

Original article

The initial care of newborn infants and subsequent hay fever

Background: Patterns of neonatal exposure to microorganisms have changed substantially over the last 100 years, and it has been suggested that this has influenced the risk of immune-mediated disease. Using a proxy measure, we tested the hypothesis that the initial handling of newborn infants, which is known to affect the pattern of exposure to microorganisms, may alter the risk of developing subsequent atopy, as indicated by hay fever.

Methods: Analysis was performed on 5519 members of the 1970 British Cohort Study, a nationally representative birth cohort. Cohort members with hay fever were identified at intervals up to the age of 26 years. Details of neonatal care and childhood circumstances were recorded prospectively. Those who had spent their first night away from their mother in the communal infant nursery were selected as likely to have experienced atypical exposure compared with infants who remained with their mother. Adjustment was made for potential confounding factors in infancy and childhood by multiple logistic regression analysis.

Results: Unadjusted relative odds (with 95% CI) for developing hay fever among those spending the first night in the communal nursery, when compared with other infants who remained with the mother, were 1.48 (1.23–1.77), $P < 0.001$. Comprehensive adjustment for the potential confounding factors, including feeding practices on the first day of life, markers of social and material circumstances, and region, did not substantially alter this relationship, with adjusted relative odds of 1.31 (1.08–1.59), $P = 0.005$.

Conclusions: While our proxy measure is associated with an increased risk of hay fever, further research is required to confirm that this is due to the pattern of infectious exposure in very early life. The results are consistent with the hypothesis that the first challenges are particularly important in the development of the newborn infant's immune system.

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The increasing incidence of atopy (1) and other immune-mediated diseases (2, 3) points toward changing environmental factors that unmask constitutive genetic tendencies. There is evidence that exposure very early in life may be of particular importance (4), suggesting that the developing immune system may be more liable to inappropriate "programming" at this time (5). Improvements in living conditions have resulted in a reduction in dose and duration of many exposures, including those to viral and bacterial antigens. We explore the hypothesis that this pattern of exposure is atypical – in evolutionary terms – and may represent a risk of subsequent immunodysfunction, defined here as self-reported hay fever used as an indicator of atopic status.

In general terms, the developing immune system is influenced most significantly by early exposures and the first exposures, after birth, when the immune system is at its most naive, may be particularly important. Although we do not have a direct measure of early

infectious exposures, we examine the relationship of a marker for pattern of exposures on the first day of life with subsequent hay fever. We selected apparently healthy infants who, during their first 24 h of life, spent the night in the communal infant nursery, but were with their mothers during the day. This group did not include those who were separated for medical reasons or who spent any time in an incubator or a special care baby unit. A limited overnight stay in the communal nursery could increase the risk of some low-dose or short-duration exposures, particularly to *nonfamilial* microorganisms. In contrast, exposure to *familial* antigens is likely to be greater in dose and duration due to prolonged and repeated contact with the mother and other family members.

The data used here were collected prospectively as part of a nationally representative longitudinal British birth cohort study (6). It was possible to perform detailed adjustment for multiple potential confounding factors in infancy and childhood.

Material and methods

The 1970 British Cohort Study

The 1970 British Cohort Study (BCS70) is an ongoing longitudinal birth cohort study, with its origins in the British Births Survey of all births ($n=17\,198$), which took place between 5 and 11 April 1970 in the UK (6). BCS70 represents the follow-up of these births, excluding those in Northern Ireland. The data used here were collected at birth by midwives and by reference to medical records, and subsequently at the ages of 5 and 10 years by interview (conducted by health visitors) and at the age of 26 years by self-completion questionnaire (7). The self-completion postal survey at 26 years, which identified cohort members with hay fever, obtained a total of 8798 complete responses, representing a 65% response rate of those who were traced (7). While attrition of the cohort has occurred, a comprehensive tracing exercise conducted prior to the 26-year survey was undertaken to minimize the loss of any specific group of individuals. Unlike most case-control or cross-sectional studies, BCS70 has detailed information for 98% of the entire target population (6) who were born during the study week; therefore, it is possible to estimate response bias and adjust for it in analysis. Despite the loss to follow-up, extensive tracing exercises have resulted in the sample at the age of 26 years being largely representative of the original birth cohort, but with some loss of the most disadvantaged groups (7).

Measures

Early exposure risks. Our measure of risk of early exposure at a low dose or for a limited duration to nonfamilial microorganisms was that the infant spent the first night of life separately from his or her mother, cared for by the maternity ward staff in the infant nursery. This did not include those in an incubator or special care baby unit, or those removed for any medical procedure or cause. The variable was divided into those who were separated from their mother only at night, those who spent both day and night by their mother's bed, and a third group who did not fit into either category. As additional indicators of early infectious exposure and microbial colonization, maternal urinary and genital tract infections were recorded, and Caesarean births were also identified.

Maternal age, parity, gestational age, delivery duration, birth weight, antibiotic administration, and head circumference. Maternal age at the cohort member's birth was classified as 30 years or below, 31–35 years, and 36 years or older. Parity was defined as mothers with no previous pregnancies, one previous pregnancy, and two or more previous

pregnancies. Gestational age was recorded in weeks from the first day of the last normal menstrual period. The durations of first-, second-, and third-stage labour were recorded separately in minutes. The cohort members' birth weight was divided into tenths of the distribution, as no assumption of linearity in relationships was made. Whether the baby was given prophylactic antibiotics in the first days of life was recorded as a binary variable. Head circumference was recorded in centimetres, but this measurement was collected only in a subset of cohort members; data from 2339 subjects were available for analysis.

Circumstances in early life. The Registrar General's measure of social class, based on father's occupation, when the infants were born, was used as an indicator of material and cultural conditions in childhood. When used in the UK, the father's class, in general, provides a more accurate indicator of the family's and indeed the mother's own circumstances than her social class (8). The class variable was divided into the following categories: I, II, IINM IIIM, IV, V, and unsupported mothers. Household crowding, as measured by the persons per room ratio divided into fifths of the distribution, was used as an additional measure of material circumstances, as well as an indicator of risk of exposure to larger doses of pathogens (9).

Breast-feeding patterns, family history of hay fever, and maternal smoking. Two measures of breast-feeding were employed. The first was from a prospective record of feeding for the first day after birth, where infants were divided into those who received colostrum (exclusively or in combination with other feeds) and those who did not. The second measure of breast-feeding was based on retrospectively collected information at the age of 5 years. This variable was divided into no breast-feeding, breast-feeding for up to 1 month of birth, breast-feeding within 3 months of birth, breast-feeding beyond 3 months, and breast-feeding of unknown duration. A family history of hay fever was considered to exist where either biological parent reported having the condition. These data were collected during the interview with health visitors when cohort members were aged 5 years. Maternal smoking was characterized as follows: nonsmokers; stopped before pregnancy; stopped during pregnancy; and smokers during pregnancy, divided into 1–4, 5–14, or 15 or more cigarettes per day.

Region and place of birth

Region of birth was divided into the 12 standard regions of Great Britain (two Welsh regions, nine English regions, and Scotland). To ensure anonymity of

cohort members, the individual hospital where a member's birth took place was not included in the data set. However, cohort members were allocated consecutive study identity numbers by hospital and district. Identity numbers numerically adjacent to the number for any cohort members are more likely to identify another cohort member born in the same hospital and health district. If the nocturnal separation of mother and baby reflected local policy, and it is hospital or district rather than the separation that is associated with hay fever, clustering by identity number should be at least as strongly associated with hay fever as the measure of separation is. A dummy variable was generated for each cohort member to indicate whether the numerically adjacent cohort members were separated from mothers on the first night of life.

Hay fever

The relevant questions in the survey conducted at the age of 26 years were as follows: "Since you were 16, have you suffered from hay fever?" and "In the last 12 months, have you suffered from hay fever?" A single binary variable for reported hay fever between the ages of 16 and 26 years was created.

Statistical analysis

Cross-tabulation and multiple logistic regression were used to investigate the associations of hay fever with spending the first night of life in the communal nursery, and the potential confounding factors. Adjustment was made for feeding on the first day of life, family history of hay fever, breast-feeding between birth and the age of 5 years, parental social class, sex, household crowding in childhood, age of mother, birth weight, parity, region of birth and the indicator of clustered handling practice by hospital, and duration of second-stage labour. The relationships of hay fever and spending the first night of life in the communal nursery with other potential confounding factors were also investigated. These measures included first and third stages of labour, mode of birth, administration of antibiotics, head circumference, maternal smoking, and maternal genital and urinary tract infections.

In the adjusted model, all variables were modelled as a series of binary dummies by SPSS software (10). Cohort members with missing values for any variable were excluded; thus, complete univariate and multivariate analysis was performed for 5519 subjects.

Because the model adjusting for *all* of the potential confounding factors was not parsimonious, an additional logistic regression was used to perform stepwise exclusion of variables that did not contribute significantly to the adjusted model.

Results

Table 1 shows the relationship of hay fever by the age of 26 years with where the infant had spent its first 24 h of life. The relative odds in this table are unadjusted and adjusted for *all* of the potential confounding factors listed. When compared with infants who remained with their mother both day and night, those who spent their first night in the nursery were more likely to develop hay fever subsequently (34.0% vs 25.9%), with relative odds of 1.48 (1.23–1.77, $P < 0.001$). After adjustment for the potential confounding factors, the relative odds were reduced to 1.31 (1.08–1.59, $P = 0.005$). Univariate analysis using the maximum number of cases ($n = 8100$) produced relative odds of 1.36 (1.17–1.57, $P < 0.001$).

A history of parental hay fever was associated with hay fever in the cohort member, with adjusted and unadjusted relative odds of 2.16 (1.86–2.50, $P < 0.001$) and 2.06 (1.77–2.40, $P < 0.001$), respectively. Univariate, breast-feeding was associated with an increased risk of hay fever, but this was not statistically significant after adjustment for the potential confounding factors. A higher social class was associated with an increased risk of hay fever, with a protective effect for those in lower social classes. The association is statistically significant when those in category III_m are compared with I, with relative odds of 0.70 (0.52–0.94, $P = 0.019$); however, this was eliminated after adjustment for the potential confounding factors. Greater household crowding was protective against hay fever, with significance, after adjustment, of $P = 0.021$.

More previous pregnancies and shorter duration of second-stage labour were both associated with a significantly smaller risk of subsequent hay fever ($P < 0.001$), before adjustment. The significance of these relationships was reduced after adjustment for the potential confounding factors, with significance levels of $P = 0.055$ and $P = 0.012$ for parity and duration of second-stage labour, respectively. This reduction in significance of association was largely due to the inclusion of both of these variables in the same model. Women who had previously been pregnant were more likely to have a shorter duration of second-stage labour; thus, colinearity of the two measures is likely to be responsible for the reduction in strength of these associations.

The highest risk of hay fever was in London and southeast England, but when compared with the southeast, only northern England was statistically significantly protective after adjustment for all of the potential confounding factors. The marker for clustering of risk by hospital was not significantly associated with risk of hay fever, with unadjusted relative odds of 1.11 (0.97–1.28, $P = 0.125$). This

Table 1. Relative odds of developing hay fever by infant handling on first day of life, with adjustment for multiple potential confounding factors

	Total no.	No. with hay fever	%	Unadjusted		Adjusted*	
				(P) Odds	95% CI	(P) Odds	95% CI
First day of life				(0.000)		(0.005)	
Mother's bed – day only	1229	418	34.0	1.48	1.23–1.77	1.31	1.08–1.59
Mother's bed – day and night	1098	284	25.9	1.00		1.00	
Other	3192	934	29.3	1.19	1.02–1.38	1.08	0.89–1.25
Parental hay fever				(0.000)		(0.000)	
No	4652	1252	26.9	1.00		1.00	
Yes	876	384	44.3	2.16	1.86–2.51	2.06	1.77–2.40
Breast-feeding				(0.000)		(0.174)	
Less than 1 month	913	316	34.6	1.37	1.18–1.60	1.16	0.96–1.40
1 month or more, <3	600	185	30.8	1.16	0.96–1.40	0.99	0.79–1.24
3 months or more	681	212	31.1	1.17	0.98–1.40	0.97	0.78–1.24
Breast-fed, duration unknown	14	1	7.1	0.20	0.02–1.53	0.19	0.03–1.46
Never breast-fed	3311	922	27.8	1.00		1.00	
Household crowding – 5ths				(0.000)		(0.021)	
1 (low)	991	318	32.1	1.00		1.00	
2	1114	366	32.9	1.04	0.86–1.24	1.11	0.92–1.34
3	1574	496	31.5	0.97	0.82–1.15	1.07	0.90–1.29
4	1139	291	25.5	0.73	0.60–0.88	0.86	0.70–1.06
5 (high)	701	165	23.5	0.65	0.52–0.81	0.82	0.64–1.05
Parity				(0.000)		(0.055)	
No previous pregnancies	2014	690	34.3	1.00		1.00	
One previous pregnancy	1884	527	28.0	0.75	0.65–0.85	0.83	0.70–0.98
2+ previous pregnancies	1621	419	25.8	0.67	0.58–0.77	0.82	0.67–0.99
Region				(0.150)		(0.542)	
North	378	89	23.5	0.65	0.50–0.86	0.71	0.54–0.93
Yorks and Humberside	511	144	28.2	0.83	0.66–1.05	0.90	0.71–1.14
North West	722	210	29.1	0.87	0.71–1.07	0.94	0.76–1.16
East Midlands	327	100	30.6	0.93	0.71–1.22	1.04	0.99–1.38
West Midlands	587	186	31.7	0.98	0.79–1.22	1.04	0.83–1.30
East Anglia	249	77	30.9	0.95	0.70–1.28	1.02	0.75–1.39
South West	391	108	27.6	0.81	0.63–1.05	0.85	0.65–1.10
South Wales	208	58	27.9	0.82	0.58–1.14	0.93	0.64–1.30
North Wales	93	23	24.7	0.70	0.43–1.14	0.76	0.46–1.24
South East	1067	342	32.1	1.00		1.00	
London	521	170	32.6	1.03	0.82–1.28	1.01	0.80–1.27
Scotland	465	129	27.7	0.81	0.64–1.03	1.00	0.77–1.29
Duration of second-stage labour (min)				(0.000)		(0.012)	
1–15	2222	597	26.9	1.00		1.00	
16–30	1406	380	27.0	1.01	0.88–1.17	1.13	0.96–1.32
31–45	699	239	34.2	1.41	1.18–1.70	1.37	1.12–1.68
46–60	394	135	34.3	1.42	1.13–1.78	1.34	1.05–1.72
61–75	244	94	38.5	1.71	1.30–2.24	1.55	1.14–2.09
76–90	162	64	39.5	1.78	1.28–2.47	1.61	1.13–2.28
> 90	223	75	33.6	1.38	1.03–1.85	1.17	0.85–1.61
Caesarean	169	52	30.8	1.21	0.86–1.70	1.21	0.84–1.74
Total	5519	1636	29.6				

*Adjustment for all measures shown and also for breast-feeding on first day of life, parental social class, sex, mother's age, birth weight, and hospital.

relationship was further diminished by adjustment for the potential confounding factors to 1.03 (0.89–1.19, $P=0.735$).

There was no significant relationship between hay fever and breast-feeding on the first day of life, sex, or mother's age. Maternal urinary infections, maternal genital tract infections, Caesarean births, gestational age, duration of first- or third-stage labour, and prophylactic antibiotic therapy in the first days of life were not significantly associated with hay fever ($P>0.1$). Neither maternal smoking nor head

circumference (modelled as five dummy variables based on fifths of the distribution or continuously) was significantly associated with spending the first night of life in the communal nursery, as opposed to staying with the mother ($P>0.1$).

A separate logistic regression model used stepwise elimination to exclude variables that did not contribute significantly to the final model. A considerably more parsimonious model was developed which retained just five of the variables as independently contributing to the risk of hay fever; namely, where the infant spent its first

24 h of life, a family history of hay fever, household crowding, parity, and duration of second-stage labour. After adjustment with the parsimonious model, the relative odds for spending the first night of life in the communal nursery were 1.34 (1.11–1.61, $P=0.001$). Parental hay fever showed the most significant relationship with hay fever in cohort members in the adjusted model ($P<0.001$), with spending the first night of life in the communal nursery as the measure with the next highest probability value for predicting subsequent hay fever.

Discussion

We have used a proposed indicator of atypical environmental exposures on the first day of life to test the hypothesis that some patterns of exposure, encountered at a time of immune immaturity, are a risk factor for subsequent disease. Self-reported hay fever by the age of 26 years was used as a marker for atopic disease, as this is a relatively common condition in these young British adults. While self-reported hay fever might result in some misclassification of disease, the risk of systematic bias is significantly reduced by the ability to adjust for multiple potential confounding factors by using the wealth of prospectively collected BCS70 data. At the age of 26 years, respondents were largely representative of the original birth cohort, with some loss of the most disadvantaged groups (7). Adjustment for multiple personal and geographic characteristics reduced the risk that the findings reported here are due to systematic bias.

Our indicator for increased risk of atypical exposures during the first 24 h of life was whether the infant spent the night in the communal nursery, compared with those who remained with their mother for the entire period. Other children were classified into a third group: those who were not born in hospital, who spent more time in the nursery, or who were removed to an incubator or special care baby unit; those who were being treated or observed for any condition; and those with a mother who had a medical problem. This is a very indirect measure of the pattern of infectious exposures in the first 24 h of life. However, we believe that, when compared with infants who remained with their mother, a higher proportion of infants who spent the night in the nursery were more likely to have experienced low-dose and short-duration exposures to nonfamilial microorganisms. The indirect nature of the measure could also result in a highly conservative estimate of risk, as individual circumstances and actual patterns of exposure will have varied considerably. Despite this, a statistically significant positive association with hay fever was observed, independent of multiple potential confounding factors.

It is possible that the relationship of spending the

night in the nursery with hay fever is due to confounding. If confounding were responsible, another factor operating on the first day of life would have been associated with both the risk of hay fever and the probability that the first night would be spent in the nursery. Of course, the causal agent may not be encountered on the first day of life, but the factor associated with nocturnal separation is predictive of a future exposure. BCS70 provides extensive information about health and circumstances on the first day of life and in later childhood; therefore, we made extensive efforts to minimize the effects of potential confounding factors. However, we could not directly identify all of the reasons why some infants spent the night in the nursery. In many cases, factors such as the personal preference of the mother or hospital staff dictated whether babies spent the night in the nursery.

Because of the indirect nature of the exposure measure, comprehensive adjustment for multiple potential confounding factors is particularly important. Parity and duration of second-stage labour were among the most significant of the potential confounding factors. There is evidence of collinearity between these two factors, perhaps indicating that some of the apparently protective effect of shorter labour reflects a larger number of previous pregnancies, and it is growing up with older siblings that confers much of the protective effect. Alternatively, a longer labour might be significant itself, or it may influence infant handling, as the mother is more likely to be tired. Potential confounding factors must show relationships with both exposure and outcome measures to influence results significantly. Thus, measures related only to the first night of life, but not risk of hay fever, or vice versa, or those related to neither, were not potential confounders, and should not be included in the adjusted model. The relationship of spending the first night in the nursery with hay fever was independent of all the potential confounding factors investigated. Variables investigated that were not related to both exposure and outcome, and therefore were not confounders, included maternal genital and urinary tract infections, head circumference, maternal smoking, use of antibiotics, and duration of first- and second-stage labour.

Variation of risk by region in Britain is likely to reflect differences in material and social circumstances, as the relationship with region of birth is weakened by adjustment for the other measures. If the relationship were due to hospital or health district-specific confounding, then infants who were not separated but were in the same hospital or health district would be at an equally high risk of developing hay fever. There was no evidence of this, supporting a direct association, rather than one caused by confounding.

The small effect of multiple adjustment on the odds of developing hay fever among those who spent the first night in the nursery is consistent with, but does not

prove, a causal relationship. The results of stepwise elimination modelling suggest that the adjusted odds presented in Table 1 may be a conservative estimate of the relationship due to a nonparsimonious model suffering from multicollinearity. The most likely consequence of this overadjustment will have been to underestimate the adjusted relative odds for hay fever associated with spending the night in the nursery. However, while the results of this study are consistent with the hypothesis that pattern of exposure to infectious agents on the first day of life influences the risk of subsequent hay fever, other, unmeasured, factors could conceivably explain the reported relationship. Even if this is the case, the possibility that exposures on the first days of life are uniquely important in influencing the developing immune system deserves further investigation.

Environmental factors, particularly in infancy and childhood, have been associated with the risk of developing an atopic disease (4, 11–14). The development of the immune system is strongly influenced by early exposures, and it is possible that some patterns of exposure, particularly to infectious agents, may lead to dysfunction (15, 16). Earlier age of entry to day nursery protects against allergy (4), suggesting that there is an important period of risk in early life when the immune system is particularly naive. Exposure to both airborne and food-borne microorganisms has been implicated in protecting against subsequent disease (13, 14, 17, 18), and it is feasible that both are able to stimulate lymphoid tissue to induce appropriate immunologic development. A small increased risk of hay fever was associated with breast-feeding for a short duration, but the strength of this association was reduced by adjustment. This relationship was also shown by a previous study (19) suggesting a sensitizing effect of limited exposure to some gut flora. However, the feeding pattern in the first 24 h of life was not associated with subsequent hay fever, suggesting that other influences, such as airborne infections, could be important on the first day. The strong protective effect of greater household crowding, lower social

class, and having older siblings, observed here and by other studies (12, 20), is consistent with a protective role for more intense infectious exposures at a younger age.

Temporal trends in material circumstances have reduced the infectious load in early life, and this may account for the rising incidence of allergic disease. But while *lack* of early infectious stimulation might be detrimental, other characteristics of the pattern of exposure may also be important. It has been proposed for other disease processes that an initial low-dose exposure may be insufficient to generate an appropriate immune response, leading to subsequent immune-mediated disease (15, 21, 22). While other explanations are possible, we hypothesize that the relatively short-duration/low-dose exposure potentially associated with a visit to the communal nursery on the first day of life may result in exposures insufficient to generate an appropriate immune response in the neonate, leading to sensitization. Children attending day nursery or exposed to *familial* infections or gut commensals, would encounter the microorganisms for a longer duration and probably at a higher dose, resulting in appropriate immune conditioning. Higher levels of household crowding are associated with higher dose exposure to antigens (9), and this may help to explain the independent protective effect of crowding.

This type of infant care on the first day of life was relatively common practice in 1970. Since then, communal nurseries have become less common, but the greater likelihood of early discharge from hospital, coupled with improving material circumstances, suggests that newborn infants continue to be exposed to low doses of nonfamilial infectious agents. While this study does not provide sufficient evidence to advise a change in neonatal handling practice, it does suggest the need for more prospective studies into the programming of the nascent immune system.

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