

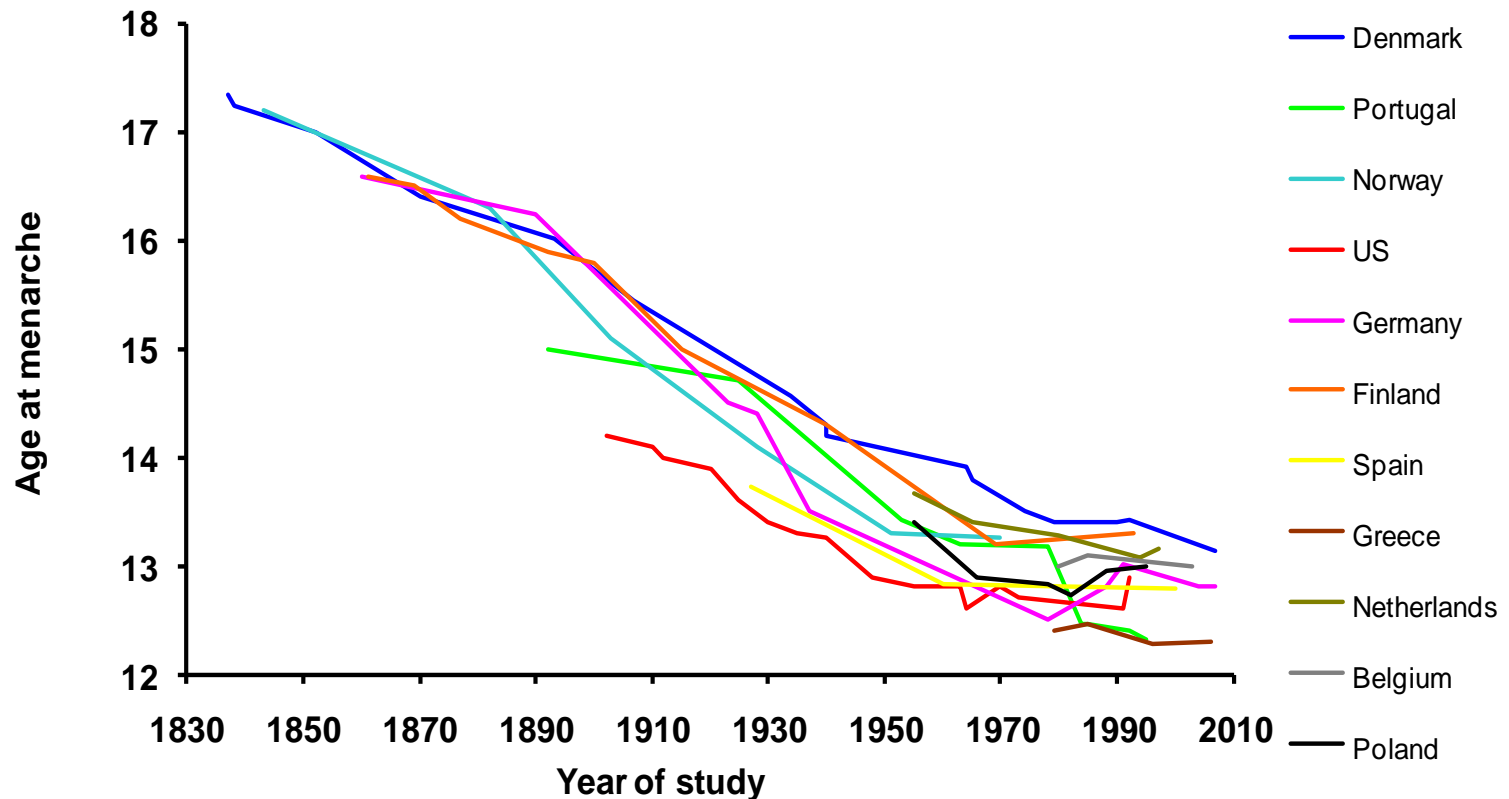
# Hormonforstyrrende stoffer og pubertet

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- 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)



## 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

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The authors have indicated they have no financial relationships relevant to this article to disclose.

### 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

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

Accepted for publication Feb 10, 2009

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PEDIATRICS® 05/11 Numbers Print 0031-4005; Online 1098-4275. Copyright © 2009 by the American Academy of Pediatrics

involved. *Pediatrics* 2009;123:

## ORIGINAL ARTICLE

## Endocrine Care

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

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**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.

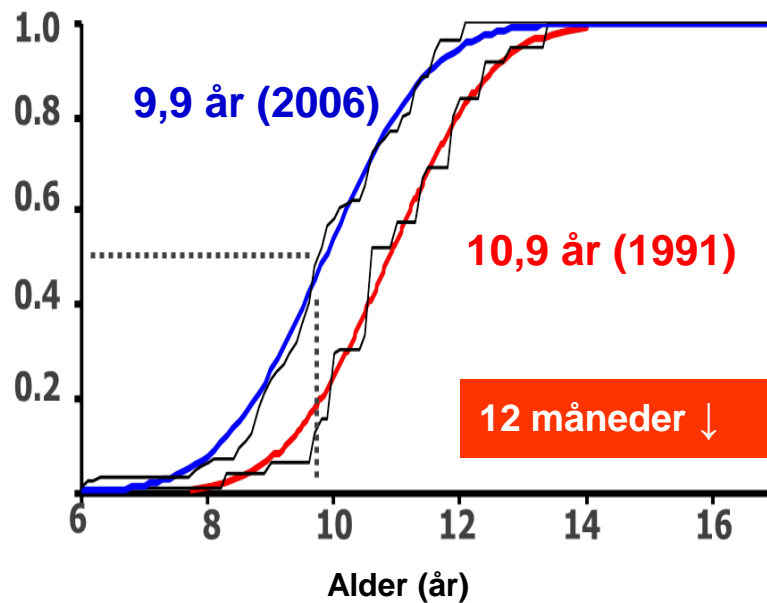
**Conclusions:** Estimated mean age at onset of puberty has declined significantly during the recent 15 yr. This decline was associated with the coincident increase in BMI. (*J Clin Endocrinol Metab* 95: 263–270, 2010)

# The COPENHAGEN Puberty Study

## Tidligere pubertetsdebut

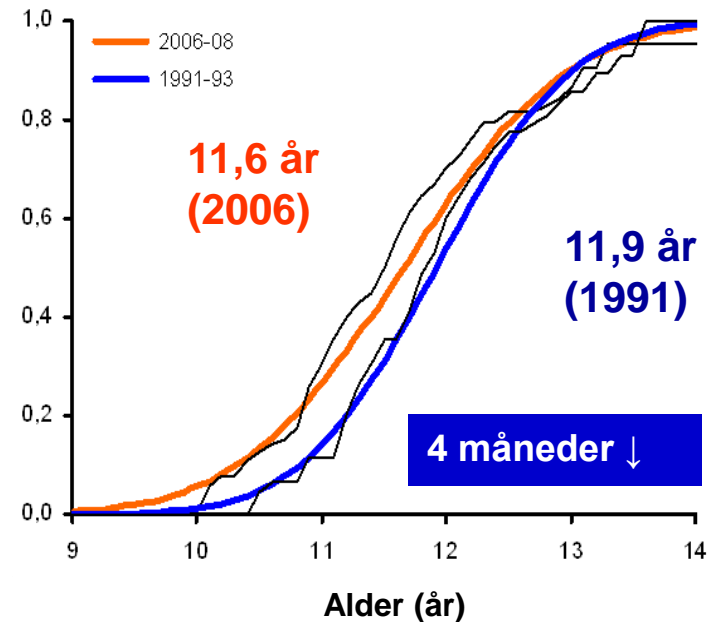
### PIGER

Sandsynlighed for B2

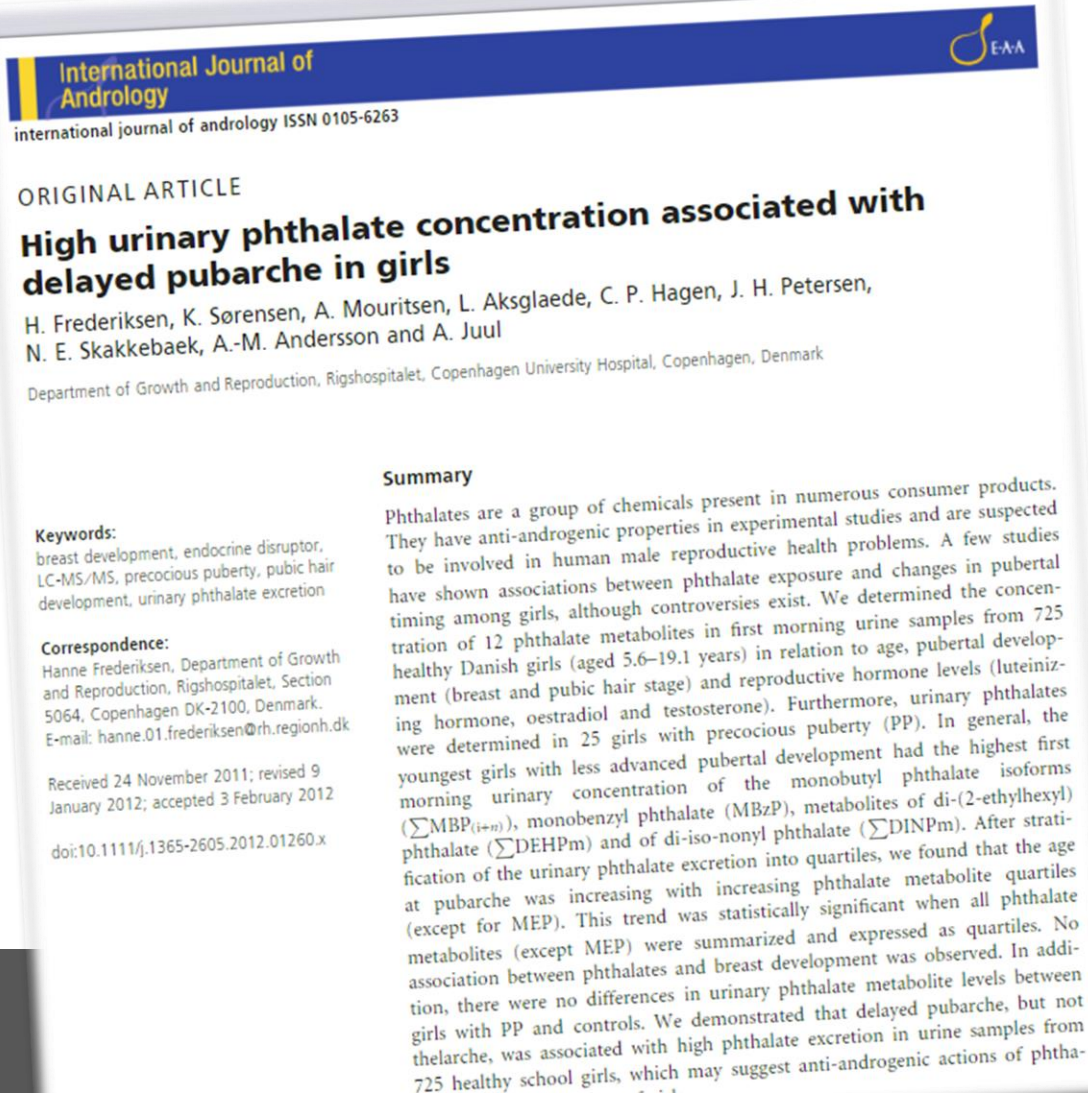


### DRENGE

Sandsynlighed for G2



# Hormonforstyrrende stoffer og pubertet Ftalater: tidligere brystudvikling og senere kønsbehåring



International Journal of  
Andrology  
international journal of andrology ISSN 0105-6263

## ORIGINAL ARTICLE

### High urinary phthalate concentration associated with delayed pubarche in girls

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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

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Received 24 November 2011; revised 9 January 2012; accepted 3 February 2012

doi:10.1111/j.1365-2605.2012.01260.x

#### 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 ( $\sum\text{MBP}_{(i+n)}$ ), monobenzyl phthalate (MBzP), metabolites of di-(2-ethylhexyl) phthalate ( $\sum\text{DEHPm}$ ) and of di-iso-nonyl phthalate ( $\sum\text{DINPm}$ ). 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 phthalates.



## Hormonforstyrrende stoffer og pubertet

### Ftalater: tidligere brystudvikling og senere kønsbehåring

Could exposure to phthalates speed up or delay pubertal onset and development? A 1.5-year follow-up of a school-based population

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## ARTICLE INFO

Article history:  
Received 14 August 2014  
Received in revised form 22 December 2014  
Accepted 1 June 2015  
Available online 12 June 2015

**Keywords:**  
Phthalates  
Sexual maturation  
Pubertal timing  
Environmental endocrine disruptors  
Antiandrogenic effect

## ABSTRACT

**Purpose:** Phthalates may interfere with the timing of pubertal development in boys. We have shown inconsistent results. This study aims to assess the associations of urinary concentrations of phthalate metabolites in school-

**Methods:** Using isotope-dilution liquid chromatography tandem mass spectrometry, we measured 18 phthalate metabolites in urine samples of 430 children (222 boys and 208 girls) aged 7–18 years in 1995 and 1996. We assessed the association of urinary concentrations of these metabolites with the age at onset of pubertal development as assessed by self-reporting of the first sexual intercourse. We also examined the association of urinary concentrations of these metabolites with the age at onset of menstruation in girls. We adjusted for baseline development stage, current chronologic age, and ethnicity.

**Results:** Urinary mono-n-butyl phthalate (MnBP) was associated with lower pubertal development stages in boys, and mono-2-ethyl-5-hydroxyhexanoate (MEHP) was associated with lower pubertal development stages in girls. MnBP was associated with 54%–63% increase in the odds of prepuberty ( $p < 0.05$ ), while MEHP and MEHP were also associated ( $p < 0.05$ ). After adjusting for potential confounding, MnBP, MEHP, and MEHP were significant. The odds ratio for MnBP, MEHP, and MEHP exposure group was 1.54, 1.54, and 1.54, respectively, compared to the reference group. Conclusions: Our findings suggest that exposure to phthalates may be associated with earlier onset of pubertal development. MnBP exposure may be associated with earlier onset of pubertal development in boys, and MEHP exposure may be associated with earlier onset of pubertal development in girls.

Human Reproduction, Vol.29, No.7 pp. 1558–1566, 2014  
Advanced Access publication on April 29, 2014 doi:10.1093/humrep/det081

**Phthalate exposure and pubertal development in a longitudinal study of US girls**

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S.M. Pinney<sup>3</sup>, M. Galvez<sup>4</sup>, A.M. Calafat<sup>4</sup>, L.H. Kushi<sup>5</sup>, and F.M. Biro<sup>6</sup>**  
**on behalf of the Breast Cancer and Environment Research Program<sup>†</sup>**

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Submitted on January 28, 2014; resubmitted on March 13, 2014; accepted on March 26, 2014

**STUDY QUESTION:** Does phthalate exposure during early childhood alter the timing of pubertal development in girls?

**SUMMARY ANSWER:** Urinary concentrations of high-molecular weight phthalate (high-MWPF) metabolites are associated with later pubertal onset.

**WHAT IS KNOWN ALREADY:** Phthalates are anti-androgenic environmental agents known to alter early development in girls!

**STUDY DESIGN, SIZE, AND DURATION:** This multi-ethnic study included 1239 girls from New York City, Greater Cincinnati, and the San Francisco Bay Area, who were 6–8 years old at enrollment (2004–2007) and who were followed up until 2011.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Phthalate metabolites were measured in urine collected at enrollment from 1,700 girls; concentrations ranged from  $<1$  to  $>10$   $\mu\text{g/g}$  creatinine. Age at breast and pubic hair stages and body size were measured to determine the age at transition from Stage 1 to 2 for breast and pubic hair development. Associations between exposure and pubertal age were estimated using Cox proportional hazard ratios (HR) with 95% confidence intervals (CI) and survival analyses. Associations were examined in respect to age-specific body mass index percentile, one of the strongest predictors of pubertal onset.

**RESULTS AND THE RISK OF CHANCE:** Urinary concentrations of high-MWPF including di(2-ethylhexyl) phthalate (DEHP) and other metabolites were associated with later pubic hair development during 7 years of observation. The relationship was stronger in normal-weight girls. Among normal-weight girls, age at pubic hair stage and age at breast stage were associated with later pubertal age and urinary 2DEHP. Among girls with overweight, age at pubic hair stage was associated with later pubertal age and urinary 2DEHP. Among girls with overweight, age at pubic hair stage was associated with later pubertal age and urinary 2DEHP. Among girls with overweight, age at pubic hair stage was associated with later pubertal age and urinary 2DEHP. Among girls with overweight, age at pubic hair stage was associated with later pubertal age and urinary 2DEHP.

**CONCLUSIONS, REASONS FOR CAUTION:** While there is

products, exposure to which may hasten and prolongation of sexual development. Gestational phthalate exposure and maternal exposure was quantified using measurements. Sexual maturation was assessed by testicular volume for boys. Data were used to model relationships between gestational age (GA) mixed model for child age (centered around the mean), and interactions between GA and gestational age. Among girls, a doubling of being at a higher Tanner stage for but with slower progression of breast development. In boys, a doubling of being at a higher Tanner stage for pubic hair progression (OR: 1.28; 95% CI: 0.97, 1.69). The onset and progression of sexual development.

**ORIGINAL ARTICLE**  
**Urine urinary phthalate concentration associated with**  
**testicular volume in girls**  
Aksgaarde, C. P., Hagen, J. H., Petersen, L. H., Jensen, T. K., & Jensen, T. K.

**High urinary phthalate concentration, delayed pubarche in girls**

**Summary** A group of chemicals present in numerous properties in experimental reproductive health

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

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Received 24 November 2011; revised 9 January 2012; accepted 3 February 2012  
doi:10.1111/j.1365-2605.2012.01260.x

## Summary

[illegible]



## Fremtidsprojekter og perspektivering Motivation for nye studier

Fortsætter denne trend?

Hvad er de sundhedsmæssige konsekvenser?

Hvad kan forklare disse trends?

Hvad bør vi gøre ved problemstillingen?

## 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**