Rigshospitalet
Juliane Marie Centret

EDMaRC
Endocrine Disruption of Male Reproduction and Child Health

REGION H Rigshospitalet

REGION H

CENTER FOR HORMONFORSTYRRENDE STOFFER

Hormonforstyrrende stoffer og pubertet

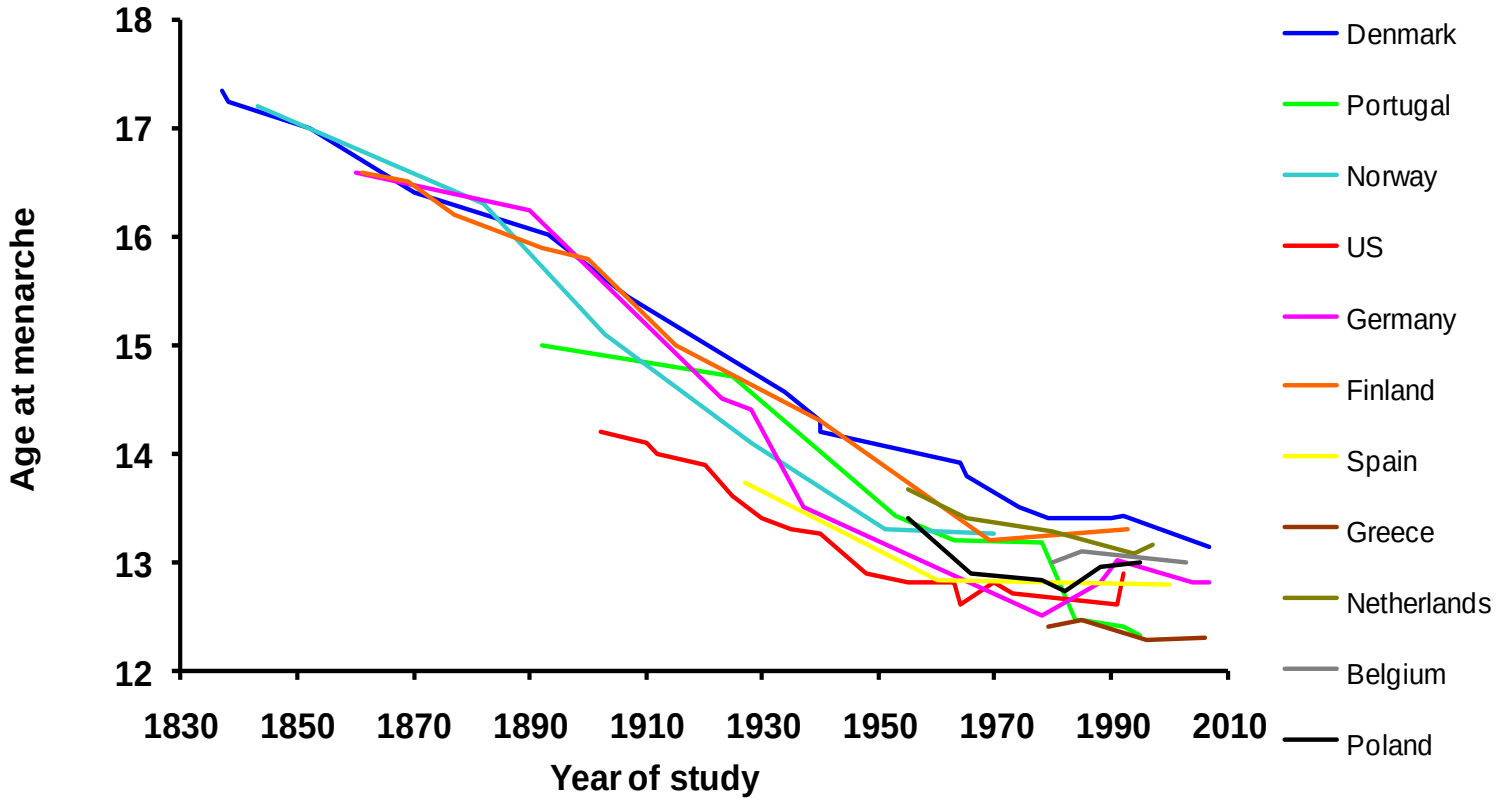
Cecilie Skaarup Uldbjerg
Afdeling for Vækst og Reproduktion, Rigshospitalet
Københavns Universitet, Danmark

UNIVERSITY OF COPENHAGEN

1. oktober 2021

- Pubertetsudvikling og globale trends
- The COPENHAGEN Puberty Study
- Hormonforstyrrendes stoffer og pubertet
- Fremtidsprojekter og perspektivering

Pubertetsudvikling og globale trends
Faldende alder for menarke (første menstruation)



Cabanes A **BMC Public Health** 2009. Fredriks AM **Pediatr Res** 2000.
Olesen AW **Ann Hum Biol** 2000. Tanner JM **Sci Am** 1973. Bau AM **Eur J Endocrinol** 2009.
Lindgren G **Acta Paediatr** 1996.

The COPENHAGEN Puberty Study
Tværsnitsundersøgelse af raske danske skolebørn i Storkøbenhavn

- ✓ 3623 raske børn
  - 2095 piger
- ✓ 10 folkeskoler
- ✓ Storkøbenhavn
- ✓ Undersøgt i:
  - 1991-3
  - 2006-8

The COPENHAGEN Puberty Study
Tidligere pubertetsdebut

ARTICLE

Recent Decline in Age at Breast Development: The Copenhagen Puberty Study

Lise Aksglaede, MD[a], Kaspar Sørensen, MD[a], Jørgen H. Petersen, PhD[a,b], Niels E. Skakkebæk, MD, DMSc[a], Anders Juul, MD, DMSc[a]

[a]University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark; [b]Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark

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What's Known on This Subject

American girls enter puberty much earlier today than has been published previously. No such trend has been documented for European girls.

What This Study Adds

We present new data on the progression in timing of puberty among European girls.

ABSTRACT

OBJECTIVE. Recent publications showing unexpectedly early breast development in American girls created debate worldwide. However, secular trend analyses are often limited by poor data comparability among studies performed by different researchers in different time periods and populations. Here we present new European data systematically collected from the same region and by 1 research group at the beginning and end of the recent 15-year period.

METHODS. Girls ($N = 2095$) aged 5.6 to 20.0 years were studied in 1991–1993 (1991 cohort; $n = 1100$) and 2006–2008 (2006 cohort; $n = 995$). All girls were evaluated by palpation of glandular breast, measurement of height and weight, and blood sampling (for estradiol, luteinizing hormone, and follicle-stimulating hormone). Age distribution at entering pubertal breast stages 2 through 5, pubic hair stages 2 through 5, and menarche was estimated for the 2 cohorts.

RESULTS. Onset of puberty, defined as mean estimated age at attainment of glandular breast tissue (Tanner breast stage 2+), occurred significantly earlier in the 2006 cohort (estimated mean age: 9.86 years) when compared with the 1991 cohort (estimated mean age: 10.88 years). The difference remained significant after adjustment for BMI. Estimated ages at menarche were 13.42 and 13.13 years in the 1991 and 2006 cohorts, respectively. Serum follicle-stimulating hormone and luteinizing hormone did not differ between the 2 cohorts at any age interval, whereas significantly lower estradiol levels were found in 8- to 10-year-old girls from the 2006 cohort compared with similarly aged girls from the 1991 cohort.

CONCLUSIONS. We found significantly earlier breast development among girls born more recently. Alterations in reproductive hormones and BMI did not explain these marked changes, which suggests that other factors yet to be identified may be involved. *Pediatrics* 2009;123: e932–e939

www.pediatrics.org/cgi/doi/10.1542/peds.2008-2491

doi:10.1542/peds.2008-2491

Key Words
puberty, breast development, menarche, obesity, endocrine-disrupting chemicals, phytoestrogen

Abbreviations
Bn—breast stage number
PHn—pubic hair stage number
FSH—follicle-stimulating hormone
LH—luteinizing hormone
PI—prediction interval
CI—confidence interval
EDC—endocrine-disrupting chemicals
BPA—bisphenol A

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Address correspondence to Lise Aksglaede, MD, Rigshospitalet, Department of Growth and Reproduction GR, Section 5064, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark. E-mail lise.aksglaede@rh.hosp.dk

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ORIGINAL ARTICLE

Endocrine Care

Recent Changes in Pubertal Timing in Healthy Danish Boys: Associations with Body Mass Index

Kaspar Sørensen, Lise Aksglaede, Jørgen Holm Petersen, and Anders Juul

Department of Growth and Reproduction (K.S., L.A., J.H.P., A.J.), Copenhagen University Hospital, DK-2100 Copenhagen, Denmark; and Department of Biostatistics (J.H.P.), University of Copenhagen, DK-1014 Copenhagen, Denmark

Context: In the 1990s, the American population-based study NHANES III renewed the focus on possible secular trends in male puberty. However, no conclusions could be made on pubertal onset due to the lack of compatible data.

Objective: The aim of the study was to evaluate secular trends in pubertal onset during the recent 15 yr and their relation to body mass index (BMI) in boys.

Design and Setting: We conducted a cross-sectional study in 1991–1993 and a combined cross-sectional and longitudinal study in 2006–2008 (The Copenhagen Puberty Study) at a tertiary center for pediatric endocrinology.

Participants: A total of 1528 boys aged 5.8 to 19.9 yr participated (n = 824 in 1991–1993, and n = 704 in 2006–2008). Genital and pubic hair stages as well as testicular volume by orchidometry were evaluated. Blood samples were analyzed for LH, FSH, testosterone, and SHBG.

Main Outcome Measures: We measured age at onset of pubertal markers.

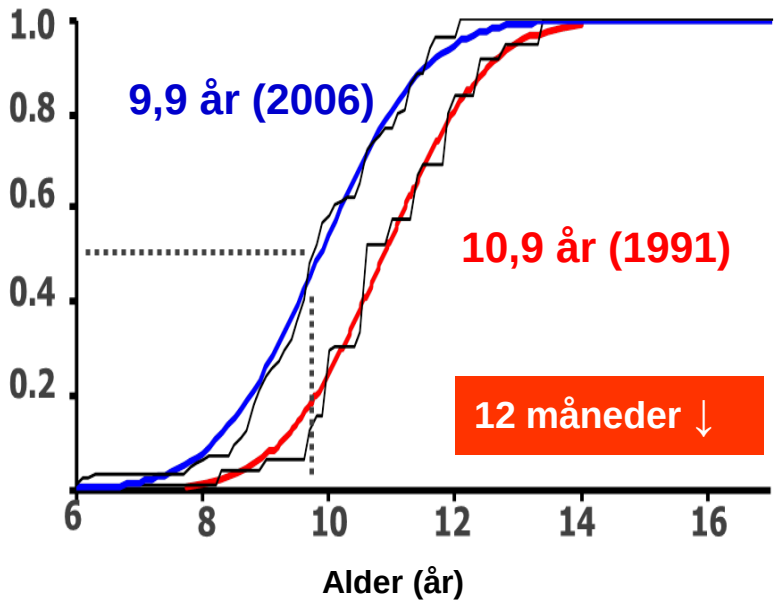
Results: Onset of puberty, defined as age at attainment of testicular volume above 3 ml, occurred significantly earlier in 2006–2008 [11.66 yr (11.49–11.82); mean (95% confidence interval)] than in 1991–1993 [11.92 yr (11.76–12.08); $P = 0.025$]. Significantly higher LH, but not testosterone, levels were found in the 11- to 16-yr-old boys from 2006–2008 compared to 1991–1993 ($P = 0.020$). BMI Z-score increased significantly from 1991–1993 [0.044 (−0.016 to 0.104)] to 2006–2008 [0.290 (0.219–0.361); $P < 0.001$]. Interestingly, pubertal onset and LH levels were no longer significantly different between study periods after adjustment for BMI.

Conclusions: Estimated mean age at onset of puberty has declined significantly during the recent 15 yr. This decline was associated with the coincident increase in BMI. (*J Clin Endocrinol Metab* 95: 263–270, 2010)

The COPENHAGEN Puberty Study
Tidligere pubertetsdebut

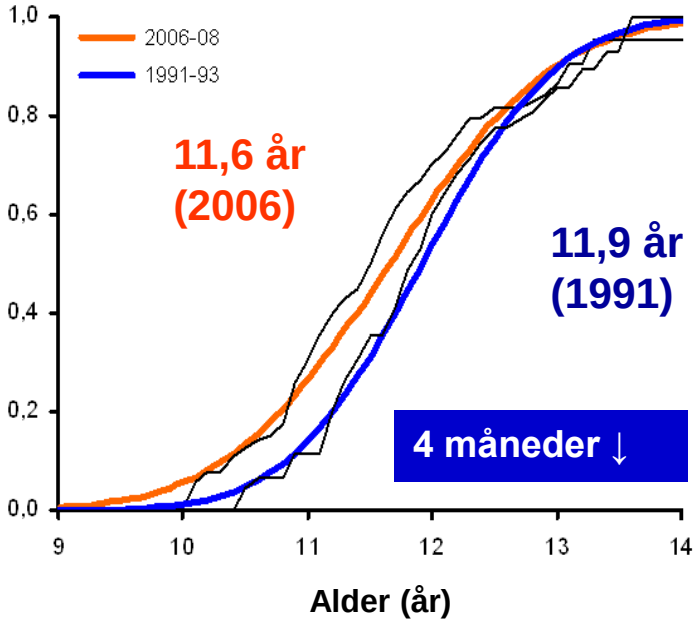
PIGER

Sandsynlighed for B2

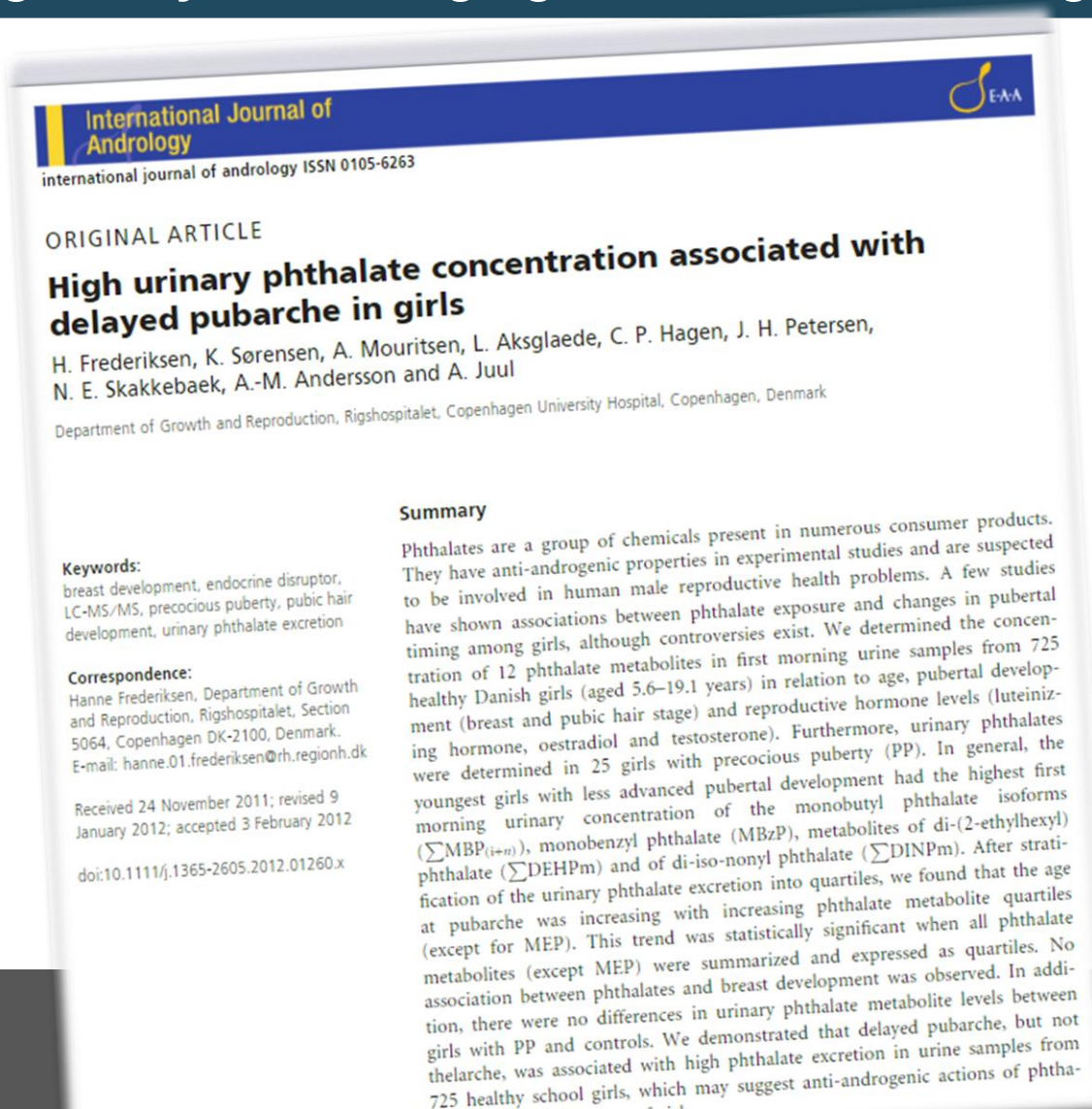


DRENGE

Sandsynlighed for G2



Hormonforstyrrende stoffer og pubertet
Ftalater: tidligere brystudvikling og senere kønsbehåring



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ORIGINAL ARTICLE

High urinary phthalate concentration associated with delayed pubarche in girls

H. Frederiksen, K. Sørensen, A. Mouritsen, L. Aksglaede, C. P. Hagen, J. H. Petersen, N. E. Skakkebaek, A.-M. Andersson and A. Juul

Department of Growth and Reproduction, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Keywords:
breast development, endocrine disruptor, LC-MS/MS, precocious puberty, pubic hair development, urinary phthalate excretion

Correspondence:
Hanne Frederiksen, Department of Growth and Reproduction, Rigshospitalet, Section 5064, Copenhagen DK-2100, Denmark.
E-mail: hanne.01.frederiksen@rh.regionh.dk

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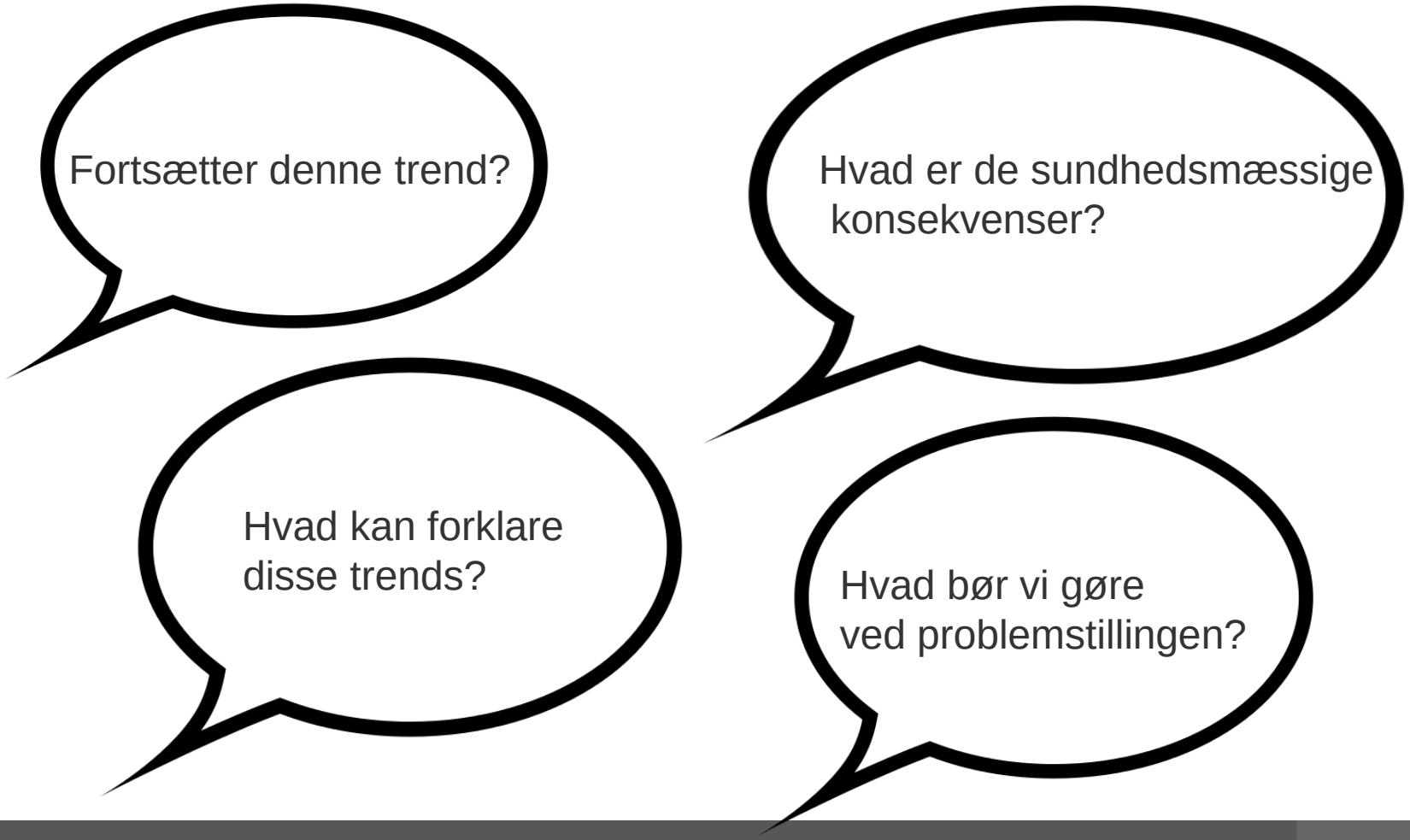
Summary

Phthalates are a group of chemicals present in numerous consumer products. They have anti-androgenic properties in experimental studies and are suspected to be involved in human male reproductive health problems. A few studies have shown associations between phthalate exposure and changes in pubertal timing among girls, although controversies exist. We determined the concentration of 12 phthalate metabolites in first morning urine samples from 725 healthy Danish girls (aged 5.6–19.1 years) in relation to age, pubertal development (breast and pubic hair stage) and reproductive hormone levels (luteinizing hormone, oestradiol and testosterone). Furthermore, urinary phthalates were determined in 25 girls with precocious puberty (PP). In general, the youngest girls with less advanced pubertal development had the highest first morning urinary concentration of the monobutyl phthalate isoforms ($\sum MBP_{(i+n)}$), monobenzyl phthalate (MBzP), metabolites of di-(2-ethylhexyl) phthalate ($\sum$DEHPm) and of di-iso-nonyl phthalate ($\sum$DINPm). After stratification of the urinary phthalate excretion into quartiles, we found that the age at pubarche was increasing with increasing phthalate metabolite quartiles (except for MEP). This trend was statistically significant when all phthalate metabolites (except MEP) were summarized and expressed as quartiles. No association between phthalates and breast development was observed. In addition, there were no differences in urinary phthalate metabolite levels between girls with PP and controls. We demonstrated that delayed pubarche, but not thelarche, was associated with high phthalate excretion in urine samples from 725 healthy school girls, which may suggest anti-androgenic actions of phtha-

Hormonforstyrrende stoffer og pubertet
Ftalater: tidligere brystudvikling og senere kønsbehåring

REGION H

Fremtidsprojekter og perspektivering
Motivation for nye studier



Fremtidsprojekter og perspektivering
The COPENHAGEN Puberty Study 2022

Formål:

Er gennemsnitsalderen for pubertetsdebut fortsat faldende i Danmark?

- Anbefalinger: nye kliniske aldersreferencer for pubertet?
- Hvad er mekanismerne bag tidlig pubertet?
- Mini-puberteten som determinant?

Fremtidsprojekter og perspektivering
Opsummering

- Børn går tidligere i puberteten, særligt piger
- Uklart om trenden fortsætter mod endnu tidligere pubertet
- Genetik og BMI kan ikke entydigt forklare trend
- Stigende interesse for betydning af hormonforstyrrende stoffer

- **The COPENHAGEN Puberty Study 2022**