

ORIGINAL ARTICLE

Impaired fetal growth decreases the risk of childhood atopic eczema: a Swedish twin study

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Summary

Background Studies have found associations between birth weight and risk of atopic eczema or allergic rhinitis (AR), although this could be due to confounding.

Objective We sought to evaluate associations between fetal growth and the risk of atopic eczema or AR in childhood, controlling for gestational age (GA), shared (familial) environmental and genetic factors.

Methods Data on atopic eczema, AR, birth characteristics and confounders were collected from registers and telephone interviews with the parents of 9- and 12-year-old twins. Firstly, cohort analyses on all twins (eczema $n = 10\,132$ and AR $n = 10\,896$) were performed. Secondly, to control for genetic and shared environment, co-twin-control analyses were performed in twin pairs discordant for atopic eczema ($n = 480$) and AR ($n = 332$).

Results The rate of atopic eczema increased with birth weight, from 12.6% in twin children < 2000 g to 17.3% in children ≥ 3500 g. The rate of AR varied between 7.8% and 8.8%. In the cohort analyses, the odds ratio (OR) for atopic eczema was 1.62 (95% CI: 1.27–2.06) for 500 g increase in birth weight and 1.00 (95% CI: 0.75–1.33) for AR. In co-twin-control analyses on atopic eczema, OR was 3.93 (95% CI: 1.55–9.98) for 500 g increase in birth weight, with no significant difference between monozygotic and dizygotic twins ($P = 0.84$).

Conclusions We found a positive association between fetal growth and childhood atopic eczema, but not AR, independent of GA, shared environmental and genetic factors. This indicates fetal growth affects the immune system, and supports further studies on early mechanisms.

Keywords allergic rhinitis, allergy, asthma, atopic dermatitis, birth weight, child, epidemiology, gestational age, twin study

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Introduction

There is evidence that factors during pregnancy indicative of disproportionate fetal growth may result in insufficient energy supply for organ development, and influence the expression of post-natal chronic disease [1]. Against the background of the hygiene hypothesis [2], a differential intrauterine 'programming' of T cell polarization in undernourished fetuses during late gestation has been proposed [3], which would later affect the development of atopic eczema and allergic rhinitis (AR).

Studies on birth characteristics and atopic eczema have shown that high birth weight [4–6] and high gestational age (GA) [4,7] increase the risk for subsequent atopic

dermatitis, while others found no significant associations [8–11]. Similarly for AR, some previous studies have shown an increasing risk with high birth weight [9, 12] and a decreased risk with low GA and low birth weight [13], while others have not found evidence of such associations [8,10,11,14]. However, because GA and birth weight are strongly correlated, it is unclear whether the associations are driven by GA, fetal growth or both.

Twin studies provide an excellent tool to study associations between fetal growth and risks of subsequent diseases, such as atopic eczema and AR. Because twin siblings share genes (half if dizygotic and all if monozygotic), intrauterine exposures, maternal and paternal factors and early environment, twin studies provide

possibilities to control for shared (familial) environmental and genetic factors [15]. Additionally, twin siblings often differ in birth weight, with one in four pairs having a discordance of $>15\%$ [16]. Because twin siblings have identical GA and the same parents, differences in birth weight within twin pairs reflect differences in fetal growth.

In a previous study, we have shown a negative association between fetal growth and the risk of asthma, which was independent of genetic factors [17]. In this study, we aim to evaluate the association between fetal growth and atopic eczema and AR when controlling for shared (familial) environmental and genetic factors in a prospective twin cohort based on the population-based Swedish Twin and Medical Birth Registers.

Methods

Study design and population

The Child and Adolescent Twin Study in Sweden, CATSS [18], is a study performed by the Swedish Twin Register, and includes all twins born between July 1992 and June 1998. In brief, data were collected by telephone interviews with the parents between October 2004 and July 2007, when the twins were 9 or 12 years old, and through linkage with the Medical Birth Register.

After exclusion of twins living abroad, twins with parents not fluent in Swedish and disabled parents or twins, 15 808 eligible twins remained in the cohort. The parents of 12 496 twins (79%) completed the interview, of whom 11 122 twins could be linked to the Medical Birth Register. After exclusion of twins with missing information on either birth weight or GA ($n = 94$) and those with a non-plausible combination of GA and birth weight according to Alexander et al. [19] ($n = 8$), 11 020 (70%) twins remained (Fig. 1). Further details regarding data collection and linkage to the Medical Birth Register are described elsewhere [17].

Variables

Data on zygosity, age, maternal education and mother's country of birth, as well as information on allergic disease and asthma were recorded during the telephone interview. Maternal education was based on self-report of educational level (≤ 9 years, 10–12 years or graduate education), and mother's country of birth was categorized into Sweden/other Nordic countries/others). The questions used for the determination of zygosity have been validated using DNA samples, showing 95% accuracy [20].

The outcome variable atopic eczema was derived from the main question 'Has NN ever had eczema?' and the sub question 'What type of eczema?' Children with a 'yes' to the main question and either or both of the alternatives

'atopic eczema' and 'flexural eczema' were classified as having atopic eczema. Furthermore, a paediatrician (C. A.) evaluated answers to an open question regarding the type of eczema, and those clearly describing an atopic eczema were classified accordingly ($n = 21$). Further, we used a question regarding doctor's diagnosis on atopic eczema/flexural eczema for secondary analyses. For our outcome variable AR, we used the question 'Has NN ever had hayfever?' (yes/no). The interview also included a question on whether the child had ever had asthma.

From the Medical Birth Register, we collected information on birth weight, birth length, GA and sex of the child as well as the maternal characteristics such as age, parity, smoking, family situation and body mass index (BMI). GA was estimated mainly from the ultrasound in weeks 16–18 (77%); otherwise, the date of the last menstrual period was used. Maternal age and parity were recorded at delivery. Mother's smoking habits (classified into 0, 1–9 or ≥ 10 cigarettes per day) and family situation (cohabits with child's father yes/no) were registered at first visit to the antenatal care clinic in weeks 8–12, along with her BMI (kg/m^2). The Medical Birth Register has been validated, and the quality of the variables included in the present study is considered high [21].

Statistical analysis

Firstly, the associations between atopic eczema and the exposure variables were analysed as a cohort, with atopic eczema and AR (yes/no) as outcome variables using generalized estimating equations with the logit link to address the correlation within twin pairs. As exposure variables, we used: (1) birth weight, (2) GA, (3) as a measure of fetal growth, birth weight by gestational week and sex in standard deviation score and (4) birth length. The exposure variables were handled both as categorized and continuous. The analyses were adjusted for the child characteristics of sex, zygosity and age, and the maternal characteristics of age at delivery, parity, education, smoking during pregnancy, family situation, country of birth and BMI. To test if there were differential effects of exposure for boys and girls, we also fitted models with interaction effects between exposure and sex.

Secondly, to study if the association between atopic eczema and birth weight or birth length was independent of GA, genetic and shared environmental factors (including maternal factors and shared childhood environment), a co-twin-control analysis was performed. Twin pairs who were discordant regarding atopic eczema/AR were thus analysed with the non-affected co-twin as a matched control to the affected twin in a conditional logistic regression with birth weight or birth length as a continuous predictor, with and without adjustment for asthma. As dizygotic twins share 50% of their segregating genes and monozygotic 100%, a smaller effect of birth weight

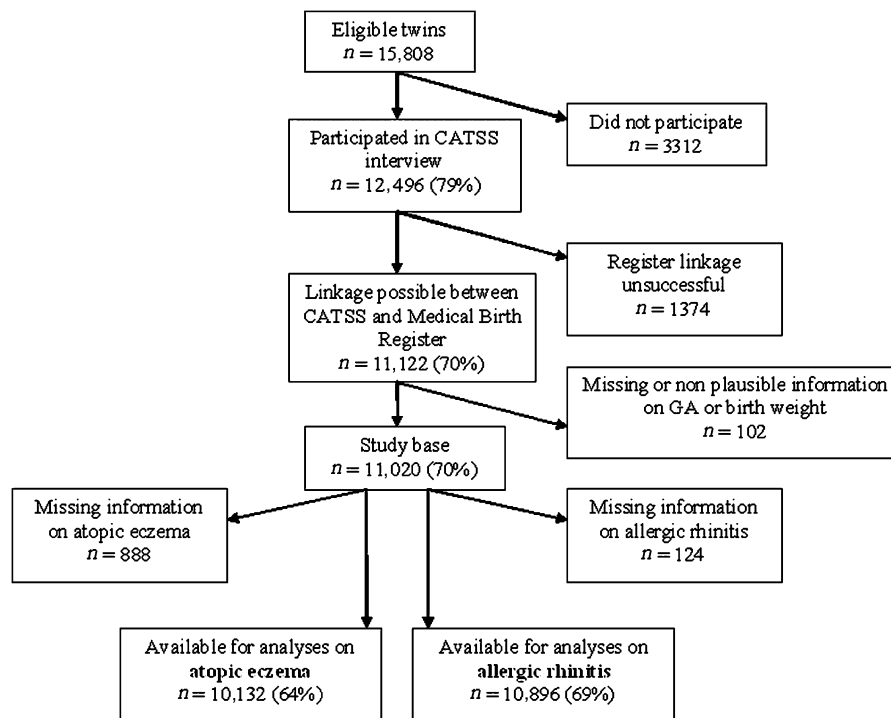


Fig. 1. Flow of subjects in the study population. Response rates are based on the number of eligible twins.

among the monozygotic twins would indicate that the association is confounded by genetic factors. Same analyses were performed for the secondary outcome atopic eczema according to the doctor's diagnosis (yes/no).

Because of our earlier finding of a negative association between fetal growth and asthma [17], we also tested if there was a differential effect of birth weight for those having asthma and those who did not in the cohort analyses, by estimating interaction effects between the exposures and asthma.

The SAS software package version 9.1 was used for all analyses and the significance level was 0.05.

Permission for the study was obtained from the Regional Ethical Review Board in Stockholm, Karolinska Institutet.

Results

Table 1 shows the rates of atopic eczema and AR by child and maternal characteristics.

The overall rate of atopic eczema was 15.6%. The rates increased with an increasing birth weight, from 12.6% in the group with a birth weight of ≤ 1999 g to 17.3% in the group with a birth weight of 3500 g and above. A similar pattern was seen for GA with 12.3% in the group with a GA of ≤ 31 weeks and 22.7% in the group with a GA of ≥ 41 weeks and for birth length, with lower rates among children with a lower birth weight. Girls had a higher rate of eczema than boys (17.3% vs. 14.1%).

The rates of atopic eczema also varied with maternal characteristics. Thus, the rate decreased with an increasing maternal age at delivery (from 19.1% to 14.0%) and was lower for twins with older siblings than for those without older siblings (14.7% vs. 16.7%). Further, the rate of atopic eczema increased with higher levels of the mother's education. The children of mothers who did not smoke during pregnancy had slightly higher rates than those with smoking mothers. Children whose mothers were born in Sweden had a higher rate of atopic eczema (16.1%) than children to mothers born outside Sweden, and the lowest rate (10.1%) was found in children to mothers born outside Scandinavia. In addition, rates of atopic eczema differed with maternal BMI, although no clear pattern was observed. There was no clear relationship between the rate of atopic eczema and the mother's BMI at the beginning of the pregnancy.

The overall rate of AR was 8.4%, with no clear relationship with birth weight, GA or birth length (Table 1). However, AR was more common among boys than girls (10.2% vs. 6.5%) and slightly more common among the 12-year-old children than the 9-year-olds (8.9% vs. 7.8%). Maternal characteristics had only a slight association with rates of AR in the offspring. First-born children had a higher rate than those with older siblings (9.5% vs. 7.4%). Rate of AR was lower in children to mothers with the lowest level of education compared with the other education groups (5.7% vs. 8.5–8.8%). Finally, regarding the mother's birth country, the rate was lowest among children of mothers born outside Scandinavia (6.6%) and

Table 1. Study population characteristics and cumulative incidence of atopic eczema and allergic rhinitis in a cohort of 10 993 Swedish twins aged 9 and 12 years, born from 1992 to 1998

	Cohort			Cohort		
	Atopic eczema			Allergic rhinitis		
	<i>N</i>	Number	%	<i>N</i>	Number	%
Total	10 132	1585	15.6	10 896	913	8.4
Child's characteristics						
Birth weight (g)						
≤ 1999	1402	177	12.6	1508	117	7.8
2000–2499	2397	370	15.4	2577	228	8.8
2500–2999	3583	580	16.2	3862	331	8.6
3000–3499	2194	362	16.5	2354	186	7.9
≥ 3500	556	96	17.3	595	51	8.6
Gestational age (weeks)						
≤ 31	594	73	12.3	639	50	7.8
32–34	1417	215	15.2	1515	138	9.1
35–36	2344	373	15.9	2519	210	8.3
37–38	3730	581	15.6	4027	330	8.2
39–40	1915	313	16.3	2057	169	8.2
≥ 41	132	30	22.7	139	16	11.5
Fetal growth*						
< –1.0	1498	209	14.0	1621	131	8.1
–1.0 to –0.5	1510	240	15.9	1614	139	8.6
–0.5–0.5	4037	636	15.8	4351	387	8.9
0.5–1.0	1505	228	15.1	1601	128	8.0
> 1.0	1582	272	17.2	1709	128	7.5
Birth length (cm)						
≤ 39	219	26	11.9	233	14	6.0
40–44	1340	203	15.1	1451	116	8.0
45–49	6148	964	15.7	6623	557	8.4
≥ 50	1756	301	17.1	1881	156	8.3
Missing	669	91	13.6	708	70	9.9
Sex						
Male	5166	726	14.1	5565	567	10.2
Female	4966	859	17.3	5331	346	6.5
Zygosity						
Monozygotic	2955	436	14.8	3198	280	8.8
Dizygotic, same sex	2869	474	16.5	3086	249	8.1
Dizygotic, different sex	3364	510	15.2	3619	309	8.5
Unknown	944	165	17.5	993	75	7.6
Age of child (years)						
9	4813	760	15.8	5176	405	7.8
12	5319	825	15.5	5720	508	8.9
Asthma						
Yes	1339	376	28.1	1477	378	25.6
No	8720	1186	13.6	6039	515	5.5
Missing	73	23	31.5	80	20	25.0
Atopic eczema						
Yes				1560	317	20.3
No				8491	477	5.6
Missing				845	119	14.1
Allergic rhinitis						
Yes	794	317	39.9			
No	9257	1243	13.4			
Missing	81	25	30.9			
Maternal characteristics						
Mother's age at delivery (years)						
≤ 19	68	13	19.1	76	4	5.3
20–24	1055	165	15.6	1163	117	10.1

Table 1. continued

	Cohort			Cohort		
	Atopic eczema			Allergic rhinitis		
	N	Number	%	N	Number	%
25–29	3361	532	15.8	3584	323	9.0
30–34	3632	593	16.3	3913	326	8.3
≥ 35	2016	282	14.0	2160	143	6.6
Parity						
1	4613	771	16.7	5003	476	9.5
> 1	5519	814	14.7	5893	437	7.4
Education						
≤ 9 years	632	83	13.1	699	40	5.7
10–12 years	5059	759	15.0	5456	464	8.5
Graduate education	4154	718	17.3	4430	390	8.8
Missing	287	25	8.7	311	19	6.1
Smoking during pregnancy (cigarettes per day)						
0	7892	1255	15.9	8471	732	8.6
1–9	1045	157	15.0	1140	86	7.5
≥ 10	588	80	13.6	638	52	8.2
Missing	607	93	15.3	647	43	6.6
Cohabits with child's father						
Yes	9030	1420	15.7	9712	805	8.3
No	325	52	16.0	361	37	10.2
Missing	777	113	14.5	823	71	8.6
Country of birth						
Sweden	9149	1476	16.1	9782	826	8.4
Denmark, Finland, Norway or Iceland	294	40	13.6	320	34	10.6
Other	656	66	10.1	756	50	6.6
Missing	33	3	9.1	38	3	7.9
BMI (kg/m ²)						
< 18.5	196	26	13.3	216	20	9.3
18.5–24.9	5416	855	15.8	5823	506	8.7
25–29.9	1999	282	14.1	2145	166	7.7
≥ 30	673	114	16.9	728	60	8.2
Missing	1848	308	16.7	1984	161	8.1

*Standard deviation score of birth weight by gestational week and sex.
BMI, body mass index.

highest among children to mothers born in Denmark, Finland, Norway or Iceland (10.6%). Children with asthma or atopic eczema had increased rates of AR and children with asthma or AR had increased rates of atopic eczema.

Of those reporting atopic eczema, 55.3% reported eczema during the last 12 months, and 65.1% reported that the child had been diagnosed by a doctor. For AR, the corresponding figures were 86.3% and 61.9%, respectively.

Table 2 shows the results from the cohort analysis on atopic eczema. After adjusting for age and sex, the OR for atopic eczema and birth weight categories consistently increased with an increasing birth weight, although it was statistically significant only for the lowest birth weight category (OR = 0.74, 95% CI: 0.61–0.90), using the 2500–2999 g category as reference. When also adjusting for maternal characteristics, it slightly decreased to 0.68 (95% CI: 0.54–0.86). The OR for the continuous birth

weight variable was also significant; OR was 1.62 for a 500 g increase (95% CI: 1.27–2.06) after adjustment for maternal characteristics. A similar pattern was observed for GA, fetal growth and birth length, with increasing ORs with increasing GA, fetal growth and birth length, although significant ORs were obtained only when the outcomes were analysed as continuous variables. Once again, ORs were slightly more pronounced when adjustments were made for maternal factors. Using the doctor's diagnosis of atopic eczema as an outcome variable, we obtained similar unadjusted and adjusted ORs of birth weight, GA, fetal growth and birth length from the cohort analyses (Appendix A).

The results from the cohort analysis for AR are shown in Table 3, with ORs for birth weight, GA, fetal growth and birth length. There were no significant associations between the exposure variables and AR, and most odds ratios (OR) were close to unity.

Table 2. OR (95% CI) for atopic eczema ever in relation to the exposure variables birth weight, gestational age, fetal growth and birth length, respectively, in the cohort analyses of Swedish twins aged 9 or 12 years

Exposure variables	Model 1* N = 10 132	Model 2† N = 7535
Birth weight (g)		
≤ 1999	0.74 (0.61–0.90)	0.68 (0.54–0.86)
2000–2499	0.94 (0.81–1.09)	0.96 (0.81–1.14)
2500–2999	Ref.	Ref.
3000–3499	1.04 (0.90–1.20)	1.08 (0.91–1.28)
≥ 3500	1.12 (0.88–1.45)	1.25 (0.94–1.66)
Birth weight per 500 g	1.43 (1.17–1.74)	1.62 (1.27–2.06)
Gestational age (weeks)		
≤ 31	0.76 (0.57–1.02)	0.74 (0.52–1.04)
32–34	0.98 (0.80–1.18)	1.00 (0.79–1.25)
35–36	1.03 (0.88–1.21)	1.08 (0.90–1.29)
37–38	Ref.	Ref.
39–40	1.07 (0.90–1.26)	1.10 (0.90–1.33)
≥ 41	1.59 (1.00–2.54)	1.62 (0.94–2.81)
Gestational age per week	1.03 (1.01–1.05)	1.03 (1.00–1.06)
Fetal growth‡		
< –1.0	0.86 (0.73–1.03)	0.78 (0.64–0.97)
–1.0 to –0.5	1.01 (0.86–1.19)	0.89 (0.73–1.08)
–0.5–0.5	Ref.	Ref.
0.5–1.0	0.96 (0.81–1.13)	0.94 (0.77–1.13)
> 1.0	1.11 (0.95–1.30)	1.11 (0.92–1.35)
Fetal growth (per standard deviation)	1.07 (1.01–1.13)	1.12 (1.05–1.20)
Birth length (cm)		
≤ 39	0.72 (0.45–1.15)	0.69 (0.39–1.21)
40–44	0.94 (0.80–1.12)	1.00 (0.82–1.22)
45–49	Ref.	Ref.
≥ 50	1.15 (0.99–1.34)	1.32 (1.11–1.57)
Birth length (per centimetre)	1.03 (1.01–1.05)	1.04 (1.01–1.06)

*Adjusted for child's sex and age.

†Adjusted for child's sex, age, zygosity and parity as well as maternal age, education, smoking during pregnancy, family situation, country of birth and BMI.

‡Standard deviation score of birth weight by gestational week and sex.

OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index.

A co-twin-control analysis was performed to analyse the association between atopic eczema/AR and birth weight, after adjustment for familial (shared genetic and environmental) factors (Table 4). The analysis showed that a 500 g increase in birth weight was associated with an almost fourfold increase in odds (OR = 3.93, 95% CI: 1.55–9.98) in same-sexed twin pairs discordant for atopic eczema. There was no significant difference in effect between monozygotic and dizygotic twins ($P = 0.84$). Moreover, the estimates in each group were very similar. For monozygotic twin pairs, the OR was 4.56 (95% CI: 0.84–24.76) and for dizygotic it was 3.69 (95% CI: 1.21–11.24). Using doctor's diagnosis of atopic eczema, corresponding OR for all disease discordant same-sexed pairs was 6.52 (95% CI: 1.94–21.86). For monozygotic twins, it was 10.02 (95% CI: 0.87–115.8) and for dizygotic

Table 3. OR (95% CI) for allergic rhinitis ever in relation to the exposure variables birth weight, gestational age, fetal growth and birth length, respectively, in the cohort analyses of Swedish twins aged 9 or 12 years

Exposure variables	Model I* N = 10 896	Model II† N = 8102
Birth weight (g)		
≤ 1999	0.90 (0.71–1.15)	0.88 (0.67–1.17)
2000–2499	1.05 (0.87–1.25)	1.07 (0.87–1.32)
2500–2999	Ref.	Ref.
3000–3499	0.89 (0.73–1.08)	0.90 (0.72–1.13)
≥ 3500	0.93 (0.68–1.28)	1.00 (0.70–1.44)
Birth weight per 500 g	0.95 (0.75–1.21)	1.00 (0.75–1.33)
Gestational age (weeks)		
≤ 31	0.93 (0.66–1.33)	0.97 (0.65–1.44)
32–34	1.11 (0.88–1.40)	1.04 (0.79–1.38)
35–36	1.01 (0.82–1.24)	1.05 (0.83–1.32)
37–38	Ref.	Ref.
39–40	0.99 (0.80–1.23)	0.91 (0.70–1.17)
≥ 41	1.47 (0.84–2.58)	1.79 (0.96–3.32)
Gestational age per week	1.01 (0.98–1.03)	1.01 (0.98–1.04)
Fetal growth‡		
< –1.0	0.90 (0.73–1.12)	0.92 (0.72–1.19)
–1.0 to –0.5	0.97 (0.79–1.18)	1.04 (0.83–1.31)
–0.5–0.5	Ref.	Ref.
0.5–1.0	0.88 (0.72–1.09)	0.95 (0.75–1.20)
> 1.0	0.83 (0.67–1.03)	0.91 (0.71–1.17)
Fetal growth (per standard deviation)	0.96 (0.90–1.03)	0.98 (0.90–1.06)
Birth length (cm)		
≤ 39	0.70 (0.37–1.34)	0.56 (0.25–1.24)
40–44	0.98 (0.78–1.22)	0.96 (0.74–1.25)
45–49	Ref.	Ref.
≥ 50	0.93 (0.76–1.13)	0.98 (0.78–1.23)
Birth length (per centimetre)	1.00 (0.97–1.02)	1.00 (0.97–1.03)

*Adjusted for child's sex and age.

†Adjusted for child's sex, age, zygosity and parity as well as maternal age, education, smoking during pregnancy, family situation, country of birth and BMI.

‡Standard deviation score of birth weight by gestational week and sex.

OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index.

same-sexed pairs 5.64 (95% CI: 1.40–22.70), but there was no significant differential effect between monozygotic and dizygotic pairs ($P = 0.69$). Similar results were obtained for the association between birth length and atopic eczema (Table 4). The co-twin-control analysis showed no evidence of association between AR and birth weight.

In the cohort analysis, the association between birth weight and atopic eczema was slightly more pronounced among children who had asthma than among those who did not, but the difference was not significant ($P = 0.08$). For doctor's diagnosis of atopic eczema, there were statistically significant interaction effects with sex regarding birth weight and birth length ($P = 0.003$ – 0.045), such that the protective effect of being small was more pronounced for boys than for girls, while the negative effect (more eczema) of being large was more pronounced

Table 4. Conditional logistic regression with birth weight and birth length as a continuous predictor for atopic eczema and allergic rhinitis ever, using the twin pairs that are discordant regarding disease in a sample of monozygotic (MZ) or dizygotic (DZ) same-sexed twins

	Zygosity	Number of pairs	OR (95% CI)	P-value for differential effect
Birth weight (per 500 g)				
Atopic eczema	All same sex	480	3.93 (1.55–9.98)	0.84
	MZ	158	4.56 (0.84–24.76)	
	DZ same sex	322	3.69 (1.21–11.24)	
Atopic eczema, diagnosis	All same sex	305	6.52 (1.94–21.86)	0.69
	MZ	91	10.02 (0.87–115.8)	
	DZ same sex	214	5.64 (1.40–22.70)	
Allergic rhinitis	All same sex	332	0.85 (0.28–2.59)	0.48
	MZ	134	1.50 (0.22–10.24)	
	DZ same sex	198	0.64 (0.16–2.52)	
Birth length (per cm)				
Atopic eczema	All same sex	480	1.14 (1.04–1.27)	0.11
	MZ	158	1.31 (1.07–1.60)	
	DZ same sex	322	1.09 (0.97–1.22)	
Atopic eczema, diagnosis	All same sex	305	1.23 (1.08–1.40)	0.37
	MZ	91	1.37 (1.05–1.79)	
	DZ same sex	214	1.19 (1.03–1.38)	
Allergic rhinitis	All same sex	332	1.02 (0.91–1.13)	0.83
	MZ	134	1.00 (0.84–1.19)	
	DZ same sex	198	1.03 (0.89–1.18)	

Odds ratios (OR) are given for an increase of birth weight in 500 g or an increase in birth length with 1 cm with 95% confidence intervals (95% CI) together with P-value for differential effect between MZ and DZ.

among girls (data not shown). The corresponding interaction effects were non-significant for our main outcomes, self-reported atopic eczema and AR, with P-values 0.058–0.15.

Discussion

In the cohort analysis, we found that the risk of childhood atopic eczema increased with an increasing birth weight. In the co-twin-control analysis, ORs did not decrease, and they did not differ between monozygotic and dizygotic pairs, indicating that genetic or shared environmental factors do not account for the association. There was no evidence of an association between birth characteristics and AR. Thus, our results, based on the largest twin study on birth characteristics and childhood atopic eczema and AR to date, support the hypothesis that fetal growth *per se* influences the risk of atopic eczema but not AR in childhood.

Atopic eczema is a multi-factorial disease, which implies that the individual propensity to become affected is influenced both by genes and environmental factors [22–24]. Although genes contribute substantially to the aetiology of the disease, they cannot explain the rapid increase in incidence in the past decades [25, 26]. Previous studies investigating the association between birth weight and atopic eczema have shown inconsistent results. Some studies have reported that high birth weight [4–6] and high GA [4, 7] lead to an increased risk of atopic eczema, while others found no significant associations [8–11]. For

AR, the results from previous studies are similar, with some studies presenting positive relations between high birth weight and AR [9,12,13], and others with no significant associations [8,10,11,14]. To our knowledge, there are no studies showing a reversed association with birth weight or GA, neither for atopic eczema nor AR. Thus, our results confirm and further strengthen some of the previous study results.

Atopic eczema is regarded as one of the first manifestations in the 'allergic march' for subsequent allergic diseases such as sensitization, asthma and AR [27–30], and additional studies have suggested that sensitization in young age may precede asthma later in life [27, 31]. We have found previously that a low birth weight and low GA increases the risk for subsequent childhood asthma [17]. However, all children with atopic eczema do not subsequently develop AR or asthma. In order to study whether the association between fetal growth and eczema differs between children who develop asthma and those who do not, we tested if there was a differential effect of birth weight. We found that the positive association between birth weight and atopic eczema was slightly, although not significantly, more pronounced among children who had asthma than among those who did not. Mechanisms to explain why the association between fetal growth and asthma or atopic eczema goes in opposite directions may be sought in the timing of the growth impairment during pregnancy. Ideally, future studies should include intrauterine measures of growth in repeated ultrasonic measures of fetal dimensions such as femur length and biparietal diameter.

The explanation of the positive association between fetal growth and atopic eczema can either be fetal growth *per se* or be found in factors that influence fetal growth. Such factors can be familial (e.g. maternal nutrition, BMI, smoking and socio-economic factors), factors specific to the fetus (e.g. individual nutrition or oxygen supply) or genetic factors. The co-twin-control analysis within twin pairs discordant for atopic eczema gave us the possibility to disentangle if the association between birth weight and atopic eczema obtained in the cohort analysis is confounded by familial (genetic and shared environmental) factors. Because twin siblings have identical GA, discordance in birth weight within twin pairs reflects factors affecting growth of each individual fetus. Moreover, because twins have the same parents, the co-twin-control analyses are adjusted for maternal and paternal anthropometric factors, which is important when studying fetal growth. In monozygotic twins, the association is also independent of genetic factors. As far as we know, this is the first study including this kind of analysis of the association between birth weight and atopic eczema.

Our results from the co-twin control analyses do not indicate a difference in strength in the association between birth weight and atopic eczema between monozygotic and dizygotic same-sexed twins, which may imply that the association between birth weight and atopic eczema is independent of genetic factors. Furthermore, because the magnitude of association did not decrease in the co-twin-control analyses compared with the cohort analyses, it indicates that fetus-specific factors are involved in the causal pathway [15]. Such fetus-specific factors could also be effects of fetal growth. One such possible explanation could be that babies with restricted fetal growth obtain a more immature immune system and will not develop sensitization and atopic eczema as easily as the fetuses without impaired fetal growth [3]. While Th2-skewed responses in the fetus is fundamental for the maintenance of pregnancy [32], a rapid suppression of Th2 responses in non-atopic and a consolidation of Th2 responses in atopic individuals can be observed during the first year of life [33]. It is possible that these immunological mechanisms are not fully developed due to impaired fetal growth.

Information on the outcome variables was collected in telephone interviews with the parents, while information on exposure was register based (Medical Birth Register). There could be a risk of misclassification of type of eczema or forgetting to report episodes of atopic eczema. The latter would probably be more likely in cases with mild symptoms. The effect of a random misclassification in the outcome variable would be an increased standard error and consequently our confidence intervals would be wider than if there had been no random misclassification. Regarding the effect of birth weight on AR, there may be limitations in assessing this outcome with questionnaires

rather than objective measures. There is also a clear risk of misclassification of AR and usual upper respiratory tract infections. Misclassifying affected children as unaffected would bias the OR estimates downwards. Thus, misclassification could be a possible explanation for the lack of association between hayfever and fetal growth.

Generalizability of our findings in twins to the general population may be a concern, due to the fact that *in utero* conditions for twins might differ from singletons. Twins are generally more growth restricted *in utero* than singletons [34]. There may also be differences in the prevalence of atopic eczema and AR between twins and singletons. In a cross-sectional study of Schultz Larsen et al. [35], cumulative incidence of atopic eczema and AR in Sweden was reported to be 15.5% and 5.9%, respectively, which correlates well to the rates of our twin study (15.6% and 8.4%). Bråbäck and Hedberg [13] have compared prevalence of AR in the past 12 months among singletons and twins in ~165 000 Swedish conscripts and found a prevalence of 15% among singletons and 11% among twins. However, the main issue is whether there are differences between twins and singletons that modify the estimates of the association between fetal growth and the disease [36], an issue that needs further attention.

In conclusion, our findings suggest that there is a positive association between fetal growth and childhood atopic eczema, which is independent of GA, shared (familial) environmental and genetic factors. This is not the case for AR, and emphasizes that atopic eczema and AR have different aetiologies.

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Appendix A

Appendix A1. OR (95% CI) for doctor's diagnosis of atopic eczema ever in relation to the exposure variables birth weight, gestational age, fetal growth and birth length, respectively, in the cohort analyses of Swedish twins aged 9 or 12 years

Exposure variable	Model I* N = 10 132	Model II† N = 7535
Birth weight (g)		
≤ 1999	0.77 (0.61–0.98)	0.79 (0.60–1.04)
2000–2499	0.86 (0.72–1.03)	0.91 (0.74–1.12)
2500–2999	Ref.	Ref.
3000–3499	1.01 (0.85–1.21)	1.09 (0.89–1.34)
≥ 3500	1.12 (0.83–1.50)	1.27 (0.91–1.79)
Birth weight per 500 g	1.43 (1.12–1.82)	1.52 (1.13–2.03)
Gestational age (weeks)		
≤ 31	0.77 (0.54–1.11)	0.90 (0.60–1.35)
32–34	1.04 (0.83–1.32)	1.13 (0.87–1.48)
35–36	0.99 (0.81–1.21)	1.14 (0.91–1.42)
37–38	Ref.	Ref.
39–40	1.15 (0.95–1.41)	1.29 (1.03–1.62)
≥ 41	1.47 (0.81–2.67)	1.41 (0.68–2.94)
Gestational age per week	1.03 (1.00–1.06)	1.03 (0.99–1.06)
Fetal growth‡		
< –1.0	0.81 (0.65–0.99)	0.74 (0.58–0.96)
–1.0 to –0.5	1.05 (0.86–1.27)	0.93 (0.74–1.17)
–0.5–0.5	Ref.	Ref.
0.5–1.0	0.84 (0.68–1.02)	0.81 (0.64–1.02)
> 1.0	1.10 (0.91–1.33)	1.12 (0.90–1.40)
Fetal growth per standard deviation	1.06 (0.99–1.14)	1.10 (1.02–1.20)
Birth length (cm)		
≤ 39	0.76 (0.44–1.34)	0.74 (0.37–1.46)
40–44	1.03 (0.84–1.26)	1.14 (0.90–1.44)
45–49	Ref.	Ref.
≥ 50	1.16 (0.97–1.39)	1.36 (1.10–1.67)
Birth length (per centimetre)	1.02 (0.99–1.04)	1.02 (0.99–1.05)

*Adjusted for child's sex and age.

†Adjusted for child's sex, age, zygosity and parity as well as maternal age, education, smoking during pregnancy, family situation, country of birth and BMI.

‡Standard deviation score of birth weight by gestational week and sex.

OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index.