The Independent and Combined Effects of Lifetime Smoke Exposures and Asthma as they Relate to COPD

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Summary
Chronic obstructive pulmonary disease (COPD) is part of a worldwide tobacco-related disease epidemic, and is associated with progressive airflow obstruction and varying degrees of emphysema and/or hyperinflation. Greater focus has been placed recently on the potential for early life factors to influence the development of COPD, based on the premise that delayed lung growth during childhood and adolescence might predispose to lung disease in later life. For most people, the adverse effects on lung function of adult and early childhood factors are additive, which provides no additional incentive for current smokers to quit. However, if there is a (synergistic) interaction between personal smoking and asthma, smoking cessation is likely to have a greater lung function benefit for the smoker who is also asthmatic, especially if quitting occurs at an early age. This article critically evaluates the evidence for the independent associations of lifetime asthma, and tobacco smoke exposures with airflow obstruction, plus their interaction when multiple factors are present.

Keywords
Interaction, asthma, tobacco, active smoking, second-hand smoke, COPD, lung function
Introduction

Chronic obstructive pulmonary disease (COPD) is an important global health issue, as it is currently the fourth leading cause of mortality, and is predicted to cause over 5.4 million deaths by 2030\(^2\). Symptoms often arise from middle-age, and progressive disability and premature death from the accelerated loss of lung function and co-morbidities such as bronchopneumonia, lung cancer and cardiovascular disease may ensue. COPD is frequently under-recognised in its earlier and milder stages, when preventive intervention would be most effective. However, only a proportion of active smokers develop COPD, and the differences in susceptibility remain largely unexplained\(^3\).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as “a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases”\(^3\). Active smoking is the primary cause of COPD in industrialised countries, whereas indoor and outdoor air pollution and occupational exposures play a greater role for men and women residing in developing countries. While irreversible airflow limitation is a well-recognised sequel of longstanding asthma\(^4\), asthma

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**Abbreviations**

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<tr>
<th>Acronym</th>
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<tr>
<td>ASM</td>
<td>Airway smooth muscle</td>
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<td>BD</td>
<td>Bronchodilator</td>
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<td>BHR</td>
<td>Bronchial hyperresponsiveness</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>ECRHS</td>
<td>European Community Respiratory Health Survey</td>
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<tr>
<td>FEF(_{25-75%})</td>
<td>Mid-expiratory flow</td>
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<tr>
<td>FEV(_1)</td>
<td>Forced expiratory volume in one second</td>
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<td>FEV(_1)/FVC</td>
<td>Ratio of the FEV(_1) to forced vital capacity</td>
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<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
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<td>SHS</td>
<td>Second-hand tobacco smoke</td>
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<td>TAHS</td>
<td>Tasmanian Longitudinal Health Study</td>
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has been regarded as a predisposing factor for spirometrically-defined COPD given the current evidence available \(^6\). For people with asthma, most doctors would give a diagnosis of COPD only if such an individual also smoked, whereas the nomenclature appropriate for non-smokers with the same spirometric abnormality is less clear \(^7\).

There has been increasing interest in the potential aetiological role of interactions between asthma and smoking as they relate to COPD in the Western world. This is in the context of bronchial hyperresponsiveness (BHR, or airway hyperreactivity), a hallmark feature of asthma, being a leading risk factor for incident airflow obstruction for people without a history of asthma \(^8\). The opportunities to investigate the potential interactions between asthma and smoking have been limited due to the frequent exclusion of asthmatics who smoke and/or COPD patients with asthma or asthma-type BHR from clinical studies with asthma-specific and/or COPD-specific endpoints \(^9,10\). Even fewer studies have examined second-hand smoke (SHS) exposures such as parental smoking and their interaction with personal smoking on lung function abnormalities. If such a multiplicative effect is present, the additional lung function loss that results from the interaction itself, provides another reason for current smokers to quit \(^11\).

Our aim is to review the evidence of these potential interactions, that is, to assess whether the strength of individual predisposing factor associations would be multiplied, rather than just added, if more than one was present. Through stratifying the population into subgroups based on statistical differences in their associations with airflow obstruction, the potential for environmental-environmental interactions to impact on the heterogeneity of COPD can be further understood.

**How is COPD defined by spirometry?**

Persistent airflow limitation that is characteristic of COPD is diagnosed by spirometry following the use of an inhaled bronchodilator. How best to define this lung function feature of COPD, especially for research purposes, has been subjected to considerable debate. The GOLD Initiative currently endorses the diagnostic criterion of post-BD ratio of the forced expiratory volume in one second to forced vital capacity (FEV\(_1\)/FVC) less than 0.70, given its simplicity and independence from reference values. However, given the physiological age-related lung function decline over time, the GOLD definition substantially underestimates
abnormality for young to middle-aged adults while overestimating abnormality for those over 50 years.

The American Thoracic Society/European Respiratory Society Task Force proposes another criterion of post-BD FEV$_1$/FVC less than the lower limit of normal, where the 5th percentile is nominated as the cut off based on the normal distribution of a healthy non-smoking population. This criterion is generally preferred for the diagnosis of mild airflow obstruction for older individuals, however most reference equations and using percent of predicted values are still subject to anthropometric-related biases. The Global Lung function Initiative has accurately constructed growth charts using over 97,000 records, and the resultant spirometric reference values that cover the age range between 3 and 95 years include appropriate age-dependent lower limits of normal. This method and using z-scores and the 5th percentile as the lower limit of normal has been validated using clinically meaningful outcomes such as all-cause mortality and prevalence of respiratory symptoms.

In addition to this “lung function criterion for COPD”, the GOLD Guidelines recommend a clinical COPD diagnosis to be based on respiratory symptoms and an established risk factor, other than asthma and SHS exposure. However, primarily due to feasibility, epidemiological studies such as Burden of Lung Disease (BOLD) and European Community Respiratory Health Survey (ECRHS) have adopted the lung function criteria only for defining and staging COPD and/or a modified GOLD definition based on pre-BD spirometry.

Pathophysiological features of Smoking and Asthma

Active Smoking

The pathogenesis of COPD in smokers has been attributed to an abnormal inflammatory and remodelling response of the airways and lung parenchyma. Smoking-related airflow limitation can result from varying degrees of fibrosis and obliteration of the small airways; inflammation and tissue remodelling of larger airways with mucus oversecretion; and parenchymal emphysematous damage and decreased elastic recoil properties of the lung tissue. Small airways obstruction and obliteration is likely to precede the parenchymal destruction, where collagen is deposited in damaged terminal bronchioles in early COPD and then the emphysematous process is initiated around the bronchioles. Smoking-related
COPD is associated with variable amounts of air-space destruction, gas transfer factor abnormality, resting and dynamic lung hyperinflation 22.

The innate immune system is the first line of lung defence, and chronic stimulation of this system by tobacco smoking results in mucus hypersecretion reduced mucociliary clearance, epithelial metaplasia, and infiltration of the airway wall by cells such macrophages and natural killer lymphocytes 23. Via dendritic cells, active smoking can stimulate the components of the adaptive immune response to generate immunological memory that ensures a more effective response to subsequent exposure. Activation of this adaptive immune response is indicated by the presence of lymphoid follicles with a germinal centre containing B and T cells. However, they are seen in only 25-30% of individuals with advanced COPD (GOLD Stages 3 and 4) and are otherwise seen in relatively few smokers 24. Neutrophils and the helper and cytotoxic T cells of the type 1 response predominate, and it is unclear whether pro-inflammatory cytokines such as tumour necrosis factor-α have a “spill-over” effect from the lung into the systemic circulation 25.

Epithelial mesenchymal transition (EMT) has been shown to be active in the airways of smokers, especially those with COPD, and might be involved in the formation of the peribronchiolar fibrosis that contributes to airway obstruction 26,27. The regulation of the modulatory protein phosphatase 2A (PP2A) has recently been identified as playing a key role in countering asthmatic and COPD-related airway inflammation and proteolytic lung destruction in response to cigarette smoke exposure 28.

**Maternal smoking**

Maternal smoking during pregnancy has been hypothesised to predispose to COPD for adult offspring through its adverse influence on intrauterine foetal growth 29. It is frequently associated with mean birth weights approximately 200 grams lower than for non-smoking mothers 30. Even for non-smoking pregnant women who were exposed to environmental SHS per se, mean birth weights were 54 grams [95%CI –98 to –8.9] lower than those not exposed, though the potential role for paternal smoking was not specified 31. Reduced foetal growth is thought to relate to chronic tissue hypoxia that results from elevated carbon monoxide levels as well as nicotine-associated vasoconstriction that adversely affects uterine and umbilical blood flow. The biological plausibility for a direct nicotine drug effect has been tested in an animal model, where nicotine-exposed foetal monkeys had similar lung
function changes to those observed for human infants in terms of forced expiratory flows and volumes\textsuperscript{33,34}. Deficits in infant lung function have been shown to track over time to effectively reduce peak lung function attainment, which in turn, adversely impacts the physiological age-related decline in adult life\textsuperscript{35}.

\textbf{Asthma}

Asthma characteristically causes acute airflow limitation, when the airways are intrinsically narrowed from smooth muscle contraction and airway inflammation. Chronic sputum plugging from thick and tenacious mucus can cause uneven ventilation and/or arterial hypoxaemia\textsuperscript{36}. Particularly for cases of fatal asthma, the airway smooth-muscle (ASM) layer is substantially thickened, and collagen is deposited in the subepithelial layer of the airway wall\textsuperscript{37}. While hypertrophy of ASM cells occurs in the large airways of non-fatal asthma cases [of predominantly moderate severity], the increase in muscle mass and likely propensity for ASM contraction that occurs in cases of fatal asthma is predominantly from ASM hyperplasia in large to small airways\textsuperscript{38}. How this airway remodelling relates to the development of asthma-related irreversible airway limitation is less clear.

The typical immunological pattern for the mild asthma phenotype is one of allergy, and includes mast cells, immunoglobulin-E-producing plasma-cells, eosinophils, and type-2 helper T cells. Severe asthma has the additional features of neutrophilic inflammation, helper and cytotoxic T-cells for both type 1 and 2 responses and increased levels of tumour necrosis factor-\(\alpha\)\textsuperscript{37}, which overlap with some immunological features of COPD. This heterogeneity of airway inflammation is acknowledged by the inflammatory-defined phenotypes that primarily include eosinophilic and non-eosinophilic asthma. While a non-eosinophilic asthma phenotype is more commonly reported for smokers than for non-smokers\textsuperscript{39}, the pro-neutrophil action of the frequently used high dose steroid asthma treatment might have confounded previous studies to some extent.

Resting hyperinflation can occur for those with asthma, but generally only during acute episodes\textsuperscript{22}. Chronic asthma is not generally associated with emphysematous destruction\textsuperscript{22,40,41}, and is typically associated with normal to high gas transfer factor levels.
What is the Interplay between Lifetime Asthma and Smoking?

Individuals who smoke and have asthma comprise a substantial proportion of the general population. For a population study that commenced in the mid-1970s, more than two-thirds of middle-aged men and women with asthma also reported being current smokers. For a cross-sectional population-based analysis of middle-aged men and women who were surveyed in 2004 (n = 5,591), 38% of asthmatics were non-smokers, 30% were past smokers and 32% current smokers, and 38% reported a smoking history of at least 10 pack-years.

Current active smokers who also have asthma report poorer symptom control, when compared to non-smokers with asthma. This predisposition might be due in part to additional increases in BHR and/or reduced efficacy of inhaled corticosteroids. In the latter study of mild asthma, the use of inhaled corticosteroids was shown to improve FEV₁ levels, but only for non-smokers (+170 ml [95%CI 80-260]). For a small number of smokers with asthma, those who quit smoking for six weeks had improvements in lung function from baseline (+407 ml [95%CI +21 to +793], p<0.05), and a fall in neutrophil count (mean – 29% difference [–51 to –8], p=0.013). A dose-response relationship has been shown between pack-years of smoking and both incident asthma and occurrence of suboptimal asthma control for atopic adults who were referred to a university clinic with allergic rhinitis.

Worse asthma control has also been associated with adult SHS exposure, where during the first three years following smoke-free legislation in England, emergency admissions for asthma decreased by 4.9% (95%CI 0.6-9.0%). Maternal smoking during childhood has been linked to increased childhood asthma incidence and prevalence, as well as to lower respiratory tract infections. There is increasing recognition of the development of asthma in genetically susceptible individuals to be potentially influenced by gene-environment interactions. Some data have linked chromosome loci 17q12-21 and 20p13 to asthma susceptibility in the context of smoke exposure, however, overall the findings have been inconsistent. While around 1% of those with COPD have α₁-Antitrypsin deficiency as their primary underlying risk factor, the genome-wide association studies (GWAS) have identified three additional genetic COPD susceptibility loci, namely IREB2, HHIP and FAM13A, which are still to validated as COPD determinants for non-smokers by large-scale genetic studies.
How do Asthma and Smoking Independently Relate to COPD?

While active smoking is the leading cause of COPD, and asthma can lead to the same spirometric abnormality that defines COPD, it remains uncertain whether maternal smoking, adult SHS exposure and asthma might be risk factors for the condition itself. A schematic summary of the main associations and potential interactions of some of these factors throughout the life-course of lung function is presented in Figure 1. Apart from the factors listed in the figure, other environmental exposures that may influence lifetime lung function include occupational exposures as well as indoor and outdoor air pollution.

Asthma

A temporal relationship between longstanding asthma and irreversible airflow limitation has been demonstrated by several studies ⁵⁶-⁶⁰. However, the heterogenous nature of asthma can pose a significant challenge to addressing its relationship to COPD, given that asthma encompasses multiple syndromes that overlap ⁶¹.

In the Tucson birth cohort study, pre-existing asthma was linked to irreversible airflow limitation in early adulthood, but only if the asthma age-of-onset was at least 16 years, or younger if taking prescription asthma medication within the year of lung function testing. The presence of current asthma symptoms was also more closely linked to adverse post-BD lung function than remitted asthma ⁶⁰, and this concept has been supported recently by the Tasmanian Longitudinal Health Study ¹¹. This latter study also provided supporting evidence for late-onset asthma, as opposed to early-onset asthma, to feature lower lung function in spite of a shorter duration of disease ¹¹,⁶¹,⁶². The clinical features of late-onset asthma have some overlap with the inflammatory phenotype non-eosinophilic asthma in terms of symptom onset and a greater likelihood for non-atopic females ⁶³. Non-eosinophilic asthma is known to be less responsive to corticosteroid therapy than eosinophilic asthma, and this might relate in part to chronic airway bacterial colonization ⁶⁴. However, severe asthma with unsuppressed eosinophilic airway inflammation has also been shown to be associated with persistent airflow limitation, based on sputum eosinophilia of at least 2% in non-smoking adults ⁵⁶. Increased eosinophil numbers in bronchoalveolar lavage specimens have been associated with lower lung function in both early and late-onset asthma phenotypes ⁶². Few studies have classified people with asthma into more than one phenotypic category, and this has limited direct comparisons across different phenotypes.
Two studies have examined the association between childhood asthma and spirometrically-defined COPD in adulthood \(^{11,65}\). These studies directly compared the strength of the asthma association with that of active smoking. For childhood asthma that was retrospectively recalled in adulthood, the equivalent smoking impact was 62 pack-years of smoking \(^{65}\), though this estimate would tend to bias towards the most severe asthma. When adjusted for atopy and childhood lung function, and with recall bias minimised through a cohort study design, the estimates for early-onset and late-onset asthma were shown to be equivalent to a 33 [95% CI 26-40] and 24 [95% CI 15-33] pack-year history of smoking respectively \(^{11}\).

The natural history of asthma-related irreversible airflow limitation for the various clinical phenotypes has not been well defined \(^{61,63,66}\). However, longitudinal data are available from the Copenhagen City Heart Study that stratified participants by gender, age, smoking status and self-reported asthma, and found smokers with asthma had an approximately 2-fold higher rate of decline of pre-BD FEV\(_1\) \(^{42}\). For middle-aged smokers with a history of asthma, this was equivalent to an annual FEV\(_1\) decline of 38 ± 3.2ml for women and 58 ± 5.8ml for men. Variation has also been described between males and females with asthma with regard to post-BD FEV\(_1\) levels regardless of smoking status, with a greater annual decline for men [41 ml (95% CI 35-47)] compared with women [29 ml (23-35)] \(^{59}\).

While there is good evidence that longstanding asthma can lead to irreversible airflow limitation, there are notable differences in physiology, airway remodelling and airways cytology between those with asthma-related irreversible airflow limitation and smoking-related COPD. In terms of lung function, subjects with asthma have a significantly greater reversibility to bronchodilators and steroids, higher gas transfer factor and lower residual volume. As the asthma-related phenotype might have different systemic co-morbidities and natural history compared to smoking-related COPD \(^{6}\), a causal role for asthma in the development of COPD remains uncertain.

**Active Smoking**

Active smoking is the main risk factor for COPD in industrialised countries, and at a population level, the deficit in FEV\(_1\) is inversely related to personal cigarette smoking duration and intensity as measured by pack-years of cigarette use. The population attributable risk of COPD mortality related to active smoking in the 30 to 69 year age group
was 84% for males and 62% for females. The corresponding estimates for developing countries were 49% and 20% respectively.\(^6^7\)

The role of active smoking in the development of COPD, emphysema, and the related symptom-syndrome of chronic bronchitis (cough and sputum production) has been extensively documented. For the 15-25% of smokers who are susceptible to developing airflow obstruction, FEV\(_1\) decline may be as high as 90 ml per year for male smokers. This compares to annual normal age-related decline in FEV\(_1\) approximating 18–21 ml from adolescence for females, and 20–27 ml for males from their early twenties.\(^6^8\) While the rate of loss of lung function was previously believed to potentially revert back to that of non-smokers or those non-susceptible to the lung function effects of smoking,\(^7^0\) it now understood that persistent airway inflammation and accelerated lung function decline continues after the cessation of smoking, albeit at a lower rate than for susceptible smokers. In comparison to never smokers aged over 65 years, smokers who quit before age 40 years have been shown to have similar FEV\(_1\) levels, whereas mean FEV\(_1\) levels were 7% lower for all smokers who quit at ages 40 to 60 years, and 14% lower for those quitting older than 60 years.\(^7^1\) Chronic bronchitis may be an independent contributor to progressive airflow obstruction for those with advanced COPD by means of higher sputum bacterial loads and recurring infective acute exacerbations.\(^7^2\)

The adverse effects of personal smoking on lung function can be evident for children and adolescents, where a reduction in expiratory flow from smoking ten or more cigarettes per week for at least one year was seen in some children by the age of 14 years.\(^7^3\) It was more marked in those with a history of respiratory illness that included asthma. While the combined effect of smoking and respiratory illness appeared additive, a synergistic interaction could have been missed in part due to the relatively short smoking history and follow-up in this study.

**Second-hand smoke exposure**

While SHS exposure is a definite risk factor for lung cancer for exposed lifetime non-smokers\(^7^4\), a causal link between SHS exposure and deficits in lung function is less clear.


**Parental smoking, regardless of sex**

A causal relationship between parental smoking and incident childhood asthma has been established, where the effects of regular maternal smoking and an allergic predisposition have been shown to synergize with regard to incident childhood allergic sensitization and wheezing during the first ten years of life. There are also some data linking maternal smoking to modest reductions in pre-BD FEV₁ levels for boys and girls, with a larger effect from prenatal maternal smoking than from postnatal exposure. For children between Grades 4 and 10 in the Southern California Children’s Health Study, the combined effect for intrauterine and postnatal SHS exposure was found to be additive. For a cohort of children, adolescents and young adults who were studied for seven years, maternal smoke exposure was associated with reductions in the expected 5-year growth in FEV₁ that were additive to the effect of personal smoking. As mentioned, a relatively short smoking history and follow-up may have prevented the detection of a smoking-smoking interaction.

In addition to associations with spirometric indices, early life SHS exposure spanning in utero to adolescence has been linked to gas trapping and a reduced gas transfer factor in a study of male adolescents. A significant trend has been reported between increasing numbers of smokers in the childhood home and a higher proportion of low attenuation areas (i.e. percent emphysema) on computed tomography scans (p < 0.01). As these middle-aged to older non-smoking adults recalled their childhood SHS exposure retrospectively, those with radiologically-identified emphysema may have preferentially recalled their childhood exposure, or alternatively, poor recall may have attenuated the true strength of the association.

**Parental smoking, sex-related differences**

Sex-related differences in lung growth provide a biologically plausible rationale for reporting lung function results for males and females separately, even if the sex-difference does not reach statistical significance. This has been adopted by several studies, with some suggesting that male children might have a greater susceptibility to the adverse lung function effects of parental smoking.

For newborn infants exposed to maternal smoking during pregnancy, reductions in expiratory flows were consistently greater for infant boys compared with girls. Other studies have suggested a predisposition for an ongoing deficit for boys in later childhood and adolescence.
For a birth cohort studied at age 21 years, prenatal maternal smoking was associated with significant reductions in pre-BD FEV\textsubscript{1} and FEF\textsubscript{25-75%} after adjustment for birthweight, personal smoking and childhood asthma, but only for males. Similarly, for study participants followed between the ages of 9 and 15 years, a mild (1.57%) non-progressive reduction in pre-BD FEV\textsubscript{1}/FVC levels was seen for non-wheezing boys who had two smoking parents. Another reported reduced mid-expiratory flows (FEF\textsubscript{25-75%}) but not FEV\textsubscript{1} for boys between 6.5 and 12 years who had mothers that smoked, regardless of the smoking habits of the father. While the ECRHS reported modest sex-specific reductions of pre-BD FEV\textsubscript{1}/FVC level for adults, the sex-differences were considered marginal. Further studies have not yet clarified whether sex-specific reductions in lung function can persist into adult life.

**Adult second-hand smoke (SHS) exposure**

There is limited evidence to support adult SHS exposure as a potential risk factor for COPD, either from studies that examined cumulative exposures or studies that measured lung function before and after workplace smoking bans were in place. Fewer data are available in terms of complex lung function, and what is available includes some paradoxical findings.

A key cross-sectional study by White and Froeb between 1969 and 1979, found adults with SHS exposure at the workplace for at least 20 years had reductions in pre-BD mid-expiratory flows that may be representative of small airways obstruction (FEF\textsubscript{25-75%}), in the absence of either personal smoking or SHS exposure in the home. Those with a history of respiratory disease/illness, occupational exposures or residing in a heavily polluted area were excluded, and statistically higher concentrations of carbon monoxide were objectively confirmed for some of the workplaces that permitted smoking. However, this study and several others did not find adverse associations between SHS exposure and FEV\textsubscript{1} levels to suggest involvement of the larger airways, though an FEV\textsubscript{1}/FVC ratio was only specified in the study by Goodman and colleagues. While adult SHS exposure may not be independently associated with fixed airflow obstruction, it remains possible that its presence might augment the effects of active smoking through an active-passive smoking interaction. Such an interaction was not examined by White et al., but could have been feasible given over 2,000 participants underwent spirometry and had a well-documented SHS exposure and active smoking history.
Interactions between the Effects of Asthma and Smoking on COPD

The Dutch Hypothesis: the first to suggest the role of interactions in COPD

In 1961, the late Professor Orie of Groningen introduced the so called “Dutch hypothesis” that conceptualised a unity between the obstructive lung diseases including asthma and COPD, as a final common path in different expressions of a primary abnormality of the airway. It was proposed that host factors such as gender, atopy and airway hyperresponsiveness interacted with environmental stimuli such as allergens, infections and tobacco smoke exposure that were encountered at specific times during an individual’s lifetime. Lung function in the short and long-term could be shaped by these interactions between host factors, the random and seasonal alterations in different environmental stimuli as well as the efficacy or long-lasting effect of any therapeutic intervention. These combined effects would influence the ultimate expression of COPD for individuals, with varying degrees of mucus hypersecretion, emphysema and small airways disease. Thus, the variation in the host response to tobacco smoke exposure might be further influenced by interactions with other environmental stimuli, and this may in part explain why only 15-25% of smokers are susceptible to developing COPD.

What are statistical interactions?

A statistical interaction is a multiplicative effect between the effects of two exposures on a disease outcome. This can also be described as “synergy” in biological systems. Each exposure, such as asthma and smoking, has an estimate for its strength of association with a lung function measure. If the combined estimate equals the sum of individual estimates, then this is termed an additive effect and only the main associations need to be reported. However, if combined estimate was statistically greater than the sum of the individual asthma and smoking estimates, the difference can be attributed to the asthma-smoking interaction itself. Stratified results for smokers with and without asthma should therefore be reported. Thus for the same smoking history, the association with adverse lung function can vary with asthma status, which may in part explain some of the natural variation of lung disease. This is summarised in Table 1.
What is the evidence for interactions between asthma, smoking and COPD?

The cohort studies that have examined interactions between the effects of asthma and smoking exposures on pre- and/or post-BD lung function have been summarised in Table 2. These studies were identified by searching the PubMed articles published from 1960 to 2013 and the following keywords were used: (((“asthma”[MeSH Terms] OR “asthma”[All Fields]) AND (“smoking”[MeSH Terms] OR “smoking”[All Fields])) AND (“respiratory physiological phenomena”[MeSH Terms] OR (“respiratory”[All Fields] AND “physiological”[All Fields] AND “phenomena”[All Fields]) OR “respiratory physiological phenomena”[All Fields] OR (“lung”[All Fields] AND “function”[All Fields]) OR “lung function”[All Fields]) AND (“Interaction”[Journal] OR “interaction”[All Fields]) AND “humans”[MeSH Terms]). Of the 73 articles identified, 11 were selected. References were also selected from a bibliographical search.

Asthma*active smoking interactions

Only two major cohort studies of adults have focussed on the possible presence of an asthma-smoking interaction on post-BD airway obstruction, namely in terms of FEV\textsubscript{1}, FEV\textsubscript{1}/FVC and FEF\textsubscript{25-75\%} levels. Tashkin and colleagues first described an interaction between the effects of BHR and smoking status on the decline of post-BD FEV\textsubscript{1}.\textsuperscript{96} It was shown that for current smokers who fulfilled the GOLD criterion of post-BD FEV\textsubscript{1}/FVC ≤ 0.70, methacholine reactivity was a strong predictor of FEV\textsubscript{1} decline during the 5-year follow-up period, but only for those who continued smoking.

This concept was extended in the population-based TAHS study, where an interaction between the effects of lifetime asthma/wheezy breathing status and pack-years of smoking on multiple continuous measures of airflow obstruction was seen.\textsuperscript{11} In other words, the strength of association varied significantly across groups depending on the combination of asthma and smoking status, and this was particularly evident for those with atopic sensitization. For the atopic subgroup, compared to non-smokers without asthma, the combined estimate for smokers with early-onset asthma and current symptoms was a −8.4% reduction in predicted post-BD FEV\textsubscript{1}/FVC levels [95% confidence interval −12 to −5.1], p<0.001), and this was greater than the sum of individual smoking and asthma (−5.7% [−8.6 to −2.8], p<0.001) associations. The estimate for active smoking alone was modestly reduced for those without atopic sensitization (−1.4% [−2.3 to −0.5], p=0.002). To date, a similar asthma-smoking interaction using post-BD FEV\textsubscript{1}/FVC levels as a categorical outcome has not been reported.
Pre-BD spirometry has been also been used as an outcome measure for longitudinal and cross-sectional studies to address asthma-related lung function changes, but is not preferred when the outcome of interest is COPD. For adults who both smoked and self-reported asthma, the combined effect on pre-BD FEV₁ decline was shown to be additive and without interaction 42,97. It is likely that this finding was influenced by the frequently inaccurate retrospective recall of childhood asthma, which is a methodological limitation in the field 98.

Multiple cross-sectional adult analyses for adult populations have emanated from the ECRHS. One of the publications reported an interaction between the effects of atopy and smoking on pre-BD lung function, when adjusting for asthma status 99. ECRHS has also reported another interaction between the effects of atopy and current asthma on lung function confounded by active smoking 100. However, both analyses were limited by the use of retrospective recall of childhood asthma and the lack of information on previous lung function. For the CARDIA study cohort of young adults, a multiplicative effect was seen between the effects of asthma and smoking at least 15 cigarettes daily on pre-BD FEV₁ decline, however the estimates may have been biased with the exclusion of those smoking less than 15 cigarettes daily 101. Gender-smoking interactions on FEV₁ have been reported for COPD participants with and without asthma in a Norwegian study by Sorheim and colleagues, though it was not clear whether the asthma-smoking interaction was statistically significant 102. For 6,126 participants of the SAPALDIA study, the association between physician-diagnosed asthma and pre-BD airflow obstruction was significantly higher for non-smokers compared with ever-smokers, however the estimates for the combined asthma-smoking subgroup did not suggest a synergistic interaction 19.

Asthma*passive smoking interaction in children

An interaction between the effects of childhood asthma and prenatal maternal smoking on reductions in spirometric indices has been suggested by the Children’s Health Study 78. The group with in utero smoke exposure and early-onset asthma had the highest decrements in FEV₁/FVC levels, which appeared statistically greater for boys than girls. For a New Zealand cohort studied from 9 to 15 years of age, those with wheezy breathing and two smoking parents had a mean decline of 3.9% and 2.3% in FEV₁/FVC levels for boys and girls respectively when compared to children without either asthma/wheezy breathing or smoking parents, and these estimates seemed greater than the individual associations combined 84.
Active/passive smoking interaction for adults

In a two-generation study that spanned 1972 to 1996, an interaction was observed between the effects of personal smoking and maternal smoking from pregnancy on pre-BD lung function for middle-aged offspring \(^{103}\). When using the equivalent of modified GOLD-defined COPD stage II or greater as the categorical outcome, an adverse effect from maternal smoking was found for current smokers without current asthma, but not for past smokers or never smokers \(^{103}\). A modest paternal-personal smoking interaction was also reported by the same study, though the above maternal-personal smoking interaction was not part of the regression model.

No parental-personal smoking interactions were identified by the ECRHS, however this may be in part explained by the parental smoking information that was retrospectively collected and subject to misclassification of those with and without the exposure \(^{18}\). Emerging data has suggested that personal active smoking might also interact with childhood exposure to parental SHS with regard to gas transfer factor measurements \(^{104}\). To date, the presence of a maternal-personal smoking interaction on post-BD spirometry or complex lung function has not been reported.

Expert commentary

Clinical Implications

The complex interplay between asthma and atopy on the one hand, and active and/or passive smoking on the other, might in part explain the considerable variation in the loss of lung function for smokers of the same age, sex and equivalent pack-year history. This is highlighted by the heterogenous nature and natural history of COPD \(^{105}\). This insight reinforces the benefits for people with asthma who smoke to quit. It also raises the possibility that the adverse “smoking effects” on lung function extend beyond that of personal smoking to include parental smoke exposure and SHS exposure in adulthood. These considerations might be useful when assessing individuals with a clinical diagnosis of COPD.

Public health Implications

The presence of increased lung function loss from an asthma-smoking or smoking-smoking interaction provides another compelling reason for people to stop smoking and avoid smoky environments. While this presents strong public health messages for the population at large,
at-risk subgroups such as asthmatics who smoke, and possibly younger individuals with a history of maternal smoke exposure who are contemplating taking up smoking, can be more specifically targeted.

**Research Implications**

By using existing asthma and smoking definitions, together with population-based data in which smokers with asthma are well represented from present and future studies, additional estimates of the associations may allow a meta-analysis to more accurately estimate interactions between active smoking and asthma phenotypes. While an interaction has been suggested for continuous measures of post-BD airflow obstruction, it is unknown whether the interaction applies to the diagnostic criterion of COPD itself, as defined by a formal cut-off of the FEV₁/FVC. If confirmed, the question remains whether the asthma-related phenotype with irreversible airflow limitation in smokers is prognostically different from that of smoking-related COPD. While non-atopic asthma of later-onset might lead to worse lung function per se, whether this impacts on the presence of severe COPD in later life is an area for further research. Cohort studies that span birth, childhood and adulthood are best suited to confirm whether the early life insult of maternal and/or paternal smoking might be a predisposing factor to the development of COPD by middle-age, perhaps through a synergistic interaction with personal smoking.

**Five-year projection**

“Fixed airflow obstruction” and “irreversible airflow limitation” refer to the same spirometric abnormality, but traditionally their application depends on whether smoking or asthma is the perceived cause. Given the likely multiplicative effect of asthma and active smoking as they relate to post-BD airflow obstruction, further work by international guideline committees for asthma and COPD can further delineate this large but previously underemphasized group to help clarify its natural history and provide more specific therapeutic recommendations. This relative exclusion challenges the conventional approach to therapeutic trials of respiratory drugs and is likely to prompt a reassessment by governmental agencies that licence therapies.

From a future viewpoint, further studies that describe the main effects and/or interactions between the effects of exposures such as asthma, active smoking, parental smoking and SHS exposure in adulthood on lung function, might potentially lead to the development of an
algorithm that can generate a tailored lung function risk profile. While the recommendation to quit smoking is important to all current smokers, the stratification by an individual’s predisposition to lung function loss might assist in guiding health professionals to target those who will gain the most lung function benefit from smoking cessation.

**Key issues**

- COPD is a major global health problem that is considered to be largely preventable and predominantly due to active smoking in Westernised countries.
- While the variation in lung function for a given smoking history might be explained by an individual’s susceptibility, interactions with environmental risk factors other than active smoking may well play a role.
- Many studies in adults that have examined asthma-smoking interactions have used pre-bronchodilator spirometry, which is not appropriate for the diagnosis of COPD.
- Asthma has been found to augment the adverse effect of active smoking on post-bronchodilator airflow obstruction when both factors are present, particularly for those with atopic sensitization and current asthma symptoms, and this might have important implications for the development of COPD at a community and individual level.
- For interactions that involve active smoking, the additional deficit in lung function beyond the sum of individual associations provides another compelling reason for current smokers to quit, especially at an earlier age.
- Further research is needed to address whether maternal smoking might be a predisposing factor in the development of COPD for adult offspring.
- Given increasing recognition of the importance of the overlap between asthma-related irreversible airflow limitation and smoking-related COPD, further revisions of the nomenclature and change in policies around therapeutic trials may well be indicated.
Definitions of abbreviations: COPD, chronic obstructive pulmonary disease; FEF, forced expiratory flows; IU, intrauterine; SHS, second-hand smoke.

Main associations are indicated by the fine blue arrows
Asthma-smoking interactions and its augmentation of the main associations are indicated by the bold doublehead and singlehead arrows respectively

? uncertainly due to lack of evidence
* current smokers
† especially for those atopic with current asthma symptoms
‡ especially for late-onset asthma
Table 1. Differences between Regression Models with and without a [Two-way] Interaction

<table>
<thead>
<tr>
<th>Statistical interaction or “synergy”</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression model</td>
<td>Additive</td>
<td>Multiplicative</td>
</tr>
<tr>
<td>Components</td>
<td>Exposure 1 + Exposure 2</td>
<td>Exposure 1 + Exposure 2 + Statistical interaction term</td>
</tr>
<tr>
<td>Combined effect</td>
<td>Equals the sum of individual estimates</td>
<td>Greater than the sum of the individual estimates, with the difference attributed to the interaction itself</td>
</tr>
<tr>
<td>Reported association</td>
<td>Association of exposure 1 across all subjects</td>
<td>Association with exposure 1 but not exposure 2, and Association with exposure 1 and exposure 2</td>
</tr>
<tr>
<td>Interpretation †</td>
<td>The main associations for exposures 1+2 are independent of each other</td>
<td>The estimate for the strength of the association for exposure 1 is statistically different in the presence or absence of exposure 2</td>
</tr>
</tbody>
</table>

† The interpretation of the interaction parameters depend on the type of regression model. For linear regression, the interaction is a difference between mean differences; for logistic regression, ratio of odds ratios; and for Poisson regression, ratio of rate ratios.
Table 2. Cohort Studies of Asthma-Smoking and Smoking-Smoking Interactions on Pre- and Post-bronchodilator Spirometry

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>Age (years)</th>
<th>Duration (years)</th>
<th>Two exposures of the interaction term</th>
<th>Main outcome variable</th>
<th>Interaction (combined effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tashkin et al 1996</td>
<td>5,733</td>
<td>Mean 48 (sd±7)</td>
<td>5</td>
<td>Active smoking status BHR</td>
<td>Post-BD FEV₁ decline</td>
<td>Yes (multiplicative)</td>
</tr>
<tr>
<td>Perret et al 2013 †</td>
<td>1,389</td>
<td>Mean 45 (sd±1)</td>
<td>37</td>
<td>Active smoking (py) Lifetime asthma</td>
<td>Post-BD FEV₁/FVC at age 45</td>
<td>Yes (multiplicative)</td>
</tr>
<tr>
<td>James et al 2005 ‡</td>
<td>9,317</td>
<td>&gt;18</td>
<td>15</td>
<td>Active smoking status Self-reported asthma</td>
<td>Pre-BD FEV₁ up to 7x over 28 years</td>
<td>No (additive)</td>
</tr>
<tr>
<td>Lange et al 1998 Δ</td>
<td>17,506</td>
<td>Mean 52 (sd±12)</td>
<td>15</td>
<td>Active smoking status Self-reported asthma</td>
<td>Pre-BD FEV₁ after 15 years</td>
<td>No (additive)</td>
</tr>
<tr>
<td>Apostol et al 2002 101β</td>
<td>3,950</td>
<td>18-40</td>
<td>11</td>
<td>Active smoking ≥15 cigs/day* Self-reported asthma</td>
<td>Pre-BD FEV₁ decline</td>
<td>Yes (multiplicative)</td>
</tr>
<tr>
<td>Bridevaux et al 2010 19Δ</td>
<td>6,126</td>
<td>30 to ≥70</td>
<td>11</td>
<td>Active smoking status Physician-diagnosed asthma</td>
<td>Pre-BD FEV₁/FVC at 11 year follow-up</td>
<td>Yes (but not synergistic)</td>
</tr>
<tr>
<td>Woolcock et al 1984 73</td>
<td>11,497</td>
<td>8-12</td>
<td>4</td>
<td>Active smoking Prospective asthma</td>
<td>Pre-BD spirometry over 4 years</td>
<td>No (additive)</td>
</tr>
<tr>
<td>Sherrill et al 1992 64†‡</td>
<td>2,413</td>
<td>3-15</td>
<td>6</td>
<td>Parental smoking Wheeze</td>
<td>Pre-BD FEV₁/FVC between 9 and 15 years</td>
<td>Yes (multiplicative)</td>
</tr>
<tr>
<td>Gilliland et al 2003 78§</td>
<td>5,933</td>
<td>7-18</td>
<td>8</td>
<td>Maternal smoking (IU) Early-onset asthma</td>
<td>Pre-BD spirometry</td>
<td>Yes (multiplicative)</td>
</tr>
<tr>
<td>Tager et al 1983 80</td>
<td>633</td>
<td>8 [range 4-23]</td>
<td>5</td>
<td>Active smoking Maternal smoking</td>
<td>Expected 5-year growth in FEV₁</td>
<td>No (additive)</td>
</tr>
<tr>
<td>Upton et al 2004 103††</td>
<td>2,000</td>
<td>30-59</td>
<td>24</td>
<td>Active smoking Maternal smoking (IU)</td>
<td>Pre-BD spirometry in middle-age</td>
<td>Yes (multiplicative)</td>
</tr>
</tbody>
</table>

Abbreviations: BD, bronchodilator; BHR, bronchial hyperresponsiveness; FEV₁, forced expiratory volume in one second; FEV₁/FVC, the ratio between FEV₁ and forced vital capacity; IU, intrauterine; SHS, second-hand tobacco smoke; py, pack-years.

† TAHS, Tasmanian Longitudinal Health Study, Australia
‡ Busselton Health Survey, WA, Australia
Δ Copenhagen City Heart Study, Denmark
β CARDIA (The Coronary Artery Risk Development in Young Adults Study), USA
Δ SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults)
†† The Dunedin Multidisciplinary Health and Development Study, New Zealand
§ Children’s Health Study, CA, USA
†† Renfrew-Paisley (Midspan) Family Study, UK
* Smokers of less than 15 cigs/day were excluded from the analysis
References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

•• #5, Eisner and colleagues 2010 -- Provides comprehensive summarises of the evidence relating to potential COPD risk factors
•• #10, Perret and colleagues 2013 -- Describes the combined and independent association between asthma, smoking and spirometrically-defined COPD
•• #39, Thomson and Chauduri 2009 -- Discusses clinical aspects, pathological mechanisms and the limited evidence available for optimal drug treatment
• #57, Brown and colleagues 1984 -- First clear documentation of this long-term sequel for asthma
• #76, Keil and colleagues 2009 -- Important interaction that provides a potential mechanism by which maternal smoking increases the risk of childhood asthma
• #78, Gilliland and colleagues, 2003 -- Describes the interplay between prenatal maternal smoking, asthma and gender on childhood lung function
• #103, Upton and colleagues 2004 -- Describes a maternal-personal smoking interaction on pre-bronchodilator spirometry for middle-aged offspring

Citations:
   http://www.who.int/mediacentre/factsheets/fs339/en/


Author/s:
Perret, JL; Walters, EH; Abramson, MJ; McDonald, CF; Dharmage, SC

Title:
The independent and combined effects of lifetime smoke exposures and asthma as they relate to COPD

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