Parental psychological distress during pregnancy and wheezing in preschool children: The Generation R Study

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Background: Maternal psychological distress during pregnancy might affect fetal lung development and subsequently predispose children to childhood asthma.
Objective: We sought to assess the associations of maternal psychological distress during pregnancy with early childhood wheezing.
Methods: We performed a population-based prospective cohort study among 4848 children. We assessed maternal and paternal psychological distress at the second trimester of gestation and 3 years after delivery and maternal psychological distress at 2 and 6 months after delivery by using the Brief Symptom Inventory questionnaire. Wheezing in the children was annually examined by using questionnaires from 1 to 4 years. Physician-diagnosed ever asthma was reported at 6 years.
Results: Mothers with psychological distress during pregnancy had increased odds of wheezing in their children from 1 to 4 years of life (overall distress: odds ratio [OR], 1.60 [95% CI, 1.32-1.93]; depression: OR, 1.46 [95% CI, 1.20-1.77]; and anxiety: OR, 1.39 [95% CI, 1.15-1.67]). We observed similar positive associations with the number of wheezing episodes, wheezing patterns, and physician-diagnosed asthma at 6 years. Paternal distress during pregnancy and maternal and paternal distress after delivery did not affect these results and were not associated with childhood wheezing.
Conclusion: Maternal psychological distress during pregnancy is associated with increased odds of wheezing in their children during the first 6 years of life independent of paternal psychological distress during pregnancy and maternal and paternal psychological distress after delivery. These results suggest a possible intrauterine programming effect of maternal psychological distress leading to respiratory morbidity. (J Allergy Clin Immunol 2014;133:59-67.)

Key words: *Anxiety, asthma, child, preschool, child development, cohort studies, depression, prospective studies, stress, psychological*

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Abnormal fetal lung and immune development in response to adverse intrauterine exposures might increase the risk of asthma and atopic disorders in childhood and adulthood.[1,2] Maternal psychological distress during pregnancy is one of these exposures that can specifically lead to developmental adaptations of the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, lung structure and function, and immune responses in the offspring.[3-8] However, any association between maternal psychological distress during pregnancy and childhood wheezing might also be explained by other mechanisms, such as social, behavioral, or environmental factors. From both a causative and a preventative perspective, it is important to explore the role of intrauterine mechanisms in this association.

We used the information of paternal psychological distress during pregnancy to address confounding, as described previously.[9-11] Stronger effect estimates for the association of maternal than paternal psychological distress during pregnancy with childhood wheezing would indicate intrauterine mechanisms. Similar associations of maternal and paternal psychological distress during pregnancy with childhood wheezing would indicate that these associations are not driven by a

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The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation, and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (STAR). The first phase of the Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam; Erasmus University, Rotterdam; and the Netherlands Organization for Health Research and Development. V. W. V. J. received an additional grant from The Netherlands Organization for Health Research and Development (ZonMw 90700303, 916.10159). L.D. is the recipient of a European Respiratory Society/Marie Curie Joint Research Fellowship, no. MC 1226-2009. The research leading to these results has received funding from the European Respiratory Society and the European Community's Seventh Framework Programme FP7/2007-2013–Marie Curie Actions under grant agreement RESPIRE, PCOFUND-GA-2008-229571 and from the seventh framework programme, project CHICOS (HEALTH-F2-2009-241504). This manuscript was written with the support of the European Child Cohort Network EUCCONET, a Research Networking Programme financed by the European Science Foundation.

Disclosure of potential conflict of interest: L. Duijts has received a European Respiratory Society/Marie Curie Joint Research Fellowship, no. MC 1226-2009. The research leading to these results has received funding from the European Respiratory Society and the European Community's Seventh Framework Programme FP7/2007-2013–Marie Curie Actions under grant agreement RESPIRE, PCOFUND-GA-2008-229571 and from the seventh framework programme, project CHICOS (HEALTH-F2-2009-241504). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 28, 2012; revised April 15, 2013; accepted for publication April 16, 2013.

Available online June 15, 2013.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.04.044

Abbreviation used
OR: Odds ratio

direct intrauterine mechanism but by residual confounding of unmeasured social, behavioral, or environmental factors within the families.

The aim of the present study was to assess the associations of maternal psychological distress during pregnancy with childhood wheezing in the first 6 years of life and to assess whether this association is independent of paternal psychological distress during pregnancy and maternal and paternal psychological distress after delivery.

METHODS

Study design and population

This study was embedded in the Generation R Study, a population-based cohort study from fetal life onward in Rotterdam, The Netherlands.[12] All children were born between April 2002 and January 2006. Assessments in pregnant women consisted of physical examination, fetal ultrasound, biological sampling, and questionnaires. In total, 8880 mothers were enrolled during pregnancy (see Fig E1 in this article's Online Repository at www.jacionline.org). For this study, 7490 mothers were eligible after excluding twin pregnancies, miscarriages, and mothers who lived outside the study area. Among them, 666 were excluded because of loss to follow-up or lack of consent for the postnatal phase of the study. In 1976 children no information on maternal psychological distress or childhood wheezing was available. Finally, 4848 (64.7%) children were included in this study. The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, The Netherlands. Written informed consent was obtained from all women.

Maternal and paternal psychological distress

Information on maternal and paternal psychological distress was obtained by using postal questionnaires at 20 weeks of gestation and at 3 years after delivery by using the Brief Symptom Inventory.[13] Information on maternal psychological distress was also obtained at 2 and 6 months after delivery by using the same questionnaire because of the critical period for maternal distress symptoms during the first 6 months after delivery.[14] The mother and father each answered their own questionnaires. The Brief Symptom Inventory is a validated self-report questionnaire with 53 items. These items define a broad spectrum of psychological symptoms in the preceding 7 days. A global index and 2 symptom scales (depression and anxiety) were defined.[13] At 6 months and 3 years after delivery, only depression and anxiety scales were measured.

The global index is a measure of the current level or depth of symptoms and denotes overall psychological distress. Each item was rated on 5-point unidimensional scales ranging from 0 (not at all) to 4 (extremely). Total scores for each scale were calculated by summing the item scores and dividing by the number of endorsed items. Higher scores represented an increased occurrence of overall distress, depression, or anxiety symptoms. Based on the Dutch cutoffs,[15] mothers were categorized as being sensitive for clinically significant psychological distress (yes/no) when having a score of greater than 0.71 on the overall distress scale, greater than 0.80 on the depression scale, and greater than 0.71 on the anxiety scale. Fathers were categorized as being sensitive for clinically significant psychological distress (yes/no) when having a score of greater than 0.66 on the overall distress scale, greater than 0.71 on the depression scale, and greater than 0.65 on the anxiety scale.[15] In the current study internal consistencies (Cronbach α) for the different scales of the mother and father ranged from 0.67 to 0.99. Spearman correlations between maternal and paternal distress scales during pregnancy and at 3 years ranged from 0.10 to 0.27, those between prenatal and postnatal maternal distress scales ranged from 0.22 to 0.58, and those between prenatal and postnatal paternal distress scales ranged from 0.14 to 0.35.

We defined patterns of paternal depression and anxiety after delivery as follows: (1) *never depression or anxiety*, no symptoms at any age after delivery; (2) *transient depression or anxiety*, symptoms at 2 or 6 months but not at 3 years after delivery; (3) *late-onset depression or anxiety*, symptoms at 3 years after delivery but not at 2 or 6 months after delivery; and (4) *persistent depression or anxiety*, symptoms at both 2 or 6 months and 3 years after delivery.

Childhood wheezing

Information on wheezing in the past year was obtained by using questionnaires adapted from the International Study on Asthma and Allergy in Childhood[16] at the ages of 1, 2, 3, and 4 years. Mothers answered 85.2%, 84.5%, 94.1%, and 88.3% of the questionnaires at the ages of 1, 2, 3, and 4 years, respectively. Response rates for these questionnaires were 71% to 76%.[17] We defined wheezing pattern categories based on Martinez et al[18] and adapted to preschool age[19,20]: (1) *no wheezing*, no recorded wheezing at any age; (2) *early wheezing*, at least 1 wheezing symptom during the first 3 years of life but no wheezing at 4 years of age; (3) *late wheezing*, no wheezing episodes during the first 3 years of age but wheezing at 4 years of age; and (4) *preschool persistent wheezing*, at least 1 wheezing episode in the first 3 years of life and wheezing at 4 years of age. Information on physician-diagnosed ever asthma was obtained by means of questionnaire at the age of 6 years, with a response rate for this questionnaire of 68%.

Covariates

Information on maternal and paternal age, smoking during pregnancy, educational level, ethnicity, history of asthma and atopy, pet keeping, and maternal parity was obtained through self-administered questionnaires at enrollment.[11,21] Maternal and paternal weight and height were measured during the first visit to the research center. Body mass index was calculated as kilograms per square meter. Gestational age, sex, and birth weight of the children were obtained from midwife and hospital registries at birth. Preterm birth was defined as less than 37 weeks of gestational age. Postal questionnaires at the ages of 6 and 12 months and 2 years provided information about breastfeeding, day care attendance, and childhood secondhand smoke at home.[21] Information on physician-attended eczema and physician-diagnosed lower respiratory tract infections was obtained by using questionnaires at the ages of 1, 2, 3, and 4 years.

Statistical analysis

Among subjects with available data on maternal psychological distress during pregnancy and childhood wheezing (n = 4848), we performed multiple imputation of missing values by using chained equations in which 25 completed datasets were generated and analyzed with the standard combination rules for multiple imputation.[22,23] Distributions in imputed datasets were similar to those observed (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org).

First, generalized estimating equations were performed to examine the associations of maternal psychological distress during pregnancy (dichotomized based on the clinical cutoffs and continuous) with the longitudinal odds of wheezing (no/yes) from the age of 1 to 4 years. These models took into account the correlations between repeated measurements of wheezing within the same subject. For optimal generalized estimating equation modeling, we selected the exchangeable correlation matrix based on the quasilikelihood under the independence model criterion and degrees of freedom.[24] Models were adjusted for several potential confounder variables selected *a priori* on the basis of previous studies.[1-3,17,21,25] We additionally adjusted the models for maternal psychological distress at 2 months, 6 months, and 3 years after delivery and for paternal psychological distress during pregnancy and 3 years after delivery by adding them one by one to the models separately. We additionally adjusted the models for patterns of maternal depression and anxiety after delivery. We used similar models to assess the associations of paternal psychological distress during pregnancy with childhood wheezing, adjusting for maternal psychological distress during pregnancy.

Second, we used generalized estimating equation models to examine the association of maternal and paternal psychological distress during pregnancy with the longitudinal odds of the number of wheezing episodes. We performed polytomous logistic regression to explore the association of maternal and