

Maternal fecundity and asthma among offspring—is the risk programmed preconceptionally? Retrospective observational study

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Objective: To evaluate the association between maternal fecundity factors and time to pregnancy and risk of asthma in offspring.

Design: Retrospective observational hospital-based birth cohort study.

Setting: A university-based obstetrics and gynecology department.

Patient(s): A total of 40,914 women, who delivered between 1989 and 2007, were linked with the register for asthma reimbursement (n = 2,577) for their offspring. Fecundity factors were recorded during pregnancy. Logistic regression analyses were used.

Intervention(s): None.

Main Outcome Measure(s): Asthma among offspring.

Result(s): The risk of asthma was significantly increased if the mother had any infertility problems (adjusted odds ratio [adjusted OR] 1.39, 95% confidence interval [CI] 1.19–1.63), medical infertility treatment (aOR 1.43, 95% CI 1.13–1.80), or any infertility treatment (aOR 1.50, 95% CI 1.26–1.79). The risk of asthma among offspring was also higher among mothers who had more than two miscarriages (aOR 1.25, 95% CI 1.04–1.51) and time to pregnancy over 3 months (aOR 1.25, 95% CI 1.07–1.45).

Conclusion(s): These findings suggest that maternal subfertility exposes offspring to an increased risk of asthma.

Clinical Trial Registration Number: The study is registered in Kuopio University Hospital register (TUTKI): ID 5302448. (Fertil Steril® 2012; ■ : ■ – ■ . ©2012 by American Society for Reproductive Medicine.)

Key Words: Asthma, fecundity, childhood, maternal subfertility, pregnancy

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Asthma and allergies are the most common chronic diseases among children. The prevalence of these diseases has substantially increased during the past few decades in several Westernized countries (1–3), including Finland (4). Intrauterine life and early infancy are suggested to be

critical time periods during which specific events and exposures may affect the risk for the development of allergic diseases in childhood (5, 6). There are some well-known strong prenatal risk factors of asthma, such as preterm birth and maternal smoking during pregnancy (2, 7, 8), and many

possible suggested risk factors such as maternal parity and age, various prenatal maternal complications, and the mode of delivery (2, 5, 8–10). However, the backgrounds to most of the prenatal and obstetric risk factors have not yet been fully explored.

Since 1978, assisted reproduction technology (ART) has evolved greatly, such that at present approximately 3% of all infants in Finland are born as a result of IVF (11). The proportion would be even higher if children born after ovulation induction were to be included. Children born after ART are generally healthy at birth and during early childhood (12, 13) and generally,

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are developmentally similar to children born after spontaneous conception (12, 14, 15). Low birth weight and prematurity contribute to the majority of early neonatal problems, being partly explained by the higher incidence of multiple pregnancies associated with ART. However, the postnatal long-term health of children conceived by ART has not been much studied.

Although the association between prenatal factors and asthma among offspring has generated interest, only three studies (8, 13, 16) as yet have focused on the association between maternal fecundity, other than parity, and the risk of asthma or wheezing disease in offspring. In the present study, using single university hospital-based birth register data on 40,914 women, we aimed to clarify whether or not maternal fertility factors before the index pregnancy were related to the risk of asthma among offspring.

MATERIALS AND METHODS

The study population was derived from a clinical birth database concerning a total population of 42,865 infants born at Kuopio University Hospital between 1989 and 2007 after 22 completed weeks of gestation. We excluded multiple pregnancies, stillbirths, and neonatal deaths. After these exclusions, data on 40,914 women with singleton live-born infants were linked with data on the register for reimbursement at the Social Insurance Institution of Finland for asthma medication for their offspring aged 1–19 years ($n = 2,577$). The study population is shown in [Supplemental Figure 1](#) (available online).

Information on maternal prepregnancy characteristics was based on data from self-administered questionnaires at 20 weeks of pregnancy. Missing data were subsequently complemented by nurse and midwife interviews at visits to prenatal maternal clinics or labor wards at Kuopio University Hospital. The questionnaire covered 75 background items. Information on pregnancy complications, pregnancy outcome, and the neonatal period was collected as part of clinical work and added to the database by the nurses and midwives who took care of delivery and the neonatal period. All childbearing women gave informed consent for the register study at the time of data collection.

Information on the need for antiasthmatic medication during childhood was obtained from the Drug Prescription Register of the Social Insurance Institution. In Finland, all medication prescribed by physicians and reimbursed by the National Sickness Insurance Scheme is registered in the Drug Prescription Register.

Logistic regression analyses were used to investigate the multivariate-adjusted associations between different predictors and the fact of having ever being diagnosed with asthma. In the analyses, all models were adjusted for the following confounding factors: child's gender, maternal asthma at the time of pregnancy (no vs. yes), maternal parity (0, 1 vs. ≥ 2), maternal age (≤ 25 , 26–35, ≥ 36 years), gestational age at birth (≤ 36 , 37–40 vs. ≥ 41 weeks), mode of delivery (vaginal vs. cesarean), smoking during pregnancy (no vs. yes, smoking >5 cigarettes per day), and prepregnancy body mass index (BMI; <21 , 22–25, >25 kg/m²).

The fecundity variables evaluated in this study were [1] previous pregnancies (0, 1, >2); [2] number of miscarriages (0, 1, ≥ 2) and [3] induced artificial abortions; [4] self-reported infertility; [5] time to pregnancy (<3 , 4–6, >7 months); [6] index pregnancy by medically assisted treatment; [7] infertility treatment in the index pregnancy by way of insemination or [8] ART (including IVF and intracytoplasmic sperm injection [ICSI] fertilization); and [9] index pregnancy by way of any infertility treatment. The cutoff level of significance was set at $P < .05$. The study was approved by Institutional Review Board and Pohjois-Savo committee of research ethics (reference 93//2008).

RESULTS

Of 40,914 live-born children, 2,577 (6.2%) had had asthma at some time, with a mean age of 4.2 years (range, 1–19 years) at the onset of asthma reimbursement. Asthmatic children were more frequently male, and they were born more frequently by cesarean delivery, with lower gestational age, with lower Apgar scores, and to younger mothers compared with controls ([Table 1](#)). No differences were detected in prepregnancy BMI, weight gain during pregnancy, or parity between cases and controls.

In multivariate analysis, the risk of asthma was significantly higher in children if the mother had had a higher number of previous pregnancies, more miscarriages, had ever experienced self-reported infertility problems, a prolonged time to pregnancy of more than 3 months, or had had any kind of infertility treatment ([Table 2](#)). The ART pregnancies were not found to increase the risk of asthma in childhood significantly and the number of induced abortions was not associated with the risk of asthma among offspring. Multivariate adjustment did not change the observed associations significantly. The risk of asthma was highest in children conceived by IUI, but the number was too low to reach statistical significance.

Because a woman's age is a strong determinant of miscarriages and infertility, we evaluated separately the effect of maternal age on selected fecundity factors ([Table 3](#)). The most significant associations were observed among mothers aged 26–35 years, whereas no significant associations were observed among mothers aged 36 years or older. Accordingly, the odds ratio for self-reported infertility was lowest in the oldest age group, suggesting that the fecundity factors might have had less importance in the oldest mothers. However, for most outcomes the odds ratios were not very divergent in the different age groups.

Similarly, because time to pregnancy is strongly correlated with ART, we evaluated separately children who were conceived spontaneously ([Table 4](#)). In this subgroup analysis, the significant associations between a higher number of earlier miscarriages and prolonged time to pregnancy versus an increased risk of asthma at any time among offspring remained.

DISCUSSION

The overall prevalence of childhood asthma was 6.3%, which corresponded well to the expected rate in Finland (17, 18). The

TABLE 1

Basic characteristics of the study population in relation to asthma at any time among offspring.

	Controls (n = 38,337)	Asthma (n = 2,577)	P value
Maternal age (y)	29.0 (±5.5)	28.7 (±5.4)	.006
Maternal parity	1.0 (±1.3)	1.0 (±1.2)	.293
No. of previous pregnancies	1.4 (±1.6)	1.5 (±1.6)	.020
Maternal asthma	1,025 (2.7)	114 (4.4)	<.001
Maternal weight gain during pregnancy (kg) ^a	13.5 (±5.3)	13.4 (±5.5)	.200
Maternal prepregnancy BMI (kg/m ²) ^b	23.2 (±4.4)	23.4 (±4.5)	.106
Maternal smoking (>5 cigarettes/d) during pregnancy	2,104 (5.5)	182 (7.1)	<.001
Men	19,313 (50.4)	1,557 (60.4)	<.001
Mean age at asthma diagnosis (y)		4.2 (±3.0)	
Gestational age at birth (wk)	39.3 (±2.0)	38.7 (±3.0)	<.001
Preterm delivery	2,094 (5.6)	284 (11.3)	<.001
Birth weight (g)	3,521 (±580)	3,399 (±767)	<.001
Head circumference at birth (cm)	35.0 (±1.7)	34.7 (±2.2)	<.001
Abdominal circumference at birth (cm) ^c	33.9 (±2.0)	33.7 (±2.1)	.419
Apgar scores at 5 min <7	652 (1.7)	67 (2.6)	<.001
Placental weight (g)	618 (±149)	610 (±150)	<.002
Vaginal delivery	31,893 (83.2)	2,046 (79.4)	
Cesarean section	6,444 (16.8)	531 (20.6)	<.001

Note: Values for controls and asthma group are mean (±2 SD) or N (%). BMI = body mass index.

^a Data available on 30,849 women.

^b Data available on 38,882 women.

^c Data available on 36,948 women.

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main finding in the present study was that the risk of asthma among offspring was significantly higher in children born to mothers who experienced fertility problems before pregnancy. This finding is based on three distinct associations. First, we found that a higher number of maternal earlier miscarriages, but not induced abortions, was a significant risk factor for developing asthma at any time among offspring, the risk being 1.25-fold higher in those children of mothers with two or more earlier miscarriages compared with those with no earlier miscarriages. Second, children born to mothers with infertility problems at any time of life before the index pregnancy had a 1.39-fold risk of asthma in childhood compared with children of mothers without such problems. Third, the risk of asthma among offspring was 1.3 times higher in children born to mothers with a prolonged time to pregnancy (>7 months) compared with mothers with 0–3 months to pregnancy. Interestingly, a history of miscarriages played a minor role in the risk of asthma among offspring in older mothers, in whom cytogenetic abnormalities are known to be a more common cause of miscarriages. Therefore, miscarriages at a younger age appeared to be the risk markers, probably reflecting immune mechanisms.

Maternal fecundity factors, other than parity, have rarely been evaluated as risk factors of asthma among offspring, probably because of long latency between exposure and outcome. We are aware of only three such studies. A large Finnish register-based case-control study showed that a higher number of maternal earlier miscarriages was associated with a risk of asthma in children diagnosed before the age of 3 years (8). In a recent Swedish population-based study Finnström et al. (13) showed an increased risk of asthma among offspring conceived by IVF and in contrast, a small Turkish study (16) showed no association between IVF and asthma among

offspring. Our study is the first to show that a prolonged time to pregnancy is also associated with an increased risk of asthma among offspring that may be partly explained by infertility treatment. On the other hand, the same was also found among children who were conceived spontaneously, suggesting that other problems in conception, such as immunologic imbalance between the mother and fetus (19, 20), might also play a role. Indeed, pregnancy complications, such as preeclampsia, miscarriage, recurrent pregnancy loss, intrauterine growth retardation, and premature birth (before 37 weeks of pregnancy), could be associated with abnormal immunologic interactions at the fetal-maternal interface (21). Such conditions are associated with low or undetectable levels of soluble HLA-G in the maternal circulation and interestingly, Ober (22) showed in 2005 that HLA-G is an asthma susceptibility gene in multiple populations (23, 24).

Maternal asthma and allergic diseases do not lower fertility in the general population (20, 25, 26) and all the analyses were adjusted for maternal asthma. Therefore, maternal asthma was unlikely to explain the present findings. One possible explanation is related to the recent suggestion that maternal stress and anxiety during pregnancy could increase the risk of asthma later among children (22–24). Maternal anxiety or stress could increase blood cortisol levels during pregnancy and furthermore, transplacental passage of cortisol could have a programming effect on development of the HPA axis in the fetus, leading to alterations of stress responses after birth. Pregnancies conceived by IVF and after miscarriages may be more stressful, with an altered antenatal programming effect (27).

Possible mechanisms behind a prenatal programming effect of infertility or subfertility with regard to the development of asthma might also operate through epigenetic

TABLE 2

Association between maternal fecundity factors at the time of index pregnancy and the risk of asthma at any time among offspring.

	Total N (%)	Asthma N (%)	OR 95% CI	aOR 95% CI
Previous pregnancies				
0	12,942 (31.6)	737 (5.7)	1	1
1	12,609 (30.8)	839 (6.7)	1.18 (1.07–1.31)	1.23 (1.05–1.43)
≥2	15,363 (37.5)	1,001 (6.5)	1.15 (1.05–1.27)	1.24 (1.03–1.48)
P value				.025
Total No. of earlier miscarriages				
0	33,568 (82.0)	2,072 (6.2)	1	1
1	5,639 (13.8)	375 (6.7)	1.08 (0.97–1.21)	1.09 (0.97–1.22)
≥2	1,707 (4.2)	130 (7.6)	1.25 (1.04–1.51)	1.25 (1.04–1.51)
P value				.034
Total No. of induced abortions				
0	36,460 (89.1)	2,310 (6.3)	1	1
1	3,794 (9.3)	230 (6.1)	0.95 (0.83–1.10)	0.93 (0.80–1.07)
≥2	660 (1.6)	37 (5.6)	0.89 (0.63–1.22)	0.81 (0.58–1.13)
P value				.28
Earlier self-reported infertility				
No	38,572 (94.3)	2,390 (6.2)	1	1
Yes	2,342 (5.7)	187 (8.0)	1.31 (1.13–1.53)	1.39 (1.19–1.63)
P value				.001
Time to pregnancy (mo) ^a				
0–3	10,615 (57.5)	660 (6.2)	1	1
4–6	3,506 (19.0)	265 (7.6)	1.23 (1.06–1.43)	1.25 (1.07–1.45)
≥7	4,345 (23.5)	331 (7.6)	1.24 (1.08–1.43)	1.30 (1.13–1.50)
P value				.001
Index pregnancy by medical infertility treatment				
No	39,932 (97.6)	2,496 (6.3)	1	1
Yes	982 (2.4)	81 (8.2)	1.35 (1.07–1.70)	1.43 (1.13–1.80)
P value				.003
Index pregnancy by intrauterine insemination				
No	40,827 (99.8)	2,568 (6.3)	1	1
Yes	87 (0.2)	9 (10.3)	1.72 (0.86–3.43)	1.88 (0.94–3.78)
P value				.076
Index pregnancy by ART ^b				
No	40,477 (98.9)	2,544 (6.3)	1	1
Yes	437 (1.1)	33 (7.6)	1.22 (0.85–1.74)	1.27 (0.89–1.83)
P value				.188
Index pregnancy by any infertility treatment ^c				
No	39,217 (95.9)	2,431 (6.2)	1	1
Yes	1,697 (4.1)	146 (8.6)	1.42 (1.20–1.70)	1.50 (1.26–1.79)
P value				.001

Note: Adjusted for the following maternal factors at birth: asthma, parity, age, smoking and prepregnancy body mass index (BMI), plus gestational weeks at birth, gender of child, and mode of delivery. P value for adjusted analysis obtained from the trend test (Wald) in logistic regression models. CI = confidence interval; aOR = adjusted odds ratio; OR = odds ratio.

^a Data available on 18,466 infants born between 1998 and 2007.

^b Assisted reproduction technology (ART) including IVF and intracytoplasmic sperm injection (ICSI).

^c Including ART, insemination, and ovulation induction by clomiphene citrate (CC) and other drugs.

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regulation of the glucocorticoid receptor gene, or changes in the neuroendocrine system or cytokine responses [9]. The ART procedures may themselves affect DNA methylation and gene expression and be disruptive to imprinted gene methylation patterns on the fetal side [9]. Similar methylation differences have been detected in cord blood samples between smoking and nonsmoking mothers and between small-for-gestational-age and appropriate-for-gestational-age infants [9, 28].

One of the strengths of this study was that our birth register data were collected from a single university hospital, with a prospective data collection system and had uniform criteria. The personal identity code system used in Finland gave us the opportunity to link our birth register cohort database to several national registers with high validity and accuracy [29–32]. Some recall bias related to questionnaire-

based data acquired by nurses and midwives cannot be avoided, but it rather underestimated than overestimated the exposure. To be eligible for special reimbursement for asthma medication, it was not sufficient that the physician diagnosed asthma in the patient. The physician, in the case of a child, mostly a pediatrician, needed to fill a special application form confirming that the patient fulfilled the strict diagnostic criteria of the Social Insurance Institution, and even then many applications were turned down. Consequently, the validity of the outcome measure is high.

In summary, our results gave new insight into the importance of the maternal preconceptional health with regard to long-term development of chronic diseases among offspring. Evidence that certain factors increase the incidence of asthma among offspring is emerging, but the results must be interpreted cautiously. To make the results applicable to clinical

TABLE 3

Association between maternal fecundity factors and risk of asthma at any time among offspring in relation to maternal age.

Fecundity variables	< 26 y (N = 11,359)			26–35 y (N = 24,375)			> 35 y (N = 5,180)		
	Total (%)	Asthma (%)	aOR 95% CI	Total (%)	Asthma (%)	aOR 95% CI	Total (%)	Asthma (%)	aOR 95% CI
Earlier miscarriages									
0	10,087 (88.8)	652 (6.5)	1	19,900 (81.6)	1,238 (6.2)	1	3,581 (69.1)	182 (5.1)	1
1	1,063 (9.4)	92 (8.7)	1.31 (1.04–1.65)	3,476 (14.2)	227 (6.5)	1.05 (0.90–1.21)	1,100 (21.2)	56 (5.1)	0.97 (0.71–1.32)
≥ 2	209 (1.8)	19 (9.1)	1.29 (0.79–2.09)	999 (4.1)	80 (8.0)	1.29 (1.02–1.64)	499 (9.6)	31 (6.2)	1.21 (0.81–1.80)
P value			.052			.106			.598
Earlier self-reported infertility									
No	11,140 (98.1)	743 (6.7)	1	22,768 (93.4)	1,405 (6.2)	1	4,664 (90.0)	242 (5.2)	1
Yes	219 (1.9)	20 (9.1)	1.50 (0.94–2.40)	1,607 (6.6)	140 (8.7)	1.48 (1.24–1.78)	516 (10.0)	27 (5.2)	1.04 (0.68–1.58)
P value			.087			.001			.763
Time to pregnancy (mo) ^a									
0–3	2,905 (61.2)	217 (7.5)	1	6,865 (57.9)	403 (5.9)	1	845 (45.2)	40 (4.7)	1
4–6	948 (20.0)	75 (7.9)	1.06 (0.81–1.40)	2,209 (18.6)	166 (7.5)	1.31 (1.09–1.58)	349 (18.7)	24 (6.9)	1.50 (0.88–2.53)
≥ 7	890 (18.8)	67 (7.5)	1.04 (0.78–1.38)	2,780 (23.5)	227 (8.2)	1.45 (1.22–1.72)	675 (36.1)	37 (5.5)	1.24 (0.78–1.98)
P value			.900			.001			.309
Index pregnancy by medical infertility treatment									
No	11,194 (98.5)	752 (6.7)	1	23,717 (97.3)	1,485 (6.3)	1	5,021 (96.9)	259 (5.2)	1
Yes	165 (1.5)	11 (6.7)	1.05 (0.57–1.95)	658 (2.7)	60 (9.1)	1.53 (1.16–2.01)	159 (3.1)	10 (6.3)	1.26 (0.66–2.48)
P value			.880			.002			.474
Index pregnancy by any infertility treatment ^b									
No	11,157 (98.2)	747 (6.7)	1	23,229 (95.3)	1,436 (6.2)	1	4,831 (93.3)	248 (5.1)	1
Yes	202 (1.8)	16 (7.9)	1.26 (0.75–2.12)	1,146 (4.7)	109 (9.5)	1.63 (1.32–2.00)	349 (6.7)	21 (6.0)	1.23 (0.77–1.96)
P value			.380			.001			.389

Note: Adjusted for the following maternal factors at birth: asthma, parity, age, smoking and prepregnancy body mass index (BMI), plus gender of child, gestational weeks at birth, and mode of delivery. P value for adjusted analysis obtained from the trend test (Wald) in logistic regression models. CI = confidence interval; aOR = adjusted odds ratio.

^a Data available on 18,466 infants born between 1998 and 2007.

^b Including assisted reproduction technology (ART), insemination, and ovulation induction by clomiphene citrate (CC) and other drugs.

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TABLE 4

Association between asthma at any time among 39,217 children and maternal fecundity factors after spontaneous conception (no assisted reproduction).

	Total N (%)	Asthma N (%)	OR 95% CI	aOR ^a 95% CI
Previous pregnancies				
0	12,292 (31.3)	673 (5.5)	1	1
1	12,106 (30.9)	795 (6.6)	1.21 (1.09–1.35)	1.25 (1.10–1.43)
≥2	14,819 (37.8)	963 (6.5)	1.20 (1.08–1.33)	1.26 (1.05–1.52)
P value			.001	.003
Total No. of earlier miscarriages				
0	32,268 (82.3)	1,957 (6.1)	1	1
1	5,347 (13.6)	353 (6.6)	1.10 (0.97–1.23)	1.10 (0.97–1.23)
≥2	1,602 (4.1)	121 (7.6)	1.27 (1.05–1.53)	1.26 (1.04–1.53)
P value			.023	.033
Total No. of earlier artificial abortions				
0	34,889 (89)	2,173 (6.2)	1	1
1	3,684 (9.4)	223 (6.1)	0.97 (0.84–1.12)	0.94 (0.82–1.09)
≥2	644 (1.6)	35 (5.4)	0.87 (0.61–1.22)	0.81 (0.57–1.14)
P value			.660	.365
Time to pregnancy (mo) ^b				
0–3	10,443 (59.8)	651 (6.2)	1	1
4–6	3,427 (19.6)	260 (7.6)	1.24 (1.06–1.43)	1.25 (1.08–1.45)
≥7	3,597 (20.6)	251 (7.0)	1.13 (0.97–1.31)	1.17 (1.01–1.37)
P value			.015	.007

Note: P value for adjusted analysis obtained from the trend test (Wald) in logistic regression models. CI = confidence interval; aOR = adjusted odds ratio.

^a Adjusted for the following maternal factors at birth: asthma, parity, age, smoking and prepregnancy body mass index (BMI), plus gender of child, gestational weeks at birth, and mode of delivery.

^b Data available on 18,466 infants born between 1998 and 2007.

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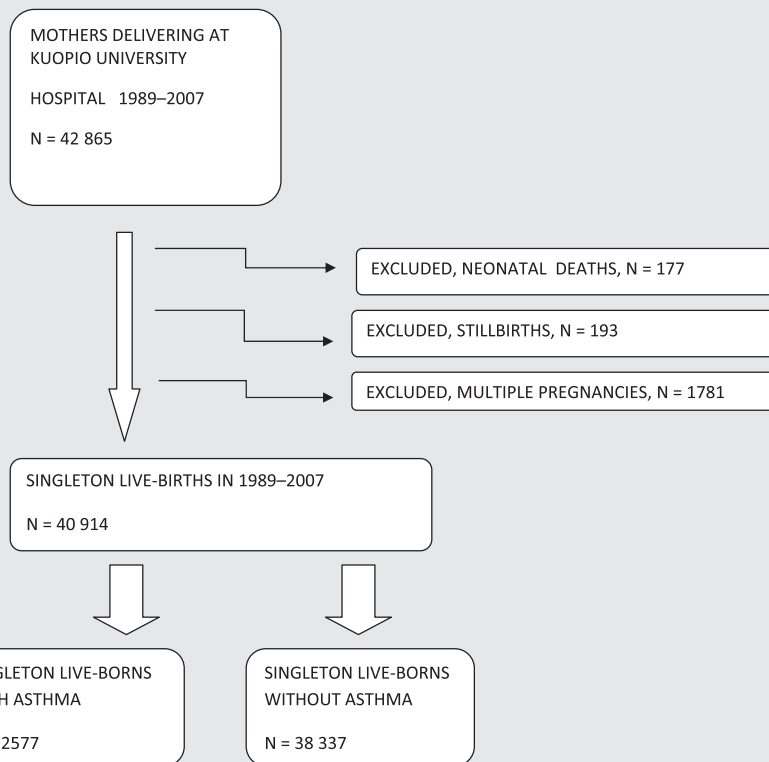
practice, changes in policy and family planning are needed. However, further research is needed to replicate the present results, validate the observed risks, and better understand how this association is mediated.

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SUPPLEMENTAL FIGURE 1



Maternal fecundity and asthma among offspring. Data from Kuopio University Hospital birth register database 1989–2007. Exclusion criteria might exist simultaneously in different groups.

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