COPD and environmental risk factors other than smoking

14. Summary

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Date : 7th March 2008

1. Objectives and general approach

The objective was to obtain a good insight from the available literature as to which environmental factors other than smoking may be causes of chronic obstructive pulmonary disease (COPD).

It was recognized that identification of all possible factors, collection of complete literature on each possible factor, entry of quantitative data onto databases and conduct of meta-analyses (analogous to the approach used in another project for summarizing the smoking data) would have been a huge and very time-consuming task. A simpler approach was used, based on PubMed searches only, with secondary references not necessarily obtained for all risk factors, and no real quantitative summarization of the data.

2. Selection of risk factors for further consideration

As a first step to deciding which risk factors other than smoking seemed possibly relevant to COPD I studied a number of published review papers, looking at which factors were referred to and, where appropriate, the authors' belief as to the strength of the evidence. I then compiled a list of possible risk factors and limited attention to 12. These are evident from the 13 previous sections of this report:

1. Identifying relevant papers
2. Diet
3. Cooking and heating
4. Alcohol
5. Eosinophilia
6. Race
7. Body mass index

8. Childhood infection
9. Outdoor air pollution
10. Socio-economic status (and related factors)
11. Atopy, allergy and hyperresponsiveness
12. Infection in adults
13. Occupation

Other factors that might have been thought relevant were not considered for the following reasons.

Genetic factors Numerous papers refer to α_1-antitrypsin deficiency as a strong (but rare) factor for emphysema. Some papers also refer to blood type and ABH secretor status and other to family history studies. However, genetic factors were not considered as the project was limited to environmental factors.

Sex, age and height Inasmuch as the definition of COPD depends on forced expiratory volume in one second (FEV_1), and FEV_1 is standardized for age, sex and height, it was decided not to pursue this area.

Respiratory diseases A number of reviews mention the problems of distinguishing asthma, cystic fibrosis, bronchiectasis and obliterative bronchiolitis, all diseases associated with airflow obstruction, from COPD. However, these were not considered environmental risk factors and were not pursued further.

Respiratory symptoms While it is clear that cough, mucous hypersecretion and dyspnoea are all strongly associated with COPD, these can be viewed as part of the disease itself, and were considered outside the scope of the project.

FEV_1 Low FEV_1 is of course a strong risk factor for COPD, but inasmuch as it is so closely linked to its definition, work here seemed unnecessary.

Environmental tobacco smoke (ETS) A quite up-to-date quantitative review of the evidence on ETS and COPD was already available[1] so it was not considered necessary to do further work. However its findings are considered below, along with those from the 12 other risk factors that were reviewed.

3. General considerations

Sources of information Based on PubMed searches (see sections 1 to 13 of this report for fuller details) an attempt was made to identify general reviews of COPD, reviews of COPD and the specific risk factors of interest, and individual epidemiological or autopsy studies presenting evidence on the relationship of COPD to one or more of the risk factors of interest. Where the evidence for a risk factor was quite limited, secondary references (of papers cited in the papers identified originally) were also obtained, though no attempt was generally made to obtain secondary references of secondary references. Where the evidence for a risk factor was already quite extensive, no attempt was made to obtain secondary references. (It would of course be possible to expand one or more of sections 2 to 13 for additional references at a later date.) Overall, about 1000 references were obtained, based on scanning of over 10000 abstracts from PubMed searches, with about 600 references used in the reviews in sections 2 to 12.

Smoking It is well known that the effects of smoking are extremely strong and a number of the general references consider that the role of some of the risk factors is to modify the effects of smoking. When considering the evidence on a risk factor from a particular study it has generally been made clear whether smoking has been taken account of in the analysis of the study. It often has been, but this is not always the case.

Types of study considered Consideration was given to epidemiological case-control, cross-sectional and cohort studies but not to studies of survival from disease. Autopsy studies comparing decedents with COPD and with control diseases, or quantifying the extent of disease in relation to the extent of exposure were also considered.

Types of endpoint Use of the term COPD has only been widespread in the last 20 years or so, and criteria used to assess this in life (e.g. the GOLD criteria) have not been standardized until quite recently. However, quite a number of the papers considered are much older than this, and too strict a criterion would lose much relevant data. Results are therefore generally considered for the following four broad types of information:

(i) Mortality from chronic bronchitis, emphysema or COPD;

(ii) Doctor diagnosis of chronic bronchitis, emphysema or COPD, whether reported by the doctor or by the subject;

(iii) COPD as defined based on lung function data, or lung function data relevant to the definition (FEV_1, forced vital capacity [FVC] or their ratio FEV_1/FVC) – but not other lung function variables; and

(iv) Chronic bronchitis, as defined by criteria involving persistent cough and phlegm, such as those defined by the Medical Research Council in their widely used respiratory symptoms questionnaire – but not other specific respiratory symptoms (e.g. cough, phlegm or wheeze on their own).

Study weaknesses Epidemiological studies are subject to a number of sources of bias and confounding, and methods used to analyse them vary in their ability to correct for these. While, on occasion, mention has been made of particular weaknesses in the design or analysis of some studies, or strengths of others, no systematic attempt has been made to evaluate study quality. However, some of the sections discuss particular problems in interpreting the data.

4. Conclusions by risk factor

ETS A review conducted in May 2007[1] identified ten published studies relating ETS exposure to risk of COPD in lifelong nonsmokers. Fourteen independent estimates of the relative risk associated with ETS exposure from the spouse or other household member gave an overall estimate of 1.38 (95% CI 1.14-1.68). There is also some evidence of a dose-relationship. Although there are a number of limitations of the evidence (including a lack of large

well-designed studies) that hinder a confident conclusion, the association observed is stronger than seen for lung cancer or heart disease and must be regarded as suggestive of a possible effect of ETS exposure, especially given the strong association of smoking with the disease.

Diet The review in section 2 summarizes evidence from 51 published papers. There are a large number of significant findings showing evidence of a beneficial effect for antioxidant vitamins, fruit, vegetables, fish and other dietary components generally considered to be part of a healthy diet. It seems clear enough that diet is relevant to the risk of COPD but, as with other health endpoints such as cancer, there remains doubt as to precisely which the relevant dietary compounds are, and a lack of good evidence from randomized controlled intervention trials.

Cooking and heating The review in section 3 summarizes evidence from 39 papers. Virtually all the studies considered are in Asia, Africa or Latin America, and the most commonly investigated exposure is use of biomass fuels, with nearly all the studies showing a significantly increased risk, particularly elevated in conditions of poor ventilation. Evidence from Western countries seems virtually non-existent.

Alcohol The review in section 4 considers 42 relevant publications. Some of the studies conducted were of the general population and some were of alcoholics. Generally, the results do not consistently show any beneficial or adverse effect of alcohol consumption. It may be that heavy consumption has a small effect on the risk of COPD, but this is not well demonstrated.

Eosinophilia The review in section 5 considers only nine papers. Studies in the Netherlands and in Tucson provide the most relevant information. While the presence of eosinophilia has been reported to predict substantially increased mortality from COPD, it remains far from clear that eosinophilia is actually a cause of increased risk, rather than a marker of the presence of the disease.

Race The review in section 6 briefly considers 25 papers. The evidence concerned a wide variety of racial comparisons and smoking was not taken account of in over half of the papers. No clear conclusions were reached. A clearer impression might be gained by analysis of national mortality data by race, or by analysis of NHANES surveys which have data on GOLD COPD morbidity, race and smoking habits, but this has not been attempted

Body mass index The review in section 7 considers 34 papers. While interpretation of the data is difficult, due to the various sources of potential bias – in particular the weight loss associated with the disease process and with smoking – the data seem reasonably consistent in indicating that low BMI is associated with poorer lung function and an increased risk of COPD. Some studies also suggest an adverse effect of obesity.

Childhood infection The review in section 8 considers 40 papers. Cross-sectional studies generally report an association between infection in childhood and presence of chronic bronchitis, COPD or reduced lung function, though these are open to potential recall bias. A number of cohort studies, predominantly conducted in the UK, also provide evidence supporting a relationship, particularly a series of studies by the Barker group in Southampton which consistently reported that pneumonia in early life predicts reduced lung function in adulthood. However, these studies provide very limited evidence on COPD mortality. Overall, the evidence is interesting and strongly suggestive, but still inconclusive. Possibilities of confounding remain, and there seem to be no data on the specific bacterium or virus involved.

Outdoor air pollution The review in section 9 considers 100 papers. In view of the substantial and complex nature of the literature, all that was attempted was a broad summary of the type of material available and the consistency of the conclusions. The evidence is difficult to interpret clearly. The evidence relating to COPD to outdoor air pollution is quite extensive and difficult to interpret clearly. There is considerable variation in the detail of the exposure measurement, varying from extensive data completed on a wide

range of pollutants to a simple comparison of residents of urban and rural populations. It is also clear that the nature of the major pollutant sources varies from region to region and over time. Add to this the variety of the indices of COPD used, and the difficulties of controlling for confounding variables, it is not surprising that a very clear answer cannot be obtained. However, there does appear to be considerable support to the idea that some air pollutants may increase the risk of COPD.

Socio-economic status (and related factors) The review in section 10 considers 61 papers. The evidence reviewed strongly indicates that there is an association of low social class (reduced income, less education) with COPD that cannot be explained by confounding by smoking. The extent to which the association is due to occupation, air pollution, or other factors, is, however, unclear.

Atopy, allergy and hyperresponsiveness The review in section 11 considers 60 papers. There are a variety of indices of allergy, atopy and bronchial hyperresponsiveness (BHR) and considerable difficulties of interpreting associations as cause and effect and difficulties in removing confounding by other factors. Even where smoking is adjusted for, this is often fairly crude. Nevertheless the strong evidence of an association of BHR with decline in FEV_1 and onset of COPD, and the weaker evidence of an association with skin test sensitivity and other indices of allergy suggest that atopy, allergy and BHR may have a causal relationship to COPD.

Infection in adults The review in section 12 considers 52 papers. Unlike other COPD risk factors, the majority of these papers are themselves reviews. While it is clear from these reviews that infections are a major cause of exacerbations of existing COPD, the evidence that infections in adulthood can lead to onset of COPD is much less convincing. In determining whether such infections have a causal role, one has to be able to exclude reverse causation, with the presence of COPD rendering patients more subject to infections (and also perhaps more likely to recall past infections). The most relevant evidence comes from the prospective studies, all conducted over 20 years ago. These

consistently show that infective episodes do not cause long-term loss of lung function, as most impressively demonstrated by Fletcher, Peto and colleagues. It also indicates that antibiotic treatment does not affect the decline of FEV_1 with advancing age. Data from other studies, mainly of case-control or cross-sectional design, are much more indicative of an association. Though many of these studies are more recent than is the case for the prospective studies, they generally do not allow one to exclude reverse causation. Nevertheless, it remains possible that some infections may help to cause COPD.

Occupation The review in section 13 is extensive, considering 202 papers, and summarizing the evidence separately for each of 21 occupations or agents to which workers were exposed. There are great problems in assessing the relationship of COPD to occupation. These include the huge size of the literature, the wide range of occupations and exposures involved, the variety of exposures within some occupations, the large changes in exposure that have occurred over time for some of the occupations, the difficulty of defining relevant comparison groups (due *inter alia* to the "healthy worker effect"), and the possibility of publication bias, where some studies consider a wide range of occupations and only report details for significant relationships. This is apart from the general problems of bias and confounding associated with epidemiological studies.

While the data relating occupation to COPD are particularly difficult to summarize and evaluate, it is clear that occupation does play a role, with exposure to a number of sources of dust, gas and fumes likely to play a part. The strongest evidence of increased risk comes for miners (clearest for coal mining and gold mining). Other occupations and exposures for which the evidence is quite strong include foundry work, welding and metal work generally, and exposure to asbestos, silica and brick dust. There are a number of other occupations where limited evidence suggests a possible effect on COPD risk.

There have been a few attempts to estimate the occupational contribution to the burden of COPD. The population-attributable risk for COPD has been

estimated as between 10 and 20%, though clearly such estimates have considerable uncertainty.

5. Overall conclusions

It is clear that a number of factors other than smoking do increase the risk of COPD. One can tentatively assess the strength of the evidence of a causal relationship, based on the studies considered, as follows:

Definite cause Cooking and heating with biomass fuels; mining (particularly coal and gold); and of course smoking.

Strongly suggestive Diet; low body mass index; childhood infection; air pollution; bronchial hyperresponsiveness; foundry work, welding and metal work generally; exposure to asbestos, silica and brick dust.

Weakly suggestive Eosinophilia; obesity; low social class; atopy and allergy; adult infection; other occupations not mentioned above.

No real indication of an effect Alcohol and race.

Clearly, many of these factors interrelate, and for a number of them additional work might produce a clearer picture.

6. Acknowledgements

I thank Philip Morris International for financial support. All opinions expressed are my own.

7. Reference

1. Lee PN, Forey BA. *Epidemiological evidence on environmental tobacco smoke and COPD*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2007. www.pnlee.co.uk/reflist.htm [Download LEE2007C]

8. Notes

For references to many of the statements made in this summary, please refer to the individual risk factor sections.