Perinatal Risk Factors for Hay Fever — A Study Among 2550 Finnish Twin Families

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Previous studies have suggested that perinatal factors influence the risk for asthma but population studies on perinatal factors and risk for hay fever are few. We studied the effect of perinatal factors on the risk for hay fever among adolescent twins by a questionnaire study involving five consecutive nation-wide birth cohorts of 16-year-old twins and their parents. The risk for parent-reported, doctor-diagnosed hay fever in the adolescents associated with several perinatal characteristics was assessed with logistic regression analysis among individuals and by a discordant pair analysis. In the univariate analysis of the birth factors, the risk for hay fever increased with increasing birth weight (p for trend = 0.048, OR for those ≥ 3000g 1.35, 95% CI 0.91–2.02 compared to those < 2000g) and gestational age (p for trend = 0.04, OR for those born after 40 weeks of gestation 2.24, 95% CI 1.03–4.86, compared to those born before 33 weeks of gestation) and was lower in those subjects hospitalised in the neonatal period (OR 0.74, 95% CI 0.58–0.93). Because of significant interactions between parental hay fever status and birth factors (ponderal index, p = 0.03 and maternal age p = 0.04), stratified analysis were performed. The positive association between birth weight and hay fever was most obvious among adolescents with no parental history of hay fever (p for trend = 0.03). Similar, though not significant, trends were found with other birth factors among these families, whereas no such trend was found among adolescents with parental hay fever, suggesting that gestational maturity increases the risk for hay fever in the absence of genetic predisposition. However, of the perinatal factors only neonatal hospitalisation (OR 0.75, 95% CI 0.59–0.96) remained a significant risk factor for the development of hay fever, when adjusted for non-perinatal factors.

Several studies have examined perinatal determinants of asthma but the perinatal risk factors for hay fever and other atopic manifestations have drawn less attention; although the environmental risk factors for hay fever have been relatively well studied, few population studies have assessed perinatal risk factors in consideration to non-perinatal factors.

Previous studies have suggested high maternal age (Bråbäck & Hedberg, 1997; Butland et al., 1997; Strachan et al., 1996) as a risk factor for hay fever, whereas high gestational age has increased the risk both for hay fever (Bråbäck & Hedberg, 1997) and atopic eczema (Olesen et al., 1997); but lack of any such association has also been reported (Fergusson et al., 1997; Svanes et al., 1998). A higher prevalence of hay fever among those of higher birth weight has also been reported (Bråbäck & Hedberg, 1997; Shaheen et al., 1999; Svanes et al., 1998). In addition, large head circumference has been associated with high total serum IgE (Godfrey et al., 1994; Gregory et al., 1999). However, the studies on perinatal factors and asthma have often shown trends opposite to those in studies on other atopic manifestations (Bråbäck & Hedberg, 1997; Frischer et al., 1993; Seidman et al., 1991).

Interestingly, multiple birth has been suggested to decrease the risk for hay fever (Bråbäck & Hedberg, 1997). This would parallel findings on the positive association between gestational age, birth weight and the risk for atopy, since prematurity and low birth weight due to preterm birth and growth retardation are common in twins (Taffel, 1995). However, the mothers of dizygous (DZ) twins tend to be older and of higher parity than mothers of singletons (Taffel, 1995). Comparative studies of atopy prevalence in twins versus singletons are scanty. Given the differences in the distribution of perinatal factors between twins and singletons, one would presume to see these differences reflected in the risk for atopic diseases.

We studied the effect of perinatal factors on the risk for hay fever in a nation-wide cohort of adolescent twins in relation to family history of hay fever and several selected social and environmental factors.

Materials and Method

The identification and characteristics of this study population, and zygosity determination have been described in detail (Räsänen et al., 1998). Briefly, for the FinnTwin16 study, Finnish families with twins born from 1975 through 1979 were ascertained from the Finnish Central Population Registry which has records of practically all twins born in Finland during that period. From 1991 through 1995, 3065 families with both twins alive and residing in Finland were

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mailed questionnaires within 2 months of the twins' 16th birthday. Each family member was mailed a personal questionnaire in addition to a family questionnaire on the birth and development of the twins. The family questionnaire was returned by 2550 (83%) families furnishing hay fever information on 4722 adolescents (93% of those in responding families).

Hay fever and asthma in these adolescents was determined by the parents' response on whether the first-born, the second-born, neither or both of the twins had been diagnosed by a doctor with either hay fever or asthma. The parents were also asked for the birth weight, birth length, and Apgar score for each twin. They stated on which gestation week the twins were born and whether the twins had to remain in hospital after birth and for what reason. Further, both parents were asked whether they themselves had been diagnosed with either hay fever or asthma, how many children they had older than the twins, and for their own occupation, smoking habits, and practice of smoking indoors when the twins were under school age (age seven). The father's occupation at the time of the survey was grouped according to the classification of the agency Statistics Finland: (1) farmers, (2) other self-employed persons, (3) upper-level employees, (4) lower-level employees, (5) manual workers, and (6) others, including students and pensioners. Because the occurrence of hay fever among adolescents with farming fathers was distinct from that of children with fathers in the other occupational groups, the other occupational groups' data were pooled. The variables and methods of the present study have been described in more detail previously (Räsänen et al., 2000).

In order to increase the reliability of the data on perinatal measures, data were examined for outliers and rechecked if necessary from the original questionnaires. Implausible perinatal data on any of the three variables (birth weight, birth length, gestational age) were excluded in 76 pairs. The ponderal index was calculated as birth weight (kg) divided by the cube of birth length (m^3; Cole et al., 1997). In order to adjust birth weight for gestation, gestation-adjusted birth weight standardised for this particular population was calculated by subtracting from the twin's birth weight the mean birth weight of all twins born in the same week of gestation and dividing this difference by the latter. The variable was then divided into fifths and grouped into three categories (lowest 1/5, second to fourth 1/5, highest 1/5).

We have used stratification by parental hay fever status as an indicator for genetic predisposition, since our previous analysis has shown a high genetic component and an almost non-existent component of shared family environment in liability to hay fever (Räsänen et al., 1998). However, we acknowledge that factors of an environmental nature may also contribute to the differences between the families with and without parental hay fever. The analysis was performed on data stratified by parental hay fever status: (1) families with unaffected parents (N = 1486) and (2) families with one parent with hay fever (N = 593). Because both parents were affected in only 86 families, these were pooled in most analyses into families with one affected parent. After stratified analysis, a similar analysis was performed on the whole data set without stratification. We also tested possible interactions between perinatal variables and parental hay fever. When testing the significance of interactions, perinatal variables were entered in the model in turn as categorised or categorised but treated as continuous with assigned rank (1, 2, 3… etc.).

Logistic regression analysis was used to calculate odds ratios (OR) for hay fever in the adolescents separately for perinatal and non-perinatal variables. First, by univariate analysis, OR's with 95% confidence intervals (CI) were calculated separately for each categorised perinatal variable: Birth weight, ponderal index, gestational age, gestation-adjusted birth weight, Apgar score, neonatal hospitalisation, and maternal age at the birth of the twins. Each variable was then adjusted by the zygosity of the twins (monozygous/ dizygous; MZ/DZ), birth order (first-born twin/ second-born twin), gender, number of older siblings (0–1/ 2 or more), and maternal smoking ever (no/ yes). Additionally, in the unstratified data set, the models were also adjusted for parental hay fever (no/ yes). For the adjusted regression models, cases with data available on all factors in each model were included. Because individual observations on twins selected as pairs may not be regarded as being totally independent, generalised estimating equations (GEE) were used in the regression analysis to correct for lack of independence (SAS Proc Genmod).

We selected as non-perinatal variables gender (male/ female), parental hay fever (no/ yes), parental asthma (no /yes), number of older siblings (0–1/ 2 or more), father's occupation (farmer/ other), parental smoking (never/ not indoors/ indoors), adolescent's own smoking status (never/ ever). The non-perinatal variables were combined in a single model to obtain the adjusted OR's. Then those perinatal and non-perinatal risk factors with at least or nearly significant ($p < 0.2$) Wald statistics were included in a single model, and backward stepwise logistic regression was performed (removal of variables based on the probability of the likelihood-ratio statistic, $p > 0.05$) in order to obtain the most parsimonious model.

For discordant pair analysis, MZ and DZ pairs discordant for hay fever were identified. Within the pairs separately for MZ and DZ birth weight, ponderal index, and Apgar score among the twins with hay fever were compared to the corresponding values among the unaffected co-twins by Wilcoxon signed rank test. In a similar fashion, categorised birth weight, ponderal index, gestation-adjusted birth weight, and neonatal hospitalisation of the twins with hay fever were compared to those of unaffected co-twins by McNemar's two-sided test.

Analyses were done with SPSS, Release 7.5.1., and SAS, Release 6.12.

Results

The overall occurrence of hay fever among the adolescents was 12.3% (582 affected individiuals). The mean birth weight of the adolescents with hay fever was 49 g higher than that of unaffected adolescents (p = 0.03), and they were less often hospitalised during the neonatal period (p = 0.04) (see Table 1). There were no statistically significant differences between the groups in birth length, ponderal index, gestational age, Apgar score, or maternal age at birth.

Table 1

Perinatal Characteristics of 16-year-old Finnish Twins by Hay Fever Occurrence

	Total number of adolescents	Adolescents without hay fever		Adolescents with hay fever		
		Mean*	(*SD*)	*n*	Mean*	(*SD*)
Birth weight (g)	4646	2663**	(526)	574	2712**	(503)
Length at birth (cm)	4546	47.2	(2.8)	564	47.4	(2.6)
Ponderal index (kg/m^3)	4540	25.2	(2.9)	563	25.4	(2.8)
Gestational age (weeks)	4101	37.0	(2.6)	509	37.2	(2.5)
Apgar score	3811	8.2	(1.8)	473	8.3	(1.8)
Neonatal hospitalisation (%)	4543	30.1***		563	25.9***	
Maternal age at birth of twins (years)	4722	28.3	(5.0)	582	28.2	(4.7)

Note: * Mean value for all variables except percentage for neonatal hospitalisation. ** Significant difference between groups ($p = 0.03$).
*** Significant difference between groups ($p = 0.04$)

Table 2

Perinatal Risk Factors for Hay Fever in 16-year-old Finnish Adolescent Twins in Families with no Parental Hay Fever. Crude and Adjusted Odds Ratios (OR) with 95% Confidence Intervals (CI) Produced by Logistic Regression Analysis and Corrected for Paired Observations by Generalised Estimating Equations.

		Proportion in category and total *N*	Occurrence of hay fever % (No. of affected)	Crude OR	95% CI	Adjusted OR*	95% CI
Birth weight (g)	<2000	11.0%	6.3% (19)	1.00		1.00	
	2000–2499	23.2%	7.8% (50)	1.09	0.65–1.82	1.05	0.62–1.79
	2500–2999	38.3%	9.2% (97)	1.25	0.78–2.03	1.28	0.77–2.11
	≥ 3000	27.5%	11.2% (85)	1.58	0.97–2.59	1.61	0.95–2.71
		N = 2753	Test for trend **	$p = 0.03$		$p = 0.03$	
Ponderal index in fourths	Lowest 1/4	25.3%	7.2% (49)	1.00		1.00	
	2nd 1/4	24.8%	8.9% (59)	1.16	0.80–1.69	1.14	0.77–1.69
	3rd 1/4	25.1%	10.3% (69)	1.34	0.92–1.95	1.36	0.92–2.00
	Highest 1/4	24.8%	10.5% (70)	1.38	0.95–2.00	1.44	0.98–2.13
		N = 2680	Test for trend	$p = 0.07$		$p = 0.04$	
Gestational age (weeks)	< 33	7.6%	8.2% (15)	1.00		1.00	
	33–36	28.9%	7.1% (50)	0.86	0.46–1.62	0.86	0.45–1.64
	37–40	60.4%	10.3% (151)	1.29	0.72–2.29	1.25	0.69–2.25
	>40	3.1%	10.5% (8)	1.33	0.47–3.73	1.32	0.46–3.78
		N = 2436	Test for trend	$p = 0.07$		$p = 0.11$	
Gestation-adjusted birth weight in fifths	Lowest 1/5	20.3%	6.5% (32)	1.00		1.00	
	2nd–4th 1/5	60.1%	9.7% (140)	1.41	0.99–2.03	1.39	0.96–2.02
	Highest 1/5	19.6%	10.6% (50)	1.54	0.97–2.44	1.49	0.92–2.43
		N = 2412	Test for trend	$p = 0.07$		$p = 0.11$	
Apgar score	≥7	90.1%	9.8% (200)	1.00		1.00	
	<7	9.9%	6.7% (15)	0.71	0.41–1.22	0.68	0.38–1.20
		N = 2262					
Neonatal hospitalisation	No	70.4%	10.0% (190)	1.00		1.00	
	Yes	29.6%	7.4% (60)	0.75	0.55–1.03	0.74	0.53–1.02
		N = 2693					
Maternal age at birth of twins (years)	<25	29.8%	8.6% (71)	1.00		1.00	
	25–30	40.3%	9.4% (106)	1.11	0.78–1.60	1.05	0.72–1.54
	>30	29.9%	9.2% (77)	1.09	0.74–1.60	1.20	0.80–1.78
		N = 2788	Test for trend	$p = 0.60$		$p = 0.30$	

Note: * OR adjusted for zygosity, birth order (A/B-twin), gender, number of older siblings, and maternal smoking. ** Wald statistic for trend in logistic regression

Table 3

Perinatal Risk Factors for Hay Fever in 16-year-old Finnish Adolescent Twins in Families with *Parental Hay Fever*. Crude and Adjusted Odds Ratios (OR) with 95% Confidence Intervals (CI) Produced by Logistic Regression Analysis and Corrected for Paired Observations by Generalised Estimating Equations.

		Proportion in category and total *N*	Occurrence of hay fever % (No. of affected)	Crude OR	95% CI	Adjusted OR*	95% CI
Birth weight (g)	<2000	8.8%	21.0% (21)	1.00		1.00	
	2000–2499	24.3%	18.9% (52)	0.83	0.49–1.39	1.03	0.58–1.83
	2500–2999	40.2%	22.0% (100)	1.08	0.65–1.79	1.33	0.75–2.34
	≥ 3000	26.6%**	19.9% (60)	0.95***	0.55–1.63	1.06	0.57–1.95
		N = 1130					
Ponderal index in fourths	Lowest 1/4	24.7%	22.5% (62)	1.00		1.00	
	2nd 1/4	24.5%	20.8% (57)	0.86	0.57–1.29	0.87	0.57–1.33
	3rd 1/4	25.2%	18.1% (51)	0.79	0.52–1.18	0.78	0.51–1.20
	Highest 1/4	25.5%**	20.4% (58)	0.90	0.60–1.35	0.87	0.56–1.34
		N = 1117					
Gestational age (weeks)	< 33	6.7%	17.6% (12)	1.00		1.00	
	33–36	28.7%	20.2% (59)	1.18	0.55–2.53	1.84	0.75–4.51
	37–40	61.8%	19.7% (124)	1.15	0.56–2.35	1.65	0.70–3.88
	> 40	2.8%	39.3% (11)	3.02	0.94–9.67	5.07	1.40–18.4
		N = 1016					
Gestation-adjusted birth weight in fifths	Lowest 1/5	18.2%	22.4% (41)	1.00		1.00	
	2nd–4th 1/5	62.2%	19.6% (123)	0.99	0.65–1.49	0.96	0.62–1.49
	Highest 1/5	19.7%**	19.7% (39)	0.97	0.57–1.63	0.89	0.50–1.57
		N = 1007					
Apgar score	≥7	89.9%	20.8% (180)	1.00		1.00	
	<7	10.1%	14.4% (14)	0.78	0.44–1.39	0.98	0.55–1.73
		N = 961					
Neonatal hospitalisation	No	70.3%	21.2% (165)	1.00		1.00	
	Yes	29.7%	19.5% (64)	0.85	0.60–1.20	0.76	0.52–1.10
		N = 1106					
Maternal age at birth of twins (years)	< 25	33.0%	22.1% (84)	1.00		1.00	
	25–30	39.1%	20.9% (94)	0.93	0.64–1.36	0.94	0.63–1.40
	> 30	27.8% ***	18.4% (59)	0.80	0.52–1.22	0.98	0.60–1.62
		N = 1150					

Notes * OR adjusted for zygosity, birth order (A/B-twin), gender, number of older siblings, and maternal smoking. ** Percentages do not add up to 100.0% due to rounding.
*** The Wald statistic for trend in logistic regression was not statistically significant for any variable.

Among the adolescents with no parental history of hay fever, there was a significant trend for higher risk for hay fever with increasing birth weight and ponderal index, when adjusted for confounders (see Table 2). The trend with increasing unadjusted ponderal index, gestational age, and gestation-adjusted birth weight was similar but did not reach statistical significance.

Among those with a parental history of hay fever, no significant trends in hay fever risk were evident (Table 3). Only those born post-term were at a higher risk for hay fever than were those born very preterm when data were adjusted for confounders.

Because interactions appeared between parental hay fever status and the assigned score for the categorised birth weight ($p = 0.07$), ponderal index ($p = 0.03$), adjusted birth weight ($P = 0.06$) and maternal age ($p = 0.04$) analysed as continuous variables, we did a further analysis in which the parental hay fever status was stratified into three categories: 1) no affected parents, 2) one affected parent, and 3) two affected parents. In the latter families, for other variables except for maternal age, the risk for any single category compared to the reference category tended to be the opposite of that observed in the families with no parental history of hay fever. However, possibly due to the small number of families with two affected parents, the results were not statistically significant.

In the data set unstratified by parental hay fever status, significant trends for increasing risk for hay fever was

Table 4

Perinatal and Non-perinatal Risk Factors for Hay Fever Combined in a Multivariate Model. Odds Ratios (OR) with 95% Confidence Intervals (CI) for Variables Selected by Backward Logistic Regression Analysis and Corrected for Paired Observations by Generalised Estimating Equations. *N* = 3438

Risk factor		Risk for hay fever	
		OR	95% CI
Neonatal hospitalisation	No	1.00	
	Yes	0.75	0.59–0.96
Gender	Male	1.00	
	Female	0.66	0.52–0.83
Parental hay fever	No	1.00	
	Yes	2.43	1.92–3.09
Number of older siblings	0–1	1.00	
	2 or more	0.68	0.50–0.94
Father's occupation	Farmer	1.00	
	Other	1.61	0.99–2.63
Parental smoking	Never	1.00	
	Ever, not indoors	1.35	0.99–1.85
	Indoors	1.01	0.70–1.45

Table 5

Perinatal and Non-perinatal Risk Factors for Hay Fever Combined in a Multivariate Model. Odds Ratios (OR) with 95% Confidence Intervals (CI) for Variables in Table 4 Additionally Adjusted for Birth Weight and Gestational Age in All Families and Stratified by Parental Hay Fever Status.

Risk factor		Risk for hay fever					
		All families (*N* = 3057)		No hay fever in the parents (*N* = 2221)		Hay fever in the parents (*N* = 836)	
		OR	95% CI	OR	95% CI	OR	95% CI
Birth weight (g)	<2000	1.00		1.00		1.00	
	2000–2499	0.94	0.59–1.49	1.01	0.51–1.99	0.84	0.44–1.59
	2500–2999	0.92	0.56–1.52	0.99	0.48–2.06	0.79	0.40–1.55
	≥ 3000	0.94	0.54–1.64	1.17*	0.52–2.62	0.64*	0.29–1.40
Gestational age (weeks)	< 33	1.00		1.00		1.00	
	33–36	1.14	0.66–1.98	0.95	0.46–2.00	1.40	0.60–3.27
	37–40	1.26	0.71–2.20	1.28	0.60–2.72	1.20	0.51–2.79
	>40	1.71	0.69–4.25	1.19*	0.35–4.10	2.89*	0.66–12.69
Neonatal hospitalisation	No	1.00		1.00		1.00	
	Yes	0.82	0.59–1.14	0.88	0.56–1.38	0.74	0.45–1.21
Gender	Male	1.00		1.00		1.00	
	Female	0.64	0.50–0.81	0.68	0.52–0.83	0.59	0.39–0.87
Parental hay fever	No	1.00					
	Yes	2.39	1.86–3.08				
Number of older siblings	0–1	1.00		1.00		1.00	
	2 or more	0.67	0.47–0.94	0.72	0.50–0.94	0.59	0.34–1.03
Father's occupation	Farmer	1.00	1.00	1.00			
	Other	1.46	0.88–2.42	2.08	1.01–4.28	0.88	0.41–1.89
Parental smoking	Never	1.00		1.00		1.00	
	Ever, not indoors	1.29	0.93–1.80	1.03	0.68–1.55	1.84	1.06–3.17
	Indoors	1.01	0.69–1.47	0.75	0.46–1.24	1.57	0.85–2.88

Note: * Test for trend was not statistically significant.

positively associated with increasing birth weight (p for trend = 0.04 before adjustment for confounders and after p = 0.048, OR for those ≥ 3000g 1.35, 95% CI 0.91–2.02 compared to those < 2000g) and with increasing gestational age (p = 0.04 after adjustment for confounders; OR for those born > 40 wk of gestation 2.24, 95% CI 1.03–4.86; data not shown). Additionally, the risk for hay fever was significantly lower among those who had been hospitalised after birth (unadjusted OR 0.80, 95% CI 0.65–0.99, adjusted OR 0.74 95% CI 0.58–0.93). Of the hospitalisations, 63% were reportedly due to prematurity.

Of those perinatal and non-perinatal variables (birth weight, neonatal hospitalisation, gender, and parental asthma and hay fever, sibship size, father's farming occupation, parental smoking) included in a single model, the following remained independent: neonatal hospitalisation, gender, parental hay fever, sibship size, father's occupation, and parental smoking (see Table 4). Gestation-adjusted birth weight was not included in the model, due to its correlation with birth weight.

When also birth weight and gestation were included in the final model, their effect on hay fever risk was not statistically significant for all families (see Table 5). The risks related to other variables remained unchanged compared to the model in Table 4. In similar multivariable models for families with and without parental hay fever, birth weight and gestational age were not significantly associated with hay fever risk; in part because the model also included the neonatal hospitalisation variable, and because sample sizes became smaller upon stratification for family history. The risks associated with gender and family size remained the same. However, father's non-farming occupation was a risk only in families without parental hay fever, while parental smoking appeared to increase the risk mostly in families with parental hay fever.

Within twin pairs discordant for hay fever, MZ twins (68 pairs) with hay fever weighed 15 grams more (median, 95% CI = –136g to 116g) than their unaffected co-twins, whereas DZ twins (253 pairs) with hay fever weighed 30 grams (95% CI = –20.0g to 82.1g) more than their unaffected co-twins. However, no statistically significant differences were observed between affected and unaffected co-twins in continuous or categorised birth weight, ponderal index, gestation-adjusted birth weight, Apgar score, or neonatal hospitalisation.

Discussion

In our study among the nation-wide birth cohort of 16-year-old twins, we relied on the parental report of both doctor-diagnosed hay fever and birth characteristics. For hay fever, this method may introduce bias towards lower occurrence with more severe cases. This should not affect the estimation of hay fever risk, since there is no reason to assume a systematic misclassification of the exposures and the outcome. We did not have access to the birth registry data on the study subjects because the Finnish Birth Registry was established only in 1987. However, birth weights of the twins participating in the study are well in accordance with the birth statistics of multiples born in Finland during that period (Anonymous, 1980). And further, studies on the accuracy of maternal recall of birth weight and gestation suggest that the method is sufficiently accurate for epidemiological purposes (McCormick & Brooks-Gunn, 1999). Recall of other birth data may be less accurate but the parents may have relied on the mother's personal maternity card for recollection.

Our results, with their consistent tendency across perinatal variables in the entire data set, show that gestational maturity increases the risk for hay fever. This is in agreement with results of birth cohort studies on allergic rhinitis (Bråbäck & Hedberg, 1997) and atopic dermatitis (Olesen et al., 1997). Other studies have shown the same tendency toward higher hay fever occurrence with higher birth weight (Butland et al., 1997; Shaheen et al., 1999; Svanes et al., 1998). Of the other hallmarks of atopy, high serum IgE levels have been associated with large head circumference (Godfrey et al., 1994; Gregory et al., 1999), and skin prick-test reactivity has been associated with low gestational age (Kuehr et al., 1992) or birth weight over 4000g (Sears et al., 1996). However, we did not observe significant differences in perinatal factors within pairs discordant for hay fever that may be due to relatively small number of discordant pairs. On the other hand, even when accounting for such known risk factors for hay fever as male gender, small sibship size, and living on a farm and surrogates of genetic predisposition (parental asthma and hay fever), neonatal hospitalisation decreased the risk for hay fever. Of the analysed perinatal exposures neonatal hospitalisation may have proved statistically more powerful due to dichotomization. It may, also, be an overall indicator of low gestational maturity – poor ability to thrive. Alternatively, it may influence the development of the immune system by giving rise to colonisation with different bacteria, infections, use of antibiotics, physical stress and different feeding practices.

Over 40% of twins are born preterm with around 50% weighing less than 2500 g at birth (Taffel, 1995). Additionally, the mothers of DZ twins tend to be older and of higher parity than mothers of singletons (Taffel, 1995). Since perinatal factors appear to modify the risk for atopic diseases and since the distributions of birth characteristics between twins and singletons differ, one would expect to see these differences reflected in the risk for atopic diseases between twins and singletons.

Unfortunately, comparative studies of atopy prevalence in twins versus singletons are scanty. Indeed, among Swedish conscripts, multiple birth was inversely related to the risk for both hay fever and asthma (Bråbäck & Hedberg, 1997) but conversely, an increased risk for eczema has been found among preterm infants (Lucas et al., 1990). However, large population-based twin studies have shown prevalences of asthma and hay fever similar to those in studies carried out by similar methods among same-aged singletons within the same countries (Laitinen et al., 1998; Rimpelä et al., 1995; Räsänen et al., 1998; Skadhauge et al., 1999). In the light of similar disease prevalences, if the effects of perinatal factors on the risk for atopic diseases are similar in twins and in singletons, postnatal factors might counterbalance the perinatal differences. However, even though the causes for intra-uterine growth retardation in twins are not well understood, their distribution in twins differs from that in singletons

(Taffel, 1995). If the development of a disease is modified by birth weight in itself, the effect of perinatal factors in twins would presumably to some extent differ from those in singletons. Nonetheless, associations between perinatal factors and hay fever found in this study among twins are parallel to those found among singletons.

In adults, atopic inflammation is characterised by a T-helper (Th) 2 cytokine profile, whereas non-atopic persons show a Th1 profile. Evidence is growing that in order to successfully complete the pregnancy, the maternal immune system deviates towards Th2 (Warner et al., 1996). It has also been shown that during the second and third trimesters of pregnancy, the immune system of the fetus develops towards the Th2 with its capability for allergen-specific reactions primed by the mother; however in those neonates with high risk for atopy the normal postnatal immune deviation towards Th1 is defective (Prescott & Holt, 1998). That gestational maturity increased the risk for subsequent hay fever may be due to atopic mothers being able to bring even a twin pregnancy closer to term or due to mature babies possibly having more Th2 skewed immunity at birth and/or more time *in utero* developing sensitisation primed by the mother.

That our result was more obvious among the families where neither parent had hay fever suggests that the genetic predisposition alone may be strong enough to cause expression of hay fever in the offspring, whereas other intra-uterine environmental effects leading to gestational maturity influence hay fever risk only in the absence of inherited risk. Our result adds more evidence that the intra-uterine environment modifies the risk for atopic diseases, and further suggests that this modification may vary according to genetic predisposition to the disease.

In summary, our study on perinatal determinants of hay fever among adolescent twins showed an increasing risk for hay fever with increasing gestational maturity almost exclusively in those with no parental history of hay fever. Whether the effect of parental hay fever status is due to strong genetic transmission of hay fever allowing weaker environmental effects to act only in the absence of genetic predisposition, remains to be shown. Nonetheless, future studies on perinatal risk factors for atopic diseases may benefit from consideration of family history.

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