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Predictors of atopic disease in children of women with asthma

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To the editor. The prevalence of atopic diseases is increasing¹, and so is the prevalence of cesarean section (CS)². The long-term consequences of CS on the infant's health are unclear, however, epidemiological studies suggest that it is associated with higher risk of obesity during infancy, type 1 diabetes, and allergic diseases³. The aim of this study was to investigate whether mode of delivery, maternal, and perinatal factors differs between asthmatic mothers of children with and without atopic diseases, and between asthmatic mothers and non-asthmatic mothers.

The Management of Asthma during Pregnancy (MAP) program was initiated in 2007 at Hvidovre Hospital, Copenhagen, Denmark and pregnant women with asthma have since then consecutively been recruited for monthly check-ups in the respiratory outpatient clinic. The prospective and still ongoing MAP program has been described in details elsewhere⁴.

All women participating in the MAP program from 2007-2013 received an invitation by letter from 2017-2018 to fill out an online questionnaire about atopic dermatitis (AD), asthma, and allergic rhinitis (AR) in their children.

Asthmatic women participating in the MAP program (i.e. cases) were matched (1:3) with consecutive women giving birth at the same hospital, i.e. representing the background population (i.e. non-asthmatic mothers) (Figure 1). AD was defined according to the U.K. Working Party

definition⁵, asthma was defined based on the question “has a doctor ever said that your child has asthma”, and allergic rhinitis was defined based on the question “has your child ever had allergic rhinitis”.

Data analyses were performed using the program editor in SAS Enterprise Guide 7.1 (SAS institute). Continuous variables were analyzed using the two-tailed Student t-test and binary variables were analyzed by the Chi-square test. For each association a crude model was first analyzed and then adjusted for potential confounders maternal age, smoking status (never smoker vs. ever smoker), marital status and primiparous.

The MAP study is approved by the Research Ethics Committee of the *Capital Region of Denmark* (H-D-2007-0051).

A total of 1,208 asthmatic women (1,283 pregnancies) were invited to fill out the questionnaire, of which 571 (46%) filled out the questionnaire; and after exclusion of 49 due to birth after 2013, 522 were included in the analysis. Women responding to the questionnaire were more often first-time mothers (70% vs 67%, $p=0.03$), and more often never-smokers (76% vs 73%, $p=0.02$) compared to non-responders. No difference was found between responders and non-responders with regards to age, pre-pregnancy weight, marital status, FEV₁/FVC-ratio, fractional exhaled nitric oxide (F_ENO), fetal sex, gestational age of the child, elective CS, maternal anemia, psychiatric co-morbidity, or year of enrolment into the MAP cohort.

The mean age of the included children were 6.7 years (SD 1.79, range 4-12).

A total of 2,782 pregnancies of non-asthmatic mothers were enrolled (32 were excluded due to missing data in the medical records). Women with asthma were more often first-time mothers (65% vs 54%, $p<0.01$) compared to non-asthmatic mothers; however, no statistically significant differences were found for age, BMI, marital status, and smoking status (Table 1).

Among the children of asthmatic mothers, 34% ($n=180$) had AD and 20% ($n=103$) had asthma. Asthmatic mothers with AD children had more often psychiatric co-morbidity compared to asthmatic mothers without AD children (OR 2.12, 95% CI (1.07-4.23)) and also compared to the background population (OR 1.81, 95% CI (1.03-3.18)). There were no significant differences regarding mode of delivery between asthmatic mothers of children with AD or asthma and non-asthmatic mothers (Table 2). There were no significant differences between asthmatic mothers with and without asthmatic children. However, higher maternal BMI was associated with asthma

in the children of asthmatic mothers compared to non-asthmatic mothers (24 kg/m² vs. 23 kg/m²). The association remained statistically significant after adjusting for maternal age, smoking status, marital status and being primiparous (OR 1.05 per BMI point, 95% CI (1.01-1.10)).

Thirteen percent (n=67) of children of asthmatic mothers had allergic rhinitis. Children with allergic rhinitis were more often delivered by elective CS (16% vs 7%, OR 2.42, 95% CI (1.16-5.08)) compared to children without allergic rhinitis in the group of asthmatic mothers. The association remained significant after adjusting for confounders.

Asthmatic women giving birth to children with allergic rhinitis more often had psychiatric co-morbidity (10% vs 5%, OR 2.39, 95% CI (1.07-5.35)) compared to non-asthmatic mothers. This association was not statistically significant after adjusting for confounders, whereas elective CS became statistically significant (OR 2.47, 95% CI (1.25-4.88)).

About 28% (n=50) of the children of asthmatic mothers had concomitant AD and asthma. Elective CS (16% vs 10%, OR 2.68, 95% CI (1.20-5.97)), and maternal pre-pregnancy BMI (OR 1.07 per BMI point, 95% CI (1.01-1.14)) were significant risk factors for AD and concomitant asthma in children of asthmatic mothers after adjusting for cofounders compared to non-asthmatic mothers. Four percent (n=23) of children of asthmatic mothers had all three atopic diseases. Pregnancies resulting in children with all three diseases were more often boys (74% vs 53%, OR 2.54, 95% CI (1.00-6.55)), and more often delivered by elective CS (30% vs 8%, OR 5.30, 95% CI (2.05-13.69)). All these associations remained significant after adjusting for confounders.

Repeating the analysis after exclusion of women (n=2) contributing with more than 1 pregnancy throughout the study period did not change any results. Further, an additional sensitivity analysis restricted to primiparous women, comparing asthmatic and non-asthmatic mothers, did not change the overall results; however psychiatric co-morbidity in the mother became statistically significant for all groups.

Elective CS was associated with development of rhinitis, concomitant AD and asthma and concomitant AD, asthma, and allergic rhinitis. Women with asthma are at increased risk of having elective CS in some studies⁶. However, we have earlier shown that CS is not overrepresented in the MAP cohort compared to the background population, nor is it associated with asthma severity (i.e. moderate/severe compared to mild asthma based on the prescribed level of treatment gathered prospectively according to the GINA guidelines)⁷. Women participating in the MAP program are

overall more resourceful, often first-time mothers and non-smokers, which might explain the lacking association between CS and asthma in the MAP cohort.

Studies so far have been contradictory regarding the association between CS and AD. Some studies have found a positive association⁸ and other have not⁹. The role of microbial colonization during delivery has been discussed in recent years. The main hypothesis is that passing through the birth canal and being exposed to the maternal gut flora might be important for the optimal formation of the child's microbiota and hence development of the immune system. Due to unbalanced bacterial colonization of children delivered by CS some studies have suggested that children are at increased risk of atopic diseases.

An important limitation that needs to be addressed is the relatively low questionnaire follow-up rate, this could result in selection bias; however, asthmatic women responding to the questionnaire are comparable to women not responding to the questionnaire on several outcomes.

In conclusion, asthmatic mothers of children with atopic diseases did not differ from asthmatic mothers with non-atopic diseases children besides that asthmatic mothers giving birth to children with AD more often had a psychiatric comorbidity compared to asthmatic mothers with non-AD children. Moreover, asthmatic mothers of children developing atopic diseases more often gave birth by elective CS compared to controls.

Keywords: Asthma, atopic dermatitis, eczema, allergic rhinitis, pregnancy, cesarean section, psychiatric co-morbidity

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Table 1

Background characteristics of the 522 asthmatic mothers compared to a random sample of non-asthmatic mothers.

	Asthmatic mothers 522	Non-asthmatic mothers 2.782
Age, yrs [#]	30 (5)	30 (4)
Body mass index, kg/cm ² [#]	23 (4)	23 (4)
Primiparity [‡] §	338 (65)	1513 (54)
Marital status Living with the child's father [‡]	503 (96)	2690 (97)
Current smokers [‡] §	33 (6)	200 (7)
Fetal sex (male) [‡]	280 (54)	1408 (52)
Birth weight [#]	3372 (572)	3438 (571)
Gestational age [#]	278 (13)	278 (13)
Elective Caesarian section [‡]	45 (9)	279 (10)
Emergency Caesarian section [‡]	58 (11)	279 (10)
Anemia [‡]	13 (3)	56 (2)
Psychiatric co-morbidity [‡]	35 (7)	129 (5)

Data are given as mean with standard deviation in brackets[#] or numbers with percentages in brackets[‡].

§ p-value<0.05

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Table 2

Association between maternal and perinatal factors, including method of delivery, and the risk of developing atopic diseases in offspring of asthmatic mothers compared to both asthmatic mothers having children without atopic diseases and non-asthmatic mothers.

		Fetal sex (male)	Birth weight	Small for gestational age	Large for gestational age	Elective caesarian section	Emergency caesarian section	Body mass index	Psychiatric co- morbidity
	Non-asthmatic mothers (n=2782)	1408 (52)	3438 (571)	1355 (50)	876 (32)	279 (10)	279 (10)	23 (4.1)	129 (5)
Atopic dermatitis (AD)	Asthmatic mothers with AD children (n=180, 34%)	104 (58)	3321 (599)	103 (59)	43 (25)	18 (10)	21 (12)	23 (4.7)	18 (10)
	Asthmatic mothers with non-AD children (n=342)	176 (51)	3398 (556)	189 (58)	107 (31)	28 (8)	37 (11)	23 (4.4)	17 (5)
	Asthmatic mothers with AD vs. asthmatic mothers with non- AD children OR _{adj} (95% CI)	1.31 (0.90-1.89)	1.00 (0.99-1.00)	1.03 (0.70-1.52)	0.70 (0.46-1.09)	1.33 (0.70-2.53)	1.05 (0.58-1.89)	0.99 (0.95-1.04)	2.07 (1.00-4.29) [§]
	Asthmatic mothers with AD children vs. Non-asthmatic mothers OR _{adj} (95% CI)	1.35 (0.99-1.86) [§]	1.00 (1.00-1.00) [§]	1.36 (0.98-1.88)	0.74 (0.52-1.07)	1.42 (0.84-2.38)	1.23 (0.75-2.01)	1.04 (1.00-1.07)	1.81 (1.03-3.18) [§]
All	Asthmatic mothers with asthma children	60 (58)	3377 (559)	58 (58)	35 (35)	10 (9)	12 (11)	24 (4.6)	9 (8)

hma	(n=103, 20%)								
	Asthmatic mothers with non-asthmatic children (n=419)	208 (52)	3362 (579)	227 (59)	107 (27)	32 (8)	44 (11)	23 (4.5)	23 (6)
	Asthmatic mothers with asthma vs. asthmatic mothers with non-asthmatic OR _{adj} (95% CI)	1.29 (0.82-2.03)	1.00 (1.00-1.00)	0.96 (0.60-1.52)	1.43 (0.88-2.34)	1.23 (0.58-2.65)	1.06 (0.52-2.16)	1.02 (0.97-1.07)	1.64 (0.70-3.88)
	Asthmatic mothers with asthma children vs. Non-asthmatic mothers OR _{adj} (95% CI)	1.42 (0.94-2.15)	1.00 (0.99-1.00)	1.30 (0.86-1.98)	1.22 (0.78-1.88)	1.39 (0.70-2.75)	1.18 (0.62-2.27)	1.12 (0.50-2.52)	1.38 (0.57-3.33)
Allergic rhinitis (AR)	Asthmatic mothers with AR children (n=67, 13%)	43 (64)	3393 (438)	36 (55)	20 (31)	11 (16)	8 (11)	23 (4.4)	7 (10)
	Asthmatic mothers with non-AR children (n=455)	221 (52)	3361 (595)	242 (59)	121 (29)	32 (7)	48 (11)	24 (4.5)	25 (6)
	Asthmatic mothers with AR vs. asthmatic mothers with non-AR children OR _{adj} (95% CI)	1.66 (0.96-2.87)	1.00 (1.00-1.00)	0.87 (0.51-1.49)	1.12 (0.62-2.02)	2.46 (1.15-5.30)	0.97 (0.42-2.27)	0.97 (0.92-1.04)	1.81 (0.70-4.67)
	Asthmatic mothers with AR children vs. Non-asthmatic mothers OR _{adj} (95% CI)	1.79 (1.07-3.01) [§]	1.00 (0.99-1.00)	1.20 (0.72-1.99)	0.99 (0.57-1.72)	2.47 (1.25-4.88) [§]	1.12 (0.50-2.52)	1.02 (0.96-1.08)	1.96 (0.82-4.69)

Data are given as mean with standard deviation in brackets or numbers with percentages in brackets.

Results are reported as odds ratio (OR) with 95% confidence interval (CI), § p-value <0.05

OR are adjusted for maternal age, smoking status (never smoker vs. ever smoker), marital status and primiparous (data from medical records)

No significant associations were found in following variables: very low birth weight, low birth weight, macrosomia, very preterm birth, preterm birth, post-term birth, umbilical cord pH, apgar score below 7, mild/moderate pre-eclampsia, severe pre-eclampsia, gestational hypertension, gestational diabetes, and maternal anemia.

Figure 1

Study flow of Management of Asthma during Pregnancy (MAP) program

**Referred to Hvidovre Hospital**

- Around 7.000/year
(around 8% have asthma)
- Receive an invitation to the MAP program

General practitioner**Non-responders**

- Around 250-300/year

Respond to the invitation

- Around 250-300/year
- Receive a scheduled appointment

Fulfill inclusion criteria

- Around 200/year
- Included in the research database
- Visit every 4. week
- Last visit 3 months post-partum

MAP cohort

- 7-year period (2007-2013)
- 1,283 pregnancies

**Non-asthmatic mothers
from hospital medical
records**

- 2,782 live born

Invited to fill
out the
questionnaire
about atopic
diseases in the
offspring

**Respond to the questionnaire
invitation**

- 522 filled out the questionnaire and
were included