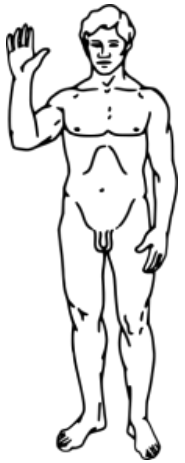
Environmental and nutritional exposures in early life:

- Methodological challenges of long term follow-up studies -

Thorhallur I Halldorsson (lur@ssi.dk, or tih@hi.is)
Faculty of food science and Nutrition, University of Iceland
Center for fetal programming, Statens Serum Institut, Copenhagen

Overview

- Background - Developmental Origins of Health and Disease (DOHAD)



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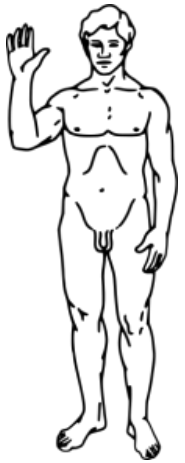
- Background - Developmental Origins of Health and Disease (DOHAD)

- Early life exposures in relation to later growth and development: Results from the Aarhus 1988-89 birth cohort

  – In utero exposures to envionmental chemicals (**PFAS**, PCBs, HCB, ...)

  – Gestational weight gain

  – Maternal diet during pregnancy (macronutriant composition)
    - Crabohydrates
    - Fats
    - Portein



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- Few results and thoughts in limitations of interventions studies in pregnancy versus observational studies and vice versa
- Summary and conclusions

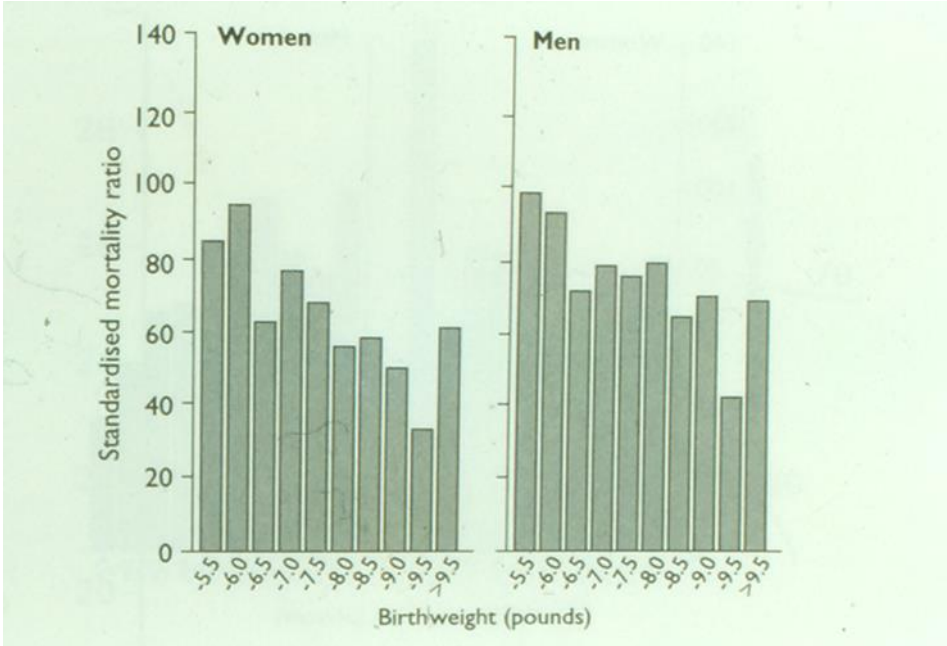
Background

Developmental Origins of Health and Disease (DOHAD)

Fetal Programming:
Initial findings in 80s and early 90s

Observations that perinatal variables are associated with adult cardiovascular diseases and cancer

- Forsdahl (JECH 1976)
  - Infant mortality and adult CVD
- Barker (Lancet, 1989)
  - Low birth weight and adult CVD
- Hales and Barker (BMJ 1991)
  - Low birth weight and T2DM
- Ekbom (Lancet 1992)
  - Perinatal variables and breast cancer

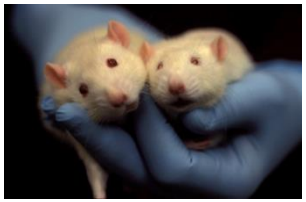


–Standardised mortality ratios for cardiovascular disease below the age of 65.

Backed by evidence from animal experiments

Maternal malnutriti

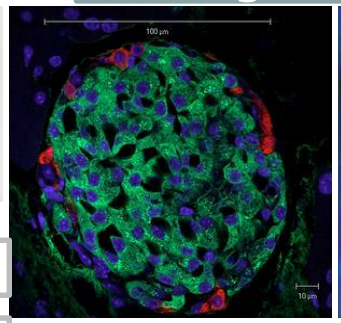
Foetal and infant



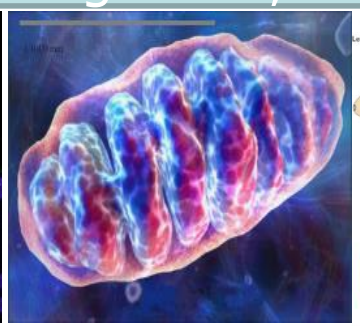
Changes in growth, metabolism, and

Hypertension

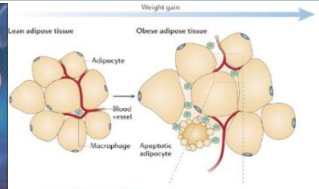
Renal failure

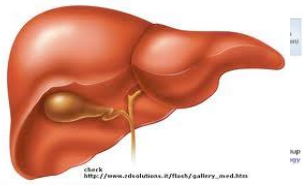


B-cell reduction



Liver mitochondria



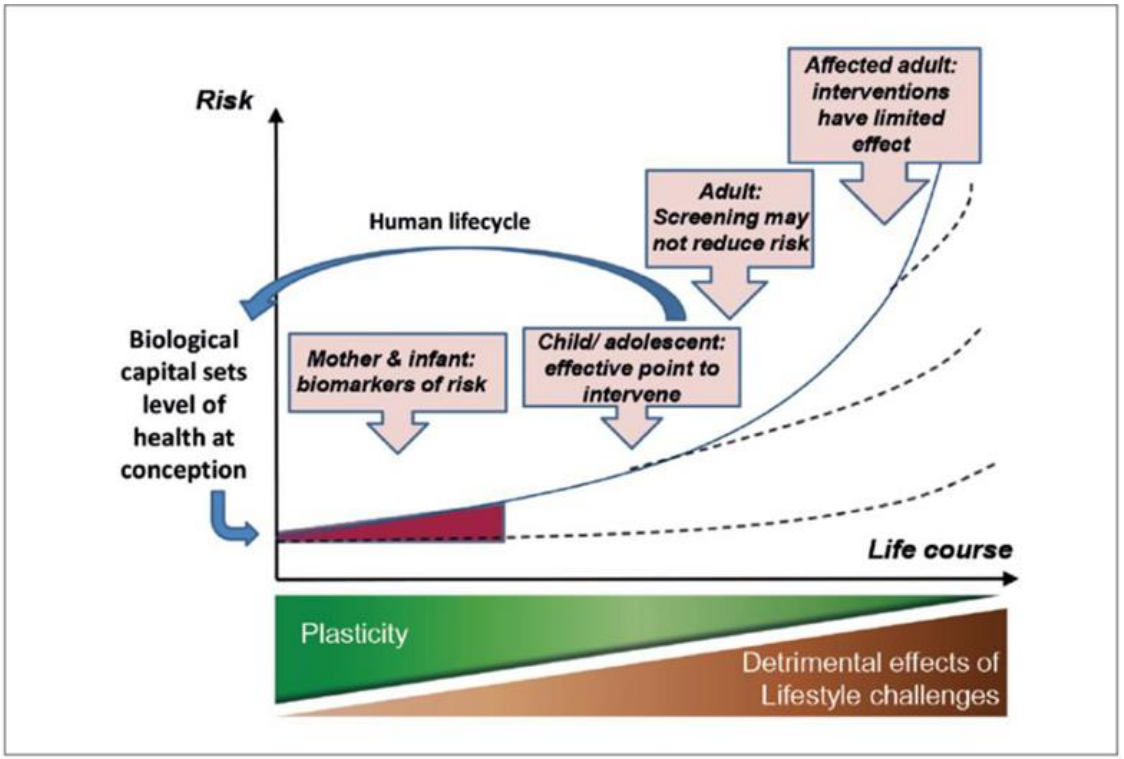


Insulin resistance

Rat studies, Sheep studies

Studies at different levels: Organs, cells, organelles

The Dohad paradigm



Postulates the existence of time windows in the early periods of any individual's life when there may be susceptibility for insults or influences that latently may determine that person's propensity for developing specific diseases many years later

Obesity and metabolic disorder

Dutch famine winter

From November 1944 to May 1945

(short period of transport embargo imposed on west Holland, until liberation from the occupation)

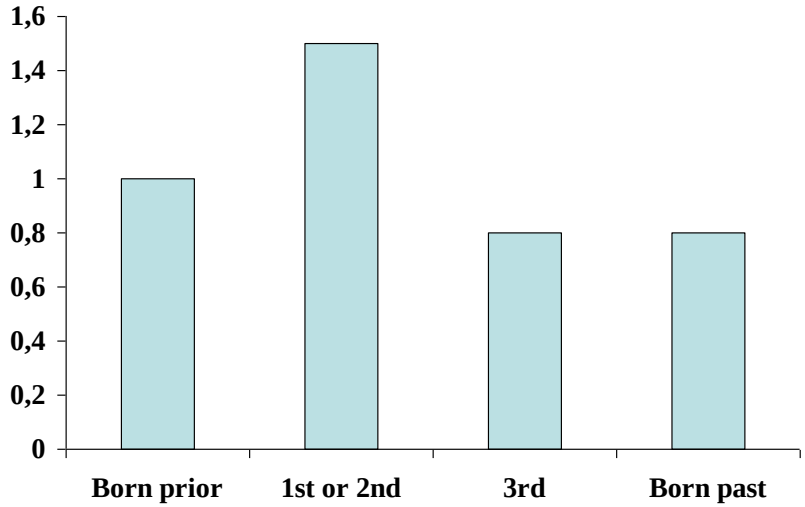
Table 1. Rations of Calories in Three-Month Averages from June, 1944, through November, 1945.[4]

Period	Calorie Ration		
	West	North	South
1944:			
Jun-Aug	1,512	1,512	1,512
Sept-Nov	1,414	1,450	1,403
1944-45:			
Dec-Feb	740	1,345	1,375
Mar-May	670	1,392	1,692
Jun-Aug	1,757	1,755	1,864
Sept-Nov	2,083	2,083	2,083

Ravelli, G.-P., et al. N Engl J Med 1976; 295:349-353

Dutch Famine

Obesity



Exposure to famine in utero and risk of obesity later in life
Thin at birth → more likely to be obese in adult life

Ravelli et al. NEJM 1976;295:349-53

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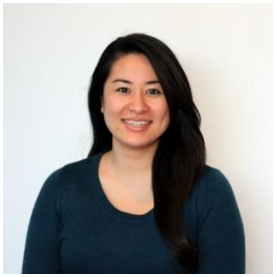
PLOS ONE

Effect of Birth Year on Birth Weight and Obesity in Adulthood: Comparison between Subjects Born Prior to and during the Great Depression in Iceland

Cindy Mari Imai[1]*, Thorhallur Ingi Halldorsson[1], Ingibjorg Gunnarsdottir[1], Vilmundur Gudnason[2,3], Thor Aspelund[2,3], Gudmundur Jonsson[4], Bryndis Eva Birgisdottir[1], Inga Thorsdottir[1]

1 Unit for Nutrition Research, Landspitali University Hospital and Faculty of Food Science and Nutrition, School of Health Sciences, University of Iceland, Reykjavik, Iceland, **2** Icelandic Heart Assocation, Kopavogur, Iceland, **3** Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland, **4** Faculty of Humanities, Department of History and Philosophy, University of Iceland, Reykjavik, Iceland



ICELANDIC HEART ASSOCIATION
HJARTAVERND

Population Science/Epidemiology

Childhood Growth and Adult Hypertension in a Population of High Birth Weight

Thorhallur Ingi Halldorsson, Ingibjorg Gunnarsdottir, Bryndis Eva Birgisdottir, Vilmundur Gudnason, Thor Aspelund, Inga Thorsdottir

Abstract—Low birth weight has consistently been associated with increased adult blood pressure. The relative importance of childhood growth is, however, less well established. This study examined sex-specific associations between childhood growth and adult blood pressure in 2120 subjects born from 1921 to 1935 in Reykjavik who were recruited into a longitudinal study in 1967–1991. Size at birth and growth at regular intervals between 8 and 13 years were

Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 730–736

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

ELSEVIER

Faster increase in body mass index between ages 8 and 13 is associated with risk factors for cardiovascular morbidity and mortality

C.M. Imai [a,*], I. Gunnarsdottir [a,b], V. Gudnason [c,d], T. Aspelund [c,d], B.E. Birgisdottir [a,b], I. Thorsdottir [a,b], T.I. Halldorsson [a,b]

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Annals of Medicine, 2013; 45: 545–550

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DOI: 10.3109/07853890.2013.852347

informa
healthcare

ORIGINAL ARTICLE

Early peak height velocity and cardiovascular disease mortality among Icelandic women

Cindy Mari Imai[1], Ingibjorg Gunnarsdottir[1,2], Vilmundur Gudnason[3,4], Thor Aspelund[3,4], Bryndis Eva Birgisdottir[1,2], Inga Thorsdottir[1,2] & Thorhallur Ingi Halldorsson[1,2]

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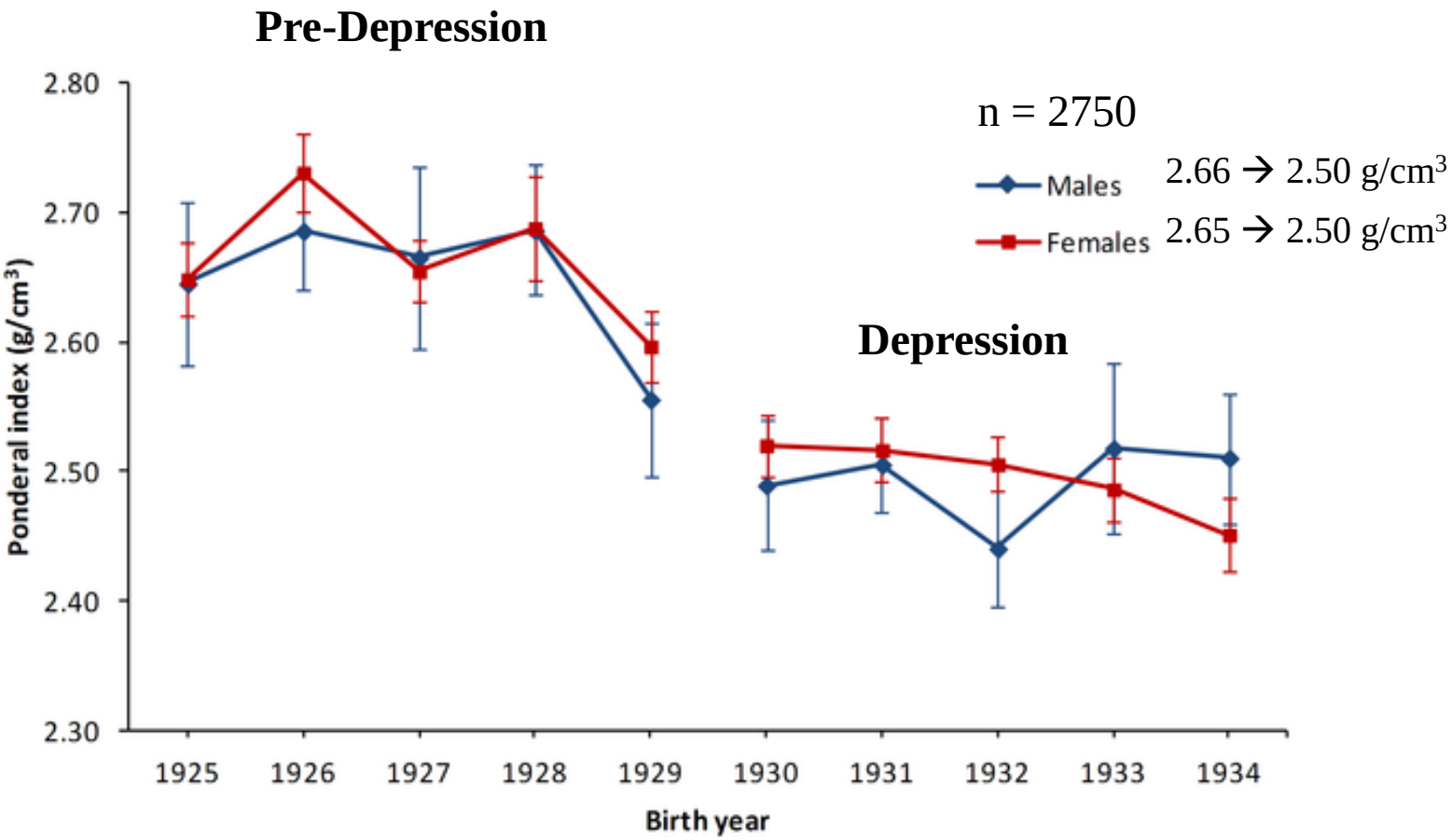

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Follow-up in 1967-1991 at the mean age of 51 years

	All		Males		Females	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Obesity (BMI ≥30 kg/m^2)	1.40	1.09, 1.77	1.27	0.89, 1.81	1.43	1.01, 2.02
Impaired fasting glucose	0.98	0.62, 1.57	0.75	0.40, 1.41	1.41	0.69, 2.90
Dyslipidemia	0.95	0.73, 1.24	0.72	0.51, 1.03	1.22	0.80, 1.86

Reference group: participants born Pre-Depression (1925-1929)

But today high birth weight is perhaps more relevant !!

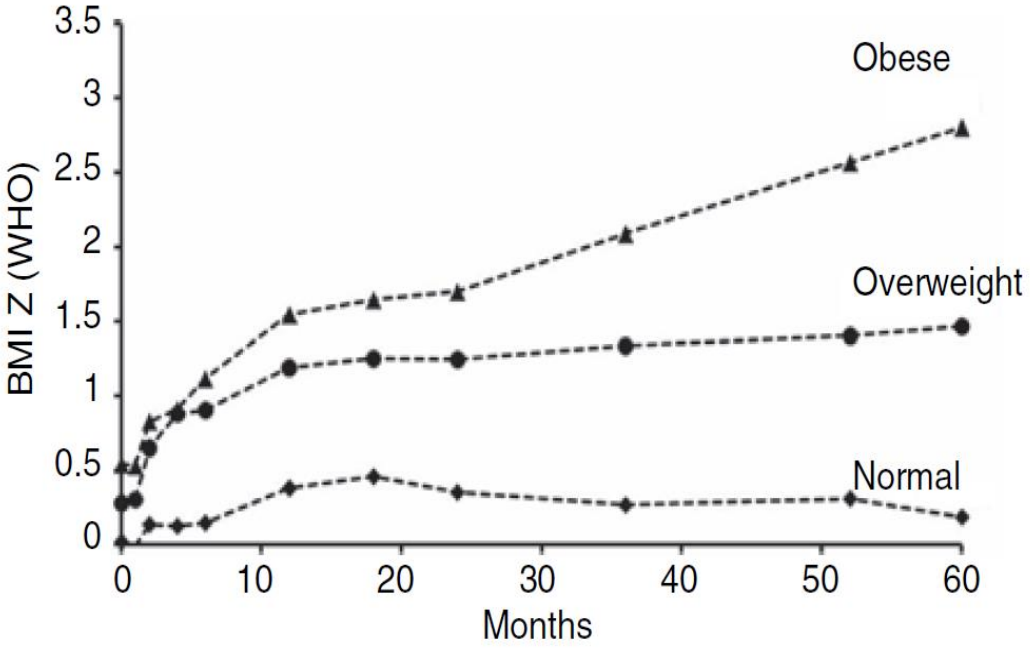

Figure 4 Evolution of BMI *z*-score from birth to 5 years in normal, overweight, and obese 5-year-old Chilean children.

~1000 Chilean children aged 0-5y

What is the source of this variation

…**and how dose it affect later growth and health**

Environmental chemicals

Maternal weight gain

Maternal diet

Smoking

Alcohol

Other factors

Cohorts and projects

- **Danish National Birth Cohort n~100.000**

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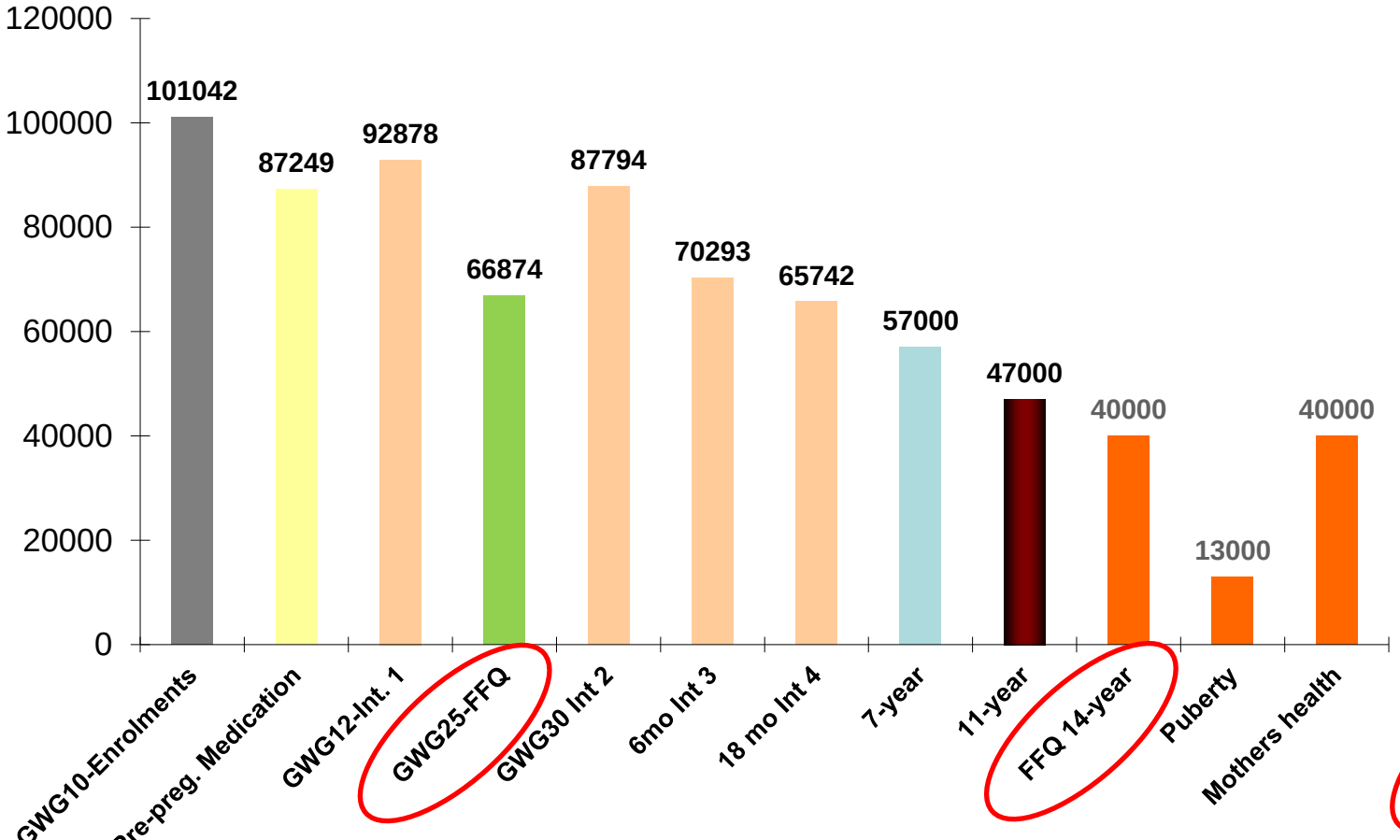
Danish National Birth Cohort

longitudinal study, data collected in waves



Cohorts and projects

- **Danish National Birth Cohort n~100.000**
- **Prospective birth Cohort in Aarhus Denmark (1998-89) n~1000**

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Cohorts and projects

- **Danish National Birth Cohort n~100.000**
- **Prospective birth Cohort in Aarhus Denmark (1998-89) n~1000**
- Randomized fish oil trail in China among pregnant women in n~5000
- Landspitali University Hospital womens birth cohort n~3000 (ongoing reqruitment)
- Icelandic Heart Association Longitudional Reykjavik study n~18.000.
- Smaller dietary observational anf intervention studies

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Collegues and co-workers

Centre for Fetal Programming

- Sjurdur F Olsen
- Dorte Rytter
- Bodil Hammer Bech
- Tine Brink Henriksen
- Marin Strøm
- Susanne Hansen
- Ekaterina Maslova
- Morten Arendt Rasmussen
- Panu Rantakokko
- Hannu Kiviranta
- Line Småstuen Haug
- Georg Becher
- Susanne Lund Christensen
- Anne Vested
- Gunnar Toft

12 partner institutions in Denmark and abroad (Shanghai, Oslo, and Reykjavik)

Centre leader Sjurdur F Olsen, Statens Serum Institut

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UNIVERSITY OF COPENHAGEN

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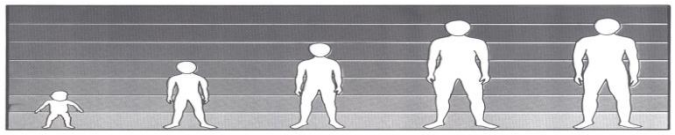
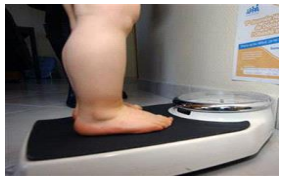
Environmental exposures in early life as determinant of overweight and obesity

Results form the Aarhus 1988-89 birth cohort



The increase in body size from birth to adult



The Aarhus 1988-89 birth cohort

Pregnancy

Offspring follow-up

1988-1989

30th week of gestation

2008

Enrollment
Women with singleton pregnancies
N=965

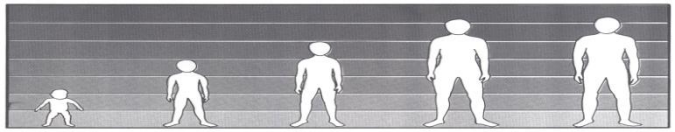
Midwife visit
Interviews, FFQ
Blood samples
N=872 (88%)

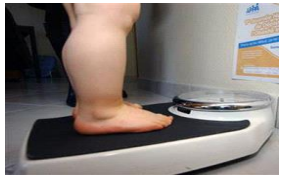
Delivery

Questionnaires (N=677, 70%)
Clinical exam (N=421, 46%)

- **Maternal diet**
- **biomarkers**
- Vitamin D3/D2
- Triglycerides , total cholestrol
- Albumin
- THS, T3, T4...
- **PFAAs, PCBs , DDE/DDT, HCB,**
- Metabolomics (in prep.)
- inflamotory biomarkers
  - CRP, SAA, sICAM1, sVCAM1, Eselectin, Pselectin sICAM3, Thromb, IL1b, IL6, IL8, TNFa

- **Offspring at 20y**
- Anthroprometry, Semen samples
- vaginal ultrasound, reproductive hormone, lung function, blood pressure
- Cardriometabolic risk factors
  - crp, ApoA ApoB alb, Chol (total, LDL, HDL), tiglicirides, insulin, fasting sugar HbA1c, leptin, adiponectin, thyroid stimulating hormone, reproductive hormones
    ....

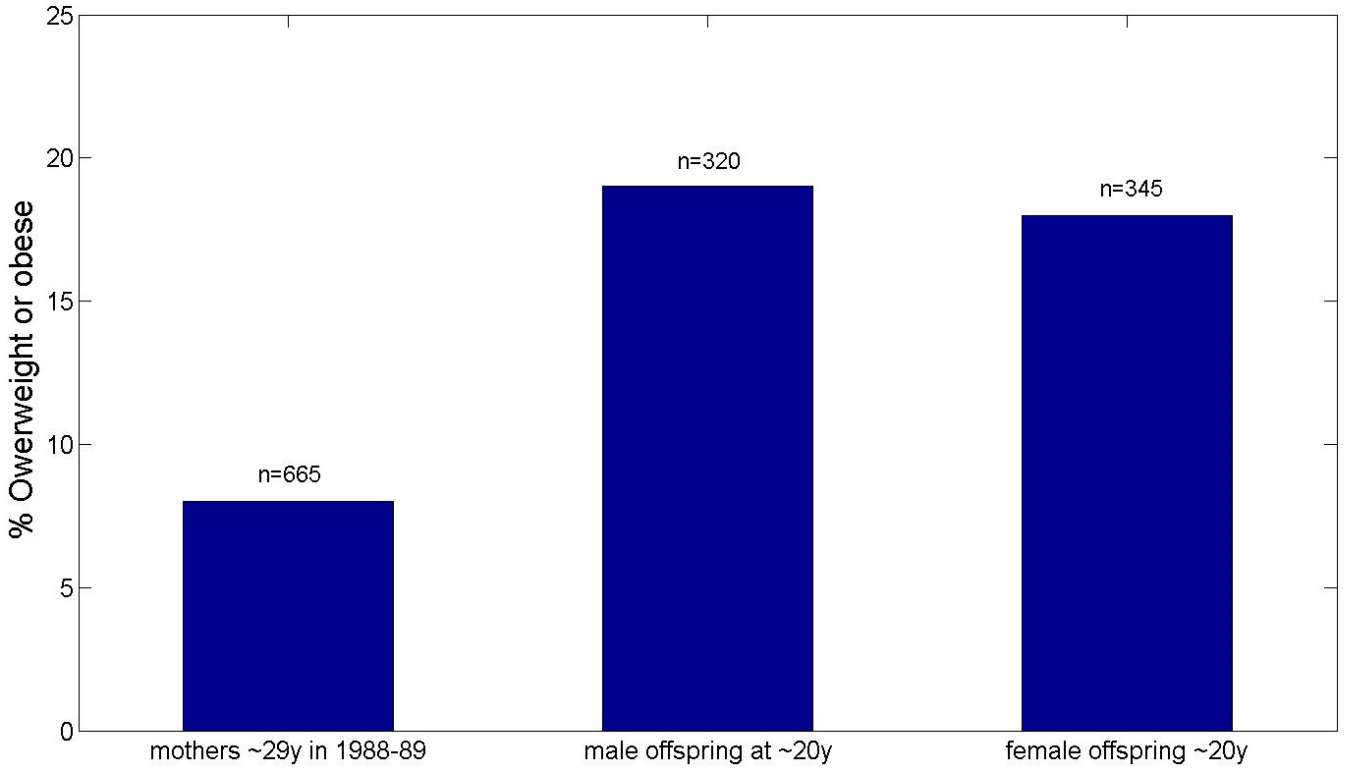




biomarkers
dietary factors
socio-economic var.
lifestyle

Offspring follow up at ~20 years

Maternal and offspring weight



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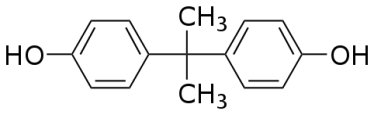
…**and how dose it affect later growth and health**

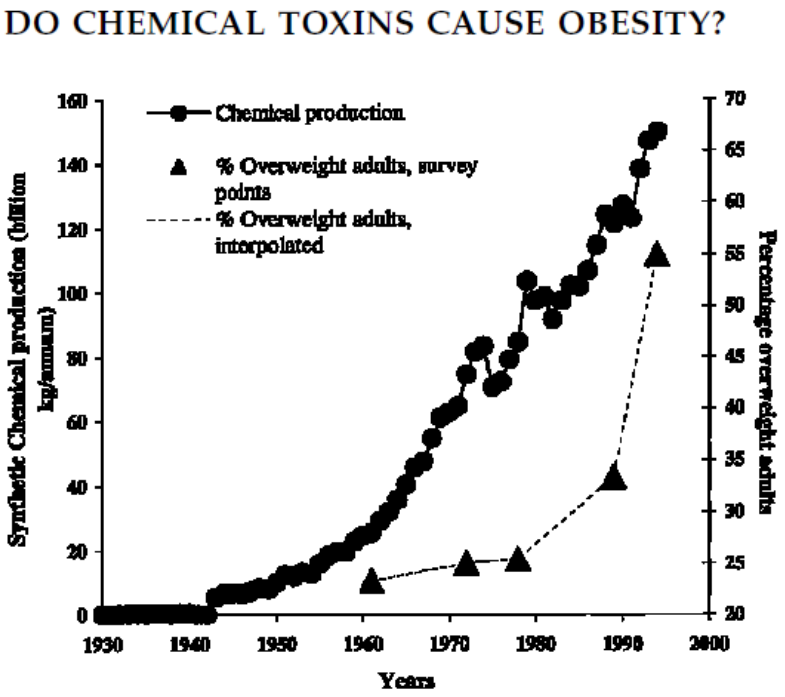
Environmental chemicals

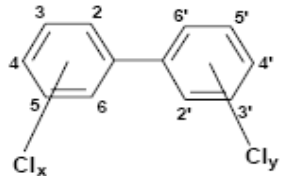
Maternal weight gain

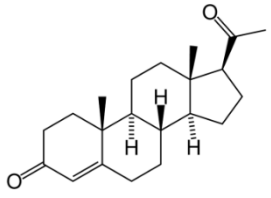
Maternal diet

Early life exposures to environmental chemicals

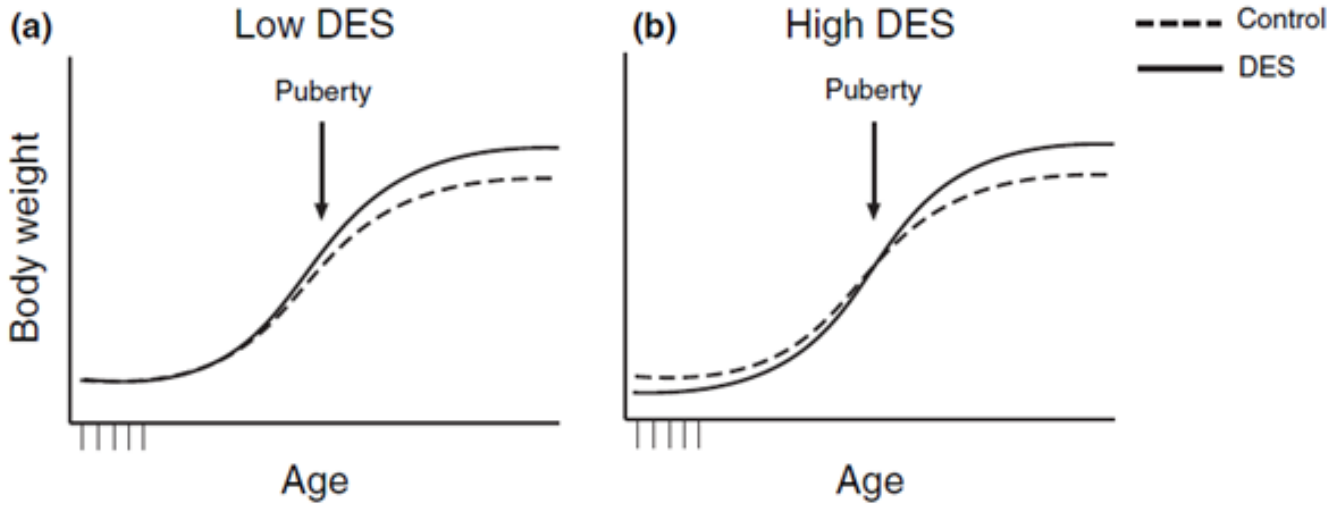


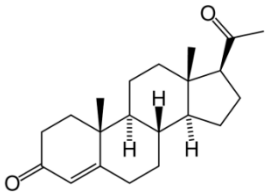






Results from animal studies diethylstibestrol (DES)





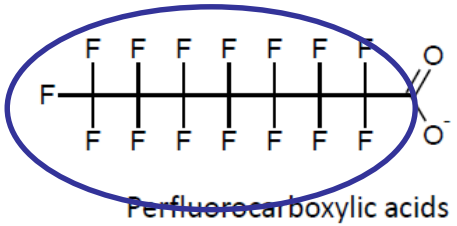
Newbold RR et al Int J Androl 2008

The new persitent compounds

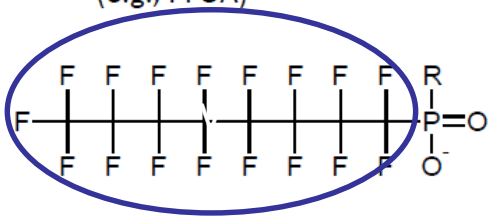
Surface active compounds are OK

Perfluoroalkyl Acids

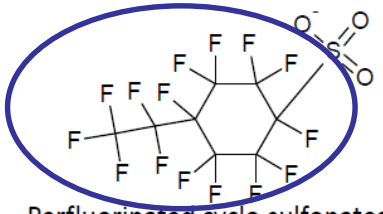
- Environmental presence :
  - direct use in various fluorochemical applications
  - degradation of precursor compounds (such as fluorotelomers)



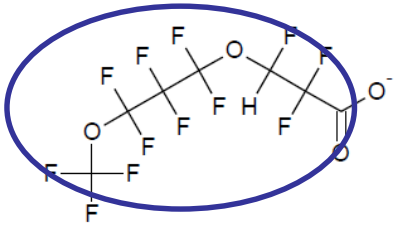
Perfluorocarboxylic acids
(e.g., PFOA)



Perfluorophosphonic/phosphinic acids
(e.g., If R=OH then PFOPA
If R=C8 perfluoroalkane then 8:8 PFPi)



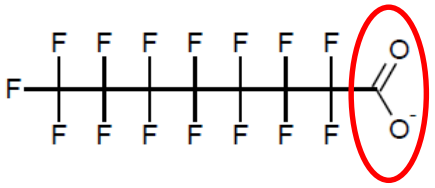
Perfluorinated cyclo sulfonates
(e.g., PFECHS)



Polyfluorinated ether carboxylates
(e.g., 4,8-dioxa-3H-perfluorononanoate)

Perfluoroalkyl Acids

- Environmental presence :
  - direct use in various fluorochemical applications
  - degradation of precursor compounds (such as fluorotelomers)



Perfluorocarboxylic acids
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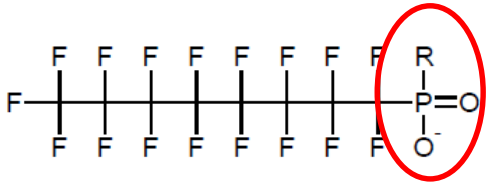
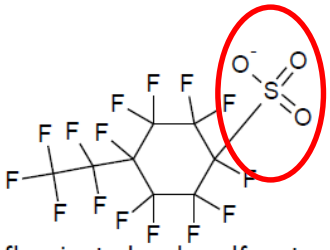
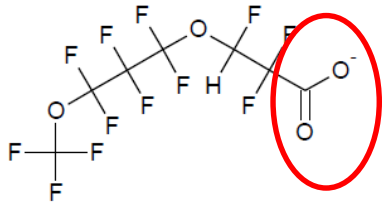


Perfluorophosphonic/phosphinic acids
(e.g., If R=OH then PFOPA
If R=C8 perfluoroalkane then 8:8 PFPi)



Perfluorinated cyclo sulfonates
(e.g., PFECHS)



Polyfluorinated ether carboxylates
(e.g., 4,8-dioxa-3H-perfluorononanoate)

Time trends

Norway – PFC levels in breast milk

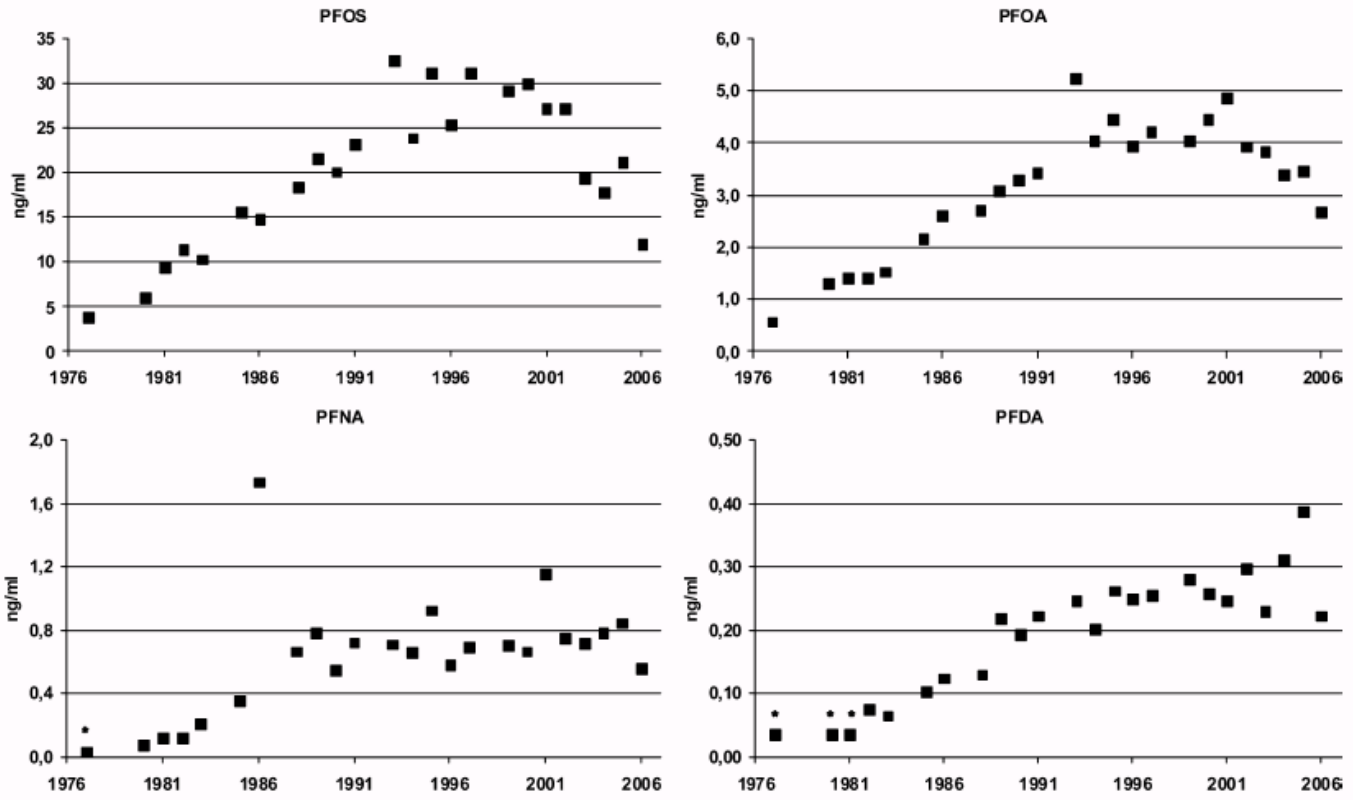
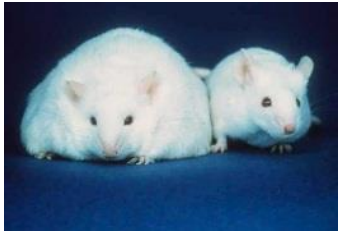


FIGURE 1. Concentrations in ng/mL of PFOS, PFOA, PFNA, and PFDA in pooled serum samples from men, age 40–50 years, in the period 1977 to 2006. Data points marked with an asterisk were below the LOQ (0.050 ng/mL serum) and are set to LOQ divided by the square root of two.

Perfluorooctanoic acid (PFOA)



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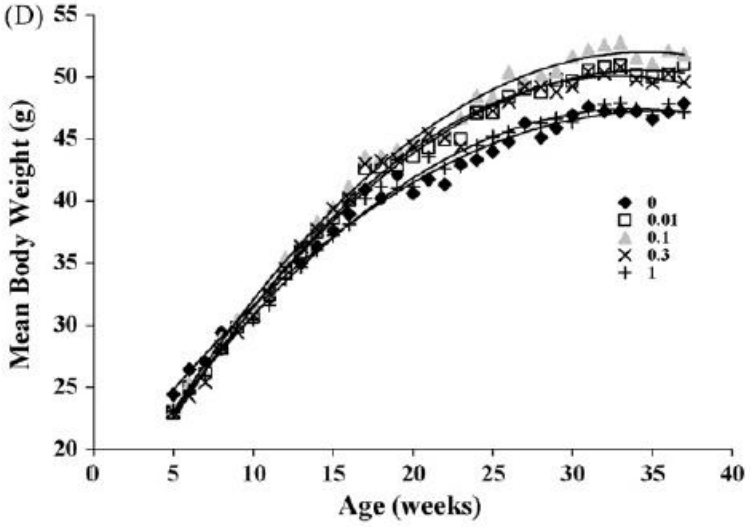
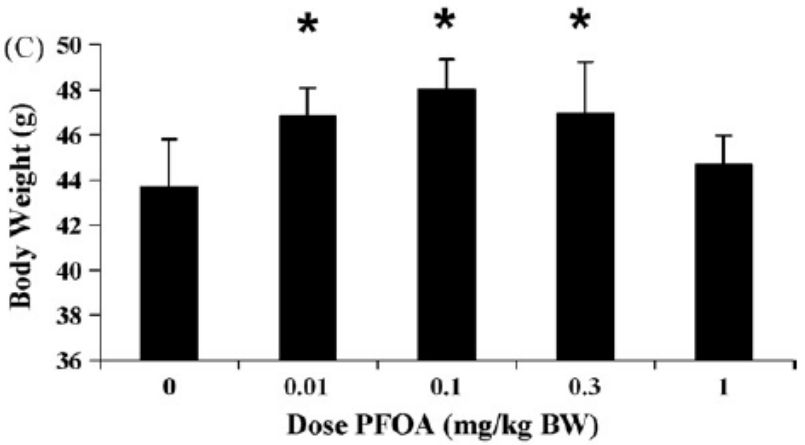
journal homepage: www.elsevier.com/locate/mce

Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life☆

Erin P. Hines[a,*], Sally S. White[b], Jason P. Stanko[a], Eugene A. Gibbs-Flournoy[c], Christopher Lau[d], Suzanne E. Fenton[d]





Research

Prenatal Exposure to Perfluorooctanoate and Risk of Overweight at 20 Years of Age: A Prospective Cohort Study

Thorhallur I. Halldorsson,[1,2,3] Dorte Rytter,[4] Line Småstuen Haug,[5] Bodil Hammer Bech,[4] Inge Danielsen,[1] Georg Becher,[5,6] Tine Brink Henriksen,[7] and Sjurdur F. Olsen[1,8]

[1]Center for Fetal Programming, Department of Epidemiology Research, Statens Serum Institute, Copenhagen, Denmark; [2]Faculty of Food Science and Nutrition, University of Iceland, Reykjavik, Iceland; [3]Unit for Nutrition Research, Landspitali University Hospital, Reykjavik, Iceland; [4]Department of Public Health, Section for Epidemiology, Aarhus University, Denmark; [5]Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway; [6]Department of Analytical Chemistry, University of Oslo, Oslo, Norway; [7]Department of Paediatrics, Aarhus University Hospital, Skejby, Denmark; [8]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA

Background: Perfluoroalkyl acids are persistent compounds used in various industrial applications. Of these compounds, perfluorooctanoate (PFOA) is currently detected in humans worldwide. A recent study on low-dose developmental exposure to PFOA in mice reported increased weight and elevated biomarkers of adiposity in postpubertal female offspring.

Objective: We examined whether the findings of increased weight in postpubertal female mice could be replicated in humans.

Methods: A prospective cohort of 665 Danish pregnant women was recruited in 1988–1989 with

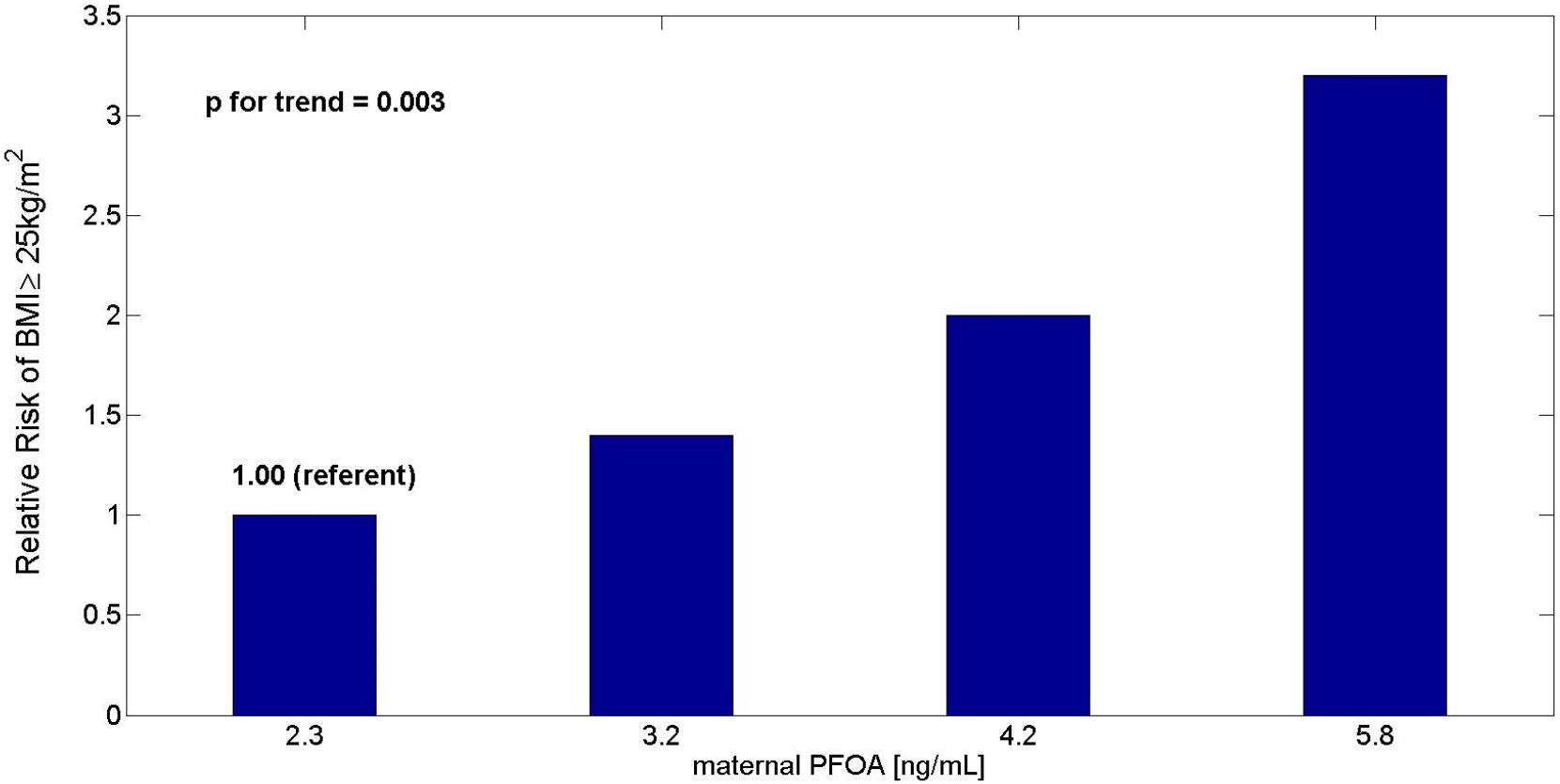
PFAAs are found in highest concentrations in the liver (Hundley et al. 2006; Maestri et al. 2006) and low-dose human exposures to PFOA and PFOS have been associated with modest increases in liver enzymes (Lin et al. 2010) and blood lipids (Nelson et al. 2010) in cross-sectional settings. The relevance of these findings is uncertain, however, because prospec-

Offspring Characteristics

	Males	Females
All offspring (mean (SD) or %)	(n=320)	(n=345)
Age (years)	19.4 (0.4)	19.4 (0.4)
Body mass index (kg/m^2)	22.8 (2.9)	22.2 (3.3)
Overweight or obese[1]	18.8%	17.7%
Waist circumference (cm)	84.3 (9.3)	79.9 (9.4)
Abdominal obesity[2]	3.5%	16.2%

[1]BMI≥25kg/m^2
[2]Waist circumference >88cm for females and >102cm for males

Relative Risk of overweight and obesity among females offspring (n=345)

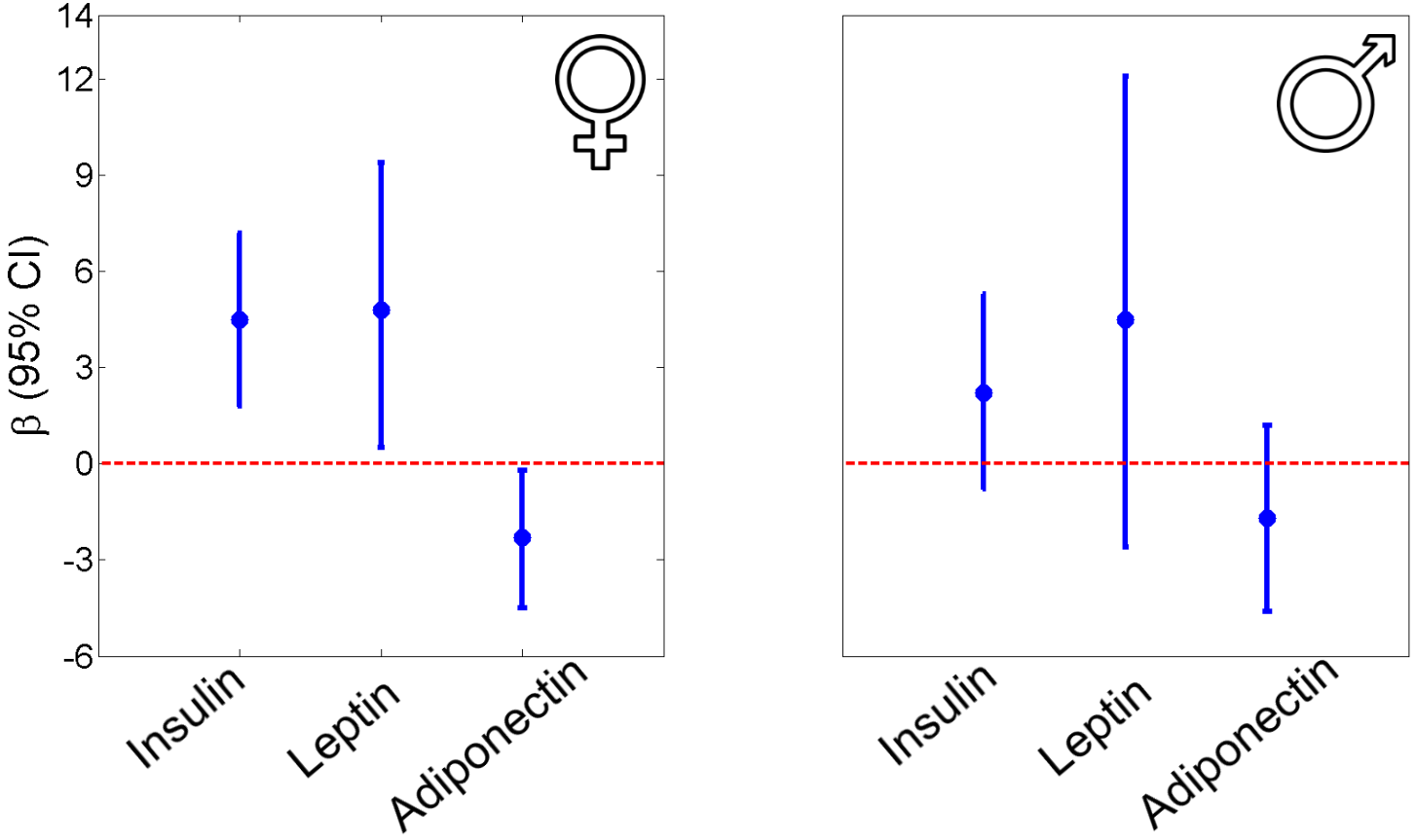


In utero epxosure to PFOA and offspring anthropometry at 20y

Maternal PFOA in quartiles (median)	Δbody mass index (kg/m^2) mean (95% CI)		Δwaist circumference (cm) mean (95% CI)	
	Females (n=345)	*Males (n=320)*	*Females (n=345)*	*Males (n=320)*
2.3 ng/mL	Referent	Referent	Referent	Referent
3.2 ng/mL	0.4 (-0.6, 1.3)	0.6 (-0.3, 1.5)	1.4 (-1.4, 4.2)	1.3 (-1.5, 4.1)
4.2 ng/mL	0.9 (-0.1, 1.9)	0.2 (-0.7, 1.1)	1.2 (-1.7, 4.0)	1.0 (-1.9, 3.8)
5.8 ng/mL	1.6 (0.6, 2.6)	0.6 (-0.3, 1.5)	4.3 (1.4, 7.3)	1.3 (-1.6, 4.1)
P valuefor trend	0.001	0.30	0.006	0.48

No association for male offspring

Maternal concentrations of PFOA and offspring CVD risk factors at 20y



β: % change in biomarker per 1-ng/mL increase in PFOA

Stabillity and confounding?

What about confounding by clustering of familial life style factors over 20 years?

What is the relevance of s small change in biomarkers of CVD risk at 20 years?

Confounding by other familial risk factors

	Females (n=345)		
	β	(95% CI)	P value
Unadjusted			
PFOA[1]	**0.43**	(0.25, 0.60)	<0.0001
Adjusted			
PFOA[1]	**0.42**	(0.25, 0.60)	<0.0001
Father considered overweight	0.99	(0.20, 1.78)	0.02
Sibling considered overweight	1.17	(-0.02, 2.37)	0.08
Maternal Pre-preg. BMI[3]	0.20	(0.04, 0.35)	0.01
Birth weight[4]	0.07	(0.002 0.14)	0.04

[1] **change in BMI at 20y in kg/m^2 per 1-ng/mL increase in PFOA**

Development of a Metabolic Syndrome Score (**by PCA**)

An alternative for examining cardiometabolic risk factors

Not published

Cardiometabolic risk fators

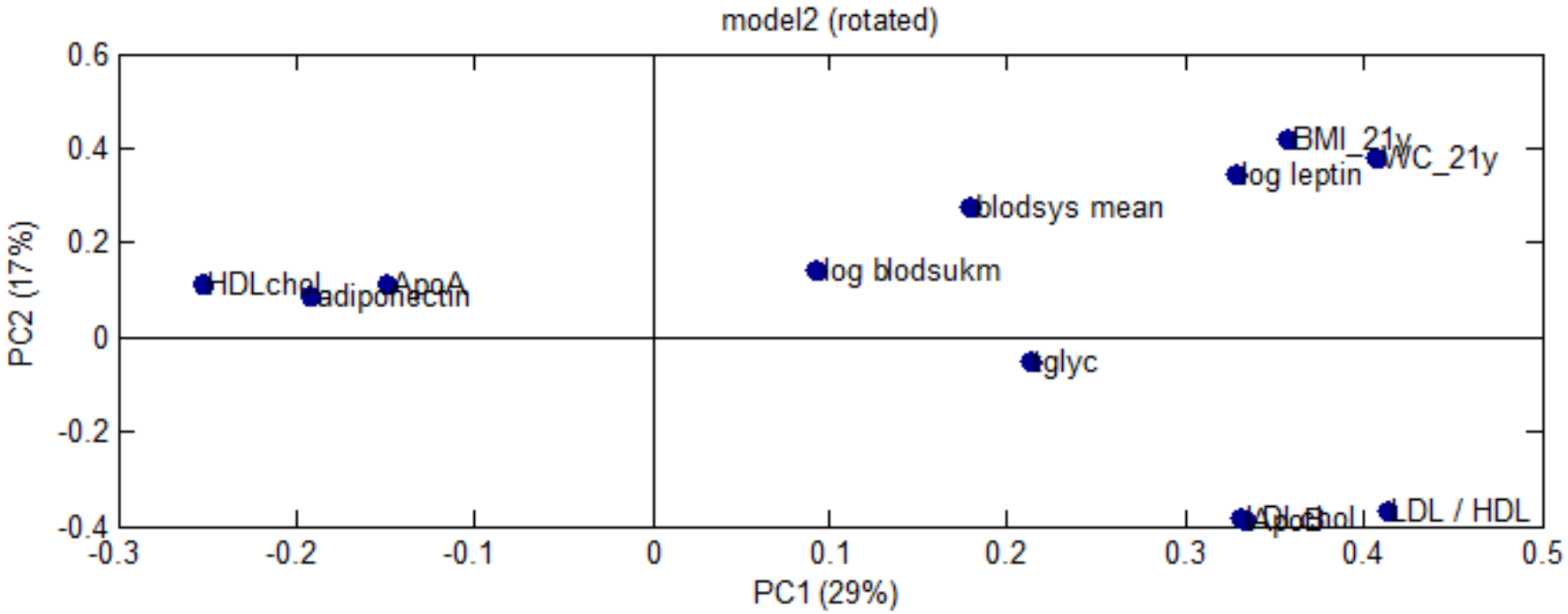
- Number of samples is 422 (170 males and 252 females)

- Included in this analysis (11 primary, 1 derived):
  - Systolic BP mean across three reg.
  - Fasting sugar
  - LDLchol
  - HDLchol
  - tglyc
  - BMI
  - Waist corcumference
  - LDL / HDL (a constructed ratio)
  - ApoA
  - ApoB
  - Adiponectin
  - leptin

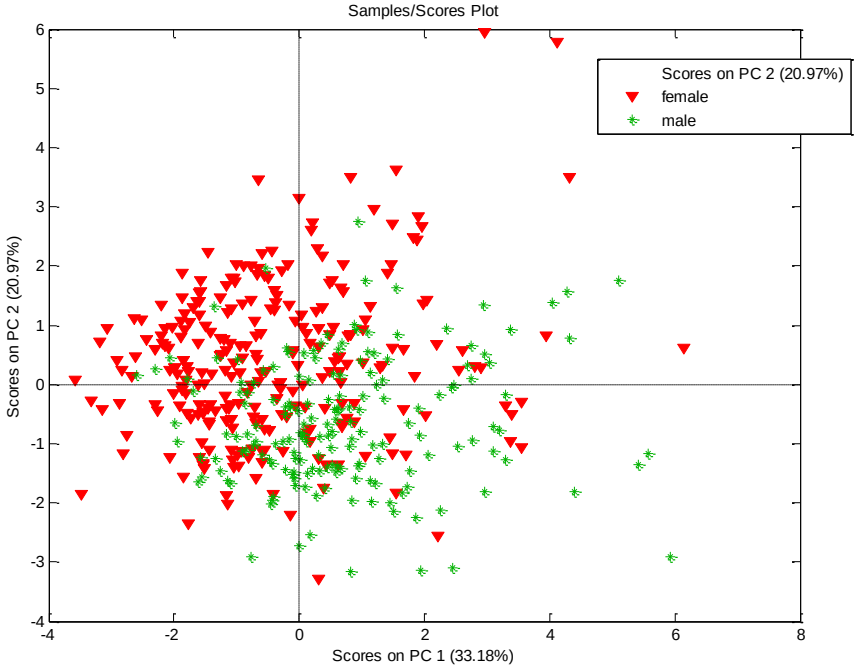
The two main components

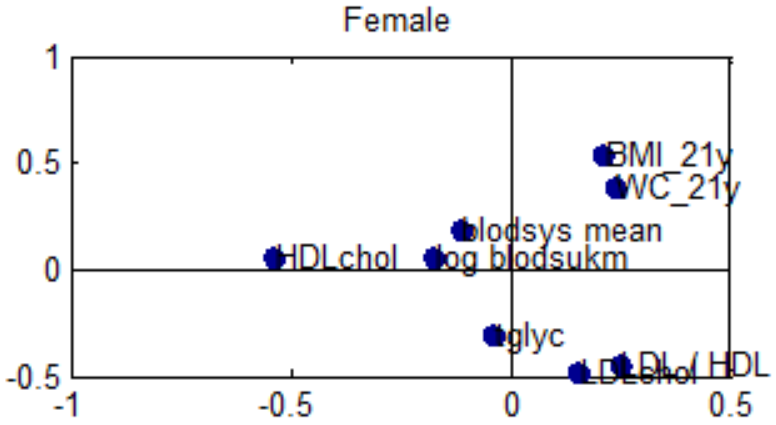
- Explainins 46% of the total variation

- PC1 (29%): Adiposity and associated cardiometabolic risk factors
- PC2(17%): normal weight but adverse lipid profile



- The patterns are consistent between the two sexes
- There is a offset between but the structure is similar





Results for the PCA

	z for BMI	z for PC1
	b[1] (95% CI)	b[1] (95% CI)
Females (n=322)		
PFOA	0.14 (0.08, 0.20)	0.20 (0.10, 0.30)
Males (n=170)		
PFOA	0.04 (-0.03, 0.10)	0.09 (-0.01, 0.20)

[1] change in z-score per 1ng/mLt increase in PFOA or PCB

Adjusted for maternal age, education, pre-pregnancy body mass index, smoking, parity, birth weight and offspring age at follow-up

Environmental Health Perspectives • VOLUME 121 | NUMBER 4 | April 2013

Associations of *in Utero* Exposure to Perfluorinated Alkyl Acids with Human Semen Quality and Reproductive Hormones in Adult Men

Anne Vested,[1] Cecilia Høst Ramlau-Hansen,[1,2] Sjurdur Frodi Olsen,[3] Jens Peter Bonde,[4] Susanne Lund Kristensen,[1] Thorhallur Ingi Halldorsson,[3,5] Georg Becher,[6] Line Småstuen Haug,[6] Emil Hagen Ernst,[7] and Gunnar Toft[1]

[1]Danish Ramazzini Centre, Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Public Health, Section of Epidemiology, University of Aarhus, Aarhus, Denmark; [3]Centre for Fetal Programming, Statens Serum Institut, Copenhagen, Denmark; [4]Department of Occupational and Environmental Medicine, Bispebjerg Hospital of Copenhagen University, Copenhagen, Denmark; [5]Faculty of Food Science and Nutrition, University of Iceland, Reykjavik, Iceland; [6]Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway; [7]Reproductive Laboratory, Institute of Anatomy, University of Aarhus, Aarhus, Denmark

Results: Multivariable linear regression analysis suggested that *in utero* exposure to PFOA was associated with lower adjusted sperm concentration (p_{trend} = 0.01) and total sperm count (p_{trend} = 0.001) and with higher adjusted levels of luteinizing hormone (p_{trend} = 0.03) and follicle-stimulating hormone (p_{trend} = 0.01). PFOS did not appear to be associated with any of the outcomes assessed, before or after adjustment.

Conclusions: The results suggest that *in utero* exposure to PFOA may affect adult human male semen quality and reproductive hormone levels.

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RESULTS: Multivariable linear regressi
was associated with lower adjusted spe
(p_{trend} = 0.001) and with higher adjuste
stimulating hormone (p_{trend} = 0.01). PFC
assessed, before or after adjustment.

CONCLUSIONS: The results suggest that
semen quality and reproductive hormone

Human Reproduction, Vol.28, No.12 pp. 3337–3348, 2013
Advanced Access publication on October 15, 2013 doi:10.1093/humrep/det382

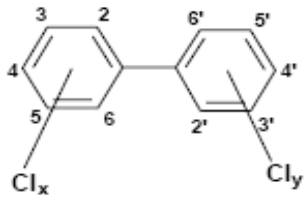
human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction

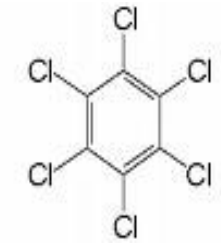
S.L. Kristensen[1,*], C.H. Ramlau-Hansen[2], E. Ernst[3], S.F. Olsen[4], J.P. Bonde[5], A. Vested[1], T.I. Halldorsson[4,6], G. Becher[7], L.S. Haug[7], and G. Toft[1]

[1]Danish Ramazzini Centre, Department of Occupational Medicine, Aarhus University Hospital, Norrebrogade 44 Build. 2C, 8000 Aarhus C DK, Denmark [2]Department of Public Health, Section for Epidemiology, Aarhus University, 8000 Aarhus C DK, Denmark [3]Department of Gynecology and Obstetrics, Aarhus University Hospital, and Institute of Anatomy, Aarhus University, 8000 Aarhus C DK, Denmark [4]Centre for Fetal Programming, Statens Serum Institut, DK-2300 Copenhagen S, Denmark [5]Department of Occupational and Environmental Medicine, Bispebjerg Hospital of Copenhagen University, DK-2300 Copenhagen S, Denmark [6]Faculty of Food Science and Nutrition, University of Iceland, 101 Reykjavik, Iceland [7]Division of Environmental Medicine, Norwegian Institute of Public Health, NO-0403 Oslo, Norway

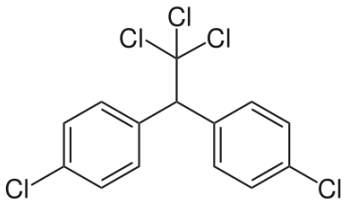
So what about other contaminants ?



PCBs

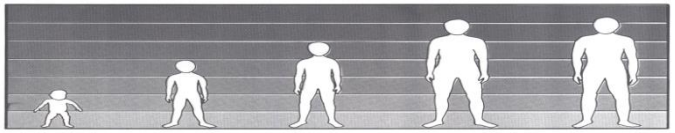


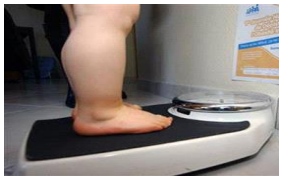
HCB



DDT

Limitations





PFOA

Offspring follow up at ~20 years

PFOA

- Despite consistent findings in one animal and one human observational study, other studies have not replicated these findings.
- Unlike those studies our opulation consisted of predominantly (92%) normal weight women.
- Exposure to PFOA could reflect unhealthy dietary habits (fast food)
- Difficult to repleicate findings of lon term-followup studies as lifestyl habits change.

In contrast to chemical exposures where we aim to minimize exposure and protect consumers …..

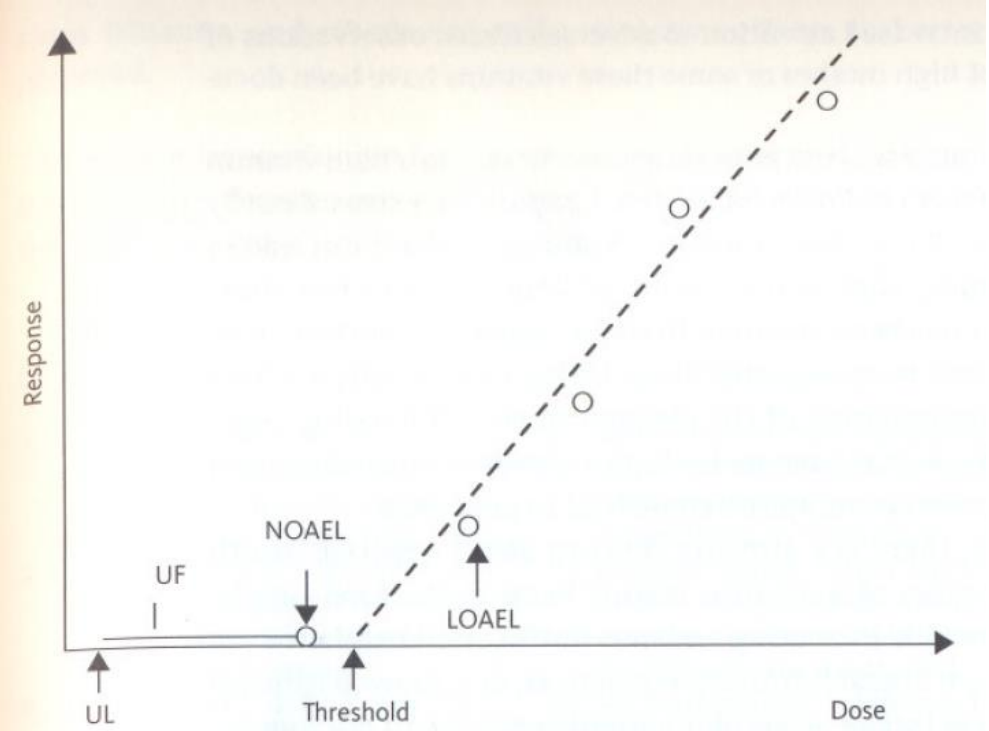
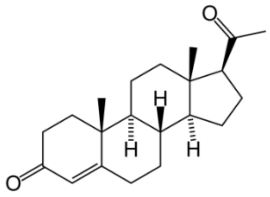
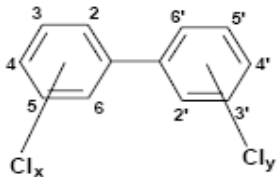


Figure 3.4 Derivation of upper intake level (UL)





PFOA (Perfluorooctanoic acid)

We are often more relaxed about unhealthy lifestyles (….although the “effects“ are no better or worse)

What is the source of this variation

…**and how dose it affect later growth and health**

Environmental chemicals

Maternal weight gain

Maternal diet

International Journal of Obesity (2015) **39,** 671–676

www.nature.com/ijo

ORIGINAL ARTICLE

Gestational weight gain in normal weight women and offspring cardio-metabolic risk factors at 20 years of age

L Hrolfsdottir[1], D Rytter[2], SF Olsen[3,4], BH Bech[2], E Maslova[3], TB Henriksen[5] and TI Halldorsson[1,3]

OBJECTIVE: Limited knowledge exists on the long-term implications of maternal gestational weight gain (GWG) on offspring health. Our objective was to examine whether high GWG in normal weight women is associated with adult offspring cardio-metabolic risk factors.

Table 3. Associations of maternal gestational weight gain with offspring BMI and waist circumference at follow-up ($n = 308$)

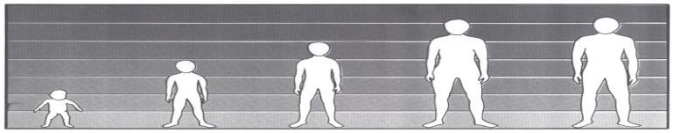
	Offspring BMI ($kg\ m^{-2}$)		*Offspring overweight*	
	β[a]	*95% CI*	*OR*[b]	*95% CI*
GWG in week 30 (per 1-kg increase)[c]	0.10	(0.01, 0.20)	1.10	(1.00, 1.20)
IOM categories:				
Suboptimal (< 11.5 kg)	−0.4	(−1.2, 0.4)	0.6	(0.2, 1.4)
Optimal (11.5–16 kg)	ref.	ref.	ref.	ref.
Excessive (> 16 kg)	0.6	(−0.2, 1.4)	1.8	(0.9, 3.8)
P for trend[d]	0.02		0.01	

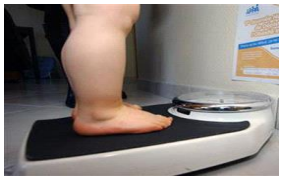
Table 4. Associations of maternal gestational weight gain during the first 30 weeks of gestation with offspring cardio-metabolic risk factors at follow-up ($n = 308$)

Outcome[a]	*All* (n = *308*)[b]			*Men* (n = *121*)[c]			*Women* (n = *187*)[c]		
	β	*95% CI*	P	β	*95% CI*	P	β	*95% CI*	P
Insulin (%)[d]	1.2	(−0.2, 2.6)	0.09	3.7	(1.4, 6.2)	< 0.01	−0.2	(−1.9, 1.5)	0.82
HOMA-IR (%)[d]	1.1	(−0.3, 2.5)	0.14	3.4	(0.8, 6.0)	0.01	−0.1	(−1.8, 1.7)	0.94
Fasting glucose (mmol l^{-1})	0.0	(−0.01, 0.01)	0.95	−0.01	(−0.04, 0.01)	0.32	0.01	(−0.00, 0.02)	0.35
Leptin (%)[d]	3.7	(1.2, 6.4)	< 0.01	10.7	(5.7, 15.9)	< 0.01	0.4	(−2.4, 3.3)	0.76
Adiponectin (%)[d]	0.5	(−0.8, 1.7)	0.45	−0.6	(−2.8, 1.6)	0.58	1.5	(0.0, 2.9)	0.04
Total cholesterol[d]	−0.9	(−1.5, −0.3)	< 0.01	−0.1	(−1.0, 0.8)	0.81	−1.3	(−2.1, −0.6)	< 0.01
LDL (%)[d]	−1.3	(−2.2, −0.4)	< 0.01	0.1	(−1.2, 1.5)	0.85	−2.2	(−3.4, −0.9)	< 0.01
HDL (%)[d]	−0.5	(−1.2, 0.1)	0.12	−1.1	(−2.1, −0.0)	0.05	−0.1	(−1.0, 0.8)	0.80
Triglyceride (%)[d]	−0.2	(−1.6, 1.2)	0.80	1.7	(−0.5, 3.9)	0.12	−1.1	(−2.8, 0.6)	0.21
SBP (mm Hg)	0.3	(0.0, 0.6)	0.03	0.4	(−0.1, 0.9)	0.09	0.2	(−0.2, 0.5)	0.30
DBP (mm Hg)	0.2	(−0.0, 0.4)	0.12	0.4	(0.0, 0.8)	0.03	0.0	(−0.2, 0.3)	0.92
Resting pulse (bpm)	0.2	(−0.1, 0.5)	0.25	0.9	(0.3, 1.5)	< 0.01	−0.3	(−0.6, 0.1)	0.17

[a]Showing increase in the outcome variable per 1-kg increase in gestational weight

Limitations





Gestational weight gain

Offspring follow up at ~20 years

- Our findings are consistent with results from other similar studies.
- The relevance of GWG as a risk factor for adverse metabolic health is still far from clear.
- Confounding due to clustering of familial lifestyle factors is difficult to account for as the offspring environment is continuously changing

What is the source of this variation

…**and how dose it affect later growth and health**

Environmental chemicals

Maternal weight gain

Maternal diet

In the case of diet, adverse consequences should in theory only occur at the extremes

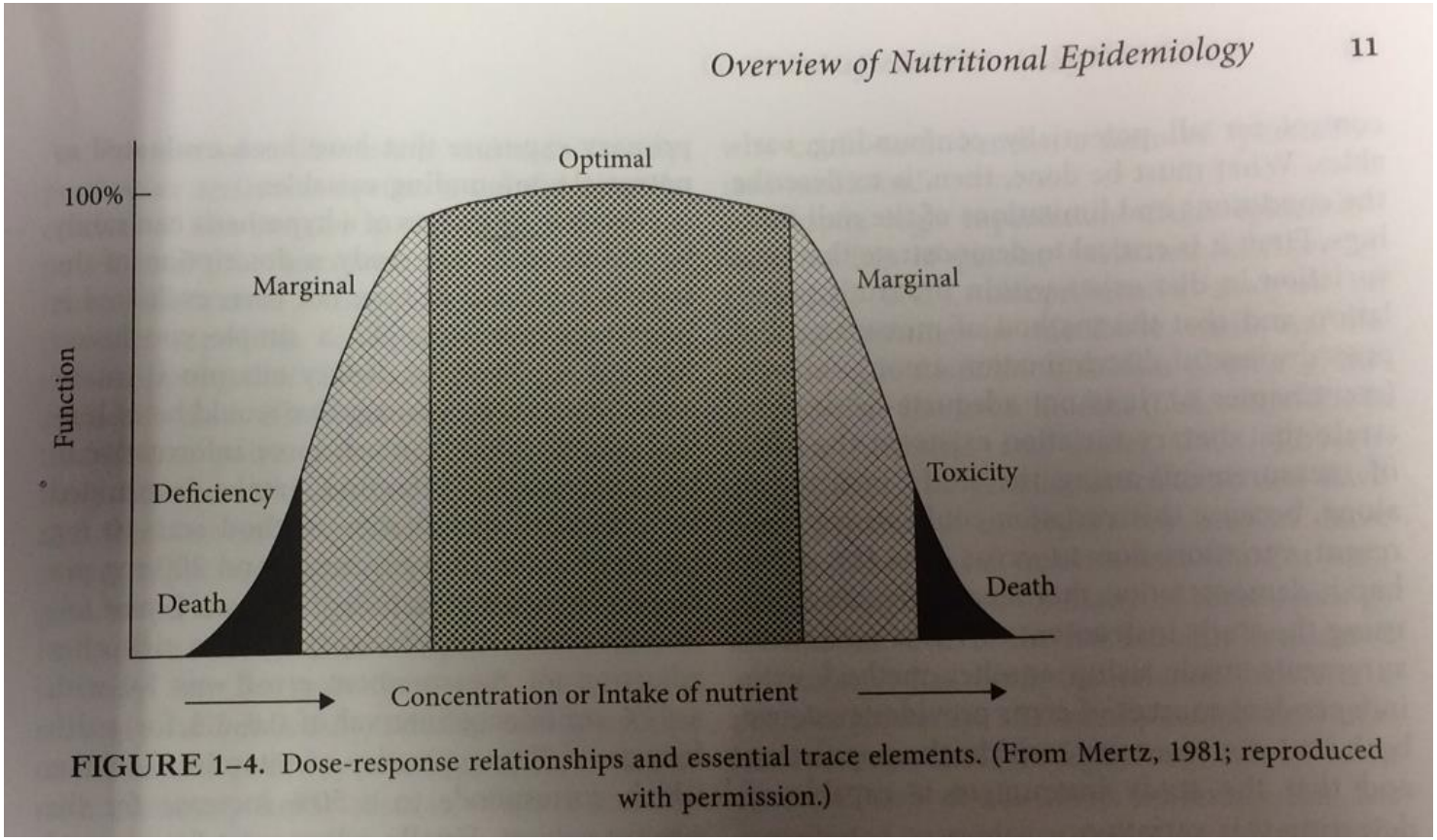


FIGURE 1–4. Dose-response relationships and essential trace elements. (From Mertz, 1981; reproduced with permission.)

Macronutrient intake

- **Protein** should provide 10-20% of total energy intake (E%).

- **Carbohydrates** 45-60 of E%
  - refined sugars < 10 E%
  - fibers should be 25-35 g/day

- **Fats** 25-40% of total energy (E%)
  - Saturated fatty acids < 10 E%
  - (Cis-)monounsaturated acids 10-20 E%
  - Polyunsaturated acids 5-10 E%,
    - icluding approx 1% from n-3 fatty acids

In historical context

- **Much emphasis of reducing intake of saturated fat (sfa) in tthe 1980s and 1990s due to its link with CVD**

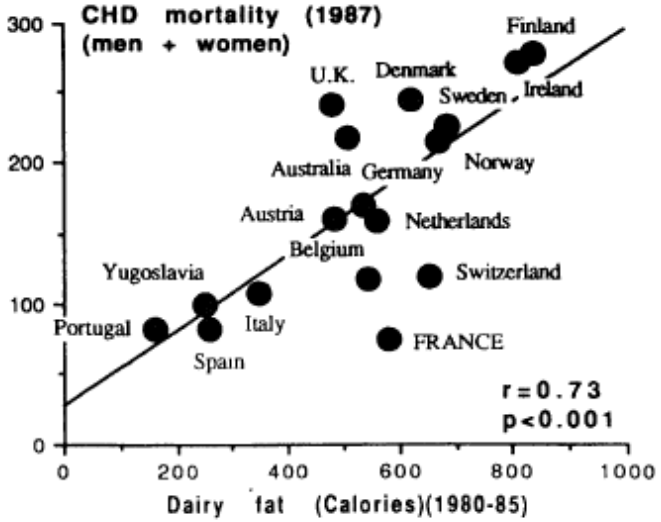


Fig 1—Relation between age-standardised death rate from CHD (mean for men and women)[1] and consumption of dairy fat in countries reporting wine consumption.

Regression equation: y = 26·3 + 0·27 dairy fat

E = constant

Fats

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Clinical Nutrition xxx (2015) 1–9

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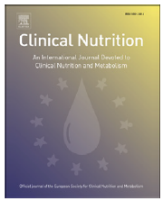


Original article

Maternal intake of fat in pregnancy and offspring metabolic health – A prospective study with 20 years of follow-up

Ekaterina Maslova [a, *], Dorte Rytter [b], Bodil H. Bech [b], Tine B. Henriksen [c], Sjurdur F. Olsen [a, d], Thorhallur I. Halldorsson [a, e, f]

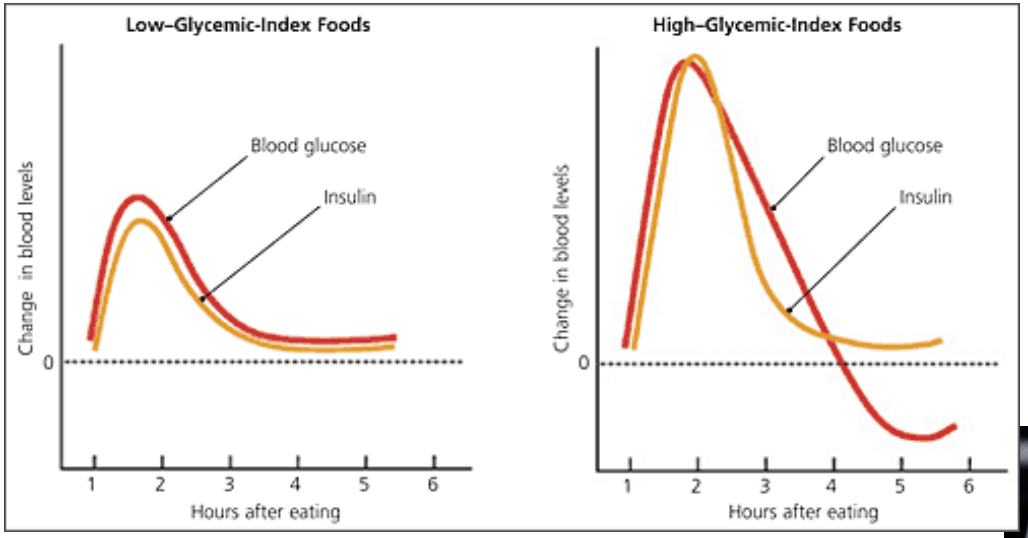
[a] Centre for Fetal Programming, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen, Denmark
[b] Section for Epidemiology, Department of Public Health, Aarhus University, Bartholins Allé 2, Building 1260, 8000 Aarhus, Denmark
[c] Department of Pediatrics, Aarhus University Hospital, Skejby, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark
[d] Department of Nutrition, Harvard T. H. Chan School of Public Health, 655 Huntington Ave, Boston, MA, USA
[e] Faculty of Food Science and Nutrition, School of Health Sciences, University of Iceland, Saemundargotu 2, 101 Reykjavik, Iceland
[f] Unit for Nutrition Research, Landspitali University Hospital, Norðurmýri, 101 Reykjavik, Iceland

Overall no association with offsspring anthroprometry or biomarkers of cardiometabolic health

(Indications of adverse associations for trans-fat)

1990s +

- Reduction in saturated fat, was unfortunately compensated by increase in charbohydrates of poor quality



Carbohydrates

OPEN ACCESS Freely available online

PLOS ONE

Dietary Glycemic Index during Pregnancy Is Associated with Biomarkers of the Metabolic Syndrome in Offspring at Age 20 Years

Inge Danielsen[1]*, Charlotta Granström[1], Thorhallur Haldorsson[1,2], Dorte Rytter[3], Bodil Hammer Bech[3], Tine Brink Henriksen[4], Allan Arthur Vaag[5,6], Sjurdur Frodi Olsen[1]

1 Centre for Fetal Programming, Department of Epidemiology Research, Statens Serum Institute, Copenhagen, Denmark, **2** The Unit for Nutrition Research, Faculty of Food Science and Nutrition, School of Health Sciences, University of Iceland, Reykjavik, Iceland, **3** Centre for Fetal Programming, Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark, **4** Department of Paediatrics, Aarhus University Hospital, Skejby, Denmark, **5** Department of Endocrinology, Rigshospitalet, Copenhagen, Denmark, **6** Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Maternal diet high of glycemic Index during pregnancy was associated with ↑ Leptin, insuling and HOMA-IR in the offspring at age 20y.

An now everyone is in love with proteins

Health & wellbeing

The ketogenic diet: high fat, high hopes

Cure for epilepsy? Radical weight-loss programme? This increasingly popular regimen could have many benefits

David Cox

Sunday 7 December 2014
18.00 GMT

Shares 4764 Comments 511

Save for later

Meta-analysis

openheart

Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis

Zoë Harcombe,[1] Julien S Baker,[1] Stephen Mark Cooper,[2] Bruce Davies,[3] Nicholas Sculthorpe,[1] James J DiNicolantonio,[4] Fergal Grace[1]

Reviews | 18 March 2014

Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk: A Systematic Review and Meta-analysis

Rajiv Chowdhury, MD, PhD; Samantha Warnakula, MPhil*; Setor Kunutsor, MD, MSt*; Francesca Crowe, PhD; Heather A. Ward, PhD; Laura Johnson, PhD; Oscar H. Franco, MD, PhD; Adam S. Butterworth, PhD; Nita G. Forouhi, MRCP, PhD; Simon G. Thompson, FMedSci; Kay-Tee Khaw, FMedSci; Dariush Mozaffarian, MD, DrPH; John Danesh, FRCP*; and Emanuele Di Angelantonio, MD, PhD*

[+] Article, Author, and Disclosure Information

See Also:
Published Letter: Willett et al
Published Letter: Dawczynski et al
Published Letter: Davidoff et al
Published Letter: Liebman et al
Published Letter: Te Morenga et al
Published Letter: Schwingshackl et al

Maternal Protein intake durng pregnany – what do we know?

- **The Harlem trail:** A RCT of nutritional supplementation conducted in 1976 in New York City

- Low income population (n=770)

- Control, balanced, high (~20%E) protein

VOLUME 65 • APRIL 1980 • NUMBER 4

Pediatrics

A Randomized Controlled Trial of Prenatal Nutritional Supplementation in New York City

David Rush, MD, Zena Stein, MA, MB, BCh, and Mervyn Susser, MB, BCh, DPH, FRCP(E)

The Harlem Trail

- *Aim of study was to increase birth weight and influence the postnatal development of the offspring of mothers at high risk of having low birth weight infants*

- 3-arm beverage supplemental trail:
  - **Controls:** received no protein supplementation
  - **Complimental group**: received balanced protein supplementation (6g/day casein)
  - **Supplemental group**: received high protein supplementation (40g day casein)

- <u>All three groups all received micronutrient supplementation</u>

The Harlem Trail

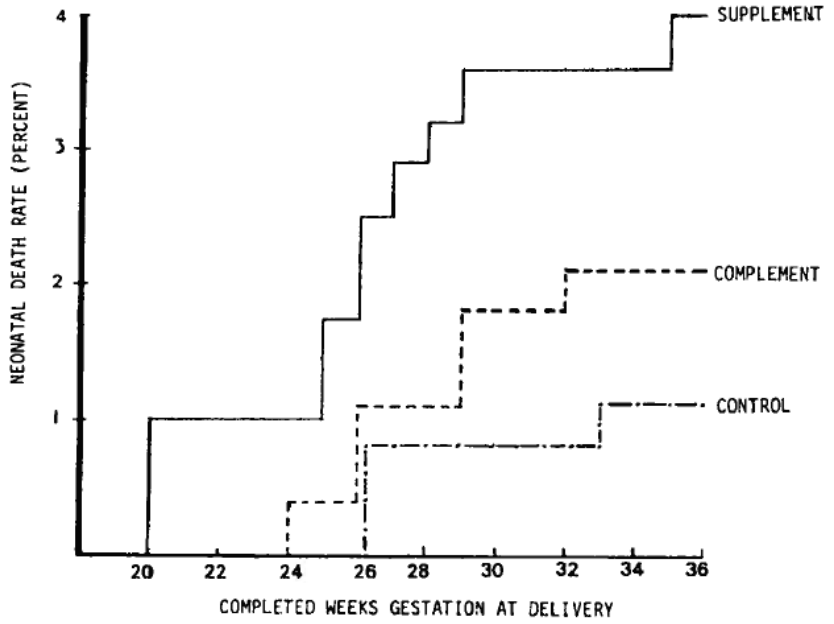


Fig 2. Treatment and neonatal death. Cumulative rates of neonatal death (percent) from life tables for each treatment group (see Appendix).

- **High protein** supplementation
  - **excess of early preterm births and associated neonatal deaths**
  - **Significant growth retardation up to week 37 of gestation**
  - borderline (not formally) significant

Preliminary results: Protein intake in the **Danish National birth cohort** (1996-2002) and the **Norwegian mother and child cohort study** (1988-2008)

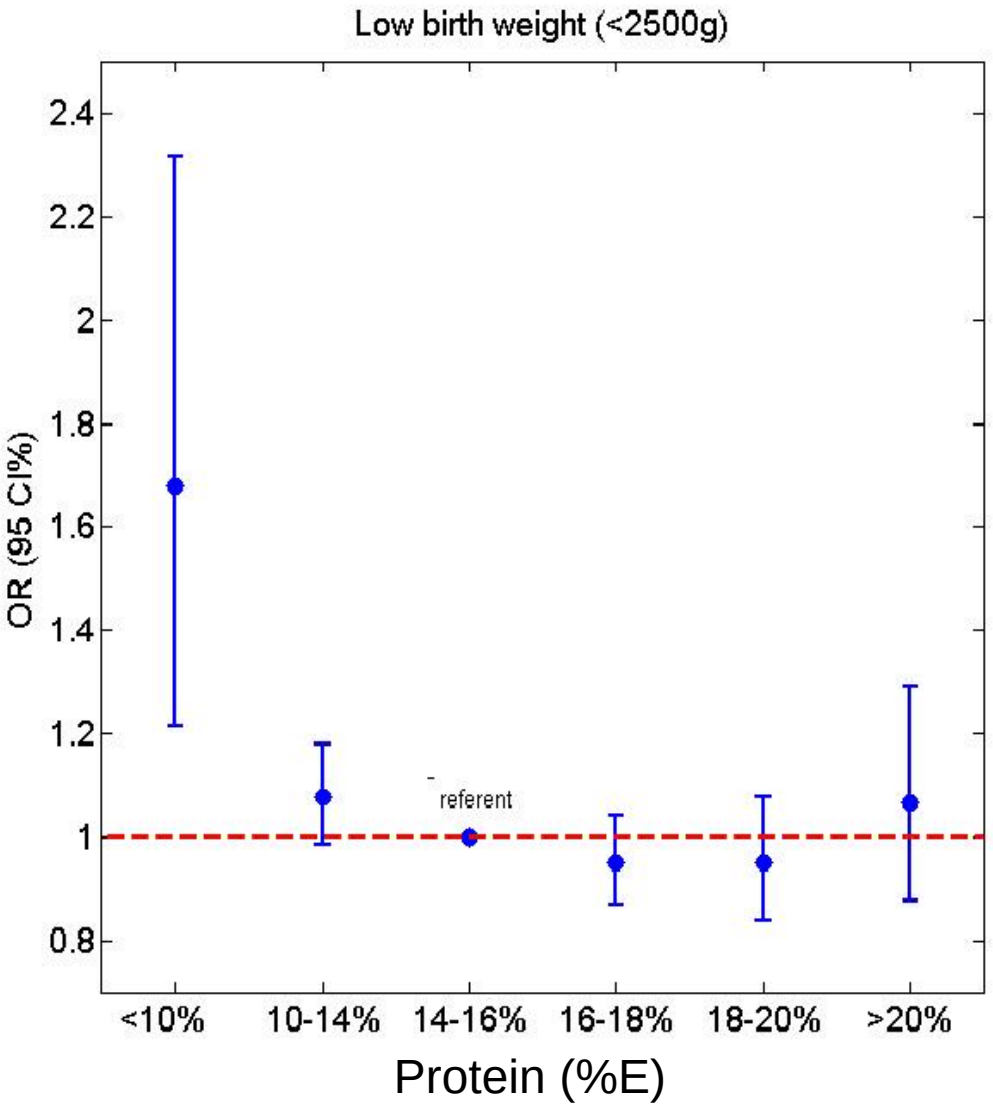
Distribution of study participants with respect to protein (%E) intake as estimated by the FFQs (n=122532)

Protein intake (%E)	Combined cohorts		DK	NO	
	N	%	%	%	
<10%	752	0.6	0.7	0.5	below recommendation
10-14%	28775	23.5	23.1	23.9	
14-16%	**42991**	**35.1**	**32.2**	**37.9**	**used as referent**
16-18%	33281	27.2	27.6	26.8	
18-20%	12718	10.4	12.0	8.8	
>20%	4015	3.3	4.4	2.2	exceeds recommendation

Danish National Birth Cohort

Norwegian **Mother and Child** Cohort Study

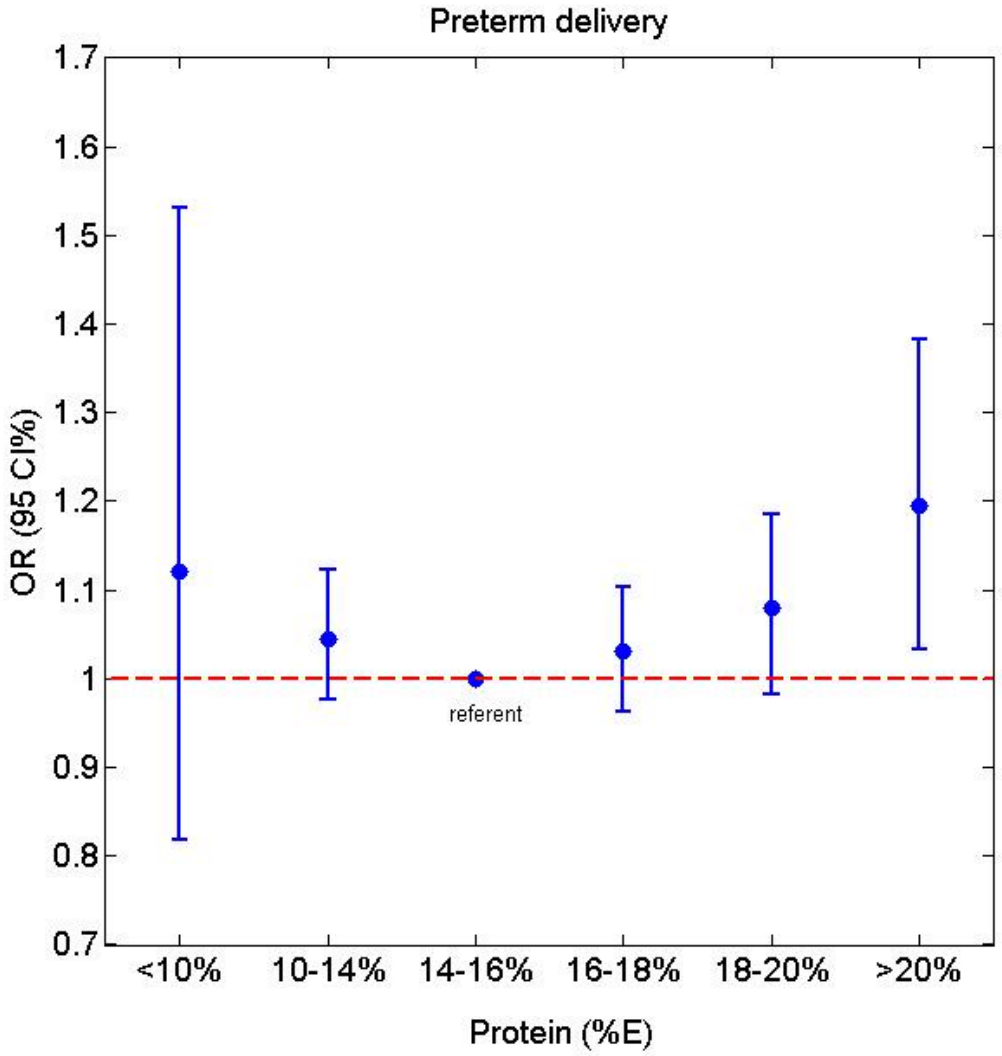
Low birth weight (LBW)



High (>20%E) protein density was not associted with LBW

Low protein density (<10%) was associated with 68% increase odds of LBW. Only 752 (0.6%) had such low intake.

Preterm delivery



- Comparde to those with protein density between 14-16% odds of preterm delivery increased at higher intakes
- A modest 20% (significant) increased odds of preterm at for >20%E
- OR in DNBC: 1.20
- OR in MoBa: 1.19

Macronturient intake in week 30 of gestation in the Aarhus 1988-89 cohort

	Percentiles		
	10th	50th	90th
Protein (%E)	13	16	20
Carbohydrates (%E)	44	51	57
Added sugars (%E)	3	7	14
Fibers (grams)	16	24	33
Total fat (%E)	24	32	40
Saturated fat (%E)	10	14	19
mono-unsaturated fat (%E)	7	9	11
Poly-unsaturated fat (%E)	3	4	5

High maternal protein intake and inflammation

Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Maternal Diet, Gestational Weight Gain, and Inflammatory Markers During Pregnancy

Laufey Hrolfsdottir[1,2], Casper G. Schalkwijk[3], Bryndis E. Birgisdottir[1], Ingibjorg Gunnarsdottir[1], Ekaterina Maslova[2,4,5], Charlotta Granström[2], Marin Strøm[2,6], Sjurdur F. Olsen[2,7], and Thorhallur I. Halldorsson[1,2]

TABLE 4 Multivariable associations of maternal protein and fiber intake with maternal inflammatory biomarkers in week 30 of gestation ($n = 671$)

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend[a]
		% Change (95% CI)				
hsCRP[b]						
Protein[c]	Ref	9 (−11 to 33)	11 (−10 to 35)	22 (−0 to 50)	26 (3 to 54)	0.026
Animal protein[c,d]	Ref	−3 (−21 to 19)	5 (−14 to 29)	19 (−3 to 46)	25 (2 to 53)	0.004
Plant protein[c,e]	Ref	−5 (−23 to 16)	−22 (−36 to −4)	−19 (−34 to 0.5)	−24 (−38 to −6)	<0.001
SAA[b]						
Protein[c]	Ref	11 (−6 to 32)	16 (−3 to 37)	16 (−3 to 37)	31 (10 to 55)	0.011
Animal protein[c,d]	Ref	3 (−13 to 23)	13 (−5 to 34)	21 (2 to 43)	23 (4 to 47)	0.003
Plant protein[c,e]	Ref	3 (−13 to 22)	−2 (−18 to 17)	−11 (−26 to 6)	−10 (−25 to 8)	0.013
IL-8[b]						
Fiber[c]	Ref	−14 (−28 to 3)	−18 (−32 to −1)	−15 (−30 to 2)	−24 (−37 to −9)	0.028

[a] *T*-test with maternal protein intake entered as continuous variable.
[b] Adjusted for maternal pre-pregnancy BMI, age, parity, smoking status, educational level, and total energy.
[c] Energy-adjusted by the residual model.
[d] Animal protein included protein from milk/milk products, cheese, ice cream, meat, fish, eggs, and related products.
[e] Plant protein included protein from cereals, vegetables, fruits, and related products.
hsCRP, high-sensitivity C-reactive protein; IL-8, interleukin 8; SAA, serum amyloid A.

High maternal protein intake and offspring later BP

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Maternal Macronutrient Intake and Offspring Blood Pressure 20 Years Later

Laufey Hrolfsdottir, MSc; Thorhallur I. Halldorsson, PhD; Dorte Rytter, PhD; Bodil Hammer Bech, MD, PhD; Bryndis E. Birgisdottir, PhD; Ingibjorg Gunnarsdottir, PhD; Charlotta Granström, MSc; Tine Brink Henriksen, MD, PhD; Sjurdur F. Olsen, MD, DMSc; Ekaterina Maslova, ScD

Conclusions—Higher maternal dietary protein intake at the expense of carbohydrates was associated with a modest increase in offspring blood pressure in young adulthood. (*J Am Heart Assoc*. 2017;6:e005808. DOI: 10.1161/JAHA.117.005808.)

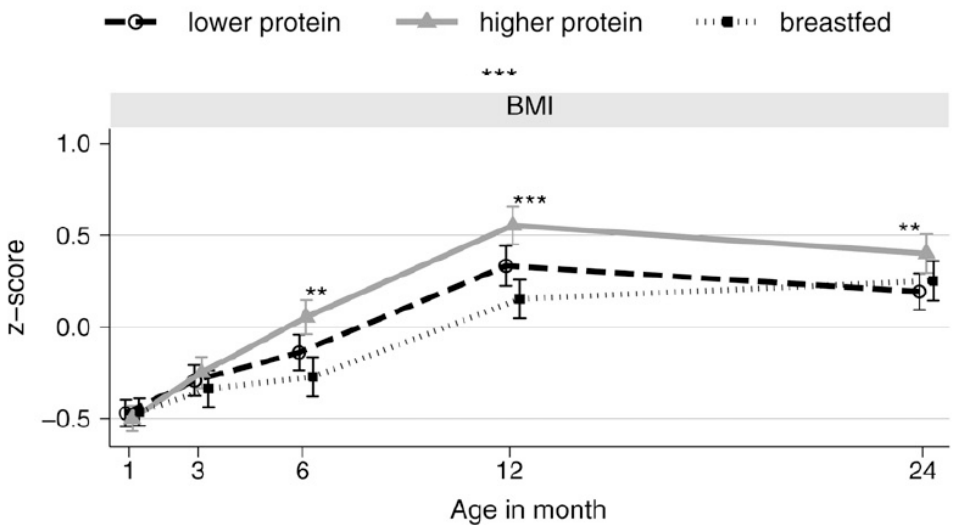
High protein intake in infancy and weight gain

Am J Clin Nutr 2009;89:1836–45.

See corresponding editorial on page 1719.

Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial[1–4]

Berthold Koletzko, Rüdiger von Kries, Ricardo Closa, Joaquín Escribano, Silvia Scaglioni, Marcello Giovannini, Jeannette Beyer, Hans Demmelmair, Dariusz Gruszfeld, Anna Dobrzanska, Anne Sengier, Jean-Paul Langhendries, Marie-Francoise Rolland Cachera, and Veit Grote for the European Childhood Obesity Trial Study Group



Intake of protein during pregnancy and offspring weight at adult age

See corresponding editorial on page 993.

Maternal protein intake during pregnancy and offspring overweight 20 y later[1–3]

Ekaterina Maslova, Dorte Rytter, Bodil H Bech, Tine B Henriksen, Morten A Rasmussen, Sjurdur F Olsen, and Thorhallur I Halldorsson

Am J Clin Nutr 2014;100:1139–48. Printed in USA.

ABSTRACT

Background: Animal studies have shown that protein intake in pregnancy may influence offspring fat metabolism and adiposity. The macronutrient ratio in human pregnancy appears to be important for offspring glucose tolerance; however, less is known about the influence on offspring adiposity.

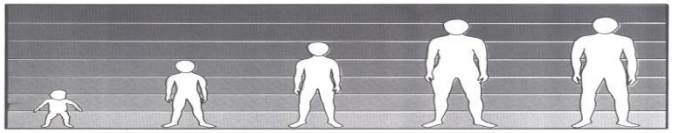
Objective: We examined the relation between maternal dietary protein intake during pregnancy and offspring anthropometric measures and biomarkers of adiposity and glucose metabolism.

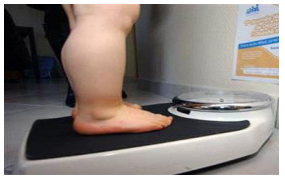
Relation between protein (substituted for carbohydrates) intake in pregnancy and risk of offspring being overweight or having waist circumference above action level II at 19–21 y of age for women (n = 361) and men (n = 325)[1]

	Overweight (BMI ≥25 kg/m^2)		High waist circumference	
	Crude	Adjusted[2]	Crude	Adjusted[2]
Women				
Total protein[3]				
Quartile 1 (median: 64 g/d; n = 80)[4]		1.00 (reference)		1.00 (reference)
Quartile 2 (median: 74 g/d; n = 94)		1.25 (0.60, 2.62)		1.24 (0.58, 2.62)
Quartile 3 (median: 82 g/d; n = 98)		1.51 (0.74, 3.07)		0.67 (0.28, 1.61)
Quartile 4 (median: 92 g/d; n = 88)		2.18 (1.11, 4.29)		1.76 (0.87, 3.57)
P-trend[5]		0.02		0.18
Animal protein[6]				
Quartile 1 (median: 36 g/d; n = 82)		1.00 (reference)		1.00 (reference)
Quartile 2 (median: 49 g/d; n = 98)		1.53 (0.70, 3.34)		1.71 (0.76, 3.85)
Quartile 3 (median: 58 g/d; n = 91)		1.64 (0.75, 3.56)		0.87 (0.34, 2.24)
Quartile 4 (median: 69 g/d; n = 89)		3.36 (1.52, 7.42)		2.20 (0.88, 5.52)
P-trend		0.003		0.15
Vegetable protein[7]				
Quartile 1 (median: 17 g/d; n = 92)		1.00 (reference)		1.00 (reference)
Quartile 2 (median: 20 g/d; n = 88)		1.14 (0.59, 2.20)		1.73 (0.89, 3.39)
Quartile 3 (median: 24 g/d; n = 86)		1.10 (0.51, 2.34)		1.98 (0.84, 4.64)
Quartile 4 (median: 28 g/d; n = 94)		1.39 (0.65, 2.99)		1.18 (0.42, 3.28)
P-trend		0.41		0.77
Men				
Total protein[3]				
Quartile 1 (median: 64 g/d; n = 83)		1.00 (reference)		1.00 (reference)
Quartile 2 (median: 74 g/d; n = 87)		1.37 (0.67, 2.78)		0.58 (0.15, 2.27)
Quartile 3 (median: 81 g/d; n = 82)		1.62 (0.82, 3.22)		1.42 (0.27, 7.50)
Quartile 4 (median: 91 g/d; n = 72)		1.74 (0.88, 3.45)		0.74 (0.12, 4.36)
P-trend		0.08		0.95
Animal protein[6]				
Quartile 1 (median: 37 g/d; n = 80)		1.00 (reference)		1.00 (reference)
Quartile 2 (median: 49 g/d; n = 89)		1.31 (0.61, 2.82)		0.67 (0.16, 2.84)
Quartile 3 (median: 57 g/d; n = 91)		1.89 (0.86, 4.19)		0.80 (0.13, 4.94)
Quartile 4 (median: 70 g/d; n = 64)		2.22 (0.92, 5.35)		0.94 (0.08, 11.69)
P-trend		0.05		0.94
Vegetable protein[7]				
Quartile 1 (median: 17 g/d; n = 68)		1.00 (reference)		1.00 (reference)
Quartile 2 (median: 20 g/d; n = 82)		2.64 (1.22, 5.69)		1.41 (0.24, 8.26)
Quartile 3 (median: 24 g/d; n = 87)		2.35 (1.00, 5.52)		0.45 (0.05, 4.35)
Quartile 4 (median: 28 g/d; n = 88)		2.51 (0.91, 6.98)		1.16 (0.08, 16.39)
P-trend		0.14		0.89

[1] All values are RRs; 95% CIs in parentheses. The total protein model was adjusted for fat intake and total energy; the animal protein model was adjusted for vegetable protein, other protein, fat, and total energy; and the vegetable protein model was adjusted for animal protein, other protein, fat, and total energy.

Limitations





In utero exposure

Offspring follow up at ~20 years

- Allot of room for confounding - **Clustering of familial lifestyle factors**
- Even with detailed information on later maternal offspring dietary habits proper adjustment may be difficult
- However, In the correlation between maternal versus offspring macronutrient intake among adolecants is often around ~0.1 to 0.3

Conclusions

- In small comprehensive birth cohort with long term follow-up a large number of associations betwene prenatal variables and ofssrping CVD-risk profile can be demonstrated.

- **Limitations**
  - As always there are questionmarks on causality of findings
  - Questions on biological relevance for some of these findings
  - Postnatal confunding cannot be exclued (unlikley to aplly for all findings)
  - Even with complete infomrmation, controling for postnatal factors is almost impossible

Conclusions

- In small comprehensive birth cohort with long term follow-up a large number of associations betwene prenatal variables and ofssrping CVD-risk profile can be demonstrated.

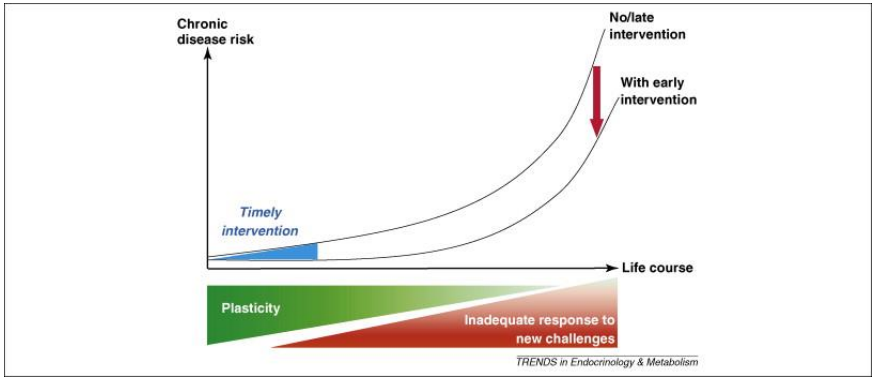
- **Strengths:**
  - Environmental exposure, maternal diet and GWG are all modifayable lifestlye habtis. Better characterisation of these factors in terms of later offspring health has clear public health relevance.
  - Our findings strongly suggest that variation in dietary and environmental exposures “within normal range“ may have biological (but not always clinically relevant) “effect“
  - Our results also higlight the need of not overinterpreting individual findings in terms of what is the “most important risk factor“!!

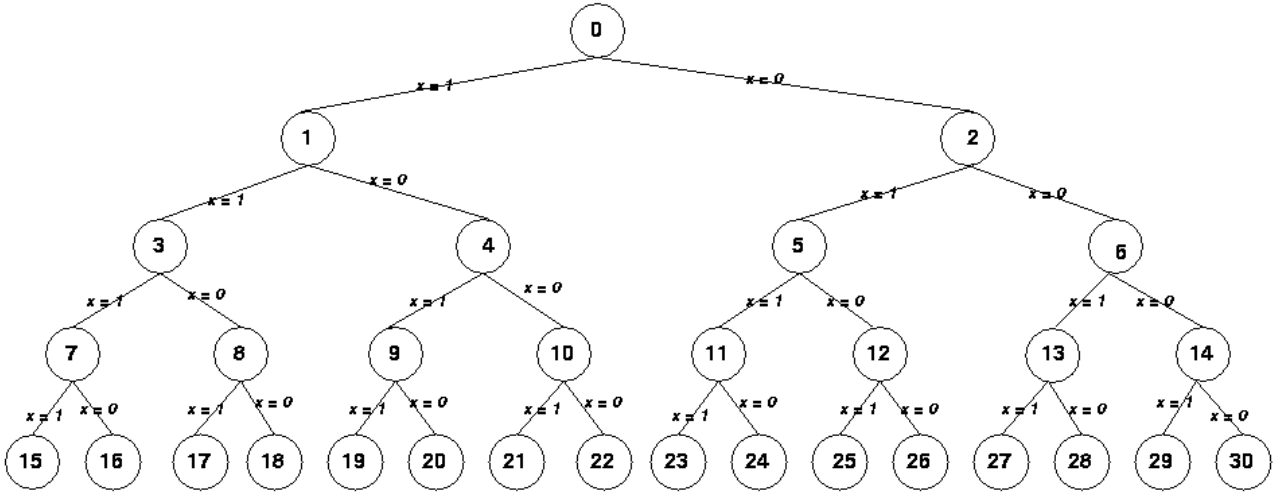
A recent reviewer coment
- to a rejected DaFo88 paper -

- A number of studies start with a cohort of births and follow the offspring over time. Perhaps the most famous of these studies is a sequence of UK birth cohort studies started in 1946 and reported on extensively in the book, The Life Project by Helen Pearson. A very large number of variables are measured on parent(s), birth characteristics, and offspring. The offspring are studied over time, usually to early adulthood.

- Given the number of variables available and the number of covariates, drawing valid conclusions is challenging. Suppose there are 10 characteristics of the parent(s), 10 birth characteristics, 10 characteristics of the newborn child and 10 characteristics measured every five years until and including 20 years old. We would have 10^7 possible relationships. Some relationships would not be of interest, but many would. The standard of 5% for statistical significance would lead to an enormous number of “statistically significant” false positive results.

- Multiple testing needs to be carefully considered and dealt with.


Chronic disease risk
No/late intervention
With early intervention
Timely intervention
Life course
Plasticity
Inadequate response to new challenges
TRENDS in Endocrinology & Metabolism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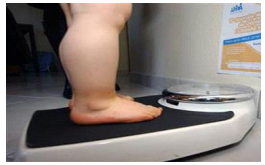

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"*Ceterum censeo Carthaginem esse delendam*"

Thank you

Antenaltal lifestyle advise for Obese pregnant women, does it work?

Popularity of antenatal lifestyle interventions

- Observational studies
  - Causality ???
  - Confounding, data diven ...!!!
  - Allot of divergent findings
  - Therefor more focus/funding of interventions

- Randomized controlled trails
  - They do say somthing on causality
  - In pinciple no confounding and NOT data driven

BMJ

BMJ 2014;348:g1285 doi: 10.1136/bmj.g1285 (Published 10 February 2014)

RESEARCH

Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial

Jodie M Dodd *professor of obstetrics and gynaecology; maternal fetal medicine specialist*[1 2], Deborah

Abstract

Objective To determine the effect of antenatal dietary and lifestyle interventions on health outcomes in overweight and obese pregnant women.

Design Multicentre randomised trial. We utilised a central telephone randomisation server, with computer generated schedule, balanced variable blocks, and stratification for parity, body mass index (BMI) category, and hospital.

Setting Three public maternity hospitals across South Australia.

Participants 2212 women with a singleton pregnancy, between 10+0 and 20+0 weeks' gestation, and BMI ≥25.

Interventions 1108 women were randomised to a comprehensive dietary and lifestyle intervention delivered by research staff; 1104 were randomised to standard care and received pregnancy care according to local guidelines, which did not include such information.

Main outcome measures Incidence of infants born large for gestational age (birth weight ≥90th centile for gestation and sex). Prespecified secondary outcomes included birth weight >4000 g, hypertension, pre-eclampsia, and gestational diabetes. Analyses used intention to treat principles.

Results 2152 women and 2142 liveborn infants were included in the analyses. The risk of the infant being large for gestational age was not significantly different in the two groups (lifestyle advice 203/1075 (19%) *v* standard care 224/1067 (21%); adjusted relative risk 0.90, 95% confidence interval 0.77 to 1.07; P=0.24). Infants born to women after lifestyle advice were significantly less likely to have birth weight above 4000 g (lifestyle advice 164/1075 (15%) *v* standard care 201/1067 (19%); 0.82, 0.68 to 0.99; number needed to treat (NNT) 28, 15 to 263; P=0.04). There were no differences in maternal pregnancy and birth outcomes between the two treatment groups.

Conclusions For women who were overweight or obese, the antenatal lifestyle advice used in this study did not reduce the risk delivering a baby weighing above the 90th centile for gestational age and sex or improve maternal pregnancy and birth outcomes.

Trial registration Australian and New Zealand Clinical Trials Registry (ACTRN12607000161426).

BMJ

BMJ 2012;345:e5605 doi: 10.1136/bmj.e5605 (Published 30 August 2012)

RESEARCH

Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial

Jennifer M Walsh *clinical research fellow, specialist registrar in obstetrics and gynaecology*, Ciara A McGowan *research dietician*, Rhona Mahony *consultant obstetrician and gynaecologist*, Michael

Abstract

Objective To determine if a low glycaemic index diet in pregnancy could reduce the incidence of macrosomia in an at risk group.

Design Randomised controlled trial.

Setting Maternity hospital in Dublin, Ireland.

Participants 800 women without diabetes, all in their second pregnancy between January 2007 to January 2011, having previously delivered an infant weighing greater than 4 kg.

Intervention Women were randomised to receive no dietary intervention or start on a low glycaemic index diet from early pregnancy.

Main outcomes The primary outcome measure was difference in birth weight. The secondary outcome measure was difference in gestational weight gain.

Results No significant difference was seen between the two groups in absolute birth weight, birthweight centile, or ponderal index. Significantly less gestational weight gain occurred in women in the intervention arm (12.2 *v* 13.7 kg; mean difference −1.3, 95% confidence interval −2.4 to −0.2; P=0.01). The rate of glucose intolerance was also lower in the intervention arm: 21% (67/320) compared with 28% (100/352) of controls had a fasting glucose of 5.1 mmol/L or greater or a 1 hour glucose challenge test result of greater than 7.8 mmol/L (P=0.02).

Conclusion A low glycaemic index diet in pregnancy did not reduce the incidence of large for gestational age infants in a group at risk of fetal macrosomia. It did, however, have a significant positive effect on gestational weight gain and maternal glucose intolerance.

Trial registration Current Controlled Trials ISRCTN54392969.

RESEARCH www.AJOG.org

OBSTETRICS

The Treatment of Obese Pregnant Women (TOP) study: a randomized controlled trial of the effect of physical activity intervention assessed by pedometer with or without dietary intervention in obese pregnant women

Kristina M. Renault, MD; Kirsten Nørgaard, DMSc; Lisbeth Nilas, DMSc; Emma M. Carlsen, MD; Dina Cortes, DMSc; Ole Pryds, DMSc; Niels J. Secher, MD

Women with pre-preg BMI>30kg/m^2

Main outcome: Gestational weight gai

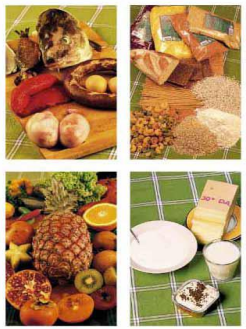
Randomised
N=425

Allocation

Intervention group
PA+D)
n=142
FFQ n=135

Intervention group PA)
n=142
FFQ n=132

Control group C)
n=141
FFQ n=129



Results: Primary outcome of the TOP-study

N=389	PA+D) Diet + Pedometer n=130	PA) Pedometer n=125	C) Control n=134	Significance
GWG: Median	**8.6 kg**	**9.4 kg**	**10.9kg**	*P*=0.024

❖Pedometer intervention reduced GWG by a mean of 1.4 kg compared to women not using a pedometer

❖Additive effect of dietary follow-up was not significant

Why are the effect estimates so unimpressive

PLOS ONE

RESEARCH ARTICLE

Intake of Sweets, Snacks and Soft Drinks Predicts Weight Gain in Obese Pregnant Women: Detailed Analysis of the Results of a Randomised Controlled Trial

Kristina M. Renault[1,2]*, Emma M. Carlsen[3], Kirsten Nørgaard[4], Lisbeth Nilas[1], Ole Pryds[3], Niels J. Secher[5], Sjurdur F. Olsen[6,7], Thorhallur I. Halldorsson[6,8]

A validated food frequency questionnaire (FFQ)

360-items

Covered the intake of food and drinks during previous 4 weeks

Baseline: Week 11-14

Endpoint: Week 36-37

Changes in diet

Table 2. Relative changes in dietary intake between baseline and endpoint among subjects reporting their diet at both time points (N = 342). The relative risk of having either low or excessive weight gain as defined by the institute of medicine[1] is also shown for each group.

	Control (n = 118)	Physical Activity (n = 110)	Physical Activity + Diet (n = 114)
Changes in dietary intake		Δ^2 (95% CI)	Δ^2 (95% CI)
Energy (MJ/day)	Reference	-0.0 (-0.7, 0.7)	0.1 (-0.5, 0.8)
Protein (%E)	Reference	0.3 (-0.4, 1.0)	**1.0 (0.3, 1.7)**
Animal protein	Reference	0.0 (-0.8, 0.9)	**1.1 (0.2, 1.9)**
Plant protein	Reference	0.3 (-0.3, 0.8)	0.0 (-0.6, 0.5)
Carbohydrates (%E)	Reference	-0.1 (-1.7, 1.8)	-0.9 (-2.6, 0.8)
added sugar	Reference	0.1 (-1.2, 1.5)	**-1.3 (-2.6, -0.0)**
form foods	Reference	0.6 (-0.3, 1.5)	-0.8 (-1.7, 0.1)
from soft drinks	Reference	-0.4 (-1.5, 0.6)	-0.5 (-1.5, 0.4)
Fat (%E)	Reference	-0.3 (-1.9, 1.3)	-0.4 (-2.0, 1.2)
saturated	Reference	-0.4 (-1.2, 0.5)	**-0.8 (-1.6, -0.0)**
Monounsaturated	Reference	0.1 (-0.6, 0.7)	0.2 (-0.5, 0.8)
Polyunsaturated	Reference	0.0 (-0.3, 0.4)	**0.4 (0.1, 0.7)**
Gestational weight gain		RR (95% CI)	RR (95% CI)
low weight gain (<5kg)	Reference	1.24 (0.73, 2.09)	1.33 (0.80, 2.21)
excessive (>9kg)	Reference	0.86 (0.68, 1.08)	0.73 (0.57, 0.94)

GWG: 10.9 kg 9.4kg 8.6kg

What about those that did not receive dietary intervention

Table 3. Dietary changes in the physically activity intervention groups stratified by median pedometer output in week 17 of gestation. Corresponding changes in GWG are also presented.

	Control	Physical Activity *low activity*[1]	Physical Activity *high activity*[1]	Physical Activity + Diet
Endpoint—baseline		Δ^2 (95% CI)	Δ^2 (95% CI)	Δ^2 (95% CI)
No.	118	60	47	114
Prot (%E)	Reference	-0.1 (-1.3, 0.7)	1.0 (0.1, 2.0)	1.1 (0.4, 1.8)
Added sugar (%E)	Reference	1.2 (-0.3, 2,8)	-1.2 (-3.0, 0.5)	-1.3 (-2.6, -0.0)
Saturated fat (%E)	Reference	-0.3 (-1.3, 0.7)	-0.5 (-1.7, 0.6)	-0.8 (-1.6, -0.0)
Poly unsaturated (%E)	Reference	0.1 (-0.3, 0.4)	-0.0 (-0.4, 0.4)	0.4 (0.1, 0.7)
Gestational weight gain				
low weight gain (<5kg)	Reference	1.22 (0.66, 2.26)	1.20 (0.61, 2.34)	1.33 (0.80, 2.21)
excessive (>9kg)	Reference	0.87 (0.66, 1.15)	0.84 (0.61, 1.15)	0.73 (0.57, 0.94)

[1]Low activity is defined as pedometer output below the median value (8725 steps/day) or missing on pedometer output (n = 13). High activity is defined as pedometer output above the median

[2] mean difference (Δ) and 95% confidence interval (95%CI). Dietary variables are adjusted for baseline BMI, maternal age, smoking, parity, and baseline energy intake

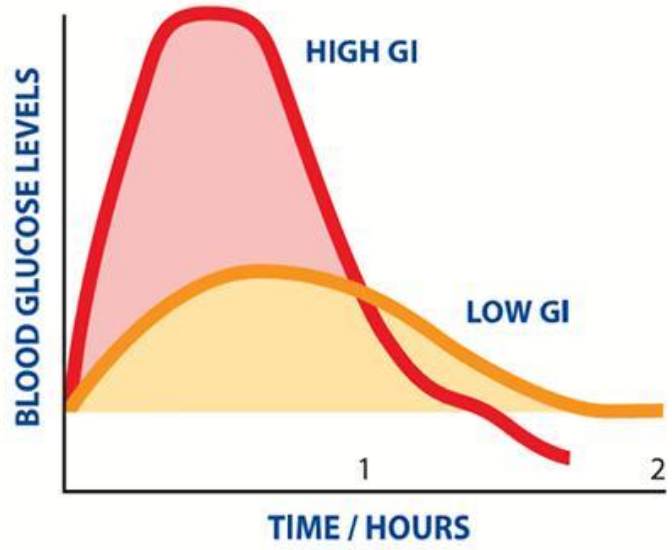
doi:10.1371/journal.pone.0133041.t003

And when we looked at diet and GWG in an observational setting

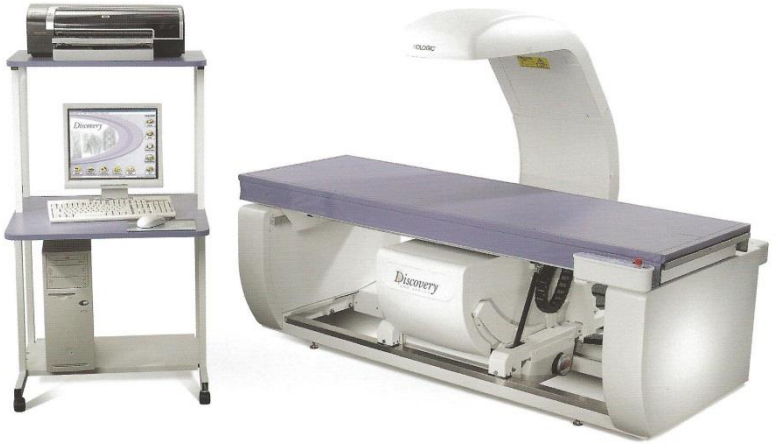
Table 5. Associations[1] between self-reported intake at baseline and endpoint of sweets snacks, cakes and soft drinks with gestational weight gain. Associations for both relative risk (RR) of excessive weight gain (>9kg) and mean increase in GWG compared to the reference category (Δ) are presented.

	Baseline (n = 366)			Endpoint (n = 347)		
	Mean change	**Excessive weight gain (>9kg)**		**Mean change**	**Excessive weight gain (>9kg)**	
Sweets	Δkg (95% CI)	Cases/n	RR (95% CI)	Δkg (95% CI)	Cases/n	RR (95% CI)
<1/wk	Reference	21/54	1.00	Reference	21/51	1.00
1–<3/wk	2.6 (0.7, 4.6)	62/131	1.28 (0.89, 1.84)	0.4 (-1.6, 2.4)	42/108	0.99 (0.66, 1.47)
3–<7/wk	3.6 (1.6, 5.6)	63/109	1.52 (1.06, 2.22)	3.3 (1.3, 5.3)	85/133	1.51 (1.06, 2.15)
1/d	4.5 (2.1, 6.9)	35/54	1.71 (1.17, 2.59)	3.2 (0.8, 5.7)	31/49	1.50 (1.01, 2.23)
≥2/d	5.4 (2.1, 8.7)	12/18	1.84 (1.14, 2.96)	5.6 (0.5, 10.8)	4/6	1.66 (0.83, 3.30)
P for trend[2]	0.0009		0.0006	<0.0001		0.001
Snacks						

Maternal diet and offpsring anthroprometry



The amount of carbohydrate in the reference and test food must be the same.



Am J Clin Nutr 2015;102:1475–81. Printed in USA.

Intake of carbohydrates during pregnancy in obese women is associated with fat mass in the newborn offspring[1]

Kristina M Renault,[2] Emma M Carlsen,[3] Kirsten Nørgaard,[4] Lisbeth Nilas,[2] Ole Pryds,[3] Niels J Secher,[5] Dina Cortes,[3] Jens-Erik Beck Jensen,[4] Sjurdur F Olsen,[6] and Thorhallur I Halldorsson[6,7]*

Departments of [2]Obstetrics and Gynaecology, [3]Paediatrics, and [4]Endocrinology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark; [5]The Research Unit Women's and Children's Health, the Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [6]Centre for Fetal Programming, Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark; and [7]Faculty of Food Science and Nutrition, University of Iceland, Reykjavik, Iceland

TABLE 2
Associations between digestible carbohydrates in early and late pregnancy in relation to the relative fat mass of offspring as measured by dual-energy X-ray absorptiometry 24 h after delivery

		Change[1] (95% CI), %	
	Median intake, g/d	Unadjusted	Adjusted[2]
Weeks 11–14			
Quartile 1	180	Referent	Referent
Quartile 2	205	0.4 (−1.2, 2.1)	1.0 (−0.5, 2.5)
Quartile 3	220	0.9 (−0.8, 2.5)	0.9 (−0.6, 2.5)
Quartile 4	244	1.2 (−0.5, 2.8)	1.2 (−0.3, 2.7)
P-trend		0.14	0.14
Weeks 36–37			
Quartile 1	188	Referent	Referent
Quartile 2	205	1.0 (−0.7, 2.6)	0.6 (−0.9, 2.1)
Quartile 3	217	1.2 (−0.5, 2.8)	0.9 (−0.7, 2.4)
Quartile 4	238	2.4 (0.7, 4.0)	2.1 (0.6, 3.7)
P-trend		0.005	0.006

[1]Mean increase in the relative percentage fat of the offspring compared with the value in quartile 1.

[2]Adjusted for maternal age, physical activity intervention, prepregnancy BMI, parity, gestational weight gain, gestational age, smoking during pregnancy, 2-h oral-glucose-tolerance test value (at approximately week 29), energy intake, and offspring sex and age at the time of the dual-energy X-ray absorptiometry measurement.

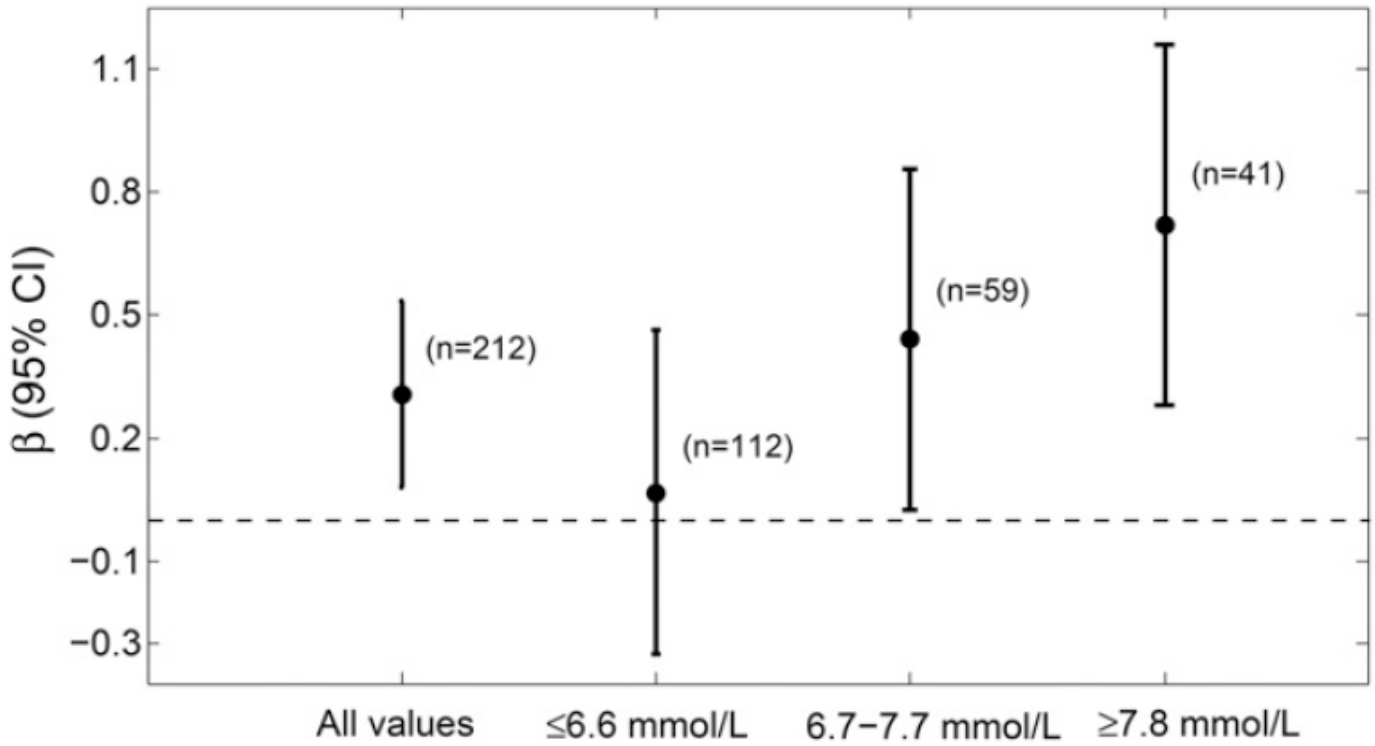


FIGURE 2 Associations between intake of digestible carbohydrates at gestational weeks 36–37 and relative fat mass of the offspring measured by dual-energy X-ray absorptiometry after birth. The regression coefficients reflect the change in relative fat mass (% on the *y* axis) per 10-g higher intake of digestible carbohydrates for all values and coefficients based on stratification by maternal 2-h oral-glucose-tolerance test values in the third trimester.

ACTA PÆDIATRICA
NURTURING THE CHILD

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REGULAR ARTICLE

Newborn regional body composition is influenced by maternal obesity, gestational weight gain and the birthweight standard score

EM Carlsen (emc@dadlnet.dk)[1], KM Renault[2], K Nørgaard[3], L Nilas[4,5], JEB Jensen[3], L Hyldstrup[3], KF Michaelsen[6], D Cortes[1,5], O Pryds[1,5]

1.Department of Paediatrics, Hvidovre University Hospital, University of Copenhagen, Hvidovre, Denmark
2.Department of Obstetrics and Gynaecology, Odense University Hospital, University of Southern Denmark, Odense, Denmark
3.Department of Endocrinology, Hvidovre University Hospital, University of Copenhagen, Hvidovre, Denmark
4.Department of Obstetrics and Gynaecology, Hvidovre University Hospital, University of Copenhagen, Hvidovre, Denmark
5.Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark
6.Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Frederiksberg, Denmark

Keywords
Abdominal fat mass, Body composition, Dual-energy X-ray absorptiometry, Gestational weight gain, Maternal obesity

Correspondence
Emma Malchau Carlsen, Hvidovre Hospital,

Table 2 Determinants of newborn birthweight, total fat-free mass, total fat mass and fat (%) (n = 311)

	Dependent	
	Fat (%)	
Determinants	β* [95% CI]	p-Value
Prepregnant obesity (y/n)	3.1 [2.0, 4.1]	<0.001
GWG (kg)	0.2 [0.1, 0.3]	<0.001
Primiparity (y/n)	0.2 [−1.2, 0.7]	0.65
Gestational age (days)	0.07 [0.02, 0.1]	0.004
Male sex (y/n)	−2.0 [−2.9, −1.1]	<0.001

GWG = Gestational weight gain.
*Multiple regression adjusted for maternal age, education and smoking.

Low GI foods ≠ better health !!

http://www.theguardian.com/commentisfree/2013/oct/21/fructose-poison-sugar-industry-pseudoscience

efsa
European Food Safety Authority
EFSA Journal 2011;9(6):2223

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to fructose and reduction of post-prandial glycaemic responses (ID 558) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

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Comment is free

Fructose: the poison index

A ruling on fructose boosts the powerful sugar industry, either by incompetence or collusion, but is based on pseudoscience

Robert Lustig
The Guardian, Monday 21 October 2013 21.00 BST
Jump to comments (721)

Fizzy drinks can have a 'serum fructose concentration of six micromolar, enough to do major arterial and pancreatic damage'. Photograph: Nathalie Louvel/Getty Images

The battle over the compound fructose now reaches new levels of obfuscation. The food industry is a strong – and loud, and rich – proponent, hard to ignore. The European Food and Safety Agency has just weighed in, in favour of the substitution of sucrose (table sugar: a disaccharide composed of the monosaccharides glucose and fructose)

Article history

World news
Food safety · European Union

Science
Food science

Business
Food & drink industry

Life and style
Food & drink

Society
Health

More from Comment is free on
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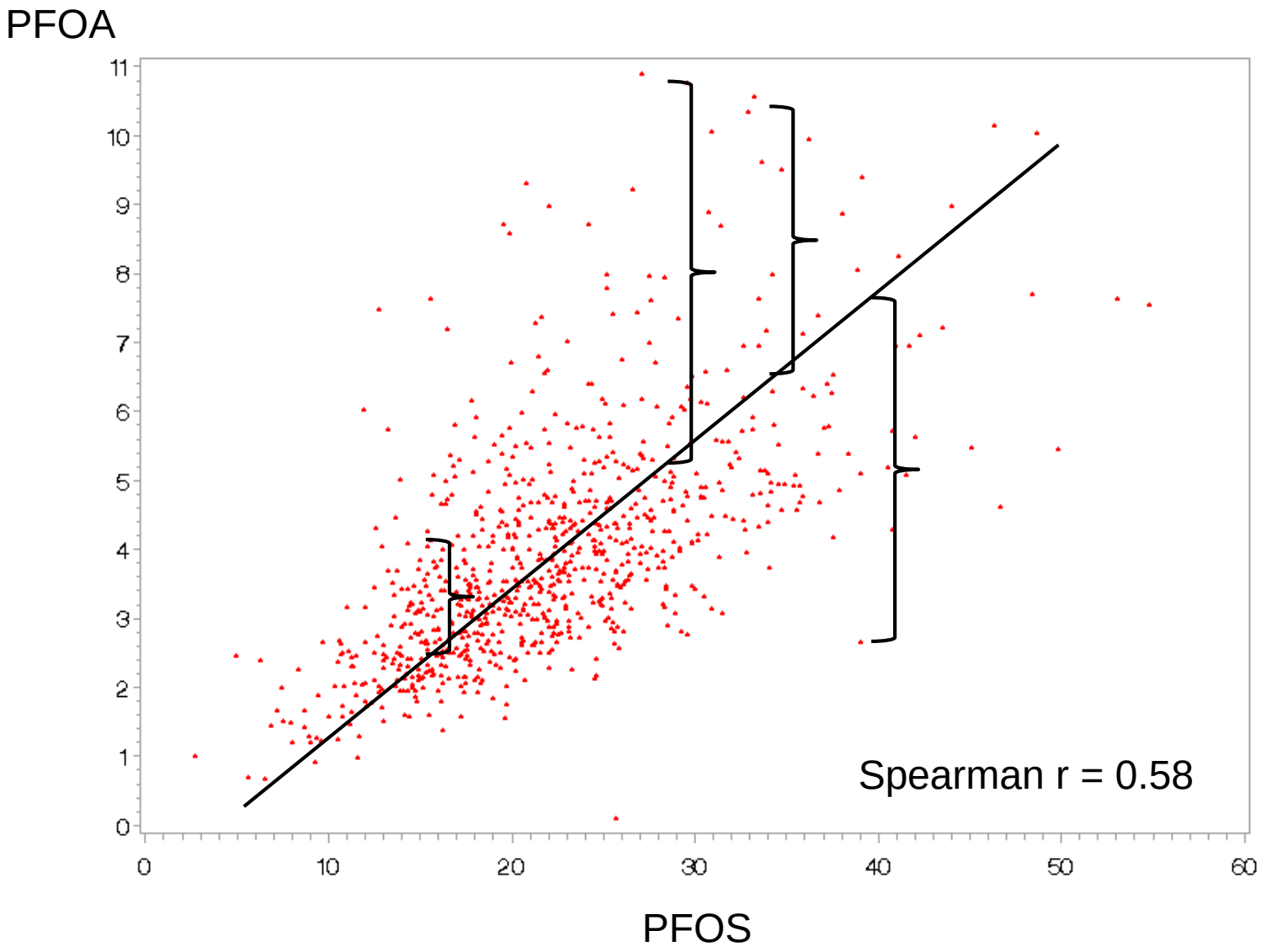
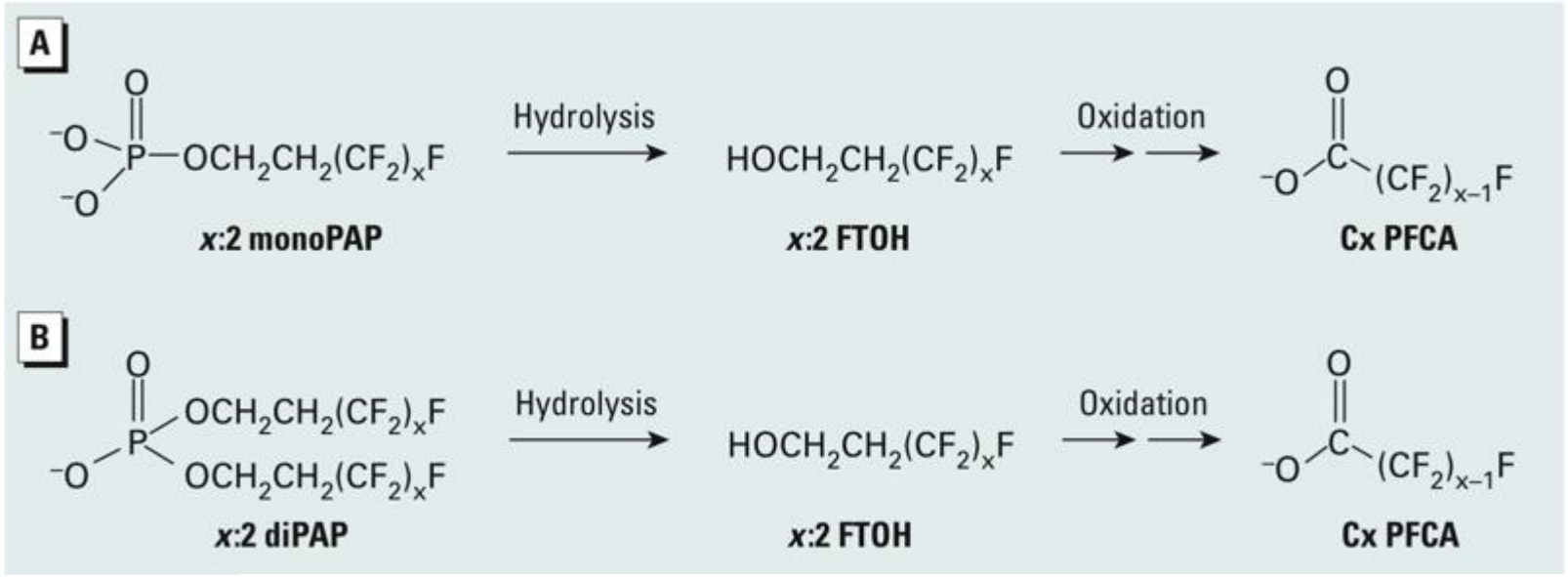
Science
Food science

The Panel considers that in order to bear the claim, glucose or sucrose should be replaced by fructose in sugar sweetened foods or beverages. The target population is individuals who wish to reduce their post-prandial glycaemic responses. The Panel notes that high intakes of fructose may lead to metabolic complications such as dyslipidaemia, insulin resistance and increased visceral adiposity.

PFOA exposure orthogonal to PFOS !!



Polyfluoroalkyl phosphate esters (PAPs) as indirect source of PFOA exposure



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