

ORIGINAL ARTICLE

Perinatal factors and the risk of atopic dermatitis: A cohort study

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Keywords

risk factors; birth weight; atopic dermatitis; breast feeding

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Abstract

Objective: To analyze the effects of pregnancy and early events in the newborn on the risk of subsequent atopic dermatitis (AD) during the first year of life.

Patients and Methods: This is a prospective multicenter cohort study of newborns during the first year of life. Newborns identified on random days in three obstetrics departments in the area of Bergamo, Lombardy, Northern Italy, were eligible. At baseline, the mothers were interviewed by medical staff during their stay in hospital after delivery. At 6 and 12 months after delivery, a postal questionnaire was sent to the parents. Relative risks were calculated with and without adjustment by multiple regression analysis.

Results: A total of 1081 newborns entered the study: 796 (74%) parents answered the 12-month questionnaire. Hundred and thirty-eight (17%) reported a diagnosis of AD at 6 months and 222 (28%) at 12 months. Parental history of AD and/or asthma was associated with an increased risk of AD (RR 1.5, 95%CI 1.1–2.0). Birth weight was slightly associated with an increased risk of AD: RR 1.04, 95%CI 1.001–1.08 (continuous variable, increment of 100 grams). No association emerged between breast feeding, smoking, and risk of AD.

Conclusions: This study in an Italian offspring cohort points to family history of atopic diseases and body weight at birth as relevant risk factors. The study was unable to document associations with other perinatal factors particularly breast feeding and parental smoking in the perinatal period.

Atopic dermatitis (AD) is the first step in the progression of atopic disorders in infants, the so-called atopic march, from AD to allergic rhinitis and asthma. Recent studies support the role of skin barrier defects (i.e., loss of function of filaggrin, an epidermal barrier protein) as facilitating entry for pathogens, allergens, and other environmental insults (toxins, irritants, pollutants). Therefore, genetic predisposition together with skin barrier defects and environmental exposure are now considered the main mechanisms of development of AD (1, 2).

The prevalence of AD has risen steeply in the last five decades, reaching about 20% in the first 2 yr of life in many industrialized countries, and becoming the most common inflammatory skin disease in childhood (3).

Thus, exposure during pregnancy or during the first weeks of life may greatly influence the risk of AD. Breast feeding and

antibiotic use in pregnancy have all been considered in relation to the risk of AD, with variable results (4).

To analyze the effects of pregnancy and early events in newborns on the risk of AD during the first year of life, we conducted a prospective cohort study. Most published studies on the epidemiology of AD have been conducted in North European and American countries, and few data are available from southern European populations for very young children. This study was conducted in the Bergamo area, Lombardy, Italy.

Methods

This was a prospective multicenter cohort study of newborns during the first year of life. Newborns identified on random

days in the three obstetric departments in the area of Bergamo, Lombardy, Northern Italy, were eligible. Subjects from families not speaking Italian or not resident in the Bergamo area were not included.

The mothers were identified and interviewed by medical interviewers during their stay in hospital after delivery. The investigator enrolled all the consecutive newborns observed from the start of the study who met the inclusion criteria on selected random days.

Enrollment started in February 2007 and was concluded in May 2009 when the number of patients established by the protocol (see below) was reached. Three questionnaires were planned: a face-to-face questionnaire with trained interviewers and two postal questionnaires sent to the parents 6 and 12 months after delivery. The baseline questionnaire collected information about the main demographic characteristics and personal habits of the parents (smoking, alcohol consumption), parents' history of allergic diseases, number of brothers and sisters of the newborn, course of pregnancy and mode of delivery, antibiotic treatment, and streptococcus prophylaxis during pregnancy, gestational age at delivery, birth weight, details of the child's home.

The follow-up questionnaires collected information about breast feeding, the home, baby's diet, selected diseases and the signs and symptoms associated with them, any hospital admission, discharge diagnosis, other health problems of the baby, parents' smoking habits during the baby's first year of life.

Diagnosis of AD

Diagnosis of AD was established when there was a history of itching skin rash (5), and a diagnosis of 'atopic dermatitis' or 'atopic eczema' made by a pediatrician or a dermatologist.

Statistical analysis

The main objective of the study was to analyze the 12-month incidence of AD in the study population and the risk factors for the development of AD. Adjusted and unadjusted relative risks (RR) and 95% confidence interval were calculated with the classical Mantel-Haenszel analysis of case-control data modified for the analysis of cohort studies (6). In the model with adjustment, we included gender, mother's and father's age and education, family history of AD (or mother's history of AD and father's history of AD or mother's history of asthma and father's history of asthma, alternatively included in the model because of the correlation), cats, or dogs in the house at birth (or cats or dogs in the house after birth), disease in pregnancy, gestational age at delivery, mode of delivery, birth weight, use of antibiotic during pregnancy, streptococcus treatment during pregnancy, antibiotic use in the newborn, breast feeding (or duration of breast feeding or duration of breast feeding/other milk).

Ethics

The study was conducted in accordance with the Declaration of Helsinki and the ICH-GCP guidelines. The study protocol

was approved by the ethics committees of the participating centers. Written informed consent was obtained from the mothers before the study.

Results

A total of 1081 newborns entered the study: 285 parents (26%, 95% CI 24–29%) did not respond to the postal questionnaire or phone interview at 12 months (Fig. 1). Thus, these analyses are based on 796 (74%, 95% CI 71–76%) newborns followed up for 12 months. The characteristics of the newborns lost to follow-up were largely similar to those for which follow-up data were available (Table 1).

A total of 222 newborns reported a diagnosis of AD, 138 (62%, 95% CI 56–69%) within 6 months, and an additional 84 (29%, 95% CI 31–44%) between 6 and 12 months. Therefore, incidence estimates were, respectively, 17% (95% CI 15–20%) and 28% (95% CI 25–31%) at 6 and 12 months. Table 2 shows the distribution of study subjects according to the diagnosis of AD at 12 months and selected factors. A family history of AD and/or asthma was associated with an increased risk of AD in the newborns (RR 1.5, 95% CI 1.1–2.0). Maternal history of AD (RR 1.8, 95% CI 1.1–2.9) and paternal history of asthma (RR 1.9, 95% CI 1.2–2.8) were significantly associated with an increased risk of AD in the newborns.

No association emerged between maternal and paternal age and education, parents' smoking habits, presence of cats and dogs in the child's house, gestational age at delivery, and the risk of AD.

Table 3 shows the relation between the risk of AD and pregnancy, delivery factors, and breast feeding.

Birth weight was slightly associated with an increased risk of AD: RR 1.04, 95%CI 1.001–1.08 (continuous variable, increment of 100 grams). The risk of AD was slightly increased with gestational age at delivery: RR 1.1, 95%CI 1.03–1.3 (continuous variable, increment of 1 wk), but with loss of significance after adjustment (RR 1.1, 95%CI 0.98–1.3).

No association emerged between a history of gestational diseases (diabetes, hypertension, liver diseases) in pregnancy, mode of delivery, and maternal use of antibiotics during pregnancy, and risk of AD. No relationship emerged between breast feeding and risk of AD.

A sample size of 796 subjects with a proportion of AD diagnosis of 27.9% (222 cases) achieve at least 80% power to detect an RR = 1.5 if the proportion of exposure in the control

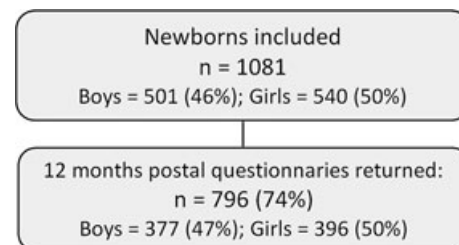


Figure 1 Flow of subjects in the study population.

Table 1 Comparison of characteristics between subjects lost to follow-up and those included in the analysis

	Lost to follow-up (12 months)				
	Yes (n = 285)		No (n = 796)		
	N*	% (95% CI)	N*	% (95% CI)	p-value
Gender					
Male	124	46.3 (40.3–52.3)	377	48.8 (45.2–52.3)	0.4799
Female	144	53.7 (47.7–59.7)	396	51.2 (47.7–54.8)	
Mother's and father's age (years)					
Mother <32 and father <35	83	39.3 (32.7–45.9)	184	30.2 (26.6–33.9)	0.0843
Mother <32 and father ≥35	21	10.0 (6.0–14.1)	60	9.9 (7.5–12.3)	
Mother ≥32 and father <35	30	14.2 (9.5–18.9)	92	15.1 (12.3–17.9)	
Mother ≥32 and father ≥35	77	36.5 (30.0–43.0)	273	44.8 (40.9–48.8)	
Mother's and father's education					
Low level**	126	48.1 (40.4–55.8)	302	39.6 (36.1–43.1)	0.0166
High level**	136	51.9 (44.2–59.6)	460	60.4 (56.9–63.9)	
Parity of the mother					
0	128	44.9 (39.1–50.7)	404	50.7 (47.3–54.2)	0.2349
1	126	44.2 (38.4–50.0)	312	39.2 (35.8–42.6)	
≥2	31	10.9 (7.2–14.5)	80	10.1 (8.0–12.1)	
Birth weight (grams)					
<2500	17	6.3 (3.4–9.2)	35	4.5 (3.05–6.0)	0.3200
2500–4000	246	90.8 (87.3–94.2)	706	91.1 (89.1–93.1)	
≥4000	8	3.0 (0.9–5.0)	34	4.4 (2.9–5.8)	
Gestational age at birth (weeks)					
<37	9	3.9 (1.4–6.4)	35	5.1 (3.5–6.8)	0.6424
37–40	175	75.8 (70.2–81.3)	523	76.5 (73.3–79.6)	
>40	47	20.3 (15.1–25.6)	126	18.4 (15.5–21.3)	
Family history of AD and/or asthma					
No	144	50.5 (44.7–56.4)	367	46.1 (42.6–49.6)	0.1996
Yes	141	49.5 (43.6–55.3)	429	53.9 (50.4–57.4)	
Mother's smoking habits					
Non-smoker	173	61.4 (55.6–67.1)	527	66.3 (63.0–70.0)	<0.0001
Ex smoker	70	24.8 (19.8–29.9)	242	30.4 (27.2–33.6)	
Current smoker after childbirth	39	13.8 (9.8–17.9)	26	3.3 (2.0–4.5)	
Father's smoking habits					
Non-smoker	108	38.9 (33.1–44.6)	417	52.7 (49.2–56.2)	<0.0001
Ex smoker	64	23.0 (18.0–28.0)	239	30.2 (14.4–19.7)	
Current smoker after childbirth	106	38.1 (32.3–43.9)	135	17.1 (27.0–33.4)	
Cats or dogs in the house at birth					
No	211	74.0 (68.9–79.2)	552	69.4 (66.1–72.6)	0.1361
Yes	74	26.0 (20.8–31.1)	244	30.7 (27.4–33.9)	
Cats or dogs in the house after birth					
No	283	99.3 (98.3–100.0)	599	75.3 (72.2–78.3)	<0.0001
Yes	2	0.7 (0.0–1.7)	197	24.8 (21.7–27.7)	

*In some cases, sum does not add up to the total because of missing values.

**Low level: mother's and father's secondary school or high school education. High level: mother's and father's high school or university.

group is assumed to be between 0.2 and 0.5. (Test statistic used: two-sided Z test with pooled variance; significance level of the test: 0.05.) (7).

Fig. 2 shows the relative risk and 95% CI of selected factors on a logarithmic scale.

Discussion

In this study, the cumulative incidence of physician-confirmed diagnoses of AD was about 28% at 1 yr. This is higher than

the prevalence estimated in other studies (8–10). For example, a cross-sectional study conducted in Italy among children aged 9 yrs reported a lifetime prevalence of AD of about 15%. (10).

In a study conducted in Verona (Northeastern Italy) and published in 2008, an incidence of 18.1% was detected among preschool children (11).

AD is a common condition in infancy and generally disappears at about 3 yrs of age in a significant proportion of children.

Table 2 Main characteristics of the study subjects according to AD diagnosis

	Diagnosis of AD								
	No (574)		Yes (222)		RR**	95%CI	RR***	95%CI	p-value
	No.	%*	No.	%*					
Gender									
Male	263	69.8	114	30.2	Ref.cat.		Ref.cat.		
Female	293	74.0	103	26.0	0.86	0.67–1.09	0.89	0.69–1.14	0.3361
Missing	18	–	5	–	–	–	–	–	–
Mother's age (years)									
Continuous variable					1.00	0.97–1.04	0.99	0.95–1.03	0.5241
<30	137	74.5	47	25.5	Ref.cat.		Ref.cat.		
30–34	236	69.2	105	30.8	1.21	0.85–1.70	1.02	0.69–1.47	0.9377
35+	180	74.4	62	25.6	1.00	0.69–1.46	0.84	0.53–1.32	0.4478
Missing	21	–	8	–	–	–	–	–	–
Mean (SD,range)	32.4 (4.2, 20–44)	32.5 (4.0, 20–43)							
Father's age (years)									
Continuous variable					1.02	0.99–1.05	1.03	0.99–1.07	0.1713
<35	210	76.1	66	23.9	Ref.cat.		Ref.cat.		
35–39	160	73.4	58	26.6	1.11	0.78–1.58	1.14	0.78–1.68	0.4997
40+	81	69.8	35	30.2	1.26	0.84–1.90	1.30	0.80–2.10	0.2841
Missing	123	–	63	–	1.42	1.00–2.00	1.53	1.05–2.22	0.0262
Mean (SD,range)	35.3 (5.0, 23–59)	35.8 (4.9, 24–50)							
Mother's education									
Secondary school	124	72.1	48	27.9	Ref.cat.		Ref.cat.		
High school	319	72.8	119	27.2	0.97	0.70–1.36	0.97	0.66–1.42	0.8833
University	131	70.4	55	29.6	1.06	0.72–1.56	1.01	0.63–1.62	0.9805
Father's education									
Secondary school	197	71.1	80	28.9	Ref.cat.		Ref.cat.		
High school	279	74.4	96	25.6	0.89	0.66–1.19	0.89	0.64–1.23	0.4732
University	92	69.7	40	30.3	1.05	0.72–1.53	1.00	0.64–1.57	0.9984
Parity of the mother									
0	296	73.3	108	26.7	Ref.cat.		Ref.cat.		
1	219	70.2	93	29.8	1.12	0.85–1.47	1.05	0.77–1.44	0.7631
>2	59	73.8	21	26.3	0.98	0.62–1.57	0.96	0.57–1.60	0.8656
Mother's smoking habits									
Non smoker	386	73.2	141	26.8	Ref.cat.		Ref.cat.		
Ex smoker	168	69.4	74	30.6	1.14	0.86–1.51	1.10	0.51–2.39	0.8092
Current smoker after childbirth	19	73.1	7	26.9	1.01	0.47–2.15	1.14	0.85–1.54	0.3843
Father's smoking habits									
Non smoker	302	72.4	115	27.6	Ref.cat.		Ref.cat.		
Ex smoker	167	69.9	72	30.1	1.09	0.81–1.47	0.94	0.62–1.41	0.7528
Current smoker after childbirth	102	75.6	33	24.4	0.89	0.60–1.31	1.13	0.83–1.55	0.4329
Family history of AD and/or asthma									
No	287	78.2	80	21.8	Ref.cat.		Ref.cat.		
Yes	287	66.9	142	33.1	1.52	1.16–2.00	1.54	1.16–2.04	0.0026
Mother's history of AD									
No	529	73.8	188	26.2	Ref.cat.		Ref.cat.		
Yes	25	53.2	22	46.8	1.79	1.15–2.78	1.81	1.13–2.89	0.0136
Uncertain/missing	20	–	12	–	1.43	0.80–2.56	1.41	0.72–2.75	0.3128
Father's history of AD									
No	507	73.7	181	26.3	Ref.cat.		Ref.cat.		
Yes	23	54.8	19	45.2	1.72	1.07–2.76	1.52	0.92–2.52	0.1061
Uncertain/missing	44	–	22	–	1.27	0.81–1.97	1.26	0.77–2.07	0.3566

Table 2. (Continued).

	Diagnosis of AD								
	No (574)		Yes (222)						
	No.	%*	No.	%*	RR**	95%CI	RR***	95%CI	p-value
Mother's history of asthma									
No	521	73.0	193	27.0	Ref.cat.		Ref.cat.		
Yes	46	64.8	25	35.2	1.30	0.86–1.98	1.26	0.82–1.94	0.2868
Uncertain/missing	7	–	4	–	–	–	–	–	–
Father's history of asthma									
No	508	73.7	181	26.3	Ref.cat.		Ref.cat.		
Yes	37	54.4	31	45.6	1.74	1.19–2.54	1.92	1.28–2.88	0.0016
Uncertain/missing	29	–	10	–	0.98	0.52–1.85	1.10	0.57–2.13	0.7744
Cats or dogs in the house at birth									
No	390	70.7	162	29.3	Ref.cat.		Ref.cat.		
Yes	184	75.4	60	24.6	0.84	0.62–1.13	0.78	0.57–1.07	0.1195
Cats or dogs in the house after birth									
No	423	70.6	176	29.4	Ref.cat.		Ref.cat.		
Yes	151	76.6	46	23.4	0.80	0.57–1.10	0.75	0.53–1.06	0.1012

RR, relative risk; CI, confidence interval.

*Row percent.

**Not adjusted.

***Adjusted (model included all variables).

This study confirmed the main recognized risk factors for AD such as family history of AD and asthma (12, 13). We found the RR of developing AD during the first year of life was 50% higher in children of parents with a history of AD than in children with no history.

The results suggested that birth weight was associated with the risk of AD. No association emerged between risk of AD and parental age, maternal and paternal smoking during pregnancy, history of gestational diseases in pregnancy, mode of delivery, treatment with antibiotics during pregnancy or delivery, and breast feeding compared with other milks feed.

The relation between birth weight and the risk of AD has rarely been analyzed (14). In a US cohort study of pregnant women and their offspring (15), birth weight was not associated with the risk of AD. A more recent cross-sectional study (16) and a case-control study (17) of AD in children older than 1 yr found a positive association between AD and obesity. A Swedish study also reported a positive relation between fetal growth and childhood atopic eczema (14).

Biologic explanations for the associations have been put forward. Impaired immune tolerance is considered to be a sequel of immune changes due to the activity of adipokines, bioactive molecules secreted in white adipose tissue. Further, obesity is related to the high levels of circulating IL6, leptin, and TNF- α , which in turn are associated with the risk of AD (18)(19–21). Birth weight has been suggested to be related with the risk of obesity (22).

Whether environmental tobacco smoke increases the risk of allergic diseases is still debated. No significant association was observed between perinatal tobacco smoke exposure and the development of AD in a prospective cohort study in Japan (23), but other studies showed positive associations (24). We

did not find any association between paternal and maternal smoking and risk of AD.

Finally, as recent studies suggest, there was no evidence of a protective effect of prolonged breast feeding (5 months or more) against AD among children at age of 12 months and it might even be a risk factor, particularly for children without family history (as an expression of genetic predisposition) (25, 26). A recent meta-analysis did not find any strong evidence of a protective effect against AD of exclusive breastfeeding for at least 3 months, even among children with a family history of atopy (27).

In the interpretation of these findings, potential limitations of the study should be considered.

First of all, 26% (95% CI 24–29%) of women were lost to follow-up. This is a high proportion, but we have to consider that this study included a non-selected population identified in a first level center at delivery, and similar dropout rates have been reported in other studies with a similar design. Moreover, the characteristics of women and newborns lost to follow-up were similar to the general and clinical characteristics of the whole study population at study entry (Table 1).

Unfortunately, no information was available on the women asked to participate that declined to enter the study.

A further concern may regard the criteria adopted for identifying new cases. We relied on a medical diagnosis by a pediatrician or a dermatologist. It is however possible that parents misunderstood the diagnosis or that a few cases had not been referred to a physician. The Italian healthcare system offers universal coverage, and primary care pediatricians are required to vaccinate all children in their area. This point is however an important limitation of this study.

Table 3 Pregnancy variables, breast feeding and diagnosis of AD

	Diagnosis of AD								
	No (574)		Yes (222)		RR**	95%CI	RR***	95%CI	p-value
	No.	%*	No.	%*					
Disease in pregnancy									
No	484	71.5	193	28.5	Ref.cat.		Ref.cat.		
Yes	77	78.6	21	21.4	0.74	0.48–1.18	0.75	0.47–1.19	0.2185
Gestational age at delivery (weeks)									
Mean (SD, range)	39.1 (1.6, 32–42)	39.5 (1.5, 33–42)			1.14	1.03–1.26	1.11	0.98–1.25	0.1016
Continuous variable									
Mode of delivery									
Spontaneous vaginal	362	72.5	137	27.5	Ref.cat.		Ref.cat.		
Induced vaginal	100	67.1	49	32.9	1.20	0.86–1.66	1.24	0.87–1.77	0.2276
Caesarean section	110	75.9	35	24.1	0.89	0.61–1.28	1.03	0.68–1.55	0.8324
Birth weight (grams)									
Mean (SD, range)	3253 (452,1290–4550)	3366 (436,1580–4750)							
Continuous variable					1.04	1.01–1.07	1.04	1.00–1.08	0.0412
Use of antibiotics during pregnancy									
No	520	73.0	192	27.0	Ref.cat.		Ref.cat.		
During whole pregnancy	54	64.3	30	35.7	1.33	0.90–1.95	1.34	0.90–2.00	0.1513
During the 1st trimester	12	54.5	10	45.5	1.66	0.88–3.13	1.85	0.96–3.58	0.0675
During the 2nd trimester	22	66.7	11	33.3	1.21	0.66–2.21	1.04	0.54–2.01	0.8965
During the 3rd trimester	32	66.7	16	33.3	1.21	0.73–2.01	1.20	0.69–2.09	0.5142
Streptococcus treatment during									
No	506	72.4	193	27.6	Ref.cat.		Ref.cat.		
Yes	68	70.1	29	29.9	1.08	0.73–1.60	0.96	0.63–1.45	0.8267
Antibiotic use in the newborn									
No	539	72.4	205	27.6	Ref.cat.		Ref.cat.		
Yes	35	67.3	17	32.7	1.19	0.72–1.95	1.12	0.65–1.91	0.6828
Breast feeding									
No	108	77.1	32	22.9	Ref.cat.		Ref.cat.		
Breast feeding only	325	69.9	140	30.1	1.32	0.90–1.93	1.34	0.90–2.02	0.1528
Breast feeding/other milks	136	73.5	49	26.5	1.16	0.74–1.81	1.13	0.71–1.80	0.6157
Missing	5	–	1	–	–	–	–	–	–
Duration of breast feeding only (months)									
Continuous variable					1.02	0.96–1.08	1.03	0.96–1.10	0.4765
0	108	77.1	32	22.9	Ref.cat.		Ref.cat.		
1–4	50	73.5	18	26.5	1.16	0.65–2.06	1.28	0.70–2.35	0.4279
5 or more	202	68.9	91	31.1	1.36	0.91–2.03	1.46	0.95–2.25	0.0877
Chi-square for trend: p-value					0.1275	0.0883			
Duration of breast feeding/other milks (months)									
Continuous variable					1.02	0.98–1.07	1.02	0.98–1.08	0.3404
0	108	77.1	32	22.9	Ref.cat.		Ref.cat.		
1–4	141	74.6	48	25.4	1.11	0.71–1.74	1.15	0.72–1.84	0.5489
5 or more	235	69.1	105	30.9	1.35	0.91–2.01	1.39	0.91–2.12	0.1264
Chi-square for trend: p-value					0.1015	0.1025			

RR, relative risk, CI, confidence interval.

€ For an increment of 100 grams.

*Row percent.

**Not adjusted.

***Adjusted (model included all variables).

Another limitation is the fact that all considered factors were self-reported. In particular, reproductive and neonatal information was self-reported by the mother. The

validity of maternally reported pregnancy and delivery information has been however reported of high reliability (28).

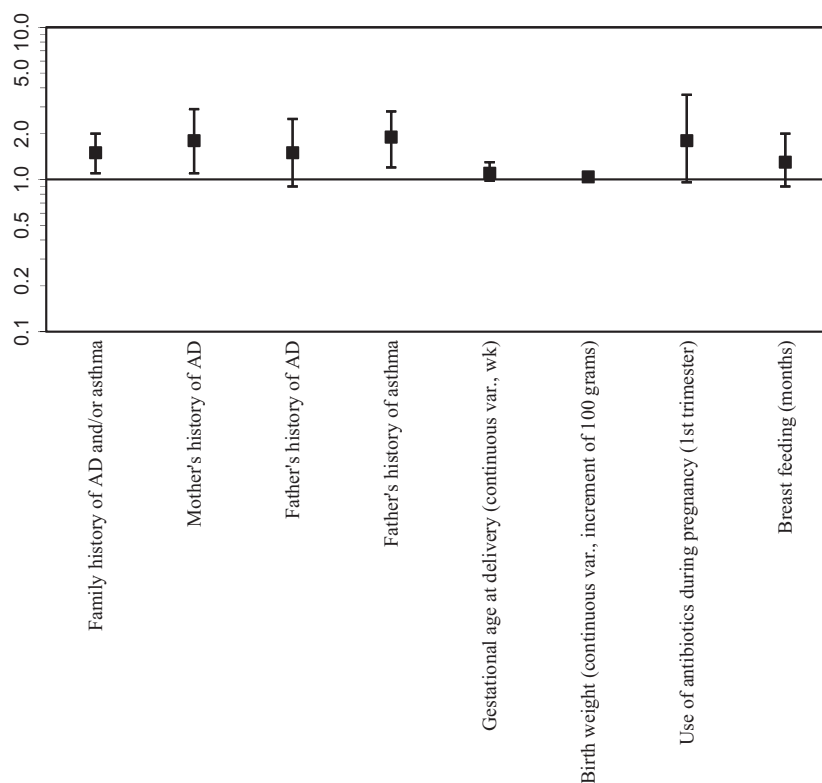


Figure 2 Relative risks (RR) and 95% confidence intervals (CI) of selected factors.

In general, any misclassification of exposures and outcomes should tend to reduce observed associations.

The strengths of this study include its prospective nature and the possibility of qualifying exposure precisely as it was not affected to any large extent by recall bias.

This study in an Italian offspring cohort points to family history of atopic diseases, gestational age, and body weight at birth as main risk factors for AD. Other perinatal factors

seemed much weaker, and no associations were found with parent education, breast feeding, and parental smoking in the perinatal period.

Conflict of interest

None to declare.

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