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Attention-Deficit/Hyperactivity Disorder and Comorbid Asthma Response

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with two-way fixed-effects estimation in R (R Foundation). Our Poisson model suggests that for every 1-log unit increase in the number of hospital discharges with an all-listed diagnosis of ADHD (a severely impaired phenotype), there is a 15% increased risk of hospitalization for an all-listed diagnosis of asthma (CCS [Clinical Classifications Software] 128) (incidence rate ratio, 1.15; 95% CI, 1.11-1.20; $P < .01$; $N = 216$). A 1-unit log increase in the annual statewide anthropogenic nitrogen use in agriculture, however, is associated with significantly reduced risk of hospitalization for all-listed asthma diagnosis (data not shown). These epidemiologic results suggest that a severe ADHD phenotype may be comorbid with autoimmune conditions, like asthma, but the association may exist on a continuum of chronic environmental exposure to trace levels of N_2O pollution.

Further analysis shows that a 1-year lag in ADHD hospitalization significantly increases risk of an all-listed asthma hospitalization (incidence rate ratio, 1.13; 95% CI, 1.09-1.17; $P < .001$; $N = 467$). Although van der Schans et al¹ indicated that the association may be direction-specific insofar as a history of asthma precedes use of ADHD medications, our ecologic results indicate the relationship could be bidirectional; confirmation with data using an individual unit of analysis is recommended. This is an important point to address considering the treatment gaps or delays that plague patients with adult ADHD. Therefore, we propose that our previously identified environmental factor in ADHD etiopathogenesis, N_2O , inhibits glutamatergic and $\alpha 7$ cholinergic signaling, inducing working memory deficits, while concomitantly remodeling bronchopulmonary architecture and increasing airway hyperactivity.⁵

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Response

To the Editor:

We appreciate the interest and additional research of Dr Fluegge and associate on our commentary regarding the association between attention-deficit/hyperactivity disorder (ADHD) and asthma in adults.¹ We agree with the authors that exposure to anthropogenic nitrogen and concomitant emission of nitrous oxide (N_2O) may mediate the association between ADHD and asthma. A bidirectional relationship between ADHD and asthma, which in part could be mediated by N_2O or other environmental factors, would be consistent with the notion of onset of ADHD in adults.² The increasing trend of drug treatment for ADHD in adults³ adds to the need to clarify the etiologic mechanism behind the asthma-ADHD association.

Since both ADHD and asthma mostly have an early onset, our main focus in earlier research was on the association between medical treatment for ADHD and atopic diseases in childhood.⁴ In this younger population a more or less artificial one-way direction of the association between both diseases exists, owing to the common restriction of making a diagnosis of ADHD before the age of 6 years. However, we agree with Drs Fluegge and Fluegge that the underlying disorder could be more bidirectionally associated with atopic diseases than would be expected based on the results of previous pharmacoepidemiologic research in children. One study showed a possible direct link between ADHD and atopic diseases by demonstrating a synergistic effect of treatment on the outcomes of both diseases.⁵ To further evaluate the direct link between ADHD and atopic diseases we are currently performing a time-series analysis to address the possible causal pathway between ADHD and atopic diseases. The objective of this study is to determine the temporal order of the co-occurring association between symptoms of atopic disease and ADHD on an individual patient level. Preliminary results provide additional evidence that the symptom expression of ADHD and atopic diseases are

interrelated. The preliminary results show that the direction of the association between symptoms of ADHD and atopic diseases is heterogeneous. It is thus plausible that multiple pathophysiologic mechanisms are underlying the comorbidity between ADHD.

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Pulmonary Rehabilitation, Exercise, and Exacerbations of COPD

Known Clinical Efficacy and the Unknown Mechanisms

To the Editor:

In a previous issue of *CHEST* (December 2017), Moore et al¹ published a large-scale cohort study of

electronic health records reporting COPD patients referred for (but who did not necessarily complete) pulmonary rehabilitation did not experience fewer general practitioner visits and hospitalizations compared with those not referred.¹ Conversely, the latest findings from a UK (National) COPD Pulmonary Rehabilitation Audit highlighted that completion of pulmonary rehabilitation is associated with reduced risk of hospitalization and time spent in hospital.² Reductions in hospital admissions and bed days were larger in those attending more sessions and/or receiving longer programs. Subsequently, we have published a meta-analysis of randomized controlled trials suggesting that the addition of supervised maintenance exercise programs following pulmonary rehabilitation decreases the risk of hospital admissions (respiratory cause) and exacerbations requiring treatment.³ Taken together, the available evidence raises the important role that exercise independently, or within pulmonary rehabilitation, can play in reducing health care use. The underlying mechanisms of action, however, remain poorly understood.

An editorial published in response to Moore et al¹ suggested that pulmonary rehabilitation (exercise) does not plausibly affect the frequency of inflammatory and infectious events but leads to reduced severity or better management of exacerbations via changes in dyspnea, physical conditioning, and enhanced disease knowledge.⁴ Although we agree that these mechanisms may be partly responsible, the additional impact of supervised maintenance exercise programs following pulmonary rehabilitation is suggestive of other unexplored mechanisms on health care use outcome data collected in the postrehabilitation period.

The evidence demonstrating the immune-regulatory and anti-inflammatory effects of regular exercise as part of short- and/or long-term training programs in older populations and those living with long-term conditions are well established.⁵ Although studies in COPD are lacking, absence of evidence is not evidence of absence. We currently have limited insight to confidently deny any plausible impact of exercise-based interventions, including pulmonary rehabilitation on the frequency of inflammatory and infectious events. Research is required using surrogate markers associated with exacerbation frequency or representing clinically relevant measures of immune function.

Although the primary purpose of pulmonary rehabilitation may not be to affect health care use,²