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Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood

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Abstract

Background: The natural history of asthma and atopic diseases begins *in utero*. Studies investigating the influence of foetal exposure to maternal stressful life events during pregnancy (SLEP) on asthma and atopic diseases are lacking.
Aim: To test whether the children of mothers who had experienced SLEP are at an increased risk for asthma, atopic eczema and allergic rhinitis.
Methods: The association between maternal SLEP (at least one among: divorce, mourning or loss of the job) and the occurrence of asthma and atopic diseases in childhood was studied in a population (n = 3854) of children, aged 3–14 yrs, living in Northern Italy. The parents filled in a standardized questionnaire about the children's health and the events occurred to their mothers during pregnancy.
Results: Three hundred and thirty-three (9%) of the mothers experienced SLEP. Their children had a statistically significantly higher lifetime prevalence of wheezing (31.6% vs. 23.1%), asthma (8.9% vs. 5.6%), allergic rhinitis (10.9% vs. 7.3%) and atopic eczema (29.7% vs. 21.1%) than those of mothers without SLEP. After adjusting for potential confounders, the foetal exposure to SLEP was positively associated with wheezing (OR: 1.41, 95% CI: 1.03–1.94), asthma (OR: 1.71, 95% CI: 1.02–2.89), allergic rhinitis (OR: 1.75, 95% CI: 1.08–2.84) and atopic eczema (OR: 1.53, 95% CI: 1.11–2.10).
Conclusion: The children of mothers who had experienced SLEP were at a moderately increased risk of having wheezing, asthma, eczema and allergic rhinitis during their childhood. Maternal stress during pregnancy might enhance the expression of asthma and atopic phenotypes in children.

Asthma and atopic diseases, such as allergic rhinitis and eczema, are common chronic conditions whose prevalence is still on the increase in many countries, and they are a significant cause of morbidity worldwide (1, 2).

The development and expression of asthma and atopic diseases is influenced by the interaction of several genetic, biological and environmental factors, many of which exert their action early in life or even during the foetal life (3).

In the last decade, several studies on children and adults have shown that the experience of stressful life events is associated with an increased risk of developing asthma and atopic diseases (4–6). Psychosocial stress might influence the onset of these diseases through multidimensional endocrine, neural, immune and behavioural processes (7).

It has also been suggested that maternal stress during pregnancy may promote the development of asthma and atopic diseases in the offspring (8). However, little is known about the relationship between gestational exposures to maternal stress and the subsequent occurrence of asthma and atopic diseases.

The aim of this study was to assess whether experiencing stressful life events during pregnancy (SLEP) (mourning, divorce or separation, loss of her or her husband's job) is associated with an increased risk of having asthma and atopic diseases in children.

Methods

Study design and participants

The association between SLEP and respiratory symptoms in the offspring was investigated using the data collected in the Viadana study. The details of this project are described elsewhere (9, 10). In brief, the Viadana study was a cross-sectional survey aimed at investigating the association between industrial pollution and the health of the children, aged 3–14, living in the district of Viadana (Mantua, Northern Italy), one of the largest wood industrial parks in Italy (9).

The survey was performed on December 2006 and involved all the children who were enrolled in the district school registers during the school-year 2006/07. Parents of all eligible children were asked to fill in a detailed questionnaire on the health and potential risk factors for the children. Complete information was collected from 3854 of 3907 eligible children (response rate of 98.6%). The local ethics committee approved the study protocol.

The questionnaire

The questionnaire, which required about 25 min to complete, investigated the presence of respiratory and allergic symptoms in children and the occurrence of specific events during pregnancy and at birth. Most of the questions were taken from the International Study of Asthma and Allergies in Childhood (ISAAC), the European Community Respiratory Health Survey (ECHRS) and the Italian Study on Respiratory Disorders in Childhood and the Environment (SIDRIA) standardized questionnaires (validated in previous international surveys), with an available Italian translation (9). Information on known or suspected risk factors and on potential confounders was collected through the questionnaire. Back-translated English and French versions of the questionnaire were also available for parents who did not speak Italian (the 3 versions are openly available at: http://biometria.univr.it/viadanastudy).

Asthma and atopic disease definitions

A child was considered to have wheezing, asthma, allergic rhinitis and atopic eczema in case of an affirmative answer to the following questions:

- 'Has your child ever had wheezing or whistling in his/her chest at any time in the past?'
- 'Has your child ever had asthma?'
- 'Has your child ever had any nasal allergies (including hay fever)?'
- 'Has your child had an itchy rash on one or more parts of the skin, which was coming and going for at least 6 months, at any time in the past?'

Stressful life events during pregnancy and prenatal and birth characteristics

The occurrence of SLEP was ascertained by the following question: 'During pregnancy, did the mother experience any situations of loss or uneasiness (mourning, loss of her or her husband's job, separation/divorce)?'

The questionnaire also collected information about prenatal and birth characteristics. The prenatal characteristics included the use of medication during pregnancy (the use of medicines for asthma, cortisone (oral or inhaled), acetaminophen (paracetamol) and antibiotics) and the following pregnancy complications: (i) hypertension for which the mother had to assume medicines, (ii) pre-eclampsia, (iii) the occurrence of fever caused by infections, (iv) the occurrence of gynaecological infections for which the mother had to take medicines and (v) risk of miscarriage or premature birth.

The birth characteristics taken from the questionnaire were the following: mother's age at child's birth (<22; 22–35; >35 yrs old), newborn weight (low: <2.5 kg; normal: 2.5–4.2 kg; high: >4.2 kg), gestational time (preterm: >3 wks before due date; post-term: >2 wks after due date; regular otherwise) and type of delivery (natural or caesarean). Finally, we collected information about duration of breastfeeding (<1 month; ≥ 1 month).

Other potential confounders

Current potential confounders for respiratory diseases included in the analyses were gender, age of the child, nationality (foreign if both parents were born abroad, Italian otherwise), self-reported traffic level (high if cars or trucks passed constantly or frequently near home; low otherwise), parental smoking (one or both parents currently smoking), parental asthma (one or both parents had asthma), parents' educational level (maximum among parents: no school/primary school, secondary school or University) as proxy of socioeconomic status, person who filled in the questionnaire (mother only, both parents, father or others). As the Viadana district is characterized by the pollution from chipboard industries, a three-level variable of proximity to industrial sources (low, intermediate and high) was used, as previously described (9, 10).

In addition, as potential confounders for atopic disorders, we considered whether the children ever kept a cat or a dog at home, and whether they shared the bedroom in their first year of life with an older sibling. Information about exposure to farm animals and presence of damp spots, mould or mildew in the child's bedroom during the first year of life was also collected.

Statistical analyses

Data were summarized with means (s.d.) or percentages as appropriate. Comparisons of variables across strata were performed by the chi-squared test and by the Wilcoxon rank-sum test according to the distribution of each considered variable.

To evaluate the association between SLEP, health outcomes, prenatal and birth factors, 3 logistic regression models were developed using a forward approach that adjusted for specific group of confounders: (i) a first model was performed adjusting for age and gender only, (ii) a second model was

estimated by adding known potential confounder factors and (iii) the third and more complete regression was computed including in the model pregnancy and perinatal conditions. Subjects with missing data to variables included in a specific regression model were excluded from the analyses. The associations were evaluated using odds ratios (OR) and 95% confidence interval (CI). p-values for significance of the tests and model parameters were set at 5%. Statistical analyses were performed with STATA 12.0 (Stata Corp. College Station, TX, USA).

Results

The children studied were 8.5 yrs old on average, and 46.5% of them were females. A total of 337 of their mothers (9.0%) had experienced SLEP (Table 1). Children exposed to maternal SLEP were slightly younger and were more frequently exposed to parental smoking and to moulds in their bedroom than children whose mothers did not experience SLEP. Maternal SLEP was also significantly associated with higher chances of keeping a cat at home.

Mothers experiencing SLEP had a greater risk (Table 2) of hypertension ($p = 0.040$), pre-eclampsia ($p = 0.007$), premature birth or miscarriage ($p < 0.001$), infection-induced fever ($p < 0.001$) and gynaecological infections ($p = 0.007$) during pregnancy. SLEP were also significantly associated with the use of paracetamol in pregnancy ($p = 0.015$), but not with the use of cortisone, anti-asthmatic drugs or antibiotics.

Children born to mothers who had experienced SLEP (Table 3) were reported to have had an increased (but not statistically significant) risk to be delivered by caesarean section or preterm. Moreover, children exposed to maternal SLEP were breastfed for significantly shorter time than children born to mothers without SLEP ($p = 0.007$).

In children, the prevalence of wheezing, asthma, allergic rhinitis and atopic eczema was 23.8% (95% CI: 22.5–25.3), 5.9% (95% CI: 5.1–6.7), 7.6% (95% CI: 6.7–8.5) and 21.9 (95% CI: 20.6–23.3), respectively. The prevalence of the four conditions was statistically significantly higher in the offspring of mothers who experienced SLEP (Fig. 1).

After adjusting for the potential confounders, the children born to mothers who had experienced SLEP had a higher risk of having wheezing (OR: 1.41, 95% CI: 1.03–1.94), asthma (OR: 1.71, 95% CI: 1.02–2.89), allergic rhinitis (OR: 1.75, 95% CI: 1.08–2.84) and atopic eczema (OR: 1.53, 95% CI: 1.11–2.10) compared to the reference group (Table 4).

There was not any statistically significant interaction between pregnancy complications (at least one among hypertension, pre-eclampsia, miscarriage, infections), SLEP and asthma or atopic diseases.

Table 1 Main characteristics of the children studied and their distribution according to the occurrence (SLEP+) or non-occurrence (SLEP–) of maternal SLEP

	Overall n = 3758	SLEP– n = 3421	SLEP+ n = 337	p-value
Age (yr, mean ± s.d.)	8.5 ± 3.2	8.6 ± 3.2	8.2 ± 3.3	0.020
Gender (female, %)	46.5	46.7	44.2	0.371
Mother's age at delivery (%)				
Under-22	78.0	78.2	75.8	0.579
22–35	12.0	11.9	13.2	
Over-35	10.0	9.9	11.1	
High traffic level near home (high, %)	58.5	58.2	60.9	0.348
Residential area (%)				
Countryside	51.3	51.6	48.6	0.426
Urban residential area	42.9	42.6	46.2	
Industrial area	5.8	5.9	5.1	
Exposure to industrial pollution (%)				
Low	35.8	35.7	36.3	0.802
Intermediate	25.5	25.7	24.0	
High	38.7	38.6	39.6	
Parents' education level (%)				
No school/primary school	35.4	35.7	31.6	0.141
Secondary school	50.7	51.3	50.6	
University	14.0	13.7	17.0	
Parental smoking (%)	41.9	41.0	51.1	<0.001
Parental asthma (%)	10.9	10.8	11.8	0.614
Ever kept a cat at home (%)	23.1	22.2	32.1	<0.001
Ever kept a dog at home (%)	23.9	23.6	26.8	0.239
Mould in child's room in his/her 1st yr (%)	16.5	16.1	21.0	0.027
Exposure to farm animals in child's 1st yr (%)	12.5	12.1	15.7	0.056
Sharing the bedroom with an older sibling in child's 1st yr (%)	26.0	25.6	30.3	0.060

p-values refer to the distribution of each variable across SLEP strata.
SLEP, stressful life events during pregnancy.

Discussion

Foetal exposure to maternal SLEP increased the risk of atopic diseases in children

A number of epidemiological studies have shown that the origins of asthma and atopic diseases may be traced back to events occurring in early life (11). The foetal stage is one of the most critical periods of developmental programming, during which maternal exposures may influence gene expressions and may result in several chronic diseases, including asthma and allergy (8, 12).

The present study is one of the first reports on the association between foetal exposure to maternal SLEP and the occurrence of asthma and atopic diseases in childhood. Our findings show that the children of mothers who had experienced a divorce, the loss of the job or a mourning during

Table 2 Percentage of adverse maternal events in women who did (SLEP+) and did not (SLEP–) report stressful life events during pregnancy and odds ratio (OR) for the association (with 95% CI) between SLEP and events during pregnancy

	SLEP–	SLEP+	OR	95% CI
Adverse maternal events during pregnancy (%)				
Hypertension	4.4	6.9	1.62	1.02–2.57
Pre-eclampsia	4.3	7.7	1.84	1.17–2.89
Risk of premature birth or miscarriage	15.7	30.3	2.34	1.81–3.03
Infection-induced fever	3.2	6.9	2.22	1.38–3.58
Gynaecological infections	5.6	9.4	1.73	1.15–2.59
Use of medicines (%)				
Paracetamol	28.5	35.0	1.34	1.05–1.71
Anti-asthmatic drugs	1.5	0.6	0.41	0.09–1.68
Cortisone	2.4	3.4	1.44	0.76–2.75
Antibiotics	5.9	6.7	1.15	0.72–1.81

SLEP, stressful life events during pregnancy.

Table 3 Distribution of birth weight, birth term, type of delivery and length of breastfeeding of children born to women who did (SLEP+) and did not (SLEP–) report stressful life events during pregnancy (SLEP), and odds ratio (OR) for the association (with 95% CI) between SLEP and perinatal characteristics

	SLEP– (%)	SLEP+ (%)	OR	95% CI
Birth weight				
<2500 g	7.4	7.6	1.04	0.68–1.60
2500–4200 g	89.2	89.3	1	–
>4200 g	3.4	3.0	0.88	0.46–1.71
Birth term				
Preterm	9.1	12.0	1.37	0.95–1.96
Regular	84.3	82.0	1	–
Post-mature	6.7	6.0	0.93	0.57–1.51
Type of delivery				
Natural	70.1	65.4	1	–
Caesarean	29.9	34.6	1.23	0.97–1.56
Breast feeding				
<1 month	30.0	37.2	1	–
≥1 month	70.0	62.8	0.73	0.57–0.92

pregnancy had a risk of having wheezing, asthma, allergic rhinitis and eczema in childhood 1.41–1.75 times higher than the children of mothers who had not experienced any stress.

This excess risk was not accounted for either by socio-demographical characteristics or known risk factors for the children and their families (e.g. parental asthma, smoking, industrial pollution, common allergens and endotoxins), or by complications or drug use during pregnancy, or by the children's characteristics at birth (e.g. weight, term and

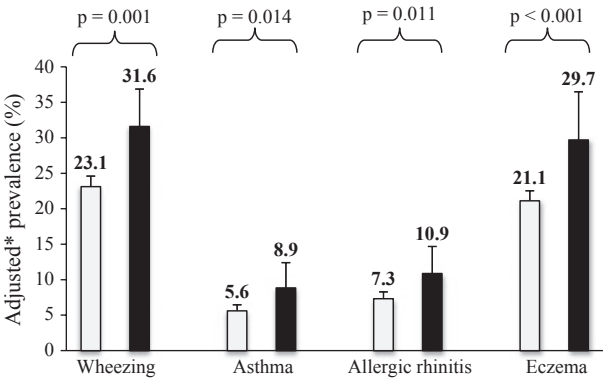

Figure 1 Prevalence* (with 95% CIs) of wheezing, asthma, allergic rhinitis and eczema in children born to mothers who did (black columns) and did not (white columns) experience SLEP. *Adjusted for gender and age.

breastfeeding). In fact, the estimates of the association between maternal SLEP and asthma and atopic diseases in children did not change after adjustment for all the previous potential confounders.

Studies examining the influence of stress during the prenatal period on atopic disorders are lacking. A recent study reported a significant association between maternal exposure to bereavement during the second gestational trimester and development of asthma in boys at 1–4 yrs (13). Another survey showed that gestational exposure to maternal psychological and physical stress was associated with a 1.5-fold increased risk of childhood eczema (14). Other studies that investigated the association of caregiver's stress and childhood wheezing (15) or the effect of stressful events in children on the onset of asthma (4) found that the exposure to stress increased the risk by 1.6–2.9 times. In adults, the incidence of asthma was increased by 1.6–2.2 times in those who had experienced stressful life events (6, 7).

Overall, our quantitative estimates of the association between prenatal exposure to SLEP and asthma and atopic diseases are consistent with those obtained from studies that assessed the effect of exposure to stressful events in children or in adults. In addition, they point out that the foetal exposure to SLEP increases the susceptibility of a child to the whole spectrum of atopic disorders.

As eczema, allergic rhinitis and asthma are inflammatory diseases largely due to an inappropriate response of the immune system, our findings suggest that prenatal stress may influence the development of foetal immunity. This hypothesis seems to be supported by evidence from animal studies (16) and by a recent cohort study that found that women who had experienced stressful events during pregnancy had an increased level of cytokines, which may enhance the polarization of the foetal immune system towards the allergic phenotype, in the cord blood (17). It is likely that the activation of the 'foetal programming' is stimulated by changes in the neuroendocrine and immune systems of the mother (18). Further studies are needed to elucidate the true pathways

Table 4 Odds ratios (OR, with 95% CI) for the association between respiratory and allergic diseases in children (wheezing, asthma, allergic rhinitis and eczema) and stressful life events during pregnancy (SLEP)

	OR–adjusted for gender and age	OR–also adjusted for socio-economic and exposure factors*	OR–also adjusted for pregnancy and birth conditions†
Wheezing	1.53 (1.20–1.96)	1.46 (1.07–1.99)	1.41 (1.03–1.94)
Asthma	1.62 (1.08–2.42)	1.70 (1.03–2.80)	1.71 (1.02–2.89)
Allergic rhinitis	1.53 (1.07–2.19)	1.78 (1.12–2.83)	1.75 (1.08–2.84)
Eczema	1.70 (1.32–2.17)	1.53 (1.13–2.09)	1.53 (1.11–2.10)

*adjusted for: gender, age, being foreign (both non-Italian parents), parental education, parental smoking, parental asthma, person who filled in the questionnaire, residential area, traffic level near home, exposure to industrial pollution, exposures to mould, farm animals, bedroom sharing with older siblings, ever had a cat at home, ever had a dog at home.
†adjusted for all the previous factors plus: pregnancy conditions (hypertension, pre-eclampsia, risk of miscarriage or premature delivery, infection-induced fever, gynaecological infection, use of paracetamol), birth conditions (mother's age at delivery, birth weight, preterm birth, caesarean birth) and breastfeeding.

through which stress-induced changes in the physiology of the mother affect the immune system of the foetus.

Maternal stress is associated with an increase in pregnancy complications and early breastfeeding cessation

In agreement with other studies, we found that pregnant women who had experienced stressful events were at an increased risk for pregnancy complications, such as miscarriage, pre-eclampsia or gestational hypertension and infections (19). These findings point out that stress exposures in this women's critical period of life are associated with multiple adverse events influencing the health status of both the mother and the foetus. Indeed, the effects of prenatal maternal stress on the foetus are physiologically mediated through alterations of maternal systems. Stress has been shown to induce changes in the hypothalamic–pituitary–adrenocortical axis (20), which may lead to hypertension and pre-eclampsia (21), and in the immune system that may increase the susceptibility to infections (22). The lack of any statistically significant interaction between pregnancy complications, the occurrence of SLEP and the development of asthma and allergy in the studied children, seems to suggest that the stress elicited disruption of neuroendocrine and immune maternal systems may be a common mechanism that independently influences the risk of complications during pregnancy and the foetal programming of the atopic phenotype.

Several studies have shown that maternal stress is associated with preterm birth and an infant's low birth weight, even if the reported associations were generally small (23). In our study, maternal SLEP were weakly associated with preterm birth, and they were not related to low birth weight. This negative finding may be due to the lack of power of our study or more likely to the fact that mothers of children with a low birth weight or delivered preterm tended to over-report the infant's birth weight (24).

In our study, SLEP were also associated with early cessation of breastfeeding. Our results are consistent with previous studies that showed that SLEP reduce maternal intention to feed at-breast (25) and the duration of breastfeeding (26), probably by impairing the release of oxytocin, which is involved in milk ejection reflex and production (27).

Strengths and limits

The strength of this study is that the survey investigated all the school-age children of the area (n = 3854) and their parents through internationally validated questionnaires, obtaining an exceptionally high response rate (98.6%). The main limitation of this study is that both maternal exposure to SLEP and outcomes were retrospectively assessed through a questionnaire administered to parents. As a consequence, recall bias might affect our results if the mothers who had troublesome pregnancies or had children with health problems over-reported the occurrence of SLEP. However, the events studied (mourning, divorce and loss of the job) have a strong impact on emotions and are likely to be recalled more accurately than other events (28). Furthermore, the agreement between medical records and perinatal factors reported by mothers has been shown to be satisfactory (29). Thus, recall bias could have influenced our estimates only to a minor extent. The use of parental-reported symptoms to identify children with asthma and atopic diseases might be considered another weakness of the survey. Nevertheless, this is the common method used in the epidemiological research on children, and the questions we used proved very reliable and valid in previous studies (30). Another limitation is that the question used to assess maternal SLEP did not permit to disentangle the three events (mourning, divorce and loss of the job). Accordingly, we were not able to study the different SLEP separately or to scale the total stress experienced by the mother for a finer measure of the exposure.

Conclusions

The children of mothers who had experienced stressful life events during pregnancy had an increased risk of having wheezing, asthma, eczema and allergic rhinitis in childhood. Maternal stress had a wide and substantial effect on preg-

nancy outcomes and enhanced the expression of asthma and atopic phenotypes in children. Our study confirms the view that the natural history of asthma and atopic diseases begins *in utero* and continues through to childhood and adolescence.

Acknowledgments

Roberto de Marco conceived the idea for this study and planned the statistical analyses. Giancarlo Pesce did the statistical analyses. All the authors cooperated in the preparation of the study instruments and questionnaires, in the interpretation of the results, drafting and revising of the present manuscript.

Disclosure

None.

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