Objective: To examine the association between early childhood respiratory disease and the risk of anxiety and depression in adulthood.

Design: Cohort study.

Setting: Providence cohort of the National Collaborative Perinatal Project.

Participants: Offspring of 1062 mothers selected for follow-up from birth through adulthood.

Main Exposure: Childhood respiratory disease.

Main Outcome Measure: Odds of developing anxiety and depression by age 34 years.

Results: Respiratory disease in childhood was associated with an elevated risk of receiving treatment for anxiety disorders but not mood disorders. Specifically, higher respiratory rate at age 4 months was associated with significantly increased odds of receiving treatment for anxiety by age 34 years (odds ratio, 2.2; 95% confidence interval, 1.1-4.4; \(P < .05\)). Respiratory disease at age 1 year was associated with significantly increased odds of receiving treatment for anxiety (odds ratio, 2.8; 95% confidence interval, 1.2-6.5; \(P = .04\)). In addition, having respiratory disease at age 1 year only was associated with increased odds of receiving treatment for anxiety (odds ratio, 3.1; 95% confidence interval, 1.1-8.7; \(P < .05\)), whereas having both respiratory disease at age 1 year and suspect (parent reported but not physician diagnosed) respiratory disease at age 7 years was associated with the greatest odds of receiving treatment for anxiety (odds ratio, 19.8; 95% confidence interval, 2.8-141.9; \(P < .05\)).

Conclusions: These results are consistent with and extend previous findings and provide prospective evidence of a link between respiratory disease in early childhood and increased risk of anxiety disorders by age 34 years. These findings may have implications for prevention or early intervention with groups at high risk for anxiety disorders.

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In recent years, interest has been growing in the relationship between respiratory disease and anxiety and depressive disorders.\(^1\)\(^-\)\(^2\)\(^2\) In parallel lines of research, results of experimental studies have shown links between respiratory abnormalities and anxiety disorders in youths and adults. Specifically, laboratory studies have provided evidence that youths with anxiety disorders have higher sensitivity to carbon dioxide inhalation compared with youths without mental disorders (eg, separation anxiety disorder).\(^2\)\(^3\)\(^-\)\(^2\) In addition, similar studies in adults have shown that panic disorder is associated with increased sensitivity to carbon dioxide and that this sensitivity is specific to panic as depression was not associated with heightened sensitivity to carbon dioxide.\(^2\)\(^6\)\(^-\)\(^2\) These results cumulatively support the hypothesis that there may be a shared vulnerability to respiratory abnormalities associated with both anxiety and respiratory disease.

Despite this growing body of evidence, several questions remain. Most notably, because most studies have been cross-sectional, it is unknown whether respiratory conditions in childhood are associated with increased rates of subsequent mental disorders.

The goal of the present study was to address 3 questions raised by the previous literature. First, are respiratory conditions in infancy and childhood associated with increased rates of mental disorders in adulthood? Second, is the association between respiratory conditions and mental disorders specific to anxiety or does it apply to depression as well?
Third, is this relationship specific to asthma or are other childhood respiratory conditions also associated with increased vulnerability to subsequent mental disorders in adulthood?

**METHODS**

**SAMPLE**

Subjects were offspring of mothers enrolled in the Providence, Rhode Island, site of the National Collaborative Perinatal Project, described in detail by Niswander and Gordon.29 In brief, this project was a multisite cohort study that involved the prospective observation and examination of more than 50,000 pregnancies and the offspring through the first 7 years of life in 12 cities across the United States. At the Providence site, 4140 pregnant women were enrolled between 1959 and 1966. Of the entire prenatal cohort of 4140 pregnancies, 3130 offspring were assessed at age 7 years and were administered the Wechsler Intelligence Scale for Children and the Wide Range Achievement Test. Subjects were matched for age, sex, and race/ethnicity to 605 control subjects with a full-scale IQ of 80 or higher who performed more than 1 SD lower on any of the academic tests were classified as having childhood learning difficulties (n = 457). These subjects were matched for age, sex, and race/ethnicity to 605 control subjects, for a final sample of 1062 subjects.

In 1996, when subjects were entering middle adulthood, 1062 individuals in the Providence cohort were selected for a follow-up study to evaluate long-term outcomes in individuals with and without childhood learning difficulties.30 All subjects selected for follow-up had a full-scale IQ of 80 or higher at age 7 years.31 Approximately 40% of the study sample included subjects whose academic tests indicated childhood learning difficulties, and 60% were control subjects matched for age, sex, and race/ethnicity. Of the 1062 subjects selected for follow-up, 47 had died or were otherwise ineligible for follow-up and 295 subjects could not be assessed. Overall, 720 of the surviving 1015 subjects (70.9%) were successfully located and interviewed at a mean (SD) age of 33.58 (1.79) years (age range, 30-39 years).

**MEASURES**

Respiratory Rate in Infancy (Age 4 Months)

Physicians examined participants at age 4 months. Respiratory rate (RR) was measured as the number of breaths per minute (bpm) (the range was from 18-96 bpm). We included RR at age 4 months because RR is a basic vital sign that is routinely measured in the medical environment. A high RR suggests dysfunction of the lungs. It is among the earliest physiologic measures of respiratory disease and can be obtained through observation and without elaborate testing.

This information was not collected for every participant because of unavailability of an assessor but was available for 390 participants. No demographic differences were noted at follow-up for those with RR measured compared with the remainder of the analytic sample (n = 321). We dichotomized the continuous measure of RR, comparing outcomes between those with higher than documented standards of mean RR for infants (44 bpm)12,13 vs others. This was done as our objective was to identify approximately the top 15% to 20% to categorize a reasonably extreme group yet with high enough prevalence to have some power to detect a 2-fold difference. This cutoff point was chosen on the basis of findings in the literature and on recommendations of clinicians (pediatricians, pediatric pulmonologists, and pediatric surgeons). Studies have documented the comparability of RR measurement by observation and auscultation.34

Respiratory Disease in Childhood (Ages 1 and 7 Years)

At ages 1 and 7 years, participants were examined by a physician, and diagnoses of croup, asthma, pneumonia, and bronchiolitis were made and rated as “definite” or “suspect.” Some children were ill at the time of assessment and were characterized as definite diagnoses based on physician evaluation. Other children were diagnosed by the physician based solely on historical information provided by their parents and were characterized as “suspect” respiratory disorders. We examined suspect and definite diagnoses at ages 1 and 7 years in relation to mental disorders at age 34 years. Analyses were run separately for each respiratory disease and for combined groups including those with any respiratory disease at age 1 or 7 years or at both examinations.

**MENTAL DISORDERS**

Diagnoses of generalized anxiety disorder (GAD) and major depression were obtained using version III-R of the National Institute of Mental Health Diagnostic Interview Schedule. Lifetime diagnoses at age onset of GAD and major depressive episode were assessed using the Diagnostic Interview Schedule at the time of the adult follow-up interview. The Diagnostic Interview Schedule is widely used in community samples, has satisfactory psychometric properties for GAD and depression, and was administered by trained reliable interviewers. The analyses presented herein combine diagnoses of major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders (Third and Fourth Editions) (DSM-III and DSM-IV), which are similar although not identical. For depression, both diagnostic systems require the presence of at least 5 of the following symptoms concurrently for longer than 2 weeks: guilt, fatigue, depressed mood, sleep disturbance, suicidal thoughts or behavior, psychomotor changes, change in weight or appetite, loss of interest or pleasure, or trouble concentrating or thinking. In the DSM-III, depressed mood is a required symptom, whereas in DSM-IV, depressed mood or loss of interest is required. In addition, DSM-IV criteria include a clinical impairment criterion and allow for a diagnosis of depression following a period of bereavement that persists for longer than 2 months. Depressive symptoms were assessed on a lifetime basis, and the age at first depressive episode was determined by asking respondents how old they were when they experienced multiple depressive symptoms for 2 weeks or longer.35

The interview included questions of whether the individual had received lifetime treatment for anxiety or depression. While there was considerable overlap, not all subjects who met criteria for a disorder received treatment, and not all who received treatment met diagnostic criteria for GAD or major depressive episode. Specifically, 54 of 79 participants with GAD (68.4%) also reported receiving treatment for anxiety, and 54 of 80 participants who received treatment for anxiety (67.5%) also met criteria for GAD. Among those meeting diagnostic criteria for major depressive episode, 136 of 230 (54.4%) reported receiving treatment for depression, and 49 of 136 (39.1%) of those who received treatment for depression also met diagnostic criteria for depression. For ease of language, throughout this article the term mental disorders is used to refer collectively to depression and anxiety outcomes at age 34 years, including both diagnoses and receipt of treatment.

Socioeconomic status (SES) at age 7 years was measured using a composite index adapted from the US Bureau of the Census that averaged percentiles derived from the educational achievement and occupation of the head of the household, as well as family income.36 Socioeconomic status at age 7 years was a continuous measure ranging from 0.3 to 9.3, with 9.3 indicating the highest SES.
We used $\chi^2$ analyses to determine the bivariate associations between high RR, respiratory conditions at ages 1 and 7 years, and mental disorders in adulthood. Tests were 2-sided, and significance was set at $P < .05$. Multiple logistic regression analyses were used to determine the association between early respiratory conditions and the risk of mental disorders in adulthood, adjusted for sex, race/ethnicity, family SES, maternal marital status, and learning disorder status. Analyses were also performed separately for subjects with and without childhood learning difficulties to determine whether learning difficulty status affected the results. Results are reported using adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Independent variables included the following: (1) RR at 4 months (high vs normal), (2) respiratory disease at age 1 year, and (3) respiratory disease at age 7 years. Respiratory disease at ages 1 and 7 years were combined to create variables examining the persistence and severity of respiratory disease in early life and risk of later mental disorders.

### Table 1. Demographic Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants (N=1062)</th>
<th>Participants Who Completed the Study (n=720)</th>
<th>Participants Who Completed the Study and Respiratory Rate Was Measured (n=399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>684 (64.4)</td>
<td>440 (61.1)</td>
<td>242 (60.7)</td>
</tr>
<tr>
<td>Female</td>
<td>378 (35.6)</td>
<td>280 (38.9)</td>
<td>157 (39.3)</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>827 (77.9)</td>
<td>555 (77.1)</td>
<td>312 (78.2)</td>
</tr>
<tr>
<td>Black</td>
<td>220 (20.7)</td>
<td>155 (21.5)</td>
<td>81 (20.5)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (1.3)</td>
<td>10 (1.4)</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Maternal educational achievement, mean (SD), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family income, mean (SD), $ (in thousands)</td>
<td>37.7 (20.3)</td>
<td>38.1 (20.7)</td>
<td>40.0 (21.6)</td>
</tr>
<tr>
<td>SES index</td>
<td>4.3 (1.9)</td>
<td>4.4 (2.0)</td>
<td>4.5 (2.1)</td>
</tr>
<tr>
<td>Learning difficulty status, No. (%)</td>
<td>394 (37.4)</td>
<td>269 (37.1)</td>
<td>142 (35.6)</td>
</tr>
</tbody>
</table>

Abbreviation: SES, socioeconomic status.

* Compared with the 342 participants who did not complete the study, the 720 participants who did were significantly more likely to be female (38.9% vs 28.7%, $P=.001$).

* Compared with the 342 participants who did not complete the study, the 720 participants who did were more likely to have higher levels of maternal education (mean [SD], 10.1 [2.5] years vs 9.6 [2.2] years, $P=.002$).

* There were no significant differences for race/ethnicity between those participants who did not complete the study (n=399) but had their respiratory rate measured at 4 months (not shown), but those who had their respiratory rate measured had higher mean maternal education compared with those who did not (n=321) (10.4 [2.6] years vs 9.8 [2.3] years, $P=.005$).

### attrition analysis

Analyses were performed to determine whether there were demographic differences between participants in the original sample who did and did not participate in the follow-up assessments (Table 1). Overall, few demographic differences were noted. Specifically, compared with the 342 participants who did not complete the adult assessment, the 720 who did were more likely to be female and to have higher maternal educational achievement, but there were no significant differences for race/ethnicity. Similarly, no significant differences were noted for sex or race/ethnicity between those participants who did (n=399) and did not (n=321) have RR measured at 4 months (data not shown). Those with RR measured at 4 months had significantly higher mean maternal educational achievement compared with those who did not have RR measured (n=321) (mean [SD], 10.4 [2.6] years vs 9.8 [2.3] years; $P=.003$). There were no significant differences between groups according to learning difficulty status.

### PREVALENECE OF RESPIRATORY DISEASE AT AGES 1 AND 7 YEARS

Any respiratory disease at age 1 year was diagnosed among 46 of 720 participants (6.4%): asthma in 6 (13%), pneumonia in 34 (74%); severe croup in 4 (9%); and bronchiolitis in 4 (9%). At age 7 years, 97 of 720 participants had either suspect or definite respiratory disease: suspect bronchiolitis in 1 (1.03%) and definite bronchiolitis in 1 (1.03%), suspect pneumonia in 34 (35.1%) and definite pneumonia in 32 (33.0%), suspect croup in 1 (1.03%) and definite croup in 7 (7.22%), and suspect asthma in 5 (5.15%) and definite asthma in 27 (27.8%).

### PREVALENCE OF MENTAL DISORDERS AT AGE 34 YEARS

Of the 720 participants, 79 (7.4%) met diagnostic criteria for GAD and 80 (7.5%) reported receiving treatment for anxiety, and 250 (23.5%) met criteria for depression and 150 (14.1%) reported receiving treatment for depression. The mean (SD) age at onset of GAD was 21.6 (7.6) years and for depression was 20.4 (7.5) years.

### RESPIRATORY CONCERNS DURING THE FIRST YEAR OF LIFE AND MENTAL DISORDERS AT AGE 34 YEARS

A higher RR at age 4 months was associated with a significantly increased likelihood of receiving treatment for anxiety by age 34 years (Table 2) compared with participants with a normal to low RR, adjusting for sex, race/ethnicity, family SES, and maternal marital status. No significant association was noted between RR and GAD, depression, or treatment of depression by age 34 years.

Respiratory disease at age 1 year was associated with a significantly increased risk of treatment of anxiety ($P=.04$) (Table 2) and a marginally elevated but not statistically significant risk of GAD ($P=.09$). When comparisons were made between each of the specific respiratory diseases diagnosed at age 1 year, that is, croup, asthma, pneumonia, and bronchiolitis (data not shown), the findings consistently showed that each condition was associated with higher rates of GAD and treatment of anxiety by age 34 years, although results failed to reach sta-
ASSOCIATION BETWEEN RESPIRATORY DISEASE AT AGES 1 AND 7 YEARS AND RISK OF MENTAL DISORDERS AT AGE 34 YEARS

Respiratory disease at age 7 years was not associated with either depression or treatment of depression (Table 3). The pattern of results for GAD and treatment of anxiety is more complicated. Overall, respiratory disease at age 7 years was not significantly associated with subsequent anxiety problems. However, children with parent-reported (suspect) respiratory disease evidenced increased risk of treatment of anxiety (OR, 3.4; 95% CI, 1.5-7.9) and a marginally increased but not significant risk of GAD (OR, 2.1; 95% CI, 0.9-5.2) compared with those without respiratory disease at 7 years. Physician-diagnosed (definite) respiratory disease at age 7 years was not associated with subsequent anxiety problems.

ASSOCIATIONS BETWEEN RESPIRATORY DISEASE AT AGES 1 AND 7 YEARS AND MENTAL DISORDERS AT AGE 34 YEARS

We compared the risk of mental disorders in adulthood in relation to respiratory disease at ages 1 and 7 years (Table 4). Respiratory disease at age 1 year in the absence of any respiratory disease at age 7 years was associated with an elevated but not statistically significant risk of GAD (OR, 2.4; 95% CI, 0.9-6.6) and significantly elevated treatment of anxiety (OR, 3.1; 95% CI, 1.1-8.7) compared with no respiratory disease at age 1 or 7 years. The risk of GAD (OR, 2.4; 95% CI, 0.8-6.9) and treatment of anxiety at 34 years (OR, 2.5; 95% CI, 0.8-7.3) among those with suspect respiratory disease at age 7 years alone was elevated but did not reach statistical significance. Having both respiratory disease at 1 year and suspect respiratory disease at 7 years was associated with the greatest risk of both treatment of anxiety (OR, 19.8; 95% CI, 2.8-141.9) and GAD, although the risk of GAD was not statistically significant (OR, 5.2; 95% CI, 0.8-34.1) owing to small sample size (n=5).

COMMENT

This study yielded 3 main findings. First, our results indicate that high RR at age 4 months, any respiratory disease by age 1 year, and parent report of respiratory disease by age 7 years are associated with increased rates of treatment of anxiety problems by age 34 years. Second, these data suggest that the association between early respiratory conditions and mental disorders appears specific to anxiety and is largely unrelated to major depression. Third, we found that the link between early
respiratory problems was not specific to asthma and that similar patterns were observable between all early respiratory diseases measured (ie, pneumonia, bronchiolitis, and croup) and later anxiety problems. To our knowledge, this is the first study to show a link between a range of respiratory concerns in the first year of life and anxiety problems over 30 years later in adulthood.

Our results suggest that individuals with respiratory problems in infancy seem to be at increased vulnerability to anxiety during adulthood. These findings are consistent with results of previous community-based studies in children, yet expand on these findings in 3 ways. First, our results suggest that the link between respiratory problems and anxiety occurs much earlier and can be observed as early as the first months of life. The earliest age at assessment in community-based studies on this topic to date has been during late childhood or early adolescence. Inasmuch as age at onset of respiratory diseases such as childhood asthma is younger than 7 years in most cases and mean age at onset of anxiety disorders is earlier than for other mental disorders, these data provide an unusual opportunity to prospectively assess this link. Second, whereas data from previous studies among children in the community have been based solely on parent report of diagnoses of respiratory disease, to our knowledge, our data are the first to show a link between respiratory problems and mental health problems using both physician-reported respiratory disease and objective measures of physiologic functioning. Third, previous longitudinal studies beginning in childhood followed up participants to age 21 years, when participants had yet to pass through the period of highest risk of mood and anxiety disorders. In our study, participants were followed up to age 34 years, after passing through the period of highest risk of mood and anxiety disorders, thereby providing a more comprehensive estimate of the risk associated with early respiratory problems.

The mechanism of the observed association between early respiratory conditions and anxiety in adulthood is unknown. One possibility is that a suboptimal immune system may predate the onset of both respiratory disease and mental disorders. It could also be that some combination of environmental and genetic risk factors lead to the co-occurrence of respiratory disease and anxiety disorders. As anxiety disorders are associated with substantially elevated rates of cigarette smoking among adults, it is conceivable that exposure to smoke in the home confers an increased risk of asthma in offspring and an increased risk of subsequent development of an anxiety disorder via genetic or familial vulnerability.

Our results suggest some specificity in the strength of the association between early respiratory problems and risk of anxiety problems compared with the risk for depression. It may be that, as predicted by laboratory data, anxiety disorders and respiratory disease share a common respiratory vulnerability.20-26 We found that early respiratory problems were more strongly and consistently associated with treatment of anxiety disorder than for the diagnosis of GAD. Some previous studies have shown stronger links between respiratory problems and panic disorder9,22,48 relative to other anxiety problems, which suggests some specificity between panic-anxiety and respiratory problems. In the present study, there was no available information about the type of anxiety disorders that were diagnosed among those who sought treatment of anxiety. It is possible that this group had high rates of panic-related anxiety disorders. This would be consistent with the suffocation alarm theory, which suggests a specific link between respiratory abnormalities and panic disorders. While this is purely speculative, it may be that the participants in the present study who sought treatment may have panic-related anxiety. Future studies to better examine the specificity of these links are needed.

As anxiety and depression are so highly comorbid, it is noteworthy that respiratory problems seem to be associated with anxiety and not depression. The reason for this apparent specificity is unknown. It may be that the mechanisms underlying the associations between respiratory disease and anxiety vs depression are different. It is conceivable that anxiety and respiratory disease share a common risk factor such as prenatal smoking or a common biological underpinning, whereas the link with depression may arise from an alternative mechanism. Previous studies of the relationships between respiratory disease, specifically asthma, have consistently found links between asthma and anxiety disorders, whereas the link between asthma and depression has been somewhat mixed. Specifically, while results have shown a link between asthma and depression among adults, the link has been observed either when the disorders were measured concurrently (both in the past year) or in close temporal proximity (within 1-3 years). In contrast, lifetime

### Table 4. Risk of Mental Disorders by Age 34 Years in Relation to Respiratory Disease at Both Ages 1 and 7 Years

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Respiratory Disease at Age 1 or Age 7 Years (n=555)</th>
<th>Respiratory Disease at Age 1 Year Only (n=29)</th>
<th>Suspected Diagnosis (Parent Report) Age 7 Years Only (n=27)</th>
<th>Definite Diagnosis at Age 7 Years Only (n=48)</th>
<th>Respiratory Disease at Age 1 Year and Suspect Diagnosis at Age 7 Years (n=5)</th>
<th>Respiratory Disease at Age 1 Year and Definite Diagnosis at Age 7 Years (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD, No. (%)</td>
<td>51 (9.2)</td>
<td>6 (20.7)</td>
<td>5 (18.5)</td>
<td>5 (10.4)</td>
<td>2 (40.0)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>1 [Reference]</td>
<td>2.4 (0.9-6.6)</td>
<td>2.4 (0.8-6.9)</td>
<td>1.3 (0.5-3.5)</td>
<td>5.2 (0.8-34.1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Treatment of anxiety</td>
<td>53 (9.5)</td>
<td>6 (20.7)</td>
<td>5 (18.5)</td>
<td>5 (10.4)</td>
<td>3 (60.0)</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>AOR (95% CI)</td>
<td>1 [Reference]</td>
<td>3.1 (1.1-8.7)</td>
<td>2.5 (0.8-7.3)</td>
<td>1.5 (0.5-4.0)</td>
<td>19.8 (2.8-141.9)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AOR, adjusted odds ratio, adjusted for sex, race/ethnicity, marital status, socioeconomic status, and learning difficulty status; CI, confidence interval; GAD, generalized anxiety disorder; NA, data not available.

*P<.05.
associations have been largely nonsignificant or mixed depending on severity of asthma. Thus, the present results are consistent with previous observations that the link between respiratory disease and depression may be time specific and limited to concurrent conditions. For example, in a study of adults in Germany, only links between an episode of asthma in the past 4 weeks and affective disorders were statistically significant, while lifetime comorbidity of asthma and affective disorders or depression were not.51 The odds ratios for a link between severe asthma and lifetime major depressive disorder were virtually identical (AOR, 0.97; 95% CI, 0.59-1.62) to those found in the present study.23 In contrast, the association between GAD and lifetime severe asthma was among the strongest of all of the associations (AOR, 5.51; 95% CI, 2.29-13.22) in that study, while the link between GAD and an episode of asthma in the past 4 weeks, either severe or nonsevere, was not significant. Thus, our findings are not inconsistent with the possibility that the timing of anxiety and depression plays a role in the link with respiratory disease.

Limitations of this study should be noted. First, the number of mental disorders assessed in adulthood was limited; thus, we could not evaluate the relation between childhood respiratory problems and the entire range of anxiety and mood disorders in adulthood. Second, although our findings are from a community-based sample, the degree to which they are generalizable may be limited as the original sample was drawn from a single city and individuals with lower SES were overrepresented. However, in the United States, asthma and other respiratory diseases are substantially more common in children of lower SES; therefore, these findings may be useful to those most likely to experience the issues we are investigating. Third, it is conceivable that there was misdiagnosis or misclassification of respiratory disease during childhood. Thus, replication of these results is needed. Fourth, the present study sample included a large percentage of subjects with and without childhood learning difficulties. This is unlikely to affect either the study findings or the generalizability of this work because childhood learning difficulties were adjusted for in all analyses and the results were unchanged when we repeated analyses for participants without learning difficulties. Fifth, respiratory diseases (eg, pneumonia, bronchiolitis, and croup) were grouped together owing to small sample size of each individual disease; however, this is not ideal owing to varied etiologies. Replication of these analyses in future studies with larger samples is recommended.

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Author Contributions: Dr Goodwin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goodwin and Buka. Acquisition of data: Buka. Analysis and interpretation of data: Goodwin. Drafting of the manuscript: Goodwin. Critical revision of the manuscript for important intellectual content: Buka. Statistical analysis: Buka. Obtained funding: Goodwin and Buka.

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REFERENCES


