



The potential impact of paternal age on risk of asthma in childhood: a study within the Danish National Birth Cohort



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ABSTRACT

Background: Advanced paternal age has been associated with offspring morbidity and mortality, possibly due to de novo mutations and epigenetic changes in male germ cells. Epigenetic changes in the cord blood cells have been linked to asthma symptoms in offspring, but the role of paternal age has been less studied.

Methods: From the Danish National Birth Cohort, 48,785 children who completed the 7-year follow-up were included. Parental reports of physician-diagnosed asthma had been obtained by a posted or web-based questionnaire. Paternal age at delivery was obtained through linkage with maternal civil registration number in the Danish Civil Registration System and classified into four groups: ≤ 24 , 25–34 (reference), 35–39, and > 40 years. We calculated the prevalence proportion of asthma and prevalence ratios (PRs) with 95% confidence intervals (CIs) using log-binomial regression, adjusting for paternal smoking, paternal asthma, and paternal socioeconomic status.

Results: At the 7-year follow-up, 5875 children (12%) had physician-diagnosed asthma. The prevalence of asthma in 7-year old children was higher with paternal age of ≤ 24 (adjusted PR 1.40; 95% CI: 1.26; 1.55) and lower with the paternal age of ≥ 35 years (adjusted PR 0.84; 95% CI: 0.78; 0.89) compared to the reference group.

Conclusions: Paternal age of ≥ 35 years was associated with a lower prevalence of asthma in childhood, and paternal age of ≤ 24 years with higher prevalence compared with paternal age of 25–34 years. The potential causes of higher asthma prevalence among offspring of young fathers warrant further investigation.

1. Introduction

Asthma is among the most common chronic diseases in childhood, and the prevalence has increased during the last decades in several Western Countries [1,2]. The disease has profound effects on quality of life in childhood and is a leading cause of school absenteeism and pediatric hospitalization [3–5].

Age of asthma onset is most commonly in early childhood. The mean age at diagnosis was 2.2 years in a population-based study of 21,038 individuals in Finland [6,7]. Several perinatal factors such as preterm delivery and maternal smoking in pregnancy have been associated with the risk of asthma [8–10]. A clear association between asthma and allergy has been identified. Most school age children and adolescents with asthma also have allergic sensitization [11,12].

Young maternal age has also been associated with an increased risk of asthma in offspring, which may reflect behavioral, social and lifestyle factors [13,14]. The role of paternal age as a risk factor for asthma in

childhood has only been evaluated in one study indicating decreased risk of asthma at increasing paternal age [15]. However, since these results were based on data from the Swedish Medical Birth register, limited ability to adjust for relevant confounders existed in that study.

During the last decades, an increasing number of couples in Europe have delayed parenthood [16]. Advanced paternal age, independently of maternal age, is associated with some offspring morbidity and mortality, including certain rare diseases and syndromes e.g., achondroplasia, neural tube defects, epilepsy, autism and schizophrenia [17–23]. The biological mechanisms behind these associations are unknown but may be related to epigenetic changes, de novo mutations in male germ cells, and DNA damage accumulations due to declining male germ line genomic stability. Potential risk factors may accumulate with age and may result from harmful environmental exposures [24,25]. Asthma may partially be induced by similar mechanisms. Specifically, one study indicated that gene-specific DNA methylation in white blood cells taken from cord blood might lead to a higher risk of asthma in

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Abbreviations list

PRs	Prevalence ratios
DNBC	Danish National Birth Cohort
CPR-number	Civil registration number
SES	Socioeconomic status
R	Correlation coefficient
SD	Standard deviation

childhood [26].

We used data from the Danish National Birth Cohort (DNBC) to examine the association between paternal age at delivery and childhood asthma. We hypothesized that advanced paternal age increased the risk of asthma in the offspring and examined, whether this potential association is modified by maternal age.

2. Materials and methods

The DNBC is a nationwide cohort study of pregnancies and children and aimed to study causes of pregnancy complications and diseases in offspring. The cohort is described in detail elsewhere [27]. Briefly, women were recruited at the first antenatal care visit (6–12 week of gestation) from 1996 to 2002 by approximately 50% of all general practitioners in Denmark: 60% of women invited agreed to participate. Women were eligible if they spoke some Danish, intended to carry their pregnancy to term, and had a permanent address in Denmark. Information on sociodemographic, perinatal, and medical factors was collected from four computer assisted telephone interviews at gestational weeks 12 and 30, postpartum months 6 and 18 and linkage to public registers. When the child was 7 years old, a follow-up was conducted by a mailed or web-based questionnaire completed by the parents about the child's health and diseases including asthma [28]. When the children reached 11 years of age, a new wave of data collection took place from 2010 to 2014. All mothers and children who were enrolled in the DNBC were invited to the 11-year follow-up, regardless of participation in previous collections (more information from www.dnbc.dk).

2.1. Study population

The DNBC included 101,041 pregnancies. We restricted the study population to 54,906 singleton live-born children for whom a mailed or web-based questionnaire at 7 years had been completed by a parent often the mother. We included only the first pregnancy in the sampling period and excluded 5370 siblings and 751 father-child pairs with no information on paternal age, because of unreported fatherhood. Thus, the final population for the analyses consisted of 48,785 children (Fig. 1).

2.2. Paternal age

Data on paternal date of birth were obtained by linkage of the maternal civil registration number (CPR-number) in the Danish Civil Registration System to the CPR-number of the fathers which include date of birth [29]. The paternal age at delivery was calculated based on the CPR-number and date of delivery and classified into four groups: ≤ 24 , 25–34 (reference), 35–39 and ≥ 40 years.

2.3. Asthma

Information on asthma was based on the 7-year follow-up questionnaire, with questions similar to validated core questions on asthma from the International Study of Asthma and Allergies in Childhood [30]. The presence of asthma in this study was defined as 'yes' to the

question 'Has your child ever been diagnosed with asthma by a doctor?'. This question had a 70% sensitivity and 99% specificity in identifying asthma cases among 7 to 8-year-old school children [31]. From the same questionnaire, we obtained information on the presence of allergy where the parent was asked about chronic illness among others allergy.

2.4. Statistical analyses and potential confounders

We estimated prevalence ratios (PRs) and 95% confidence intervals (CIs) using log-binominal regression adjusted for confounding factors. The main determinants of asthma were identified in the literature and obtained primarily from interview 1 (gestational week 12) and included: parental smoking (yes/no) [10], parental asthma (yes/no) [10], parental allergy (yes/no) [32], time to pregnancy (months) [33], family size (2,3, ≥ 4) [34], maternal fish-oil supplementation during pregnancy (yes/no) [35] and paternal socioeconomic status (low, middle or high based on the father's education and income reported at child's birth) [36]. We evaluated "change in estimate" of the selected individual potential confounders and included only variables that changed the estimate $> 5\%$ in the final multivariate regression model (paternal smoking, paternal asthma and paternal SES) [37]. Maternal and paternal age were highly correlated ($r = 0.70$) which call for

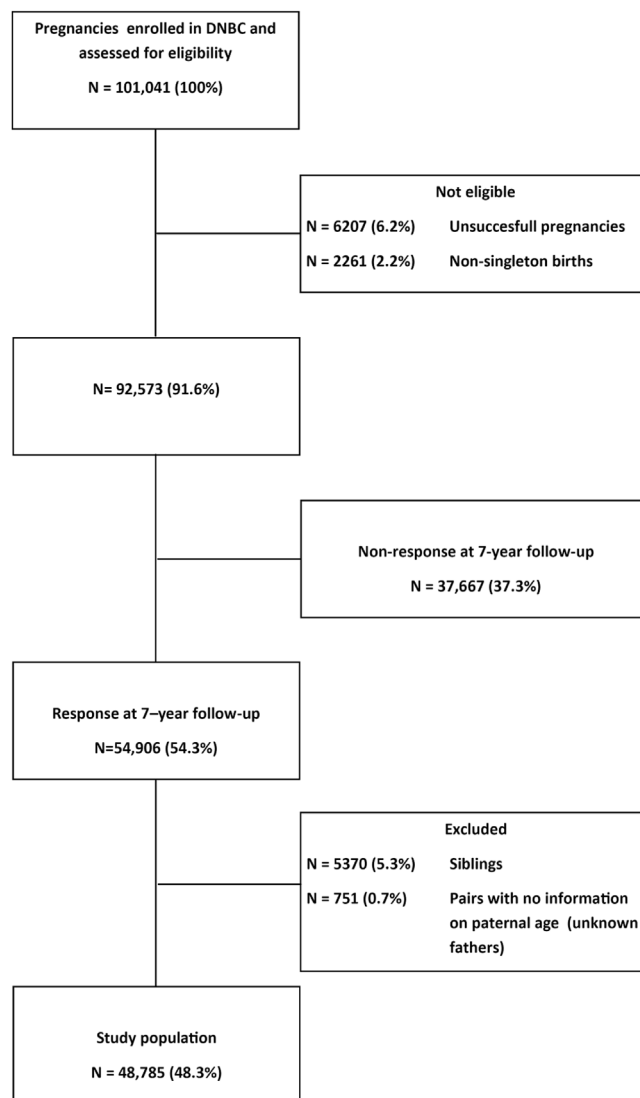


Fig. 1. Selection of mother/child pairs from the Danish National Birth Cohort (DNBC) for the current study.

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