Maternal age at menarche and pubertal development in sons and daughters: a Nationwide Cohort Study

S. Sørensen*, N. Brix, A. Ernst, L.L.B. Lauridsen, and C.H. Ramlau-Hansen

Department of Public Health, Section for Epidemiology, Aarhus University, DK-8000 Aarhus C, Denmark

*Correspondence address: sorensen_signe@hotmail.com

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STUDY QUESTION: Is maternal age at menarche associated with pubertal development in sons and daughters?

SUMMARY ANSWER: Maternal age at menarche was associated with pubertal development in both sons and daughters.

WHAT IS KNOWN ALREADY: Studies have shown that age at menarche is greatly inherited from mother to daughter, but it remains largely unknown to what extent age at menarche in mothers is associated with timing of puberty in sons.

STUDY DESIGN, SIZE, DURATION: In this population-based study we used data from the Puberty Cohort nested within the Danish National Birth Cohort. Live-born singletons aged 11 were followed from 2012 to 2016.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In total, 15 822 children (7697 sons and 8125 daughters) gave half-yearly information on puberty from the age of 11 years until full sexual maturity or 18 years of age through self-administrated questionnaires (participation rate 71%). Information on maternal age at menarche was reported by the mothers during pregnancy. Maternal age at menarche was used both as a continuous and as a categorical variable (earlier, same time or later than peers). A multivariable regression model for interval-censored data was used.

MAIN RESULTS AND THE ROLE OF CHANCE: Maternal age at menarche was positively associated with timing of genital development, pubic hair development, first ejaculation of semen, voice break, axillary hair development and acne in sons, and with timing of breast development, pubic hair development, menarche, axillary hair development and acne in daughters. In sons, the associations were of similar strength for all pubertal markers, whereas in daughters, the associations were strongest for breast development and menarche.

LIMITATIONS, REASONS FOR CAUTION: Age at menarche was recalled during pregnancy. However, studies indicate that age at menarche is recalled moderately in adulthood. Information on puberty was self-reported, but inaccuracy of data would probably cause non-differential misclassification.

WIDER IMPLICATIONS OF THE FINDINGS: Early maternal age at menarche was associated with earlier pubertal development, and late maternal age at menarche was associated with later pubertal development in both sons and daughters. The largest effect-estimates were for the associations between maternal age at menarche and the daughters’ age at menarche and age at breast development.

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Introduction

During the last century, the timing of puberty seems to occur at still younger ages which may be partly explained by improved general health and living standards (Juul et al., 2007; Aksela et al., 2008, 2009b). This is a public health concern, as earlier age at puberty has been linked to increased risk of frequent and serious diseases in adulthood, such as breast cancer, testicular cancer, diabetes mellitus and cardiovascular diseases (Golub et al., 2008).

Both genetic and environmental factors influence the timing of puberty (Abreu and Kaiser, 2016). A recent genome-wide association study (GWAS) showed a substantial overlap of genes suggested to influence timing of puberty in both boys (age at voice break) and girls (menarche) (Day et al., 2015). This genetic overlap indirectly suggests that maternal timing of puberty may be related to timing of puberty in both sons and daughters.

Many studies have shown that age at menarche (AAM) in mothers is associated with AAM in daughters (Brooks-Gunn and Warren, 1988; Malina et al., 1994; Graber et al., 1995; Cameron and Nagdee, 1996; Salces et al., 2001; Ersy et al., 2005; Pouta et al., 2005; Chang and Chen, 2008; Tehrani et al., 2010; Wohlfahrt-Veje et al., 2016).

However, only a single study has investigated the impact of maternal timing of puberty on the age at onset of genital development and pubic hair in sons (Wohlfahrt-Veje et al., 2016).

The aim of this study is to examine the associations between maternal AAM and pubertal development in sons and daughters by use of longitudinally collected information on several markers of pubertal development self-reported half-yearly throughout puberty.

Materials and methods

Study population

The present study used data from the Puberty Cohort nested within the Danish National Birth Cohort (DNBC) which is a cohort of approximately 100,000 mother-child pairs. In the DNBC the mothers were interviewed twice during pregnancy, and at the time the child was 7 years old, the parents filled in a questionnaire concerning their child’s health and development. At the age of 11 years, the children were invited to fill in a questionnaire including questions on puberty.

The Puberty Cohort was established in August 2012, and eligible children for this cohort included live-born singletons born between 2000 and 2003 whose mothers had participated in the first maternal interview during pregnancy and had not withdrawn from the DNBC. In total, 56,641 children were eligible for the Puberty Cohort. To improve the exposure contrast, we sampled the eligible children according to 12 different exposures of interest. Hence, 22,439 children were sampled and invited to participate in the Puberty Cohort with the end of follow-up for the present study in October 2016. During this follow-up a total of 15,822 children provided information on puberty (Fig. 1).

Exposure: maternal age at menarche

Information on maternal AAM was collected through a computer-assisted telephone interview around gestational week 17. The mother was asked: ‘How old were you when you had your first menstrual bleeding (in years)?’ If she did not remember, she was asked: ‘At what grade did you have your first menstrual bleeding?’, and if she did not remember that either, she was asked to indicate whether her first menstrual bleeding came earlier, later, or at the same time as her peers.

Outcomes: markers of pubertal development

Information on pubertal development in sons and daughters was collected through web-based, self-administered questionnaires at 11 years of age in the DNBC, and from 11.5 years of age and every 6 months in the Puberty Cohort. The questionnaires included a short description and line drawings of each Tanner stage: genital development (Tanner G1–G5), breast development (Tanner B1–B5), and pubic hair development (Tanner PH1–PH5) (Marshall and Tanner, 1969, 1970). The children were also asked to report their status on first ejaculation of semen (years and months), voice break (yes or no), AAM (years and months), axillary hair (yes or no) and acne (yes or no).

Covariates

Information on sociodemographic and maternal lifestyle during pregnancy was available from the maternal interviews conducted in pregnancy. Information on social class was retrieved from Statistics Denmark, whereas information on childhood height and weight was retrieved from the
7-years questionnaire in the DNBC. Potential confounders were identified a priori according to existing literature (Windham et al., 2004; Keim et al., 2009; Shrestha et al., 2011; Ernst et al., 2012; Deardorff et al., 2013, 2014; Culpin et al., 2014; Hakonsen et al., 2014; Hougaard et al., 2014; Gollenberg et al., 2015; Kim et al., 2017) and included maternal pre-pregnancy body mass index (BMI; classified according to WHO (World Health Organization, 2000)), cohabitation status during pregnancy, highest social class of parents, maternal smoking during first trimester, maternal alcohol consumption during first trimester and childhood BMI (classified according to the International Obesity Task Force (Cole et al., 2000)).

### Statistical analyses

As the children in the Puberty Cohort were asked to report their pubertal status half-yearly, the observations were either left, interval or right censored. We used the intreg package in Stata/MP 13.1 to perform a
parametric multivariable censored regression model based on the normal distribution fitted by maximum likelihood estimation (Sun, 2006). The assumption of normal distribution was evaluated by plotting the non-parametric cumulative incidence function and comparing it to the normal distribution using the LcencReg package in R x64 3.3.1.

Sampling weights were used to account for the sampling procedure. Robust standard errors were used to account for the use of sampling weights and clustering of the siblings.

In our analyses we used maternal AAM both as a categorical variable (‘Maternal AAM earlier than peers’, ‘Maternal AAM same time as peers’ and ‘Maternal AAM later than peers’) and as a continuous variable (in years). The results for the categorical maternal AAM are presented as mean monthly differences in timing of puberty in sons and daughters of mothers with AAM earlier or later than peers, compared to the timing of puberty in sons and daughters of mothers with AAM same time as peers.

The results for the continuous maternal AAM are presented as the slope of the regression line ($\beta$) with 95% CI between maternal AAM (in years) and the age of the sons or daughters (in months) at attaining each pubertal marker, where $\beta$ presents the mean monthly change in timing of puberty in sons and daughters per one-year increase in maternal AAM.

In a sub-analysis, childhood BMI was included in the models as it may confound the associations, although we consider childhood BMI to be an intermediate variable (Juul et al., 2007; Ong et al., 2007; Kaplowitz, 2008; Akslaaede et al., 2009a).

**Ethics**

The pregnant women gave their written informed consent at the enrollment in the DNBC. The study was approved by the Committee on Biomedical Research Ethics in Denmark (KF 01-471/94), the Danish Data Protection Agency (j.no. 2012-41-0379 and 2015-57-0002) and the steering committee of the DNBC (2012-04 and 2015-47).

**Results**

Characteristics of the study population, according to the maternal age at menarche, are presented in Table I.
We found that sons of mothers who reported AAM earlier than peers, had earlier age at all markers of pubertal development than sons of mothers with AAM same time as peers, except for genital development Tanner stage 2. The largest difference in months was observed for axillary hair (−2.60 (95% CI: −3.86; −1.34) months), meaning that sons of mothers who reported AAM earlier than peers started development of axillary hair 2.6 month earlier than sons of mothers who reported AAM same time as peers. Sons of mothers who reported AAM later than peers, attained first ejaculation of semen, axillary hair and acne later than sons of mothers with AAM same time as peers. Analyses on genital development, voice break and pubic hair development showed tendencies towards later attainment.

**Figure 2** Timing of puberty in sons according to maternal age at menarche, the Puberty Cohort.
AAM, age at menarche; CI, confidence interval; G2, genital development Tanner Stage 2; G3, genital development Tanner Stage 3; G4, genital development Tanner Stage 4; G5, genital development Tanner Stage 5; PH2, pubic hair development Tanner Stage 2; PH3, pubic hair development Tanner Stage 3; PH4, pubic hair development Tanner Stage 4; PH5, pubic hair development Tanner Stage 5.
*Adjusted for the following covariates: maternal pre-pregnancy BMI, cohabitation status, highest social class of parents, maternal smoking and maternal alcohol consumption during first trimester.

**Figure 3** Timing of puberty in daughters according to maternal age at menarche, the Puberty Cohort.
AAM, age at menarche; CI, confidence interval; B2, breast development Tanner Stage 2; B3, breast development Tanner Stage 3; B4, breast development Tanner Stage 4; B5, breast development Tanner Stage 5; PH2, pubic hair development Tanner Stage 2; PH3, pubic hair development Tanner Stage 3; PH4, pubic hair development Tanner Stage 4; PH5, pubic hair development Tanner Stage 5.
*Adjusted for the following covariates: maternal pre-pregnancy BMI, cohabitation status, highest social class of parents, maternal smoking and maternal alcohol consumption during first trimester.
in sons of mothers with AAM later than peers, although they were not statistically significant (Table II and Fig. 2).

Daughters of mothers who reported AAM earlier than peers, had earlier age at all markers of pubertal development than daughters of mothers with AAM same time as peers, with the largest difference in months observed for breast development Tanner Stage 5 (−6.06 (95% CI: −7.92; −4.20) months). Daughters of mothers reporting a later AAM than peers were older at the time of onset of all pubertal markers (Table II and Fig. 3).

We found that maternal AAM was associated with all pubertal markers in both sons and daughters (Table III).

Adjustment for childhood BMI did not change the results, indicating that childhood BMI did not mediate or confound the associations of interest (data not shown).

Discussion

This cohort study of 15,822 Danish children, mainly of Caucasian origin (Olsen et al., 2001) is, to our knowledge, the largest published study investigating the associations between maternal AAM and pubertal development in both sons and daughters. We found that maternal AAM was associated with all pubertal markers in both sons and daughters.

Our results are consistent with a recent GWAS that found a great overlap in genes influencing both male and female timing of puberty (Day et al., 2015), thereby suggesting that maternal timing of puberty should be associated with timing of puberty in daughters as well as sons. Furthermore, our results fit well with the neuroendocrine regulation of puberty. In females, the development of pubic hair, axillary hair and acne is a result of the androgen surge at adrenarche, while breast development and menarche are results of the oestrogen surge at gonadarche. In contrast, all male pubertal markers are sensitive to androgens produced by the testis at gonadarche (Despopoulos and Silbernagl, 2003), and we speculate that these regulatory differences may account for some of the observed discrepancy between sons and daughters.

Though genes influencing timing of puberty in both sexes are overlapping, some genes mainly affect males and other genes mainly affect females (Day et al., 2015). This implies that maternal timing of puberty should be more strongly associated with the timing of puberty in daughters than in sons, which also was observed in our study.

Previous studies on maternal timing of puberty and pubertal development in sons and daughters are sparse, especially regarding sons (Wohlfahrt-Veje et al., 2016). The study by Wohlfahrt-Veje et al. examined maternal pubertal timing in relation to age at menarche and age at onset of the development of genitals, breasts and pubic hair (Tanner Stage 2), and their results were consistent with ours.

Important strengths of our study are the longitudinal design with detailed information on puberty and covariates, the high participation rate (71%), the substantial number of participants, and the close to complete data on maternal AAM.

As a limitation, our study used recalled information on maternal AAM. Maternal AAM was reported during pregnancy, and the potential misclassification is thereby most likely non-differential. Previous prospective studies indicate that AAM is recalled in adulthood with moderate accuracy (Damon and Bajema, 1974; Dorn et al., 2013). In addition, the maternal AAM in our study population was recalled at levels comparable to other contemporary cohorts (13.17 and 13.6 years, respectively (Ersoy et al., 2005; Wohlfahrt-Veje et al., 2016)). We also used self-reported information on puberty. A recent evaluation of the self-assessment of pubertal development among late adolescents in the Puberty Cohort showed that boys tended to underestimate their genital stage (Ernst et al., 2018). However, in our study it seems unlikely that self-reported information should be related to the maternal AAM, and thereby it would probably only cause non-differential misclassification. This provides an alternative explanation for the weaker associations observed in sons. Participation in the Puberty Cohort was not related to maternal AAM (data not shown), thereby reducing the risk of selection bias.

In conclusion we found that maternal AAM was associated with age at attaining various pubertal markers in both sons and daughters. As maternal AAM was associated with timing of puberty in sons as well as daughters, this study provides epidemiologic support for shared genes for the timing of puberty in boys and girls.

Authors’ roles

Contributions to conception, design, data interpretation and approval of the version to be published: S.S., N.B., A.E., L.L.B.L. and C.H.R.H.
Data acquisition: C.H.R.H.
Data management: N.B., A.E. and L.L.B.L.
Critical review of the manuscript: N.B., A.E., L.L.B.L. and C.H.R.H.
Data analysis and drafting of the article: S.S.

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Conflict of interest
None declared.

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Danish Ministry of Education. Databanken. 03/26; 2017.


