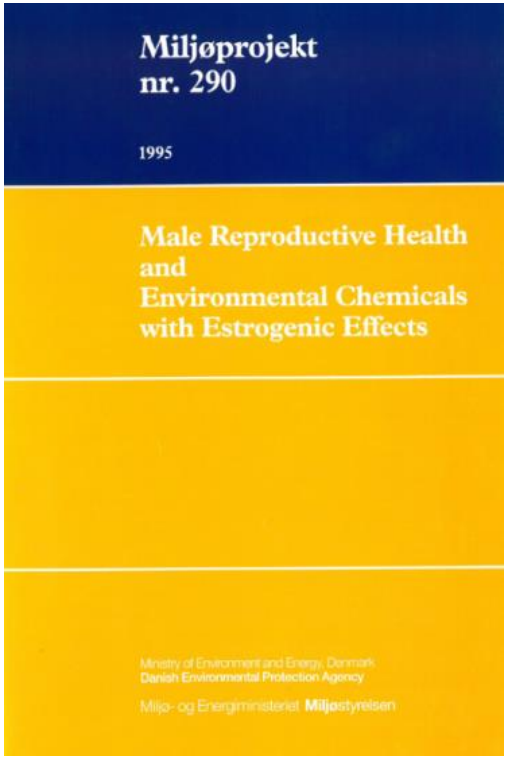
CEHOS

Hormonforstyrrende stoffers betydning for sundhed og sygdom

Anders Juul
Afdeling for Vækst og Reproduktion,
Rigshospitalet

REGION

1991 WHO workshop arrangeret af forskerteam på Rigshospitalet satte fokus på miljøets påvirkning af human reproduktion



1995 Forskergruppen stod bag MST rapport

COW 8th Copenhagen Workshop on Endocrine Disrupters 2015 · April 27 - 30

Siden 2000 Vært for 7 internationale konferencer om hormonforstyrren de stoffer

REGION

Reproduktivt Helbred

en livslang proces

Hvornår starter den reproduktive periode ?

Hos mennesket ?

I puberteten? Når man er 20 år? Før eller senere?

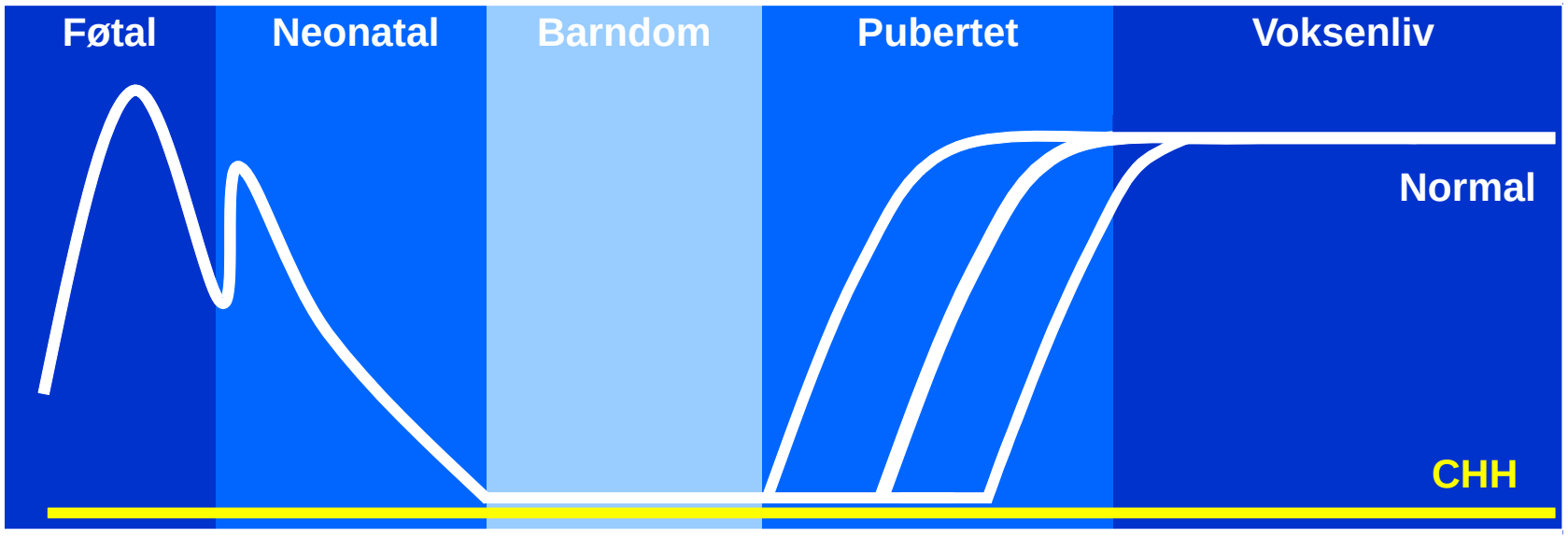
Svaret er lige efter fødslen.

Reproduktivt Helbred

en livslang proces

Fødsel

Reproduktionen starter i fostertilværelsen



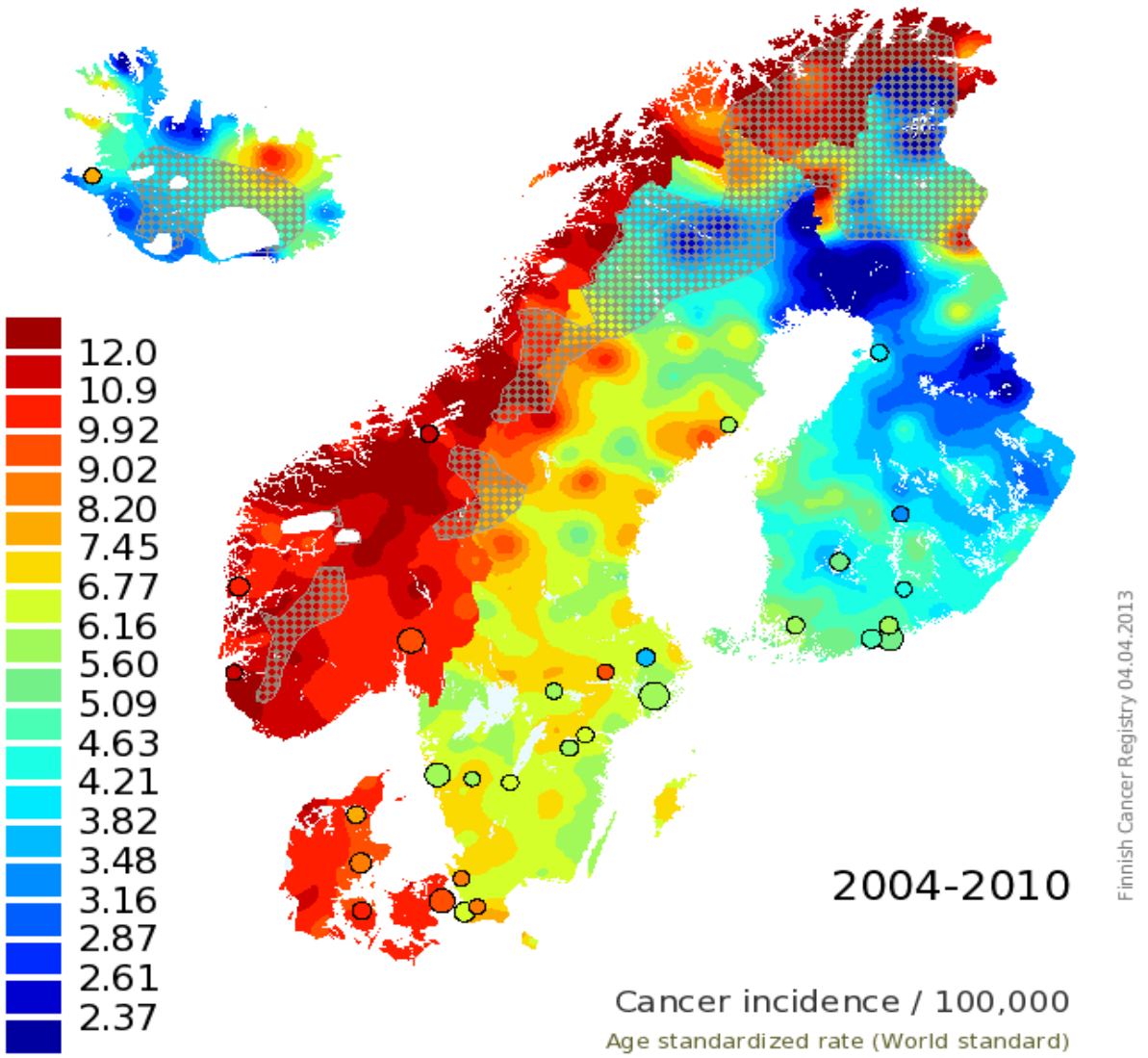
Reproduktivt Helbred

en livslang proces

Når testikeludviklingen i fostertilværelsen går galt – har det konsekvenser resten af livet:

- Kryptorkisme
- Hypospadi
- Nedsat testosteron dannelse
- Kort Anogenital Distance (AGD)
- Dårlig sædkvalitet
- Testikelkræft

Scandinavian incidence in Testicular Cancer



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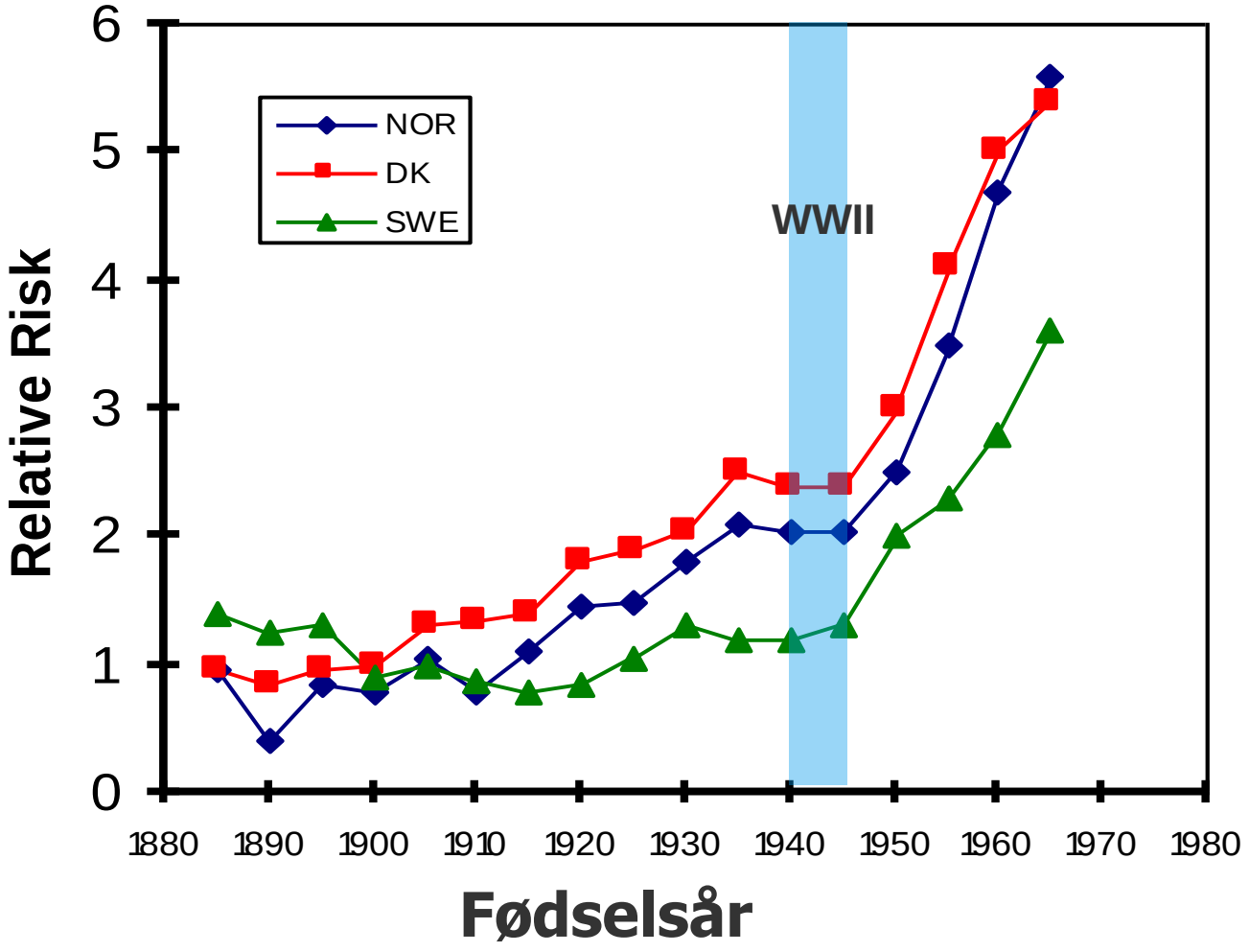
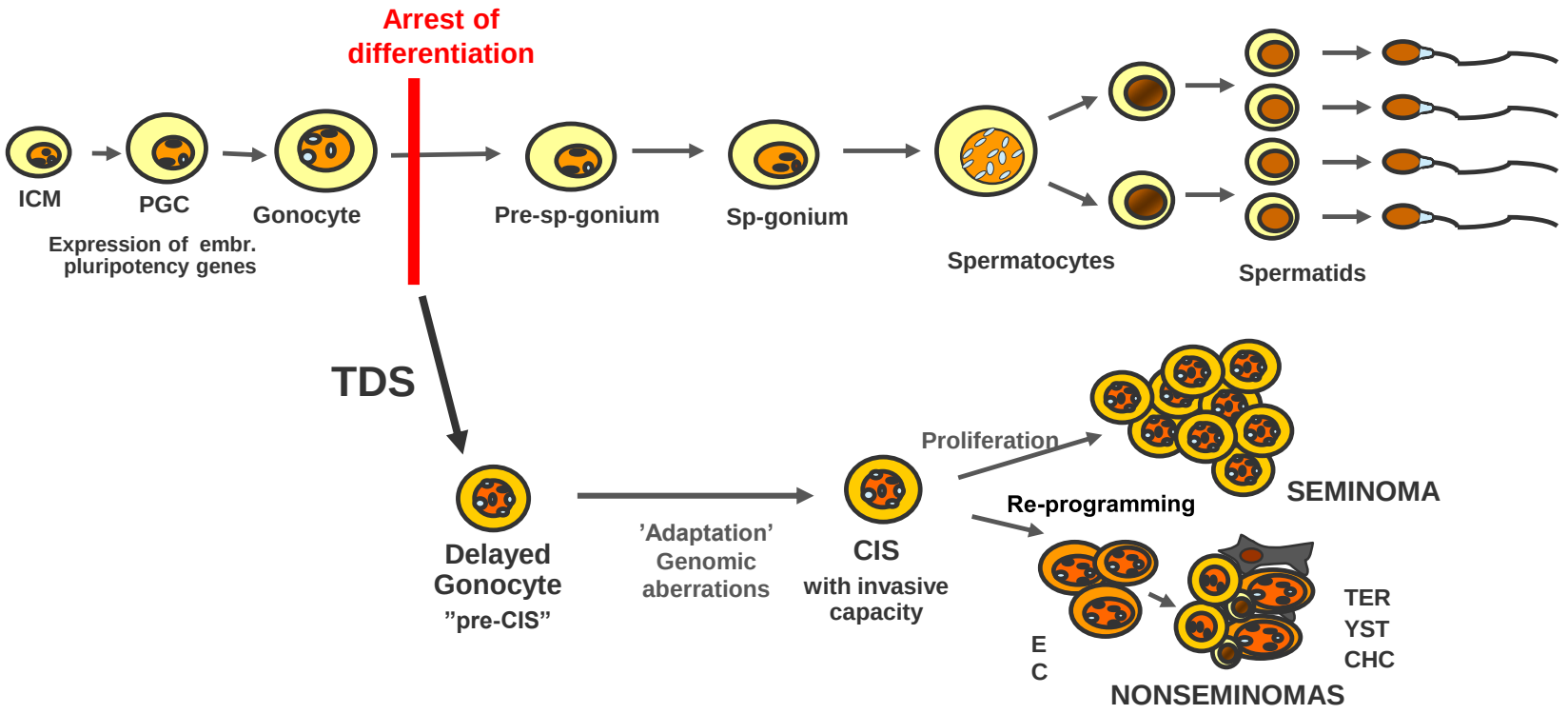
Risiko for Testikelkræft
fødselskohorte effekt



Redrawn from Bergström et al, JNCI 1996; 88: 727-33

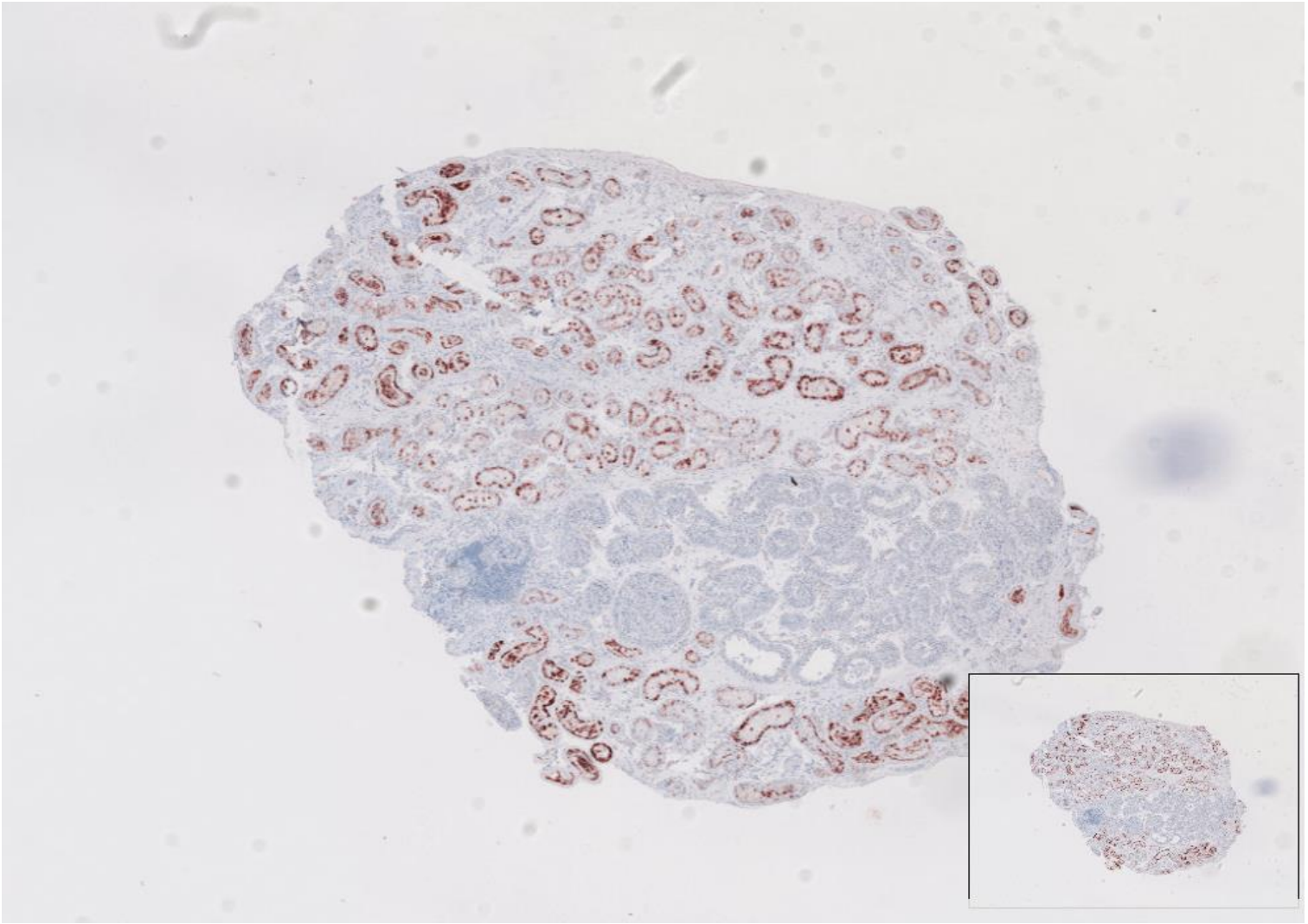
Udvikling af testikelkræft



Updated from Rajpert-De Meyts, Hum Reprod Upd 2006

GCNIS in adult testis

Arrested fetal gonocytes



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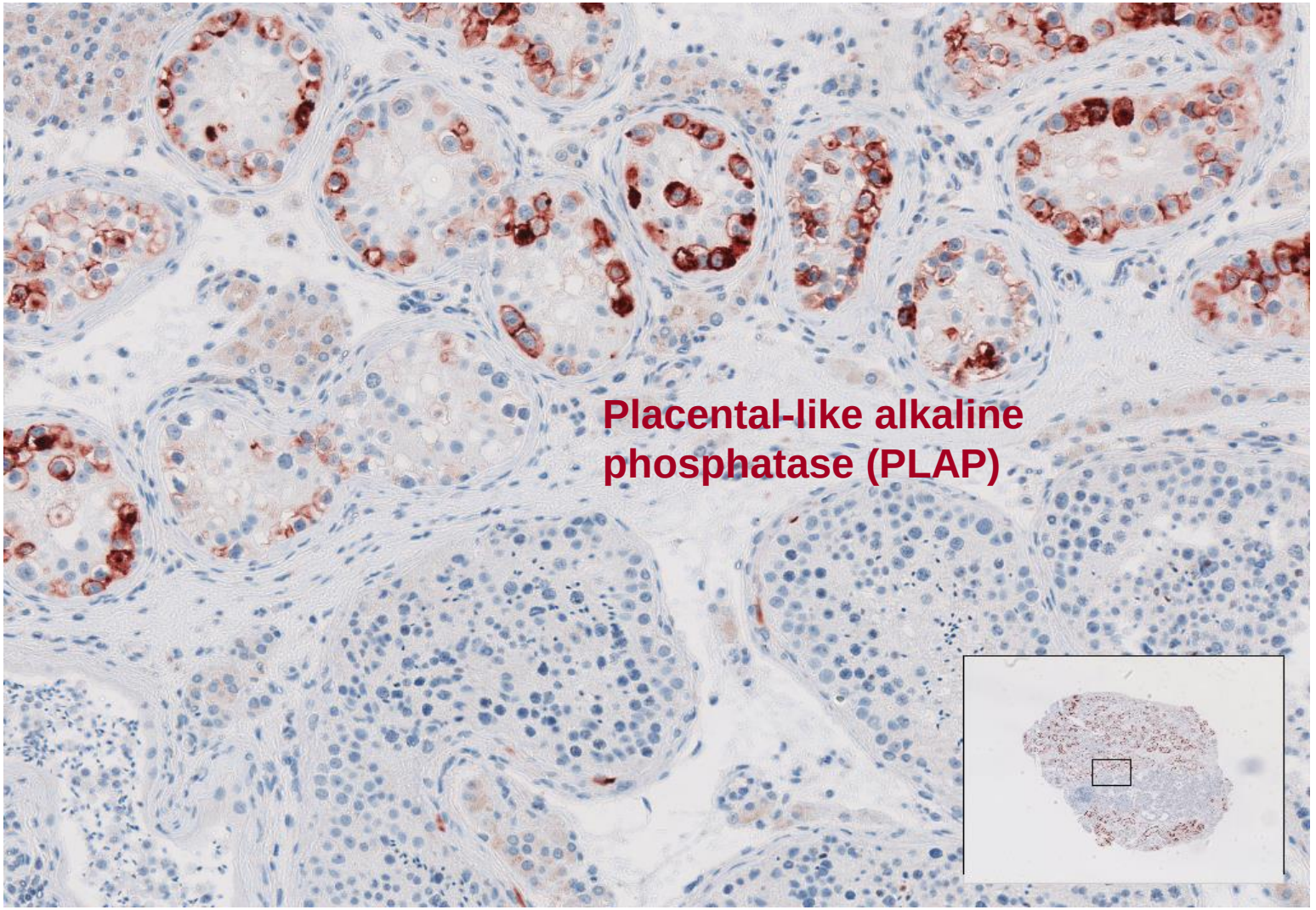
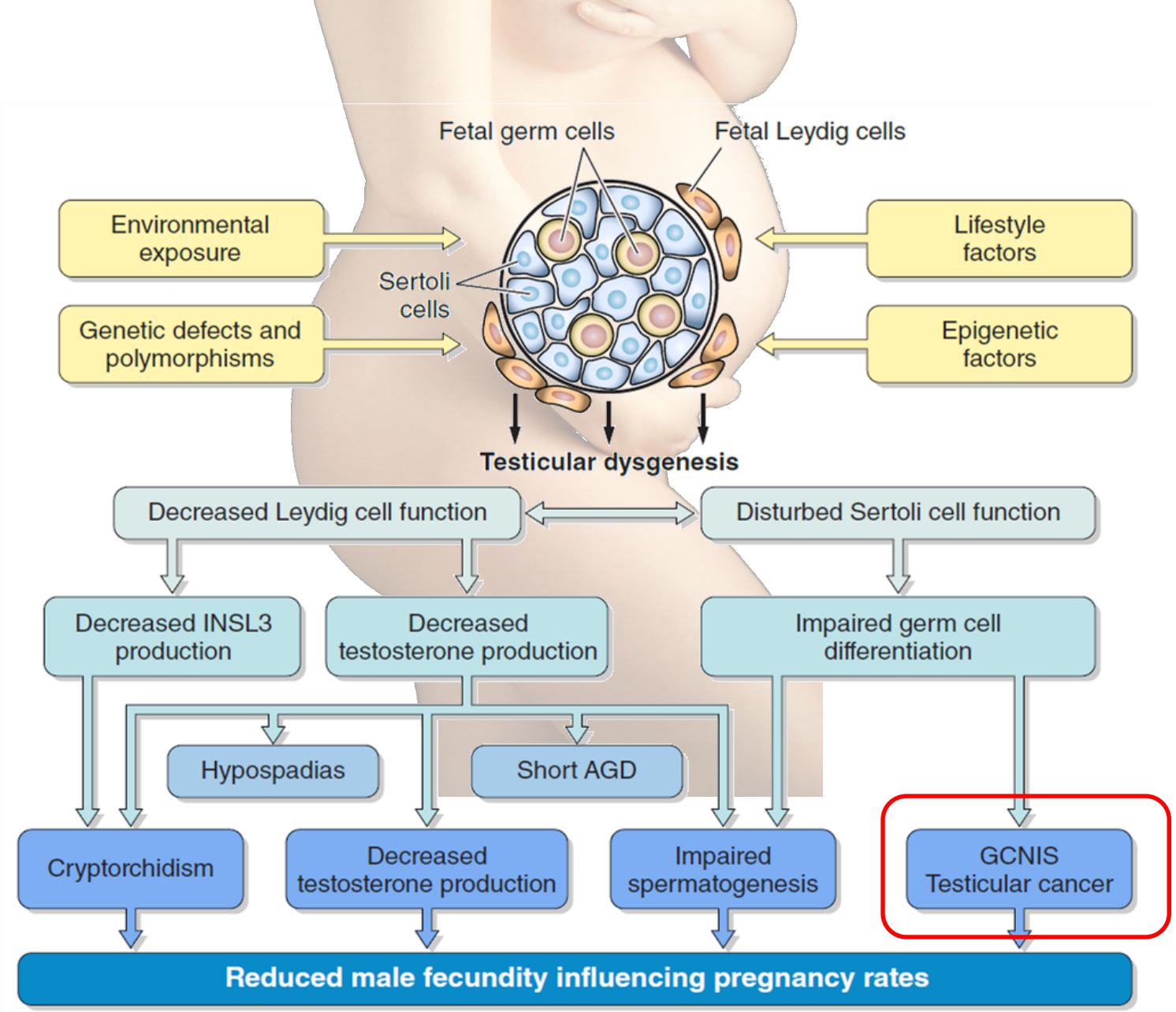




Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM..., **Juul A**.
Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility.
Physiol Rev 2016, 96(1):55-97

Hyppigheden af kryptorkisme

ARTICLES

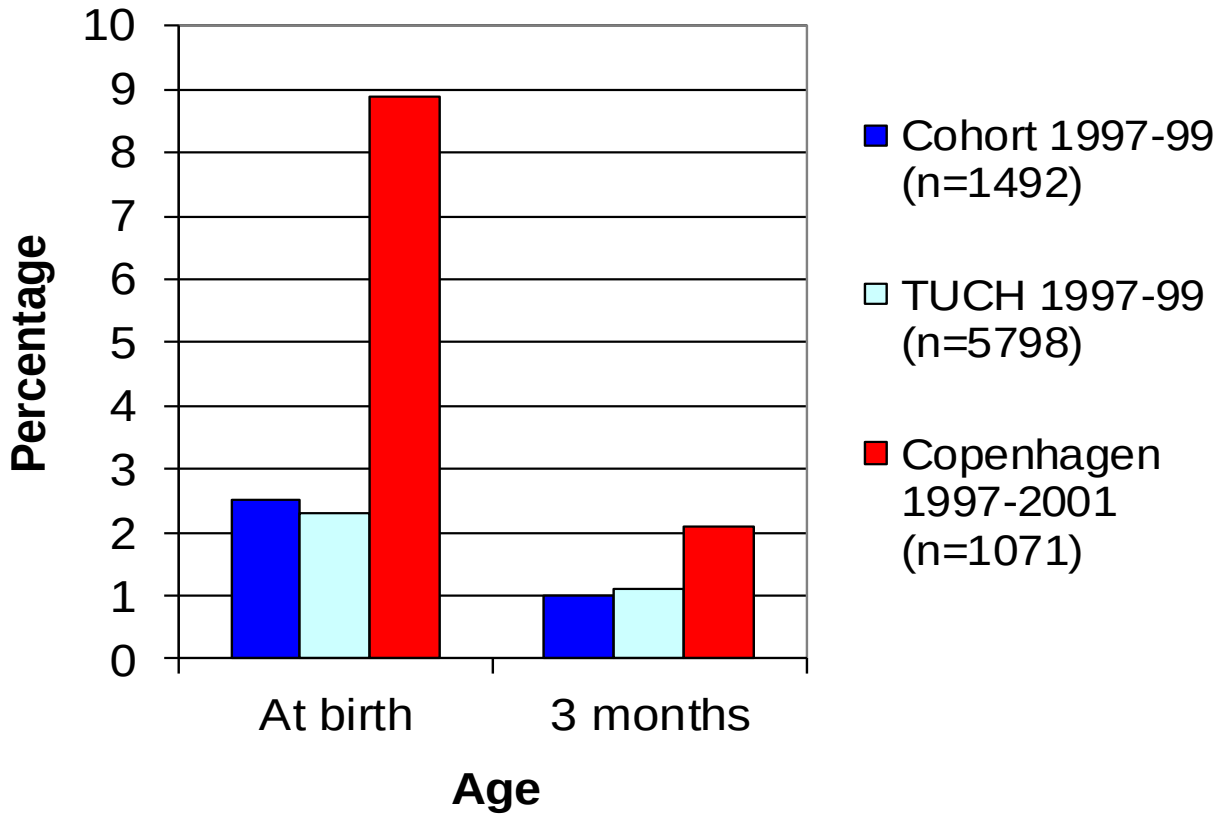
Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries

K A Boisen, M Kaleva, K M Main, H E Virtanen, A-M Haavis M Reunanen, N E Skakkebaek, J Toppari

Summary

Background Several investigators have shown striking differences in semen quality and testicular cancer rate between Denmark and Finland. Since maldescent of the testis is a shared risk factor for these conditions we undertook a joint prospective study for the prevalence o congenital cryptorchidism.

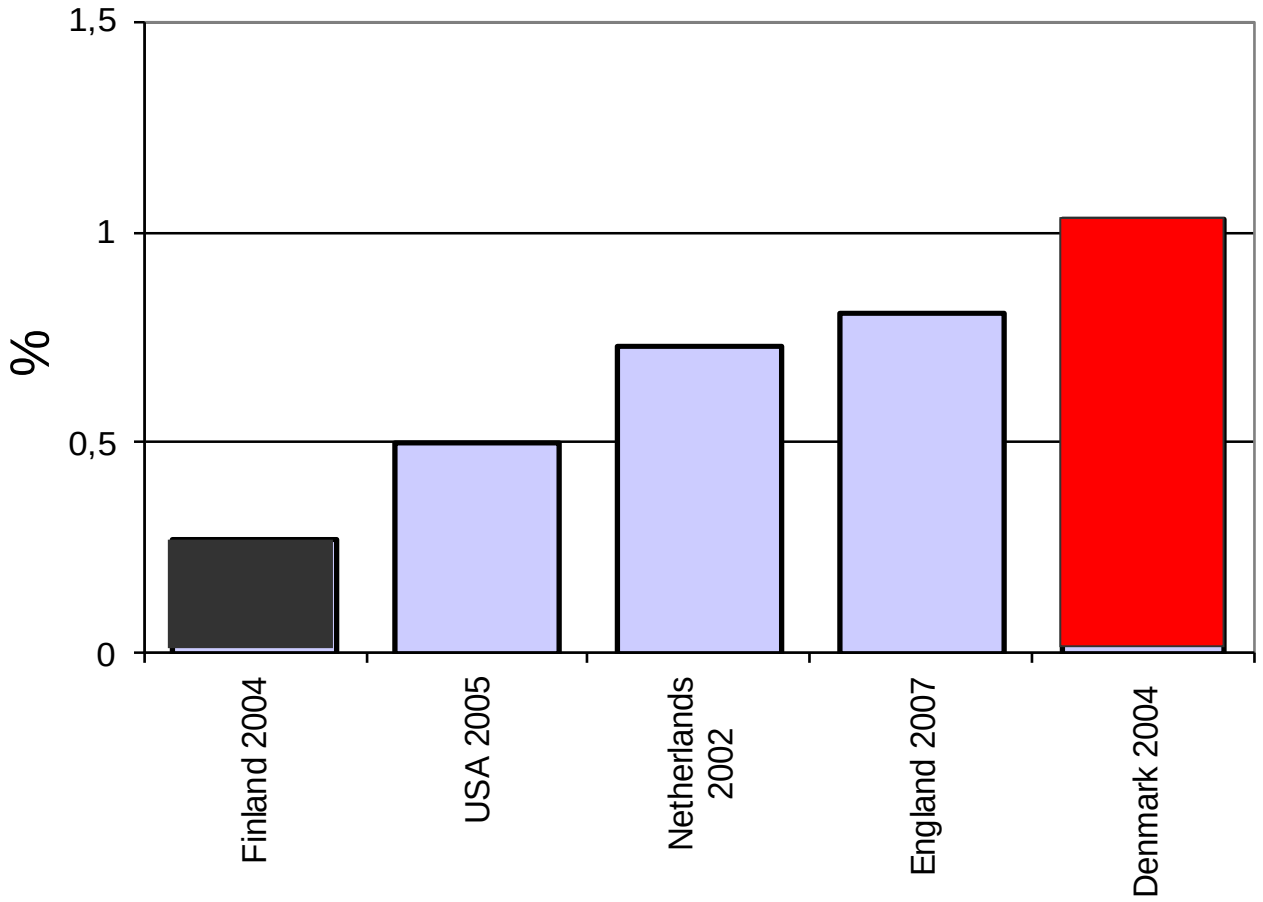
Methods 1068 Danish (1997–2001) and 1494 Finnish boys (1997–99) were consecutively recruited prenatally. We also established prevalence data for all newborns at Turku University Central Hospital, Finland (1997–99, n=5798). Testicular position was assessed by a standardised technique. All subtypes of congenital cryptorchidism were included, but retractile testes were considered normal.



Boisen et al. Lancet 2004

Hypospadi

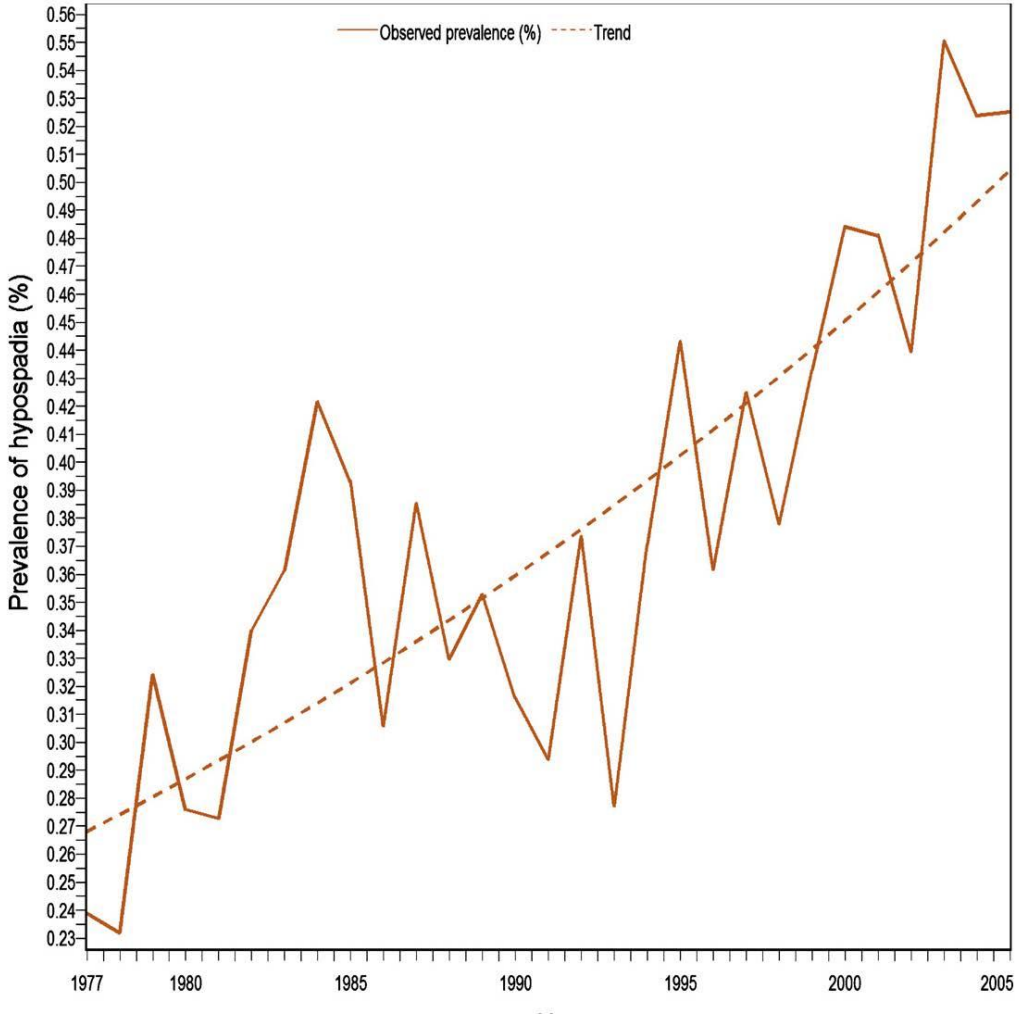
Hyppighed i forskellige populationsstudier



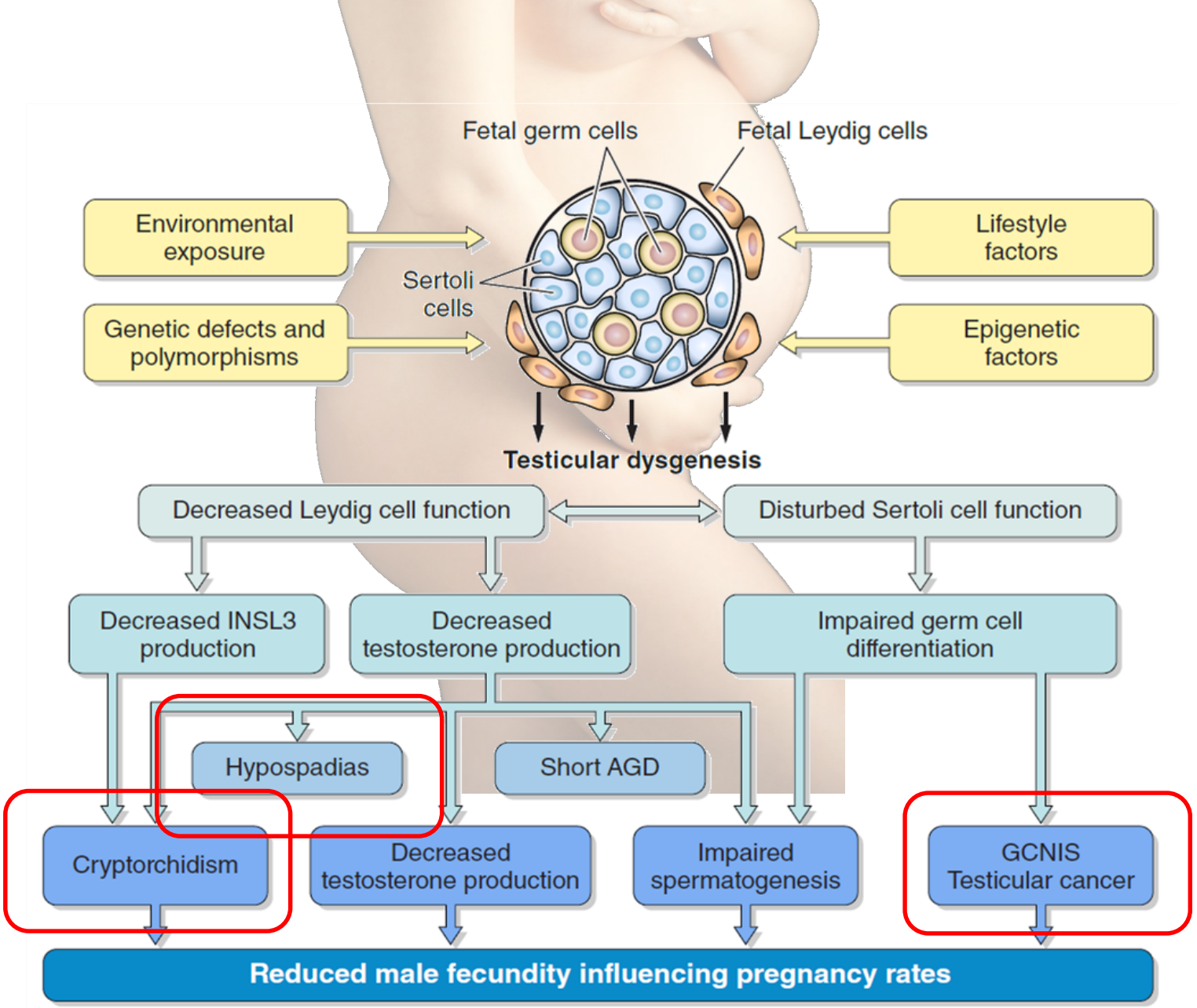
Boisen et al. JCEM 2005

Hypospadier

Forekomst i Danmark

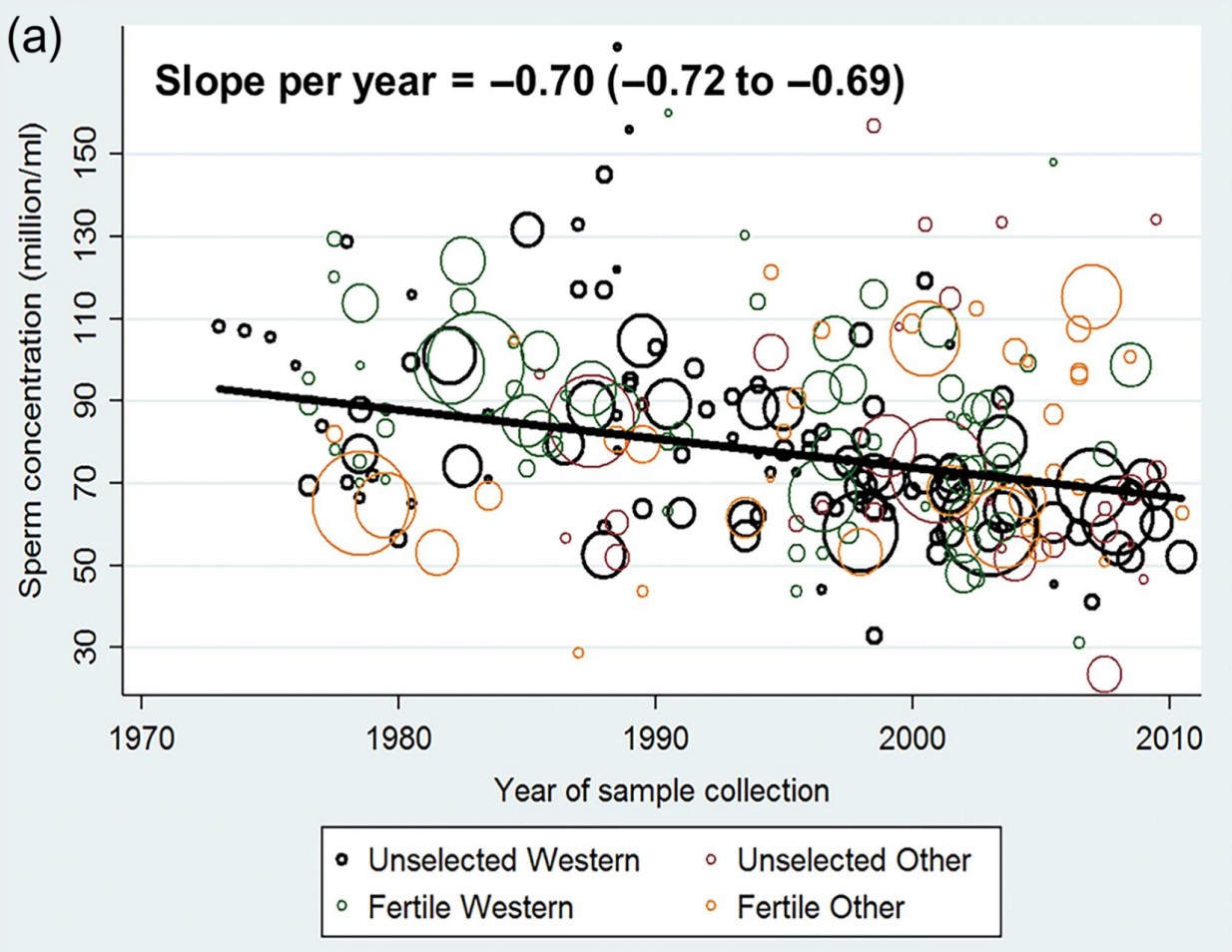


Lund et al. Eur Urol 2009

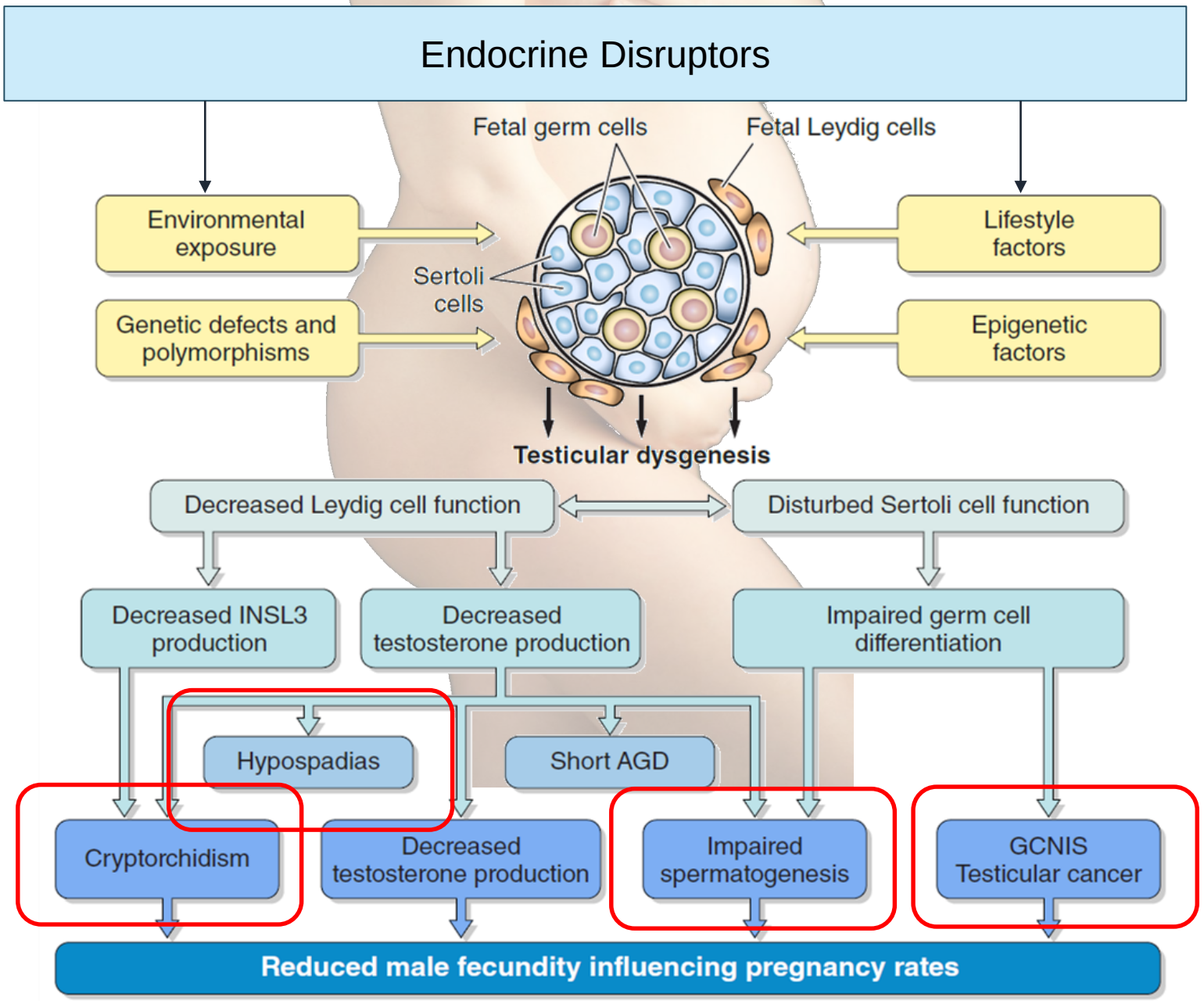


Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM..., **Juul A**.
Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility.
Physiol Rev 2016, 96(1):55-97

Faldende sædkvalitet
worldwide



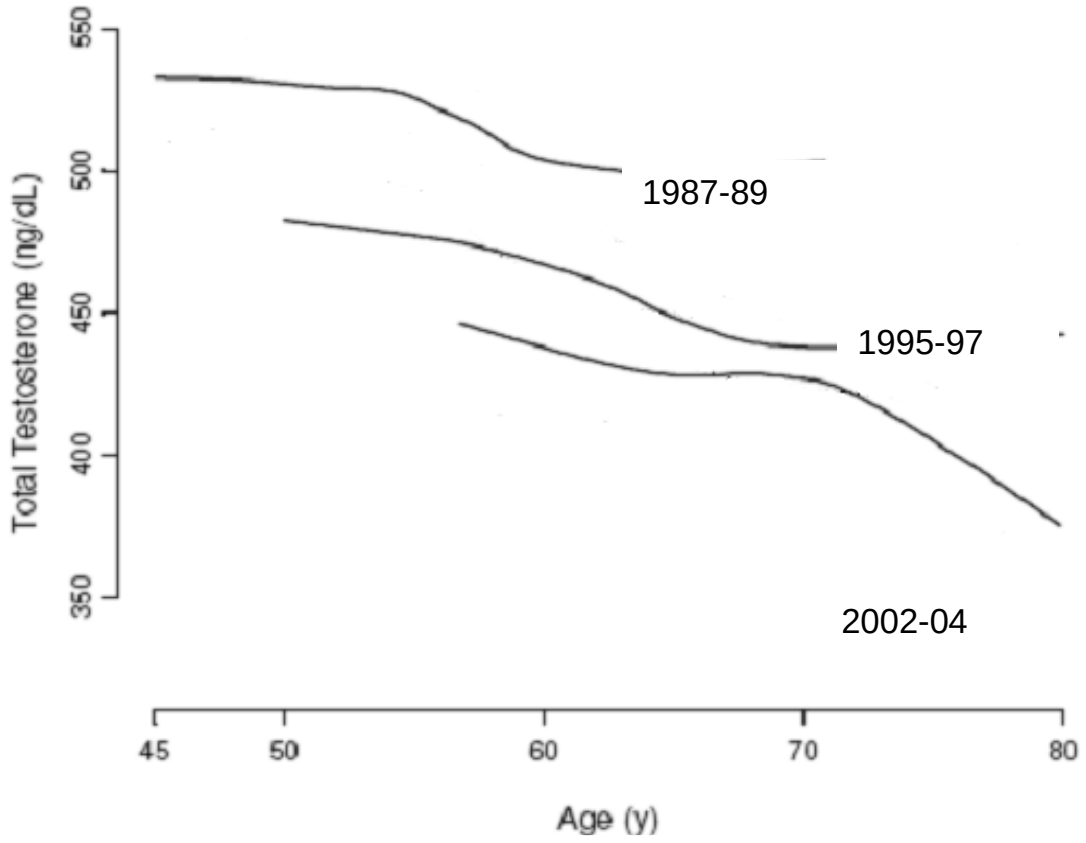
Levine, Jørgensen et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. **Hum Reprod Update. 2017** Nov 1;23(6):646-659.



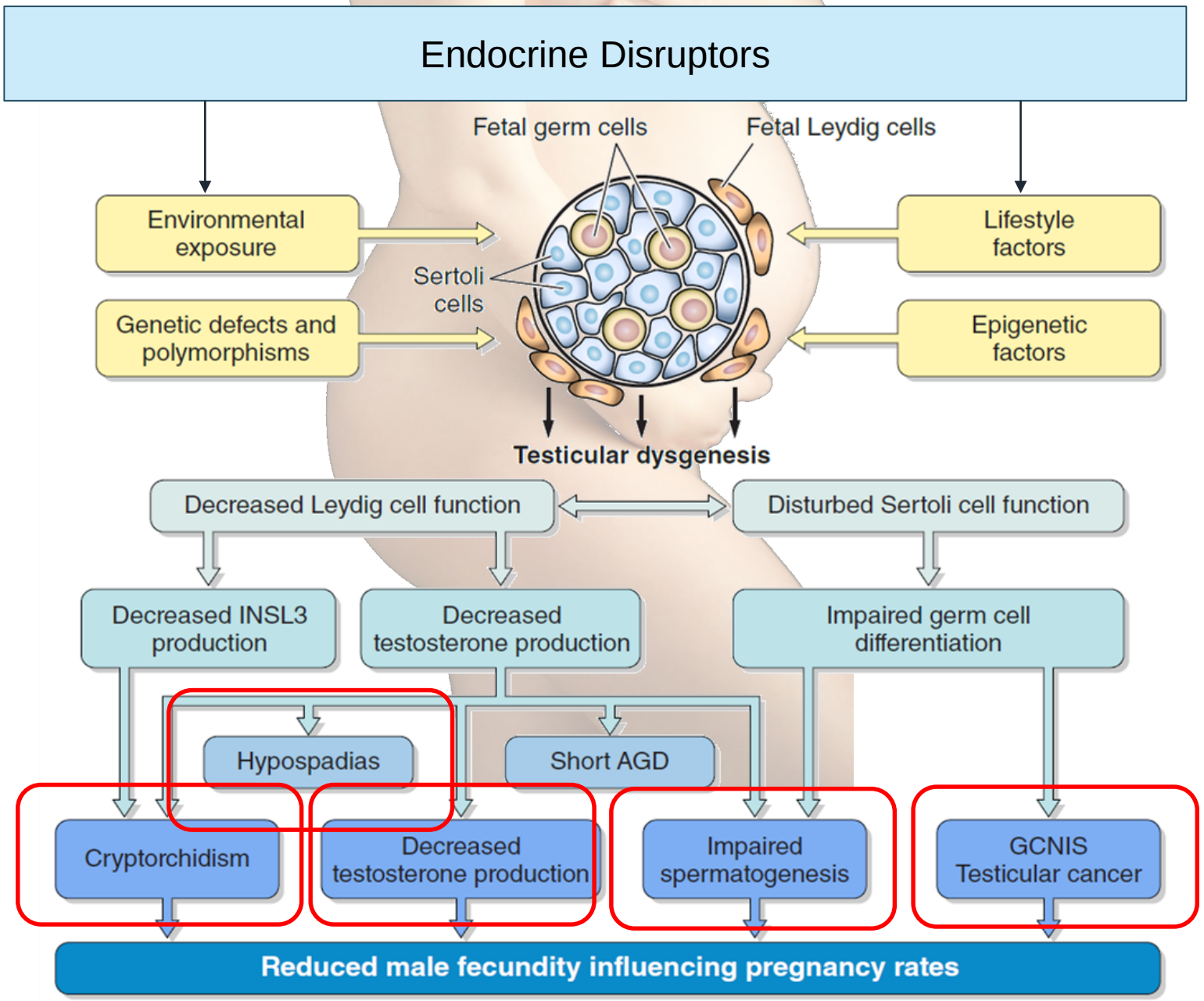
Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM..., **Juul A**.
Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility.
Physiol Rev 2016, 96(1):55-97

Serum Testosteron falder

Fødselskohorte effekter i USA, DK, FIN



Travison, JCEM 2007, Andersson et al, JCEM 2007 and Perheentupa et al, EJE 2013



Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM..., **Juul A**.
Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility.
Physiol Rev 2016, 96(1):55-97

Konklusion

Reproduktion er programmeret i fostertilværelsen

Mandlige reproduktive sygdomme i stigning

Skyldes ændringer i miljø og livsstil

Konklusion

Reproduktion er programmeret i fostertilstanden

Mandlige reproduktive sygdomme i stigning

Skyldes ændringer i miljø og livsstil

Hvordan undersøger vi om det er rigtigt?

Konklusion

Reproduktion er programmeret i fostertilstanden

Mandlige reproduktive sygdomme i stigning

Skyldes ændringer i miljø og livsstil

Hvordan undersøger vi om det er rigtigt?
Tre eksempler

- Timetrend studiet
- DISRUPT
- Minipubertet studiet

CeHoS-EDMaRC projekt

"Undersøgelse af ændringer over tid i graden og mønstret af eksponering for phthalater, bisphenoler og andre phenoler"

~

Timetrend studiet

Hanne Frederiksen

Afdeling for Vækst og Reproduktion, Rigshospitalet

Center for Hormonforstyrrende Stoffer, Informationsdag

Formål

- at undersøge befolkningens eksponeringsmønster phthalater og bisphenol A (BPA), samt for nye substitutter for disse stoffer

- ændringer i eksponeringsmønstret ?

Studie design

- 300 unge danske mænd fra den generelle befolkning
- Urinprøver indsamlet i 2009, 2013 og 2017

Phthalate diesters and phthalate substitutes and their metabolites

	Phthalate diester		Human urine metabolite	Abbreviation
Phthalates				
	Di-methyl phthalate	DMP	Mono-methyl phthalate	MMP
	Di-ethyl phthalate	DEP	Mono-ethyl phthalate	MEP
	Di-iso-propyl phthalate	DiPrP	Mono-iso-propyl phthalate	MiPrP
	Di-n-propyl phthalate	DPrP	Mono-propyl phthalate	MPrP
	Di-iso-butyl phthalate	DiBP	Mono-iso-butyl phthalate	MiBP
	Di-n-butyl phthalate	DnBP	Mono-n-butyl phthalate	MnBP
			Mono-(3-hydroxybutyl) phthalate	MHBP
	Butylbenzyl phthalate	BBzP	Mono-benzyl phthalate	MBzP
	Di-n-pentyl phthalate	DnPeP	Mono-n-pentyl phthalate	MnPeP
			Mono-(4-hydroxypentyl) phthalate	MHPeP
	Di-(2-ethyl-hexyl) phthalate	DEHP	Mono-(2-ethyl-hexyl) phthalate	MEHP
			Mono-(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
			Mono- (2-ethyl-5-oxohexyl) phthalate	MEOHP
			Mono-(2-ethyl-5-carboxypentyl) phthalate	MECPP
			Mono-(2-carboxymethyl-hexyl) phthalate	MCMHP
	Di-n-hexyl phthalate	DnHxP	Mono-n-hexyl phthalate	MHxP
			[illegible]	[illegible]
	Di-cyclohexyl phthalate	DCHP	Mono-cyclohexyl phthalate	MCHP
	Di-n-heptyl phthalate	DnHpP	Mono-n-heptyl phthalate	MHpP
			Mono-(6-hydroxyheptyl) phthalate	MHHpP
			Mono-(6-carboxyhexyl) phthalate	MCHxP
	Di-octyl phthalate	DnOP	Mono-n-octyl phthalate	MnOP
			Mono-3-(carboxypropyl) phthalate	MCPP*
	Di-iso-nonyl phthalate	DiNP	Mono-iso-nonyl phthalate	MiNP
			Mono-hydroxy-iso-nonyl phthalate	MHiNP
			Mono-oxo-iso-nonyl phthalate	MOiNP
			Mono-carboxy-iso-octyl phthalate	MCiOP
	Di-iso-decylphthalate	DiDP	Mono-iso-decyl phthalate	MiDP
			Mono-(9-hydroxydecyl) phthalate	MHiDP
			Mono-(9-oxodecyl) phthalate	MOiDP
			Mono-(9-carboxynonyl) phthalate	MCiNP
Phthalate substitutes				
	Di-2-ethylhexyl terephthalate	DEHTP	Mono-(2-ethyl-5-hydroxy-hexyl) terephthalate	MEHHTP
			Mono-(2-ethyl-5-oxo-hexyl) terephthalate	MEOHTP
			Mono-(2-ethyl-5-caboxyl-pentyl) terephthalate	MECPTP
			Mono-(2-caboxyl-methyl-hexyl) terephthalate	MCMHTP
	Di-iso-nonyl-cyclohexane-1,2-dicarboxylate	DINCH	Cyclohexane-1,2-dicarboxylate-mono-(hydroxyl-iso-nonyl) ester	MHiNCH
			Cyclohexane-1,2-dicarboxylate-mono-(carboxy-iso-octyl) ester	MCiOCH

* MCPP is the major metabolite of DnOP but are not specific for DnOP

32 metabolitter fra 15 phthalater og 6 metabolitter fra 2 phthalat substitutter (DINCH og DEHTP)

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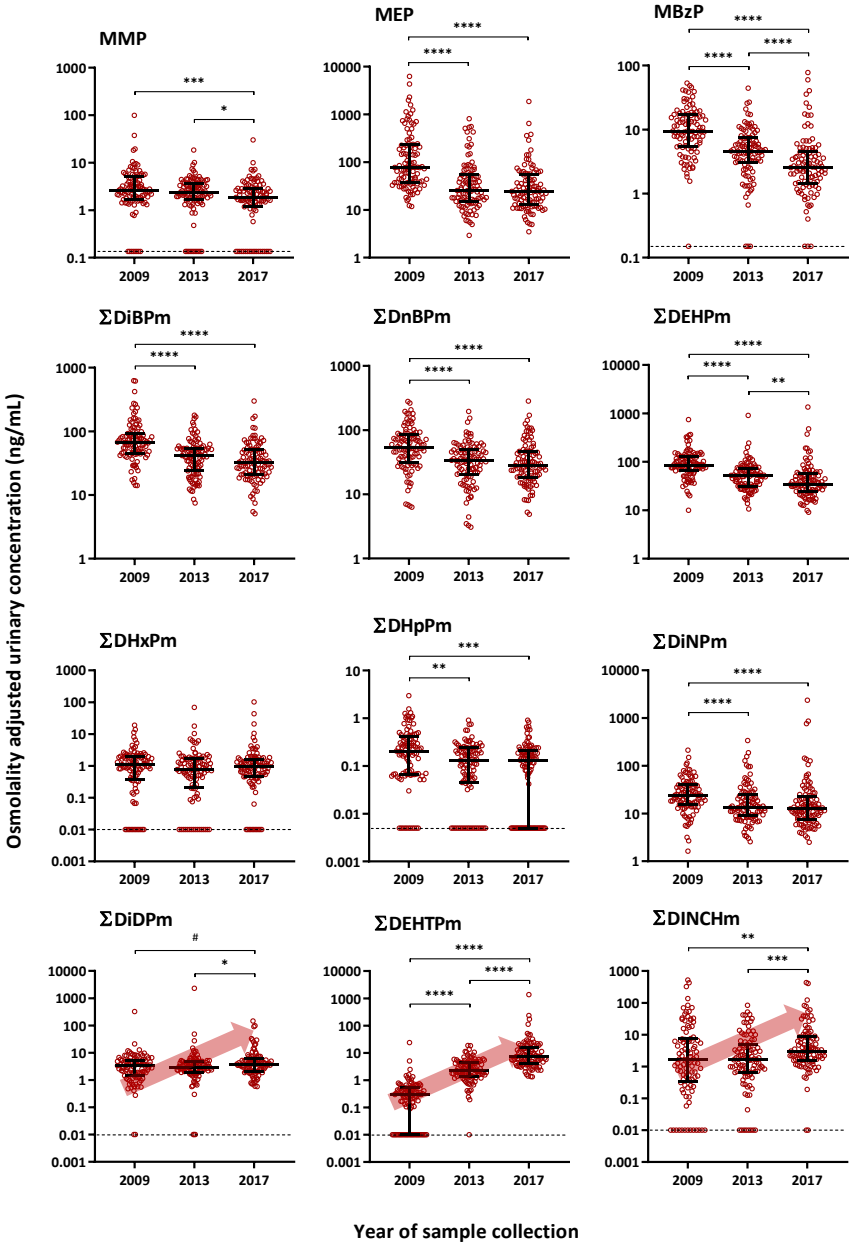

Forbud og udfasning af nogle stoffer hjælper

De falder fra 2009 til 2017

Nye stoffer i stigning....

Frederiksen et al, 2019, in press

*REACH (Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals),
**SVHC substance (Substance of very high concern)

International Journal of Hygiene and Environmental Health xxx (xxxx) xxx-xxx

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journal homepage: http://ees.elsevier.com

Changes in urinary excretion of phthalates, phthalate substitutes, bisphenols and other polychlorinated and phenolic substances in young Danish men; 2009–2017

Hanne Frederiksen [a,b,*], Ole Nielsen [a], Holger M. Koch [c], Niels E. Skakkebaek [a,b], Anders Juul [a,b], Niels Jørgensen [a,b], Anna-Maria Andersson [a,b]

[a] Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Denmark
[b] International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Rigshospitalet, University of Copenhagen, Denmark
[c] Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr, University Bochum (IPA), Bochum, Germany

ARTICLE INFO

Keywords
endocrine disruptor
human biomonitoring
phthalate
DINCH
di-2-ethylhexyl terephthalate (DEHTP)
phenol

ABSTRACT

During the past two decades human exposure to bisphenol A (BPA) and phthalates such as di-iso-butyl phthalate (DiBP), di-n-butyl phthalate (DnBP), butylbenzyl phthalate (BBzP) and di-(2-ethyl-hexyl) phthalate (DEHP) has received substantial interest due to widespread population exposures and potential endocrine disrupting effects. Therefore, these chemicals have gradually been restricted and phased out through legislation. However, humans are still exposed to a wide range of other less studied phthalates, phthalate substitutes and BPA analogues as well as other polychlorinated and phenolic substances. In this study, we investigated human exposure to these chemicals over the past decade. Three hundred urine samples collected in 2009, 2013 and 2017 (100 samples each year) from young Danish men of the general population, participating in a large on-going cross-sectional

Tak for økonomisk støtte til:

- Velux Fondene
- Lundbeck Fonden
- Augustinus Fonden
- Svend Andersens Fond

NIH National Institutes of Health

NIH projekt

"Er hormonforstyrrende stoffer højere hos gravide kvinder hvis sønner udvikler testikelkræft ?"

~

DISRUPT

Elvira Braüner, Cecilie Uldbjerg, Anders Juul

Afdeling for Vækst og Reproduktion, Rigshospitalet

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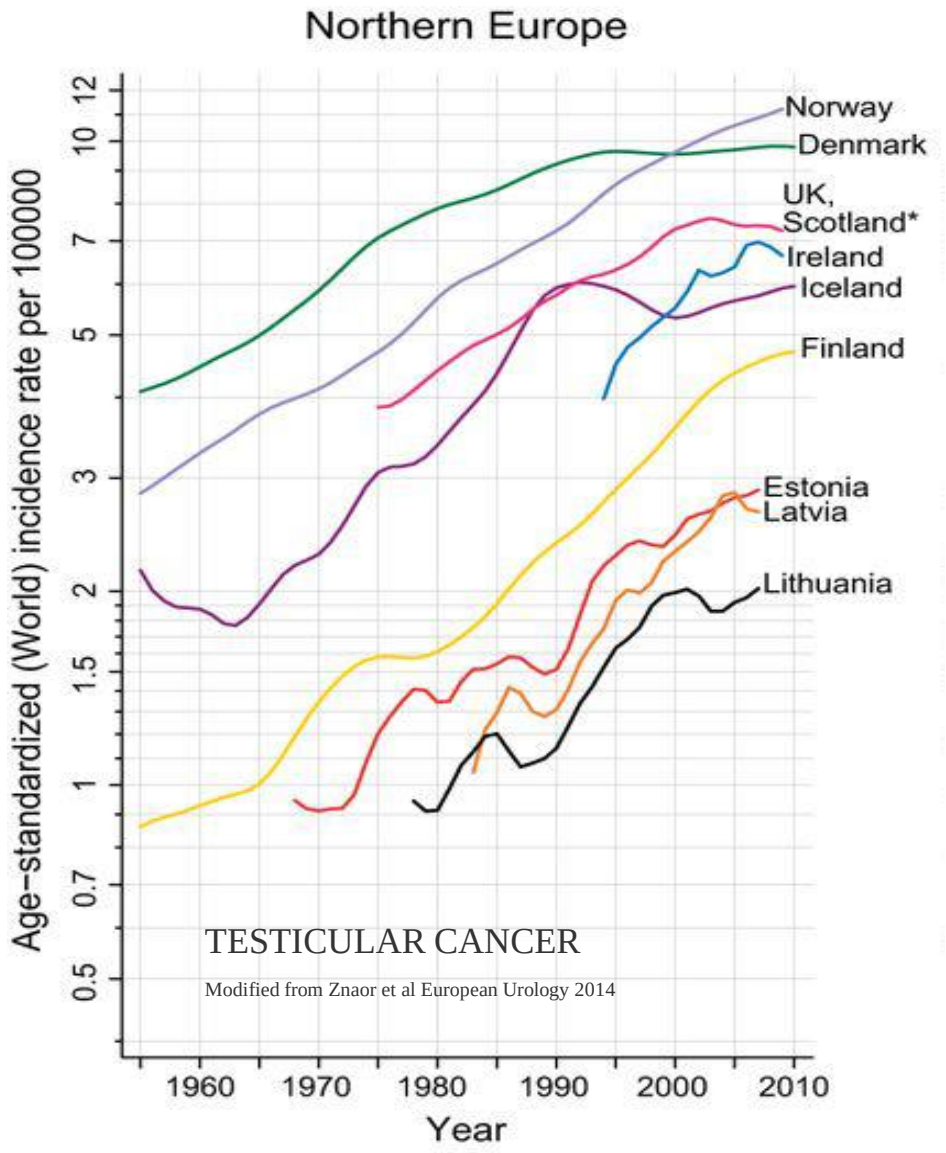

Skyldes stigningen i testikelkræft hormonforstyrrende stoffer ?

REGION

Systemat
Review a
analysis

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ACCEPTED MANUSCRIPT

Endocrine Disrupting Chemicals and Risk of Testicular Cancer A Systematic Review and Meta-analysis

Elvira V Bräuner, Youn-Hee Lim, Trine Koch, Cecilie S Uldbjerg, Laura S Gregersen, Marc K Pedersen, Hanne Frederiksen, Jørgen H Petersen, Brent A Coull, Anna-Maria Andersson, Martha Hickey, Niels E Skakkebæk, Russ Hauser, Anders Juul

The Journal of Clinical Endocrinology & Metabolism, dgab523, https://doi.org/10.1210/clinem/dgab523

Published: 16 July 2021 **Article history** ▾

Abstract

The incidence of many hormone-dependent diseases, inclu
cancer, have sharply increased in all high-income countries during the 20th century. This is not fully explained by established risk factors. Concurrent, increasing exposure to antiandrogenic environmental endocrine disrupting chemicals (EDCs) in fetal life may partially explain this trend. This systematic review assessed available evidence regarding the association between environmental EDC exposure and risk of testicular cancer (seminomas and

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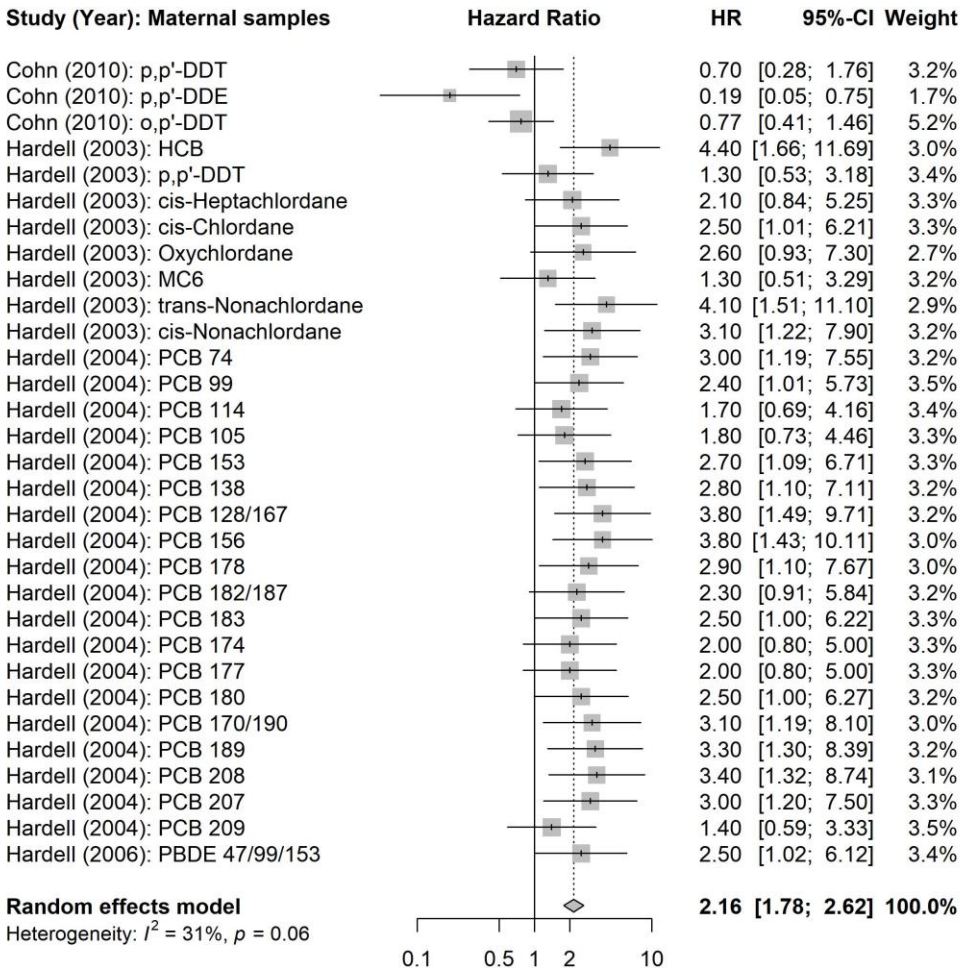
Braüner et al, JCEM 2021, in press



Konklusion: Højere eksponering af mødre til EDC associeret med højere risiko for testikelkræft – få studier

Braüner et al, JCEM 2021, in press

DISRUPT – et unikt dansk studium

Prøver indsamlet
1st trimester
N=128,702 graviditeter
1976-96

2019
194 Cases: sønner med testikelkræft
Kontroller: 5:1

Første resultater
2022

National Institute of Health – 04/15/20- 2020-04/14/2022 Funding USD 867.000
Project Title: Prenatal Exposure to Endocrine Disrupting Chemicals and Risk of Testicular Cancer (DISRUPT). NoA: 1 R01 CA236816-01A1 PI: Juul, Anders

EDMaRC

Endocrine Disruption of Male Reproduction and Child Health

EDMaRC projekt

Hvad regulerer hormonerne i minipuberteten?

COPENHAGEN Minipuberty Study

The COPENHAGEN minipuberty study

REGION

COPENHAGEN
Minipuberty Study

Received: 15 January 2021 | Revised: 25 April 2021 | Accepted: 27 April 2021
DOI: 10.1111/ppe.12777

ORIGINAL ARTICLE

Paediatric and Perinatal Epidemiology WILEY

Cohort profile: The COPENHAGEN Minipuberty Study—A longitudinal prospective cohort of healthy full-term infants and their parents

Alexander Siegfried Busch[1,2] | Marie Lindhardt Ljubicic[1,2] | Emmie N. Upners[1,2] | Margit Bistrup Fischer[1,2] | Nanna Kolby[1,2] | Camilla Eckert-Lind[1,2] | Kirstine Jespersen[1,2] | Anna-Maria Andersson[1] | Hanne Frederiksen[1,2] | Trine Holm Johannsen[1,2] | Hanne Kristine Hegaard[3,4] | Heidi Sharif[3] | Casper P. Hagen[1,2] | Anders Juul[1,2]

[1]Department of Growth and Reproduction, Copenhagen University Hospital - Rigshospitalet, Copenhagen O, Denmark

[2]International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC, Copenhagen University Hospital - Rigshospitalet, Copenhagen O, Denmark

[3]Department of Obstetrics, Copenhagen University Hospital - Rigshospitalet, Copenhagen O, Denmark

[4]The Research Unit Women's and Children's Health, Juliane Marie Center for Women, Children and Reproduction, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark

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Email: anders.juul@regionh.dk

Funding information
The COPENHAGEN Minipuberty Study received support from the Candy Foundation, Nos. 2017-224 and 2020-344 (ENU); Absalon Foundation, No. F-23653-01 (MLL); The European Union's Horizon 2020 research and innovation program, No. 733032 HBM4EU (AMA); The Danish Environmental Protection Agency (Miljøstyrelsen: MST-621-00012 Center on Endocrine Disrupters) (AJ, HF); The Research council of Capital Region of Denmark: No. E-22717-11 (AJ); Research council of Rigshospitalet: Nos.

Abstract

Background: The hypothalamic-pituitary-gonadal (HPG) axis governs sexual maturation and reproductive function in humans. In early postnatal life, it is transiently active during which circulating sex steroids reach adult levels. While this so-called minipuberty represents a universal phenomenon in infants of both sexes, its role for early maturation and growth remains incompletely understood.

Objectives: To provide normative data on auxology as well as serum and urinary hormone levels in healthy, full-term infants throughout the first year of life and to investigate associations of postnatal HPG axis dynamics as well as hormonal, genetic and environmental exposures with early genital development and growth.

Population: Healthy, Danish, full-term, singleton newborns including their parents.

Design: Single-centre, prospective, observational longitudinal pregnancy and birth cohort.

Methods: Newborns were followed with six repeated clinical examinations during a one-year follow-up period. An umbilical cord blood sample was drawn at birth. At each visit, infants underwent a clinical examination focusing on auxology and genital development. Further, blood (serum, plasma, DNA) and urine samples were collected at each visit. Mothers and fathers underwent a clinical examination and provided blood samples prior to and after birth. A subset of parents provided urine samples and breast milk samples. Pregnancy and obstetrical outcomes, and detailed parental questionnaires were compiled.

Preliminary results: Between August 2016 and August 2018, 2481 women with singleton pregnancies were invited to participate of which 298, including their partners, were enrolled (12.0%). A total of 268 healthy, full-term newborns born appropriate for gestational age (AGA) were included at birth, 233 newborns participated in the postnatal follow-up period and 186 completed the one-year follow-up period (9.4% and 7.5%, respectively).

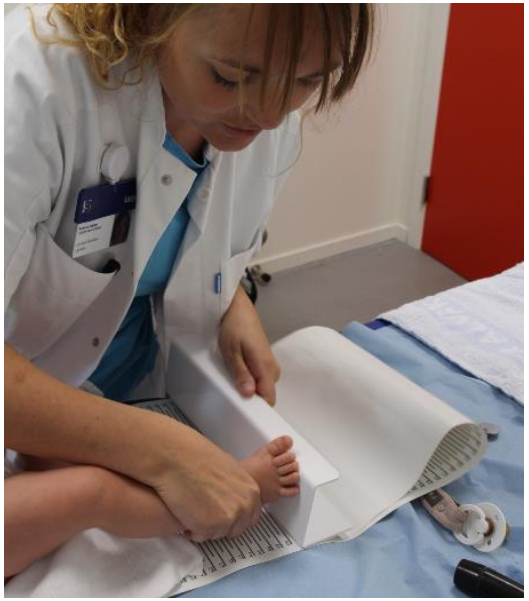
ClinicalTrials.gov ID: NCT01411527

REGION

Metoder

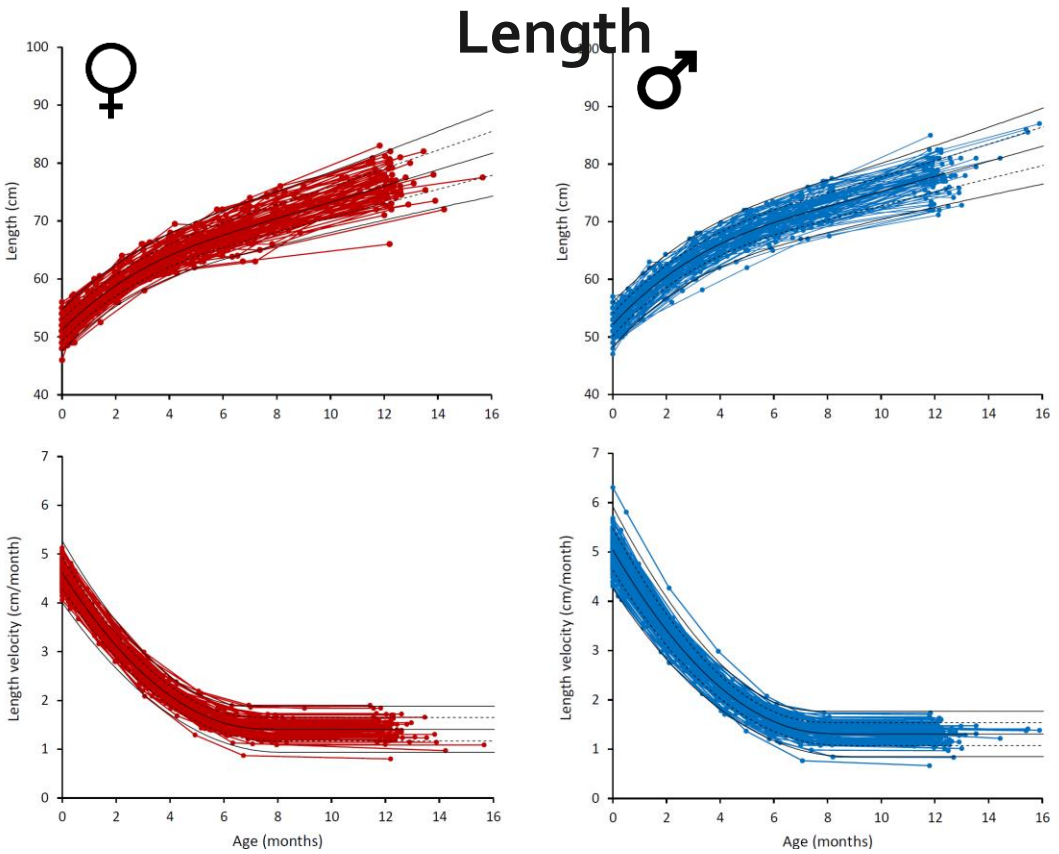
- Longitudinel, observational studie ('16 – '19)
- 233 nyfødte til termin
- 6 undersøgelser i 1. leveår

COPENHAGEN
Minipuberty Study



Results

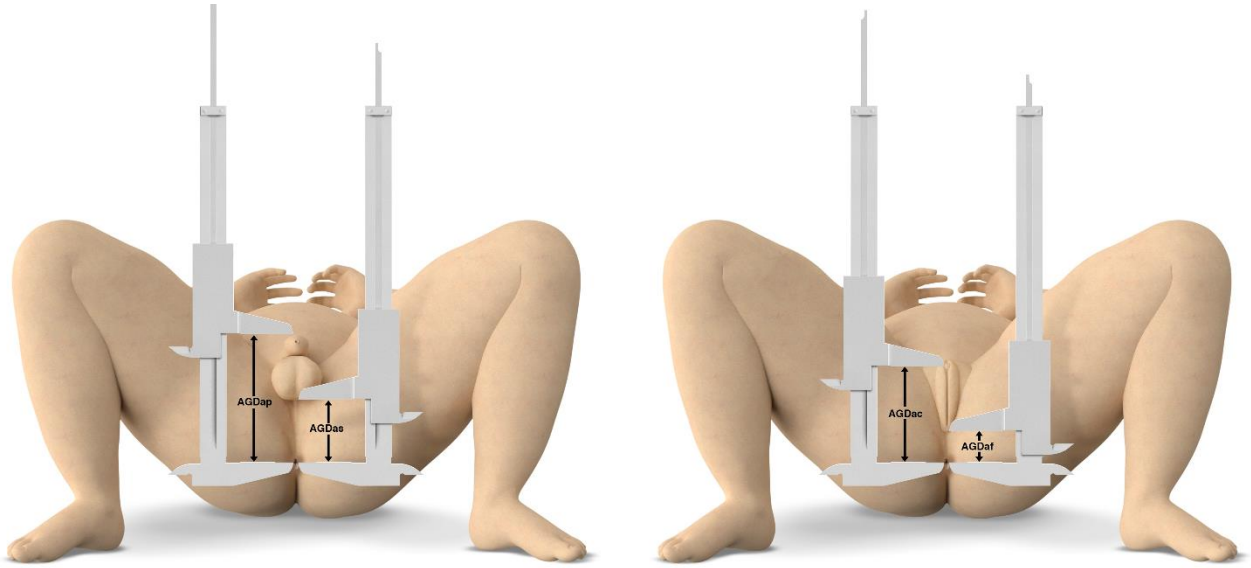
Boys and girls with distinct growth patterns



J Clin Endocrinol Metab. 2020 Sep 1;105(9):2996-3004. doi: 10.1210/clinem/dgaa393.

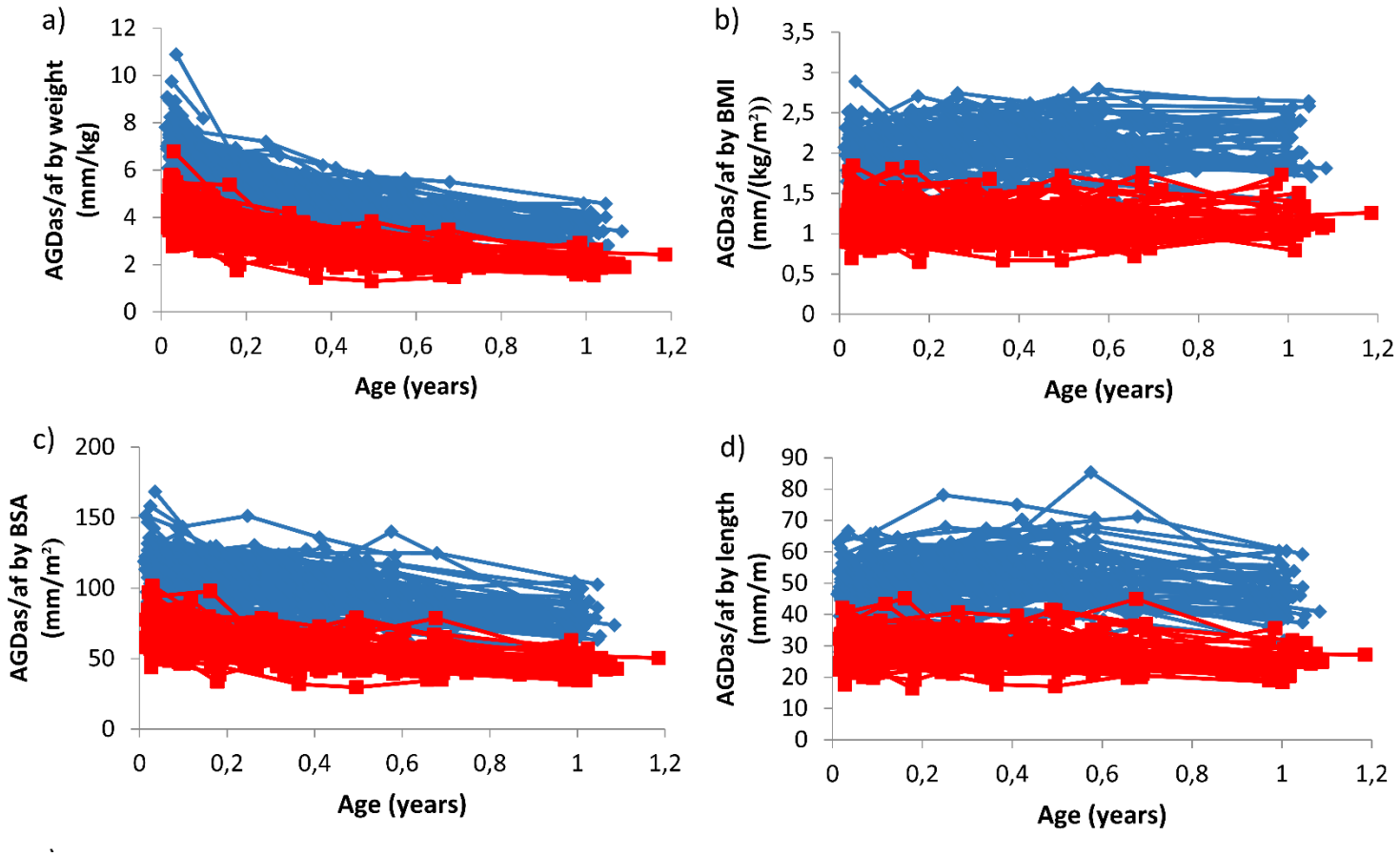
Anogenital Distance in Healthy Infants: Method-, Age- and Sex-related Reference Ranges

Margit Bistrup Fischer [1 2], Marie Lindhardt Ljubicic [1 2], Casper P Hagen [1 2], Ajay Thankamony [3], Ken Ong [3 4], Ieuan Hughes [3], Tina Kold Jensen [5 6], Katharina M Main [1 2], Jørgen Holm Petersen [7], Alexander S Busch [1 2], Emmie N Upners [1 2], Sheela Sathyanarayana [8 9], Shanna H Swan [10], Anders Juul [1 2]



Fischer et al. JCEM. 2020

Anogenital distance – COPENHAGEN Minipuberty Cohort



Fischer et al. JCEM 2020

Påvirker eksponering til hormonforstyrrende stoffer (barn, mor, far (TRIO) hhv AGD, penis, testikel, hormoner, vækst ….?

Første resultater dec 2021…

COPENHAGEN
Minipuberty Study

Mathilde Lærkeholm Pedersen

REGION

Tak for børnene og deres familier

EDMaRC

Endocrine Disruption of Male Reproduction and Child Health

CEHOS

Konklusion

Alle danskere er eksponeret til tusindvis af hormonforstyrrende stoffer, som har skadelige effekter i dyrestudier

Særligt gravide og børn bør beskyttes mod de værste stoffer – som kan have livslange skadelige konsekvenser

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