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Maternal depressive symptoms, maternal asthma, and asthma in school-aged children

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ABSTRACT

Background: Little is known about joint effects of maternal asthma and maternal depression on childhood asthma.

Objective: To examine whether maternal depression and maternal asthma lead to greater risk of childhood asthma than maternal asthma alone.

Methods: Cross-sectional studies of children (ages 6-14 years) in San Juan, Puerto Rico (n=655) and Sweden (n=6,887). In Puerto Rico, maternal depressive symptoms were defined using the Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire. In Sweden, maternal physician-diagnosed depression was derived from national registries, and maternal depressive symptoms were defined using an abbreviated CES-D questionnaire. Childhood asthma was defined as physician-diagnosed asthma, plus current wheeze (in Puerto Rico) or medication use (in Sweden). Logistic regression was used for the multivariable analysis.

Results: Compared to Puerto Rican children whose mothers had neither asthma nor depressive symptoms, those whose mothers had asthma but no depressive symptoms had 3.2 times increased odds of asthma (95% confidence interval [CI]=2.1-4.8), and those whose mothers had both asthma and depressive symptoms had 6.5 times increased odds of asthma (95% CI=3.3-13.0). Similar results were obtained for maternal depression and maternal asthma in the Swedish cohort (odds ratio [OR] for maternal asthma without maternal depression= 2.8, 95% CI=2.1-3.7; OR for maternal asthma and maternal depression=4.0, 95% CI=1.7-9.6). Although the estimated effect of maternal asthma on childhood asthma was increased when maternal depressive symptoms (Puerto Rico) or maternal depression (Sweden) was present, there were no statistically significant additive interactions.

Conclusion: Maternal depression may further increase the risk of asthma in children with maternal history of asthma.

INTRODUCTION

Asthma is the most common chronic disease of childhood and a major public health problem in the United States (U.S.) and worldwide (1, 2). In the U.S., the burden of childhood asthma is unequally distributed across racial or ethnic groups, with Puerto Ricans and non-Hispanic Blacks being more affected with this disease than non-Hispanic whites or Mexican Americans (3). In Nordic countries, including Sweden, the incidence of childhood asthma increased until the 1990s, and then reached a plateau in the 2000s (4).

Depression is a common mental illness that affects 8-16% of women of reproductive age (5). Depression is frequent during and after pregnancy, affecting 10-15% of all gravid and post-partum mothers (6, 7) Among Hispanics, Puerto Rican mothers have twice the risk of mental health disorders (including depression) as Mexican Americans (8). In large studies of adults, depression has been associated with asthma (9, 10).

The high frequency of comorbid depression and asthma in women of reproductive age may increase the risk of childhood asthma. Maternal depression may affect asthma in pre-school and school-aged children through indirect mechanisms, including second-hand smoke and non-adherence to prescribed controller medications. If present during pregnancy, maternal depression has been associated with increased odds of wheeze (an asthma symptom) from ages 1 to 4 years (odds ratio [OR]=1.5, 95% confidence interval [CI]=1.2-1.8)(11), with one study suggesting a dose-response relationship between maternal depressive symptoms and severity of childhood wheeze (12).

Maternal history of asthma is one of the strongest risk factors for childhood asthma. Children born to mothers with a history of asthma have up to fivefold higher odds of asthma than those born to mothers without history of asthma (95% CI for OR=1.7-14.9) (13).

Even though depression and asthma are common in women of reproductive age (1, 14-17), no study has assessed whether maternal depressive symptoms or maternal depression accentuates the detrimental effects of maternal asthma on childhood asthma. We hypothesized that maternal depressive symptoms or maternal depression further increases the risk of asthma in children whose mothers have asthma. We examined this hypothesis using two different study populations, first in a cohort of Puerto Rican children living in San Juan, Puerto Rico, and then in a cohort of Swedish children. By replicating the study in two populations that differ with regard to genetics, environmental exposures and socioeconomic factors, cultural practices, and diet, we hoped to reduce false positive findings and confounding bias.

METHODS

Puerto Rican Cohort

Subject Recruitment

Details on study design and subject recruitment have been previously reported (18, 19). In brief, from March 2009 to June 2010, children were chosen from randomly selected households in the metropolitan area of San Juan (Puerto Rico), using a multistage probability design. Primary sampling units were randomly selected neighborhood clusters based on the 2000 U.S. Census, and secondary sampling units were randomly selected houses within each primary sampling unit. A household was eligible if ≥1 resident was a child aged 6 to 14 years old. In households with >1

eligible child, only one child was randomly selected for screening. On the basis of the sampling design, 7,073 households were selected and 6,401 (90.5%) were contacted. Of these 6,401 households, 1,111 had ≥1 child within the age range of the study who met other eligibility criterion (see below). In an effort to reach a target sample size of ~700 children (which would give us ≥90% power to detect an OR ≥2 for exposures with a prevalence ≥25%), we attempted to enroll a random sample (n=783) of these 1,111 children. Parents of 105 of these 783 eligible households refused to participate or could not be reached. There were no significant differences in age, gender, or area of residence between eligible children who did (n=678 [86.6%]) and did not (n=105 [13.4%]) agree to participate.

The main recruitment tool was a screening questionnaire given to parents of children ages 6 to 14 years to obtain information about the child's general and respiratory health. We selected as cases children with parental report of physician-diagnosed asthma and wheeze in the previous year. We selected as control subjects children who had neither parental report of physician-diagnosed asthma nor wheeze in the prior year. All participants had to have four Puerto Rican grandparents, to ensure their Puerto Rican descent. Of the 678 study participants, 655 (~97%) had complete information on maternal depressive symptoms and were included in the current analysis.

Study Procedures

Study participants completed a protocol that included administration of questionnaires, and measurement of height and weight. One of the child's parents (usually [>93%] the mother) completed a questionnaire that was slightly modified from the one used in the Collaborative Study of the Genetics of Asthma (20). This questionnaire was used to obtain information about

the child's general and respiratory health, socio-demographic characteristics, and family history. In children, asthma was defined as physician-diagnosed asthma and wheeze in the previous year. Maternal history of asthma was defined as a positive answer to the question: "Has the child's mother ever had asthma?" Maternal depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD), a 20-item questionnaire that has been widely used and validated for epidemiologic studies in the general population.(21, 22) The overall CESD score is calculated by summing the scores for each item, and ranges from 0 to 60 points. Maternal depressive symptoms were considered present if the CESD score was ≥ 21 points, an adequate cutoff score for significant depressive symptoms in Puerto Rican adults, and an indicator of severe depressive symptoms in non-Puerto Rican adults (21, 22).

Written parental consent was obtained for participating children, from whom written assent was also obtained. The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Juan, PR; protocol #0160507), Brigham and Women's Hospital (Boston, MA; protocol #2007-P-001174/9), and the University of Pittsburgh (Pittsburgh, PA; protocol #PRO-10030498).

Statistical Analysis

We used two-sample t-tests to compare pairs of binary and continuous variables, and chi squared tests for comparison of binary variables. A stepwise approach was used to build the multivariable logistic regression models of maternal depressive symptoms, maternal asthma and childhood asthma. Because of their well-established association with depression and/or asthma, all final models included age, gender (23), household income (< vs. ≥ $15,000/year [near the median

income for households in Puerto Rico in 2008-2009])(24-26) and early-life exposure (in utero or in the first two years of life) to environmental tobacco smoke (ETS) (27). Other covariates considered in the initial multivariate models included body mass index (BMI) as a z-score (based on 2000 CDC growth charts) and current exposure to ETS; these covariates were removed from the final models, as they were neither associated with asthma at $P<0.05$ nor changed the parameter estimate (β) for maternal depressive symptoms by ≥10%. After the final multivariable models were built, we tested for a first-order interaction (on a multiplicative scale) between maternal depressive symptoms and maternal asthma on childhood asthma. Next, we examined the odds of childhood asthma in four subgroups: 1) no maternal asthma and no maternal depressive symptoms, 2) no maternal asthma but maternal depressive symptoms, 3) maternal asthma but no maternal depressive symptoms, and 4) both maternal asthma and depressive symptoms. Additive interactions were then examined using the Relative Excess Risk due to Interaction (RERI)(28).

All statistical analyses were performed with SAS version 9.4 software (SAS Institute, Cary, NC).

Swedish Cohort

Subject Recruitment

The Study of Twin Adults: Genes and Environment (STAGE) study population was derived from the Swedish Twin Registry (STR). During 2005-2006, all twins born between 1959 and 1985 were invited to participate in an extensive telephone interview or web-based questionnaire on habits, diseases, diet, living conditions and work (29). Children who were aged 6-14 years during 2005-2006 and had a mother in the STAGE cohort were eligible for this analysis.

Children of twins were identified using the Swedish Multi-Generation register. Adopted children were excluded, as were parents who emigrated after completing the questionnaire. In total, 25,383 twins (59.6%) responded to the questionnaire. Registry data were available for 24,685 twins: 15,720 of these had 32,561 biological children. After applying the eligibility and exclusion criteria, 6,887 children were included in the current analysis.

Study Procedures

Study participants completed questionnaires as part of the STAGE and Swedish Multi-Generation Registry. Maternal physician-diagnosed depression was defined as a diagnosis of depression from a hospital or outpatient clinic, derived from the Swedish Patient register (PAR) from 2005-2010. The ICD-10 diagnoses codes included: F32.0-F32.3, F32.8, F32.9, F33.1-F33.4, F33.8, F33.9, F34.1, and F41.2. Maternal depressive symptoms were measured using the previously validated eleven-item Iowa short version of the CES-D, an index of self-reported depressive symptoms in the last week (30). We allowed up to two missing items, and the scores of these two items were calculated using imputation of the mean of the individual's response to the non-missing items of the scale. Each item gives a score of 0-3 points, for a maximum possible total score of 33 points. A score larger than 8 was classified as depressive symptoms (30, 31). Maternal asthma was self-reported asthma in the STAGE questionnaire, defined as a positive answer to the question "Do you have asthma?" Early exposure (*in utero*) to ETS was derived from the MBR, and determined during pregnancy by midwives asking mothers about their smoking status at the first antenatal visit. Socio-economic status, defined as the highest educational attainment of the mother at the time of the STAGE questionnaire, was taken from the Swedish Longitudinal integration database for health insurance and labor (LISA) register.

In children, asthma was derived using PAR and the Swedish Prescribed Drug Registers (SPDR) between 2005 and 2010. Asthma was defined as an asthma diagnosis (ICD code J45 or J46) in the PAR, AND/OR: 1) any asthma medication except β2- agonist dispensed at least twice from July 2005, or 2) any asthma medication dispensed at least thrice during one calendar year from 2006-2010, identified with the Anatomical Therapeutic Chemical (ATC) codes R03BA (inhaled corticosteroids), R03AK (fixed combinations of β2-agonist and corticosteroids), R03DC (leukotriene receptor antagonists) or R03AC (β2- agonist). Dispensed asthma medication from the SPDR and register-based asthma diagnoses in PAR are suitable proxies for an asthma diagnosis (32).

Permission for the study was obtained from the Regional Ethical Review board in Stockholm, Sweden.

Statistical Analysis

Logistic regression was used for the multivariable analysis of maternal physician-diagnosed depression (heretofore called "maternal depression", for ease of exposition) or maternal depressive symptoms, maternal asthma and childhood asthma, using a similar approach to that used for the Puerto Rican cohort. All models were adjusted for offspring age, gender, early exposure to ETS and maternal educational level. All analyses used robust standard errors to

account for clustering of observations within twin pairs. Statistical analyses were conducted using Stata release 14.1 (Stata Corp, College Station, TX, USA).

RESULTS

Table 1 shows the main characteristics of the Puerto Rican (n=655) and Swedish (n=6,887) study participants. In the Puerto Rican cohort, children with asthma (cases) were significantly younger and more likely to be male, to have been exposed to ETS, to have a maternal history of asthma, and to have a mother with depressive symptoms. There were no significant differences in household income or maternal education between cases and control subjects.
In the Swedish cohort, those with asthma (cases) were more likely to be male and to have a maternal history of asthma. There were no significant differences in maternal education, early or current ETS, maternal depression or maternal depressive symptoms between children with and without asthma. By design, the age of study participants was similar across study cohorts. Compared with cases in the Swedish cohort, those in the Puerto Rican cohort were more likely to be exposed to ETS, and to have a maternal history of asthma.

Table 2 shows the results of the analysis of maternal depressive symptoms and asthma among Puerto Rican children. In the unadjusted analysis, maternal depressive symptoms were significantly associated with 1.4 times increased odds of childhood asthma. After adjustment for age, gender, household income, and early-life ETS, maternal depressive symptoms remained significantly associated with 1.5 times increased odds of childhood asthma (Model 1). After additional adjustment for maternal asthma, the association between maternal depressive symptoms and childhood asthma was nearly unchanged in magnitude but became non-

statistically significant (P=0.05, Model 2). We found no significant interaction between maternal depressive symptoms and maternal asthma on childhood asthma in a multiplicative scale (P= 0.3, tested in Model 2).

Figure 1 shows the proportion of children with asthma in four subgroups of Puerto Rican and Swedish children, classified according to the presence of maternal asthma and maternal depressive symptoms or maternal depression. In Puerto Rico, 40% of children with no maternal asthma and no maternal depressive symptoms had asthma, and 81% of those with maternal asthma and maternal depressive symptoms had asthma (**Figure 1A**). In Sweden, 6% of children with no maternal asthma and no maternal depression had asthma, and 18% of those with both maternal asthma and maternal depression had asthma (**Figure 1B**).

Given the results shown above and our a priori hypothesis, we next examined the relation between categories of maternal depressive symptoms and maternal asthma, and asthma in Puerto Rican children (**Table 3**). Compared with children without maternal asthma or maternal depressive symptoms, those with maternal asthma had 3.1 times significantly increased odds of asthma, and those with both maternal asthma and maternal depressive symptoms had 6.4 times significantly increased odds of asthma. Maternal depressive symptoms were not significantly associated with childhood asthma in the absence of maternal asthma. Nearly identical findings were obtained in a multivariable analysis. In this analysis, the RERI between maternal asthma and maternal depression was positive (and thus suggestive of an additive interaction), but not statistically significant (3.0, 95% CI= -1.4 to 7.4).

Table 3 shows the results of the unadjusted and adjusted analyses of categories of maternal asthma and maternal depression, and asthma in Swedish children. Consistent with our findings in Puerto Rico, maternal depression was not significantly associated with childhood asthma in the absence of maternal asthma. In a multivariable analysis, maternal asthma was significantly associated with 2.8 times increased odds of childhood asthma in the absence of maternal depression. In this analysis, maternal asthma was significantly associated with 4.0 times increased odds of childhood asthma in the presence of maternal depression. In the multivariable model, the estimated RERI was positive, but not statistically significant for an additive interaction between maternal asthma and maternal depression (1.5, 95% CI= -1.0, 4.0). As in Puerto Rico, there was no significant interaction between maternal asthma and maternal depression on a multiplicative scale.

Supplementary Table 1 shows the results of the unadjusted and adjusted analyses of categories of maternal asthma and maternal depressive symptoms, and asthma in Swedish children. Compared with children without maternal depressive symptoms or maternal asthma, those with maternal asthma had threefold significantly increased odds of asthma, and those with maternal asthma and maternal depressive symptoms also had threefold significantly increased odds of asthma. Similar results were obtained in a multivariable analysis. In this analysis, maternal depression alone was not significantly associated with childhood asthma. Consistent with no additive interaction, the estimated RERI was not significant (-0.24, 95% CI= -1.27 to 0.80).

DISCUSSION

Among Puerto Ricans, we show that maternal depressive symptoms are not significantly associated with asthma in children without maternal history of asthma, but that the association between maternal asthma and childhood asthma appears stronger when maternal depressive symptoms are present (aOR=6.5) than when such maternal symptoms are absent (aOR=3.3). Consistent with our findings in Puerto Ricans, maternal physician-diagnosed depression was not significantly associated with asthma in Swedish children without maternal history of asthma. However, the association between maternal asthma and asthma in Swedish children seems stronger when maternal depression is present (aOR=4.0) than when maternal depression is absent (aOR=2.8). In contrast to findings for maternal depression (which indicates more severe depressive symptoms), the association between maternal asthma and asthma in Swedish children was similar in the presence or absence of maternal depressive symptoms. Although we found no statistically significant additive or multiplicative interaction between maternal asthma and maternal depressive symptoms or maternal depression in Puerto Ricans or Swedes, we had limited statistical power to detect such an interaction.

Our negative results for an association between maternal depressive symptoms or maternal depression and asthma in the absence of maternal asthma differ from those in an Australian study, which reported an association between maternal depressive symptoms and asthma in children ages 6 to 7 years old, regardless of maternal history of asthma (33). In addition to differences in geographic location and the race or ethnicity of study participants, the Australian study examined repeated measures of depressive symptoms between the first year of life and school-age, which we lacked. To our knowledge, however, this is the first report of potential

joint detrimental effects of maternal asthma and maternal depressive symptoms or maternal depression in school-aged children.

Several plausible mechanisms could explain a particularly strong association between maternal asthma and childhood asthma in the presence of maternal depressive symptoms (in Puerto Rico) or maternal depression (in Sweden). Depressive symptoms or clinical depression may alter the mother's ability to care for her children. Maternal depression could thus influence asthma in children through poor healthcare utilization or reduced adherence to controller medications (34). Moreover, parental mental illness has been linked to poor asthma management in children, leading to increased risk of hospitalization (35). Maternal depression in caregivers has been associated with increased asthma morbidity in children in some studies (36) but not in others (10). Alternatively, some of the women with asthma and depressive symptoms or clinical depression may have been depressed during pregnancy, and perinatal stressors may increase the risk of childhood asthma by altering immune responses (37) or the hypothalamic-pituitary-adrenal (HPA) axis (35). However, we cannot test this hypothesis in our cross-sectional study.

Maternal asthma has been a strong risk factor for childhood asthma in cross-sectional (38) and birth cohort studies (13, 37), which have estimated ORs for maternal asthma ranging between 3.3 and 5.0. Consistent with those findings, we found that maternal asthma was associated with 3.5 times increased odds of asthma in Puerto Rican children, and with 2.7-2.8 times increased odds of asthma among Swedish children. Our results extend those from prior studies, and suggest that maternal depressive symptoms or maternal depression increases the risk of childhood asthma conferred by maternal asthma alone.

Our study has several strengths, including replication in two ethnically divergent populations living in markedly different geographic locations and thus exposed to different environments, and ability to account for confounding factors (including gender, household income and early-life ETS). However, we recognize several study limitations. First, maternal depression was assessed 6 to 14 years after the birth of study participants, and thus we cannot assess the role of prenatal or perinatal depression, or treatment of maternal depression, on childhood asthma. Second, we used a cutoff score of 21 points for depressive symptoms, based on our prior work in Puerto Rican adults, instead of a cutoff score of 16 points (used in non-Puerto Rican women). However, we obtained similar results using a cutoff score of 16 points (data not shown), and a cutoff score of 21 points has been previously used to indicate more severe depressive symptoms in non-Puerto Rican women (40, 41). Maternal asthma was associated with similarly increased odds of asthma in Swedish children regardless of concurrent depressive symptoms, but we observed a difference in the magnitude of the association between maternal asthma and asthma between Swedish children who did and did not have a mother with physician-diagnosed depression (a marker of more severe depressive symptoms), albeit smaller than that found in the Puerto Rican cohort.

In summary, our findings suggest that maternal depressive symptoms (in Puerto Rico) or maternal depression (in Sweden) further increases the risk of asthma among children with a maternal history of asthma. Our results need confirmation in longitudinal studies with adequate statistical power to detect additive interactions between maternal asthma and maternal depression. Such studies should help further elucidate whether maternal depression (during or after pregnancy) interacts with maternal asthma on the pathogenesis of childhood asthma.

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Table 1: Main characteristics of study participants

	Puerto Rico		Sweden	
	Controls (n=314)	**Cases (n=341)**	**Controls (n=6,401)**	**Cases (n=486)**
Age (years)	10.9 (2.7)	10.4 (2.6) ‡	9.84 (2.6)	10.2 (2.6) ‡
Male gender	153 (48.7 %)	194 (56.9 %) ‡	3225 (50.4%)	307 (63.2%) §
Early-life environmental tobacco smoke*	122 (38.8 %)	168 (49.3 %) §	629 (9.8%)	44 (9.1%)
Current environmental tobacco smoke	107 (34.1 %)	152 (44.6 %) §	1545 (24.1%)	128 (26.3%)
Household income >$15,000 per year	110 (36.7 %)	116 (34.6 %)	--	--
Maternal education				
Middle school only	99 (31.5 %)	108 (31.7 %)	337 (5.3%)	25 (5.1%)
High school graduate	91 (29.0 %)	96 (28.2 %)	3089 (48.3%)	235 (48.4%)
Less than 3 years of college	56 (17.8 %)	55 (16.1 %)	1133 (17.7%)	91 (18.7%)
3 or more years of college	68 (21.7 %)	82 (24.1 %)	1793 (28%)	135 (27.8%)
Maternal asthma	66 (21.0 %)	166 (48.7 %) §	600 (9.4%)	108 (22.2%) §
Maternal depression				
*Depressive symptoms***	67 (21.3 %)	96 (28.2 %) ‡	1937 (30.3%)	169 (34.8%)
Physician-diagnosed depression			154 (2.4%)	14 (2.9%)

Data are presented as mean (SDs) for continuous variables or number (percentage) for binary variables.

*Early-life environmental tobacco smoke: In utero or before age 2 years.

**Depressive symptoms: A full Center for Epidemiologic Studies Depression (CESD) score ≥ 21 points in Puerto Rico, or an abbreviated CESD score >8 points (in Sweden)

‡P-value <0.05 for the comparison between cases and controls at each location

§P-value <0.01 for the comparison between cases and controls at each location

Table 2: Maternal depressive symptoms and asthma among participating children in Puerto Rico

	Unadjusted	Model 1*	Model 2*
	Odds ratio (95% confidence interval), P value		
Maternal depressive symptoms	1.4 (1.0-2.1), 0.04	1.5 (1.0-2.2), 0.04	1.5 (1.0-2.2), 0.05
Age (years)		0.9 (0.9-1.0), 0.02	0.9 (0.9-1.0), 0.01
Male gender		1.4 (1.0-1.9), 0.05	1.5 (1.1-2.1), 0.02
Household income >$15,000/year		1.2 (0.8-1.6), 0.42	1.2 (0.8-1.7), 0.37
Early-life environmental tobacco smoke		1.6 (1.1-2.2), 0.01	1.5 (1.1-2.1), 0.02
Maternal asthma			3.5 (2.5-5.1), <0.001

Maternal depressive symptoms: A Center for Epidemiologic Studies Depression (CESD) score ≥ 21 points. Early-life ETS (environmental tobacco smoke): In utero or before age 2 years

*Model 1 was adjusted for age, gender, household income, and early-life ETS. Model 2 was additionally adjusted for maternal asthma.

Table 3: Analysis of categories of maternal asthma and maternal depressive symptoms, and asthma among participating children in Puerto Rico and Sweden (STAGE)

	Maternal history of:		Unadjusted	Adjusted
	Asthma	**Depressive symptoms^**	Odds ratio, 95% confidence interval, P value	
Puerto Rico	*No*	*No*	1.0	1.0
	No	*Yes*	1.2 (0.8-1.9)	1.3 (0.8-2.1)
	Yes	*No*	**3.1 (2.1-4.6)**	**3.2 (2.1-4.8)**
	Yes	*Yes*	**6.4 (3.3-12.4)**	**6.5 (3.3-12.9)**
	Asthma	**Physician-diagnosed depression**	Odds ratio (95% confidence interval), P value	
Sweden	*No*	*No*	1.0	1.0
	No	*Yes*	0.6 (0.2-1.5)	0.4 (0.1-1.3)
	Yes	*No*	**2.7 (2.1-3.5)**	**2.8 (2.1-3.7)**
	Yes	*Yes*	**3.3 (1.4-7.8)**	**4.0 (1.7-9.6)**

^Depressive symptoms: A Center for Epidemiologic Studies Depression (CESD) score ≥ 21 points

*Adjusted for age, gender, household income and early-life (in utero or before age 2 years) environmental tobacco smoke