Perinatal maternal mental health is associated with both infections and wheezing in early childhood

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Abstract

Background

Wheezing and infections are common during infancy, and the role of early-life exposures in their development is still under investigation. We examined associations between maternal mental health in pregnancy and after delivery and subsequent offspring wheezing and infections.

Methods

We studied 2314 mother-child pairs recruited in the Piccolipiù birth cohort (Italy) from 2011 to 2015. Maternal mental health was assessed in pregnancy and 12 months after delivery via the General Health Questionnaire-12 (GHQ-12). GHQ-12 Likert scores were collapsed into low (below the upper tercile) and high (above). Risk ratios (RR) and 95% confidence intervals (CI) between each combination of scores—during pregnancy and 1 year after delivery—and outcomes were computed by log-binomial regression models.

Results

High scores both in pregnancy and after delivery, compared with low scores in both periods, were associated with wheezing (RR: 1.35; 95% CI: 1.08, 1.69), recurrent (≥2 episodes) wheezing (1.35; 0.99, 1.83), any and recurrent (≥4 episodes) upper respiratory infections (1.20; 1.04, 1.41, and 1.45; 1.07, 1.97, respectively), lower respiratory infections (1.31; 1.08, 1.61), and diarrhea (1.49; 1.23, 1.80). High scores either during pregnancy or 1 year after delivery only were less consistently associated with outcomes.

Conclusions

Maternal mental health problems extending from pregnancy to the first year after delivery are associated with development of both wheezing and infections. As wheezing is mostly triggered by infections, increased infection susceptibility could represent a possible common biologic mechanism. This study confirms the importance of early-life exposures on childhood health.

Key Message

This is the first study that demonstrated in the same population of infants the association of maternal mental health problems in pregnancy and in the first year after delivery with both wheezing and infections, raising a hypothesis of a possible common biologic mechanism. As both maternal mental health problems perinatally and wheezing and infections in infancy are common findings these results might be important also for prevention.

1 INTRODUCTION

There is consistent evidence that pre- and postnatal maternal stress is associated with mental health problems and negative health outcomes in children, especially developmental and psychologic disorders [1]. Two recent meta-analyses and one systematic review showed that prenatal psychologic stress is associated also with the risk of both asthma and wheezing [2-4]. Types of stress indicators included experience of negative life events, doctor diagnosis of maternal anxiety and depression, and stress perception. On the other hand, studies evaluating mental health and stress exposure both during and after pregnancy yielded inconsistent results [5-9]. Thus, the contribution of prenatal and postnatal exposure on offspring asthma and wheezing development remains inconclusive.

Few previous studies also suggested a relationship between maternal mental health and common childhood infections [10-13].

Given that childhood respiratory infections often trigger wheeze [14], we hypothesized that there might be a common mechanism, namely an enhanced susceptibility to infections related to maternal stress and mental health problems, which could explain the association with both childhood infections and wheezing.

The present study was carried out in the Italian multicenter birth cohort Piccolipiù. We aimed at evaluating the relationship of maternal mental health at the end of pregnancy and 1 year after delivery not only with offspring wheezing but also with respiratory infections and gastroenteritis, which are the most common infections in early childhood.

2 METHODS

2.1 Study population

Piccolipiù is a birth cohort recruited between November 2011 and January 2015 in five Italian cities [15]. Women were contacted in pregnancy and were asked to complete a baseline questionnaire, with information on demographics, environmental exposures, and health before pregnancy. Additional information was obtained either from the medical records or directly from the mother within the 48 hours after delivery. Mothers were then contacted at 6, 12, 24, and 48 months after delivery when information on child health was collected through questionnaires.

Of the 3337 mothers who completed the baseline questionnaire, 597 did not fill in the 24-month questionnaire, while 426 did not complete one or both questionnaires on mental health (General Health Questionnaire-12 [GHQ-12]).

A total of 2314 mother-child pairs with available data both on maternal GHQ-12 and on child outcomes were included in the analyses.

The Piccolipiù study was approved by the Ethics Committee of Lazio Regional Health Service—ASL ROMA1, national coordinator of the project, and by the Ethics Committee of each local center. Parental informed consent was obtained at recruitment.

2.2 Exposure variables

Maternal mental health was ascertained via the GHQ-12, which is a self-administered questionnaire of 12 items used as a screening instrument for general non-psychotic psychiatric morbidity. The GHQ-12 has been validated worldwide [16, 17], and it has been used also in the perinatal period [18].

In the Piccolipiù cohort, the GHQ-12 questionnaire was completed twice: (a) within 48 hours after delivery, evaluating mental health during the last 4 weeks of pregnancy, and (b) 12 months after delivery, evaluating mental health in the 2 weeks before the assessment.

Mothers were asked to rate the degree to which they had experienced the following symptoms and/or mood states: loss of sleep; feelings of being under stress; unable to play a useful role; unhappy, depressed; feeling unable to face problems, to concentrate, to make decisions, to overcome difficulties; lack of enjoyment in day-to-day activities; lack of confidence; and feelings of worthlessness. Responses were recorded as “not at all,” “same as usual,” “slightly more than usual,” and “much more than usual” and were scored on a 4-point Likert-type scale from 0 to 3. The total score ranged from 0 to 36, higher scores indicating worse mental health.

2.3 Outcome variables

Childhood outcomes, including wheezing, upper and lower respiratory tract infections, and diarrhea occurring between 12 and 24 months were assessed from the questionnaire completed at 24 months.

Wheezing was defined, according to the standardized ISAAC questionnaire [19], as at least one episode of wheezing or whistling in the chest in the past 12 months, while recurrent wheezing was defined as at least two episodes of wheezing. Upper respiratory tract infection was defined as at least one episode of otitis or pharyngitis, while we considered as recurrent upper infections at least four episodes [20]. Lower respiratory tract infection was defined as at least one episode of bronchitis or bronchiolitis or pneumonia. Finally, diarrhea, which is commonly caused by a viral gastroenteritis in young children, was used as a proxy for gastroenteric infections and was defined as at least one episode of at least six stools a day.

2.4 Statistical analysis

GHQ-12 scores were categorized according to the terciles of the distribution (0-7, 8-10, or ≥11 in pregnancy, and 0-6, 7-8, or ≥9 after delivery); a chi-square test for trend was used to assess an exposure-response relationship between GHQ-12 terciles and outcomes.

We next collapsed GHQ-12 scores into low (below the upper tercile) and high (above the upper tercile) and categorized maternal mental health into four combinations: (a) low prenatal-low postnatal (reference category); (b) high prenatal-low postnatal; (c) low prenatal-high postnatal; and (d) high prenatal-high postnatal. Associations between the three exposure categories compared with the unexposed group and the outcomes were assessed by univariable and multivariable log-binomial regression models estimating risk ratios (RR) and 95% confidence intervals (CI). Multivariable models were adjusted for the following confounding factors selected based on prior knowledge: maternal age at delivery, maternal citizenship (Italian or foreign), maternal smoking during pregnancy, maternal education (<13 and ≥13 years of schooling), parity, parental history of asthma or atopy, infant's sex, and center. To account for loss to follow-up and possible selection bias, we conducted the same analyses using an inverse probability weighting (IPW) methodology [21].

We also tested if the association between maternal GHQ-12 and the outcomes was different in boys and girls by adding a gender interaction term in the multivariable analyses.

The potential effect modification of breastfeeding at 6 months on the association between maternal GHQ-12 and the outcomes was assessed by an interaction test and stratified analysis.

Statistical analyses were conducted with STATA 11.0 software (StataCorp).

3 RESULTS

Characteristics of mother-child pairs included in the analyses are reported in Table 1. Maternal age at delivery, citizenship, maternal education, history of asthma or atopy, parity, and maternal smoking in pregnancy were different in mother-child pairs included and in those excluded from the analyses (Table S1).

Table 1. Main characteristics of the 2314 mother-child pairs included in the analysis

	No (%)a
Maternal age at delivery (y)	
<30	410 (17.7)
30-34	794 (34.3)
≥35	1110 (48.0)
Citizenship	
Italian	2195 (95.0)
Maternal education (y)	
≤13	1194 (51.7)
Parental diagnosis of asthma or atopy	
Yes	1187 (51.4)
Nulliparity	
Yes	900 (39.0)
Maternal smoking during pregnancy	
Yes	210 (9.1)
Caesarean section	
Yes	629 (27.3)
Child sex	
Male	1173 (50.8)
Birth weight (g)	
<2500	62 (2.7)
2500-3499	1437 (62.4)
3500-4499	788 (34.2)
≥4500	15 (0.7)
Any breastfeeding at 6 mo	
Yes	1496 (64.7)
Day care attendance	
Yes	1327 (57.7)

	No (%)a
Children outcomes at 12-24 mo	
Wheezing	414 (18.0)
Recurrent wheezing	239 (10.4)
Upper respiratory infections	1153 (49.9)
Recurrent upper respiratory infections	246 (10.7)
Lower respiratory infections	505 (22.0)
Diarrhea	558 (24.2)
Recruitment centers	
Torino	429 (18.5)
Trieste	379 (16.4)
Viareggio	294 (12.7)
Firenze	471 (20.4)
Roma	741 (32.0)

- [a] Total number may vary across variables due to missing values.

4 DISCUSSION

In this study, we found that children of mothers with higher scores at the GHQ-12 both at the end of pregnancy and 1 year after delivery had an increased risk of wheezing disorders and respiratory and gastroenteric infections at 12-24 months. The evidence on the associations between high maternal mental health score in only one of the two periods and the outcomes was less strong. Nevertheless, the association between high GHQ-12 in pregnancy only and wheezing disorders in addition to diarrhea confirms that pregnancy is a particularly vulnerable period.

Several studies suggested that children exposed to stress or mental health problems during pregnancy had an increased risk of wheezing and asthma; in most studies, the outcome was wheezing in pre-schoolers. Our results on wheezing are consistent with those of Chiu et al that assessed the association of perinatal negative life events with offspring wheezing symptoms from birth to age 2 years. They found that children of mothers with high scores for maternal negative life events both prenatally and between 12 and 18 months postpartum had the greatest risk of recurrent wheezing. An Editorial [22] accompanying the paper raised the problem of possible reverse causation, as childhood wheezing, which was assessed every 3 months postpartum, might have predated postnatal stress ascertainment. We studied instead offspring wheezing disorders and infections occurring in the second year of life, that is after evaluation of postnatal maternal mental health, thus establishing a clear temporal relationship.

Another prospective cohort study from Mexico showed that both prenatal exposure and postnatal exposure to negative life events were independently associated with wheezing in pre-schoolers, while a study from the Netherlands showed an association only for exposure to prenatal psychologic distress and not for distress in the first 6 months after delivery. Two other studies found an association between both pre- and postnatal stress and asthma in the first 7 years of life.

To our knowledge, an association of maternal depression, stress, or exposure to negative life events with respiratory, gastroenteric, or other unspecified infections was reported only in few studies with study designs and settings different from our study. In the Danish National Birth Cohort, a positive

association was found between life stress assessed by questionnaires in pregnancy and hospitalization for infectious diseases when the children were 4-8 years old. In Denmark, children of mothers exposed to stressful events in pregnancy had an increased risk of hospitalization for infections especially in the first year of life. In these studies, the outcomes were assessed using registries. In the Norwegian Mother and Child Cohort Study, the researchers found a weak association between exposure to negative life events in pregnancy and infections in the first 12 months of infant's life. Finally, in a study based on a database of primary care medical records in the United Kingdom, children of mothers with perinatal depression had an increased risk of gastrointestinal and lower respiratory tract infections.

In our study, we investigated whether there was a different association with children outcomes if mothers experienced mental health problems both in pregnancy and 1 year after delivery (long-standing problems), or in one of the two periods only.

Analyzing maternal mental health only during pregnancy or only after pregnancy does not take into account that depression, anxiety, and psychologic stress in pregnancy often continue after birth, as evidenced by the high GHQ-12 scores association. With our approach, we could, therefore, better specify the vulnerable periods and speculate that mothers with high GHQ-12 scores in both periods are possibly more severely affected.

We also found that the pattern of association of persistent high maternal mental health scores with outcomes was very similar for wheezing disorders and infections, possibly indicating an involvement of maternal mental health in an increased susceptibility to infections.

Wheezing during early childhood is a common clinical condition, triggered by viral infections in 80%-90% of episodes. There are plausible biologic mechanisms that could explain the associations between maternal mental health problems and offspring infections. It has long been known that psychologic stress is associated with changes in immune function [23, 24] and to an increased susceptibility to infections [25].

In the Canadian Healthy Infant Longitudinal Development cohort, infants born to mothers with prenatal depressive symptoms only and those with both pre- and early postnatal depressive symptoms had reduced secretory IgA in stools [26]. This was possibly due to a lowering of plasma cells in Peyer's patches as a consequence of glucocorticoid and catecholamine release after exposure to stress [27]. Infants' secretory IgA is a first-line defense of the immature immune system against infections with the capacity to influence the composition of gut microbiota, a potential pathway linking maternal prenatal stress and infant health [28, 29]. The relationship between postnatal stress and infections in offspring might be due to an increased susceptibility of stressed mothers themselves to common infections [30], and transmission of infective agents to their children.

Putative mechanisms linking stress in pregnancy and childhood wheezing and asthma—independent of an effect on infections—include a dysregulation of maternal and child hypothalamic-pituitary-adrenal axes and an immune dysregulation in offspring [31, 32]. However, this mechanism more easily explains an enhanced susceptibility to childhood atopic disorders, including asthma, rather than wheezing in infancy.

The main strength of our study is its prospective design: Since outcomes were ascertained after the occurrence of exposures, we could establish a clear temporal relationship between maternal mental health and childhood outcomes. We accounted for many important confounding factors. To our knowledge, this is also the first study that assessed in the same population of infants the association

of maternal mental health problems in two sensitive periods of child development with both wheezing and infections.

We also acknowledge some limitations. A substantial number of mothers did not complete the GHQ-12 questionnaire or did not participate in the 24-month follow-up. However, IPW analysis supported the findings of the complete case analysis. Mental health during the last 4 weeks of pregnancy was assessed within 48 hours after birth, which might be a very hectic period for the mothers that may influence reporting and mental health assessment. We relied only on the GHQ-12 questionnaire and not on a clinical psychiatric diagnosis that might better characterize long-standing attributes of the respondent (trait), nor we had information on stressful life events experienced by mothers over their life course; these would lead to correlates of stress long after exposure, including altered cortisol levels and immune disruption. Information on outcomes was collected by self-administered questionnaires, which is a widely accepted method of data collection in epidemiologic studies. Wheezing might be overestimated, as parents might label a single episode of noisy breathing as wheezing [33]. Recurrent wheezing is less affected by this source of bias and is more likely to identify a pathologic condition, as well as recurrent upper respiratory infections. Mothers with higher GHQ12 scores could have been more likely to over-report their offspring symptoms. On the other hand, some studies reported the associations between maternal mental health or bereavement and offspring asthma and infections in early childhood even when the exposures and the outcomes were assessed from registries [10, 12, 34]. Finally, we had no data on paternal mental health during the pregnancy period, which could have been considered as a negative control exposure in order to test for confounders shared by the mother and father [35].

In conclusion, in our cohort, young children born to mothers with high scores at the GHQ-12 both in pregnancy and 1 year after delivery are at increased risk of infections and wheezing. A positive association for wheezing outcomes and diarrhea was found also for exposure in pregnancy only, thus supporting previous results on wheezing disorders. We also showed that maternal postnatal mental health problems likely play a role in the onset of offspring infections. Given the relatively high prevalence of mothers with mental health problems and stress during pregnancy and in the post-pregnancy period, our findings indicate that these conditions might substantially contribute to common offspring disorders in the first years of life.

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