The Childhood of Adult-Onset Asthma and the Asthma/Chronic Obstructive Pulmonary Disease Overlap

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ABSTRACT

Adult asthma is a heterogeneous condition and, in a significant proportion of patients, the disease first manifests during childhood. Recent evidence suggests, however, that even in bona fide adult-onset asthma, the roots of the disease may be found in early life. In longitudinal studies, patients with adult-onset asthma were more likely to have early life wheezing and bronchial hyperresponsiveness at age six than subjects without asthma. Adult-onset asthma has also been consistently associated with preceding reports of both atopic and non-atopic rhinitis, suggesting that an alteration in mucosal/innate immunity may be common to both conditions. Of particular interest are the potential early origins of the asthma/chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS). Many patients with childhood-onset asthma reach the plateau phase of lung function with significant airflow limitation and are thus likely to eventually reach the levels of forced expiratory volume in 1 second and forced expiratory volume in 1 second/forced vital capacity ratio that codify the diagnosis of COPD, even after normal rates of age-related lung function decline. Active smoking has been shown to have synergistic effects with both a history of childhood asthma and with a history of lower respiratory illnesses due to the respiratory syncytial virus in determining increased airway narrowing and a diagnosis of asthma in early adult life. Asthma diagnosis, in this case, could potentially be a surrogate for the first clinical manifestations of chronic obstructive pulmonary disease. It is thus plausible to surmise that strategies for the
The prevention of ACOS will need to reach back to active avoidance of risk factors that may predispose for this condition during the growing years. Among these strategies, development of a vaccine against respiratory syncytial virus, decreased exposure to air pollution, and smoking cessation targeted to adolescents and young adults with asthma should be major priorities. (BRN Rev. 2016;2:159-169)

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**INTRODUCTION**

Although most cases of asthma begin in childhood, there is now clear evidence that the disease first manifests in adult life in a significant proportion of patients. Moreover, significant attention has been paid lately to patients who have airflow limitation and a diagnosis of chronic obstructive pulmonary disease (COPD), but who also appear to have many shared characteristics with asthma, including sputum or peripheral eosinophilia, partial reversibility of airway obstruction, and clinically significant response to inhaled corticosteroids. Several reviews have recently addressed the potential role of early life factors in the development of COPD, but there has been no systematic assessment of the potential childhood roots of adult-onset asthma and the so-called asthma/COPD overlap syndrome (ACOS). This is an important challenge, because there are currently no strategies for the primary prevention of these two conditions as compared with childhood asthma, for which promising new approaches are emerging and are being actively pursued.

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**OBSTACLES FOR THE STUDY OF THE NATURAL HISTORY OF ADULT-ONSET ASTHMA**

A major barrier to the understanding of the lifetime risk factors for adult-onset asthma is the paucity of longitudinal studies of respiratory disease that extend from infancy all the way into adult life. Such studies are very expensive, are usually subjects to attrition and losses to follow-up, and often face major organizational challenges that lead to early termination and disbandment. As a result, most studies of adult-onset asthma are based on samples recruited in adult life, with information about the natural history of the disease based on questionnaires. Shaaban, et al., for example, reported that 8.8-year incident asthma among 20-44-year-old subjects “without asthma at baseline” was three times higher in subjects with non-atopic rhinitis and four times higher in subjects with atopic rhinitis than in subjects without rhinitis. This study thus strongly suggested that rhinitis, with or without skin test positivity to allergens, is a risk factor for the subsequent development of adult-onset asthma. However, retrospective assessment is subject to recall bias and thus
determination of age of onset in adult patients may be highly inaccurate, especially regarding potential symptoms occurring in early life. In the Tasmanian Longitudinal Health Study, for example, 32% of all 46-year-olds who had asthma at any time after age 7 (as ascertained prospectively) denied ever having had the disease. Had their asthma subsequently relapsed, they would have been erroneously classified as cases of adult-onset asthma. The most reliable data, therefore, come from the few longitudinal studies with follow-up from birth.

**RESULTS OF LONGITUDINAL STUDIES OF ADULT-ONSET ASTHMA**

The first comprehensive longitudinal study of childhood risk factors for adult-onset asthma was published by Strachan, et al. in 1996. They used data from the British National Child Development Study (also called 1958 cohort), which followed all persons born in England, Scotland, and Wales during one week in March 1958. They defined “adult-onset wheezing” to be present in subjects without a history of asthma or wheezy bronchitis at previous follow-ups at ages 7, 11, and 16 years who reported having ever had asthma or wheezing, or both, at age 33. Almost 25% of participants reported incident wheezing between ages 17 and 33. Factors independently and strongly associated with adult-onset wheezing were active smoking and “hay fever” reported at any previous follow-up. A limitation of this study was that no objective assessment was made of atopic status (e.g. by skin testing) and a report of hay fever or eczema was equated with “allergies”. Analysing data from the Tasmanian study mentioned earlier, Burgess, et al. reported the association between parental reports of “allergic rhinitis” starting at different ages at or after age 7 years and incident asthma between 20 and 44 years. As in the previous study, no objective assessment of atopic status was available. Children who had allergic rhinitis by age 7 were seven times and four times more likely to have incident asthma at ages 8-12 and 13-20, respectively, but were also twice as likely to have adult-onset asthma by age 44.

A clear pattern emerges from these studies: children who have nasal symptoms without lower airway manifestations are more likely to have subsequent asthma, and this increased risk decreases with age but extends up to adult life. One possible interpretation of these findings is that the allergic process purportedly inducing nasal symptoms initially is causally associated with the extension of these symptoms to the lower airways. Unfortunately, it is not possible to determine the role of childhood atopy from the available longitudinal studies because none of them performed skin tests or assays for specific serum immunoglobulin E (IgE) levels.

Evidence against the proposal that atopic status is the link between rhinitis and the subsequent development of adult-onset asthma was provided by Guerra, et al. These authors assessed the association between rhinitis and subsequent incident asthma at a mean age of approximately 50 years in a case control study nested into the Tucson Epidemiologic Study of Obstructive Airway Disease. In agreement with Shaaban, et al., they found that rhinitis increased the risk of development of asthma by about three times both among atopic and non-atopic patients, as assessed by skin prick
test. There was also a “dose-response” effect, with subjects with more severe and persistent rhinitis having the highest likelihood of subsequent incident asthma. Although this study did not specifically assess the association between childhood rhinitis and adult-onset asthma, longitudinal studies starting in childhood have shown that complete remission of rhinitis from four years up to early adult life is rare\textsuperscript{10}, suggesting that it may be a persistent condition with roots in early life.

If the association between rhinitis and subsequent asthma is independent of atopy, processes not mediated by IgE responses may be at play. Neural nasal-bronchial reflex inducing bronchoconstriction or increasing bronchial responsiveness has been invoked as a possible mechanism\textsuperscript{11}. Postnasal drip of inflammatory cells and mediators and their absorption from the nasal mucosa into the systemic circulation may also influence airway tone\textsuperscript{12}. Much more likely, however, is the existence of a common mucosal, innate immune derangement affecting subjects with rhinitis and asthma\textsuperscript{13}, and this derangement is expressed clinically in both the upper and lower airway in subjects who have additional risk factors for the development of asthma.

**ROLE OF CHILDHOOD LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS IN ADULT-ONSET ASTHMA**

Strong indirect support for this hypothesis was provided by an analysis of early life risk factors for adult-onset asthma as part of the Tucson Children’s Respiratory Study\textsuperscript{1}. Among subjects with no reports of asthma up to age 16, 5.8% (49/845) developed new asthma by age 22, and 35/49 (71%) were females. Major independent risk factors for adult-onset asthma were low lung function and cold-air bronchial hyperresponsiveness at age 6, parental asthma, and late-onset and persistent wheezing before age 6. Adult-onset asthma was not associated with either eczema by age 2 or skin test reactivity at age 6. Previously, Wright, et al.\textsuperscript{14} had shown that, in this same cohort, allergic rhinitis at age 6 was associated with subsequent development of asthma during childhood, and this association was independent of skin test reactivity. Subsequent analyses showed that the association between rhinitis at age 6 and incident asthma persisted up to adult life (unpublished observations).

Taken together, these results suggest that a putative, common mucosal alteration unrelated to atopy underlies the adult-onset asthma/rhinitis connection, and that a second, lower-airway specific derangement is needed for the clinical expression of asthma in subjects with a previous history of rhinitis. What this common mucosal alteration may be is still undetermined, but it is of interest that adult-onset asthma is also related to wheezing during the preschool years, as summarized earlier. Since most wheezing and rhinitis in that age group is caused by viral infection\textsuperscript{15}, it is tempting to speculate that the derangement consists of inappropriate innate immune responses to viral and possibly bacterial infection, starting in early life. Detailed discussions of the molecular mechanisms that may cause such inappropriate responses go beyond the scope of this paper and have been addressed elsewhere\textsuperscript{13,16}. Briefly, alterations in type I interferon responses have been reported in both subjects with asthma\textsuperscript{17} and in those with rhinitis\textsuperscript{18}. In
addition, type-2 innate lymphoid cells are part of a family of innate lymphocytes that have been implicated in the pathogenesis of asthma, rhinitis, and atopic dermatitis\textsuperscript{13}. These cells provide a potent source of immune effector cytokines at the initiation of immune responses, and they could be a potential common link between these three conditions.

**THE CONUNDRUM OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP SYNDROME (ACOS)**

The above assessment of childhood risk factors for adult-onset asthma cogently sets the stage for a discussion of the potential early origins of ACOS. Although the fact that there may be overlap between asthma and COPD has been known for some time and is at the roots of the so-called Dutch hypothesis of COPD\textsuperscript{19}, the fact that there could be a specific group of patients in whom asthma and COPD coexist has only become part of consensus guidelines in the last few years. The exact definition of this “syndrome” is still under debate, and two major recent reviews suggested that ACOS should not be designated “as a disease entity in primary and specialist care”\textsuperscript{20} and “be abandoned as a specific phenotype in favour of a multidimensional assessment and management of complex obstructive airway diseases”\textsuperscript{21}. There is also confusion as to how to classify never-smoking patients with asthma and airflow limitation levels compatible with the Global Initiative for Chronic Obstructive Lung Disease (GOLD)-based definition of COPD. Some authors believe that these patients cannot be classified as having either ACOS or COPD\textsuperscript{22} because such diagnoses have to be limited to smokers (or those exposed to biomass fuel). Nevertheless, as outlined by the joint document between the Global initiative for Asthma (GINA) and GOLD\textsuperscript{23}, it is evident that many patients with airflow limitation have features that are common in asthma and, concomitantly, features that are common in COPD. Most of the discussion about ACOS is centred on the potential for there to be specific therapeutic strategies for this still insufficiently defined condition. Gibson and McDonald\textsuperscript{21}, however, have added a new dimension to this discussion by suggesting that ACOS may have its origins, at least in part, during childhood. They identified three possible expressions of the heterogeneity of ACOS: severe asthma with incomplete airflow reversibility; childhood asthma among adult smokers; and eosinophilic COPD. I will further explore the potential early life risk factors involved in the first two of these three situations.

**CHILDHOOD ASTHMA AMONG ADULT SMOKERS**

There is now unequivocal evidence indicating that childhood asthma is associated with the development of statistically and clinically significant airflow limitation. One of the largest and most thoroughly phenotyped cohorts of children with mild-to-moderate asthma followed prospectively was the Childhood Asthma Management Program (CAMP)\textsuperscript{24} in the USA. Lung function measured repeatedly between ages 6-18 for a total of 1,041 children enrolled in CAMP was compared with that of 5,415 children without asthma from the Harvard Six Cities Study (as a control group). For both genders, the forced expiratory volume in 1 second/forced vital capacity (FEV\textsubscript{1}/FVC) ratio was...
significantly lower in CAMP than in controls, and the deficits were already present, to a large extent, at age 5, but tended to increase slightly with age thereafter (Fig. 1). As a result, children with asthma attained a lower plateau of lung function: mean FEV$_1$/FVC ratio at age 18 years was 10% lower in males and females with asthma than in controls (76.5 versus 86.3% in males, 79.4 versus 89.5% in females, respectively). These deficits in lung function are similar to those reported by others$^{25}$. It is plausible to surmise that the effects of active smoking on airway structure and function could be more severe in adults with a history of childhood asthma than in those without such a history. Results from the Busselton longitudinal study in Western Australia suggested that this may indeed be the case$^{26}$. Adults with (n = 713) and without (n = 4,058) asthma or without asthma with a mean age of approximately 40 years were followed for more than 20 years and lung function measured up to seven times during that time interval. Smokers with asthma had the steepest decline in lung function during follow-up (Fig. 2): both males and females who were heavy smokers and had asthma at the beginning of follow-up showed a 3.7 ml/year larger decline in FEV$_1$ than heavy smokers without asthma. Age at onset of asthma was not assessed in this study. Diaz, et al.$^{27}$ compared lung function and airway size by CT scan in 590 smokers with a history of childhood asthma (mean age and pack years of smoking 57 and 37, respectively) with smokers without childhood-onset asthma (60 years and 40 pack years, respectively). Smokers with childhood-onset asthma had 6% lower FEV$_1$/FVC ratio and 9% lower FEV$_1$ percentage predicted than smokers without a history of childhood-onset asthma. As a result, 61% of the former and 47% of the latter had evidence of airflow limitation.
Apparently opposite to this conclusion, however, are the results of a recent study using data from the Dunedin longitudinal study\textsuperscript{28}. The authors assessed the effects of smoking and asthma on the development of airflow obstruction in a population followed from ages 9 to 38. Using data from childhood and adult questionnaires, they identified participants with childhood-onset persistent asthma (n = 91), adult-onset asthma (n = 93), asthma in remission (n = 85), and non-asthmatics (n = 572). Cumulative smoking history and childhood-onset persistent asthma were both associated with lower FEV\textsubscript{1}/FVC ratios, but associations between smoking and FEV\textsubscript{1}/FVC ratios differed between asthma subgroups (interaction p < 0.001). Smoking was associated with lower pre- and post-bronchodilator FEV\textsubscript{1}/FVC ratios among non-asthmatics and those with late-onset or remitted asthma, but smoking was not associated with lower FEV\textsubscript{1}/FVC ratios among those with childhood-onset persistent asthma. If these results should be interpreted as meaning that childhood-onset persistent asthma somehow “protects” against the ill effects of smoking remains speculative. It is also possible that subjects with childhood asthma may be more likely to quit or never start smoking. In the European Community Respiratory Health Survey, a recalled history of maternal asthma, paternal asthma, childhood asthma, maternal smoking, and childhood respiratory infections were significantly associated with lower FEV\textsubscript{1} and larger FEV\textsubscript{1} decline at ages.
20-45 years\textsuperscript{29}. Finally, the data from the Bus- selton study (Fig. 2) suggest that the increased airflow obstruction present in patients with asthma at the start of follow-up is more clearly observed after age 40.

Of interest is the potential role of early life wheezy lower respiratory illnesses (WLRI), especially those due to the respiratory syncytial virus (RSV), as risk factors for childhood asthma and potentially COPD. It has been well established for decades that infants who have RSV-WLRI are more likely to subsequently wheeze during the school years as compared with children without RSV-WLRI, but also that this increased risk wanes with age\textsuperscript{30}. More recently, studies that followed children with a history of severe RSV-WLRI into adult life observed a relapse of asthma-like symptoms during the third decade of life in these subjects\textsuperscript{31} (Fig. 3). Until recently, the explanation for this rebound in risk associated with RSV-WLRI in early life was elusive. Using data from the Tucson Children’s Respiratory Study, Voraphani, et al.\textsuperscript{32} reported that neither smoking nor RSV-WLRI were separately associated with asthma during the third decade of life. However, adults who had a history of RSV-WLRI as infants and smoked were 1.6 times more likely to have asthma and more likely to have increased daily variability of peak flow than those with the same history who did not smoke. No association between smoking and either asthma or peak flow variability was found among subjects without a history of RSV-WLRI. These results thus suggest that subjects who had a history of RSV-WLRI may have increased susceptibility to the ill effects of smoking, and the first manifestations of this increased susceptibility are often called “asthma” by practitioners among such subjects. This interaction between early life RSV-related events and smoking may thus be a major determinant of the ACOS overlap described among active smokers.

The mechanisms through which RSV-WLRI could enhance the deleterious effects of cigarette smoking are only partially understood. In some studies, RSV has been detected just as frequently in stable COPD patients as in those suffering disease exacerbations, leading to the suggestion that RSV may persist in COPD\textsuperscript{33}. If subjects with a history of RSV-WLRI in early life may harbour RSV chronically is an intriguing and still controversial hypothesis\textsuperscript{34}. Animal models have shown that RSV infection enhances the influx of macrophages, neutrophils, and lymphocytes to the airways of cigarette smoke-exposed mice\textsuperscript{35}. Cigarette smoke also accentuated airspace enlargement and fibrosis caused by RSV in mice. Combined stimulation with both smoke and
RSV synergistically induced cytokine (interleukin [IL]-1α, IL-17, interferon-γ, KC, equivalent to IL-8, IL-13, chemokine [C-X-C motif] ligand 9, RANTES, migration inhibitory factor, and granulocyte-macrophage colony-stimulating factor) and protease expression. In addition, RSV exposure caused marked apoptosis within the airways of infected mice, which was augmented by cigarette smoke exposure. It is tempting to speculate that if RSV persists more frequently in subjects with a history of RSV-WLRI than in those without such a history, reactivated RSV may enhance the deleterious effects of cigarette smoke.

**SEVERE ASTHMA WITH INCOMPLETE AIRFLOW REVERSIBILITY**

Postma and Rabe have suggested that asthma and COPD cannot be considered as entirely separable entities, but more as a spectrum of conditions associated with, at the one extreme, intermittent and fully reversible airflow obstruction and at the other, patients with irreversible airway obstruction and chronic respiratory failure. Which subjects are at a given point in this spectrum depends on the constellation of risk factors (genetic, environmental, and developmental) that have influenced their lifelong course. Within this framework, severe asthma associated with incomplete airway reversibility is indeed placed somewhere in a central position and could justifiably be considered a subform of ACOS, as suggested by Gibson, et al.

In the Dunedin study, both subjects with asthma who had persistent symptoms from age 9 into adult life and those whose asthma remitted during adolescence but relapsed in adult life had significant airflow limitation from age 9 up to adult life. Recently, Tagiyeva, et al. reported on the long-term outcome of children who had asthma during the school years, a large proportion of whom still had asthma in adult life. These children had a sixfold increased risk of having COPD at age 60-65 as compared with those without childhood asthma. In the Tasmanian study, subjects with childhood-onset asthma had fixed airflow obstruction in adult life that was equivalent to a 33 pack-year history of smoking. In the Melbourne longitudinal study, 41% of children who had severe asthma at age 10 had asthma at age 50, and 44% had COPD at that same age.

In the Tucson Children’s Study, we found that the level of post-bronchodilator FEV1/FVC ratio subjects with asthma at age 22 was strongly and linearly related to age of onset of the disease, both in patients whose asthma persisted from childhood into adult life and in those whose asthma remitted during adolescence. As a result, the lowest levels of lung function among patients with current asthma were observed among those who were first diagnosed before age 6. Interestingly, as explained earlier, we found that subjects with newly diagnosed asthma in adult life also had significant airflow limitation as a group, but that airflow limitation and bronchial hyperresponsiveness were already observed by age 6 in these subjects, over a decade before their asthma symptoms justified being diagnosed with the disease.

The association between asthma and airflow limitation, as suggested by these studies, may have its origins, at least partially, in early life and this has important implications for long-term survival. Prospective studies...
have shown that among adult subjects who had asthma at the onset of follow-up, those with airflow limitation had the highest risk of subsequent 30-year mortality, after adjusting for cigarette smoking40.

**CONCLUSIONS AND FUTURE STUDIES: PREVENTING ADULT ASTHMA AND ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP SYNDROME IN CHILDHOOD**

There is mounting evidence indicating that adult onset asthma and ACOS have their origins, at least in part, during the first two decades of life. “Childhood disadvantage factors”29 such as impaired lung function and bronchial responsiveness in early life, early onset of upper airway inflammation, severe childhood asthma, and lower respiratory tract illnesses predispose for both the persistence of asthma symptoms and for the development of ACOS and new cases of asthma in adult life. Future studies ought to explore the cogent hypothesis that fostering lung health during childhood may be critical for the prevention of ACOS and adult-onset asthma. Three areas in which prevention strategies seem feasible are air pollution, smoking, and prevention of WLRI caused by RSV. Subjects exposed to higher levels of fine particulate matter (PM$_{2.5}$) and ozone had nearly three-fold greater odds of developing ACOS than those not exposed41. Recent improvements in air pollution in the Los Angeles area have been associated with significant reversion of the lung function impairment associated with particulate matter exposure in children42,43. Smoking cessation strategies particularly targeted to young adults with a history of childhood asthma could prevent the increased decline in lung function observed in smokers with such a history. Finally, major advances have been recently made in the development of vaccines against RSV44, and studies are needed to determine if such vaccines could prevent at least in part the deficits in lung function growth observed in young patients with RSV-WLRI.

**DECLARATION OF INTEREST**

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**REFERENCES**