

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

Mònica Guxens, MD, MPH, PhD,^{a,b,c,d} Agnes M. M. Sonnenschein-van der Voort, MSc,^{a,e,f} Henning Tiemeier, MD, PhD,^{f,g} Albert Hofman, MD, PhD,^f Jordi Sunyer, MD, PhD,^{b,c,h} Johan C. de Jongste, MD, PhD,^e Vincent W. V. Jaddoe, MD, PhD,^{a,f,i} and Liesbeth Duijts, MD, PhD^{e,f,j} Rotterdam, The Netherlands, and Barcelona, Spain

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* 2013;■■■■:■■■■-■■■■.)

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

From ^athe Generation R Study Group, Erasmus Medical Center, Rotterdam, The Netherlands; ^bthe Center for Research in Environmental Epidemiology (CREAL), Barcelona; ^cHospital del Mar Research Institute (IMIM), Barcelona; ^dCIBER Epidemiología y Salud Pública (CIBERESP), Barcelona; ^ethe Department of Pediatrics, Division of Respiratory Medicine, ^fthe Department of Child & Adolescent Psychiatry, ^gthe Department of Pediatrics, and ^hthe Department of Pediatrics, Division of Neonatology, Erasmus Medical Center–Sophia Children's Hospital, Rotterdam; ⁱthe Department of Epidemiology, Erasmus Medical Center, Rotterdam; and ^jPompeu Fabra University, Barcelona.

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.

Corresponding author: Liesbeth Duijts, MD, PhD, Erasmus Medical Center–Sophia Children's Hospital, Sp-3435, PO Box 2060, 3000 CB Rotterdam, The Netherlands. E-mail: l.duijts@erasmusmc.nl.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaci.2013.04.044

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 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.

Abbreviation used

OR: Odds ratio

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 Childhood¹⁶ 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 al¹⁸ 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 quasilielihood 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 paternal psychological distress during pregnancy with preschool wheezing patterns. We used logistic regression to examine the association of maternal and paternal psychological distress during pregnancy with physician-diagnosed ever asthma at 6 years. The goodness of fit of the logistic and polytomous logistic regression models (R^2) was estimated.

Finally, we tested the interaction between maternal psychological distress during pregnancy and maternal history of asthma or atopy as a proxy for atopy susceptibility in children, as well as the interaction between maternal psychological distress during pregnancy and maternal smoking during

TABLE I. Maternal and paternal characteristics of the study population (n = 4848)

	Distribution (%)	
	Mother	Father
Age at enrollment (y)*		
<20	1.9	0.6
20-24.9	11.1	4.9
25-29.9	25.4	18.5
30-34.9	44.3	41.2
≥35	17.4	34.8
Body mass index at enrollment (kg/m ²)†		
Underweight (<20)	9.1	4.0
Normal weight (20-24.9)	56.0	47.4
Overweight (25-29.9)	24.5	41.2
Obese (≥30)	10.4	7.4
Smoking during pregnancy (yes vs no)*	13.7	42.1
Educational level*		
Primary education	6.6	5.8
Secondary education	40.2	37.7
Higher education	53.2	56.5
Ethnicity (non-European vs European)*	31.5	31.4
Parity (multiparous vs nulliparous)*	40.6	—
History of asthma and atopy (yes vs no)*	35.0	29.2
Pet keeping during pregnancy (yes vs no)*	32.6	—
Overall psychological distress during pregnancy (yes vs no)‡	8.1	2.6
Depression during pregnancy (yes vs no)‡	8.0	2.9
Anxiety during pregnancy (yes vs no)‡	9.3	6.4
Overall psychological distress at 2 mo after delivery (yes vs no)‡	7.1	—
Depression symptoms at 2 mo after delivery (yes vs no)‡	7.3	—
Anxiety symptoms at 2 mo after delivery (yes vs no)‡	7.4	—
Depression symptoms at 6 mo after delivery (yes vs no)‡	7.6	—
Anxiety symptoms at 6 mo after delivery (yes vs no)‡	9.0	—
Depression symptoms at 3 y after delivery (yes vs no)‡	4.2	3.2
Anxiety symptoms at 3 y after delivery (yes vs no)‡	4.3	3.8
Patterns of depression symptoms after delivery§		
Never depression symptoms	87.1	—
Transient depression symptoms	9.5	—
Late-onset depression symptoms	1.8	—
Persistent depression symptoms	1.6	—
Patterns of anxiety symptoms after delivery§		
Never anxiety symptoms	86.2	—
Transient anxiety symptoms	10.2	—
Late-onset anxiety symptoms	1.9	—
Persistent anxiety symptoms	1.7	—

*Information obtained through self-administered questionnaire at enrollment.

†Maternal weight and height were measured during the first visit to the research center, and body mass index was calculated.

‡Information obtained by means of postal questionnaires with the Brief Symptom Inventory; the mother and father each answered their own questionnaires.

§Patterns of depression and anxiety symptoms after delivery defined separately according to the history of maternal depression/anxiety symptoms at 2 and 6 months and 3 years after delivery: (1) *never depression/anxiety symptoms*, mothers without depression/anxiety at any age after delivery; (2) *transient depression/anxiety symptoms*, mothers with depression/anxiety symptoms at 2 or 6 months but not at 3 years after delivery; (3) *late-onset depression/anxiety symptoms at 3 years*, mothers with depression/anxiety symptoms at 3 years after delivery but not at 2 or 6 months after delivery; and (4) *persistent depression/anxiety symptoms*, mothers with depression/anxiety symptoms at 2 or 6 months and at 3 years after delivery.

pregnancy, on childhood wheezing. Moreover, we performed a sensitivity analysis focused on the associations of maternal and paternal psychological distress during pregnancy with childhood wheezing, in which we included only those subjects with complete data of maternal and paternal psychological distress during pregnancy and at 3 years after delivery and wheezing at 1, 2, 3, and 4 years (n = 2098). Maternal, paternal, and child characteristics of this subsample were compared with the original population for analysis (n = 4848). Statistical tests of hypotheses were 2-tailed, with the significance level set at a *P* value of less than .05. Statistical analyses were conducted with STATA 11.0 software (StataCorp, College Station, Tex).

RESULTS

Children included in the present analysis were more frequently from parents with a higher educational level, and their mothers

and fathers showed less psychological distress during pregnancy (see Table E3 in this article's Online Repository at www.jacionline.org) compared with those lost to follow-up. No differences on maternal and paternal history of asthma and atopy were found.

Of the study participants, 7.8% mothers had overall psychological distress during pregnancy (Table I). Wheezing prevalences of the children were 29.1%, 19.5%, 12.4%, and 12.6% at 1, 2, 3 and 4 years, respectively (Table II). Concerning preschool wheezing patterns, 53.7% of children were classified as never wheezing, 33.0% as having early wheezing, 2.6% as having late wheezing, and 10.7% as having persistent wheezing. Prevalence of physician-diagnosed ever asthma at 6 years was 6.0%.

TABLE II. Child characteristics of the study population (n = 4848)

	Distribution (%)
Sex (female vs male)*	50.9
Preterm birth (<37 vs ≥37 wk)*	4.1
Birth weight (g)*	
<2500	3.9
2500-3499	47.6
3500-4499	46.1
≥4500	2.5
Breast-feeding (yes vs no)†	92.0
Day care attendance (yes vs no)†	59.2
Secondhand smoke at home (yes vs no)†	17.4
Physician-attended eczema from 1 to 4 y (ever vs never)‡	27.8
Physician-diagnosed lower respiratory tract infections from 1 to 4 y (ever vs never)‡	20.4
Wheezing‡	
First year	
No episodes	70.9
1-3 episodes	22.8
≥4 episodes	6.3
Second year	
No episodes	80.5
1-3 episodes	16.3
≥4 episodes	3.2
Third year	
No episodes	87.4
1-3 episodes	10.3
≥4 episodes	2.3
Fourth year	
No episodes	87.4
1-3 episodes	10.3
≥4 episodes	2.3
Wheezing patterns§	
Never wheezing	53.7
Early wheezing	33.0
Late wheezing	2.6
Persistent wheezing	10.7
Physician-diagnosed ever asthma at 6 y	6.0

*Information obtained from midwife and hospital registries at birth.

†Information obtained by means of postal questionnaires at the ages of 6 and 12 months and 2 years.

‡Information obtained by means of postal questionnaires at the ages of 1, 2, 3, and 4 years.

§Wheezing patterns categories based on Martinez et al¹⁸ and adapted to preschool age,^{19,20} according to the history of wheezing from the age of 1 to 4 years: (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 obtained by means of postal questionnaire at the age of 6 years.

Compared with mothers without psychological distress during pregnancy, mothers with overall distress, depression, or anxiety during pregnancy had increased odds of wheezing in their children overall 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]) based on generalized estimating equation models (Fig 1). Paternal overall distress, depression, and anxiety during pregnancy were not associated with an increased odds of wheezing yearly from 1 to 4 years of life based on generalized estimating equation models (Fig 1). We did not observe major differences in the size of the

effect estimates between the unadjusted and adjusted models (see Fig E2 in this article's Online Repository at www.jacionline.org). Additional adjustment of maternal psychological distress during pregnancy in generalized estimating equation models for maternal psychological distress at 2 months, 6 months, and 3 years after delivery; for the patterns of maternal psychological distress after delivery; and for paternal psychological distress during pregnancy and at 3 years after delivery one by one separately did not materially affect the results (see Tables E4 and E5 in this article's Online Repository at www.jacionline.org). None of the paternal psychological distress variables after delivery were associated with childhood wheezing (all $P > .05$). Compared with children from mothers without psychological distress during pregnancy, children of mothers with overall distress had higher odds of having 1 to 3 wheezing episodes (OR, 1.56 [95% CI, 1.27-1.90]) and 4 or more wheezing episodes (OR, 1.71 [95% CI, 1.20-2.43]) from 1 to 4 years of life based on generalized estimating equation models (Table III). Table IV shows that children of mothers with overall distress during pregnancy had 1.20 (95% CI, 0.86-1.67) times more odds of having early wheezing, 2.46 (95% CI, 1.28-4.70) times more odds of late wheezing, and 2.73 (95% CI, 1.90-3.94) times more odds of persistent wheezing compared with children from mothers without psychological distress during pregnancy based on polytomous logistic regression models. Similar results were found for depression and anxiety (Tables III and IV). Maternal overall psychological distress during pregnancy was borderline associated with physician-diagnosed ever asthma at 6 years (Table V) based on logistic regression models. We did not observe associations between paternal psychological distress during pregnancy and childhood wheezing episodes and patterns or physician-diagnosed ever asthma (Tables III-V).

Associations of maternal psychological distress during pregnancy with wheezing from 1 to 4 years in generalized estimating equation models were similar among children of mothers with a history of asthma and atopy compared with those of mothers without, as well as among children of mothers who were smokers and nonsmokers (P for interaction $> .50$). Compared with children in our original population for analysis, children included in the complete case analysis were more often from parents with a higher educational level who tended to smoke less frequently, were born more frequently in The Netherlands, had a lower body mass index, reported more frequently a history of asthma and atopy, and reported less psychological distress during pregnancy (see Table E6 in this article's Online Repository at www.jacionline.org). Results from the complete case analysis (see Fig E3 and Tables E7 and E8 in this article's Online Repository at www.jacionline.org) showed effect estimates mostly in the same direction as the previous analysis, but the effect sizes differed, and the associations were less often statistically significant.

DISCUSSION

Our results suggest that children exposed to maternal psychological distress during pregnancy have increased odds of childhood wheezing until the age of 6 years. The strength of the associations after adjusting for paternal psychological distress during pregnancy and maternal and paternal psychological distress after delivery, the lack of association of paternal psychological distress during pregnancy and maternal and paternal psychological distress after delivery with childhood

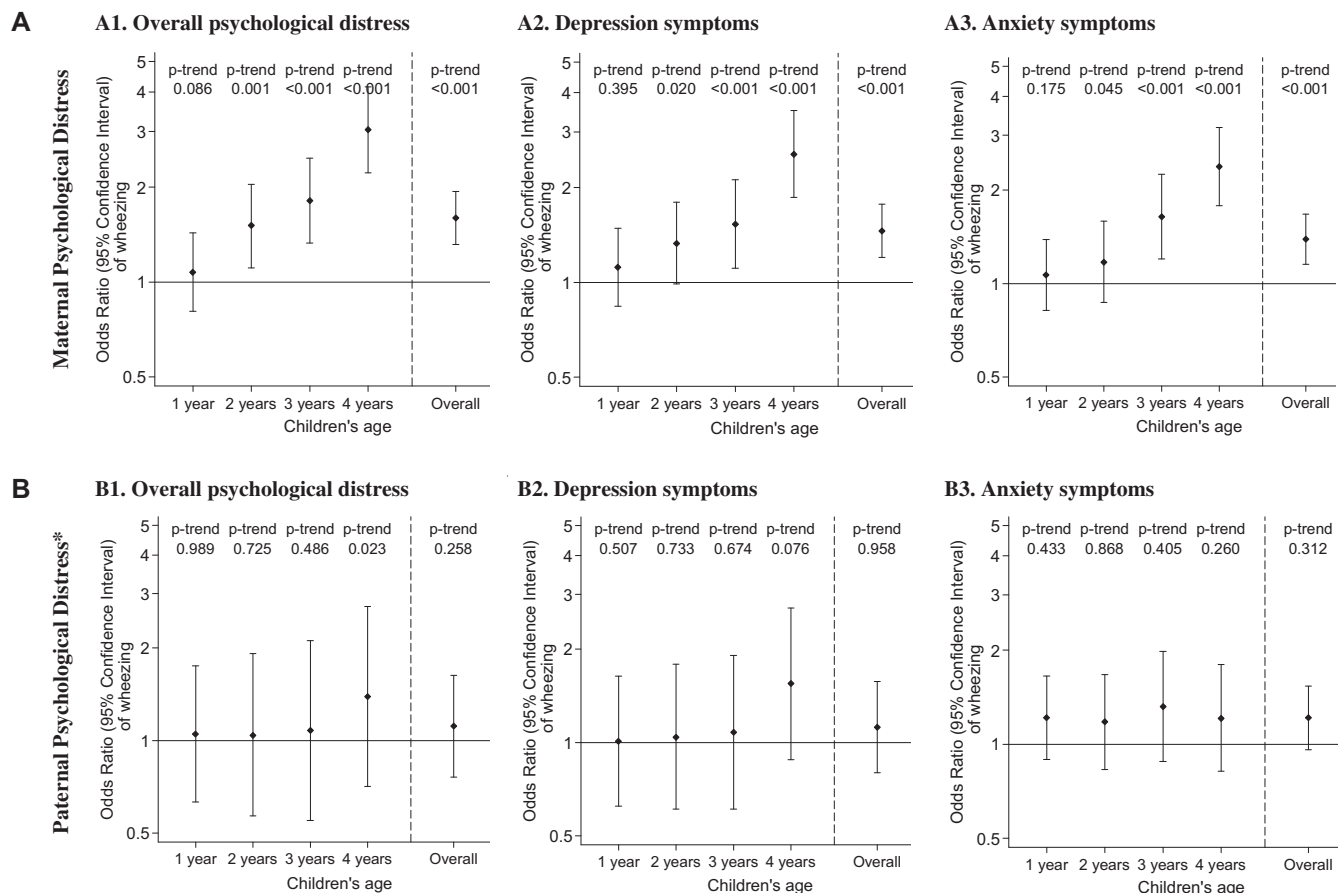


FIG 1. Associations of maternal and paternal psychological distress during pregnancy with wheezing from 1 to 4 years. Odds ratios (95% CIs) from generalized estimating equation models represent the odds of wheezing for the children of mothers or fathers with psychological distress (no, yes). *P* value trend (*p-trend*) represents the linear trend per unit increase on the psychological distress scales. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breastfeeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections. *Models additionally adjusted for maternal psychological distress during pregnancy.

wheezing, and the robustness of the results after adjusting for a large set of potential confounding variables support an intra-uterine programming effect of maternal psychological distress during pregnancy on fetal lung development and subsequent respiratory morbidity.

The strengths of our study were its population-based prospective design, large sample size, assessment of maternal and paternal exposures during pregnancy with the same instrument at the same time point, assessment of maternal and paternal exposures after delivery, and repeated measures of wheezing. In addition, we adjusted for many socioeconomic and lifestyle variables known to affect maternal psychological distress and childhood wheezing. However, residual confounding cannot be completely ruled out. Therefore we used paternal psychological distress during pregnancy as an indirect control for unmeasured variables and shared family factors.

The present study has some limitations. Information on wheezing was mainly based on maternally reported questions.²⁶ Objective tests for assessing asthma are difficult to perform in young children and have limited applicability. In preschool children a diagnosis of asthma is based on symptoms.²⁷ Maternal

psychological distress could have influenced the recognition and reporting of symptoms in their child. Information about maternal psychological distress at the same time as childhood wheezing questionnaires would be of interest and could have reduced potential information bias. Information about maternal psychological distress was available from repeated measurements during the preschool period. Additional adjustment for postnatal maternal psychological distress did not materially change the effect estimates of maternal psychological distress during pregnancy with childhood wheezing. Wheezing during preschool ages might be partly caused by viral infections, and this phenotype is mostly neither persistent nor related to asthma at later ages.²⁸ This is in line with our observations of stronger effects for wheezing at 4 years than at 1 year and for late-onset compared with early-onset wheezing and of a consistency of the association with physician-diagnosed ever asthma at 6 years. Also, adjustment for lower respiratory tract infections did not change the effect estimates. Follow-up studies at older ages with more detailed assessments of asthma and atopy phenotypes are needed. Maternal psychological distress was measured at 1 time point during pregnancy. We do not know whether maternal distress varied in

TABLE III. Associations of maternal and paternal psychological distress during pregnancy with number of wheezing episodes from 1 to 4 years

	No. of wheezing episodes			
	1-3 Episodes per year		≥4 Episodes per year	
	OR	95% CI	OR	95% CI
Maternal psychological distress				
Overall psychological distress				
No	Reference		Reference	
Yes	1.40	1.15-1.71	1.58	1.14-2.20
Per 1-unit increase	1.41	1.20-1.66	1.51	1.16-1.95
<i>P</i> value trend		<.001		.002
Depression symptoms				
No	Reference		Reference	
Yes	1.28	1.05-1.55	1.54	1.11-2.13
Per 1-unit increase	1.20	1.06-1.36	1.27	1.04-1.55
<i>P</i> value trend		.004		.018
Anxiety symptoms				
No	Reference		Reference	
Yes	1.26	1.05-1.50	1.37	1.00-1.88
Per 1-unit increase	1.23	1.09-1.40	1.30	1.06-1.60
<i>P</i> value trend		.001		.012
Paternal psychological distress*				
Overall psychological distress				
No	Reference		Reference	
Yes	1.15	0.79-1.68	0.87	0.41-1.84
Per 1-unit increase	1.18	0.86-1.63	1.27	0.72-2.23
<i>P</i> value trend		.304		.412
Depression symptoms				
No	Reference		Reference	
Yes	1.11	0.79-1.56	1.18	0.62-2.24
Per 1-unit increase	1.01	0.80-1.27	1.06	0.70-1.61
<i>P</i> value trend		.957		.766
Anxiety symptoms				
No	Reference		Reference	
Yes	1.18	0.93-1.49	1.41	0.91-2.16
Per 1-unit increase	1.09	0.88-1.34	1.22	0.84-1.78
<i>P</i> value trend		.426		.291

ORs (95% CIs) from generalized estimating equation models represent the odds of wheezing episodes for the children of mothers or fathers with psychological distress during pregnancy. Maternal and paternal psychological distress were treated as dichotomized based on the clinical cutoffs (no, yes) and as continuous (per 1-unit increase). *P* value trend represents the linear trend per unit increase on the psychological distress scales. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breast-feeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections.

*Models additionally adjusted for psychological distress during pregnancy.

intensity or persistence throughout pregnancy. Cookson et al³ showed similar effect estimate sizes between anxiety measured at week 18 and week 32 of pregnancy. Observational measurements of parental psychological distress were not feasible in this large birth cohort, and we relied on self-reports. Nevertheless, all scales showed an acceptable internal validity; the Brief Symptom Inventory was validated in The Netherlands, and Dutch clinical cutoffs were available.^{12,13} Finally, not all mothers and children recruited were included in this analysis, and loss to follow-up was related to lower socioeconomic position. This might have affected our findings, although the inclusion in the analysis of a large set of variables related to participation could have reduced the likelihood that nonresponse biased the results. We observed differences between the effect estimates of our original population of analysis and the complete case analysis. These differences might be due to both a reduction of the sample size and a selected subsample that seemed biased and not representative. For that reason, we consider results based on the multiple imputation dataset more valid.²²

Only a few previous studies have assessed the relation between maternal psychological distress during pregnancy and childhood wheezing.³⁻⁶ Cookson et al³ found a positive association of maternal anxiety symptoms during pregnancy with subsequent childhood physician's diagnosis asthma at the age of 7.5 years in 5810 children. Similar to our study, they did not observe an association of paternal anxiety symptoms with childhood asthma. Moreover, when maternal anxiety symptoms both during pregnancy and after delivery were taken into account, only symptoms during pregnancy were associated with childhood asthma. In addition to their study, we showed that maternal psychological distress affects asthma symptoms already from a young age onward, and because of our longitudinal design with repeatedly measured outcomes, we observed that these adverse effects became stronger with increasing age. Also, we were able to adjust for more potential confounders, such as maternal prepregnancy body mass index, paternal smoking, or pet keeping at home and to examine important possible modifying effects of genetic susceptibility and secondhand smoke exposure. In another population-based

TABLE IV. Associations of maternal and paternal psychological distress during pregnancy with wheezing patterns from 1 to 4 years

	Early wheezing		Late wheezing		Persistent wheezing	
	OR	95% CI	OR	95% CI	OR	95% CI
Maternal psychological distress						
Overall psychological distress						
No	Reference		Reference		Reference	
Yes	1.23	0.89-1.69	1.94	1.04-3.60	2.15	1.47-3.13
Per 1-unit increase on the scale	1.51	1.16-1.97	2.14	1.29-3.54	2.18	1.60-2.98
<i>P</i> value trend		.002		.003		<.001
Depression symptoms						
No	Reference		Reference		Reference	
Yes	1.31	0.97-1.76	2.04	1.14-3.64	1.84	1.24-2.72
Per 1-unit increase on the scale	1.28	1.05-1.57	1.69	1.18-2.43	1.51	1.18-1.93
<i>P</i> value trend		.015		.004		.001
Anxiety symptoms						
No	Reference		Reference		Reference	
Yes	1.17	0.88-1.55	1.81	1.05-3.12	1.72	1.22-2.43
Per 1-unit increase on the scale	1.27	1.04-1.56	1.71	1.18-2.49	1.66	1.31-2.10
<i>P</i> value trend		.022		.005		<.001
Paternal psychological distress*						
Overall psychological distress						
No	Reference		Reference		Reference	
Yes	1.29	0.74-2.29	2.12	0.79-5.665	1.12	0.46-2.70
Per 1-unit increase on the scale	1.06	0.68-1.66	1.92	0.83-4.48	1.33	0.72-2.48
<i>P</i> value trend		.789		.128		.359
Depression symptoms						
No	Reference		Reference		Reference	
Yes	0.99	0.59-1.67	1.72	0.67-4.42	1.23	0.60-2.52
Per 1-unit increase on the scale	0.86	0.61-1.22	1.44	0.81-2.59	1.10	0.68-1.78
<i>P</i> value trend		.402		.215		.706
Anxiety symptoms						
No	Reference		Reference		Reference	
Yes	1.24	0.89-1.71	1.29	0.58-2.85	1.24	0.74-2.09
Per 1-unit increase on the scale	1.12	0.84-1.55	1.31	0.66-2.63	1.13	0.73-1.76
<i>P</i> value trend		.438		.437		.585

ORs (95% CIs) are from polytomous logistic regression models. Maternal and paternal psychological distress were treated as dichotomized based on the clinical cutoffs (no, yes) and as continuous (per 1 unit-increase). *P* value trend represents the linear trend per unit increase on the psychological distress scales. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breast-feeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections. Goodness of fit (R^2) was 0.10 for all models.

*Models additionally adjusted for psychological distress during pregnancy.

study of 653 mother-child pairs, although both prenatal and postnatal maternal stress were independently associated with increased recurrent wheezing during the first 2 years of life, children born to mothers experiencing higher stress in both periods were particularly at risk.⁶ These effects remained when adjusting for several confounders and pathway variables. These findings are not in accordance with our results in which prenatal maternal psychological distress seemed to have a greater effect than postnatal maternal psychological distress. A smaller sample size study based on 279 children observed that maternal demoralization during pregnancy predicted overall, transient, and persistent wheezing in the first 5 years of life.⁵ In this study no information on paternal demoralization during pregnancy was available, and models were not adjusted for maternal demoralization after delivery. Because maternal demoralization was a stable trait in their cohort, the authors could not separate pregnancy and early postnatal effects. A previous case-control study including 247 subjects did not observe a significant relationship between maternal depression and anxiety during pregnancy and the infant's wheezing.⁴ The main limitation was that mothers were asked retrospectively whether depression or anxiety constituted

a problem during pregnancy. Other previous studies explored the associations of maternal stress, depression, anxiety, or cortisol levels during pregnancy with general childhood respiratory diseases and observed an association of higher maternal stress at pregnancy with an increased risk of childhood respiratory illness.^{29,30}

The mechanisms underlying the associations of prenatal psychological distress exposure with childhood wheezing are still unclear. A possible programming effect by maternal stress during pregnancy is pointed out by studies reporting that adult mammals prenatally exposed to psychological distress have an altered hypothalamic-pituitary-adrenal axis after birth and might be predisposed to airway inflammation and hyperresponsiveness.^{31,32} Stress-induced alterations in maternal cortisol levels might influence fetal immunomodulation and T_H2 lymphocyte predominance through a direct influence on cytokine production.³³ Stress was also associated with increased proportions and altered function of natural killer lymphocytes.³⁴ Recently, it was shown in human subjects that maternal stress during pregnancy was associated with altered innate and adaptive immune responses in cord blood of infants at high risk of atopic diseases.³⁵

TABLE V. Associations of maternal and paternal psychological distress during pregnancy with physician-diagnosed ever asthma at 6 years

	Physician-diagnosed ever asthma	
	OR	95% CI
Maternal psychological distress		
Overall psychological distress		
No	Reference	
Yes	1.45	0.91-2.31
Per 1-unit increase	1.27	0.88-1.84
<i>P</i> value trend		.201
Depression symptoms		
No	Reference	
Yes	1.33	0.82-2.16
Per 1-unit increase	1.17	0.88-1.57
<i>P</i> value trend		.276
Anxiety symptoms		
No	Reference	
Yes	1.19	0.76-1.86
Per 1-unit increase	1.15	0.86-1.55
<i>P</i> value trend		.344
Paternal psychological distress*		
Overall psychological distress		
No	Reference	
Yes	0.72	0.22-2.36
Per 1-unit increase	1.08	0.51-2.28
<i>P</i> value trend		.837
Depression symptoms		
No	Reference	
Yes	1.06	0.41-2.72
Per 1-unit increase	1.01	0.53-1.90
<i>P</i> value trend		.982
Anxiety symptoms		
No	Reference	
Yes	0.95	0.53-1.68
Per 1-unit increase	0.88	0.49-1.56
<i>P</i> value trend		.651

ORs (95% CIs) from logistic regression models represent the odds of physician-diagnosed asthma for the children of mothers or fathers with psychological distress during pregnancy. Maternal and paternal psychological distress were treated as dichotomized based on the clinical cutoffs (no, yes) and as continuous (per 1-unit increase). *P* value trend represents the linear trend per unit increase on the psychological distress scales. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breast-feeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections. Goodness of fit (R^2) was 0.15 for all models.

*Models additionally adjusted for maternal psychological distress during pregnancy.

Furthermore, the stress hormone adrenaline stimulates β_2 -adrenoreceptors that are expressed throughout the body.³⁶⁻³⁸ The effects on the adrenergic receptors of the lungs might predispose to later respiratory problems.^{36,37}

Next to programming effects, a hypothesized mechanism was the intermediate role of fetal growth. Maternal psychological distress during pregnancy might impair fetal growth,³⁹ and low-birth-weight children with smaller lungs and airways seem to have a higher risk of wheezing.^{25,40} However, in our study results remained after adjusting for birth weight and gestational age at birth.

The programming effect of maternal psychological distress can also operate through epigenetic programming.⁷ Differential methylation patterns in the glucocorticoid receptor related to

postnatal maternal care was shown recently in a rodent model and cultured cell lines.⁴¹⁻⁴³ In human subjects methylation of the glucocorticoid receptor was sensitive to maternal mood in the perinatal period and the infant's hypothalamic-pituitary-adrenal axis stress reactivity.⁴⁴ Further studies are needed to identify the underlying mechanisms.

In conclusion, our results suggest intrauterine effects of maternal psychological distress during pregnancy on the presence of wheezing at early ages. Further studies are needed to explore underlying biological mechanisms and long-term consequences.

We gratefully acknowledge the contribution of all the children and their parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

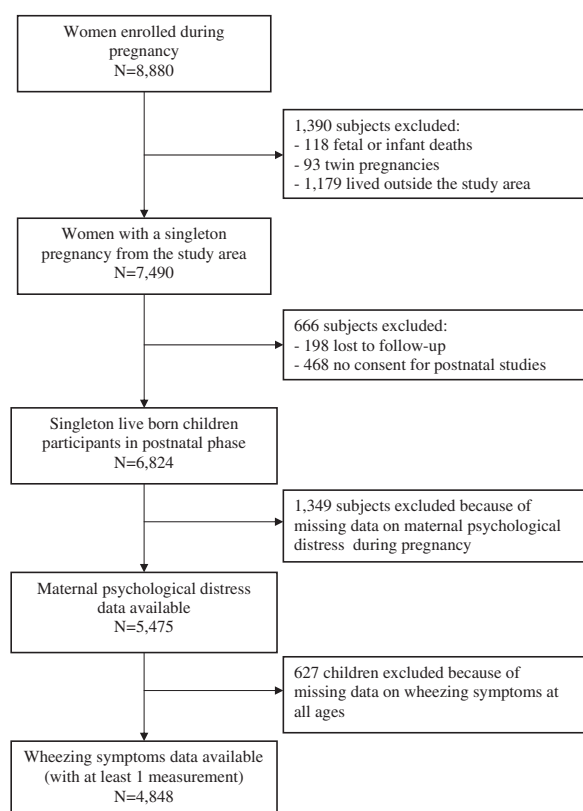
Key messages

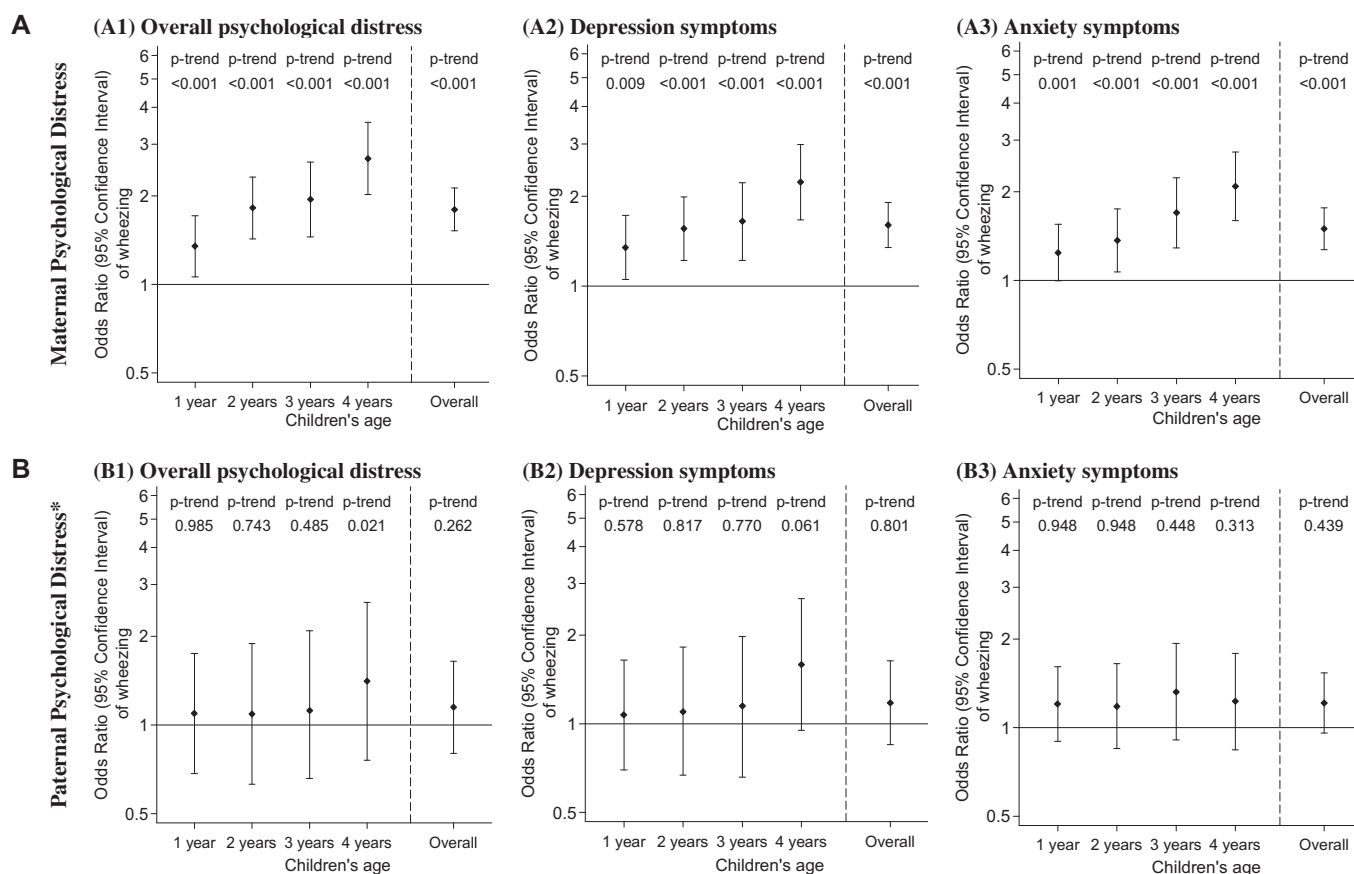
- Maternal psychological distress during pregnancy is associated with increased odds of wheezing in the child during the first 6 years of life independent of paternal psychological distress during pregnancy and maternal and paternal psychological distress after delivery.
- These results suggest a direct intrauterine programming effect of maternal psychological distress on respiratory morbidity.

REFERENCES

- Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med* 2012;17:82-91.
- Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol* 2012;27:5-14.
- Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol* 2009;123:847-53.
- Lefevre F, Moreau D, Sémon E, Kalaboka S, Annesi-Maesano I, Just J. Maternal depression related to infant's wheezing. *Pediatr Allergy Immunol* 2011;22:608-13.
- Reyes M, Perzanowski MS, Whyatt RM, Kelvin EA, Rundle AG, Diaz DM, et al. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. *Ann Allergy Asthma Immunol* 2011;107:42-9.
- Chiu YH, Coull BA, Cohen S, Wooley A, Wright RJ. Pre- and postnatal maternal stress and wheeze in urban children: effect of maternal sensitization. *Am J Respir Crit Care Med* 2012;186:147-54.
- Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. *Immunol Allergy Clin North Am* 2011;31:19-39.
- Wright RJ. Perinatal stress and early life programming of lung structure and function. *Biol Psychol* 2010;84:46-56.
- Davey Smith G. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol* 2008;102:245-56.
- van Batenburg-Eddes T, Brion MJ, Henrichs J, Jaddoe VW, Hofman A, Verhulst FC, et al. Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study. *J Child Psychol Psychiatry* 2012 [Epub ahead of print].
- Brion MJ, Zeegers M, Jaddoe V, Verhulst F, Tiemeier H, Lawlor DA, et al. Intrauterine effects of maternal prepregnancy overweight on child cognition and behavior in 2 cohorts. *Pediatrics* 2011;127:e202-11.
- Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JO, Moll HA, Steegers EA, et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol* 2010;25:823-41.
- De Beurs E. Brief Symptom Inventory, handleiding [Dutch manual]. Leiden (The Netherlands): PITS BV; 2004.
- Munk-Olsen T, Laursen TM, Pedersen CB, Mors O, Mortensen PB. New parents and mental disorders: a population-based register study. *JAMA* 2006;296:2582-9.
- De Beurs E. Brief Symptom Inventory, handleiding addendum. Leiden (The Netherlands): PITS BV; 2009.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.

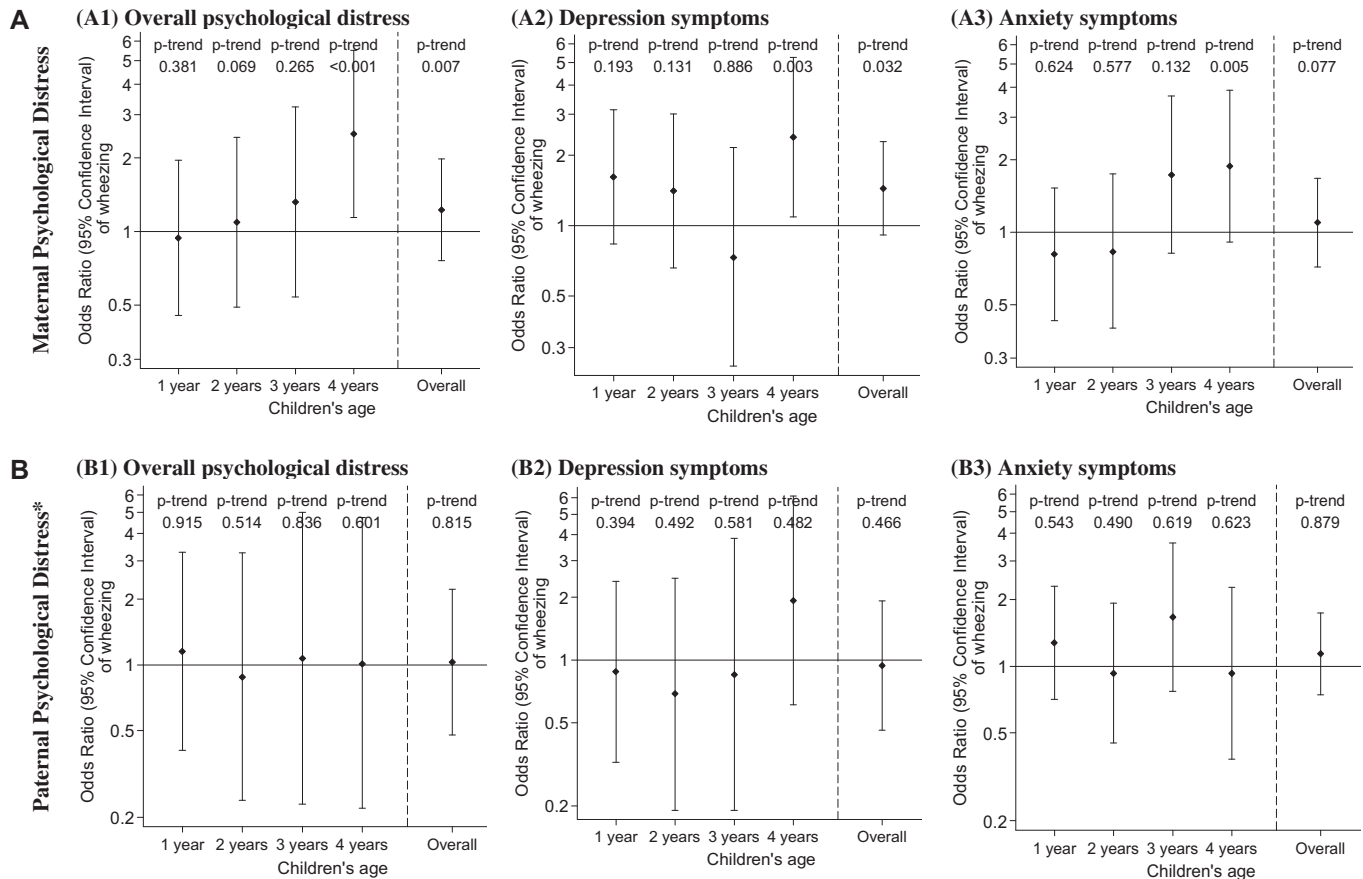
17. Sonnenschein-van der Voort AM, Jaddoe VWV, van der Valk RJ, Willemsen SP, Hofman A, Moll HA, et al. Duration and exclusiveness of breastfeeding and childhood asthma-related symptoms. *Eur Respir J* 2012;39:81-9.
18. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8.
19. Brussee JE, Smit HA, Koopman LP, Wijga AH, Kerkhof M, Corver K, et al. Inter-rupter resistance and wheezing phenotypes at 4 years of age. *Am J Respir Crit Care Med* 2004;169:209-13.
20. Oostveen E, Dom S, Desager K, Hagendorens M, De Backer W, Weyler J. Lung function and bronchodilator response in 4-year-old children with different wheezing phenotypes. *Eur Respir J* 2010;35:865-72.
21. Duijts L, Jaddoe VW, van der Valk RJ, Henderson JA, Hofman A, Raat H, et al. Fetal exposure to maternal and paternal smoking and the risks of wheezing in pre-school children. The Generation R Study. *Chest* 2011;141:876-85.
22. Spratt M, Carpenter J, Sterne JA, Carlin JB, Heron J, Henderson J, et al. Strategies for multiple imputation in longitudinal studies. *Am J Epidemiol* 2010;172:478-87.
23. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
24. Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics* 2001;57:120-5.
25. Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, Moll HA, Hofman A, de Jongste JC, et al. Fetal and infant growth and asthma symptoms in preschool children. The Generation R Study. *Am J Respir Crit Care Med* 2012;185:731-7.
26. Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25:609-16.
27. Edwards CA, Osman LM, Godden DJ, Douglas JG. Wheezy bronchitis in childhood: a distinct clinical entity with lifelong significance? *Chest* 2003;124:18-24.
28. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3:193-7.
29. Beijers R, Jansen J, Riksen-Walraven M, de Weerth C. Maternal prenatal anxiety and stress predict infant illnesses and health complaints. *Pediatrics* 2010;126:e401-9.
30. Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Stress during pregnancy and offspring pediatric disease: a National Cohort Study. *Environ Health Perspect* 2011;119:1647-52.
31. Joachim RA, Handjiski B, Blois SM, Hagen E, Paus R, Arck PC. Stress-induced neurogenic inflammation in murine skin skews dendritic cells towards maturation and migration: key role of intercellular adhesion molecule-1/leukocyte function-associated antigen interactions. *Am J Pathol* 2008;173:1379-88.
32. Pincus-Knackstedt MK, Joachim RA, Blois SM, Douglas AJ, Orsal AS, Klapp BF, et al. Prenatal stress enhances susceptibility of murine adult offspring toward airway inflammation. *J Immunol* 2006;177:8484-92.
33. von Hertzen LC. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. *J Allergy Clin Immunol* 2002;109:923-8.
34. Oya H, Kawamura T, Shimizu T, Bannai M, Kawamura H, Minagawa M, et al. The differential effect of stress on natural killer T (NKT) and NK cell function. *Clin Exp Immunol* 2000;121:384-90.
35. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* 2010;182:25-33.
36. Hara MR, Kovacs JJ, Whalen EJ, Rajagopal S, Strachan RT, Grant W, et al. A stress response pathway regulates DNA damage through β 2-adrenoreceptors and β -arrestin-1. *Nature* 2011;477:349-53.
37. Spasojevic N, Gavrilovic L, Dronjak S. Regulation of atrial catecholamine enzymes and adrenoceptor gene expression after chronic stress. *Acta Physiol Hung* 2011;98:433-41.
38. Xiang L, Del Ben KS, Rehm KE, Marshall GD. Effects of acute stress-induced immunomodulation on TH1/TH2 cytokine and catecholamine receptor expression in human peripheral blood cells. *Neuropsychobiology* 2012;65:12-9.
39. Henrichs J, Schenk JJ, Roza SJ, van den Berg MP, Schmidt HG, Steegers EA, et al. Maternal psychological distress and fetal growth trajectories: the Generation R Study. *Psychol Med* 2010;40:633-43.
40. Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M, et al. Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA Birth Cohort. *Am J Respir Crit Care Med* 2007;175:1078-85.
41. Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM. Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. *J Clin Invest* 2004;114:1146-57.
42. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. *Nat Neurosci* 2004;7:847-54.
43. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labont'e B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009;12:342-8.
44. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics* 2008;3:97-106.

**FIG E1.** Flowchart of participants in the study.



Odds ratio (95% Confidence Interval) from generalized estimating equation models represents the odds of wheezing for the children of mothers or fathers with psychological distress during pregnancy (no, yes). *P* value for trend (p-trend) represents the linear trend per unit increase on the psychological distress scales. *Models additionally adjusted by maternal psychological distress during pregnancy

FIG E2. Unadjusted association between maternal (A) and paternal (B) psychological distress during pregnancy and wheezing from 1 to 4 years.



Odds ratio (95% Confidence Interval) from generalized estimating equation models represents the odds of wheezing for the children of mothers or fathers with psychological distress during pregnancy (no, yes). *P* value for trend (p-trend) represents the linear trend per unit increase on the psychological distress scales. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity, parental history of asthma or atopy, pet keeping, and children's sex, preterm birth, birth weight, breastfeeding, day care attendance, second hand smoke at home, eczema and lower respiratory tract infections. *Models additionally adjusted by maternal psychological distress during pregnancy

FIG E3. Complete case analysis: adjusted associations of maternal (A) and paternal (B) psychological distress during pregnancy with wheezing from 1 to 4 years.

TABLE E1. Details of the imputation modeling**Software used and key setting:** STATA 12.0 software (StataCorp, College Station, Tex)—Ice command (with 10 cycles)**Number of imputed datasets created:** 25**Variables included in the imputation procedure:**

Variables used in the main analyses (outcome, exposure, and potential confounders): Child wheezing symptoms at 1st, 2nd, 3rd, and 4th years of life; child wheezing symptoms at 6 months and 1st, 2nd, 3rd, and 4th years of life; physician-diagnosed ever asthma at 6 years, maternal and paternal overall psychological distress during pregnancy; maternal and paternal depression symptoms during pregnancy; maternal and paternal anxiety symptoms during pregnancy; maternal overall psychological distress at 2 months after delivery; maternal depression symptoms at 2 months after delivery; maternal anxiety symptoms at 2 months after delivery; maternal depression symptoms at 6 months after delivery; maternal anxiety symptoms at 6 months after delivery; maternal depression symptoms at 3 years after delivery; maternal anxiety symptoms at 3 years after delivery; paternal depression symptoms at 3 years after delivery; paternal anxiety symptoms at 3 years after delivery; maternal age; maternal and paternal educational level; maternal body mass index at enrollment; parity; maternal and paternal smoking during pregnancy; family history of asthma or atopy; pet keeping during pregnancy; child sex; child ethnicity; child low birth weight; child preterm birth; child breast-feeding; child day care attendance; and child secondhand smoke at home

Variables only used for the imputation models: Child shortness of breath symptoms at the 1st, 2nd, 3rd, and 4th years of life; child cough at night at the 1st, 2nd, 3rd, and 4th years of life; child phlegm at the 1st, 2nd, 3rd, and 4th years of life; child bronchiolitis at 6 months and the 1st and 2nd years of life; child pertussis at 6 months and the 1st, 2nd and 3rd years of life; child bronchitis at the 1st, 2nd, 3rd, and 4th years of life; child pneumonia at the 1st, 2nd, 3rd, and 4th years of life; maternal and paternal ethnicity; maternal alcohol use during pregnancy; paternal body mass index; paternal age; maternal gestational diabetes; maternal hypertension; marital status; main caregiver of the child; family stress during pregnancy reported by the mother and father; maternal and paternal somatization symptoms during pregnancy; maternal and paternal obsession-compulsion symptoms during pregnancy; maternal and paternal interpersonal sensitivity symptoms during pregnancy; maternal and paternal hostility symptoms during pregnancy; maternal and paternal phobic anxiety symptoms during pregnancy; maternal and paternal paranoid ideation symptoms during pregnancy; maternal and paternal psychoticism symptoms during pregnancy; maternal somatization symptoms at 2 months after delivery; maternal obsession-compulsion symptoms at 2 months after delivery; maternal interpersonal sensitivity symptoms at 2 and 6 months after delivery; maternal hostility symptoms at 2 and 6 months after delivery; maternal phobic anxiety symptoms at 2 months after delivery; maternal paranoid ideation symptoms at 2 months after delivery; maternal psychoticism symptoms at 2 months after delivery; maternal and paternal interpersonal sensitivity symptoms at 3 years after delivery; and maternal and paternal hostility symptoms at 3 years after delivery

Treatment of binary/categorical variables: logistic and multinomial models**Statistical interactions included in imputation models:** none

TABLE E2. Distribution of study variables in the imputed and observed datasets

	Data missing (%)	Imputed dataset*	Observed dataset*
Maternal characteristics			
Age at enrollment (y)†	0.0	—	—
Prepregnancy body mass index (kg/m ²)‡	0.6		
Underweight		9.2	9.2
Normal weight		55.9	55.9
Overweight		24.5	24.5
Obese		10.4	10.4
Smoking during pregnancy (yes vs no)†	10.2	13.6	13.6
Education level†	2.8		
Primary education		6.5	6.3
Secondary education		40.4	39.9
Higher education		53.1	53.8
Ethnicity (non-European vs European)	1.4	28.4	28.1
Parity (multiparous vs nulliparous)†	0.3	40.4	40.4
History of asthma and atopy (yes vs no)†	20.6	37.1	35.0
Pet keeping during pregnancy (yes vs no)†	13.9	34.3	32.9
Overall psychological distress during pregnancy§	0.1	0.26 (0.00)	0.26 (0.01)
Depression symptoms during pregnancy§	0.2	0.20 (0.01)	0.20 (0.01)
Anxiety symptoms during pregnancy§	0.2	0.26 (0.01)	0.26 (0.01)
Overall psychological distress at 2 mo after delivery§	21.2	0.24 (0.00)	0.23 (0.01)
Depression symptoms at 2 mo after delivery§	21.4	0.21 (0.01)	0.20 (0.01)
Anxiety symptoms at 2 mo after delivery§	21.2	0.24 (0.01)	0.22 (0.01)
Depression symptoms at 6 mo after delivery§	30.7	0.23 (0.01)	0.22 (0.01)
Anxiety symptoms at 6 mo after delivery§	30.7	0.27 (0.01)	0.26 (0.01)
Depression symptoms at 3 y after delivery§	22.6	0.14 (0.00)	0.13 (0.01)
Anxiety symptoms at 3 y after delivery§	22.6	0.18 (0.00)	0.17 (0.01)
Paternal characteristics			
Smoking during pregnancy (yes vs no)†	9.5	41.9	41.8
Education level†	24.1		
Primary education		6.9	5.7
Secondary education		40.0	37.5
Higher education		53.1	56.8
History of asthma and atopy (yes vs no)†	33.0	32.1	29.4
Overall psychological distress during pregnancy§	26.5	0.14 (0.00)	0.13 (0.01)
Depression symptoms during pregnancy§	26.6	0.09 (0.00)	0.09 (0.01)
Anxiety symptoms during pregnancy§	26.5	0.17 (0.00)	0.16 (0.01)
Depression symptoms at 3 y after delivery§	35.4	0.11 (0.00)	0.10 (0.01)
Anxiety symptoms at 3 y after delivery§	35.3	0.17 (0.00)	0.16 (0.01)
Child characteristics			
Sex (female vs male)	0.0	—	—
Preterm (<37 vs ≥37 wk)	0.0	—	—
Birth weight (g)	0.0	—	—
Breast-feeding (yes vs no)¶	3.1	92.0	92.1
Day care attendance (yes vs no)¶	21.6	58.1	59.2
Postnatal smoking exposure (yes vs no)¶	13.9	18.6	17.4
Physician-attended eczema from 1 to 4 y (ever vs never)#	3.3	35.0	27.8
Physician-diagnosed lower respiratory tract infections from 1 to 4 y (ever vs never)#	3.8	26.9	20.4
Wheezing#			
First year	13.2		
No episodes		71.0	70.9
1-3 episodes		22.6	22.8
≥4 episodes		6.4	6.3
Second year	14.6		
No episodes		80.3	80.5
1-3 episodes		16.4	16.3
≥4 episodes		3.3	3.2
Third year	20.7		
No episodes		87.1	87.6
1-3 episodes		10.4	10.1
≥4 episodes		2.5	2.3
Fourth year	20.6		
No episodes		86.8	87.4

(Continued)

TABLE E2. (Continued)

	Data missing (%)	Imputed dataset*	Observed dataset*
1-3 episodes		10.7	10.3
≥4 episodes		2.5	2.3
Wheezing patterns**	33.2		
Never wheezing		56.7	53.7
Early wheezing		30.1	33.0
Late wheezing		3.1	2.6
Persistent wheezing		10.1	10.7
Physician-diagnosed asthma during first 6 y (yes vs no)††	31.1	6.5	6.0

*Values are percentages for categorical variables and means (SEs) for continuous variables.

†Information obtained through self-administered questionnaire at enrollment.

‡Maternal weight and height were measured during the first visit to the research center, and body mass index was calculated.

§Information obtained by means of postal questionnaires using the Brief Symptom Inventory; the mother and father each answered their own questionnaires.

||Information obtained from midwife and hospital registries at birth.

¶Information obtained by means of postal questionnaires at the ages of 6 and 12 months and 2 years.

#Information obtained by means of postal questionnaires at the ages of 1, 2, 3, and 4 years.

**Wheezing patterns categories based on Martinez et al¹⁸ and adapted to preschool age,^{19,20} according to the history of wheezing from the age of 1 to 4 years: (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 obtained by means of postal questionnaires at the age of 6 years.

TABLE E3. Comparison of the maternal, paternal, and child characteristics between those included and those not included in the study among the 6824 eligible subjects*

	Included (n = 4848)	Not included (n = 1976)	P value differences
Maternal characteristics			
Age at enrollment (y)†	30.8 (4.7)	28.5 (5.7)	<.001
Prepregnancy body mass index (kg/m ²)‡			<.001
Underweight	9.1	9.4	
Normal weight	56.0	47.0	
Overweight	24.5	27.6	
Obese	10.4	16.0	
Smoking during pregnancy (yes vs no)†	13.7	20.4	<.001
Education level†			<.001
Primary education	6.6	20.6	
Secondary education	40.2	51.2	
Higher education	53.2	28.1	
Ethnicity (non-European vs European)†	31.5	61.8	<.001
Parity (multiparous vs nulliparous)†	40.6	53.4	<.001
History of asthma and atopy (yes vs no)†	35.0	33.2	.236
Pet keeping during pregnancy (yes vs no)†	32.6	25.2	<.001
Overall psychological distress during pregnancy§	0.26 (0.34)	0.46 (0.50)	<.001
Depression symptoms during pregnancy§	0.20 (0.44)	0.44 (0.70)	<.001
Anxiety symptoms during pregnancy§	0.26 (0.43)	0.45 (0.56)	<.001
Paternal characteristics			
Smoking during pregnancy (yes vs no)	42.1	47.4	<.001
Education level			<.001
Primary education	5.8	11.8	
Secondary education	37.7	44.4	
Higher education	56.5	43.8	
History of asthma and atopy (yes vs no)	29.2	29.4	.935
Overall psychological distress during pregnancy§	0.13 (0.21)	0.18 (0.29)	<.001
Depression symptoms during pregnancy§	0.09 (0.27)	0.13 (0.22)	.001
Anxiety symptoms during pregnancy§	0.16 (0.28)	0.20 (0.37)	.003
Child characteristics			
Sex (female vs male)	50.9	46.9	<.001
Preterm (<37 vs ≥37 wk)	4.2	5.9	.002
Birth weight (g)	3458 (545)	3363 (556)	<.001

*Values are percentages for categorical variables and means (SDs) for continuous variables.

†Information obtained through self-administered questionnaire at enrollment.

‡Maternal weight and height were measured during the first visit to the research center, and body mass index was calculated.

§Information obtained by means of postal questionnaires using the Brief Symptom Inventory; the mother and father each answered their own questionnaires.

||Information obtained from midwife and hospital registries at birth.

TABLE E4. Associations of maternal psychological distress during pregnancy with overall wheezing from 1 to 4 years adjusted for maternal psychological distress at 2 months, 6 months, and 3 years after delivery

	Model 1*		Model 1* + maternal psychological distress after delivery							
			At 2 mo		At 6 mo		At 3 y		Patterns†	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Overall psychological distress‡										
No	Reference		Reference		—	—	—	—	—	—
Yes	1.44	1.20-1.74	1.40	1.15-1.71	—	—	—	—	—	—
Per 1-unit increase on the scale	1.46	1.25-1.70	1.44	1.36-1.14	—	—	—	—	—	—
<i>P</i> value trend		<.001		.001		—		—		—
Depression symptoms										
No	Reference		Reference		Reference		Reference		Reference	
Yes	1.34	1.11-1.62	1.31	1.08-1.60	1.25	1.02-1.53	1.29	1.06-1.57	1.23	1.01-1.51
Per 1-unit increase on the scale	1.23	1.09-1.38	1.21	1.06-1.38	1.17	1.02-1.34	1.18	1.03-1.36	1.16	1.01-1.33
<i>P</i> value trend		.001		.006		.002		.016		.033
Anxiety symptoms										
No	Reference		Reference		Reference		Reference		Reference	
Yes	1.27	1.07-1.52	1.24	1.03-1.49	1.20	1.00-1.45	1.24	1.03-1.49	1.18	0.97-1.42
Per 1-unit increase on the scale	1.26	1.12-1.42	1.19	1.04-1.37	1.21	1.05-1.40	1.21	1.06-1.38	1.21	1.05-1.39
<i>P</i> value trend		<.001		.014		.009		.006		.009

ORs (95% CIs) from generalized estimating equation models represent the odds of wheezing episodes for the children of mothers with psychological distress during pregnancy. Maternal psychological distress was treated as dichotomized based on the clinical cutoffs (no, yes) and as continuous (per 1-unit increase). *P* value trend represents the linear trend per unit increase on the psychological distress scales.

*Adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, parity, parental history of asthma or atopy, pet keeping, children's sex, preterm birth, birth weight, breast-feeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections.

†Patterns of maternal psychological distress after delivery (never distress, only postpartum distress, only distress at 3 years, and persistent distress).

‡Not available at 6 months and 3 years after delivery.

TABLE E5. Associations of maternal psychological distress during pregnancy with overall wheezing from 1 to 4 years adjusted for paternal psychological distress during pregnancy and at 3 years after delivery

	Model 1*		Model 1* + paternal psychological distress			
			During pregnancy†		At 3 y after delivery‡	
	OR	95% CI	OR	95% CI	OR	95% CI
Overall psychological distress‡						
No	Reference		Reference		—	—
Yes	1.44	1.20-1.74	1.44	1.19-1.74	—	—
Per 1-unit increase on the scale	1.46	1.25-1.70	1.44	1.23-1.68	—	—
<i>P</i> value trend		<.001		<.001		—
Depression symptoms						
No	Reference		Reference		Reference	
Yes	1.34	1.11-1.62	1.33	1.10-1.62	1.35	1.12-1.63
Per 1-unit increase on the scale	1.23	1.09-1.38	1.23	1.08-1.39	1.22	1.08-1.38
<i>P</i> value trend		.001		.002		.001
Anxiety symptoms						
No	Reference		Reference		Reference	
Yes	1.27	1.07-1.52	1.26	1.06-1.50	1.27	1.06-1.52
Per 1-unit increase on the scale	1.26	1.12-1.42	1.25	1.10-1.41	1.24	1.10-1.41
<i>P</i> value trend		<.001		<.001		.001

ORs (95% CIs) from generalized estimating equation models represent the odds of wheezing episodes for the children of mothers with psychological distress during pregnancy. Maternal psychological distress was treated as dichotomized based on the clinical cutoffs (no, yes) and as continuous (per 1-unit increase). *P* value trend represents the linear trend per unit increase on the psychological distress scales.

*Adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breast-feeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections.

†Models additionally adjusted by maternal psychological distress during pregnancy.

‡Not available at 3 years after delivery.

TABLE E6. Comparison of the maternal, paternal, and child characteristics between those included in the complete case analysis and those not included among the 4848 subjects*

	Included (n = 2098)	Not included (n = 2750)	P value differences
Maternal characteristics			
Age at enrollment (y) [†]	31.7 (4.0)	30.1 (5.1)	<.001
Prepregnancy body mass index (kg/m ²) [‡]			<.001
Underweight	9.0	9.2	
Normal weight	60.4	52.7	
Overweight	22.7	25.9	
Obese	7.9	12.2	
Smoking during pregnancy (yes vs no) [†]	9.5	16.9	<.001
Education level [†]			<.001
Primary education	1.8	10.4	
Secondary education	30.6	47.8	
Higher education	67.6	41.8	
Ethnicity (non-European vs European) [†]	16.1	43.7	<.001
Parity (multiparous vs nulliparous) [†]	35.6	44.4	<.001
History of asthma and atopy (yes vs no) [†]	36.8	33.5	.034
Pet keeping during pregnancy (yes vs no) [†]	35.5	30.3	<.001
Overall psychological distress during pregnancy§	0.19 (0.24)	0.31 (0.40)	<.001
Depression symptoms during pregnancy§	0.12 (0.29)	0.26 (0.51)	<.001
Anxiety symptoms during pregnancy§	0.19 (0.32)	0.31 (0.50)	<.001
Paternal characteristics			
Smoking during pregnancy (yes vs no)	36.4	46.6	<.001
Education level			<.001
Primary education	3.3	9.2	
Secondary education	33.5	43.2	
Higher education	63.2	47.6	
History of asthma and atopy (yes vs no)	29.3	29.1	.896
Overall psychological distress during pregnancy§	0.12 (0.17)	0.16 (0.25)	<.001
Depression symptoms during pregnancy§	0.09 (0.22)	0.12 (0.33)	<.001
Anxiety symptoms during pregnancy§	0.15 (0.26)	0.18 (0.31)	.017
Child characteristics			
Sex (female vs male)	50.1	51.5	.352
Preterm (<37 vs ≥37 wk)	3.4	4.7	.029
Birth weight (g)	3519 (526)	3412 (555)	<.001

*Values are percentages for categorical variables and means (SDs) for continuous variables.

[†]Information obtained through self-administered questionnaire at enrollment.[‡]Maternal weight and height were measured during the first visit to the research center, and body mass index was calculated.

§Information obtained by means of postal questionnaires using the Brief Symptom Inventory; the mother and father each answered the questionnaires.

||Information obtained from midwife and hospital registries at birth.

TABLE E7. Complete case analysis: Associations of maternal psychological distress during pregnancy with overall wheezing from 1 to 4 years adjusted for maternal psychological distress at 3 years after delivery

	Model 1		Model 1 + maternal psychological distress at 3 y	
	OR	95% CI	OR	95% CI
Overall psychological distress*				
No	Reference		—	—
Yes	1.23	0.76-1.98	—	—
Per 1-unit increase on the scale	1.77	1.20-2.63	—	—
<i>P</i> value trend		.004		—
Depression symptoms				
No	Reference		Reference	
Yes	1.44	0.91-2.29	1.38	0.86-2.21
Per 1-unit increase on the scale	1.43	1.05-1.95	1.36	0.98-1.88
<i>P</i> value trend		.023		.064
Anxiety symptoms				
No	Reference		Reference	
Yes	1.10	0.72-1.68	1.03	0.66-1.60
Per 1-unit increase on the scale	1.31	0.98-1.74	1.26	0.93-1.71
<i>P</i> value trend		.066		.143

ORs (95% CIs) from generalized estimating equation models represent the odds of wheezing episodes for the children of mothers with psychological distress during pregnancy. Maternal psychological distress was treated as dichotomized based on the clinical cutoffs (no, yes) and as continuous (per 1-unit increase). *P* value trend represents the linear trend per unit increase on the psychological distress scales. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breast-feeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections.

*Not available at 3 years after delivery.

TABLE E8. Complete case analysis: Associations of maternal psychological distress during pregnancy with overall wheezing from 1 to 4 years adjusted for paternal psychological distress during pregnancy and at 3 years after delivery

	Model 1		Model 1 + paternal psychological distress			
			During pregnancy		At 3 y after delivery	
	OR	95% CI	OR	95% CI	OR	95% CI
Overall psychological distress*						
No	Reference		Reference		—	—
Yes	1.23	0.76-1.98	1.26	0.78-2.04	—	—
Per 1-unit increase on the scale	1.77	1.20-2.63	1.79	1.20-2.67	—	—
<i>P</i> value trend		.004		.004		—
Depression symptoms						
No	Reference		Reference		Reference	
Yes	1.44	0.91-2.29	1.50	0.95-2.39	1.51	0.95-2.40
Per 1-unit increase on the scale	1.43	1.05-1.95	1.46	1.07-2.00	1.47	1.08-2.00
<i>P</i> value trend		.023		.018		.015
Anxiety symptoms						
No	Reference		Reference		Reference	
Yes	1.10	0.72-1.68	1.10	0.72-1.69	1.10	0.72-1.68
Per 1-unit increase on the scale	1.31	0.98-1.74	1.31	0.98-1.75	1.31	0.98-1.74
<i>P</i> value trend		.066		.065		.069

ORs (95% CIs) from generalized estimating equation models represent the odds of wheezing episodes for the children of mothers with psychological distress during pregnancy. Maternal psychological distress was treated as dichotomized based on the clinical cutoffs (no, yes) and as continuous (per 1 unit increase). *P* value trend represents the linear trend per unit increase on the psychological distress scales. Models were adjusted for maternal age, body mass index, smoking during pregnancy, educational level, ethnicity, and parity; parental history of asthma or atopy and pet keeping; and children's sex, preterm birth, birth weight, breast-feeding, day care attendance, secondhand smoke at home, eczema, and lower respiratory tract infections.

*Not available at 3 years after delivery.