Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition

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Background: There is evidence to suggest an association between prenatal maternal stress and the development of asthma or other atopic diseases in offspring. Yet, insights on the lasting effect of multiple, common prenatal stressors are rare, and the effects of prenatal timing are poorly understood. Further, it remains elusive if prenatal life events modify the risk for atopic diseases in the context of a parental predisposition to atopy.

Objective: We tested whether women's experiences of common, adverse life events during the first or second half of pregnancy predicted the risk of developing atopic diseases in their children and whether a reported parental atopic disease moderated this association.

Methods: We calculated the odds of a child developing asthma, eczema, and/or allergic rhinitis at ages 6 or 14 years, depending on maternal prenatal exposure to negative life events in a sample of 1587 children from the Western Australian Pregnancy Cohort (Raine) Study by using multivariable logistic regression.

Results: We observed that the likelihood of asthma and eczema at age 14 years was significantly increased in children of mothers who had experienced adverse life events during the second half of gestation (1 life event: adjusted odds ratio for asthma, 2.08 [95% CI, 1.22-3.54]). A stronger increase in the odds to develop asthma upon prenatal life events was present in children of mothers without asthma compared with mothers with asthma.

Conclusions: Maternal adverse life events during the second half of gestation are linked to an increased risk for the development of atopic disorders, asthma, and eczema, in the case of asthma, particularly in the absence of a maternal asthma. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Atopic disease, eczema, asthma, allergic rhinitis, negative life events, prenatal programming, child, pregnancy*

An unprecedented increase in prevalence of asthma and atopic diseases has been observed worldwide over the past decades.[1,2] This trend is notably apparent in Westernized societies, where often one-third of the children are reported to have an atopic disease.[1] Despite considerable research efforts, there is no unifying hypothesis to explain this "atopic epidemic." Clearly, a strong hereditary component is associated with atopic diseases.[3,4] However, genetic factors alone do not suffice to explain these recent increases because such substantial changes to the human genome are not presumed to emerge over a few decades. Accordingly, the causes of asthma and atopic diseases have been hypothesized to be related to changing environmental challenges observed over the past decades, such as pollution, microbial exposure, diet, and psychosocial factors (eg, high stress perception).[5-15] Moreover, a stronger maternal parent-of-origin effect has been reported in the context of determining the risk for asthma.[3] This observation strongly supports that *in utero* challenges significantly determine the later risk for atopic diseases.[5,12,16-18] Indeed, the prenatal period has recently been identified as particularly susceptible to environmental challenges and exposures, that is, smoking during pregnancy has been shown to increase the risk for atopic diseases in children later in life.[5,12,17,18]

Strikingly, in coinciding with the increased prevalence of atopic diseases, an increase in psychosocial stresses in populations of varying socioeconomic conditions also has been reported.[19,20] These findings have been amalgamated and fostered epidemiologic studies that aimed to test an association between prenatal psychosocial stress and an increased risk for atopic diseases in children later in life.[21,22] Published evidence available to date on this presumed association reports rather ambiguous findings, which range from a significantly increased risk, for example, for childhood asthma, to only weak evidence for an association.[22,23] This ambiguity of findings likely results from the differences in study designs used in respective epidemiologic studies, that is, the gestational periods examined or the definition or measurement of stress. For example, maternal prenatal anxiety symptoms have been used to index prenatal stress and revealed a strong association with childhood asthma.[22,23] However, anxiety, defined as manifest feelings of fear and insecurity, may be a limited proxy for stress perception. Alternatively, prenatal

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Abbreviation used
OR: Odds ratio

bereavement, which was weakly associated with childhood asthma in boys only, is a very severe yet rare stressor. Other studies investigated the effect of prenatal life events in a selected, potentially biased population, for example, in low-income minority groups.[24,25] Hence, extrapolation of these findings for other social groups may be limited. Another recent study showed that children of mothers who experienced prenatal negative life events are at greater risk to develop repeated wheezing within the first 2 years of life.[26] However, wheezing early in life may be a transient phenomenon, and evidence for an association between prenatal negative life events and a long-term manifestation of asthma would be helpful to strengthen these findings. Moreover, little is known on whether or not prenatal psychological challenges affect the risk for children's atopic diseases irrespective of a pre-existing maternal atopic disease. Thus, here we aimed to test for a differential effect of prenatal maternal stress, depending on the presence or absence of maternal or paternal atopic disease.

Thus, evidence from large, prospectively designed birth cohorts to support an association between prenatal stressors and the risk for manifest atopic diseases in children later in life is still limited. Given the reported rise in stress levels among Western societies today, additional studies in which such limitations have been addressed as much as possible are urgently required to validate the alleged association. In this context, the evaluation of common adverse life events may serve as a suitable proxy for stress perception and physiological stress response because adverse life events have previously been associated with increased levels of cortisol in pregnant women.[27]

In the present study, we evaluated the associations among common adverse life events (eg, a residential move, economic or marital problems, job loss) in a prospectively designed large pregnancy cohort. Life events were assessed at 2 critical time points during gestation: (1) at mid gestation (gestation week 18), when the development of the fetal immune system is completed, and (2) at week 34, when the fetal airway epithelial development has occurred, lung air spaces have expanded, and production of a surfactant factor has begun. The onset of atopic diseases in children was evaluated twice, at 6 years of age to identify a possible effect of prenatal life events on early life atopic diseases, and at age 14 years to unveil an association between prenatal life events and a manifestation of atopic diseases (asthma, eczema, and allergic rhinitis) during puberty. Further, we determined whether parental atopic disease modifies any effect of prenatal maternal life events. We investigated these associations in a population-based birth cohort from Australia, in which women's life events were self-reported both during pregnancy and after birth.

METHODS

We conducted a longitudinal evaluation of 1587 children and their mothers from the Western Australian Pregnancy Cohort (Raine) Study. Both mother and child completed a questionnaire at follow-up and the children took part in a clinical examination at the Telethon Institute for Health Research at the age of 14. In the Raine Study, between 1989 and 1991, mothers between 16 to 20 weeks of gestation were enrolled by research midwives at antenatal clinics at the main tertiary maternal hospital or nearby medical practices in Perth, Western Australia. The original purpose of the study was to determine the effects of intensive fetal monitoring on pregnancy outcomes. Full details regarding recruitment are outlined by Newnham et al.[28] The study protocol was approved by the human ethics committee at King Edward Memorial Hospital and/or Princess Margaret Hospital in Perth. Details of pregnancies, deliveries, and neonatal outcomes were taken from hospital notes. The cohort initially consisted of 2860 live born children. These children were followed-up at 1, 2, 3, 6, 8, 10, and 14 years of age. At 14 years of age, 1587 children still participated in the assessments, whereas 1273 were lost to follow-up. Complete data were available for 994 mothers and their children. Measures for this investigation were obtained from parent surveys administered during the Raine Cohort study and from clinical examinations at age 6 years and 14 years, which included allergy and lung function testing.

Prenatal negative life events

Prenatal stress was evaluated via questionnaire as part of the study protocol and comprised 10 typically stressful life events taken from a broader life-stress inventory.[29] Pregnant women were assessed twice during pregnancy, first, at gestational week 18 when the women were asked whether or not they had experienced any of the life events since the beginning of pregnancy and, second, at gestational week 34 when the women were asked whether any of these events had been experienced since the last survey at gestational week 18. This ensured that the same event was not recorded twice. Negative life events surveyed were separation or divorce, marital problems, problems with the children, pregnancy problems, experience of involuntary job loss, partner experienced involuntary job loss, money problems, a residential move, death of a close relative, and death of a close friend. These items were selected because they were deemed the most salient for a population-based sample and to save space in the larger health and lifestyle questionnaire that mothers completed during pregnancy.[30] Moderately stressful life events, such as a residential move, money problems, and pregnancy problems were among the life events most often experienced, whereas more-severe life events, such as death of a relative or friend, were rare. An overview of the frequency of the individual life events is shown in Table E1 (in this article's Online Repository at www.jacionline.org). Further some life events were significantly associated with each other, that is, separation or divorce and residential move or money problems and partner's involuntary job loss. The frequency of co-occurrences of life events is shown in Table E2 (in this article's Online Repository at www.jacionline.org) for life events from conception to gestational week 18 and between gestational week 18 and 34, respectively.

In the Raine study, no additional information is available that would allow us to appraise the stress level perceived in response to the respective life events or the duration of the stressful experience. Thus, we could not assign predetermined weights to life events. Therefore, we postulated an additive effect of multiple life events and evaluated the total number of life events experienced during the first (until gestational week 18) as well as the second half of pregnancy (gestational week 18 to 34) for each woman.

Atopic disease outcomes

Current asthma at ages 6 and 14 years was defined as ever having been diagnosed with asthma by a physician and the presence of a wheeze or nocturnal cough in the absence of respiratory infection, in addition to receipt of asthma medications (controller and reliever drugs) in the previous 12 months. One might argue that this definition for asthma is rather stringent because so-called wheezers were excluded. However, because we observed that, in only 18.5% of the 54 children who experienced only wheezing at age 6 years, a manifestation of asthma could be detected at age 14 years, we gave the stringent definition our preference. Moreover, children who met the stringent definition of current asthma used in this study exhibited significant deficits in lung function and greater sensitivity to methacholine challenge tests for bronchial hyperreactivity.[31,32]

Atopy was assessed at ages 6 years and 14 years, and was defined as a specific IgE level of more than or equal to 0.35 kU/L for any of the following allergens: house dust mite (*Dermatophagoides pteronyssinus*), rye grass pollen (*Lolium perenne*), cat, couch grass (*Cynodon dactylon*), mold mix-2