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PERSPECTIVE

Tobacco use in relation to COPD and asthma

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ABSTRACT: Smoking is the leading cause of preventable death worldwide. Hundreds of millions of individuals still smoke, affecting their health as well as that of their peers, family and offspring. Smoking is a well-established prime risk factor for chronic obstructive pulmonary disease and hampers the response to treatment in asthma and chronic obstructive pulmonary disease. In the present paper, new concepts are discussed with respect to pathology, treatment, smoking cessation and tobacco control. Recommendations for future directions are given.

KEYWORDS: Asthma, chronic obstructive pulmonary disease, cigarette smoke

Smoking is the major risk factor for the development of chronic obstructive pulmonary disease (COPD) and hampers the response to treatment in both asthma and COPD [1, 2]. Despite the worldwide research related to various aspects of smoking and the efforts from organisations like the European Respiratory Society (ERS) and the World Health Organization (WHO) to curb tobacco use and prevent people from starting to smoke, the global epidemic of tobacco-associated disease has progressively worsened. Recently, a report of the Smokefree Partnership (made up of the ERS, the French Institute National du Cancer and Cancer Research UK) and the European Heart Network entitled *Lifting the smokescreen: 10 reasons for a smoke free Europe* was published [3] and launched at the European Parliament in Brussels, Belgium, aiming to assist European and other national politicians and policy makers to promote and implement comprehensive smoke free legislation. Only new laws, promoting smoke free environments and smoking cessation will help to reduce the smoking prevalence and limit the increases in death rates from smoking-related diseases.

In November 2005, clinicians, pathologists, psychologists, epidemiologists and basic scientists met at the Lunteren-V Symposium (Groningen, the Netherlands) ''Smoking as target in asthma and COPD''. Participants discussed the effects of smoking in relation to asthma and COPD, including the epidemiology, genetics and psychology of tobacco addiction, the effects of smoking in pregnancy and childhood, the effects of smoking on the pathogenesis and treatment of asthma and COPD, smoking cessation and perspectives of smoking control in the future. The present article summarises important aspects that were discussed and recommendations for future actions are given.

TRENDS OF TOBACCO USE IN EUROPE

According to data from the WHO, at the beginning of 2002 ~30% of the adult populations of the European Member States were regular smokers. Figure 1 shows that highest numbers of smokers are found in Greece (almost half of males and nearly 30% of females smoke) and the lowest numbers are found in Sweden [4]. In all countries except Sweden, the prevalence of smoking is higher in males than in females. However, the graph shows a north–south gradient, *i.e.* in the northern countries (*e.g.* Scandinavian countries and the United Kingdom) the prevalence is almost similar in males and females. In central Europe the prevalence of smoking in males and females is of an intermediate difference, *e.g.* the habit is more common in males than in females (13.9 *versus* 5%). Interestingly, in southern Europe, there is a still larger difference with regard to smoking habits in males and females; this difference being largest in Portugal, where 37% of males and only 13% of females smoke. Finally, ~60% of children are exposed to parental smoking in Europe, with harmful effects as discussed later. Expectations for the future are that the prevalence of smokers will decline in the ''Western'' part of the world, but that tobacco addiction will increase in low-income countries that can least afford its toll of disability, disease and death. In the Western

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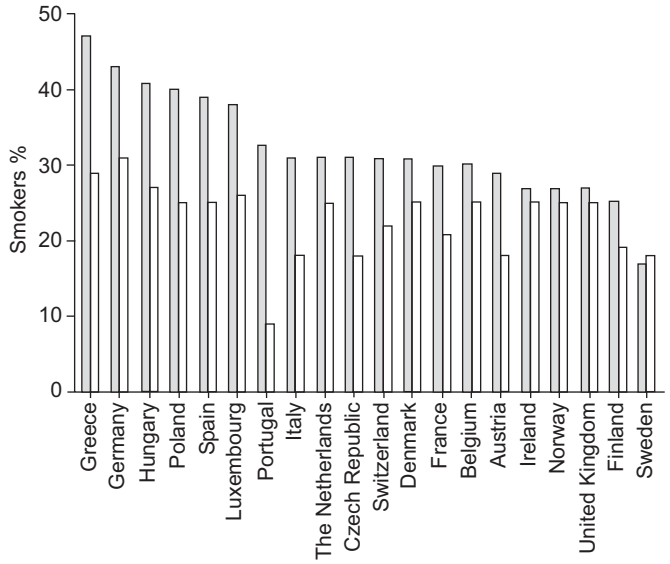

FIGURE 1. Prevalence of smokers in Europe in 2005. Data originally taken from [4]. Figure reproduced from [5] with permission from the publisher. ■: males; □: females.

world, smoking rates are on the decline, thanks in large part to tobacco taxes. However, low-income countries are facing the temptation of billions of dollars of potential investment from multinational tobacco companies. Governments in the Western world could help their counterparts in low-income countries to resist the influence of tobacco companies by creating alternative investment opportunities and suggesting that the aid will be increased if tobacco taxes are raised [6].

GENETICS AND PSYCHOLOGY OF TOBACCO ADDICTION

It is generally accepted that smoking cessation is the most significant measure that can be taken to reduce morbidity and mortality. Notwithstanding this, physicians find themselves frequently frustrated as patients with respiratory disease continue smoking. Understanding this behaviour requires understanding of the effect that nicotine exerts on instinctual motivation centres of the brain. Smoking behaviour has traditionally been viewed as the manifestation of either a biological dependence to nicotine or a learned habituated routine. Emerging evidence suggests that biology and psychology may not be so distinctly independent in this phenomenon. Three fundamental concepts help to develop a deeper understanding. First, the magnitude of nicotine's impact on the brain relates to the rate of its delivery to the brain, suggesting that characteristics of the delivery device may also contribute to the motivating potential of the drug [7]. Second, nicotine bypasses normal sensory input pathways to directly affect the organism's most fundamental survival instincts and thereby influences behavioural decisions more profoundly than even starvation or pain [8]. Finally, exposure to nicotine can result in long-term changes in structure and function of the brain, suggesting that tobacco use should be viewed as an exposure that may increase lifelong risk of relapse [9, 10].

Clinical research has highlighted individual differences for nicotine dependency as well as success in smoking cessation. This can be partly attributed to polymorphisms in several genes, *e.g.* dopaminergic genes that may influence the dopamine receptor number and/or function and cytochrome P450 enzymes (CYP2A6 and CYP2D6) that lead to more rapid nicotine metabolism [11]. COPD develops primarily in heavy smokers, suggesting that smoking behaviour regulated by the serum nicotine level may be associated with the development of COPD. However, the *CYP2A6del* polymorphism may inhibit smokers from giving up smoking, yet it appears to function as a protective factor against the development of pulmonary emphysema independent of smoking [12]. There are a number of other confounding factors related to the development of emphysema and airflow limitation, such as race, sex, air pollution and social status, indicating that further investigations are needed to clarify the relationship between this polymorphism and the development of pulmonary emphysema.

Insights into the genetic contribution to smoking addiction can potentially lead to more effective strategies for smoking reduction.

EFFECTS OF SMOKING IN PREGNANCY AND EARLY CHILDHOOD

With the dramatic rise in asthma and allergic disease there is an urgent need to understand the early contributing events. While the development of allergic disease is multifactorial, the contribution of maternal smoking is a major adverse, and yet avoidable, environmental factor. The foetus is exposed directly (systemically) to the toxic effects of cigarette smoke and is uniquely vulnerable because of its immature state. Developing systems are more susceptible to damage given their high numbers of actively dividing cells and a weaker ability to detoxify and to repair DNA damage. In particular, effects on developing airways and immune function could contribute to an increased risk of susceptibility to asthma and allergic disease [13].

Smoking in pregnancy is associated with significant effects on neonatal lung function, and many of these effects persist into later childhood. Reduced lung function in school-aged children with smoking parents appears to be especially linked to *in utero* exposure, next to additional effects of post-natal exposure [14, 15]. These children have significantly higher rates of respiratory infections and asthma, and are eventually more likely to smoke as adults. This, together with developmental abnormalities in airway structure and function, has major implications for chronic airways diseases in later adulthood. There is accumulating evidence that maternal smoking in pregnancy is associated with effects on neonatal immune function (*e.g.* increased cord blood immunoglobulin E [16]), on cytokine production [17] and on lymphoproliferative responses [18] in the offspring. These effects may be mediated by increased oxidative stress, which is evident in infants exposed to passive smoking in the early post-natal period [19].

Adverse effects on immune function could also account for increased susceptibility to infection in infants of smokers, which may by itself contribute to the development or prevention of allergy and asthma. Innate toll-like receptor

(TLR) pathways provide the first defence against microbes but also modulate subsequent antigen-specific adaptive immune responses, essential for normal post-natal immune maturation. Factors that alter these signals have been implicated in the increase in numbers of patients with allergy and other immune diseases, and smoke constitutes one such factor [20].

INTERACTION OF SMOKING WITH GENES THAT PREDISPOSE TO ASTHMA AND COPD

Epidemiological and family studies have indicated that genes that predispose to asthma interact with environmental tobacco smoke (ETS) exposure in early life. At least one of those genes resides on chromosome 5q, as it was shown that linkage to chromosome 5q was only present in families with children exposed to ETS [21]. Two studies provide some support, one of which suggests this may be the *CD14* gene [22] and the other that it may be the *betareceptor* gene [23]. Both studies are inconclusive as they have not yet been replicated or are based on a small sample size. *Glutathione* S-*transferase (GST)* genes are implicated in several detoxification pathways, including response to oxidative stress. Deletions in *GSTM1* and *GSTT1* are rather prevalent and these loss-of-function mutations may result in impaired detoxification of toxic substances, such as those present in ETS. A study of 2,950 children in the USA showed that the association of ETS on asthma and wheezing was restricted to children with *GSTM1* null genotype gene [24]. In 3,054 German schoolchildren, ETS was significantly associated with lower lung function in children carrying the *GSTT1* null alleles [25]. Moreover, current smoking ($\geqslant$20 cigarettes·day^{-1}) was associated with a higher frequency of self-reported asthma and wheeze in carriers of *GSTM1* null genotype compared to the nonsmokers. Further genetic studies need to be carried out in order to explain why only a subset of smokers develops COPD. It will be intriguing to see if gene–ETS interactions that associate with low lung function in childhood are associated with COPD in adulthood.

Altogether, these studies clearly show the harmful effects of ETS as an environmental factor. It is essential that greater effort is directed towards better strategies for the prevention of this readily avoidable toxic exposure. The aforementioned report *Lifting the smokescreen* [3] includes an estimate of 79,000 deaths·yr^{-1} attributable to passive smoking in Europe. It also analysed the economics of smoke free policies and the impact of smoking bans in restaurants and bars, showing an increase of occupation and employment in bars and restaurants in New York (NY, USA) since March 2003 when the smoke free law came into force. This means that measures to prevent passive smoking are feasible and popular.

SYSTEMIC EFFECTS OF SMOKING

COPD is increasingly regarded as a systemic disorder, associated with, amongst others, muscle wasting and bone loss. It is likely that the systemic component constitutes a risk factor for development of, for example, cardiovascular events [26, 27]. The underlying mechanisms are unclear, yet increased levels of the acute-phase C-reactive protein (CRP) has linked COPD with cardiovascular disease [28]. Elevated CRP levels were found in ex-smokers with COPD [29] and are a predictor of acute exacerbations in COPD [30]. In stable disease, increased levels of CRP could be explained by genetic determinants or by a response to infections or the damaged lung tissue itself, generating endogenous TLR ligands such as fibronectin, which triggers inflammation [31, 32]. Cardiovascular literature shows that high CRP level predicts incident myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death among healthy individuals with no history of cardiovascular disease [33]. Interestingly, systemic corticosteroids reduce CRP and other circulating inflammatory cytokine levels in COPD [34]. However, there is so far no evidence that a reduction in CRP will lead to an improvement in outcome of COPD. An important lesson was learned with chronic heart failure (CHF). Publications from three randomised, controlled trials of anti-tumour necrosis factor (TNF) treatments (etanercept and infliximab) in CHF showed reduced serum CRP, interleukin (IL)-6 and TNF levels but no measurable benefits for the patients [35, 36]. These data show the enormous complexity of the inflammatory cascades and networks involved in chronic diseases such as cardiovascular disease and COPD [37]. The interaction between cardiac and pulmonary disease may have important implications for the development of novel therapies. Well-conducted, long-term interventional studies are needed for better understanding of the mechanistic and epidemiological link between steroid therapy, COPD and cardiovascular disease.

SMOKING AND SMALL AIRWAYS

Smokers with and without COPD specifically show inflammation and fibrosis in the small airways [38, 39]. Small airways disease correlates with impaired lung function and most strongly with uneven ventilation as measured by the single-breath nitrogen washout test [40]. However, small airways geometry (wall thickness) is more closely related to lung function impairment than inflammatory cell counts in the small airways of smokers and ex-smokers with COPD [39].

There are multiple ways to approach the small airways noninvasively (lung function, computed tomography (CT), hyperpolarised helium) but none of them seems completely satisfactory [41]. Together with the forced expiratory volume in one second/vital capacity ratio, the single-breath nitrogen test shows predictive power for COPD development in susceptible smokers [42]. Data suggest that the multiple-breath nitrogen washout test constitutes the optimal way to assess small airways (dys)function at present, showing significant abnormalities in smokers [43]. Smoking cessation induced persistent improvements in the conductive airway compartment, in contrast to the acinar airways malfunction that quickly returned to baseline after a transient improvement [44]. Yet this test awaits anchoring to small airways pathology. What else can be used to monitor small airways? Measuring dimensions of large and intermediate airways by high-resolution CT scanning allows accurate estimation of small airways dimensions in smokers [45]. Air trapping thus measured is associated with small airways inflammation, in particular with the inflammatory cell infiltrate within the smooth muscle layer [46]. In addition, it was recently demonstrated that airflow limitation in COPD is more closely related to the dimensions of the distal (small) airways than proximal (large) airways [47]. Taken together, smoking seriously affects the histology and function of small airways. A new ''small airways era'' is starting, thanks to technical

developments in the noninvasive assessment of small airways. Small airways techniques cannot be used today for screening purposes but are valuable for (sub)phenotyping COPD. Integrative studies on the histology, cellular phenotypes, gene expression and function of small airways are urgently needed.

SMOKING AND TREATMENT OUTCOME IN ASTHMA AND COPD

While cigarette smoking is common in asthmatics, with prevalence rates similar to the general population, studies in asthma have tended to concentrate on never-smokers. However, asthmatics who smoke have an increased risk of death [48], more severe asthma symptoms, an accelerated decline in lung function, increased hospital-based care and increased mortality following hospital admission with an episode of near-fatal asthma, compared with nonsmoking asthmatics [49–51]. Furthermore, they have a different inflammatory pattern in the airways. Smoking asthmatics have increased numbers of neutrophils and levels of IL-8 but decreased numbers of eosinophils in sputum [52]. Also, in mouse models of asthma, a decrease in ovalbumin-induced airway eosinophilia was found after smoking [53, 54]. Smoking may thus shift the inflammatory phenotype found in asthma from eosinophilia towards neutrophilia, which may have implications for clinical manifestations of disease as well as for therapy. Smoking also has implications for treatment response, since it may confer a degree of steroid-resistance in asthma [55]. The underlying mechanisms are poorly understood but may include differences in drug access or clearance from the lungs due to increased mucus secretion or airway permeability, increased oxidative stress, abnormalities in glucocorticoid receptor function or altered corticosteroid pharmacokinetics. There is increasing evidence that histone acetylation and deacetylation by histone deacetylases (HDACs) plays a critical role in the regulation of inflammatory genes and in mediating the anti-inflammatory effects of corticosteroids. Disruption in the nuclear histone acetylation/deacetylation balance (chromatin remodelling) by cigarette smoke may result in excessive transcription of specific proinflammatory genes in the lungs. Therapeutic strategies to increase HDAC activity may, therefore, be expected to reduce inflammation and restore steroid responsiveness [56]. These strategies include low doses of theophylline or antioxidants and nitric oxide synthase inhibitors [57, 58]. However, the best therapy would be encouraging these patients to quit smoking since there is some evidence that smoking cessation may at least partially restore steroid responsiveness in asthma.

There is also evidence that steroids have less effect in smoking COPD patients. SIN *et al.* [59] showed in a pooled meta-analysis that mortality was reduced by inhaled steroids, a beneficial effect that was especially notable in former smokers.

SMOKING CESSATION

Smoking cessation in teenage subjects

Among adults who have smoked daily, 82% first tried cigarettes when aged <18 yrs and 53% smoked daily before that age. Many teenage smokers want to stop smoking and they do so once they receive the right kind of help at the right time. Most smoking research on teenage subjects has focused on school-based programmes to prevent teenagers from starting to smoke. Unfortunately, these prevention programmes have had little long-term effect and currently about one out of every four teenagers still start smoking. A different approach using brief counselling and an interactive computer program during routine medical care showed that 24% of teenage smokers had stopped smoking after 2 yrs. This quit rate was more than double that of similar teenage smokers who did not receive the intervention (11%) [60]. This brief antismoking intervention included a 30-s clinician advice message, a 10-min interactive computer program, a 5-min motivational interview, and up to two 10-min telephone or in-person booster sessions. Unfortunately, the programme was not effective in preventing nonsmoking teens from starting to smoke over the next 2 yrs. This implies that more effort must be undertaken in developing school-based prevention programmes. The social influences of smoking on teens must be better examined and behavioural sciences should be involved to come up with a better approach. School-based tobacco prevention programmes must also include prohibiting tobacco use at all school facilities and events, helping students to quit and preventing them from starting smoking.

Smoking cessation in COPD

Smoking cessation can slow the progression of COPD at all stages of disease. There are the first indications that confrontation with a diagnosis of COPD in new patients increases smoking cessation rates [61]. It is important to start smoking cessation as early as possible as patients with COPD stop smoking less easily than smokers without COPD. Reimbursement of smoking cessation treatment clearly increases smoking cessation rates [62].

Notwithstanding its beneficial effect on progression of COPD, many sustained ex-smokers remain symptomatic and experience frequent exacerbations of their disease [63]. They also have persistent airway wall inflammation [64, 65]. The latter could signify that inflammatory cells are an integral part of the repair process taking place after smoking cessation. Investigations of changes in repair and remodelling processes, especially in the small airways after smoking cessation, may elucidate the discrepancy between the ongoing and increased airway inflammation and the improvement in clinical variables after smoking cessation. More detailed information on the exact role of inflammatory markers in repair and remodelling processes in COPD could result in new (anti-inflammatory) therapy strategies.

Effects of smoking (cessation) in males and females

The prevalence of COPD is higher in males than females, which is generally attributed to higher historical rates of cigarette smoking in males [66, 67]. However, some studies suggest that females are more susceptible to the deleterious effects of cigarette smoke, which may partly contribute to an observed recent increase in female prevalence rates of COPD [66]. This may vary from country to country, with the sex difference being present in some countries but not in others. The Lung Health Study [68] showed that females who quit smoking gain over twice as much lung function as males who quit. Conversely, if females do not quit they lose more lung function than males. This is important to explain to females, since they are less successful in their attempts at smoking cessation. The amount of lung function gained in females who

quit strongly depends on how much they smoked. This relationship is less pronounced in males. Greater airways reactivity accentuates the effects of quitting and continuing to smoke in both sexes [68]. It has been shown by DOLL *et al.* [69] that even among middle-aged smokers cessation is effective albeit that cessation at earlier ages is even more so. Doctors and other health professionals should point this out very clearly in order to encourage the patient to quit smoking. More prospective studies are needed with respect to smoking cessation and mortality.

Smoking cessation advice

From the literature it is clear that smoking cessation advice has a certain demand on the healthcare givers [70]. It is therefore important to have effective strategies. A minimal smoking cessation advice session (<3 min) is already effective, there is a dose–response effect of these sessions that varies from person to person, and more than four smoking cessation sessions are especially effective. Furthermore, additional treatment with nicotine replacement and/or bupropion may further help to improve smoking cessation success rates, albeit with variable efficacy in individual persons.

PERSPECTIVES OF SMOKING AND TOBACCO CONTROL IN THE FUTURE

Cigarette smoking is one of the biggest threats to current and future world health. According to WHO projections, there will be 2 billion smokers and 10 million smoke-related deaths annually by 2050. PETO *et al.* [71] have estimated that mortality in the next 50 yrs can be affected more by the numbers of adult current smokers who stop than by the numbers of young people starting smoking. Although the prevalence of smoking among adults has declined steadily over the last decades, smoking has declined much more slowly among young adults and, sadly, smoking has remained at ~28% since 1994 in UK adults [72].

Since smoking cessation and prevention programmes have shown limited success, policy makers must be stimulated to strengthen governmental actions of smoking control. This has to be done in addition to continuing encouragement of smoking cessation by doctors and other health professionals.

Since 1997, the majority of the European Union members have strengthened their policies on tobacco control. This included increasing taxation of tobacco products, introduction of age restriction on tobacco sales, introduction of a complete ban or strict restrictions on direct advertising and improvement of regulations on smoking in public places. In addition, there have been better information campaigns, introduction of large warning labels on tobacco products and nicotine replacement therapy products have been made available without prescription in pharmacies. However, no attempts have been made on the regulation of the tobacco product itself. National economic interests and political influence of the tobacco industry may be fundamental to the latter. The amount of tar, nicotine and other toxic ingredients in cigarettes are not regulated and information on this is confidential. Information on the constituents of cigarettes needs to be present on the package label. Importantly, policy makers should be strongly encouraged to ban the tobacco industry or at least establish comprehensive smoke free policies, like smoke free environments in all public places and workplaces, bans on tobacco advertising and large clear graphic health messages on tobacco packaging. The report *Lifting the smoke screen* [3] showed that the public supports and complies with smoke free legislation and that smoke free laws do not result in negative economic effects.

CONCLUSIONS

Smoking is a serious healthcare problem that needs to be addressed more aggressively by clinicians and governments. Smoking cessation, at any age, is the most effective way to reduce disease progression in chronic obstructive pulmonary disease, improve steroid responsiveness in asthma and chronic obstructive pulmonary disease, reduce the risk for development of many forms of cancer and cardiovascular diseases and improve overall health and survival. In particular, nonsmoking teenagers need attention to prevent them from starting to smoke. As long as cigarette smoking remains a normal and acceptable behaviour in adults, preventing children and adolescents from experimenting is difficult. Schools can provide an ideal venue to teach about the harmful effects of smoking and the behaviour of the tobacco industry in manipulating young people. In addition, the public attitude to smoking must change, and scientific researches, health professionals and society must take their responsibility to call upon policy makers and governments to support implementation of comprehensive smoke free laws. A real threat is the estimate that the prevalence of smokers will increase in low-income countries where the tobacco industry is consolidating due to less governmental control and absent public debate on the role of tobacco companies. These countries, whose economies are tobacco dependent, should be assisted in diversifying.

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