Familial Depression and Respiratory Illness in Children

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Objective: To determine the relationship between parental major depression and respiratory illness in youth.

Design: Three-generation family cohort study.

Setting: Baseline study initiated at the Yale University Depression Research Unit.

Participants: One hundred sixty-one children and their parents and grandparents.

Main Exposure: Family history of major depression.

Main Outcome Measures: We studied the lifetime prevalence of respiratory illness and a range of other physical disorders, including gastrointestinal, neurodevelopmental, and cardiovascular diseases, in offspring of parents with and without major depression. Analyses were also stratified by parental and grandparental major depression status and were adjusted for age, sex, parental prenatal smoking, and parental functional impairment.

Results: Parental major depression is associated with a significantly increased likelihood of respiratory illness in youth (odds ratio, 3.7; 95% confidence interval, 1.6-8.6). This association persists after adjusting for age, sex, parental prenatal smoking, parental respiratory disease, and parental functional impairment.

Conclusions: Our results suggest that youth of parents with major depression may have heightened vulnerability to respiratory illness. Neither parental respiratory illness, prenatal smoking, nor functional impairment appears to explain this link.

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I N RECENT YEARS, THERE HAS BEEN growing interest and evidence in support of a relationship between respiratory illness and mental disorders in youth.[1-16] The mechanism of this association remains unknown. Investigators have examined a possible familial association between parental mental health and childhood respiratory illness from a variety of perspectives. Available data suggest an association between maternal mental health problems and childhood respiratory illness. Several questions about this potential association remain unanswered. Specifically, previous studies have examined the relationship between caregiver mental health problems and asthma morbidity among pediatric patients with asthma[17-21] and the relationship between caregiver mental health problems and the development of asthma,[22-24] with the exception of a study in Puerto Rico that included a community-based sample.[25] To our knowledge, the relationship between mental disorders in parents and childhood respiratory illness has not been examined. Previous studies have included self-reports of depressive symptoms in caregivers, yet these studies have not included diagnoses of major depression[26] diagnosed using *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) criteria with clinic interviews; nor have other specific diagnoses been available.

In addition, previous studies have not examined possible mechanisms such as prenatal smoking or functional impairment in the association between caregiver cigarette smoking and mental health problems and childhood respiratory illness. Prenatal nicotine dependence is associated with both major depression[27] and increased risk of childhood respiratory illness.[28,29] Therefore, this is one possible pathway that might explain the association. Another possibility is that the behavioral manifestations of major depression, which include functional impairment,[26] lead to increased exposure to risk factors for respiratory illness in the home, such as cockroach allergens,[30,31] which in turn increase the risk of respiratory illness in

youth. Previous investigations on this topic have focused on outcomes related to respiratory disease; yet, information has not been available on whether this effect is specific to respiratory illness or whether the effect may be more general, where parental psychopathology may be associated with a generally increased risk of any physical disorder in youth. Also, previous studies have examined this association in 2 generations. There is evidence that grandparental behavior, directly and in combination with parental behavior, may be associated with increased risk of respiratory illness in offspring.[32]

The purpose of the current study was to address some of these informational gaps by using data from a 3-generation study with *DSM* (Third Edition)[33] diagnoses of major depression. We analyzed the effects of familial major depression on the risk of respiratory illness in children by examining generational trends. The outcome of interest was respiratory illness in the third generation. The main focus of the study was third-generation participants (grandchildren), hereinafter called "subjects" for clarity. Second-generation participants are referred to as "parents," and third-generation participants as "grandparents."

First, we examined the relationship between family history of major depression and respiratory illness by examining parental major depression and the odds of respiratory illness in subjects. Second, the study examined the role of potentially explanatory factors (eg, parental respiratory illness, prenatal smoking, and functional impairment) in the association between parental major depression and respiratory illness in subjects. Third, we examined whether or to what degree there appears to be specificity in the association between parental major depression and respiratory illness compared with other physical disorders in subjects. Based on findings of previous studies, we hypothesized that parental major depression would be associated with a significantly increased likelihood of respiratory illness in subjects.

METHODS

Grandparents, parents, and subjects participated in a 20-year follow-up study of offspring of depressed (high-risk families) and nondepressed (low-risk families) probands. The study design and sample assessments are described in detail elsewhere.[34-37] In the baseline study, the depressed grandparents had moderate to severe major depressive disorder that resulted in impairment and were receiving treatment at the Yale University Depression Research Unit. The control group was recruited at the same time from a sample of adults in the same community. They underwent at least 4 direct interviews and were required to have no lifetime history of psychiatric illness. The study was initiated in 1982 (baseline) and, with few exceptions, the procedures remained unchanged across waves to avoid introducing method variation bias. Grandparents, parents, and subjects were interviewed separately, and the interviewers of subjects were blind to the clinical status of the parents. In addition, parents were blind to the clinical status of grandparents concerning major depression. For the purposes of these analyses, family history of major depression was present if either grandparent had major depression. Full details of methods for wave 1 (baseline), wave 2 (2-year follow-up), wave 3 (10-year follow-up), and wave 4 (20-year follow-up) can be

found elsewhere.[32,35,36,38,39] All psychiatric diagnoses are those made during an individual's lifetime and include all diagnoses up to the last interview (wave 3 or 4). The study was approved by the institutional review board at the New York State Psychiatric Institute, Columbia University, and all participants provided written informed consent or assent with parental consent.

SAMPLE

The present report is based on 182 of the original 220 subjects from a total of 83 of the original 91 families, including 125 subjects from 61 high-risk families and 57 subjects from 22 low-risk families. High-risk families were defined as those with a depressed grandparent in the first cohort of the study, while low-risk refers to a nondepressed community control grandparent. The baseline sample (wave 1) consisted of 220 offspring aged 6 to 23 years from 91 families.[34] They were interviewed again 2, 10, and 20 years later (waves 2, 3, and 4, respectively). Parents were interviewed at all waves.

ASSESSMENTS

Psychiatric Diagnoses

Adult psychiatric diagnoses of major depression were obtained using a semistructured diagnostic assessment (Schedule for Affective Disorders and Schizophrenia, Lifetime Version for Adults [SADS-LA]).[40]

Medical Illness

Medical illness data were collected using a standard medical checklist that includes 57 conditions categorized according to the site or system affected. Information was collected at each wave from grandparents, parents, and subjects; for minor subjects, parents completed the forms of medical conditions. The data from all waves were pooled to create a lifetime history medical condition for parents and subjects. Ambiguous reports of medical problems were coded during the best-estimate process by a physician blinded to the major depression status of the family.

Prenatal Smoking

Mothers from the grandparent cohort were asked whether they had ever smoked more than 10 cigarettes per day during their pregnancy with each child. The same criteria were used for categorizing smoking during pregnancy in the mothers in the parent cohort.

Functional Impairment

The Global Assessment Scale was completed by the best estimator at each wave.[41,42] This instrument is rated on a scale of 0 to 100 and provides an overall estimate of a person's current functional adjustment based on all available information.

INTERVIEWERS AND BEST-ESTIMATE PROCEDURES

The diagnostic assessments of parents were administered by mental health professionals with doctorates or master's degrees, trained as previously described.[35] When a history of mental health treatment was reported, study participants were asked to consent to have the relevant information examined and

Table 1. Association Between Grandparental and Parental Major Depression and Odds of Respiratory Illness in Subjects*

Factor Measured	No Grandparental Major Depression				Grandparental Major Depression				Interaction *P* Value
	No Parental Major Depression (n = 35)	Parental Major Depression (n = 25)	χ^2_1; *P* Value	OR (95% CI)†	No Parental Major Depression (n = 28)	Parental Major Depression (n = 70)	χ^2_1; *P* Value	OR (95% CI)†	
Respiratory illness in subjects	6 (16.6)	5 (20.0)	0.3;.70	1.5 (0.40-5.9)	2 (6.7)	27 (38.0)	7.9;.004	5.6 (1.5-20.2)	.17

Abbreviations: CI, confidence interval; OR, odds ratio.
*Data are given as number (percentage) unless otherwise indicated.
†Adjusted for age and sex.

released for use in our study. Two experienced clinicians, who were not involved in the interviewing, independently and blinded to the diagnostic status of the previous generation or prior assessments, reviewed all of the material and assigned a *DSM* (Fourth Edition) diagnosis based on the best-estimate procedure,[36] as reported elsewhere.[36,37] In the best-estimate procedure, 2 senior clinicians review extensive interview data and the case history and reach a consensus diagnosis. The diagnoses are cumulative across all waves.

STATISTICAL ANALYSIS

Initially, univariate analyses to test for the association between parental major depression and respiratory illness in subjects were performed using χ^2 tests. The same procedure was used to determine the association between grandparental major depression, parental prenatal smoking and grandparental prenatal smoking, parental respiratory illness, parental functional impairment, and respiratory illness in subjects. The univariate models were followed by multivariate models to adjust for the effect of potential confounders. Logistic regression analyses were performed to examine the association between parental major depression and respiratory illness in subjects, adjusting for differences in age, sex, parental and grandparent prenatal smoking, parental respiratory illness, and parental functional impairment. All analyses were adjusted for grandparental major depression to reflect the original design of the study. We then reran the final model using the generalized estimating equation procedure (GEE) to adjust for possible correlation of outcomes in siblings.

RESULTS

The 182 subjects included 151 interviewed at wave 4 (20 years after the baseline interview; mean age, 34.1 years) and 31 interviewed at wave 3 but not interviewed at wave 4 (mean age, 27.7 years). Ten years after the baseline assessment, there was no significant difference in attrition rate by parental diagnosis.[34] One hundred fifty-one (70%) of the original available cohort of 220 subjects were reinterviewed approximately 20 years after the initial interview (wave 4). There were no significant differences between interviewed and noninterviewed subjects by age, parental diagnosis, and major depression status of the subject at last interview. Significantly more female (58%) than male (43%) individuals were interviewed at wave 4 (*P* = .02).[37] Grandparents were interviewed at each wave except wave 4 because they were, on average, 63 years old and past the age of risk of first onset of major depression.

DEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE

Grandparents (n = 47) in the depressed (high-risk) and nondepressed (low-risk) groups at the last interview did not vary by sex (58% female), age (mean age, 56 years at wave 3 because the first generation was not interviewed at wave 4), marital status (81.2% were married), employment status (60% were employed full-time), mean household income ($42 570), and mean number of children (3.7).

Parents (n = 86) did not vary by their own parents' (grandparents) depression status, sex (64.8% female), age (mean age, 38 years), marital status (70.5% were married), employment status (66.7% were employed full-time), mean years of education (13.8 years), mean household income ($62 559), or mean number of children (2.1).

Subjects (n = 151) did not differ by their grandparents' depression status or by sex (54% female). They did, however, differ by age: subjects from the low-risk group had a mean age of 10.7 years, and those from the high-risk group had a mean age of 13.8 years. All analyses were adjusted for age. Further details of the original sample are provided by Weissman et al.[36]

ASSOCIATION BETWEEN GRANDPARENTAL AND PARENTAL MAJOR DEPRESSION, PRENATAL SMOKING, AND RESPIRATORY ILLNESS IN SUBJECTS

Among those with a family history of major depression (ie, grandparental major depression), parental major depression was associated with a significantly increased odds of respiratory illness in subjects (odds ratio [OR], 5.6; 95% confidence interval [CI], 1.5-20.2) compared with those without parental major depression (**Table 1**). Among those without a family history of major depression, indicated by a history of major depression in either grandparent, parental major depression was not significantly associated with elevated respiratory illness in subjects compared with those without parental major depression. The association between parental major depression and respiratory illness in subjects seems to vary by history of grandparental major depression. Specifically, when 2 generations (grandparents and parents) were affected with major depression, the risk of res-

Table 2. Association Between Parental Major Depression and Respiratory Illness in Subjects*

Factor Measured	No Parental Major Depression (n = 63)	Parental Major Depression (n = 95)	Unadjusted OR (95% CI)	AOR† (95% CI)	AOR‡ (95% CI)	AOR§ (95% CI)	AOR‖ (95% CI)	AOR¶ (95% CI)	AOR# (95% CI)
Respiratory disease in subjects	8 (12.7)	33 (34.7)	3.66 (1.56-8.59)	3.17 (1.32-7.64)	3.02 (1.25-7.34)	5.80 (1.35-24.98)	4.03 (1.55-10.51)	2.89 (1.17-7.11)	2.65 (1.05-6.69)

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.
*Data are given as number (percentage) unless otherwise indicated.
†Adjusted for grandparental major depression.
‡Adjusted for grandparental major depression, age, and sex.
§Adjusted for grandparental major depression, age, sex, and parental prenatal smoking.
‖Adjusted for grandparental major depression, age, sex, and prenatal smoking.
¶Adjusted for grandparental major depression, age, sex, and parental functional impairment.
#Adjusted for grandparental major depression, age, sex, parental functional impairment, and respiratory impairment.

piratory illness in subjects was increased 5-fold compared with those without affected grandparents and parents. However, a formal test of interaction, testing whether these 2 ORs were significantly different from each other, did not reach statistical significance.

The association between parental prenatal smoking and respiratory illness in subjects (OR, 2.6; 95% CI, 0.9-7.5) compared with those without parental prenatal smoking was not statistically significant. When parental prenatal smoking was examined with major depression in parents, the association between parental major depression and respiratory illness in subjects was reduced but remained statistically significant (**Table 2**).

There were no statistically significant associations between parental respiratory disease and parental depression (P=.29), parental prenatal smoking (P=.70), or respiratory disease in offspring (P=.60). There did not appear to be a statistically significant relationship between parental respiratory disease and respiratory illness in subjects (data not shown but available from the authors on request).

In the final model, we examined the relationship between parental major depression and odds of respiratory illness in subjects, examining the role of prenatal smoking, parental respiratory disease, and functional impairment related to major depression as possible mediating factors and age and sex as potential confounding factors (Table 2). Before investigating prenatal smoking and functional impairment as potential mediators rather than confounders, we examined whether each was significantly related to both the independent variable (ie, parental major depression) and the dependent variable (ie, respiratory illness in subjects). Univariate comparisons revealed that the relationship between parental prenatal smoking and parental major depression was statistically significant (P<.001). Also, a slight association between parental prenatal smoking and respiratory illness in subjects indicated that, with further research, it may be possible to consider parental prenatal smoking a potential mediator of this relationship due to the marginal significance demonstrated (P=.07). However, in this study, the association between either parental respiratory illness or prenatal smoking and respiratory illness in subjects was not found to be statistically significant. In addition, the relationship between parental functional impairment and parental major depression was found to be statistically significant (P=.003), and parental functional impairment appears to be related to an increased rate of respiratory illness in subjects, though this difference did not reach statistical significance (23.9% [33] vs 40.0% [8]; P=.12), yet the difference appears considerable; therefore, we measured parental respiratory illness, and functional impairment, a potential mediator in these analyses, to be conservative, though the results need to be interpreted with caution.

Results of our analyses showed that parental major depression was associated with significantly increased odds of respiratory illness in subjects, and this relationship remained significant after adjusting for grandparental major depression (OR, 3.17; 95% CI, 1.32-7.64). The association persisted further, though the association was slightly attenuated after adjusting for age and sex (OR, 3.02; 95% CI, 1.25-7.34). The association between parental major depression and respiratory illness in subjects remained statistically significant after adjusting for the effect of parental prenatal smoking, grandparental prenatal smoking, parental respiratory illness, and parental functional impairment, suggesting that parental prenatal smoking, parental respiratory illness, and parental functional impairment do not mediate the relationship between parental major depression and respiratory illness in subjects.

FAMILY HISTORY OF MAJOR DEPRESSION AND PHYSICAL DISORDERS IN SUBJECTS: SPECIFICITY

In an additional analysis, the odds of a range of physical disorders was examined in subjects with and without a history of parental and grandparental major depression (**Table 3**). Results of this analysis showed that the relationship between family history of major depression and respiratory illness was specific in that family history of major depression within the 2 previous generations was associated with increased odds of respiratory illness in subjects but the odds of other physical disorders were not increased.

Table 3. Family History of Depression (Grandparental and Parental) and Rates of Physical Disorders in Subjects*

Factor Measured	Parental Major Depression				χ^2_3	*P* Value
	No Grandparental Major Depression		Grandparental Major Depression			
Parental depression	No	Yes	No	Yes		
No. of subjects	35	25	30	71		
No. of families	9	7	12	26		
Mean age (SD) of subjects, y	10.4 (4.4)	11.1 (4.6)	12.7 (6.5)	14.3 (5.7)		
Subject disorders						
Physical illness						
Cancer	0	1 (4.0)	0	0	5.6	.14
Cardiovascular illness	0	2 (8.0)	1 (3.3)	5 (7.0)	3.1	.37
Dermatologic illness	4 (11.1)	2 (8.0)	5 (16.7)	8 (11.3)	1.1	.78
Endocrine-related illness	0	0	0	1 (1.4)	1.3	.74
Gastrointestinal tract illness	0	0	1 (3.3)	6 (8.3)	5.6	.13
Genitourinary tract illness	0	0	0	2 (2.8)	2.5	.46
Hematologic illness	0	1 (4.0)	1 (3.3)	1 (1.4)	1.8	.63
Infectious disease	0	0	0	1 (1.4)	1.3	.74
Metabolic illness	0	0	1 (3.3)	2 (2.9)	1.9	.60
Musculoskeletal illness	0	0	1 (3.3)	3 (4.2)	2.5	.47
Neuromuscular illness	2 (5.6)	3 (12.0)	4 (13.3)	17 (23.9)	6.3	.11
Headache	1 (2.8)	0	3 (10.0)	11 (15.5)	7.5	.06
Respiratory illness	6 (16.7)	5 (20.0)	2 (6.7)	27 (38.0)	14.5	.002
Systematic illness	10 (27.8)	8 (32.0)	5 (16.7)	24 (33.8)	2.9	.40
Neurodevelopmental disorder	3 (9.1)	3 (13.6)	2 (8.0)	6 (8.5)	1.6	.66
Any physical illness	16 (44.4)	15 (60.0)	16 (53.3)	51 (71.8)	9.0	.03

*Data are given as number (percentage) unless otherwise indicated. Ten stepgrandchildren are excluded. Parents are biological children of grandparents. Number may vary because of missing data in some categories. Instruments used were the K-SADS (Kiddie-Schedule for Affective Disorders and Schizophrenia) or the SADS-LA (Lifetime Version for Adults). Analysis is based on analysis of covariance with adjustment for sex and age at the interview for continuous outcomes (F test) and χ^2 analysis for dichotomous outcomes.

COMMENT

These data are consistent with and extend previous results with 4 main findings. First, parental major depression is associated with significantly increased odds of respiratory illness in subjects. Second, the association between parental major depression and odds of respiratory illness in subjects persists after adjusting for parental prenatal smoking, parental respiratory illness, and parental functional impairment, as well as age, sex, and grandparental major depression. Third, the association between parental major depression and odds of respiratory illness in subjects appears to be somewhat specific to respiratory illness, inasmuch as parental major depression does not appear to similarly increase the odds of a wide range of other physical disorders in subjects. Fourth, this link appears stronger in those with a history of grandparental major depression compared with those without such history.

Our results suggest that parental major depression is associated with a significantly increased likelihood of respiratory illness in offspring. To our knowledge, this is the first study to document a relationship between parental major depression and increased odds of respiratory illness in youth. This finding is consistent with and extends previous results showing associations between depressive symptoms and stress in caregivers and higher levels of asthma morbidity in youth.[14-25] If replicated in general community and other clinical samples, these findings suggest that offspring of parents with major depres-sion may be at high risk for vulnerability to respiratory illness. Identifying a relationship between specific mental disorders in parents, as compared with general mental health symptoms or perceived environmental stress, and risk of respiratory illness in youth is useful for both research and clinical purposes. From a research perspective, understanding potentially common risk factors including familial risk for both specific mental disorders and respiratory illness is only possible if specific mental disorders are identified that then can be used to perform comparisons and attempt replication of results (eg, common genetic vulnerability to major depression and respiratory illness). Future studies need to include specific diagnostic groups so that replication is possible. From a clinical perspective, major depression is a treatable disorder,[38,39] with guidelines for recommended treatment. Similar treatment approaches for depressive symptoms and perceived stress are not as clear. Therefore, if future results confirm an association between parental major depression and increased risk of respiratory illness in youth and young adults, treatment of parental major depression may ultimately be a potential prevention strategy.

The mechanism of the observed association between parental major depression and respiratory illness in subjects cannot be determined based on these data alone. By examining the potentially mediating role of prenatal smoking, respiratory illness, and functional impairment in parents in the association between the two, we have made some progress in ruling out the possibility that these factors completely explain the association. Further inves-

tigation of the potential role of these factors in the link between parental major depression and respiratory illness among youth in a representative community-based sample may be informative in revealing whether and to what degree our findings are generalizable to other groups. By adjusting for respiratory illness in parents, we were also unable to find evidence suggesting that respiratory illness in parents explained the association between parental major depression and respiratory illness in subjects. There are numerous alternative possibilities. It may be that the association is explained by shared genetic vulnerability to respiratory illness and major depression. Several studies have shown evidence suggestive of such an association between depressive symptoms and atopy[43,44] and a familial relationship between panic disorder and respiratory illness.[45] Future studies that can examine a potentially genetic link between major depression and respiratory illness will be useful. Another possibility is that parents with major depression smoke cigarettes while children are in their first few months and years of life, thereby exposing them to environmental tobacco smoke, a known risk factor for childhood respiratory illness.[46] Exposure to environmental tobacco smoke is one of few risk factors documented to increase the risk for the onset of asthma in early life.[47,48] Future studies will be needed to explore this potential pathway as the current study did not include information on parental smoking or exposure to enviromental tobacco smoke after the child was born.

Our results also suggest that the association between parental major depression and odds of respiratory illness in subjects appears to be somewhat specific to respiratory illness as parental major depression does not appear to similarly increase the likelihood of a wide range of other physical disorders in subjects. While a number of previous studies have examined associations between parental mental health problems and asthma or respiratory illness in youth, it has not been clear whether and to what degree it is simply the case that parental major depression is associated with elevated rates of a wide range of physical disorders in offspring or whether there is some specificity in the link between parental mental health problems and respiratory illness. The reason for this specificity is not known. Previous data have suggested common neurobiological pathways for asthma and major depression,[49] and it may be that those are unique to this association. This finding will need to be replicated in community-based samples.

A novel finding presented by our results is that, while the association between parental major depression and respiratory illness in subjects persists after adjusting for grandparental major depression, the strength of the link between parental major depression and respiratory illness in subjects appears to be much stronger among those with a family history where 2 generations have been affected by major depression. This has not previously been reported as no prior study has examined this association in a 3-generation study, though it is also consistent with findings indicating a common familial risk for both major depression and atopy.[50,51] There are several possible explanations for this result. First, it may be that if there is a common genetic vulnerability to both major

depression and respiratory illness, those with a family history of 2 generations with major depression have greater vulnerability to respiratory illness because of greater risk of both resulting from having a family history of both. Alternatively, it may be that the home environments of those with a strong family history of major depression are more likely to contain risk factors for the development of respiratory illness in offspring. For instance, major depression and cigarette smoking are strongly linked in adults.[52,53] It may be that there were higher rates of cigarette smoking in nuclear and extended families with a history of major depression and, therefore, greater opportunity for infants and young children to be exposed to environmental tobacco smoke early in life.

Some features of this study design limit the generalizability of the findings and should be considered when interpreting these results. First, our results are not generalizable to the community; therefore, future studies that can replicate these findings with community-based samples are needed. In addition, the sample was entirely white, and since prevalence of respiratory illness differs among children of various minorities, it is unclear whether the results would be generalizable among all races/ethnicities. Second, because diagnoses of respiratory illness are by parent's report and self-report, there is the possibility of report bias owing to lack of data directly from physician diagnoses. In addition, the measure of respiratory illness in subjects was somewhat vague and did not differentiate between specific types of respiratory illness. Future studies that investigate associations with greater specificity of illness will be needed. Third, small cell sizes in several of the comparisons may have limited our ability to detect significant differences in a number of cases. These results should be interpreted with caution and need replication. Fourth, because the precise temporal sequence of parental major depression, parental functional impairment, and parental prenatal smoking is not known, conclusions about parental prenatal smoking and functional impairment being mediators of the relationship between parental major depression and respiratory illness in subjects are not possible because a mediator must occur temporally between a risk factor and the outcome for this definition to be precise.[54] Fifth, we were not able to test all potential mediating or confounding factors in the relationship between parental major depression and respiratory illness in subjects, such as postnatal parental cigarette smoking during childhood and adolescence, as well as exposure to environmental tobacco smoke. Therefore, all potential mediators could not be investigated in this study.

There are also several notable strengths of this investigation. First, no previous investigation has used data from 3 generations to investigate the association between parental psychopathology and respiratory illness in offspring. Therefore, our study provides new evidence of this multigenerational association. Second, previous studies have not been able to investigate potentially mediating environmental and social factors in the association between parental psychopathology and respiratory illness in subjects. Third, the availability of data on a wide range of physical disorders in offspring enable an investigation of the level of specificity of the

association between parental major depression and respiratory illness in subjects, which has not previously been available.

These findings are consistent with and extend previous results by providing evidence that parental major depression is associated with increased likelihood of respiratory illness in children. The increased odds of respiratory illness among subjects associated with parental major depression does not appear to be explained by parental prenatal smoking, parental respiratory disease, or parental functional impairment. The link between parental major depression and increased odds of respiratory illness in offspring appears to be specific in that parental major depression was not associated with any other physical disorders in subjects. Our results suggest that this association is much stronger in those with a family history of 2 generations affected by major depression. Future research will be important to replicate these findings in other populations. Studies that include diverse community-based samples (particularly, youth in urban settings, who may have heightened vulnerability to respiratory illness early in life) and that further investigate potential social, biological, environmental, and genetic mechanisms that may explain the link between parental major depression and respiratory illness in youth are needed.

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