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## Early identification of children likely to develop persistent asthma: atopy is an integral component of the high risk phenotype

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### Summary

There is a growing consensus that the long term solution to the asthma epidemic lies in prevention and not in treatment of established disease. Atopic asthma arises from gene  $\times$  environment interactions which most commonly occur during a relatively narrow window period in pre- and postnatal development. These interactions are incompletely understood, and hence the holy grail of primary prevention remains an elusive goal. We contend that a lack of understanding of the role of atopy in early life in the development of persistent asthma in children exists amongst primary care physicians, paediatricians and specialists. In this review we argue that early identification of high risk children is feasible based on currently available technology, and worthwhile in relation to potential benefits to the children so identified. Knowledge of an asthmatic child's atopic status in early life has practical clinical and prognostic implications, as well as forming the basis for future preventative strategies.

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#### Author's contributions:

The idea for this review came from Pat Holt and Peter Sly and they wrote the first draft. They then invited a group of peers to join with them and assimilated their comments into the final version. Authors were invited based on their contribution to the literature in this area, especially in relation to major prospective birth cohort studies.

#### Conflict of Interest statement

No commercial entity was involved in the development or production of this article. The undersigned authors declare that they have no commercial relationship with any entity that could benefit from publication of this article and have no actual or perceived conflict.

## Introduction

There is a growing consensus that the long term solution to the asthma epidemic lies in prevention and not in the development of increasingly more sophisticated anti-inflammatory drugs for treatment of established disease<sup>1</sup>. International research over the last 20 years has tracked the roots of the most common form of this disease, atopic asthma, to *gene x environment* interactions which most commonly occur during a relatively narrow window period in pre- and postnatal development<sup>1</sup>. These interactions are incompletely understood, and hence the holy grail of primary prevention remains an elusive goal. However the progress that has been achieved in this area is sufficient to justify a more structured approach to early identification of high risk children. Current treatment strategies do not alter the long term outlook for children with asthma despite controlling symptoms and improving quality of life<sup>2</sup>, implying that a different approach is necessary. We argue below that early identification of high risk children is feasible based on currently available technology, and worthwhile in relation to potential benefits to the children so identified.

### **Asthma related phenotypes in childhood: insights into the role of atopy from prospective birth cohort studies**

A number of epidemiologically distinct wheezing phenotypes have been recognised in childhood<sup>3</sup>, the most common being: *transient infantile wheeze*, where children have recurrent wheeze during the first two to three years of life but rarely afterwards; *viral-associated wheeze*, where children typically have episodic wheeze associated with respiratory viral infections and may not wheeze at other times; and *atopic asthma*, where children have wheeze associated with sensitization to aeroallergens and frequently have features of other atopic diseases such as dermatitis and rhino-conjunctivitis. While all of these wheezing phenotypes add to the burden of disease imposed on families and the community, asthma that persists throughout childhood and into adulthood imposes the greatest burden and, as such, is the major target for prevention programs. In this review, the term “persistent asthma” will be used to describe asthma that persists from early childhood into adult life and is not a description of symptoms as for staging asthma in clinical guidelines. The association between asthma and sensitization to aeroallergens continues through adolescence into the teen years<sup>4-11</sup> and in many cases into early adulthood<sup>12</sup>, at least in the developed world<sup>13</sup>.

Physiologically, the presence of wheeze implies expiratory flow limitation but the symptom does not give any clue about the underlying cause. Any insult that decreases airway calibre or alters airway wall compliance can potentially result in wheeze. Wheezing is more common in the first years of life in boys<sup>4</sup>. One potential mechanism underlying this gender imbalance is that boys are thought to have relatively smaller airways than girls when related to lung size<sup>14</sup>, however, direct proof of this is lacking. Wheeze with viral infections is common during childhood, especially during the first years of life. Viral lower respiratory infections (LRI) are likely to result in wheezing if they induce inflammation and oedema of the airway epithelium, resulting in a decrease in airway calibre. At least 20% of all children have one or more episodes of LRI with wheezing (wLRI) in the first year of life and up to 90% of these cases are associated with documented viral infections<sup>15</sup>. Thirty percent of

children enrolled in the Tucson Children's Respiratory Study had 1 wLRI in the first three years of life<sup>3</sup>. Cohort studies in different parts of the world have shown that such wLRI are most commonly caused by rhinoviruses (RV), respiratory syncytial virus (RSV), parainfluenza viruses, and to a lesser extent, adenoviruses, human metapneumo virus and influenza virus<sup>16-20</sup>.

The majority of children with viral-induced wheeze lose their symptoms in their early school years<sup>21,22</sup>. These children generally have normal spirometry and are more commonly nonatopic<sup>21</sup>. In contrast children who become sensitized to common aeroallergens are more likely to retain their symptoms and have lower lung function at school age<sup>3,10,16,21</sup>. In a cohort of children enrolled between the age of 7 and 17 years and re-evaluated 6 years later, subjects with either persistent or new atopy to house dust mites (HDM) had lower lung function compared to those who remained unsensitized. The loss in lung function was greater in those with persistent as opposed to new onset of atopy<sup>23</sup>. Furthermore, the loss of lung function reported in the first six years of life<sup>3</sup> continues in allergic asthmatics during adolescence<sup>24</sup>. Longitudinal follow up of birth cohorts in Europe, USA and Australia shows that early sensitization<sup>10,16,21,25,26</sup>, and more severe sensitization<sup>27</sup>, are risk factors for persistence of asthma. Interestingly, while transient sensitization conveys increased risk of wheezing<sup>10</sup> the risk for persistence of symptoms is more pronounced if sensitization itself is also persistent<sup>10,21,28</sup>. The enhanced asthma risk associated with early sensitization may be related to the fact that this is associated with more intensely Th2-polarised long-term memory responses<sup>29</sup>, and/or interactions with other risk factors during the early postnatal period (see below).

### **The role of the environment: a differential response to allergen and bacterial products**

A recent prospective cohort study assessed postnatal development of lung function in high risk children raised in normal UK household environments versus those subject to a strict environmental controls to reduce exposure to indoor allergens and airborne irritants<sup>30</sup>. While these measures did not improve sensitization rates (in fact the opposite result was seen), children living in the clean environment had better lung function at 3 years of age than children in the control group. Lung function was not different between the groups at 4 weeks of age, showing that this was a postnatal effect. These data raise the intriguing suggestion that the more “pro-inflammatory” conventional environment was associated with decreased lung growth. The potential significance of these findings is not known, however, studies (e.g.<sup>31,32</sup>) have demonstrated that low lung function in early life is an independent risk factor for persistent asthma. The precise mechanisms underlying these effects of early environmental control are incompletely understood, but the clear association between indoor allergen levels and frequency of wheezing episodes<sup>10,21,33</sup> and development of new sensitizations, persistent bronchial responsiveness, and doctor-diagnosed asthma<sup>34</sup> in sensitised subjects suggests that successful reduction of allergen exposure leading to reduced allergy-mediated airway inflammation, may be one factor.

Atopic sensitization also increases the susceptibility of the airways to non-allergenic but nevertheless pro-inflammatory components of house dust such as microbial lipopolysaccharide (LPS)<sup>35</sup>, and reduction of exposure to these in early life may also be a

contributing factor. Exposure to LPS prior to sensitization is associated with reduction in risk for sensitization<sup>36</sup>. Active exposure to immunogenic levels of aeroallergen seems to be a prerequisite for the development of normal immunological tolerance, which provides protection against *de novo* sensitization<sup>37</sup>. This implies that an understanding of the significance of exposure to these agents to asthma pathogenesis in individual children can only be gained in light of knowledge of their current atopic status. Similar conclusions can be drawn for the role of viral infections in early life as risk factors for asthma (detailed discussion below).

### **Respiratory viral infections: direct and atopy-dependent roles in asthma development**

The bulk of wheeze in the first few years of life is attributable to viral infection. Acute LRI, including bronchiolitis, resulting from RV and RSV, account for the majority of hospitalisations in children under 3 years of age<sup>20,38</sup>. The mechanism(s) underlying the wheeze-promoting effects of these infections are only partially understood, but they are associated with the spread of infections to the lower airways and subsequent intensification, presumably resulting in inflammatory damage to airway tissues. Animal studies support a role for neurogenic inflammation resulting from RSV infection<sup>39</sup>.

The contribution of individual inflammatory effector mechanisms to the host response to respiratory viruses is controversial, exemplified by the ongoing saga surrounding RSV. On the one hand, a prominent contribution from recruited neutrophils to the anti-RSV response in the airways of human infants has been reported<sup>40,41</sup>, but the role of these cells in viral clearance is unknown<sup>40</sup>. The presence of an underlying Th2 “signature” in the lung response to RSV in the form of local IgE production has also been reported<sup>42</sup>. This Th2 signature has become a repeating theme in much of the literature on RSV infection in children and in murine models, particularly in relation to the apparent link between Th2-dependent eosinophil responses and infection severity. Reports to this effect include the presence of eosinophil secretory products in airway secretions of infants during acute infection<sup>43-46</sup>, the presence of eosinophils in nasal secretions<sup>46</sup>, and accompanying changes in the activation status of eosinophils in the blood<sup>47,48</sup>. A consistent finding has been that circulating eosinophil numbers transiently drop during acute RSV infection<sup>48-51</sup>, which has been widely interpreted as indicating active migration to the site of infection. The possibility that such recruitment may be a normal part of the host anti-viral defence response in this age group<sup>50</sup> is indirectly supported by recent findings from a murine RSV model demonstrating a direct role for eosinophils in accelerating viral clearance via a TLR-7-dependent pathway<sup>52</sup>. In this context cytokine receptor expression on blood borne eosinophil precursors in infants differs markedly from the IL-5-dominant pattern characteristic of older age groups, and is dominated by receptors for the ubiquitous cytokines IL-3 and GM-CSF<sup>53</sup> which are “first line” cytokines produced early in most classes of cellular immune responses including those against pathogens. This may contribute to the increased prominence of eosinophils in inflammatory exudates in general in early life<sup>53,54</sup>.

Severe viral bronchiolitis is more frequent in infants with elevated IgE<sup>46,55</sup> suggesting that predisposition to both states may involve common genetic or epigenetic mechanisms<sup>1</sup>. These factors may act in concert with others involving innate mechanisms (such as type III

IFN production) more specifically related to host anti-viral defense<sup>56</sup>. Severe asthma exacerbations in older children are commonly associated with respiratory viral infections and the susceptible subgroup is again dominated by those sensitised to aeroallergens<sup>20,57-60</sup>. These and other findings suggest that inflammatory pathways triggered by viral infections and inhalant allergy can function independently or in combination to drive asthma symptomatology in subjects with established disease<sup>1,20</sup>.

The results of a series of prospective cohort studies that have tracked large groups of children over varying periods indicate that the effects of these pathways are not restricted to asthma exacerbations but may also be central to disease aetiology. The bulk of the early studies in this area<sup>5</sup> focused primarily on the role of atopy in isolation whereas more recent prospective birth cohort studies have examined the role of atopy and viral infections in asthma aetiology in parallel<sup>3,9,10,16,21,22,61</sup>. Collectively, these findings are consistent with a “two hit” model for asthma<sup>1</sup> in which airways inflammation triggered by viral infection or allergy during postnatal lung growth disrupts underlying tissue differentiation programs, leading to aberrations in respiratory function which “track” over prolonged periods into later life<sup>1,62</sup>. While both allergy and respiratory infections during early life are independently associated with risk for subsequent development of asthma, the highest odds ratios for persistent asthma are observed in children who suffer both stresses<sup>1,9</sup>(Fig. 1).

The precise nature of the interactions between atopy and infections in this context are unclear. The finding in a high risk cohort that early RV/RSV infections impose the greatest risk on development of persistent asthma in children who are sensitised by two years suggests that the mechanism may involve cumulative airway damage accruing from the two pathways<sup>16</sup>. However, other manifestations of the atopic phenotype, in particular excessively Th2-polarised cellular immune responses to the infecting virus in high risk infants<sup>63</sup>, may also contribute. In this context it is of interest to note that developmental deficiencies in capacity to produce Th1 cytokines exemplified by interferon  $\gamma$ , which are a hallmark of infants at high risk of atopy<sup>64</sup>, are also associated with risk for RSV<sup>65,66</sup> or RV infection in infancy<sup>67</sup>. It is additionally noteworthy that respiratory viral infection markedly upregulates local innate immune functions in particular the activity of airway mucosal dendritic cell (DC) populations<sup>68,69</sup> which control development and expression of adaptive cell-mediated immunity against the pathogen. These DC also provide the initial trigger for the CD4+ Th2-cell component of the asthma late phase response in atopics<sup>37</sup>, and via this route the viral infection may thus enhance the immunopathogenic potential of pre-existing inhalant allergy (see scheme in Fig 1) creating a heterogeneous inflammatory milieu which, as noted above, is associated with maximal risk of asthma development<sup>9,70</sup>.

The role of atopy in asthma on a population basis has been clarified by a recent analysis of the Third National Health and Nutrition Examination Survey (NHANES III) which concluded that 56.3% of the cases of asthma in the USA were attributable to atopy<sup>71</sup>. This report included data from people aged between 6 and 59 year old and found that the proportion of asthma attributable to atopy was higher in males (74.1% vs 43.2% in females), with further variations related to education and housing status.<sup>71</sup> Initial analyses of 1400 subjects from the 14yr follow-up of the community-based birth cohort from Perth (6yr data in<sup>9</sup>) indicate that the proportion of current asthma attributable to atopy is 52% overall.

However, in contrast to the NHANES III data, the atopy accounts for more asthma in females (65.6%) than in males (46.4%). It is intriguing to speculate that this pattern of gender difference may be specific to adolescence and thus not seen in populations with wider age ranges. It is also important to note that these data all come from developed Western countries and that the relationship between atopy and asthma may not be the same in populations from developing countries<sup>13</sup>. However, even under conditions where non-atopic asthma is the most common phenotype, atopy is still associated with more severe asthma<sup>13</sup>.

### **Predicting children at risk of persistent asthma: developing clinical indicators**

A number of attempts have been made to produce models or clinical indicators of risk of persistent asthma at early ages<sup>32,72,73</sup>. These models have used asthma risk factors identified in epidemiological studies, including: parental history of asthma and atopy; wheeze history; the presence of other atopic conditions such as eczema, rhino-conjunctivitis or food allergy; increased serum IgE antibodies; and *in vitro* cytokine production. In general, while children identified via these models do have a higher risk of developing persistent asthma, the negative predictive values are higher than the positive predictive values<sup>32,72,73</sup>, indicating that they are better at excluding asthma than predicting it and are thus not suitable for identifying the high risk children likely to benefit from prevention strategies.

Longitudinal follow-up in a range of birth cohort studies have demonstrated that optimal utilisation of atopy indices for assessment of asthma risk can only be achieved in an appropriate clinical context. In particular, they need to be considered against a background of information including family history, age and gender which is collected under standardised conditions. This list is expanding with new candidate markers such as Body Mass Index<sup>71</sup>, race-ethnicity<sup>71</sup>, sleep quantity and quality<sup>74,75</sup> environmental pollution such as traffic noise and fumes<sup>76</sup>, and will undoubtedly eventually include genetic markers<sup>77</sup>.

Accumulating evidence suggests that quantitative measures of atopy<sup>27,78-81</sup> in particular cumulative titres of IgE specific for perennial inhalant allergens<sup>82,83</sup>, provide more robust assessments of atopy associated risk than simple binary classifications such as sensitised/non sensitised. In a large birth cohort from Perth Australia, the severity of atopy, judged from both the number of positive SPT and the wheal size, was related to both the risk of current asthma and severity of asthma at 6 years of age<sup>7</sup>. Linear trends were also seen between serum levels of eosinophil cationic protein, a biomarker of eosinophil activation, and SPT wheal size as well as to asthma severity<sup>7</sup>. Associations between quantitative measures of atopy and an increased risk of asthma, severity of food allergy<sup>27</sup>, and responsiveness to bronchial allergen challenge have been reported in other paediatric cohorts<sup>79</sup>. These findings suggest that there is little justification for the continued use of atopy as a binary variable for assessing asthma risk.

Personal atopic history in early life appears to be one of the most important factors determining an individual's risk of persistent asthma. Recent data from longitudinal cohort studies address the inter-relationships between different clinical manifestations of atopy<sup>27,84</sup>. The German Multicentre Allergy Study (MAS) reported a cumulative

prevalence of atopic dermatitis (AD) in the first 2 years of life of 21.5%<sup>84</sup>. When associated with allergic sensitization, AD was a significant predictor of asthma at school age; this risk was not seen with AD in the absence of sensitization. However, in many of the children in this cohort wheeze was seen before or at the onset of AD rather than as a progression of atopic disease. The finding that AD *per se* does not constitute a risk for asthma, but only when associated with allergic sensitization was supported by the findings a cohort of high risk Australian children<sup>27</sup>. The latter study also demonstrated a significant risk for asthma [odds ratio (OR) 3.52, 95%CI 1.88-6.59] at early school age in children with AD and sensitization to food allergens in the first 2 years of life. The risk was greater with large wheal size predictive of clinical food allergy [OR 4.61, 2.34-9.09]. They also found no increased risk of asthma with AD in the absence of allergic sensitization. These data, and others from high risk cohorts<sup>85</sup>, demonstrate that infantile eczema and genuine AD (i.e. that associated with allergic sensitization) are not synonymous, and that non-atopic eczema does not convey a risk for asthma. Thus, objective measurement of atopic status including quantification of markers of sensitization is required to quantify asthma risk. Sensitization to hen's egg appears to convey the greatest risk<sup>27,84</sup>. These conclusions come from both high-risk<sup>27,85</sup> and community-based cohorts<sup>84</sup> suggesting that they are applicable to the general population.

In addition to atopy and respiratory infections, a range of environmental factors contribute to risk for asthma development through pre- or postnatal exposures, including: ETS<sup>86-88</sup>, type of bedding<sup>89,90</sup>, indoor and outdoor air pollutants<sup>91-94</sup>, psychosocial factors<sup>95</sup>, and bioaerosols containing microbial breakdown products<sup>36</sup> and/or allergens<sup>37</sup>. The effects of these exposures may be modified by genetic<sup>96,97</sup> and epigenetic<sup>98,99</sup> factors. *In vitro* models suggest that environmental conditions that compromise the barrier function of the airway epithelium could enhance replication of respiratory viruses<sup>100,101</sup> and, consequently, respiratory morbidity. We must, however, acknowledge that the role of some environmental exposures in inducing asthma is not clear. In particular, exposure to pets or farm animals is protective in many but not all studies and controversy still exists regarding whether prolonged breast feeding increases the risk of persistent asthma in all children or only in those with atopic mothers.

At present it may not be possible to accurately define a “high risk” child with absolute certainty. Current research points to some indicators, including: family history of asthma and allergies, especially a maternal history; early and more severe sensitisation to some food antigens, especially hen's egg, and to aeroallergens; early viral infection associated with wheeze and adverse environmental exposures. However, further comprehensive studies are needed to develop good clinical indicators of high risk.

### **What would early identification of high risk children achieve?**

A significant proportion of children who develop persistent disease are not being detected until their disease has already consolidated, thus denying them any potential benefits of early intervention. But are these potential benefits *real* or *imagined*? One argument in support of *reality* is the “Hawthorne effect” which is seen in the control arm of intervention studies and in observational studies, notably the improved disease outcomes (relative to the

community at large) which accrue from nothing other than the provision of “current best practise” care to at-risk subjects<sup>102</sup>. We argue that the ability to identify at-risk children with a high degree of certainty would potentially allow a number of important interventions to be undertaken, including: early institution of appropriate therapy in children destined to suffer persistent asthma which can control asthma symptoms and reduce the burden imposed on the child and the family<sup>2</sup> and the community<sup>103</sup>; provision of appropriate advice to parents of wheezing children, including advice of allergen avoidance in sensitized children<sup>104</sup>; and potentially institution of specific allergen immunotherapy in children most likely to benefit<sup>6,8</sup>. In addition, routine advice that should be given by all primary care physicians and paediatricians to avoid exposing young children to environmental contaminants, such as cigarette smoke, pollutants and noxious chemical, could be further strengthened for parents of high risk children. However, ensuring that high risk children are actively engaged with clinical follow-up may also provide an important benefit.

Intensive research is in progress internationally on a broad range of more aggressive early intervention strategies (discussed in<sup>62</sup>), including: immunotherapy; immunoprophylaxis; and prevention of wLRI with immunomodulatory approaches and/or antiviral approaches. Testing these strategies requires identification of those children most likely to benefit. It is clear that at present our capacity to accurately define the high risk state is limited and is an issue requiring further research. Nevertheless, the approach discussed above, which includes as a cornerstone the early identification and quantification of specific allergic sensitization, together with accurate assessment of severity and stability of sensitization, represents a logical step in this direction.

In conclusion, objective assessment of atopy by quantitating allergen-specific IgE levels in serum to common food allergens (e.g. hens egg and cows milk) and local aeroallergens (e.g. house dust mite, alternaria, etc) by two years of age in conjunction with the presence of other atopic manifestations (e.g. AD, or clinical food allergy) can help identify which wheezing children are at high risk of developing persistent asthma. The ability to identify high risk children may provide individual benefit by ensuring they are actively engaged with clinical monitoring and providing them with current “best practice” management. This will also facilitate appropriate selection of subjects for clinical trials designed to evaluate new prevention strategies.

### **Search strategy and selection criteria**

The OVID search engine was used to find articles in the Medline database using key words related to childhood asthma, allergic sensitization, longitudinal cohort studies and asthma risk factors. This general search was supplemented by specific searches for articles addressing particular points of relevance to the review. As this was not a systematic review conducted using Cochrane guidelines, no “selection” or “rejection” criteria were used.

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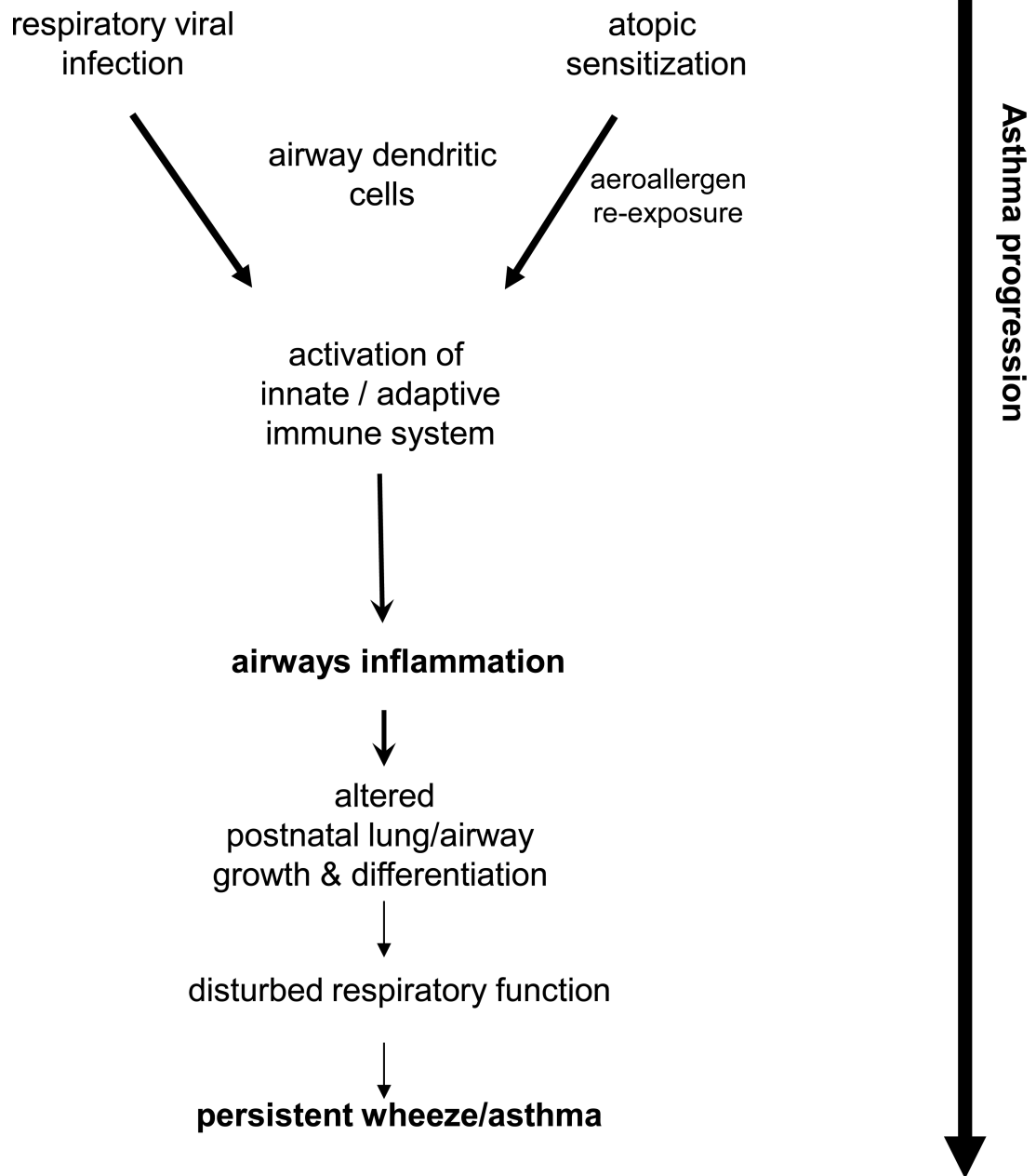
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**Figure 1.** Schematic representation of the interactions between early respiratory viral infections and atopic sensitization on the pathway to persistent wheeze/asthma. The link between activation of immune defence mechanisms to viral infections and activation of airway dendritic cells (DC) is highlighted.