



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

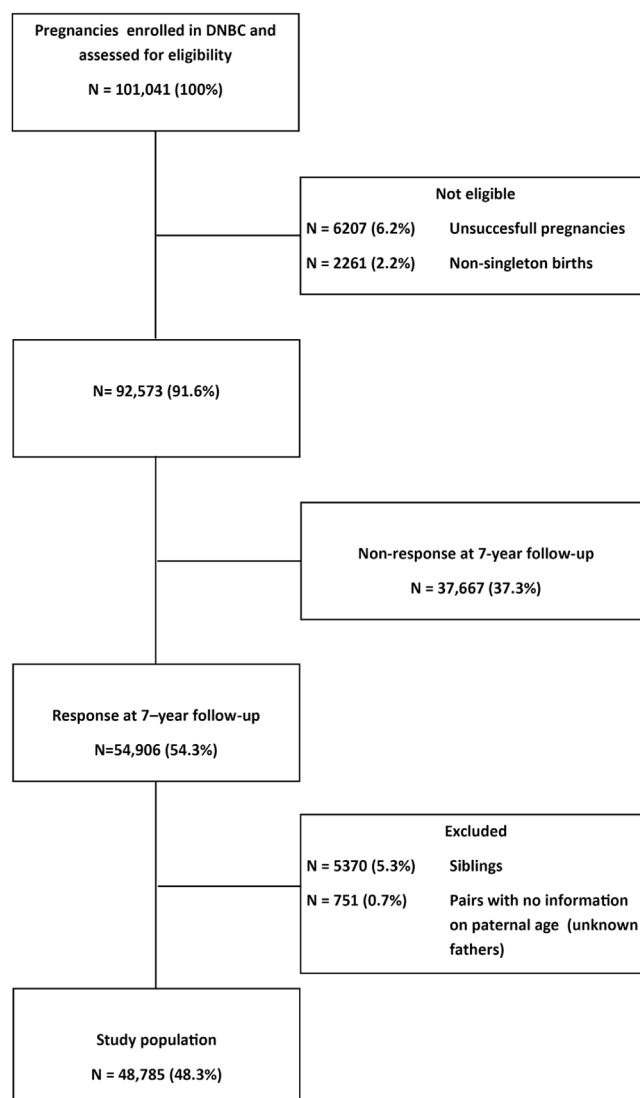


Fig. 1. Selection of mother/child pairs from the Danish National Birth Cohort (DNBC) for the current study.

caution in inclusion of maternal age into the model. We evaluated the interaction between the paternal age and the covariates including maternal age and found no clear evidence of effect measure modification on the multiplicative scale. In a sensitivity analysis, we evaluated adjustment for maternal age in the model. In another sensitivity analysis, we included information on asthma in children from the 11-year follow-up to calculate the prevalence of childhood asthma under the assumption that these children also had asthma at 7-year of age. Finally, we assessed the association of paternal age and risk of allergy among 7-year old children without asthma adjusted for paternal allergy, paternal smoking and paternal SES. All analyses were performed in STATA 11.0 (STATA Corp., Texas, USA).

3. Results

Of the 48,785 included children, 5875 (12%) reported physician diagnosed asthma. The mean paternal age at the time of birth of the child was 32.3 years with a standard deviation (SD) of 5.3 years. Table 1 shows the paternal and maternal characteristics assessed at interview 1 for the children included in the 7-year follow-up. The paternal age group of ≥ 40 years had in comparison with the reference group a higher socioeconomic status (SES), less allergy, longer TTP, were from larger families, and their partners were older. A greater proportion of the paternal age group of ≤ 24 years smoked, had a smoking partner, had more often asthma, but less allergy and lower SES compared with the reference group.

Table 2 shows the number of asthma cases and prevalence of 384 (19%) in the paternal age group of ≤ 24 years, 4021 (12%) in the reference group, 1049 (10%) in the paternal age group of ≥ 35 –39 years, and 421 (10%) in the paternal age group of ≥ 40 years. The prevalence of asthma in 7-year old children was higher in the paternal age group of ≤ 24 years (adjusted PR 1.40; 95% CI: 1.26; 1.55) and lower for the

paternal age group of ≥ 35 years (adjusted PR 0.84; 95% CI: 0.78; 0.89) compared with the reference group.

In a sensitivity analysis, we adjusted for maternal age in the multivariate analysis, and we found similar prevalences in the paternal age groups, but the adjusted PR was attenuated in the paternal age group ≤ 24 years (adjusted PR 1.23; 95% CI: 1.11; 1.37) and lower for the paternal age group of ≥ 35 years (adjusted PR 1.00; 95% CI: 0.89; 1.11) compared with the reference group. In another sensitivity analysis, we included information on asthma in children from the 11-year follow-up leading to a higher prevalence of childhood asthma, but the estimated PR's were similar to the above reported results (data not shown). Finally, we found a tendency towards a higher prevalence of allergy in 7-year old children of the paternal age group of ≤ 24 years (adjusted PR 1.17; 95% CI: 0.67; 2.06) and lower for the paternal age group of ≥ 35 years (adjusted PR 0.92; 95% CI: 0.69; 1.22) compared with the reference group, though the 95% CI included null.

4. Discussion

Paternal age of ≥ 35 years at the time of child's birth was associated with a lower prevalence of asthma in 7-year old children, and paternal age of ≤ 24 years with a higher prevalence of asthma children compared with the paternal age of 25–34 years. Paternal characteristics such as smoking, asthma or SES seemed not to confound this association although residual confounding can not be excluded.

To our knowledge, only one Swedish study has examined the association between paternal age and risk of asthma in offspring and found a slightly decreased risk of asthma in early childhood for fathers ≥ 35 years, which was more pronounced for fathers ≥ 50 years [15]. In our study, we examined advanced paternal age ≥ 40 years. Unfortunately, only 0.4% of the fathers in our study population were ≥ 50 years, and therefore we could not make a separate analysis for this age

Table 1
Paternal and maternal characteristics of 48,785 7-years old children.

Paternal age (years)	≤ 24 n = 1991	Reference 25–34 n = 32,415	35–39 n = 10,267	≥ 40 n = 4112	All N = 48,785
Paternal smoking (N) (%)					
Yes	740 (42.2)	8767 (28.5)	2851 (29.3)	1241 (32.5)	13599 (29.6)
No	1015 (57.8)	21942 (71.5)	6875 (70.7)	2574 (67.5)	32406 (70.4)
Paternal socioeconomic status (N)(%)					
High	255 (15.1)	13816 (46.3)	5303 (56.3)	2241 (60.8)	21615 (48.4)
Middle	1077 (64.0)	12677 (42.4)	2970 (31.5)	1007 (27.3)	17731 (39.7)
Low	352 (20.9)	3366 (11.3)	1151 (12.2)	440 (11.9)	5309 (11.9)
Paternal asthma (N) (%)					
Yes	232 (12.6)	2579 (8.3)	694 (7.1)	243 (6.2)	3748 (8.1)
No	1614 (87.4)	28339 (91.7)	9116 (92.9)	3680 (93.8)	42749 (91.9)
Paternal allergy (N)(%)					
Yes	386 (21.0)	7574 (24.5)	2277 (23.3)	793 (20.3)	11030 (23.8)
No	1452 (79.0)	23288 (75.5)	7497 (76.7)	3107 (79.7)	35344 (76.2)
TTP (months) (N) (%)					
0	351 (27.8)	6781 (24.7)	1990 (23.8)	590 (18.9)	9712 (24.2)
1–5	619 (49.1)	12572 (46.0)	3238 (38.8)	1120 (35.9)	17549 (43.8)
6–12	197 (15.6)	4449 (16.3)	1401 (16.8)	577 (18.5)	6624 (16.5)
> 12	94 (7.5)	3554 (13.0)	1719 (20.6)	832 (26.7)	6199 (15.5)
Family size (persons in household) (N) (%)					
2	1554 (83.3)	17544 (56.5)	2932 (29.7)	1194 (30.3)	23224 (49.7)
3	311 (16.7)	13505 (43.5)	6928 (70.3)	2753 (69.7)	23497 (50.3)
≥ 4	≤ 5 (0.0)	7 (0.0)	≤ 5 (0.0)	≤ 5 (0.0)	12 (0.0)
Maternal age (years)					
Mean (sd)	23.8 (3.3)	28.9 (3.4)	32.8 (3.5)	35.0 (4.0)	30.0 (4.3)
Maternal BMI (kg/cm ²)					
Mean (sd)	23.5 (4.3)	23.4 (4.1)	23.3 (3.9)	23.2 (4.4)	23.4 (4.1)
Maternal smoking (N) (%)					
Yes	771 (41.4)	7286 (23.5)	2251 (22.8)	977 (24.7)	11285 (24.1)
No	1093 (58.6)	23775 (76.5)		2974 (75.3)	35454 (75.9)
Maternal allergy (N)(%)					
Yes	602 (32.3)	9708 (31.3)	3072 (31.2)	1234 (31.3)	14616 (31.3)
No	1261 (67.7)	21298 (68.7)	6772 (68.8)	2706 (68.7)	32037 (68.7)

Table 2
Prevalence ratios (PRs) for asthma in 7-year old offspring according to subgroups of paternal age.

		N	Asthma cases	Prevalence	Crude PR	Adjusted PR ^a
Paternal age (years)	≤ 24	1991	384	0.19	1.55	1.40 (1.26,1.55)
	Ref 25–34	32415	4021	0.12	1	1
	35–39	10267	1049	0.10	0.82	0.84 (0.78,0.89)
	≥ 40	4112	421	0.10	0.83	0.85 (0.77,0.94)

^a Adjusted for paternal smoking, paternal asthma and paternal SES.

group.

Our finding of a positive association between paternal age of ≤ 24 years and childhood asthma was also reported in the above mentioned study where they found a tendency towards a slight positive association between paternal age in mid-childhood for fathers ≤ 24 years and risk of childhood asthma. Previous studies have also found that younger paternal age has been associated with increased risk of adverse birth outcomes independently of maternal confounders [38,39]. We found that the young paternal age effect was independent of maternal age in interaction tests, while adjustment for maternal age in the sensitivity analysis attenuated the effect estimates most likely due to the strong correlation between paternal and maternal age. Young maternal age is associated with adverse child outcomes such as asthma in offspring, and our result indicates that also young paternal age could be a risk factor for asthma in offspring [13,14]. We adjusted for paternal factors such as paternal SES and smoking in the multivariate analysis, but we had no information on alcohol use. Alcohol use has been associated with some adverse reproductive outcomes and is more prevalent in young fathers especially teenage fathers [40]. Moreover, we could not account for emotional and financial support which may affect the fathers' and mothers' emotional, physical and reproductive health differently across age groups. The mechanisms by which being a young father may contribute to an increased risk of asthma in offspring are not known and warrant further investigation. The same mechanism could be applied to allergy in the offspring, and this further support that asthma is correlated with allergy and may have similar causes.

The strengths of the study include the use of prospectively collected data from a large and well-documented birth cohort (DNBC) which provided sufficient statistical power to detect even relatively weak associations and reduced the risk of bias by adjusting for a large number of potential confounders.

Our main concern in this study is selection bias due to attrition related to the outcome of interest. It might be possible that included parents to the children who developed asthma obtained from completing the 7-year follow-up due to lack of resources of having a sick child. However, there is no reason to believe that this attrition related to asthma in childhood should differ by the age of the father leading to non-differential selection. Also, we found no indication of selection bias in the sensitivity analysis with inclusion of information on asthma in children from the 11-year follow-up. The participation rate went from 63% to 48%, but the estimated PR's were similar in the two data collections.

Information about doctor-diagnosed asthma was based on maternal reports. Although standardized and validated asthma questions were used, we can not rule out the risk of non-differential misclassification. We only included information provided by the parents, and no diagnoses were therefore confirmed or provided directly by a physician. Information on paternal age is accurate because the information was extracted from the Danish Civil Registration System. We have no reason to believe that the quality of the data depends on the age of the father, and any random misclassification will often bias the results toward the null.

5. Conclusions

Our findings suggest that paternal age ≥ 35 years may be associated with a decreased prevalence of asthma in childhood, and paternal age ≤ 24 years is associated with an increased prevalence compared with children born of fathers of 25–34 years of age. The potential causes of higher asthma prevalence among offspring of young fathers warrant further investigation.

Ethical approval

All women in the DNBC gave written informed consent at the entry to the cohort. Data were analyzed encrypted without direct personal identification. The storage and linking of the data in this study were approved by the Danish Data Protection Agency (J.nr. 2015-57-0002) and by the DNBC Steering Committee (project.nr. 2016-33).

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Authors' contributions

AMLT, JO, AND VE all substantially contributed to study idea, design and interpretation of data. AHR performed expert statistical support. AMLT drafted the article and analyzed the data. All authors revised the paper critically and gave their approval of the final version.

Conflicts of interest

None.

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