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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.

1 **INTRODUCTION**

2 Asthma is the most common chronic disease of childhood and a major public health problem in
3 the United States (U.S.) and worldwide (1, 2). In the U.S., the burden of childhood asthma is
4 unequally distributed across racial or ethnic groups, with Puerto Ricans and non-Hispanic Blacks
5 being more affected with this disease than non-Hispanic whites or Mexican Americans (3). In
6 Nordic countries, including Sweden, the incidence of childhood asthma increased until the
7 1990s, and then reached a plateau in the 2000s (4).

8
9 Depression is a common mental illness that affects 8-16% of women of reproductive age (5).

10 Depression is frequent during and after pregnancy, affecting 10-15% of all gravid and post-
11 partum mothers (6, 7) Among Hispanics, Puerto Rican mothers have twice the risk of mental
12 health disorders (including depression) as Mexican Americans (8). In large studies of adults,
13 depression has been associated with asthma (9, 10).

14
15 The high frequency of comorbid depression and asthma in women of reproductive age may
16 increase the risk of childhood asthma. Maternal depression may affect asthma in pre-school and
17 school-aged children through indirect mechanisms, including second-hand smoke and non-
18 adherence to prescribed controller medications. If present during pregnancy, maternal depression
19 has been associated with increased odds of wheeze (an asthma symptom) from ages 1 to 4 years
20 (odds ratio [OR]=1.5, 95% confidence interval [CI]=1.2-1.8)(11), with one study suggesting a
21 dose-response relationship between maternal depressive symptoms and severity of childhood
22 wheeze (12).

23

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

27
28 Even though depression and asthma are common in women of reproductive age (1, 14-17), no
29 study has assessed whether maternal depressive symptoms or maternal depression accentuates
30 the detrimental effects of maternal asthma on childhood asthma. We hypothesized that maternal
31 depressive symptoms or maternal depression further increases the risk of asthma in children
32 whose mothers have asthma. We examined this hypothesis using two different study populations,
33 first in a cohort of Puerto Rican children living in San Juan, Puerto Rico, and then in a cohort of
34 Swedish children. By replicating the study in two populations that differ with regard to genetics,
35 environmental exposures and socioeconomic factors, cultural practices, and diet, we hoped to
36 reduce false positive findings and confounding bias.

37

38 ***METHODS***

39 **Puerto Rican Cohort**

40 **Subject Recruitment**

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

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

56
57 The main recruitment tool was a screening questionnaire given to parents of children ages 6 to 14
58 years to obtain information about the child's general and respiratory health. We selected as cases
59 children with parental report of physician-diagnosed asthma and wheeze in the previous year.
60 We selected as control subjects children who had neither parental report of physician-diagnosed
61 asthma nor wheeze in the prior year. All participants had to have four Puerto Rican grandparents,
62 to ensure their Puerto Rican descent. Of the 678 study participants, 655 ($\sim 97\%$) had complete
63 information on maternal depressive symptoms and were included in the current analysis.

64

65 **Study Procedures**

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

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

80
81 Written parental consent was obtained for participating children, from whom written assent was
82 also obtained. The study was approved by the Institutional Review Boards of the University of
83 Puerto Rico (San Juan, PR; protocol #0160507), Brigham and Women's Hospital
84 (Boston, MA; protocol #2007-P-001174/9), and the University of Pittsburgh (Pittsburgh, PA;
85 protocol #PRO-10030498).

86
87 **Statistical Analysis**
88 We used two-sample t-tests to compare pairs of binary and continuous variables, and chi squared
89 tests for comparison of binary variables. A stepwise approach was used to build the multivariable
90 logistic regression models of maternal depressive symptoms, maternal asthma and childhood
91 asthma. Because of their well-established association with depression and/or asthma, all final
92 models included age, gender (23), household income ($<$ vs. \geq \$15,000/year [near the median

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

106

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

108

109 **Swedish Cohort**

110 **Subject Recruitment**

111 The Study of Twin Adults: Genes and Environment (STAGE) study population was derived
112 from the Swedish Twin Registry (STR). During 2005-2006, all twins born between 1959 and
113 1985 were invited to participate in an extensive telephone interview or web-based questionnaire
114 on habits, diseases, diet, living conditions and work (29). Children who were aged 6-14 years
115 during 2005-2006 and had a mother in the STAGE cohort were eligible for this analysis.

116 Children of twins were identified using the Swedish Multi-Generation register. Adopted children
117 were excluded, as were parents who emigrated after completing the questionnaire. In total,
118 25,383 twins (59.6%) responded to the questionnaire. Registry data were available for 24,685
119 twins: 15,720 of these had 32,561 biological children. After applying the eligibility and
120 exclusion criteria, 6,887 children were included in the current analysis.

121

122 **Study Procedures**

123 Study participants completed questionnaires as part of the STAGE and Swedish Multi-
124 Generation Registry. Maternal physician-diagnosed depression was defined as a diagnosis of
125 depression from a hospital or outpatient clinic, derived from the Swedish Patient register (PAR)
126 from 2005-2010. The ICD-10 diagnoses codes included: F32.0-F32.3, F32.8, F32.9, F33.1-
127 F33.4, F33.8, F33.9, F34.1, and F41.2. Maternal depressive symptoms were measured using the
128 previously validated eleven-item Iowa short version of the CES-D, an index of self-reported
129 depressive symptoms in the last week (30). We allowed up to two missing items, and the scores
130 of these two items were calculated using imputation of the mean of the individual's response to
131 the non-missing items of the scale. Each item gives a score of 0-3 points, for a maximum
132 possible total score of 33 points. A score larger than 8 was classified as depressive symptoms
133 (30, 31). Maternal asthma was self-reported asthma in the STAGE questionnaire, defined as a
134 positive answer to the question "Do you have asthma?" Early exposure (*in utero*) to ETS was
135 derived from the MBR, and determined during pregnancy by midwives asking mothers about
136 their smoking status at the first antenatal visit. Socio-economic status, defined as the highest
137 educational attainment of the mother at the time of the STAGE questionnaire, was taken from the
138 Swedish Longitudinal integration database for health insurance and labor (LISA) register.

139
140 In children, asthma was derived using PAR and the Swedish Prescribed Drug Registers (SPDR)
141 between 2005 and 2010. Asthma was defined as an asthma diagnosis (ICD code J45 or J46) in
142 the PAR, AND/OR: 1) any asthma medication except β 2- agonist dispensed at least twice from
143 July 2005, or 2) any asthma medication dispensed at least thrice during one calendar year from
144 2006-2010, identified with the Anatomical Therapeutic Chemical (ATC) codes R03BA (inhaled
145 corticosteroids), R03AK (fixed combinations of β 2-agonist and corticosteroids), R03DC
146 (leukotriene receptor antagonists) or R03AC (β 2- agonist). Dispensed asthma medication from
147 the SPDR and register-based asthma diagnoses in PAR are suitable proxies for an asthma
148 diagnosis (32).

149
150 Permission for the study was obtained from the Regional Ethical Review board in Stockholm,
151 Sweden.

152

153

154

155 **Statistical Analysis**

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

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

163

164 **RESULTS**

165 **Table 1** shows the main characteristics of the Puerto Rican (n=655) and Swedish (n=6,887)
166 study participants. In the Puerto Rican cohort, children with asthma (cases) were significantly
167 younger and more likely to be male, to have been exposed to ETS, to have a maternal history of
168 asthma, and to have a mother with depressive symptoms. There were no significant differences
169 in household income or maternal education between cases and control subjects.

170 In the Swedish cohort, those with asthma (cases) were more likely to be male and to have a
171 maternal history of asthma. There were no significant differences in maternal education, early or
172 current ETS, maternal depression or maternal depressive symptoms between children with and
173 without asthma. By design, the age of study participants was similar across study cohorts.

174 Compared with cases in the Swedish cohort, those in the Puerto Rican cohort were more likely to
175 be exposed to ETS, and to have a maternal history of asthma.

176

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

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

187

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

195

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

206

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

218
219 **Supplementary Table 1** shows the results of the unadjusted and adjusted analyses of categories
220 of maternal asthma and maternal depressive symptoms, and asthma in Swedish children.
221 Compared with children without maternal depressive symptoms or maternal asthma, those with
222 maternal asthma had threefold significantly increased odds of asthma, and those with maternal
223 asthma and maternal depressive symptoms also had threefold significantly increased odds of
224 asthma. Similar results were obtained in a multivariable analysis. In this analysis, maternal
225 depression alone was not significantly associated with childhood asthma. Consistent with no
226 additive interaction, the estimated RERI was not significant (-0.24, 95% CI= -1.27 to 0.80).

227

228 **DISCUSSION**

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

243
244 Our negative results for an association between maternal depressive symptoms or maternal
245 depression and asthma in the absence of maternal asthma differ from those in an Australian
246 study, which reported an association between maternal depressive symptoms and asthma in
247 children ages 6 to 7 years old, regardless of maternal history of asthma (33). In addition to
248 differences in geographic location and the race or ethnicity of study participants, the Australian
249 study examined repeated measures of depressive symptoms between the first year of life and
250 school-age, which we lacked. To our knowledge, however, this is the first report of potential

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

253

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

266

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

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

290
291 In summary, our findings suggest that maternal depressive symptoms (in Puerto Rico) or
292 maternal depression (in Sweden) further increases the risk of asthma among children with a
293 maternal history of asthma. Our results need confirmation in longitudinal studies with adequate
294 statistical power to detect additive interactions between maternal asthma and maternal
295 depression. Such studies should help further elucidate whether maternal depression (during or
296 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				
<i>Middle school only</i>	99 (31.5 %)	108 (31.7 %)	337 (5.3%)	25 (5.1%)
<i>High school graduate</i>	91 (29.0 %)	96 (28.2 %)	3089 (48.3%)	235 (48.4%)
<i>Less than 3 years of college</i>	56 (17.8 %)	55 (16.1 %)	1133 (17.7%)	91 (18.7%)
<i>3 or more years of college</i>	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				
<i>Depressive symptoms**</i>	67 (21.3 %)	96 (28.2 %) ‡	1937 (30.3%)	169 (34.8%)
<i>Physician-diagnosed depression</i>			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	<i>No</i>	<i>No</i>	1.0	1.0
	<i>No</i>	<i>Yes</i>	1.2 (0.8-1.9)	1.3 (0.8-2.1)
	<i>Yes</i>	<i>No</i>	3.1 (2.1-4.6)	3.2 (2.1-4.8)
	<i>Yes</i>	<i>Yes</i>	6.4 (3.3-12.4)	6.5 (3.3-12.9)
Sweden	Asthma	Physician-diagnosed depression	Odds ratio (95% confidence interval), P value	
	<i>No</i>	<i>No</i>	1.0	1.0
	<i>No</i>	<i>Yes</i>	0.6 (0.2-1.5)	0.4 (0.1-1.3)
	<i>Yes</i>	<i>No</i>	2.7 (2.1-3.5)	2.8 (2.1-3.7)
	<i>Yes</i>	<i>Yes</i>	3.3 (1.4-7.8)	4.0 (1.7-9.6)

[^]Depressive symptoms: A Center for Epidemiologic Studies Depression (CESD) score \geq 21 points

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