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Mental Health

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

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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.

Key words: Asthma, mothers, depression, anxiety, children

Key Messages

- Chronic exposure to maternal depression or anxiety, rather than critical exposure in any particular period, is associated with offspring asthma.
- We find no evidence to support that exposure to maternal depression or anxiety *in utero* is more sensitive than any other period of exposure. However, sub-analysis with only acute cases of depression or anxiety suggests that exposure to maternal depression or anxiety in infancy may be a sensitive period, but this needs further exploration.
- Paternal and cousin analyses did not find evidence of residual confounding for chronic maternal depression or anxiety and offspring asthma.

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[20] (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, short-acting β2 agonists, 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.[21]

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).[13] 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.[22] 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 exposure contributed information to the odds ratios for the exposure. We decided not to include a sibling analysis, as we could not be sure the mother would be discordant for depression or anxiety from pregnancy to pregnancy, due to the chronic nature of these diseases.

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.

Table 1. Description of Swedish children born July 2006-December 2009

	Full Cohort *N* (%)	*N* (%) with asthma
	N = 360 526	*N* = 31 351 (8.7)
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	233 394(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)

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.

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 0 = no maternal distress, 1 = maternal distress (*n*)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	Model fit (QIC) and comparison with saturated model[g]
Saturated model[b]	Trajectory across 4 time points (pre-conception, pregnancy, postnatal, current)	0,0,0,0 (284 028)	1	1	204 985.5
		1,0,0,0 (11 473)	1.31 (1.23, 1.39)	1.23 (1.16, 1.31)	
		0,1,0,0 (1121)	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)	
		1,0,0,1 (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)	
		0,1,0,1 (319)	1.51 (1.08, 2.12)	1.42 (1.00, 2.02)	
		0,0,1,1 (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 model[c]	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 model[d]	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		1.17 (1.16, 1.19)	1.14 (1.12, 1.15)	205 073.9, $P < 0.0001$
Sensitive period model[e]	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 model[f]	None		–		205 496.6, $P < 0.0001$

[a]Adjusted for maternal education, maternal asthma, number of siblings, gender.
[b]Each possible trajectory assumed unique and estimated separately in one fully saturated model.
[c]Each time period modelled as the main effect in four separate models.
[d]Summed score of number of times exposed, one model, assume all time periods have equal importance, interchangeable effect sizes.
[e]All time periods in one model, assume all time periods have equal importance, effect sizes may differ.
[f]One model, no exposure variables included.
[g]Large *P*-values ($P > 0.1$) indicate a better fit of the more parsimonious model.

Table 3. Cumulative model for paternal distress and childhood asthma. Odds ratios (OR) and 95% confidence intervals (CI)

Number of times exposed	Number of children per category (%)	UnadjustedOR (95% CI)	Adjusted[a]OR (95% CI)	*P*-values	Mutually adjusted[b] OR (95% CI)	*P*-values
0	311 478 (86.4)	1	1		1	
1	27 826 (7.7)	1.11 (1.06, 1.16)	1.09 (1.04, 1.13)	0.0002	1.05 (1.00, 1.09)	0.04
2	9852 (2.7)	1.16 (1.09, 1.25)	1.13 (1.06, 1.21)	0.0004	1.06 (0.99, 1.14)	0.09
3	5315 (1.5)	1.13 (1.03, 1.24)	1.08 (0.98, 1.19)	0.10	0.99 (0.90, 1.09)	0.89
4	6055 (1.7)	1.14 (1.05, 1.25)	1.11 (1.01, 1.21)	0.03	1.01 (0.92, 1.11)	0.80

[a]Adjusted for paternal and maternal education, paternal asthma, number of siblings, gender.
[b]Adjusted as above and mutually adjusted for maternal distress and maternal asthma.

Table 4. Cumulative model for maternal distress and childhood asthma in cousins whose mothers are sisters. Odds ratios (OR) and 95% confidence intervals (CI) ($N = 42\,950$)

Number of times exposed	Number of children from discordant families[a] per category	UnadjustedOR (95% CI)	Adjusted[b]OR (95% CI)	*P*-values
0	1191	1	1	
1	819	1.32 (1.15, 1.53)	1.27 (1.10, 1.47)	0.0015
2	360	1.34 (1.08, 1.67)	1.31 (1.05, 1.64)	0.02
3	174	1.12 (0.82, 1.51)	1.07 (0.78, 1.46)	0.68
4	135	1.11 (0.79, 1.58)	1.08 (0.76, 1.55)	0.68

[a]Cousins are discordant for asthma, mothers are discordant for distress.
[b]Adjusted for maternal education, maternal asthma, number of siblings, gender.

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 at 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 modelling. 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.* 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.* 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.[6,9] 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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