Mental Health

Longitudinal depression or anxiety in mothers and offspring asthma: a Swedish population-based study

Bronwyn K Brew,1* Cecilia Lundholm,1 Alexander Viktorin,1,2 Paul Lichtenstein,1 Henrik Larsson1,3 and Catarina Almqvist1,4

1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, 2Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA, 3School of Medical Sciences, Örebro University, Örebro, Sweden and 4Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden

*Corresponding author. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, SE-171 77, Stockholm, Sweden. E-mail: bronwyn.haasdyk.brew@ki.se

Abstract

Background: Previous research has found that maternal stress during pregnancy increases the risk of offspring asthma. However, whether this association is consistent with a causal interpretation has never been tested. The objective is to determine whether there is a critical exposure period for maternal depression or anxiety on offspring asthma or whether cumulative exposure is most important, and to investigate evidence of confounding.

Methods: The study population included all children born in Sweden from July 2006 to December 2009 (n = 360,526). Information about childhood asthma, maternal depression or anxiety (diagnosis or medication) and covariates was obtained from the Swedish national health registers. The associations between exposure periods (pre-conception, pregnancy, postnatal or current) and childhood asthma were estimated using structured life course approach hypothesis testing. Paternal and cousin analyses were used to test for evidence of confounding from shared genes and environment.

Results: For childhood asthma, cumulative exposure best described the effect of exposure to maternal depression or anxiety up to a maximum of any two exposure periods [adjusted odds ratio 1.44, 95% confidence interval (CI) 1.38, 1.52]. The hypotheses of a critical period were not supported. The paternal and cousin analyses indicated minimal influence from familial confounding.

Conclusions: These findings support an association between cumulative exposure to maternal depression or anxiety and asthma development in offspring. This association is unique for maternal depression or anxiety and not due to familial confounding. The clinical implication is that effective psychological management of women with chronic distress may reduce offspring asthma risk.

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Introduction

Asthma continues to be the most prevalent childhood chronic disease. Attention to environmental and social determinants such as poverty, prenatal smoking and distress provide scope for intervention to reduce asthma risk.1–4 Studies have shown that infants exposed to maternal distress (depression or anxiety) during pregnancy are at increased risk for wheeze and asthma during childhood.5–9 Other studies have found that postnatal, or cumulative, distress exposure is most important for the development of childhood asthma.10–12 However, few studies have investigated multiple exposure periods around pregnancy. In order to determine whether there is a critical period of exposure (only one period contributes), a sensitive period of exposure (all periods contribute but one period contributes more) or a cumulative (chronic) effect,13 it is crucial to study a cohort of women in a longitudinal manner from before pregnancy to after pregnancy. Importantly, the timing of exposure could suggest different mechanisms by which maternal distress may cause offspring asthma, which in turn informs clinical management of distress in women.

Another issue inherent to observational studies is the possibility of confounding that could be masking a true association. Previous studies have attempted to control for potential confounding, using measured factors such as socioeconomic background and maternal asthma, but the possibility of bias due to confounding by unmeasured factors remains. Familial confounding, i.e. confounding due to unmeasured genetic and shared environment in families, can be detected using children of maternal siblings (cousins), or analyses using paternal distress as the exposure.14 Cousins share 12.5% of segregating genes and mothers with a similar environment of origin. Therefore a cousin comparison that shows a lower or no association between distress and asthma compared with a population-wide comparison suggests that the main analysis with unrelated cases is subject to familial confounding.14,15 Paternal distress analysis is especially useful for in utero and preconception comparisons, when the paternal exposure is not expected to have a direct association with the outcome.16 An association between paternal distress and the outcome could imply confounding in the association between maternal distress and offspring asthma.17

This study aims to determine whether there is a critical, sensitive or cumulative exposure period of maternal depression or anxiety for childhood asthma risk. Maternal depression or anxiety in four exposure periods are investigated: preconception, pregnancy (in utero), postnatal and current. Familial confounding is explored using paternal and cousin analyses.

Methods

Study population

A Swedish nation-wide cohort was established using the Swedish personal identity number that enables unambiguous linkage between the administrative registers held by the Swedish National Board of Health and Welfare and Statistics Sweden.18 This included children born between 1 July 2006 and 31 December 2009, identified in the Swedish Medical Birth Register.19 The date of conception was estimated using the birth date and gestational age at birth in days provided in the Medical Birth Register. Linkage to the Multi-Generation Register allowed identification of the mother’s sisters. Stillbirths, as well as deaths or emigrations before the age of five years, were excluded.

Exposure

Medication for depression and anxiety
Dispensation dates of anxiolytic and antidepressant medications were identified in the Swedish Prescribed Drug
Register (SPDR) using ATC codes N05B and N06A, respectively (see Supplementary data at IJE online for more information on the SPDR and the medication groups covered by N05B and N06A).

**Diagnosis of depression or anxiety**

For the purpose of studying exposure to maternal ‘depression or anxiety’, broad parameters were applied to identify relevant diagnoses. Exposure was defined by having at least one diagnosis during the exposure period, recorded in the National Patient Register (NPR) with an ICD-10 code for depressive disorder according to : F30-F34, F38 and F39 and for anxiety according to: F40–42, F44, F45, and F48 (see Supplementary data, available at IJE online for more information on the NPR and for a list of each ICD-10 code used). In this study, the term ‘depression or anxiety’ was defined as medication for, or a diagnosis of, an anxiety or depressive disorder.

**Outcome**

To be classified as having asthma, one of the following criteria had to be met: (i) an asthma diagnosis in the 12 months before the 5th birthday (ICD-10 code J45 in the NPR); or (ii) an asthma medication prescription in the 12 months before the 5th birthday (in the SPDR), AND either: (iia) a second asthma medication prescription between ages 1 and 5 years (inhaled corticosteroids, leukotriene receptor antagonists, fixed combinations of β2 agonists and corticosteroids, from the SPDR), or (iib) an asthma diagnosis between ages 1 and 5 years (in the NPR). One year of age was chosen as a cut-off to avoid misclassification of wheezing illness in the first year of life. The register-based asthma outcomes were originally validated based on medical records using clinical criteria, with high predictive values for clinically relevant paediatric asthma.

**Covariates**

Information on the birth date, birthweight, gestational age, parity, child gender and maternal smoking at the first antenatal appointment was obtained from the Medical Birth Register. The education of the mother and father (completed: year 9 or below, year 12 or more than 2 years tertiary) was retrieved from the Longitudinal Integration database for Health Insurance and Labour Market Studies, held by Statistics Sweden.

Maternal and paternal history of asthma was defined as fulfilling one of the following criteria: an asthma diagnosis preceding the child’s birth (from the NPR); or two prescriptions for an asthma medication (inhaled corticosteroids, leukotriene receptor antagonists, fixed combinations of β2 agonists and corticosteroids, from the SPDR) since July 2005 (when the SPDR started) and before the child’s birth; or, self-reported asthma ‘ever’ at the first antenatal appointment (from the Medical Birth Register, for mothers only).

**Statistical analysis**

To test which life course model provided the best fit to the data, we compared a fully saturated model (with regard to the exposure) with a set of nested generalized estimating equations (GEEs) representing either: (i) a critical period model; (ii) a cumulative model; (iii) a sensitive period model; or (iv) a no effects model as proposed by Mishra et al. (known as the structured life course approach). The four exposure periods included: preconception (2 years preceding pregnancy); pregnancy; postnatal (2 years after childbirth); and current (3rd and 4th years after childbirth). The saturated model includes all possible exposure combinations and interactions. In the critical period models, four separate models were fitted for exposure at each of the four time points. These models test if each exposure period is associated with offspring asthma. The cumulative model was tested by summing the number of periods during which an individual was exposed to maternal depression or anxiety, which was then used in a single GEE first as a categorical variable and then as a linear variable. This model tests if there is a chronic association of maternal depression or anxiety with offspring asthma, with each exposure period assumed to have the same effect. The sensitive period model was tested by including all four exposure periods in one single model, which allows the effects of each exposure to vary over the life course. This model tests if one exposure period has more of an effect on offspring asthma than the other periods. The GEEs used the logit link function, and exchangeable covariance structure was used to model the correlation amongst siblings. We compared the nested and saturated models using Wald tests, where large P-values (P > 0.1) indicated a better fit of the more parsimonious model. If the Wald test was found to be similar between various nested models and the saturated model, we selected the model with the lowest quasi-likelihood under the independence model criterion (QIC). Directed acyclic graphs were used to identify potential confounders for the association between maternal depression or anxiety and childhood asthma. Adjusted analyses included gender, parity, maternal asthma and maternal education.

Since we could not be sure that a woman who had a dispensed medication or a diagnosis for depression or anxiety actually had symptoms for anxiety or depression, we also repeated the life course hypothesis testing those with an
acute diagnosis (an unplanned visit to an outpatient clinic or emergency ward) as the exposure variable in a sensitivity analysis.

As the categorical cumulative model was found to be the best fit model for maternal depression or anxiety and childhood asthma, only this model was tested in subsequent analyses. Interaction by maternal asthma or gender was tested in the cumulative model for maternal depression or anxiety and childhood asthma. Smoking during pregnancy was added in a separate model to test for mediation due to smoking.

Paternal depression- or anxiety-adjusted analyses also included paternal history of education and paternal asthma instead of maternal asthma. Mutual maternal depression or anxiety and maternal asthma during the same exposure period were added to the paternal model, to block a possible indirect pathway between paternal depression or anxiety and offspring asthma via paternal influence on maternal mental state.17,23

Cousin analysis included all offspring of maternal siblings who had a child during the study period. The analysis was stratified by cousin group and therefore only those cousins who were discordant for asthma outcome and maternal depression or anxiety and maternal asthma during the same exposure period were added to the paternal model, to block a possible indirect pathway between paternal depression or anxiety and offspring asthma via paternal influence on maternal mental state.17,23

Data management and statistical analyses were conducted using SAS 9.4 and SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA). The study was approved by the regional ethics review board in Stockholm, Sweden. The requirement for informed consent was waived because the study was based on population registers. Individuals in the study population were not identifiable at any time.

Results

Descriptive statistics

The cohort included 360 526 children aged four years, of whom 8.7% had asthma (Table 1). Depression or anxiety occurred in one-fifth (22.2%, n = 76 498) of all women during the entire study period. This consisted of 9.1% of women during pre-conception, 3.3% during pregnancy, 9.9% during the postnatal period and 14.2% during the current exposure period. Table S1 in the Supplementary data (available at IJE online) displays the population sizes for each of the exposure trajectories across the four periods, as well as for increasing number of exposures (cumulative). Fathers had less recorded depression or anxiety than mothers overall, (13.6%, n = 49 048). Among the mothers, 4.6% (n = 12 878) had an acute diagnosis for depression or anxiety.

| Table 1. Description of Swedish children born July 2006-December 2009 |
|---------------------------------------------------------------|
| **Full Cohort N (%)** | **N (%) with asthma** |
| **Gender** | |
| Male | 185 481 (51.5) | 19 062 (60.8) |
| Female | 175 045 (48.5) | 31 351 (39.2) |
| **Birthweight (grams)** | |
| ≤2999 | 55 449 (15.4) | 6113 (19.5) |
| 3000–3499 | 115 871 (32.1) | 9659 (30.8) |
| 3500–3999 | 123 721 (34.3) | 10 025 (32.0) |
| 4000–4499 | 52 790 (14.6) | 4409 (14.1) |
| ≥4500 | 12 695 (3.5) | 1145 (3.7) |
| **Gestational age (weeks)** | |
| ≤34 | 8483 (2.4) | 1642 (5.2) |
| 35–37 | 31 094 (8.6) | 3490 (11.1) |
| 38–40 | 233 397 (64.7) | 19 507 (62.2) |
| ≥41 | 87 555 (24.3) | 6712 (21.4) |
| **Number of older siblings** | |
| 0 | 160 213 (44.4) | 14 058 (44.8) |
| 1 | 130 939 (36.3) | 11 542 (36.8) |
| ≥2 | 69 374 (19.2) | 5 751 (18.3) |
| **Mother’s education** | |
| Year 9 | 38 724 (11.0) | 3334 (10.8) |
| Completed Year 12 | 140 668 (39.8) | 12 916 (41.8) |
| Tertiary | 173 773 (49.2) | 14 640 (47.4) |
| **Smoking during pregnancy** | |
| 0 | 319 791 (93.0) | 27 400 (91.9) |
| 1–9 cigarettes/day | 18 688 (5.4) | 1806 (6.1) |
| ≥9 cigarettes/day | 5565 (1.6) | 611 (2.1) |
| **Maternal history of asthma** | |
| Yes | 37 909 (10.5) | 6325 (20.2) |
| **Paternal history of asthma** | |
| Yes | 21 535 (6.0) | 3255 (10.4) |

Life course hypothesis testing

Testing each exposure period as a ‘critical period’ revealed an association between maternal depression or anxiety and offspring asthma of approximately the same magnitude for each exposure period: adjusted odds ratio (OR) 1.29–1.35 (Table 2). However, using the structured life course approach to select the best fitting model, none of the critical period models nor the sensitive period models were found to be the best fit of the data (P < 0.0001). The best-fitting model was the cumulative model (categorical, P = 0.29) as shown in Table 2. Exposure to depression or anxiety at any single period was associated with offspring asthma with an OR estimated at 1.30 (95% CI 1.26, 1.35), and OR 1.44 (95% CI 1.38, 1.52) for exposure during two
Table 2. Saturated model and alternative life course models for maternal distress exposure and childhood asthma. Odds ratios (OR) and 95% confidence intervals (CI)

| Model type               | Exposure variables included | Level of exposure  | Unadjusted OR (95% CI) | Adjusted OR (95% CI)a | Model fit (QIC) and comparison with saturated modelb |
|--------------------------|-----------------------------|--------------------|-------------------------|------------------------|-----------------------------------------------------|
| Saturated modelb         | Trajectory across 4 time points | 0,0,0,0 (284 028) | 1                       | 1                      | 204 985.5                                            |
|                          | (pre-conception, pregnancy, postnatal, current) | 1,0,0,0 (11 473) | 1.31 (1.23, 1.39)       | 1.23 (1.16, 1.31)      |                                                     |
|                          |                             | 0,1,0,0 (121)     | 1.36 (1.13, 1.65)       | 1.33 (1.10, 1.62)      |                                                     |
|                          |                             | 0,0,1,0 (8431)    | 1.38 (1.28, 1.48)       | 1.31 (1.22, 1.41)      |                                                     |
|                          |                             | 0,0,0,1 (22 595)  | 1.38 (1.32, 1.44)       | 1.34 (1.28, 1.40)      |                                                     |
|                          |                             | 1,1,0,0 (1064)    | 1.33 (1.09, 1.61)       | 1.22 (1.00, 1.49)      |                                                     |
|                          |                             | 1,0,1,0 (1934)    | 1.68 (1.47, 1.92)       | 1.58 (1.38, 1.82)      |                                                     |
|                          |                             | 0,1,0,1 (3673)    | 1.65 (1.49, 1.82)       | 1.52 (1.37, 1.68)      |                                                     |
|                          |                             | 0,1,1,0 (353)     | 1.52 (1.09, 2.11)       | 1.50 (1.08, 2.09)      |                                                     |
|                          |                             | 0,0,1,1 (319)     | 1.51 (1.08, 2.12)       | 1.42 (1.00, 2.02)      |                                                     |
|                          |                             | 0,0,1,0 (10 270)  | 1.50 (1.41, 1.60)       | 1.42 (1.33, 1.51)      |                                                     |
|                          |                             | 1,1,1,0 (798)     | 1.72 (1.40, 2.12)       | 1.58 (1.28, 1.95)      |                                                     |
|                          |                             | 1,0,1,1 (6358)    | 1.46 (1.35, 1.58)       | 1.36 (1.08, 1.70)      |                                                     |
|                          |                             | 0,1,1,1 (784)     | 1.49 (1.20, 1.86)       | 1.36 (1.08, 1.70)      |                                                     |
|                          |                             | 1,1,0,1 (607)     | 1.60 (1.25, 2.05)       | 1.55 (1.21, 2.00)      |                                                     |
|                          |                             | 1,1,1,1 (6718)    | 1.59 (1.48, 1.71)       | 1.44 (1.34, 1.56)      |                                                     |
| Critical period modelc  | Pre-conception              | 0                  | 1                       | 1                      | 205 315.7, \(P < 0.0001\) |
|                          |                             | 1                  | 1.39 (1.34, 1.44)       | 1.29 (1.24, 1.34)      |                                                     |
|                          | Pregnancy                   | 0                  | 1                       | 1                      | 212 895.4, \(P < 0.0001\) |
|                          |                             | 1                  | 1.43 (1.34, 1.51)       | 1.32 (1.24, 1.40)      |                                                     |
|                          | Postnatal                   | 0                  | 1                       | 1                      | 205 225.0, \(P < 0.0001\) |
|                          |                             | 1                  | 1.42 (1.37, 1.47)       | 1.33 (1.28, 1.38)      |                                                     |
|                          | Current                     | 0                  | 1                       | 1                      | 205 118.7, \(P < 0.0001\) |
|                          |                             | 1                  | 1.42 (1.37, 1.46)       | 1.35 (1.30, 1.39)      |                                                     |
| Cumulative modeld        | Number of times exposed, categorical | 0                  | 1                       | 1                      | 204 978.1, \(P = 0.29\) |
|                          |                             | 1                  | 1.36 (1.32, 1.41)       | 1.30 (1.26, 1.35)      |                                                     |
|                          |                             | 2                  | 1.54 (1.47, 1.62)       | 1.44 (1.38, 1.52)      |                                                     |
|                          |                             | 3                  | 1.49 (1.40, 1.60)       | 1.39 (1.30, 1.49)      |                                                     |
|                          |                             | 4                  | 1.59 (1.48, 1.71)       | 1.44 (1.34, 1.56)      |                                                     |
|                          | Number of times exposed, linear | 1                  | 1.17 (1.16, 1.19)       | 1.14 (1.12, 1.15)      | 205 073.9, \(P < 0.0001\) |
| Sensitive period modelf  | Pre-conception              | 0                  | 1                       | 1                      | 205 045.3, \(P < 0.0001\) |
|                          |                             | 1                  | 1.17 (1.12, 1.28)       | 1.13 (1.08, 1.18)      |                                                     |
|                          | Pregnancy                   | 0                  | 1                       | 1                      |                                                     |
|                          |                             | 1                  | 1.00 (0.94, 1.08)       | 0.96 (0.93, 1.07)      |                                                     |
|                          | Postnatal                   | 0                  | 1                       | 1                      |                                                     |
|                          |                             | 1                  | 1.16 (1.10, 1.21)       | 1.12 (1.07, 1.18)      |                                                     |
|                          | Current                     | 0                  | 1                       | 1                      |                                                     |
|                          |                             | 1                  | 1.27 (1.22, 1.32)       | 1.23 (1.19, 1.28)      |                                                     |
| Empty modelf             | None                        | –                  | –                       | –                      | 205 496.6, \(P < 0.0001\) |

aAdjusted for maternal education, maternal asthma, number of siblings, gender.
bEach possible trajectory assumed unique and estimated separately in one fully saturated model.
cEach time period modelled as the main effect in four separate models.
dSummed score of number of times exposed, one model, assume all time periods have equal importance, interchangeable effect sizes.
eAll time periods in one model, assume all time periods have equal importance, effect sizes may differ.
fOne model, no exposure variables included.
gLarge \(P\)-values \((P > 0.1)\) indicate a better fit of the more parsimonious model.
periods. However, exposure to more than two periods did not increase the OR further; therefore there was a saturation effect seen at two periods of exposure. Testing for interaction by maternal asthma and gender revealed small but clinically insignificant differences. Adding smoking during pregnancy to the models as a potential mediator did not alter effect estimates.

Analysis of those with an acute diagnosis of depression or anxiety as the exposure revealed that the categorical and linear cumulative models, the postnatal critical period model and the sensitive period model were all a better fit of the data than the saturated model (Table S2, in Supplementary data available at IJE online). However, the best model fit was the sensitive period model ($P = 0.79$), with the strongest association with offspring asthma found for the postnatal period (adjusted OR 1.26, 95% CI 1.15, 1.38).

### Paternal Analysis

Analysis of paternal depression or anxiety and childhood asthma found a small association for one, two and four exposure periods with adjusted OR estimated at 1.09–1.13 (Table 3). Adjustment for mutual maternal depression or anxiety and maternal asthma reduced the effect sizes and only exposure to one paternal period remained (OR 1.05, 95% CI 1.00, 1.09).

### Cousin analysis

Among the offspring, 42,950 had cousins born within the study period. The demographics for the cousin cohort did not differ from the main cohort (Table S3, in Supplementary data, available at IJE online). Of these cousins, there were 1265 cousin groups (2679 individuals) discordant for both asthma and maternal depression or anxiety. Cousin analysis revealed slightly smaller estimates than the original maternal analysis for one and two exposure periods and childhood asthma (Table 4). Exposure to one period of maternal depression or anxiety resulted in an OR of asthma estimated at 1.27 (95% CI 1.10, 1.47) and 1.31 (95% CI 1.05, 1.64) for two periods. The estimates for three and four periods of exposure were not increased and had wide confidence intervals due to low power.

### Discussion

This register-based study found that cumulative, or chronic, maternal depression or anxiety before childbirth and during the child’s early life is associated with the risk
of offspring asthma. Analysis of paternal depression or anxiety supported that this association is unique for maternal depression or anxiety, and the cousin analysis suggests that the association is not due to familial confounding.

Although there are a number of studies that have assessed the association between maternal distress during pregnancy and offspring asthma,\(^7\)-\(^9\),\(^24\) this is the first study that has assessed the periods before, during and after birth and applied hypothesis testing based on life course modeling. Our findings do not support the hypothesis that in utero exposure to depression or anxiety is a critical or sensitive period for asthma development.\(^7\)-\(^9\) Rather, our results support the literature that has found a cumulative exposure at several periods to be a better predictor of offspring asthma.\(^10\),\(^25\),\(^26\) Although there is biological plausibility in the hypothesis that in utero exposure to distress influences the development of offspring asthma,\(^27\) the majority of epidemiological studies in this field have only assessed this period exclusively (sometimes extending the period to 1 year preceding birth). Thus it cannot be assumed that in utero exposure to distress is more critical than other periods surrounding pregnancy, for asthma development. Dreger et al.\(^28\) found that exposure to recurrent maternal stress was associated with increased cortisol (a glucocorticoid released in response to stress) levels in children without asthma but was lowered in children with asthma.\(^28\) This was not seen for those exposed in only the 1st year of life. These findings support other research that has found that children with atopic disease have lower cortisol levels\(^29\) and suggests that chronic maternal stress may dysregulate the hypothalamic-pituitary-adrenal axis (HPA axis), which in turn alters the immune response to become more Th-2 in nature, increasing IgE-mediated responses such as atopic disease.\(^30\) In addition, several studies by Wright et al.\(^31\) have found that exposure to care-giver stress and cumulative stress are associated with immune modulation in the offspring towards an atopic immune profile.\(^31\),\(^32\)

We found a weak association for paternal analysis that suggests the presence of some residual confounding, but on the whole this analysis supports the maternal-offspring association, as others have found.\(^6\) As far as we are aware, this is the first study to test cousins, the children of mothers who are sisters. This is also known as a family design or genetically informed study, and essentially reduces the unmeasured shared genetic and environmental confounding.\(^15\),\(^33\) for example if the mothers had grown up in poverty which could lead to distress or a propensity for asthma in the extended family. This analysis showed that the child of a woman with chronic exposure to depression or anxiety was more likely to develop asthma, compared with their cousin whose mother did not have depression or anxiety, regardless of shared genes or environment.

Sensitivity analyses for the acute cases gave some support for the cumulative model; however, the results for the postnatal critical and sensitivity models suggested that postnatal depression or anxiety in the mother may be an important period in asthma development, particularly when the distress level is severe. This needs to be explored further. Unfortunately, due to the low numbers in the acute analyses, we did not have power to also perform a cousin analysis.

The main strength of this study is that we were able to employ several different methods in a total population, with prospectively collected measures of exposures and validated outcomes.\(^21\) Since it is unfeasible to do randomized controlled trials for distress exposure in early programming, and observational studies have inherent weaknesses, the best approach is to use a variety of methods to help strengthen causal inference.\(^34\) Using a structured approach to test various life course models (critical, sensitive and cumulative periods) allowed us to test the best statistical fit for the data, rather than making our own inferences from the data.\(^13\),\(^35\) Another strength was the paternal and cousin analyses which tested for evidence of residual confounding, that is unmeasured, shared confounders such as genetic variants or shared environment that may explain the maternal-offspring association.

The main limitation in this study is the definition of the exposure variable, particularly during pregnancy. The rate of depression or anxiety seen in our study is much lower (3.3%) than the rate of psychiatric disorders reported in a population-based sample of pregnant Swedish women (14.1%).\(^36\) Fortunately the rates during the other periods were more comparable, especially during the current period (14.2%). We hypothesize that pregnant women are less inclined to take medication and seek help from a doctor during pregnancy, for fear of harming the baby. Second, the diagnosis data in this study came from inpatient and outpatient hospital registers; we were unable to access primary health care records, and therefore we are missing a large proportion of diagnoses. However, we attempted to overcome this by including prescribed medications from any source. Although our classification of depression or anxiety will be missing some women, the advantages of our study are that it does not suffer from selection bias since it is based on the total population, and there is less risk of reporting bias by mothers reporting negatively for both depression or anxiety and their child’s asthma status. It is also important to note that given the limitations of our exposure definition, the associations found in this study are likely to be pushed towards the null and therefore in an ideal study we would expect to see stronger associations. Nevertheless, given the low prevalence of depression or anxiety in pregnant women, we
cannot completely rule out the possibility of a critical in utero exposure period for offspring asthma development.

In conclusion, this study supports a chronic rather than critical model of exposure to maternal depression or anxiety and asthma development in offspring. This association is unique for maternal depression or anxiety and not due to familial confounding. Thus, ensuring that women have timely access to integrated medical, mental and social health care before pregnancy, during pregnancy and in the early years, will maximize their potential for good respiratory health in their offspring.

Supplementary Data
Supplementary data are available at IJE online.

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