Longitudinal assessment of maternal depression and later life childhood asthma and wheeze: effect modification by child sex

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Abstract

Background: Studies report associations between maternal mental health and adverse respiratory outcomes in children; however, the impact of timing and duration of maternal distress remains understudied. We sought to longitudinally examine associations between maternal depression and childhood asthma and wheeze, and explore sex differences. **Methods:** Maternal depression (n=605) were assessed using the Edinburgh Depression Scale questionnaire, dichotomized at a clinically relevant cutoff (>12) a) during pregnancy, b) postpartum, and c) postpartum and subsequent time points postnatally (recurrent depression). Report of wheeze in the past 12 months (current wheeze) and asthma were obtained using a validated survey at 48 and 72 months. Associations were analyzed using a modified Poisson regression adjusted for covariates, and in interaction models. **Results:** Both postpartum and recurrent depression were associated with higher risk of current wheeze (RR: 1.88, 95% CI: 1.21, 2.92; RR: 2.39, 95% CI: 1.52, 3.78) and asthma at 48 months (RR: 2.79, 95% CI: 1.13, 6.87; RR: 3.14, 95% CI: 1.26, 7.84). In interaction analyses, associations were stronger in females. Postpartum and recurrent depression were associated with higher risk of current wheeze at 48 months in females (RR: 3.06, 95% CI: 1.48, 6.32; RR: 4.02, 95% CI: 1.91, 8.46) when compared to males RR: 1.47, 95% CI: 0.84, 2.56; RR: 1.86, 95% CI: 1.04, 3.34). **Conclusions:** Postpartum and recurrent depression were associated with higher risk of wheeze and asthma in children, and associations were stronger in females than males. Understanding the temporal- and sex-specific effects of maternal depression may better inform prevention strategies.

Introduction

Accumulating evidence has shown that prenatal and early life psychological stress and stress correlates, like maternal depression and anxiety, are linked to an increased risk of respiratory disorders including wheeze and asthma[1] in the offspring. Psychological stress can affect the individual biology, progression, and management of respiratory disease throughout the lifespan[2, 3]. Maternal psychological functioning has been linked to the alteration of the immune system and lung development[4] prenatally and in early childhood. Both prenatal and postnatal maternal psychological functioning is associated with higher risk of allergy, asthma, and wheezing development in infants[5]. The effects of prenatal and postnatal maternal stress have been

examined independently from one another but the influence of the timing of exposure during critical periods of development has not been completely elucidated[6-8].

A few recent studies have examined the impact of prenatal and postnatal maternal distress on childhood risk of atopic and respiratory disease[9-11]. Van der Leek et al[11]reported significant associations between maternal prenatal, recurrent postpartum, and late onset postpartum distress and higher risk of atopic dermatitis at age 5 years[11]. Prenatal maternal distress and late onset postnatal distress were also associated with asthma at 7 years of age[11]. Brew et al[9] examined the association between maternal depression or anxiety during different exposure periods (pre-conception, pregnancy, postnatal, or current) and childhood asthma development. They did not identify a critical exposure period but rather reported that chronic exposure to maternal depression and anxiety is associated with offspring asthma. Ramratnam et al[12] concluded that maternal stress and depression in the first 3 years were positively associated with respiratory illnesses and a moderate-wheeze-low-atopy-phenotype[12].

Growing evidence has also demonstrated that critical windows of vulnerability may differ by sex of the offspring[10]. Our group reported stronger associations between higher prenatal maternal stress and childhood wheeze in males while the association between postnatal maternal stress and wheeze was stronger among females[13]. Similarly, Lee and colleagues reported that males were more vulnerable to stress during the prenatal period and females were more impacted by postnatal and cumulative maternal stress when examining asthma risk[10].

While the majority of these studies have been conducted in high-income countries, maternal stress and depression is of particular concern in low- and middle-income countries given its high prevalence and the limited resources for its diagnosis and management[14-16]. Furthermore, studies have shown the prevalence of asthma has increased worldwide, especially in non-industrialized countries[17, 18]. Understanding the impact of timing and duration of symptoms of maternal psychosocial distress during and post pregnancy and the development of childhood respiratory disease would fulfill a research gap. We leveraged existing data from an established population-based prenatally enrolled longitudinal cohort in Mexico City. We examined the association between maternal depression, assessed during pregnancy and postnatally, and the risk of respiratory disease in early childhood. We also examined whether these effects differed by child sex.

Methods

Study Population

Between July 2007 and February 2011, pregnant women receiving health service and prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social –IMSS) were recruited into the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study. The inclusion criteria were: <20 weeks gestation, at least 18 years old, planned to stay in Mexico City for the next 3 years, had telephone access, reported no medical history of heart or kidney disease, no daily alcohol consumption, and no use of any steroid or anti-epilepsy medications. Following birth, 681 mother-child dyads are actively followed, 605 completed the 48 month visit and 569 completed the 72 month visits and has the necessary covariates for analyses. The institutional review boards at the Harvard School of Public Health, Icahn School of Medicine at Mount Sinai, and the Mexican National Institute of Public Health approved the procedures of the study. Women provided written informed consent.

Maternal Depression

A trained psychologist administered the validated Spanish version[19, 20] of the Edinburgh Depression Scale questionnaire (EDS) during the second or third trimester of pregnancy (prenatal period), and the 1, 6, 12, 18, 24, and 48 month postnatal study visits. The 10-item EDS asks about depression symptoms in the past 7 days, including: "1: I have laughed and been able to see the funny side of things," "2: I have looked forward with enjoyment to things," "3: I have blamed myself unnecessarily when things went wrong," "4: I have been anxious or worried for no good reason," "5: I have felt scared or panicky for no very good reason," "6: Things have been getting on top of me," "7: I have been so unhappy that I have had difficulty sleeping," "8:

I have felt sad or miserable," "9: I have been so unhappy that I have been crying," and "10: The thought of harming myself has occurred to me." Participants rated the severity or frequency of each item based on 4 levels scored from 0 (indicating the most favorable condition) to 4 (indicating the least favorable condition) for each item. Total scores can range from 0 to 30.

Maternal depression were examined as a dichotomous outcome using EDS scores at a clinically-relevant cutoff (EDS score > 12)[21]. Maternal depression was examined at three time specific categories: a) depression only during pregnancy, b) postpartum depression, and c) recurrent depression. Depression during pregnancy was defined as depression during the second or third trimester of pregnancy and at no other subsequent time point. Postpartum depression was defined as depression during the first or sixth month postpartum. Lastly, recurrent depression was defined as postpartum depression and depression at any subsequent time point postnatally.

Respiratory outcomes

The validated Spanish version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was administered at the 48 month and 72 month visit. The following outcomes were assessed during both visits, ever wheeze, current wheeze, and asthma. Ever wheeze was defined as caregiver report of "Has your child ever had wheezing or whistling in the chest at any time in the past?" and current wheeze was defined based on response to "In the past 12 months, did your child have wheezing or whistling in the chest?" To measure asthma, caregivers responded to the following question, "Has your child ever had asthma in their life?" Repeated wheeze was defined as caregivers reporting wheeze during both 48 month and 72 month visits. Any ever wheeze was defined as caregiver reporting ever wheeze at 48 or 72 months and any current wheeze was identified as wheeze in the past 12 months at 48 or 72 months. Lastly, ever asthma was defined as asthma at either 48 or 72 months.

Covariates

Child's sex was obtained from delivery records. Mother's age at delivery was calculated by subtracting child's birthdate from mother's birthdate collected at enrollment. Caregiver's report of ever having asthma was collected through questionnaires at enrollment (second or third trimester). Maternal education was categorized into three levels: less than high school, high school, or greater than high school. Breastfeeding was assessed at 1 month postpartum and categorizes as, never/ no attempt to breastfeed and attempted to breastfeed up to 1 month. Socioeconomic status (SES) was assessed utilizing 13 variables derived from prenatal questionnaire results which were used to classify study participant families into six levels based on the SES index created by the Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública (AMAI)[22]. These levels were then collapsed into lower, medium, and higher socioeconomic status. Exposure to particulate matter <2.5 microns in diameter ($PM_{2.5}$) was estimated at each participant's residenceduring pregnancy and over the first two postnatal years using a novel spatio- temporal model incorporating Moderate Resolution Imaging Spectroradiometer (MODIS) satellite- derived Aerosol Optical Depth (AOD) measurements at a 1x1km spatial resolution[23]. These remote sensing data are calibrated with municipal ground level monitors of $PM_{2.5}$, land use and meteorological data to yield estimates of daily residential $PM_{2.5}$ levels for each study participant[23]. Daily particulate matter during the first year of life was averaged for the entire gestational period and over the first and second year postpartum[13].

Statistical Analyses

Data were analyzed using a modified Poisson regression approach that allowed for estimation of risk ratios instead of odds ratios[24]. Models were adjusted for child's sex, maternal education level (<high school, high school, >high school), mother's age, average $PM_{2.5}$ during pregnancy, and average $PM_{2.5}$ during the first year postpartum. We then examined effect modification by child sex (male/female) for respiratory outcomes by including the relevant interaction terms. Models with p-values <0.1 for interaction terms were then stratified by child sex. In sensitivity analysis, we also adjusted for average $PM_{2.5}$ during the first two years postpartum, breastfeeding, and for SES instead of maternal education. Analyses were performed in R Version 3.5.1 (R Development Core Team) and SPSS version 24 (Chicago, IL).

Results

A total of 605 mother- child dyads from the PROGRESS cohort were included in this study. Table 1 shows the distribution of exposure, outcomes, and covariates of the study population as a whole and then stratified by child sex. Child sex was evenly distributed within this population. The average maternal age was 27 years of age. The majority of participants had a lower SES (52%), and no more than a high school education (40%). Only 8 women reported ever having asthma at enrollment. Prenatal depression were observed in 16% of mothers, postpartum depression in 25% of mothers, and recurrent depression in 17% of mothers. Overall, at the 48 month assessment 26%, 13%, and 3% of the children had a caregiver report ever wheeze, current wheeze, and asthma, respectively. The distribution of respiratory outcomes in children at 72 months were as follows: a) ever wheeze in 16%, b) current wheeze in 6%, and c) asthma in 4%. Additionally, overall 29% of the study participant's caregivers reported any ever wheeze, 14% any current wheeze, and 5% ever asthma.

Table 1: Characteristics of mother–child dyads in the PROGRESS cohort, n=605

Characteristics	**Total Sample**	**Male Children 304 (50%)**	**Female Children 301 (50%)**
Maternal age at enrollment (years), median (IQR)	27.00 (23.00, 31.00)	27.00 (24.00, 31.00)	27.00 (23.00, 31.00)
Maternal breastfeeding, n (%)	Maternal breastfeeding, n (%)	Maternal breastfeeding, n (%)	Maternal breastfeeding, n (%)
Never/ no attempt to breastfed	33 (6%)	8 (4%)	14 (7%)
Attempted to exclusively breastfed	542 (94%)	209 (96%)	200 (93%)
Maternal education at enrollment, n (%)	Maternal education at enrollment, n (%)	Maternal education at enrollment, n (%)	Maternal education at enrollment, n (%)
< High school	242 (40%)	130 (43%)	112 (37%)
High school	221 (37%)	103 (34%)	118 (39%)
> High school	142 (23%)	71 (23%)	71 (24%)
Maternal ever asthma at enrollment, n (%)	Maternal ever asthma at enrollment, n (%)	Maternal ever asthma at enrollment, n (%)	Maternal ever asthma at enrollment, n (%)
Ever had asthma, yes	8 (4%)	7 (7%)	1 (1%)
Socioeconomic status, n (%)	Socioeconomic status, n (%)	Socioeconomic status, n (%)	Socioeconomic status, n (%)
Lower	314 (52%)	156 (51%)	158 (52%)
Medium	230 (38%)	117 (38%)	113 (38%)
Higher	61 (10%)	31 (10%)	30 (10%)
Average $PM_{2.5}$ during pregnancy, median (IQR)	22.78 (20.58, 24.19)	22.76 (20.65, 24.36)	22.78 (20.38, 24.12)
Average $PM_{2.5}$ during the first year of life, median (IQR)	22.73 (20.54, 23.88)	22.73 (20.65, 23.95)	22.76 (20.36, 23.83)
Maternal Depression, n (%)	Maternal Depression, n (%)	Maternal Depression, n (%)	Maternal Depression, n (%)
Prenatal depression, yes	104 (17%)	57 (19%)	47 (16%)
Postpartum depression, yes	145 (25%)	76 (26%)	69 (24%)
Recurrent depression, yes	92 (16%)	49 (17%)	43 (15%)
Respiratory Outcomes (48M), n (%)	Respiratory Outcomes (48M), n (%)	Respiratory Outcomes (48M), n (%)	Respiratory Outcomes (48M), n (%)
Ever wheeze, yes	150 (25%)	86 (28%)	64 (21%)

Current wheeze, yes	72 (12%)	44 (14%)	28 (9%)
Asthma, yes	20 (3%)	11 (4%)	9 (3%)
Respiratory Outcomes (72M), n (%)	Respiratory Outcomes (72M), n (%)	Respiratory Outcomes (72M), n (%)	Respiratory Outcomes (72M), n (%)
Ever wheeze, yes	85 (15%)	47 (16%)	38 (13%)
Current wheeze, yes	31 (5%)	20 (7%)	11 (4%)
Asthma, yes	23 (4%)	17 (6%)	6 (2%)
Any ever wheeze	176 (29%)	96 (32%)	80 (27%)
Any current wheeze	79 (14%)	47 (16%)	32 (11%)
Any ever asthma	30 (5%)	19 (6%)	11 (4%)

Table 2: Association of maternal depression and adverse respiratory outcomes in children, n=605

Outcome measures	**Maternal depression measures RR (95% CI)**	**Maternal depression measures RR (95% CI)**	**Maternal depression measures RR (95% CI)**
	Prenatal depression	Postpartum depression	Recurrent depression
Ever wheeze at 48M	1.00 (0.95, 1.06)	1.24 (0.92, 1.67)	1.48^{*} (1.07, 2.03)
Current wheeze at 48M	1.02 (0.93 1.13)	1.88^{+} (1.21, 2.92)	2.39^{++} (1.52, 3.78)
Asthma at 48M	1.09 (0.80, 1.48)	2.79^{*} (1.13, 6.87)	3.14^{*} (1.26, 7.84)
Ever wheeze at 72M	1.04 (0.95, 1.14)	1.54^{*} (1.02, 2.32)	1.76^{*} (1.12, 2.77)
Current wheeze at 72M	0.99 (0.87, 1.13)	1.19 (0.55, 2.59)	1.48 (0.63, 3.48)
Asthma at 72M	1.73 (0.81, 3.69)	1.86 (0.79, 4.36)	2.25 (0.91, 5.59)
Any ever wheeze	1.02 (0.97, 1.08)	1.27 (0.97, 1.66)	1.53^{+} (1.15, 2.03)
Any current wheeze	1.02 (0.93, 1.12)	1.59^{*} (1.03, 2.46)	2.08^{+} (1.32, 3.28)
Ever asthma	1.12 (0.87, 1.45)	2.15^{*} (1.06, 4.39)	2.46^{*} (1.16, 5.21)
Models adjusted for child's sex, mother's age and educational level at enrollment, average $PM_{2.5}$ exposure during pregnancy, and average PM2.5 at 1st year postpartum. $^{*}p < 0.05$ $^{+}p < 0.01$ $^{++}p < 0.001$	Models adjusted for child's sex, mother's age and educational level at enrollment, average $PM_{2.5}$ exposure during pregnancy, and average PM2.5 at 1st year postpartum. $^{*}p < 0.05$ $^{+}p < 0.01$ $^{++}p < 0.001$	Models adjusted for child's sex, mother's age and educational level at enrollment, average $PM_{2.5}$ exposure during pregnancy, and average PM2.5 at 1st year postpartum. $^{*}p < 0.05$ $^{+}p < 0.01$ $^{++}p < 0.001$	Models adjusted for child's sex, mother's age and educational level at enrollment, average $PM_{2.5}$ exposure during pregnancy, and average PM2.5 at 1st year postpartum. $^{*}p < 0.05$ $^{+}p < 0.01$ $^{++}p < 0.001$

Table 2 shows the results of the modified Poisson regression analysis in the overall population. We did not observe significant associations between prenatal depression and childhood respiratory outcomes. Postpartum depression was significantly associated with increased risk of current wheeze (RR: 1.88, 95% CI: 1.21, 2.92) and asthma (RR: 2.79, 95% CI: 1.13, 6.87) at 48 months. We observed an association between postpartum depression and any current wheeze (RR: 1.59, 95% CI: 1.03, 2.46) and ever asthma (RR: 2.15, 95% CI: 1.06, 4.39). Lastly, a statistically significant association was observed between postpartum depression and ever wheeze at 72 months (RR: 1.54, 95% CI: 1.02, 2.32).

Maternal recurrent depression was associated with an increased risk of ever wheeze at 48 months (RR: 1.48, 95% CI: 1.07, 2.03) and 72 months (RR: 1.76, 95% CI: 1.12, 2.77). It was also associated with increased risks of current wheeze (RR: 2.39, 95% CI: 1.52, 3.78) and asthma at 48 months (RR: 3.14, 95% CI: 1.26, 7.84). Additionally, we found that recurrent depression was associated with increased risks of any ever wheeze (RR:

1.53, 95% CI: 1.15, 2.03), any current wheeze (RR: 2.08, 95% CI: 1.32, 3.28), and ever asthma (RR: 2.46, 95% CI: 1.16, 5.21).

In two-way interaction models, we found evidence for effect modification by sex for postpartum ($p_{interaction}$= 0.06) and recurrent depression ($p_{interaction}$= 0.06) on current wheeze at 48 months. As shown in figure 1, postpartum depression were associated with higher risk of current wheeze at 48 months in females (RR: 3.04, 95% CI: 1.47, 6.27) when compared to males (RR: 1.53, 95% CI: 0.87, 2.68). We observed a similar pattern for recurrent depression, with females having a higher risk of current wheeze (RR: 3.95, 95% CI: 1.86, 8.36) when compared to males (RR: 1.92, 95% CI: 1.06, 3.46). We also found interactions between child sex and postpartum depression ($p_{interaction}$= 0.05) on current wheeze at 72 months (figure 2). Sensitivity analyses including additional adjustment for average $PM_{2.5}$ in the first 2 postnatal years, breastfeeding, and SES showed similar results (results not shown).

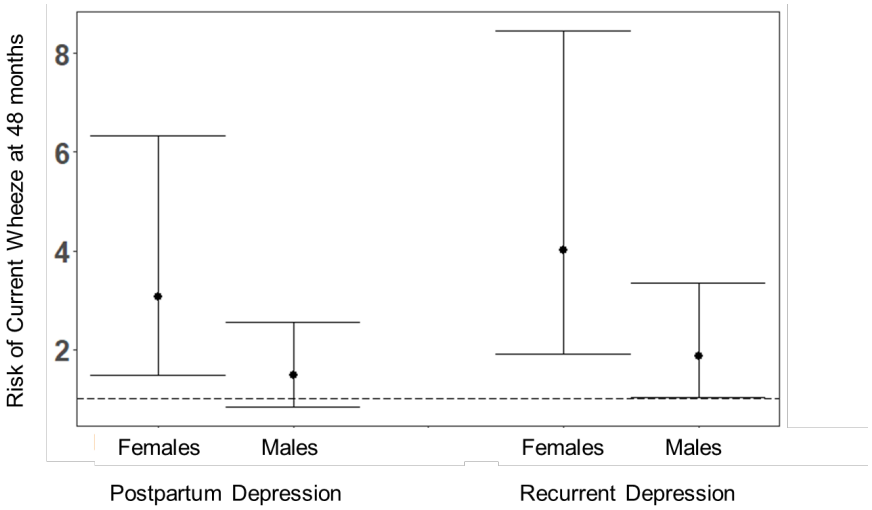

Figure 1: Sex-stratified associations between postpartum and recurrent depression and risk of current wheeze at 48 months. Models adjusted for mother's age and educational level at enrollment, average $PM_{2.5}$ exposure during pregnancy, and average $PM_{2.5}$ at 1st year postpartum.

Figure 2: Sex-stratified associations between postpartum depression and risk of current wheeze at 72 months. Models adjusted for mother's age and educational level at enrollment, average $PM_{2.5}$ exposure during pregnancy, and average $PM_{2.5}$ at 1st year postpartum.

Discussion

Our analyses leveraged longitudinal data to examine associations between maternal psychological functioning and respiratory outcomes in childhood. Our findings suggest that exposure to postpartum and recurrent maternal depression are associated with higher risk of wheeze and asthma in childhood. The observed associations remained significant after adjustment for a number of important potential confounders and covariates. We also found that child sex modified the association between maternal depression and respiratory outcomes; the association between postpartum and recurrent depression and higher risk of current wheeze was stronger in females when compared to males.

Prospective birth cohorts examining maternal depression at different time points in relation to wheeze and asthma development in childhood have produced mixed results[5, 9, 12]. A Canadian population based birth cohort study found that continued exposure to maternal anxiety or depression from birth into early childhood was associated with a twofold increase in the risk of asthma at age 7 years[5]. This is fairly consistent with

the results our study although we observed an association earlier at 48 months (4 years of age)[5]. Also in line with our results, Ramratnam et al. assessed the associations between maternal stress and depression during pregnancy and early life, and recurrent wheezing utilizing the Urban Environment and Childhood Asthma (URECA) birth cohort[12] and found an association between cumulative maternal depression in the first 3 years of life and recurrent wheezing[12]. However, we did not find any associations between prenatal depression and any of our outcomes like previous studies have reported[9, 11]. Differences in our findings may be attributable to our classification of depression (e.g., limited only to the prenatal period), the prevalence of our outcome and sample size.

The assessment of maternal mental health in the first postnatal year signifies an important critical window as the biological systems of children are rapidly maturing within the first two years of life, and may be compromised by exposure to more severe and enduring maternal mental health problems beyond the first postnatal year[25]. A potential mechanism for the observed relationships between postpartum and recurrent maternal depression and respiratory outcomes in our study may be through dysfunction of the hypothalamic pituitary adrenal (HPA) axis. McLearn *et al* reported that depressed women had reduced odds of playing or talking with their infants [4, 26] and animal studies have reported that decreased maternal attention enhanced hypothalamic-pituitary-adrenal (HPA) axis stress response in their offspring[4, 27, 28]. These interactions could be associated with symptoms of distress and raised cortisol levels in infants[4, 29] and recurrent infections and asthma in preschool children[4, 30]. Additionally, previous studies have reported that maternal postnatal depression and anxiety strongly correlate with infant cortisol levels[31, 32]. HPA dysregulation and the production of proinflammatory cytokines could increase children's susceptibility and sensitivity to persistent maternal distress and other co-occurring sources of chronic stress throughout the early childhood period[32, 33]. As a result, this could manifest as high allostatic load or a blunted cortisol response, increasing children's vulnerability for the development of asthma[5, 34, 35].

There is also growing evidence that the effects of maternal mental health on children's health outcomes may differ by sex. Previous studies have shown that the prenatal environment seems to impact males more than females whereas, females may be more susceptible to the postnatal environment. Lee et al. examined the associations between pre- and/ or postnatal stress and children's asthma, along with their effect modification by sex in a prospective cohort study utilizing the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project[10]. Increased maternal stress during the postnatal period was more strongly associated with higher odds of asthma in females[10], which is in line with our study findings. Previous studies have also shown that females may be more adaptive in utero, though at a cost of adverse health effects later in life[10, 36]. As a result, the usual increase in stress reactivity in females exposed to in utero stress could explain their greater vulnerability to stress- induced health effects after birth[10, 36]. Alton et al concluded that wheeze at 3 years of age was nearly 5 times more likely in girls of mothers who experienced postpartum depression, which is fairly similar to the results seen in this paper[4].

Utilizing the PROGRESS cohort in Mexico City is an important contribution to this growing body of work as the prevalence of postnatal and recurrent depression varies widely across cultures and geographic regions[10]. This study has several strengths, which include a prospective study design, large urban population and sample size of participants, and validated methods for measuring maternal depression and childhood respiratory health outcomes. Additionally, we had the ability to adjust for important environmental factors, including prenatal and early life exposure to $PM_{2.5}$.

Our study also had some limitations. Asthma and wheeze outcomes are based on caregiver report which might be subject to recall bias. However, given the logistical and technical complexity of objectively recording asthma and wheeze in children, caregiver-reported wheeze and asthma is commonly utilized in moderate- to larger-sized population level studies. The ISAAC survey has been validated internationally and in Spanish-Speaking populations[37]. Future work should examine more objective respiratory outcomes, such as lung function as these children continue to be followed. As with any observational study, we cannot rule out residual confounding due to unmeasured factors that may influence depression and wheezing/asthma in childhood. PROGRESS is composed of urban, low-income families and our results may translate to other

populations who face similar rates of depression. Research into the respiratory childhood health risks of maternal depression may be particularly clinically relevant in countries with high maternal depression such as the United States where 1/8 women experience symptoms of postpartum depression[23].

Conclusion

Postpartum and recurrent depression were associated with higher risk of wheeze and asthma in childhood. Our results, support the importance of researching the critical windows of maternal mental health during pregnancy and postnatally. Moreover, in order to more fully understand the influence of maternal mental health childhood respiratory disease risk, the modifying effects of child sex should be taken into account. This enhanced knowledge may benefit prevention and intervention strategies like maternal mental health surveillance programs.

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