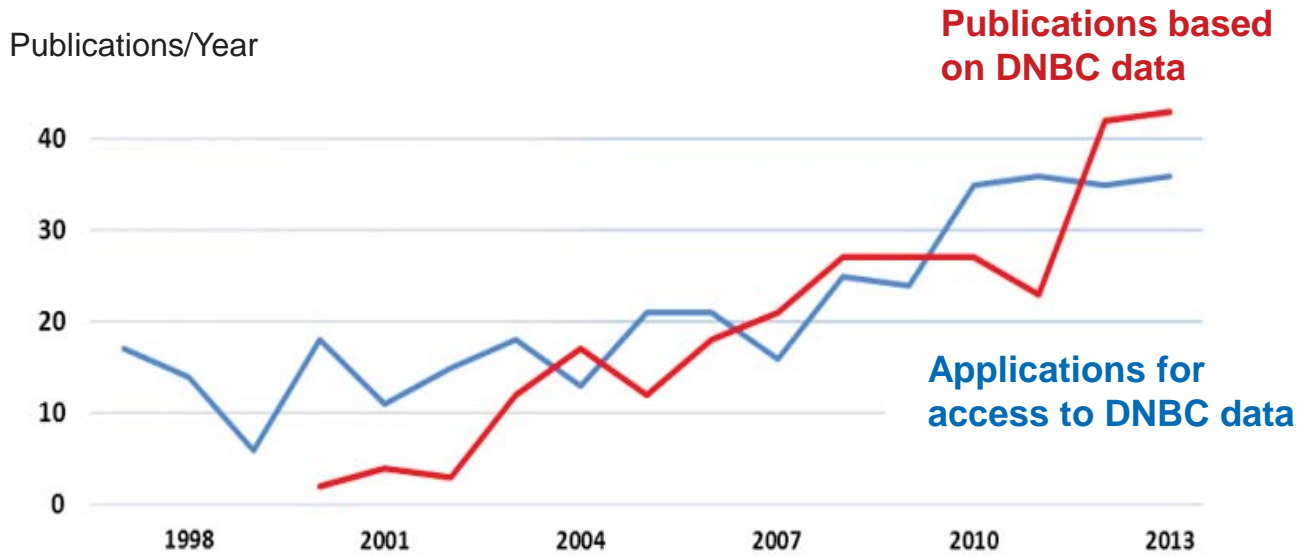
Dietary questionnaire at 14 years

- ❖ 146 food items divided in to 8 food groups:
 - Beverages
 - Dairy products
 - Bread and cereals
 - Spread on bread
 - Lunch and dinner meals
 - Side dishes
 - Fruit and vegetables
 - Snack and desserts
- ❖ 19 questions regarding height, weight, physical activity level, meal habits, use of supplements and sleep patterns

❖ ~40,000 DNBC children have completed the questionnaire by now

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DNBC publications



Danish National
Birth Cohort

**INTERNATIONAL COLLABORATION ACROSS COHORTS
ON THE HEALTH IMPACT OF DIET IN PREGNANCY**



very large

INTERNATIONAL COLLABORATION ACROSS COHORTS ON THE HEALTH IMPACT OF DIET IN PREGNANCY

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PERSPECTIVE FOR INTERNATIONAL COLLABORATION

- **At present, three very large cohorts exist where diet has been assessed concurrently during pregnancy – each with around 100,000 mother child pairs:**
 - Danish National Birth Cohort (DNBC), 1996-2003
 - Norwegian Mother-Child Cohort (MoBa), 1999-2008
 - Japanese Environment Childrens Study (JECS), 2011-14
- **Important potential for coordinated analyses between the cohorts, examining impact on health of the diet consumed in pregnancy**

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The two cohorts have common history

Share many design features

Particularly, the two FFQs have many similarities

- ❖ Both FFQs have comparable time scales
- ❖ They have similar general structure
- ❖ They have many identical or near-identical food items
- ❖ Possible to define food groups that are comparable, or roughly comparable

MoBa women had, compared to DNBC women, on average:

- Lower intake of
 - Milk, by 39%
 - Butter, by 54%
 - Potatoes, by 65%
- Higher intake of
 - Fish, by 39%
 - Rice, by 41%
- Most other differences were below 20%

Olsen, Birgisdottir, Halldorsson, Brantsæter, Haugen, Strøm, Meltzer.
Acta Obstetricia et Gynecologica Scandinavica 2014; 93:1131-40.

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❖ Foundations

- March of Dimes Birth Defects Foundation
- Danish Council for Strategic Research
- Danish Council for Independent Research
- Nordea-fonden
- European Union
- National Institutes of Health

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THANK YOU FOR YOUR ATTENTION

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