Update on the “Dutch hypothesis” for chronic respiratory disease

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Introductory article
Airways responsiveness and development and remission of chronic respiratory symptoms in adults
X Xu, B Rijcken, JP Schouten, ST Weiss

Background. Many patients with chronic obstructive lung disease show increased airways responsiveness to histamine. We investigated the hypothesis that increased airways responsiveness predicts the development and remission of chronic respiratory symptoms.

Methods. We used data from 24-year follow-up (1965–90) of 2684 participants in a cohort study in Vlagtwedde and Vlaardingen, Netherlands. Increased airways responsiveness was defined as a PC_{10} value (concentration of histamine for which challenge led to a 10% fall in forced expiratory volume in 1 s) of less than 8 mg/ml. Information on respiratory symptoms was collected by means of a standard questionnaire every 3 years. Logistic regression was used to control for age, area of residence, cigarette smoking status, and sex.

Findings. Participants with increased airways responsiveness (1281 observations) were more likely than those without increased airways responsiveness (5801 observations) to develop the following symptoms during any 3-year follow-up interval: chronic cough (odds ratio 1.9 [95% CI 1.2–2.9]), chronic phlegm (2.0 [1.3–3.0]), dyspnoea (2.3 [1.5–3.5]), asthmatic attacks (3.7 [2.2–6.1]), and persistent wheeze (2.7 [1.7–4.4]). The estimate of the odds ratio for the development of any of the six symptoms was 1.7 (1.2–2.3). Participants with increased airways responsiveness were less likely than those without this characteristic to show remission of these respiratory symptoms. The estimate of the odds ratio for the remission of any of the six symptoms was 0.42 (0.28–0.61).

Interpretation. These prospective analyses show that increased airways responsiveness is positively associated with the development of chronic respiratory symptoms and negatively associated with the remission of these symptoms in adults. (Lancet 1997; 350:1431–34)

The “Dutch hypothesis” was originally put forward by Orie et al. They postulated that airway hyperresponsiveness (AHR) and atopy were markers of a basic disturbance or constitution which predisposed to the development of chronic non-specific lung disease characterised by cough, sputum production, dyspnoea, and often airflow limitation. This disease, later termed CARA in Dutch, included both chronic asthma and what we would today label as chronic obstructive pulmonary disease (COPD). Retrospectively, it seems that this lack of distinction between asthma and COPD—at a time when most British, other European, and American studies made a clear distinction—was a major hindrance for communication between the Dutch group and others. Also, the “Dutch hypothesis” was not a term proposed by Orie et al but by others contrasting it with the “British hypothesis” which focused on chronic mucus hypersecretion as a marker of recurrent airway infections causing chronic airflow limitation.

The core point at the beginning of the 1960s was that the Dutch hypothesis pointed to endogenous factors which might play an important role in the development of COPD. This contrasted with the view that exogenous factors—particularly tobacco smoke—were the overwhelming causes of COPD.

Atopy, airways hyperresponsiveness, and the risk of COPD
The role of atopy has gradually been separated from that of AHR, at least in epidemiological studies. In several studies total IgE has been used as a marker of atopy. In general, smokers have an increase in total IgE and also in blood eosinophil count compared with non-smokers. In the absence of clinical asthma there is, however, no indication that atopy interacts with tobacco
FEV\textsubscript{1} is not without pitfalls, and the association between metric values or peak flow measurements of peripheral airways is largest in populations of elderly subjects. AHR risk links with other established risk factors; however, the decline in FEV\textsubscript{1} has been made by Rijcken and Holland. Increased airways responsiveness to histamine explains a significant part of the FEV\textsubscript{1} variation, the association between forced expiratory volume in one second (FEV\textsubscript{1}) and apparent AHR appears to add approximately 10 ml/year to the decline in FEV\textsubscript{1}. The effect is largest in populations of elderly subjects. A review of the epidemiological literature on AHR and the decline in FEV\textsubscript{1} has been made by Rijcken and Weiss, co-authors of the introductory article.

The above studies all looked at lung function data measured on two or more occasions, the first with concurrent measures of AHR and FEV\textsubscript{1}. With subsequent FEV\textsubscript{1} measurements the initial AHR from such studies can be related to the change in FEV\textsubscript{1}. If it explains a significant part of the FEV\textsubscript{1} variation, the hypothesis that AHR is a risk factor for an excess FEV\textsubscript{1} decline is supported. Although analysing this decline in FEV\textsubscript{1} is not without pitfalls, an association between AHR and subsequent FEV\textsubscript{1} decline now seems established. It should be noted, however, that AHR—like all other biological phenomena—varies over time. A given threshold may lead subjects to be labelled “hyper-reactive” at some times and “normal” at others. For this reason there is a need for studies which are able to look at changes in AHR and changes in FEV\textsubscript{1}, as well as other disease outcomes in order to demonstrate consistency.

The introductory article

The introductory article by Xu and colleagues stems from an almost ideal cohort study which has measured AHR every third year for a 24 year period in the rural Villagewide and urban Vlaardingen populations of Holland. Increased airways responsiveness to histamine was defined as a provocative concentration causing a fall in FEV\textsubscript{1} of 10% or more (PC\textsubscript{20}) \textless 8 mg/ml. Subjects with increased airways responsiveness were more likely than subjects without to develop a variety of respiratory symptoms (chronic cough, chronic sputum expectoration, dyspnoea, asthmatic attacks, persistent wheeze) in any following three year period (odds ratios of 1.4–3.7 adjusted for age, sex, smoking status, and area of residence). Odds ratios tended to be larger for asthma-like symptoms, persistent wheeze, and asthma attacks than for “bronchitis” which was defined as episodes of cough and phlegm lasting for at least three weeks in the past three years. Furthermore, patients with increased airways responsiveness were less likely to report remission of symptoms than those without increased responsiveness.

The strength of the study lies in its sample size, its two distinct cohorts, and the appropriate use of advanced statistical methods. It does, however, have one limitation. The results were said to be uninfluenced by the exclusion of “asthmatics” but no definition of the latter was provided. Presumably the authors relied on self-reported physician made diagnoses. The relationship between AHR and the clinical symptoms of asthma is well founded and so the inclusion of asthmatic subjects is likely to have introduced some bias. We would have expected, conversely, some weakening of the demonstrated associations after exclusion of asthmatic subjects. The authors have nevertheless collected and analysed invaluable data which strengthen the overall credibility of AHR as an important aetiological factor in chronic respiratory disease.

Airways hyperresponsiveness and other risk factors for COPD

Thus, AHR seems to be an independent risk factor for the development of FEV\textsubscript{1} decline. The longitudinal observation of an excessive decline in FEV\textsubscript{1} being a “constitutional factor” as suggested by the Dutch hypothesis. This poses the further interesting question of how the AHR risk links with other established risk factors.

It is worth noting that the clinical diagnosis of COPD is usually “cross-sectional”—that is, the diagnosis is made after demonstrating irreversable airflow limitation after the apparent exclusion of a few (and rare) specific conditions that can also cause fixed airway obstruction. It is not generally diagnosed after the longitudinal observation of an excessive decline in FEV\textsubscript{1}. The distinction from asthma is most often achieved from the clinical history, a history of smoking and other exposures such as dust and fumes, serial measurements of spirometric values or peak flow, measurements of parenchymal lung function, or (when doubt remains) corticosteroid reversibility or the quantification of airway responsiveness. This clinical approach does not always distinguish between the several ways in which the affected individual may have acquired a low level of lung function. The different possibilities are shown in fig 1 where the normal course of growth and decline in FEV\textsubscript{1} is shown.

One of the main obstacles for the acceptance of the Dutch hypothesis has always been the “downgrading” of the role of tobacco smoking. In the literature on COPD the attributable risk of tobacco smoking is generally believed to be 80–90%. At the same time only 15% of smokers develop COPD, a phenomenon generally ascribed to the presence or absence of various degrees of “susceptibility.”

The growth phase for the lungs (or at least lung function) has recently been shown to be affected by smoking, especially in girls. In cross-sectional studies it seems that AHR is associated with a
lower maximally attained level of FEV1. The growth pattern is largely unknown, but the association is readily observed in growing children with persistent asthma. No studies have looked at interactions between AHR and smoking although the growth of lung function seems to be more markedly reduced in symptomatic smokers than in asymptomatic smokers.

It is generally believed that in healthy non-smokers a plateau phase of lung function occurs in early adulthood, generally spanning the ages 25–35 years, but this belief may be partly the result of combining measurements of continued slow growth in some subjects with those of slow decline in others. Smoking shortens the plateau phase whereas little is known about the influence of AHR.

Recent work has suggested that, contrary to previous "common knowledge", female gender seems to be a further risk factor for COPD. From the viewpoint of the Dutch hypothesis a higher prevalence of AHR in women provides the means for greater susceptibility to the harmful effects of smoking. Such an increased prevalence was reported from the Lung Health Study but this was interpreted in terms of geometric differences in airways caliber. However, subsequent analyses have shown that the difference cannot be explained solely by geometric factors. In a recent French paper Leynaert et al found that young women were more hyperreactive than men. With AHR defined as a provocative dose of methacholine causing a 20% fall in FEV1, (PD20) of <4 mg/ml, 37.3% of women were hyperreactive and 18.6% of men. The difference could not be attributed to differences in height. The study also suggested that a larger proportion of the AHR found in women was associated with smoking. This implies that this greater susceptibility to smoking might be mediated by AHR, though the introductory article does not support such a hypothesis.

While statistical interactions are often treated with little attention, we find this lack of interaction disturbing and we believe it represents a major obstacle to accepting AHR as the underlying marker of susceptibility. Without a demonstrable interaction between AHR and a strong environmental factor such as tobacco smoke, AHR should be seen as no more than a further independent risk factor for COPD along with smoking, rather than as a more fundamental mechanism by which smoking exerts its influence. Another way of demonstrating that AHR and smoking interact in causing airway obstruction would be by determining whether attenuation of AHR can slow down the progression of airflow obstruction in continuing smokers. This is being tested in ongoing studies. At present, however, there is insufficient epidemiological or scientific evidence to regard AHR as the mechanistic pathway for constitutional susceptibility to exogenous factors such as tobacco smoke. Studies focusing on this point are clearly needed.

Chronic mucus hypersecretion has re-emerged as a risk factor for an accelerated FEV1 decline and recent studies have suggested a more obvious impact of smoking on lung function in symptomatic than in asymptomatic subjects. No studies have looked at interactions between mucus hypersecretion and AHR, and both may represent markers of an inflammatory component in the disease.

The heterogeneity of COPD and the Dutch hypothesis

Another impediment to widespread acceptance of the Dutch hypothesis has been the reluctance to accept a common background for diseases with such differing pathophysiology as asthma and emphysema. Instead of rejecting the hypothesis on these grounds it may be worthwhile taking a broader view.

From clinical and pathological studies it is clear that COPD may arise as a consequence of emphysema with destruction of lung tissue and loss of elastic recoil, a dramatic example of this being the terminal phase of α1-antitrypsin deficiency. On the other hand, end stage COPD may be seen with virtually no emphysema, the severe airflow limitation being a consequence of small airways dysfunction. This is due to thickening of the airway wall and fibrotic changes following remodelling processes—an obstructive bronchiolitis. With growing recognition of this heterogeneity of COPD (quite apart from COPD + asthma) it is clear that no one hypothesis will be able to fully explain its pathogenesis; it may be fruitful to consider the many pathways to or causes of COPD, or the spectrum of COPD, rather than COPD alone. While it may be appropriate for initial diagnosis and management to regard COPD as a single entity and proceed according to guidelines recently published, the search for underlying mechanisms needs to follow other leads. In this respect the Dutch hypothesis can make a valuable contribution.

The close connection between AHR and asthma and its apparent additional relation to COPD requires comment in any update on the Dutch hypothesis. In a further paper to the introductory article, Ricksten et al argued that distinguishing between asthma and COPD in epidemiology is of little use. This may be so, particularly for studies looking strictly at FEV1, decline or mortality. For the clinician, however, the clinical picture is often distinguishable and it makes sense to separate asthma from COPD in terms of treatment strategies, treatment goals, etc. Nevertheless, the traditional view that lung function in asthma typically remains normal...
between asthma attacks is now discarded, and it is generally accepted that processes of airflow remodelling often lead to permanent damage to the airway wall and to fixed obstruction. Thus, an increased longitudinal decline in FEV1 in adult life— in et al. to fixed obstruction. Thus, an increased longitudinal

**LEARNING POINTS**

- Airway hyperresponsiveness (AHR) is associated with respiratory symptoms, level of lung function, and decline in lung function.
- Changes in AHR are associated with changes in respiratory symptoms, seemingly in both asthmatic and non-asthmatic subjects.
- AHR is a risk factor for COPD, independent of age and tobacco consumption.
- The reported relationship of AHR with gender needs further evaluation.
- Future studies of respiratory epidemiology may benefit from looking at changes in the risk factor of interest as well as at changes in the outcome variable—for example, the methodology reported in the introductory article.

**Conclusions**

We conclude that the “Dutch hypothesis” is still with us. After more than 35 years of increasing awareness of COPD and increasing research, the “hypothesis” is now being tested. Its components and the ideas behind it are playing an influential and important role in understanding the underlying mechanisms of chronic airflow limitation.

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doi: 10.1136/thx.53.2008.S15

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