Vitamin D during fetal life and long term health consequences – the D-tect study

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Background – D-tect study

Low vitamin D early in life may play a role to development of abnormalities or diseases in these organs/tissue

- Nutrient and pro-hormone
- Actions mediated via nuclear vitamin D receptors (VDR)
- Vitamin D receptors found from most tissues and organs of the body
  - Bone, Brain, Breast, Heart, Immune cells, Placenta, Pancreas, Prostate, Etc.
Vitamin D in Northern European populations

Most obtained through sunlight induced skin synthesis, smaller amount from diet/supplements

- Synthesized in skin after UVB exposure – can occur only 6 months of the year
- Dependent during winter on supplies from food and/or supplements/fortification
Results – BSMB study

Vitamin D intake from diet

Among the 68,447 participating Danish pregnant women the mean daily vitamin D intake from the diet was: 3.56 ± 2.05 μg
Among the 68,447 participating Danish pregnant women the mean daily vitamin D intake from supplements was: 5.67 ± 5.20 μg
In 68,447 Danish pregnant women the mean vitamin D intake was 9.23 ± 5.60 μg per day.
Fortification policies

- 1961 – 85 vitamin D fortification of margarine was mandatory (1.25µg/100g)
- 1972 – 76 vitamin D fortification of low fat milk was permitted (2.5 – 3.8µg/1000g)
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- Fortified margarine → 15 % of the dietary vitamin D
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– Fortified margarine → 15 % of the dietary vitamin D
– Fortified low fat milk → unknown (not mandatory)
Figur 3: Forsyningen af smør og margarine m.m.

Kilde: Statistik. årbog, diverse årgange. Veterinærdirektorats margarineproduktionsstatistik ’91 og ’92


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Concept:

1) low vitamin D intake and status prevalent - also among pregnant women and their offspring
2) some results show that foetal vitamin D status is relevant for birth outcomes (birth weight)
3) few studies available to examine if foetal vitamin D is also relevant for future health (obesity and diabetes type 1)
4) generally long term health consequences of low vitamin D in fetal life unknown
D – testing disease study idea:

• A societal intervention study that examines effects on health outcomes occurring up to 50 year later, of *low vitamin D during growth spurts*, such as foetal life, adiposity rebound and puberty, while also taking secular trends, season and trimester into account,

• Fractures, birth weight, TD1 and obesity
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• A means to examine if exposure to *vitamin D fortified foods* has beneficial affects the development of health outcomes (fractures, birth weight, TD1 and obesity) in child- and adulthood

• A case-cohort study that examines *foetal* serum 25(OH)D levels (blood from babies taken within 72 hours after birth) among those developing adverse health outcomes compared to random controls
Idea: D – tecting disease

- **1961 – 85** vitamin D fortification of margarine was mandatory (1.25µg/100g)
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- foetal life, adiposity rebound and puberty

Includes approx. 3 mio. individuals born 1930 – 90
Entire birth cohorts followed from birth till 2013
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Entire birth cohorts followed from birth till 2013

(PKU cards: stored blood from individuals born since 1981 – we can examine development of health outcomes (Diabetes, fractures, obesity pre-eclampsia) as children or adults, in relation to levels of vitamin D at birth)
Seasonal variation in serum 25(OH)D

Hyppönen and Power, AJCN 2007
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The D tect study – Timing of vitamin D fortification of margarine and milk

- Initiation of mandatory fortification of margarine ('61)
- Initiation and termination of permission to fortify low fat milk ('72 & '76)
- Termination of mandatory fortification of margarine ('85)

- 45 years of follow-up
- Approx. 35 years of follow-up
- Approx. 30 years of follow-up
- 20 years of follow-up

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Data usability –
National Patient Registry

Diagnosed since 1977 in LPR

Initiation of mandatory fortification of margarine ('61)
Initiation and termination of permission to fortify low fat milk ('72 & '76)
Termination of mandatory fortification of margarine ('85)

Diagnosed from 18 years around 1961
Diagnosed from 7 years around 1977
Diagnosed from 2 years around 1976
Diagnosed since birth around 1985

45 years of follow-up
Approx. 35 years of follow-up
Approx. 30 years of follow-up
20 years of follow-up

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Definition of exposure groups – each 2 full years. Vertical lines: timing of vitamin D fortification events. Margarine fortification was initiated on the 1\textsuperscript{st} January 1961 and terminated on the 1\textsuperscript{st} June 1985. Milk fortification was permitted from the 1\textsuperscript{st} January 1972 to the 1\textsuperscript{st} January 1976.
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Washout period
6 months to establish margarine on the shelves + 9 months pregnancy
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Washout period 6 months to establish margarine on the shelves + 9 months pregnancy

Washout period 6 months shelf life eliminations + 9 months pregnancy

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The D tect study – Timing of vitamin D fortification of margarine and milk

Initiation of mandatory fortification of margarine ('61)
Initiation and termination of permission to fortify low fat milk ('72 & '76)
Termination of mandatory fortification of margarine ('85)

- 45-50 years of follow-up
- 35-40 years of follow-up
- 30-35 years of follow-up
- 20-25 years of follow-up

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D – tecting disease

- Registries:
  - The Civil Registration System (Unique CPR number)
  - Danish National Patient Registry (all hospitalisations, incl. fractures)
  - Danish diabetes registry
  - Danish MS registry
  - Danish RA registry
  - The Danish Childhood Diabetes Registry (T1D)
  - The Danish Diabetes registry (T1D and T2D)
  - The Copenhagen School Health Record Registry (obesity and birth weights)
  - National Birth Registry (maternal obesity, birth complications, birth weight)
  - Statistics Denmark Fertility Database (socio economic status)
  - Biological Specimen Bank for Neonatal Screening (blood from all new born babies)
D-tect study

Pros
- **No need for** information on *individual* food intake
- Confounders will be equally distributed
- The only difference is exposure to intervention/fortification

Cons
- Possibility of *other* societal or environmental change *simultaneous* with the change in fortification practice = other exposure
- Steady yearly changes in disease = outcomes prevalence/incidence -> secular trend
Sun exposure around fortification initiation and termination

• 24 months exposure before and after initiation in 1961 (including washout period)
D – tecting disease

The D-tecting disease study (D-tect)

Funded by DSF
Halfway through the 4 year project period

Obesity, diabetes1 and fractures

Obesity (PhD student Camilla Bjørn Jensen)
T1D (Post doc. Ramune Jacobsen)
Fractures (wrist, arm and clavicle, PhD student Mina Hændel)

Schizophrenia (Senior researcher Joachim Knop),
T2D (PhD student Amelie Keller),
pre-eclampsia (PhD student Maria Stougaard)
- Astma, MS, RA, gestational diabetes,
Preliminary Results

• Variations in 25(OH)D by season before and after the termination of the mandatory fortification program
• Results for risk of T1D before and after the termination of the mandatory fortification program
• Results for risk of schizophrenia before and after the termination of the mandatory fortification program
Variations in 25(OH)D by season before and after the termination of the mandatory fortification program
These early results (with limited power) suggest:

– Season variation in 25(OH)D measured in DBS (PKU cards) from Danish newborns

– A tendency towards Higher 25(OH)D extracted from DBS for those that got extra vitamin D from fortification compared to those who did not – particularly those born Aug-Dec
Results for risk of T1D before and after the termination of the mandatory fortification program
T1D or insulin dependent diabetes

- Multifactorial aetiology:
  - environmental risk factors
  - genetic predisposition
- Insulin-secreting beta cell destroyed due to Th1-mediated immunity up-regulation
Vitamin D and T1D

- Vitamin D
- Th2
- Th1
- Type 1 diabetes ↓
- Pre-eclampsia ↓
Importance of adjustment for secular trends in T1D in the D tect study
Analysis

• Cox regression with time to first incidence
  – Exposure
  – Exposure + sex + month of birth
  – Exposure + secular trend
  – Exposure + secular trend + sex + month of birth
vitamin D and Type-1 diabetes

• These early results suggest:
  – Extra vitamin D in foetal life seems to reduce the risk of incident type-1 diabetes before age 15 years
  – These effects may be stronger for girls than boys
Approach: Secular trend

- Secular trend -> Birth cohort effect
- T1D risk depends on the year of birth - > the later in 1980’ies you’re born, the higher the risk of T1D

Svensson et al. Diabetes Care, 2002
Approach: Linear spline modelling 1
Approach: Linear spline modelling 2
Approach: Linear spline modelling

Diagram showing periods of gestational exposure to margarine fortified with vitamin D.
Approach: statistical method

- Cox regression
  - time to first T1D incident
  - covariates
    - Month and year of birth numerical scale
    - Sex
• These early results suggest:
  – Extra vitamin D in foetal life do not seem to reduce the risk of incident type-1 diabetes before age 15 years.
Results for risk of schizophrenia before and after the termination of the mandatory fortification program
Seasonal variation in serum 25(OH)D

Hyppönen and Power, AJCN 2007
Schizophrenia

• New results of risk of incident schizophrenia related to vitamin D exposure in foetal life around the time of termination of the mandatory vitamin D fortification in June 1st 1985
• Children born May/July were expected to have the lowest vitamin D levels
• 249.753 individuals followed for around 27 years
• These early results suggest:
  – Extra vitamin D in foetal life seems to reduce the risk of getting schizophrenia before age 27 years
• More information: www.Detectingdisease.dk

• Thank you for your attention😊