

Perinatal characteristics and obstetric complications as risk factors for asthma, allergy and eczema at the age of 6 years

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Summary

Background Considerable effort has been put into identifying early determinants for atopic disorders. Many studies have evaluated the role of fetal development and obstetric complications. However, the results are not unequivocal.

Study objective To assess the relationship between perinatal characteristics and obstetric complications, and the presence of reported current asthma, allergy and eczema at the age of 6 years in the framework of a previously conducted study.

Method Seven hundred families in the Netherlands with index children born in 1988–1990 were retrospectively selected. Data were extracted from the Municipal Health Service's records of health examinations of these children and their siblings. These examinations were carried out at the age of 6 years. The records contained data on reported atopic disorders and perinatal characteristics.

Results Gestational age was inversely related to the risk of asthma (P for trend: 0.03). Children with low birth weight tended to have a lower risk of any allergy, albeit not significant ($P = 0.07$). However, no link was found between neonatal head circumference and atopic disorders. The ratio of neonatal head circumference to birth weight was positively associated with the risk of atopic disorders, especially with the risk of asthma (odds ratio (OR) = 1.87; 95% confidence interval (CI_{95%}) = [1.11, 3.15]).

Vacuum extraction was a risk factor for allergy (OR = 1.84, CI_{95%} = [1.03, 3.28]), but not for asthma. Induced labour was positively associated with the risk of inhalant allergy (OR = 2.22, CI_{95%} = [1.09, 4.51]) and, to a lesser extent, asthma (OR = 1.72, CI_{95%} = [0.95, 3.10]). For caesarean section and forcipal extraction there were no such relationships.

Conclusions Prematurity is a risk factor for asthma reported at 6 years. A high ratio of head circumference to birth weight is a risk factor for any atopic disorder. Vacuum extraction was associated with a higher risk of allergy, and induced labour is a risk factor for inhalant allergy. All results should be viewed with the possibility of residual confounding.

Keywords allergy, asthma, birth weight, eczema, gestational age, neonatal head circumference

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Introduction

The prevalence of asthma and allergic disorders has increased over the past decades and much effort has gone into identifying risk factors for these disorders. The relationship between fetal development and obstetric complications with childhood asthma and atopic disorders has been studied extensively [1–27]. Results are not unequivocal: although several studies have reported that low gestational age (or low birth weight) is a risk factor for the development of subsequent asthma [3, 4, 6, 11, 20, 21], others could not confirm this relationship [8, 10, 13, 16, 27]. Similarly, although some studies have found a link between high

gestational age (or high birth weight) and either a high risk of asthma, atopic disease or a high IgE concentration [5, 9, 16, 21], other studies have not [7, 8, 12, 13]. A positive association between neonatal head circumference and total IgE concentration was first reported in 1994 [5] and confirmed by others [12–14]. This finding raised the hypothesis that this positive association might reflect the long-term effect of sustaining fetal brain growth at the expense of the trunk, in particular the thymus [5]. More recently, this hypothesis was challenged by the finding that thymus size is not related to allergic disease [18] and that the relationship between the ratio of head circumference to birth weight and hayfever is negative [24].

Several studies found that caesarean section is a risk factor for subsequent development of asthma [15, 19, 20, 23, 26] and allergic disease [18, 23, 24], although this last result was not confirmed by Xu et al. [19]. Other complications during

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labour (vacuum extraction, forcipal extraction and induced labour) were also found to be positively related to the risk of asthma [15, 20].

Within the framework of a retrospective study of birth order and sibship size as risk factors for reported asthma, allergy and eczema in children [28] we recorded various perinatal characteristics (gestational age, birth weight and neonatal head circumference) and obstetric complications. Because of the lack of consensus mentioned above, we aimed to contribute a piece of evidence to the bulk of results that already exists. The current study focused on the relationships between perinatal characteristics and obstetric complications on the one hand and asthma, allergy and eczema as reported during health examinations at age 6 years on the other.

Methods

Study area and population

Population, sample size calculation and blinding have been described in detail elsewhere [28]. Briefly, data on health check-ups in children of 700 families were extracted from the files of a Municipal Health Service in the Netherlands. Only families with at least two children were included and index children were born in 1988–1990. The files contained health data from birth up to the examination at the age of 6 years. These examinations are approximately monthly during the first year of life, but primary schoolchildren get only one routine comprehensive examination at 6 years.

Data extraction

All data, including those on current atopic disorders, were extracted from the records as reported by the physician who did the check-up, or as reported in a questionnaire filled out by the parents, or as reported in letter(s) from a paediatrician/pulmonologist that was included in the file. The following items were extracted: gestational age, birth weight, neonatal head circumference, any obstetric complications, birth order, sibship size, date of birth, gender, year of birth of the mother, ZIP code, parents' country of birth, breadwinner's occupation, atopic disorders in the parents, diphtheria tetanus pertussis poliomyelitis (DTPP) vaccination status and duration of breastfeeding, diagnosis of current asthma, allergy, eczema and specific medication for these disorders at the age of 6 years and date of check-up. Length at birth was also recorded in the files, but we did not use this characteristic, as it is an unreliable measure [29].

Statistical analysis

We evaluated the relationship between perinatal characteristics (gestational age, birth weight, neonatal head circumference and the ratio of neonatal head circumference to birth weight) and obstetric complications (caesarean section, vacuum extraction, use of forceps, induced labour) on the one hand and, on the other, reported asthma, inhalant allergy (including house-dust mite, pollen, furry pets, hayfever, rhinitis), eczema (including food allergy), allergy (inhalant allergy and/or eczema), and any atopic disorder (asthma and/or allergy). Gestational age was categorized as follows: <36,

36–<41 and ≥ 41 weeks. Birth weight was categorized in <2500, 2500–<4500 and ≥ 4500 g, head circumference in <37 and ≥ 37 cm, and the ratio of head circumference and birth weight in below the median and greater than or equal to the median. The analysis was carried out within families by means of logistic regression for correlated measurements (generalized estimating equations) [30]. With this technique correlation between family members is taken into account. Analyses were performed both in univariate and multivariate models with adjustments for the subset of the following possible confounders which changed the univariate point estimate by at least 10% [31]: sibship size, birth order, year of birth, season of birth, gender, age at the time of check-up, atopic disease of the parents, level of occupation of the breadwinner, age of the mother at the time of delivery, level of urbanization, country of origin and DTPP vaccination status. For the relationships with obstetric complications we also considered gestational age, birth weight, neonatal head circumference and the ratio of neonatal head circumference to birth weight as possible confounders. However, because obstetric complications are likely to be intermediate variables in the relationship between perinatal data and atopic disorders, these complications were not considered as confounders. Similarly, in the relationships between perinatal data and atopic disorders, we did not consider the remaining perinatal data as confounders, because these variables are very likely to be strongly correlated and including them in the model could obscure possible relationships. A two-sided *P*-value of 0.05 was considered significant. For the risk factors with more than two categories (gestational age and birth weight) we also performed tests for linear trend. Breastfeeding was excluded from the model for two reasons: Firstly, the causal pathway between breastfeeding and atopy is unclear, and may be in two directions: breastfeeding may have implications for the development of atopic disorders [32, 33], but on the other hand mothers of children who are at risk of developing an atopic disorder are commonly advised to breastfeed [34]; secondly, breastfeeding may act as an intermediate variable in the relationship between perinatal factors and allergic disorders: adjustment for this variable could conceal any of the relations studied.

For many children one or more of the perinatal characteristics was missing and consequently sometimes an adjusted analysis became problematic. In case no adjusted analysis was feasible we used a multiple imputation technique with five imputed data sets [35]. Analyses were carried out for these five sets and results were pooled. Imputation was done with IVEware version 2.0. For all other analyses SPSS (version 11) and SAS (version 8.2) were used.

Results

Data were obtained on 1961 children from 700 families. At least one atopic parent was present in 150 families (21%); of 606 families (87%) both parents were born in the Netherlands. Health check-up data at the age of 6 years were available for 1727 of the children (88%). The average age at which the health check-up was performed was 5.9 years (SD: 0.6 years). Gestational age was recorded for 1666 children

Table 1. Perinatal data and obstetric complications

Perinatal data	<i>n</i>	%
Gestational age (weeks)		
< 36	62	3
36 – < 41	1250	64
≥ 41	354	18
Unknown	295	15
Birth weight (g)		
< 2500	81	4
2500 – < 4500	1601	82
≥ 4500	28	1
Unknown	251	13
Neonatal head circumference (cm)		
< 37	788	40
≥ 37	73	4
Unknown	1100	56
Ratio head circumference to birth weight (cm/g) (median = 0.01015)		
< median	429	22
≥ median	432	22
Unknown	1100	56
Obstetric complications		
Caesarean section		
Yes	85	4
No	1627	83
Unknown	249	13
Vacuum extraction		
Yes	92	5
No	1620	83
Unknown	249	13
Forciple extraction		
Yes	26	1
No	1686	86
Unknown	249	13
Induced labour		
Yes	129	7
No	1583	81
Unknown	249	13

(85%), birth weight for 1710 children (87%) and neonatal head circumference for 861 children (44%). For 246 children (14%) at least one of the atopic disorders under study was reported. For further details of the 700 families and their 1961 children we refer to a previous publication on this study [28]. Perinatal characteristics and obstetric complications are presented in Table 1, data on the health examinations at age 6 years in Table 2.

Relations of perinatal data and atopy

Table 3 shows the relationships (prevalences, odds ratios (ORs) and adjusted ORs) between the perinatal data and asthma, inhalant allergy, eczema, any allergy or any atopic disorder.

Gestational age was inversely related to the risk of asthma (*P* for trend: 0.03): children born after a gestational period of less than 36 weeks had a higher risk of asthma (OR = 2.03, 95% confidence interval (CI_{95%}) = [1.03, 4.01]), whereas

Table 2. Data on health check-ups at age 6 years in 1727 of the 1961 children included in the study

	<i>n</i>	%
Health check-up file		
Available	1727	88
Not available	234	12
Data on 1727 children from available health check-up records		
Asthma		
Yes	153	9
No	1574	91
Inhalant allergy		
Yes	77	4
No	1650	96
Eczema		
Yes	106	6
No	1621	94
Allergy (inhalant allergy and/or eczema)		
Yes	160	9
No	1567	91
Atopic disorder (any)		
Yes	246	14
No	1481	86
	<i>n</i>	Mean (SD)
Age (years) at check-up	1727	5.9 (0.6)

children born after a gestational period of 41 weeks or more had a lower risk (OR = 0.71, CI_{95%} = [0.44, 1.14]).

Children with low birth weight tended to have a lower risk of allergy compared with children with normal birth weight, although the relationship was not significant (*P* = 0.07). This relationship was of similar magnitude in the subgroup of children of normal gestational age (data not shown).

Neonatal head circumference showed no significant relationships with the outcome variables. However the ratio of neonatal head circumference to birth weight showed a significant relationship with atopic disorders: children born with a large head circumference relative to their weight had a higher risk of asthma and 'any atopic disorder'.

Obstetric complications

After adjustment for confounders neither caesarean section nor forciple extraction were related to the outcome variables (Table 4). However, vacuum extraction was related to a higher risk of allergy, whereas induced labour was associated with a higher risk of inhalant allergy. There was some evidence of a higher risk of asthma in children delivered after induced labour, although this was not significant in the adjusted model (*P* = 0.07).

Discussion

The present study showed that gestational age is inversely related to the risk of asthma and that a high ratio of neonatal head circumference to birth weight is a risk factor for atopic disorders, especially asthma. Both vacuum extraction and induced labour appeared to be related to a higher risk of allergic disease.

Table 3. Atopic disorders by perinatal data: prevalences (%) and crude and adjusted (adj) odds ratios (ORs) with 95% confidence intervals (CI_{95%})

	Asthma				Inhalant allergy				Eczema				Allergy (inhalant allergy and/or eczema)				Any atopic disorder			
	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}
Gestational age (weeks)																				
<36	18.3	2.28	2.03	1.03–4.01	3.3	0.67	0.58	0.17–1.96	1.7	0.27	0.30	0.14–1.97	3.3	0.32	0.32	0.09–1.17	18.3	1.29	1.13	0.55–2.32
36–<41*	9.2	1.00	1.00	–	5.1	1.00	1.00	–	6.1	1.00	1.00	–	9.8	1.00	1.00	–	14.8	1.00	1.00	–
≥41	6.0	0.73	0.71	0.44–1.14	3.2	0.63	0.60	0.31–1.16	6.3	1.04	1.06	0.64–1.74	8.0	0.81	0.78	0.50–1.20	11.2	0.77	0.77	0.53–1.12
P-value for trend		0.03	0.03			0.24	0.22			0.37	0.39			0.92	0.77			0.12	0.16	
Birth weight (g)																				
<2500	12.3	1.32	1.35	0.60–3.00	3.7	0.75	0.67	0.20–2.25	2.5	0.40	0.38	0.09–1.57	3.7	0.37	0.34	0.11–1.09	12.3	0.81	0.79	0.37–1.69
2500–<4500*	8.6	1.00	1.00	–	4.7	1.00	1.00	–	6.2	1.00	1.00	–	9.5	1.00	1.00	–	14.1	1.00	1.00	–
≥4500	3.7	0.55	0.41	0.07–2.44	0.0	0.37†	–	–	7.4	1.21	1.54	0.35–6.76	7.4	0.77	0.95	0.22–4.10	7.4	0.52	0.52	0.13–2.05
P-value for trend		0.33	0.24			0.75				0.12	0.09			0.09	0.05			0.98	0.93	
Head circumference (cm)																				
<37 cm*	8.7	1.00	1.00	–	4.7	1.00	1.00	–	6.3	1.00	1.00	–	9.7	1.00	1.00	–	14.3	1.00	1.00	–
≥37 cm	9.1	1.11	1.02	0.34–2.80	4.5	0.92	0.72	0.20–2.55	4.5	0.75	0.72	0.22–2.32	9.1	0.94	0.82	0.33–1.99	12.1	0.87	0.80	0.34–1.84
P-value		0.81	0.96			0.89	0.61			0.63	0.58			0.89	0.66			0.73	0.59	
Ratio of head circumference/birth weight																				
<median*	6.3	1.00	1.00	–	3.4	1.00	1.00	–	5.1	1.00	1.00	–	7.5	1.00	1.00	–	11.1	1.00	1.00	–
≥median	11.1	1.80	1.87	1.11–3.15	6.0	2.01	1.61	0.81–3.19	7.2	1.46	1.25	0.20–2.24	11.8	1.68	1.50	0.93–2.44	17.1	1.68	1.68	1.11–2.54
P-value		0.02	0.02			0.03	0.17			0.20	0.45			0.03	0.10			0.01	0.01	

*Reference category.

†Because of the absence of children allergic for airborne allergens in the group with high birth weight (both in the original and in the imputed data) no OR could be estimated by the usual method. We omitted the multivariate analysis for this relation and only estimated a univariate OR and CI_{95%} (0.02–6.11) by adding 0.5 to all cells, also ignoring the correlation between family members.**Table 4.** Atopic disorders by obstetric complications: prevalences (%) and crude and adjusted (adj) odds ratios (ORs) with 95% confidence intervals (CI_{95%})

	Asthma				Inhalant allergy				Eczema				Allergy (inhalant allergy and/or eczema)				Any atopic disorder			
	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}	%	OR	OR _{adj}	CI _{95%}
Caesarean section																				
No*	8.5	1.00	1.00	–	4.7	1.00	1.00	–	6.1	1.00	1.00	–	9.2	1.00	1.00	–	13.8	1.00	1.00	–
Yes	12.3	1.31	1.03†	0.51–2.08	2.5	0.41	0.57	0.12–2.76	4.9	0.80	0.94	0.26–3.33	7.4	0.73	0.86	0.31–2.40	17.3	1.14	1.12†	0.56–2.24
P-value		0.50	0.93			0.28	0.48			0.73	0.40			0.53	0.77			0.71	0.74	
Vacuum extraction																				
No*	8.7	1.00	1.00	–	4.3	1.00	1.00	–	5.8	1.00	1.00	–	8.7	1.00	1.00	–	13.7	1.00	1.00	–
Yes	8.7	1.03	0.92†	0.43–1.98	8.7	2.20	1.53	0.68–3.44	9.8	1.83	1.67	0.83–3.35	17.4	2.29	1.84	1.03–3.28	19.6	1.61	1.68	1.01–2.79
P-value		0.94	0.83			0.04	0.31			0.08	0.15			0.003	0.04			0.05	0.04	
Forcible extraction																				
No*	8.6	1.00	1.00	–	4.6	1.00	1.00	–	6.0	1.00	1.00	–	9.2	1.00	1.00	–	13.9	1.00	1.00	–
Yes	15.4	1.14	1.44†	0.48–4.28	3.8	0.88	0.77†	0.10–5.93	3.8	0.74	0.59	0.09–3.94	7.7	0.91	0.62†	0.14–2.65	19.2	1.22	0.98	0.30–3.14
P-value		0.84	0.52			0.90	0.80			0.74	0.59			0.89	0.52			0.71	0.97	
Induced labour																				
No*	8.1	1.00	1.00	–	4.2	1.00	1.00	–	6.1	1.00	1.00	–	9.1	1.00	1.00	–	13.5	1.00	1.00	–
Yes	17.2	1.78	1.72	0.95–3.10	8.6	1.93	2.22	1.09–4.51	5.2	0.86	1.47	0.50–4.36	10.3	1.07	1.25	0.66–2.37	20.7	1.42	1.49	0.91–2.44
P-value		0.04	0.07			0.07	0.03			0.72	0.49			0.83	0.50			0.15	0.12	

*Reference category.

†Because of lack of data no estimations were possible in the adjusted model; we used the five imputed data sets in order to estimate ORs and CI_{95%}.

Perinatal data

Gestational age was in the present study shown to be related to a higher risk of asthma at 6 years. This is a confirmation of earlier findings [4, 6]. One study relating gestational age to asthma in adulthood reported a similar result [11], but two other studies did not find this relation [10, 16]. Kuehr et al. [2] reported an increased sensitization to aeroallergens in children born with a low gestational age. High gestational age was found to be associated with the risk of atopic dermatitis [9] and atopy [16], low gestational age was reported to be protective for rhinitis [11]. Even though the observed

relationships were not significant, our data tend to support these findings. A lack of association was reported earlier: between gestational age and the risk of sensitization to aeroallergens [7] and the risk of any atopy [8].

Low birth weight has been shown to be associated with a higher risk of asthma [1, 3, 4, 6, 20, 21], whereas high birth weight has been shown to be positively related to total IgE [5], the risk of atopic dermatitis [9] and the risk of asthma [12, 21]. The result of the present study, showing an inverse relationship between birth weight and the risk of asthma, although not statistically significant, is in concordance with the literature. Although a higher risk of asthma or a higher risk

of atopic dermatitis in children with high birth weight could not be confirmed in this study, we observed a lower risk of eczema in low birth weight children. This was also reported by Siltanen et al. [17]. An explanation for the higher risk of asthma in prematurely born children and low birth weight children might be that these conditions are characterized by disturbed lung growth and result in reduced lung function. Small airway size gives rise to wheezing symptoms during viral infections, especially in the first year of life, and this is often labelled as asthma [36].

Neonatal head circumference was not found to be related to any of the outcome variables in the present study. Several studies have reported positive relationships between neonatal head circumference and the risk of asthma or increased total IgE [5, 8, 12–14], although the findings are not unequivocal. Some studies reported the lack of a relationship with asthma [10, 12, 13] or atopic disorders [8, 12, 13]. The positive relationship between neonatal head circumference and total IgE concentration has raised the hypothesis, put forward by Godfrey et al. [5], that a sustaining brain growth at the expense of the trunk, in particular the thymus, promotes the development of atopic disease. However, this hypothesis has been falsified by Benn et al. [18] who found a positive relationship between neonatal head circumference and thymus size in the first week of life. He also showed that neonatal thymus size is not associated with allergic disease at the age of 5 years. Katz et al. [24] examined the relationship between hayfever and the ratio of neonatal head circumference to birth weight, a measurement which better reflects the relative growth of the brain than absolute neonatal head circumference. They found that children with a high ratio had a lower risk of hayfever. Our own results suggest an increased risk of atopy in newborns with a relatively large ratio of neonatal head circumference to birth weight and hence support the hypothesis put forward by Godfrey et al. [5].

Obstetrical complications

Children delivered by caesarean section have a higher risk of asthma [15, 19, 23, 26], and allergy [18, 23]. Other obstetric complications are also reported to be associated with an increased risk of asthma [15, 20]. Although, in line with other studies [15, 19, 23, 26], we found a 50% higher prevalence of asthma in children delivered by caesarean section, the relationship disappeared after adjustment for confounding factors. One of these confounding factors was the ratio of neonatal head circumference to birth weight in the multivariate model. However, neither this measure nor neonatal head circumference alone was considered as a confounder in the four studies mentioned. We therefore suggest that the excess risk found in other studies may be because of residual confounding.

Like Xu et al. [19] we did not observe a relationship between caesarean section and allergy. Unlike them [15], however, we did not find an excess risk of asthma in children delivered with vacuum extraction, although we did find an increased risk of allergy in such children. Children delivered after induced labour had a higher risk of inhalant allergy and (to a lesser extent) asthma; Annesi-Maesano et al. [20] also found a weak relationship with asthma. The mechanisms underlying the relationships between obstetric complications

and atopic disorders are unclear. It has been suggested that incubator care, being more probable after a delivery with complications, might delay the contact of the newborn with microbes and thus affect the Th2 → Th1 shift [15].

Limitations of this study

As stated before [28] the data used in this study were obtained from routinely collected records and we cannot exclude inaccuracy of data, including under- or overreporting of the diseases under study. Therefore it is possible that some of the relationships found in this study are due to residual confounding.

Selection bias cannot be excluded, because, due to the study design, families with only one child were not included. Consequently possibly atopic children with perinatal problems are underrepresented in this study. This may have attenuated the resulting relationships.

Neonatal head circumference was often not recorded, because this measurement is generally not performed in home deliveries. Firstly, this affected the power of the statistical tests. Secondly, while analyses with this variable were probably restricted to a selected population (i.e. hospital deliveries), this could have yielded spurious results. However, missing data on neonatal head circumference was not related to any of the outcome measures, and hence selection bias can be excluded. Provided a report of the delivery was available, the other perinatal variables were complete. The lack of a delivery report is unlikely to be related to the health status of the newborn or the child at the age of 6 years: files with missing delivery reports were either very old or contained data of children born in a different region or country.

No data were available on smoking by the mother during pregnancy. Intrauterine exposure to tobacco components is related to both birth weight and childhood respiratory symptoms [37] and should therefore be considered as an important confounder in the relationship between asthma and birth weight. Therefore the weak relationship observed between birth weight and asthma could be because of residual confounding. However, other studies which did adjust for smoking during pregnancy reported the same relationship.

Because no distinction could be made between the different phenotypes of asthma at the age of 6 years and observations at earlier ages were lacking, we could not examine associations pertaining to a specific phenotype.

Conclusion

Prematurity is a risk factor for asthma at 6 years, and special procedures during delivery, such as vacuum extraction and induced labour, are associated with a higher risk of atopic disorders. We also demonstrated that a high ratio of neonatal head circumference to birth weight is related to a higher risk of atopic disorders. Although some of these results confirm earlier findings, all results should be viewed with the possibility of residual confounding. Therefore further research into these relationships and their underlying mechanisms is needed. A better understanding could contribute to the prevention of atopic diseases.

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