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Title

Causal links between RSV infection and asthma – no clear answers to an old question

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“We have shown strong evidence for a causal relationship of winter viruses with early childhood asthma” – concluded Wu in a recent issue of this Journal. (1) “RSV infection does not cause asthma but is an indicator of the genetic predisposition to asthma” counter Thomsen and colleagues in this issue. (2) The two papers follow up on a discussion that has been going on for decades. It is undisputed that infants hospitalized with a lower respiratory tract infection caused by respiratory syncytial virus (RSV) more often report subsequent childhood wheeze. What remains unclear is the direction of causation: does RSV infection confer a long-term change in the host which increases the risk of subsequent asthma? Or is a hospitalization with RSV bronchiolitis simply an early marker of an underlying predisposition for reversible airway disease (i.e. asthma)?

What do the two new papers contribute to this debate? Wu and colleagues, analyzing data from 95,000 infants from a state-based health-care program in Tennessee, found that children aged four months at the winter virus peak had an increased risk of bronchiolitis in infancy and of asthma during childhood. (1) These results add convincing evidence to another old dispute – whether there is an association between season of birth and risk of asthma (3, 4) - but contribute little to clarify causation. The smoothed curves suggesting that children born in September bear the highest risk of later asthma could be explained, as the authors suggest, by the timing of birth 4 months prior to the winter virus peak. Other explanations include birth 8 months prior to the pollen peak, or some critically timed exposure during fetal life, (5) in short, any seasonally varying exposure. Although the authors point out that that the curves shifted with changing virus peaks from year to year, a statistical test supporting this statement, e.g. comparing the infants' age at the winter virus peak to their age at a fixed calendar date, is missing. Moreover, in the 20% of children who had had clinical bronchiolitis, risk of asthma was not predicted by the age they were ill, but by their age when the national virus peak occurred. This is surprising. If we hypothesize that RSV bronchiolitis confers developmental damage, this should happen when the child itself is ill, but not when other children are ill. Finally, the parallel trend in hospitalizations for bronchiolitis and asthma in the US is prone to ecological fallacy and provides no evidence for an association between the RSV and asthma at the individual level, much less for causality.

The current paper by Thomsen and colleagues makes a more convincing attempt to detect causality in the RSV-asthma association. (2) Using a large dataset of 8,280 twin pairs in Denmark, they fitted genetic variance components and direction of causation models to their data. This method draws on cross-trait cross-twin correlations to resolve both the genetic relatedness and the direction of causation between two traits, in this case RSV hospitalization and asthma. (6, 7) The authors found that the association between RSV and asthma was essentially due to genetic effects shared between these traits. Furthermore, a model in which RSV hospitalization causes asthma could be rejected by statistical testing, while one in which
asthma causes RSV could not. These twin data thus quite clearly contradict the hypothesis of a causal effect of RSV on asthma, suggesting that the observed association is due to shared genetic predisposition.

Both papers suffer from poor phenotype definitions for RSV infections and for asthma, which makes the findings hard to interpret. An RSV infection was simply defined as discharge diagnosis with verified RSV infection. While 70% of infants have experienced an RSV infection by age one year, and 100% by age two, the host response to the virus varies greatly, including upper respiratory tract infections, typical bronchiolitis (with crepitations but no wheeze), or RSV-induced wheezy bronchitis. It has been suggested that RSV-associated wheezy bronchitis, but not typical bronchiolitis might be associated with subsequent atopy and asthma. (8, 9) On the other hand, infections by other viruses, particularly rhinoviruses, are followed by recurrent wheeze, (10) suggesting that the host response, rather than the type of virus, predicts later outcome.

Asthma phenotype was poorly defined in both studies. There is much evidence suggesting that there are several phenotypes of early childhood wheezing disease. (11, 12) Using the old umbrella term “asthma” which ignores this heterogeneity may be misleading, particularly when investigating pathways and causation. In the Danish paper, asthma was defined as a discharge diagnosis of asthma at any time, or a parent report of “asthma ever in life” collected at age 3-5 years. Another recently published manuscript from the Danish group, which analyzed causality by applying a different statistical approach (time to event analysis) to the same twin dataset, reveals that a large proportion of these “asthma” hospitalizations occurred in one year olds and that the relative risk of “asthma” falls to unity one year after RSV infection. (13) This suggests that most children with so-called “asthma” might have had recurrent viral wheeze, a largely self-limiting disorder of which RSV lower airway disease may simply be one manifestation. Indeed the Danish studies provide further indirect evidence in support of the contention that there are several phenotypes of early childhood wheezing disease. Cohort studies assessing asthma outcomes at different ages have in fact suggested that the association between RSV infections and later wheeze wanes with time, and that there is no association with atopy (14) (15).

To summarize, we think these new data are more in favor of the hypothesis that the association between RSV and asthma is due to shared predisposition rather than to a causal effect of RSV. However, clearer phenotype definitions both of early childhood viral disease (“bronchiolitis”) and of subsequent recurrent wheezing disorders (“asthma”) are absolute requisites for making any further progress in discovering the pathways leading to childhood asthma. Without specifying what disorders we are dealing with, this type of epidemiological or genetic research will remain inconclusive.
References


