

Letter to the Editor

Association between parental age and asthma in a population-based register study

To the Editor:

Asthma is one of the most common chronic diseases in childhood and adolescence. Risk factors have been sought *in utero* and in the early fetomaternal environment.¹ Some studies have suggested that children of very young mothers are at increased risk of asthma.^{2,3} Others claim that the risk is not related to the age of the mother but rather report bias for health outcomes in firstborns as opposed to younger siblings.⁴ Paternal age as a risk factor for asthma in offspring has not yet been studied and could shed additional light on mechanisms related to fetomaternal effects or bias.

Parental age as a risk factor for negative health outcomes has obtained much interest in the area of neuropsychiatric disease, including bipolar disorder and academic morbidity. Although the mechanism behind this association is unknown, a causal link involving *de novo* mutations, epigenetic alterations, and/or fetal programming has been suggested.⁵ There are also recent data to support that the diversity in the mutation rate of single nucleotide polymorphisms is dominated by the father's age at the child's conception.⁶ It has been suggested that the negative health outcomes related to parental age are confounded by parental or family characteristics. By using family designs, we can rule out all genetic and environmental factors shared by siblings, half-siblings, or cousins and thus strengthen causal inferences.⁷

The aim of this study was to (1) estimate the association between parental (both maternal and paternal) age and asthma in offspring by using a family design (half-siblings and cousins from the mother's sister and father's brother)⁸ and (2) to explore potential confounders, mediators, and effect modifiers related to the association.

The Swedish Medical Birth Registry (MBR) was used to establish 2 cohorts of children, one consisting of children born during July 2005-2009 (early-childhood cohort) and another of children born during 1999-2002 (midchildhood cohort). We excluded children with unknown fathers and multiple births, leading to 445,727 children in the early-childhood cohort and 333,032 children in the midchildhood cohort.

Asthma was defined by using the National Patient Register (NPR) and the Swedish Prescribed Drug Register (SPDR). Asthma in the early-childhood cohort was defined as a diagnosis from the NPR combined with dispensed asthma medication in the SPDR. Asthma in the midchildhood cohort was defined as either a diagnosis from the NPR during the seventh year of life or dispensed asthma medication in the SPDR during the seventh year of life.⁹

We used parental age both as continuous variables and categorized into 5-year intervals, with age of 25 to 29 years at the offspring's birth as the reference category. Continuous age variables per 5-year increase were also used.

For the early-childhood cohort, we used Cox regression with attained age as the underlying time scale to estimate hazard ratios of the association between parental age and asthma in offspring. Because of nonproportional hazards, age-specific hazard ratios are presented. For the midchildhood cohort, we used logistic regression to estimate the prevalence of odds ratios of the association between parental age and asthma in offspring.

Robust SEs were used to account for familial clustering of observations.

We used family designs to account for unmeasured confounding shared within families with asthma-discordant half-siblings/cousins. This was implemented by using stratified Cox regression and conditional logistic regression with conditioning on half-sibling or cousin pairs. Details on Methods, Family design, and Statistical analysis are provided in this article's Online Repository at www.jacionline.org.

The study was approved by the Regional Ethical Review board in Stockholm, Sweden.

Cumulative asthma incidence in the early-childhood cohort was 3.9% during follow-up, whereas asthma prevalence in the midchildhood cohort was 6.3%. Parental age distributions in both cohorts were similar, as were other background characteristics of children (sex and birth weight) and parents (parental education, maternal body mass index [BMI], and parity; see [Table E1](#) in this article's Online Repository at www.jacionline.org).

Estimates of age-specific hazard ratios for the early-childhood cohort and odds ratios for the midchildhood cohort adjusted for parental education, maternal BMI, and parity are presented in [Fig 1](#). During the first year of life, higher maternal and paternal age were associated with lower rates of asthma in offspring. This pattern was more pronounced for incidence at age 1 to 4.5 years. In analysis of the midchildhood cohort, maternal age groups of 24 years or younger were associated with lower odds of asthma in offspring, whereas the odds of asthma decreased with higher paternal age.

In analyses using parental age as a continuous measure and family designs to account for unmeasured confounding shared within families, lower rates of asthma in offspring with advancing parental age remained in the early-childhood cohort after adjustment for confounders, which were statistically significant for asthma-discordant cousins ([Table I](#)). In the midchildhood cohort the lower odds were stable only for paternal but not maternal age in the cohort analyses. Subanalyses in both cohorts showed that the results were not driven by the oldest age category.

We found an association between decreasing parental age and asthma in early childhood. This effect was independent of familial and other potentially confounding factors, such as parity and the other parent's age. In midchildhood there were no consistent associations.

Previous studies have not accounted for factors shared within families and are thus comparable primarily with the cohort results in this study, with which the previously seen patterns generally agree for factors shared within families.^{2,3}

The strengths of this study are that we had access to population-based data with rich information about covariates and, importantly, information on family relations, allowing several analyses that extend beyond previous publications. The limitations of family designs include the requirement of exposure- and outcome-discordant sib or cousin pairs.⁸ When individual subjects within a family have children together with partners within the same age range, exposure discordance becomes less common, and larger populations are needed to reach statistical significance. Family designs allow us to rule out shared environmental factors but do not tell us which within-family environmental factors were of importance.

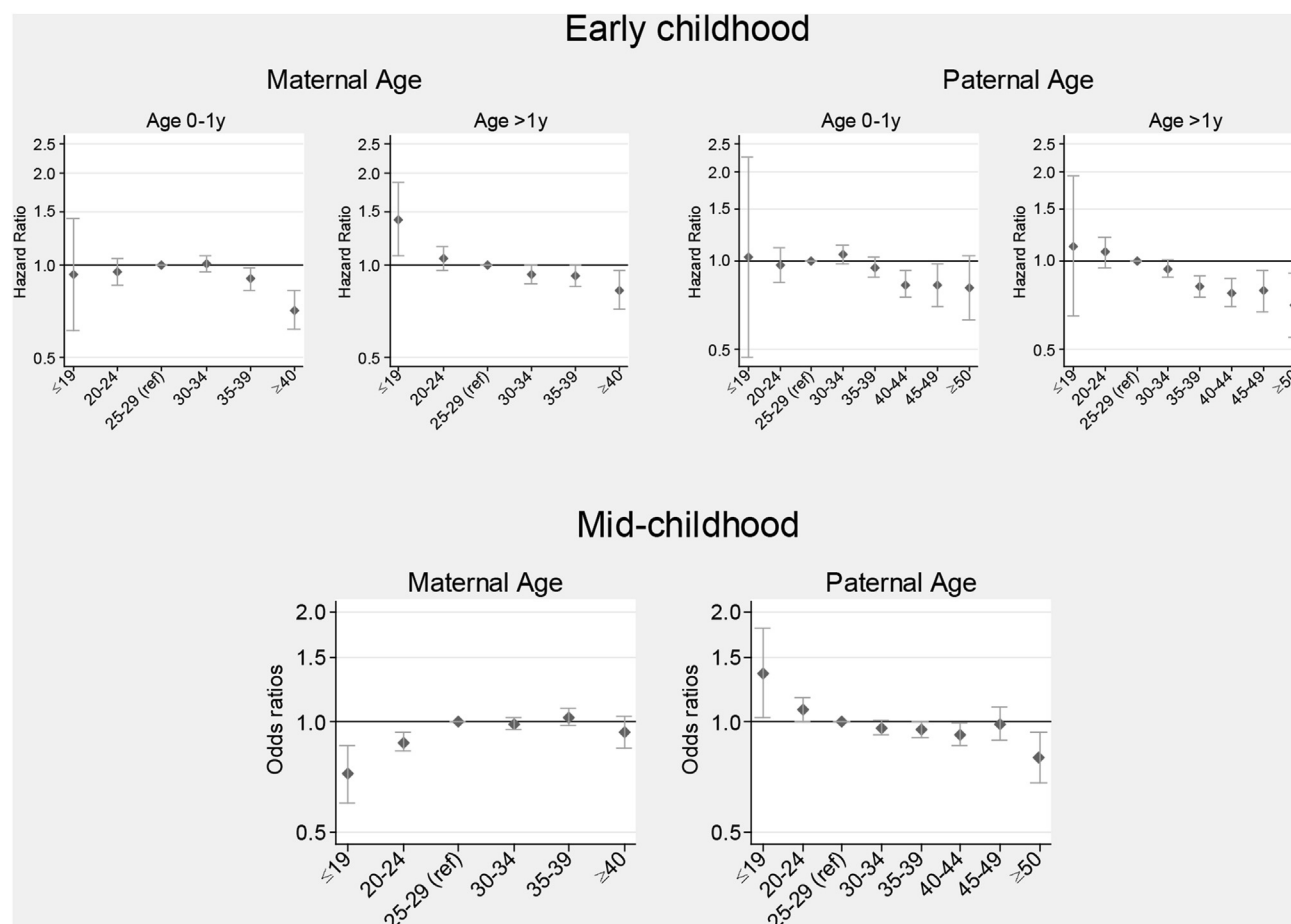


FIG 1. Association between parental age and asthma in offspring. Hazard ratios for the early-childhood cohort and odds ratios for the midchildhood cohort with associated 95% CIs using the age group of 25 to 29 years as a reference category are shown. Hazard ratios and odds ratios of maternal and paternal ages were mutually adjusted for each other, parity, socioeconomic factors, and maternal BMI in early pregnancy.

TABLE I. Within-family associations between parental age (per 5-year increase) and asthma in offspring from stratified Cox regression and conditional logistic regression, conditioning on half-sibling or cousin pairs

	Early childhood				Midchildhood		
	Adjusted HR (95% CI)*	Adjusted HR (95% CI)†	Adjusted HR (95% CI)‡		Adjusted OR (95% CI)*	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡
Cohort analysis				Cohort analysis			
Maternal age	0.99 (0.97-1.01)	0.95 (0.93-0.97)	0.94 (0.92-0.97)	Maternal age	1.00 (0.98-1.02)	1.02 (1.00-1.04)	1.03 (1.00-1.05)
Paternal age	0.95 (0.93-0.96)	0.93 (0.92-0.95)	0.94 (0.92-0.96)	Paternal age	0.96 (0.95-0.98)	0.97 (0.95-0.98)	0.97 (0.96-0.99)
Half-sibling analysis				Half-sibling analysis			
Maternal age	0.92 (0.65-1.31)	0.83 (0.56-1.24)	0.45 (0.19-1.09)	Maternal age	1.41 (1.02-1.96)	1.45 (0.99-2.11)	1.37 (0.83-2.25)
Paternal age	0.83 (0.57-1.21)	0.83 (0.57-1.20)	0.54 (0.26-1.14)	Paternal age	0.93 (0.67-1.28)	0.93 (0.68-1.29)	0.94 (0.60-1.46)
Cousin analysis				Cousin analysis			
Maternal age	0.95 (0.89-1.01)	0.88 (0.82-0.94)	0.85 (0.78-0.93)	Maternal age	0.97 (0.91-1.03)	1.00 (0.94-1.06)	1.01 (0.93-1.08)
Paternal age	0.97 (0.91-1.02)	0.95 (0.90-1.00)	0.95 (0.89-1.02)	Paternal age	1.01 (0.96-1.06)	1.01 (0.96-1.07)	1.00 (0.95-1.07)

HR, Hazard ratio; OR, odds ratio.

*Maternal and paternal age are mutually adjusted for each other.

†Maternal and paternal age are mutually adjusted for each other, with additional adjustment for parity.

‡Maternal and paternal age are mutually adjusted for each other, with additional adjustment for parity, socioeconomic status, and maternal BMI in early pregnancy.

In conclusion, this study confirms the decreasing risk of early-childhood asthma with maternal age and reports that this is also true for paternal age and that the association is independent of shared familial factors. We were not able to

identify important mediators and effect modifiers related to the association, which calls for studies to explore mechanisms related to *de novo* mutations and the fetomaternal and early-life environment.

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Supported through the Swedish Research Council through grant no. 2011-3060 and the Swedish Initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) through framework grant no. 340-2013-5867, the Swedish Heart-Lung Foundation, the Åke Wiberg Foundation, Sällskapet Barnavård, grants provided by the Stockholm County Council (ALF project nos. 520344 and 530422), the Strategic Research Program in Epidemiology at Karolinska Institutet, and the National Institute of Child Health and Human Development.

Disclosure of potential conflict of interest: C. Almqvist has received research support from the Swedish Research Council, the Swedish Heart-Lung Foundation, the Åke Wiberg Foundation, Sällskapet Barnavård, the Stockholm County Council (ALF project), and the Strategic Research Program in Epidemiology at Karolinska Institutet. The rest of the authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2015.04.006>

METHODS

Family design

Family design provides the opportunity to study the association between parental age and asthma, adjusting for familial factors.^{E1} We aimed to address the association between exposure to parental age and subsequent asthma by examining a prospective nationwide cohort of children followed from the start of pregnancy up to school age. By exploring the association within families using half-sibling and cousin control subjects, we adjust for familial factors, thereby further assessing causality.

To contribute new knowledge on the causes and consequences of childhood health problems requires use of methods that account for familial confounding. A traditional between-family analysis compares unrelated subjects from different families. A within-family analysis compares subjects within the same family (eg, twins, siblings, and/or cousins), thus adjusting for all potential confounders that are constant within the family.

Sibling comparison is one of the strongest family designs for studying early risks that can vary among siblings. It can rule out alternative mechanisms that confound associations between parental age and subsequent childhood asthma, including all unmeasured genetic and environmental factors shared by siblings. Full siblings share half of their segregating genes and some intrauterine exposures and parental factors. Other type of relatedness (eg, half-siblings who share 25% of their segregating genes and full cousins who share 12.5% of their segregating genes) can be used to compare multiple groups of relatives who differ in their exposure to the putative environmental risk and their genetic risk.^{E1} If associations seen in a cohort of siblings remain in within-family analyses, then factors specific to each subject are assumed to be involved in the underlying causal pathways. On the contrary, if the statistical association is diluted in the within-family analyses, it is a sign of confounding by familial factors. Comparison of these differentially exposed relatives, who share different amounts of genes and environmental factors, will help identify whether these confounding factors are genetic or environmental in origin, which will elucidate the underlying mechanisms.

Statistical methods

The MBR was used to establish 2 cohorts of children, one consisting of children born during July 2005-2009 (early-childhood cohort) and another of children born during 1999-2002 (midchildhood cohort). We excluded children with unknown fathers and multiple births, leading to 445,727 children in the early-childhood cohort and 333,032 children in the midchildhood cohort. For the within-family analyses, we identified subsamples of half-sibling and cousin pairs discordant on asthma within these cohorts. In the early-childhood cohort we identified 232 half-sibling pairs and 6,347 cousin pairs discordant

on asthma. In the midchildhood cohort we identified 195 half-sibling pairs and 5,579 cousin pairs discordant on asthma.

We used parental age both as a continuous variable and categorized into 5-year intervals, with age 25 to 29 years at birth of offspring as the reference category. Continuous age variables per 5-year increases were also used.

Confounding factors that we considered were pre-pregnancy maternal BMI retrieved from the MBR, educational level, disposable income of fathers at year of the offspring's birth, and a neighborhood deprivation index.^{E2}

For the early-childhood cohort, we used Cox regression with attained age as the underlying time scale to estimate hazard ratios of the association between parental age and asthma in offspring. Each subject was followed for his or her first asthma event or censored at emigration, death, or end of follow-up at December 31, 2009, whichever came first. Schoenfeld residuals together with likelihood ratio tests of interaction terms between parental age variables and the underlying time scale were used to evaluate the proportional hazards assumption. The hazard rates for both variables were significantly nonproportional over follow-up, and thus we estimated age-specific hazard ratios (<1 year of follow-up and ≥1 year of follow-up). For the midchildhood cohort, we used logistic regression to estimate prevalence odds ratios of the association between parental age and asthma in offspring. Robust SEs were used in the analyses to account for familial clustering of observations.

For the half-sibling/cousin analyses, we used stratified Cox regression and conditional logistic regression with conditioning on half-sibling/cousin pairs discordant on asthma, thereby adjusting for all factors that are shared within each half-sibling/cousin set.

We used several models with different levels of confounding adjustment. First, we fitted a model including maternal and paternal age. Second, we fitted a model with maternal and paternal age adjusted for parity. Third, we fitted a model with maternal and paternal age adjusted for parity, socioeconomic factors, and maternal BMI in early pregnancy. We also studied possible effect modification by birth order of children, stratifying on firstborns and children of higher birth order, respectively. Likelihood ratio tests of interaction terms showed no significant effect modification.

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TABLE E1. Characteristics of offspring and parents

	Early-childhood cohort, no. (%)	Midchildhood cohort, no. (%)
No.	445,727	333,032
Sex		
Boy	229,361 (51.5)	171,366 (51.5)
Girl	216,366 (48.5)	161,666 (48.5)
Birth weight (g)		
≤2,999	59,789 (13.4)	41,737 (12.5)
3,000-3,499	144,277 (32.4)	100,993 (30.3)
3,500-3,999	157,322 (35.3)	118,664 (35.6)
4,000-4,499	67,461 (15.1)	55,460 (16.7)
≥4,500	16,350 (3.7)	14,593 (4.4)
Missing	528 (0.1)	1,585 (0.5)
Maternal BMI (kg/m ²)		
<18.5	9,720 (2.2)	7,015 (2.1)
18.5-24.9	247,727 (55.6)	179,401 (53.9)
25.0-29.9	99,093 (22.2)	70,990 (21.3)
≥30	46,727 (10.5)	29,301 (8.8)
Missing	42,460 (9.5)	46,325 (13.9)
Educational level of mothers in 2004		
Elementary/high school	216,075 (48.5)	200,390 (60.2)
College/university	187,822 (42.1)	129,387 (38.9)
Missing	41,830 (9.4)	3,255 (1.0)
Educational level of fathers in 2004		
Elementary/high school	304,932 (68.4)	256,705 (77.1)
College/university	119,207 (26.7)	75,079 (22.5)
Missing	21,588 (4.8)	1,248 (0.4)
Parity		
1	200,116 (44.9)	146,588 (44.0)
2	164,120 (36.8)	119,804 (36.0)
3	57,894 (13.0)	46,337 (13.9)
4	15,339 (3.4)	13,362 (4.0)
≥5	8,258 (1.9)	6,941 (2.1)
Maternal age (y)		
0-19	5,114 (1.1)	4,451 (1.3)
20-24	50,074 (11.2)	39,318 (11.8)
25-29	121,041 (27.2)	106,912 (32.1)
30-34	161,868 (36.3)	116,563 (35.0)
35-39	87,482 (19.6)	54,924 (16.5)
40-44	20,148 (4.5)	10,864 (3.3)
Paternal age (y)		
0-19	2,056 (0.5)	1,763 (0.5)
20-24	22,744 (5.1)	17,956 (5.4)
25-29	85,067 (19.1)	76,252 (22.9)
30-34	152,687 (34.3)	117,881 (35.4)
35-39	113,315 (25.4)	76,753 (23.0)
40-44	48,390 (10.9)	28,710 (8.6)
45-49	14,846 (3.3)	9,438 (2.8)
50-54	6,622 (1.5)	4,279 (1.3)
Maternal age (y), median (IQR [range])	31 (27-34 [14-55])	30 (27-34 [14-55])
Paternal age (y), median (IQR [range])	33 (30-37 [14-80])	32 (29-36 [14-75])
Asthma		
No	428,494 (96.1)	312,130 (93.7)
Yes	17,233 (3.9)	20,902 (6.3)