Outcome measures in COPD

Outcome measures in chronic obstructive pulmonary disease (COPD)

A Dirksen

Lung density determined by CT scanning may be a useful outcome measure in COPD

Forced expiratory volume in 1 second (FEV_1) is by far the most well established outcome variable in obstructive pulmonary disease. Numerous studies have documented the correlation of this parameter with clinical variables such as severity of disease and mortality,[1] and spirometric measurements have been standardised by international recommendations on lung function testing.[2] Nevertheless, in real life the relevance of a maximal blow through a narrow tube is not always self-evident, and the intuitive clinical meaningfulness of this surrogate parameter is therefore perhaps less obvious. FEV_1 has further limitations in chronic obstructive pulmonary disease (COPD). In general, dynamic lung volumes such as FEV_1 and forced vital capacity (FVC) are highly effort dependent. However, in emphysematous subjects an abnormally low FEV_1 is partly caused by the dynamic collapse of the airways which is also effort dependent. Therefore, in COPD the result of a more moderated manoeuvre is usually superior to the result of a maximal effort. This phenomenon adds to the variability of repeated measurements and, in COPD, the standard deviation of repeated measurements of FEV_1 is larger than the annual decline, even in heavy smokers.[3] For these reasons there is an increasing interest in other measures such as number of exacerbations or disease specific questionnaire scores as alternative outcome measures for monitoring the progress of emphysema in randomised clinical trials.

Another new outcome measure is lung density as determined by computed tomographic (CT) scanning. Although the scanner has mainly been used as an imaging device, in the 1970s when Hounsfield developed CT scanning for clinical use he envisaged the scanner as a measuring device as well, because it provides precise information on the density of tissues derived from the attenuation of *x* rays. In this context it should be noted that pulmonary emphysema is defined pathologically as ''the abnormal permanent enlargement of airspaces distal to the terminal bronchioles due to destruction of their walls, without obvious fibrosis''.[4] In other words, loss of lung tissue is an essential and inevitable part of the emphysematous process, and no other reasonably common and diffuse lung disease shares this feature with emphysema. CT based densitometric parameters therefore have the potential to be both sensitive and specific outcome measures for monitoring the progress of emphysema.

Even in the late 1970s and early 1980s emphysema was described by CT scanning.[5 6] Since that time, several studies have compared CT and pathological findings and—with improved resolution, faster scan times, and thinner collimation—the correlation between CT scores and pathological grading has improved. Furthermore, recent studies seem to indicate that CT lung density is more reproducible than traditional spirometric variables such as FEV_1.[7]

Two papers in this issue of *Thorax* add important data to the validation of CT lung density as an outcome measure for monitoring the progress of emphysema. In both studies participants suffered from severe α_1-antitrypsin (AAT) deficiency (assumed PI*ZZ genotype) and both studies included St George's Respiratory Questionnaire (SGRQ) data, lung function tests (FEV_1 and transfer coefficient (KCO)), and CT lung density measurements. Dawkins *et al*[8] followed about 200 subjects for a mean of 2 years. Twenty subjects who died after enrolment in the study had lower FEV_1 (percentage predicted), KCO (percentage predicted), higher CT emphysema index (threshold –910 HU), and higher SGRQ scores indicating worse health status than survivors. Subsequent multiple regression analysis (Cox survival) showed that the CT emphysema index was the most powerful predictor of mortality followed by the SGRQ activity score, whereas age and lung function measurements had no independent influence on survival. In the study by Stolk *et al*[9] 22 individuals were followed for 30 months and a significant correlation was found between changes in CT lung density (percentile density) and changes in health status (SGRQ) but, surprisingly, no correlation was seen between these variables and changes in pulmonary function measurements (FEV_1 and KCO).

Patients with severe AAT deficiency provide a good model for studies of emphysema because they develop the disease at a relatively young age when health status is less affected by comorbidities that become more prevalent with increasing age. However, these studies do also have limitations. Although 200 subjects is a large group for studies of AAT deficiency, it is a more moderate number compared with other studies in usual COPD and the results obtained in AAT deficiency may not necessarily be applicable to the much larger population of smokers with usual COPD.

From a methodological point of view, it is interesting to note the difference between the two studies in the selection of the CT densitometric parameter and CT protocol for image acquisition. Thus, Dawkins *et al* used the emphysema index and an HRCT protocol (that is, thin slices and a hard reconstruction) whereas Stolk *et al* chose the percentile density and a volume scan protocol (that is, thick slices and a soft reconstruction algorithm). Owing to photon statistics, thick collimation and soft reconstruction usually give more reliable results and the percentile density seems to be more robust than the emphysema index, at least in longitudinal studies of the progress of emphysema.[10]

The radiation burden is always an important consideration when using *x* rays for monitoring disease, and the radiation dose of a standard CT scan of the chest is by no means negligible. However, by reducing the current of the *x* ray tube, it is possible to keep the total radiation dose of a full volume scan of the lung below 1 mSv without significant loss of information on lung density. This low dose technique opens up the possibility for longitudinal studies with repeated CT scans in the same subject. Volume scanning has two important advantages: (1) using modern multislice techniques the scan can be performed in one breath hold, and (2) the amount of air in the lungs can be calculated from the images. Lung density is obviously very dependent on inspiratory level, and the volume of air in the lungs can be used to adjust lung density for the inspiratory level.[10] When analysing trends in longitudinal data such as in the study by Stolk *et al*, adjustment for lung volume is unavoidable because the total lung volume of a subject may vary significantly from one

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examination to the next.[10] This kind of noise reduction may be less important in cross sectional studies such as the one by Dawkins *et al*,[8] and it may even introduce new errors. An increase in total lung volume is an inherent part of the emphysematous process and, by eliminating that aspect of the disease, volume adjustment may in fact weaken the correlation between CT lung density and other measures of disease severity (unpublished data). Thus, adjustment of lung density for lung volume is not always to be recommended.

The two studies published in this issue of *Thorax* underline the urgent need for standardisation and international agreement on recommendations for lung density measurement based on CT scanning. However, provided CT lung density can be standardised and validated against traditional clinical outcome variables, it may prove to be a new measurement that is objective, specific, and sensitive for monitoring the effect of new drugs on the progress of emphysema in future randomised clinical trials.

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Asthma and obesity

Asthma and obesity: where are we now?

S Chinn

The importance of the reported association between obesity and asthma is still unclear

An association between asthma and overweight or obesity was first reported in adults in the 1980s.[1 2] The papers were concerned with chronic disease in general and excited little attention in the respiratory field at the time. In children concern had been over growth retardation in those with asthma.[3] In 1984 Somerville *et al*[4] reported a weak association between symptoms of asthma and increasing weight for height, but again this provoked little interest.

In the last 5 years there have been numerous reports of an association in adults and in children—too many to cite directly.[5 6] Even since the later of these two reviews there have been further reports in children,[7] in adults,[8] and specifically in women.[9] The lack of earlier reports does not necessarily imply that the association is recent because, when the prevalence of obesity was lower, there was less power to detect a raised prevalence or incidence in obese subjects. However, in addition to this indirect evidence, there is some direct evidence for the association being recent in origin. In a study of children aged 5–11 years in Britain carried out over 23 years, in contrast to the weak association in the 1977 data cited above, a strong association was found in data collected in 1994.[10] In adults there is evidence for an association between asthma and obesity in Britain as early as 1982, but no other reports to show whether the relation existed earlier.[6] Obesity, defined as a body mass index (BMI) of 30 or more, had already reached 14% in adults in the US by the early 1970s,[11] a figure comparable to that reached in England in 1993,[12] so it seems likely that the association, if present, could have been detected in the US earlier than the 1980s.

THE EVIDENCE

Confounding

Studies in adults have found associations between reported asthma or symptoms (rather than doctor diagnosed asthma) and BMI and, in a few studies, height and weight were also self-reported. This has led to some scepticism that the association is spurious or due to confounding[13] or, at most, the result of increased perception of symptoms among those who are overweight.[14] Schachter *et al* found an association between symptoms and medication for asthma and increasing BMI, but not airway responsiveness (AHR), in 1971 adults aged 17–73 years,[14] and in this issue of *Thorax* they present similar findings in 5993 children aged 7–12 years.[15]

The association is not simply due to concomitant trends in asthma and obesity, as suggested by Wilson.[13] The association is not ecological but is found in individual data and, while in the UK the trends in BMI and asthma have been concurrent in children, the trend in BMI does not explain the trend in asthma due to the recent nature of the association.[10] Wilson's alternative explanation was that it was due to confounding. Confounding can never be completely ruled out in observational studies, but the factors suggested by Wilson—gastro-oesophageal reflux and obstructive sleep apnoea—are not potential confounders but intervening variables on putative causal pathways.[13]

Increased perception

That the association may be due to increased perception of symptoms in obese individuals is much more difficult to rule out. Indeed, it can be assumed

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that part of the association is due to perception as lung function decreases with increasing BMI within individuals,[16 17] although in cross sectional data an increase in lung function may be seen at lower BMI and a decrease only at higher values.[18] The question is whether the association is entirely due to increased perception. The conclusions of Schachter *et al* were based on finding no trend of increasing AHR with greater BMI.[14 15] However, in 11277 participants in the European Community Respiratory Health Survey (ECRHS) a statistically significant trend was found even after adjusting for lung function,[19] and a case-control study of men in the Normative Aging Study found a U-shaped relation with greater AHR at high and low BMI, also adjusted for lung function.[20]

There is other evidence for not dismissing the association as being entirely due to increased perception. In children, case-control studies comparing those with diagnosed asthma and those without showed that the asthmatic children had greater mean BMI.[21 22] Furthermore, at least six longitudinal studies have shown an increased incidence of asthma in overweight or obese children and adults.[6 7] A delayed effect is more difficult to explain away than an immediate one by increased perception. In these studies incidence was calculated in those disease or symptom free at baseline. The lack of an agreed definition of asthma, and the difficulty of differentiating true incident asthma from recurrence of quiescent asthma, have provoked criticism of this approach.[23] However, the studies do make the reverse causation hypothesis—that lack of exercise in asthmatic patients promotes obesity—an unlikely explanation. These studies also provide evidence against the mechanical effects of obesity being the sole explanation, by the same argument as against increased perception and against a combination of perception and mechanical effects alone.

Studies of change in symptoms in obese asthmatic patients who lose weight have the potential to overcome the above scepticism. The one randomised controlled trial of 38 obese patients showed a reduction in symptoms and improvement in health status in the treated group compared with the control group, and an increase in lung function.[24] However, at high BMI a reduction in weight is likely to increase lung function irrespective of symptoms,[16 17] so this may not have convinced the sceptics. Airway responsiveness was not measured. A large trial including AHR as an outcome could provide evidence that the change in reported symptoms is not entirely due to reduced perception with weight loss, although on its own it cannot determine whether obesity is a cause of asthma.

Dietary factors

Review articles have considered many possible explanations apart from confounding, mechanical effects, and perception.[5 6] Obesity may modify the immune system, female sex hormones may play a role, physical inactivity may independently promote obesity and asthma, and a large number of dietary factors may be implicated.[5] In the randomised controlled trial weight reduction was achieved through a diet which was modified in content as well as in calories,[24] and surgical reduction may lead to dietary changes. It may be feasible to collect dietary data in asthmatic patients motivated to lose weight, but a large study will be required to disentangle the candidate explanatory factors.

Sex differences

A number of studies have found an association between the prevalence or incidence of asthma in women but not in men, prompting a discussion of the mechanisms involving female sex hormones. However, the finding was not universal and, in the ECRHS, the association between AHR and obesity was, if anything, greater in men,[18] but associations between symptoms and obesity were almost identical in men and women.[25] Part of the explanation for this heterogeneity in the findings may be in study size and methodology. In order to conclude a different effect in men and women, a statistically significant interaction is required. It is not sufficient to observe a statistically significant relation in one group and not in the other, but studies may lack the power to detect an interaction.[26] A number of studies have not reported a test of interaction but analysed data for men and women separately on a priori grounds because of the previous reports of differing associations. Others have reported a combined effect, so the evaluation of the evidence for and against a sex difference is quite difficult. In addition, some of the larger studies of adults showing a greater association in women analysed reported height and weight[27 28] which may have different validity in men and women. Only a large study with the power to detect an interaction effect can answer the question, but the interaction may genuinely differ between studies if the association is due to multiple mechanisms with difference contributions in different places.

Schachter *et al* found an association between BMI and atopy in girls,[15] while Jarvis *et al* found no association with atopy in men or women, and no interaction between BMI and atopy on symptoms.[25] Huang *et al* found an association between high BMI and both atopy and AHR in girls but not boys in Taiwan,[29] the association with atopy explaining that with AHR. An association between BMI and atopy was reported in a study in Finland but no symptom data were included.[30]

WHERE ARE WE NOW?

The scientific community is divided over the importance of the reported association between obesity and asthma, over whether the association is confined to women and girls or not, and whether atopy is also associated and perhaps on a causal pathway. In addition, there are a number of plausible mechanisms with little or no evidence for or against their role. Only large studies which include AHR as an outcome are likely to add further to the debate. However, we can surely all endorse the plea made by Redd and Mokdad[23] not to delay intervention programmes to tackle the obesity epidemic while we argue over the mechanisms for an association with asthma.

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Air pollution and lung cancer

Air pollution and lung cancer: what more do we need to know?

A J Cohen

Further work is needed to quantify the effect of outdoor air pollution on lung cancer

Lung cancer accounts for 1.2 million deaths yearly worldwide, exceeding mortality from any other cancer in the developed countries.[1] The vast majority are caused by tobacco smoking, but environmental causes of cancer, including air pollution, have long been a concern also.[2] Outdoor air pollution has received particular attention lately as research has proliferated linking exposure, even at low ambient levels, to a wide range of adverse health effects including increased mortality and morbidity from non-malignant cardiovascular and respiratory disease and lung cancer. In response, international agencies such as the World Health Organization and governments in Europe, the US and Canada have reviewed existing air quality standards and, in many cases, moved to strengthen them. In the developed countries, where air quality has generally improved in recent decades, the scientific basis and public health efficacy of these actions have been questioned by industries whose emissions are regulated and others. In this context, reports linking air pollution and lung cancer are likely to attract attention and generate controversy. The publication of the paper by Nafstad and colleagues in this issue of *Thorax* is an occasion to consider both the contribution of this study to the evidence linking air pollution and lung cancer and what additional research may be needed.[3]

Exposure to outdoor air pollution has been associated with small relative increases in lung cancer in studies conducted over the past four decades.[4] The epidemic of lung cancer emerging in the 1950s in the US and Europe motivated early research on the role of air pollution, including studies of migrants and urban-rural comparisons but, as the role of cigarette smoking became increasingly clear, interest in air pollution waned. However, recent prospective cohort and case-control studies which have taken into account tobacco smoking, as well as occupational and other risk factors, have continued to report increases in lung cancer associated with air pollution.[5–7] The American Cancer Society (ACS) study, which included 10 749 lung cancer deaths, reported that each 10 μg/m^3 increment of fine particles ($PM_{2.5}$) was associated with an 8–14% increase in lung cancer.[7] A causal interpretation is buttressed by other evidence. Urban air contains known and suspected human carcinogens such as benzo[α]pyrene, benzene, and 1,3-butadiene, together with carbon based particles onto which carcinogens may be adsorbed, oxidants such as ozone and nitrogen dioxide, and oxides of sulphur and nitrogen in particle form. Increased lung cancer has also been reported among workers occupationally exposed to components of urban air pollution such as polycyclic aromatic hydrocarbons and diesel exhaust.[8 9]

In light of this evidence, the question is arguably not ''Does air pollution cause some lung cancers?'', but rather ''How many excess cases is it likely to cause?''. The answer to this question, and another—''Which pollutants, emitted by which sources, may be responsible?''—can potentially inform regulatory action to improve air quality and public health.

The current evidence suggests that lung cancer attributable to air pollution may occur among both smokers and non-smokers, and therefore both residual confounding and effect modification of the air pollution relative risk due to cigarette smoking must be considered. Nafstad *et al*[3] report the relative risks of air pollution adjusted for cigarette smoking, but adjustment may not have controlled completely for potential confounding. The authors acknowledge that their study, like most other cohort studies, has information on cigarette

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smoking only at the beginning of the follow up period. The possibility that changes in tobacco use are correlated with exposure is difficult to rule out, although the association of lung cancer with air pollution was largely unaffected in the Six Cities study[5] when longitudinal information on cigarette smoking was used in a recent reanalysis,[10] and several case-control studies have found an increased risk following adjustment using time varying information.[6] Several studies, including the one reported here by Nafstad *et al*, show an increased risk of lung cancer among self-reported never smokers, but the numbers in any single study are very small and the estimates imprecise. This also complicates efforts to estimate the numbers of cases in which both air pollution and smoking play a role. A study that includes large numbers of well documented never smokers may be the only approach that could address these concerns, if feasible.

Past approaches to exposure measurement also contribute to uncertainty in risk estimates. The ACS and Six Cities studies estimated the exposure of each participant based solely on long term average concentrations in their metropolitan area of residence. This approach may accurately reflect exposure to pollutants distributed homogenously over large areas for several decades but, if exposure at finer spatial and temporal scales is important, the estimates of relative risk may be inaccurate. Newer European and North American studies have begun to use spatial statistical methods to estimate individual long term exposure histories, linking residential histories, measurements of traffic density on nearby streets, and long term records of specific air pollutants, and can estimate how the size of the relative risk varies in time and space.[6 11 12] Hoek *et al*[11] observed larger relative effects on mortality from cardiopulmonary diseases as a result of air pollution near to major roads than from larger scale urban and regional air pollution, and Nyberg *et al*[6] estimated the highest relative risks of lung cancer for exposure 20 years or more before diagnosis. By providing exposure estimates at the individual level, these studies also reduce the possibility of aggregate level (ecological) bias.[10 13]

The effect of air pollution on lung cancer, fully manifest only decades after exposure, is a moving target. The emergence of cars and trucks as dominant modes of transportation and the decline in heavy industrial manufacturing in some developed countries since the mid 20th century, combined with effective air quality regulations, have changed both the nature of urban air pollution and patterns of human exposure. Over the time course of many recent lung cancer studies, decreases in larger respirable and fine particles as well as some gaseous pollutants and carcinogens have been documented,[7] although concentrations of the fine, and arguably more toxic, particles may have declined to a lesser extent than other pollutants,[5] increased in some locations,[14] or changed their spatial distributions. Epidemiologists must rely on whatever components of the air pollution mix have been measured over extended periods, and consequently have reported associations of lung cancer with long term exposure to particles, ozone, sulphur dioxide, and nitrogen dioxide, but not known carcinogens. No mechanisms by which these pollutants per se cause cancer have been identified, and although some cancer biomarkers have been associated with air pollution exposure in non-smokers, they have not been used in large studies designed to estimate lung cancer risk. Nafstad *et al*[3] and Nyberg *et al*[6] used ambient concentrations of nitrogen dioxide and sulphur dioxide as surrogates for air pollution from mobile sources and residential heating, respectively. Each observed an increased risk of lung cancer associated with the nitrogen dioxide based indicator but not with the sulphur dioxide based indicator, but neither of these pollutants is specific to either source. As technological improvements and regulatory efforts continue to change the nature of air pollution, estimating current and future impacts on lung cancer will remain a challenge.

Exposure to air pollution is estimated to contribute to 62 000 lung cancer deaths per year worldwide—a large number of deaths, to be sure, but considerably less than the 712 000 deaths from non-malignant cardiac and respiratory disease attributable to air pollution.[15] These impacts are largely borne by the populations of highly polluted cities in developing countries—roughly 60% of the world's burden of air pollution attributed disease. In Chinese cities, where air pollution levels are many times greater than those in the cities of the developed West, outdoor air pollution may contribute to as much as 10% of lung cancer overall, and perhaps a larger proportion in non-smoking women. Unfortunately, because there is a lack of suitable studies in developing countries, these estimates are based on extrapolating the relative risk estimates from the ACS study to China, India, and other settings where differences in health status and the air pollution mixture introduce large uncertainties.

Opportunities to strengthen the scientific evidence on air pollution and lung cancer should be pursued, including in developing countries where the estimated health impact of air pollution and the need for accurate risk estimates are greatest. Studies should be designed to address, in addition to lung cancer, other arguably more important knowledge gaps such as the effect of long term exposure on the incidence of chronic non-malignant cardiorespiratory disease. Beginning large studies de novo would entail major financial and opportunity costs, so identifying existing cohorts, especially those with large numbers of non-smokers and for whom biological samples have been stored, may be the best option. Studies of outdoor air pollution and lung cancer in developing countries will need to account for past or concurrent exposures to indoor air pollution, particularly from use of coal for cooking and heating, a major cause of lung cancer in poor rural women in China and elsewhere,[16] and changing patterns of tobacco smoking.

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Nitrogen dioxide

Hypothesis: Ill health associated with low concentrations of nitrogen dioxide—an effect of ultrafine particles?

A Seaton, M Dennekamp

The epidemiological associations between illness and nitrogen dioxide may be the consequence of confounding by particle numbers

In 1996 the Expert Panel on Air Quality Standards (EPAQS) recommended an ambient air standard for nitrogen dioxide (NO_2) in the UK of 150 ppb measured hourly.[1] This recommendation, like those for carbon monoxide (CO) and sulphur dioxide (SO_2) that had preceded it, was based on human toxicology rather than on epidemiology. The EPAQS was unable to find evidence that these gases were likely to be toxic to humans at the recommended concentrations. However, at the time of the NO_2 recommendation there was already epidemiological evidence that effects on *populations* rather than *individuals* might be associated with much lower concentrations and the EPAQS recommended that steps be taken to reduce annual average concentrations, although without proposing a long term standard. The UK government has subsequently adopted, as targets to be achieved by 2005, World Health Organization NO_2 guideline standards of 105 ppb (200 μg/m^3) over 1 hour and 21 ppb (40 μg/m^3) as an annual average, the latter having been based on possible relationships between exposure to the gas and respiratory illness in children.[2] Achievement of a long term standard does, of course, have the desirable consequence of reducing peaks and therefore short term exceedences. However, compliance with a very low average concentration of NO_2 implies a substantial reduction in the concentration of the primary pollutant released from vehicle exhausts—that is, nitric oxide (NO). Since NO reacts with ozone to form NO_2, lower concentrations will result in raised urban ozone concentrations, a gas that also has known toxic effects on the lungs and that, until now, has been seen primarily as a rural pollutant in the UK.

Progressive reductions in pollution are welcomed by many because of a belief that human health and the ecology of the planet will benefit, but it must be remembered that they are attained at a cost to industry and thus to society. That cost may be offset by reductions in health expenditure, by increases in life expectancy and crop productivity, and by opportunities for the innovative in designing more efficient engines and fuels. The components of this equation can at present only be estimated very uncertainly, therefore setting tight standards tends to be an act of faith, typically driven by political balancing of the exhortations of pressure groups on both sides. This makes it particularly important to attempt to quantify the health effects of pollutants, a process that has traditionally been based on known toxicological effects but now increasingly relies on epidemiological relationships.

TOXIC EFFECTS OF NITROGEN DIOXIDE: EPIDEMIOLOGY OR TOXICOLOGY?

Scientific confusion arises from the different viewpoints of toxicologists and epidemiologists which may be illustrated by considering NO_2. Human inhalation challenge studies have shown that normal healthy individuals do not show adverse effects to NO_2 below concentrations of about 2000 ppb (about 4000 μg/m^3). Asthmatic subjects may react to concentrations as low as 250 ppb (about 500 μg/m^3), either by alterations in bronchial reactivity or by increased sensitivity to inhaled allergens. Such subclinical changes might reasonably be expected to be associated with occasional exacerbations of asthma in very susceptible individuals in an exposed population. However, it is difficult to imagine that concentrations less than half of this could be responsible for clinically measurable episodes of illness, or that concentrations around a fifth of this could cause chronic health problems. While epidemiological studies have sometimes been able to detect associations that suggest health benefits may accrue by adhering to standards set at such very low concentrations, the overall message from these studies is confusing. For example, the WHO review in 2000[3] concluded that ''the most consistent general impression is of increased respiratory illness in older children''. The report goes on to speculate that such episodes may set the scene for chronic lung disease in later life. This conclusion was weighted by consideration of studies of children living in houses with and without gas cookers. However, such studies have shown equivocal results, one meta-analysis having shown a significant effect[4] and another not.[5 6] As we have shown, gas cooking may entail very high acute exposures to both NO_2 and particles.[7] In fact, the heterogeneity of epidemiological findings with respect to NO_2 led the UK Department of

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Health's Committee on the Medical Effects of Air Pollutants to conclude in 1998 that this pollutant should not be included in its quantitative estimates of the effects of pollutants on health.[8] It is plain that the evidence on which the long term NO_2 standard is based is insecure.

Epidemiological studies usually rely on the assumption that the exposures of all individuals in the population may be taken as those measured by one or a few city centre monitors. This method has the incidental effect of obscuring any threshold that may be present,[9] leading to the possibly erroneous conclusion that there is no absolutely safe level of the gas in population terms. The epidemiologist may argue, with justification, that the toxicologist can only study relatively small numbers of subjects who are well enough to take part, and thus cannot comment on effects on the very vulnerable who comprise a small but critical proportion of any population studied. Faced with such conflicting evidence, what action should governments take?

CONFOUNDING AND EFFECT MODIFICATION

There are many problems in interpreting epidemiological studies of air pollution, but perhaps the most important are confounding and effect modification. There are relatively few important sources of pollution in cities—vehicles, industrial and domestic combustion processes outdoors, and cooking and smoking indoors. All produce a mixture of pollutants including particles, NO (oxidised by atmospheric ozone to NO_2), and CO. Particles, with which adverse health effects have been associated most consistently, are usually measured as PM_{10} (the mass of those that are less than 10 μm in aerodynamic diameter), a metric that includes a varying contribution from non-combustion sources. There are plausible hypotheses to explain the association of exposure to low concentrations of particles with both respiratory and cardiovascular illness and death[10–12]; this cannot be said of any associations between NO_2 and such illnesses.

It is apparent that, in urban pollution episodes, particles and NO_2 rise and fall together, making it difficult or impossible to separate their effects. Some studies have been particularly interesting in this regard. One observed an association between the triggering of implanted defibrillators and ambient concentrations of both particles and NO_2, the latter effect appearing to be somewhat stronger.[13] If NO_2 was indeed responsible, individuals with such devices would be well advised to avoid entering kitchens containing gas cookers where NO_2 concentrations may rise to 1000 ppb (approximately 2000 μg/m^3).[7] Another study in eight European cities showed that the association between particle concentrations (as PM_{10}) and acute cardiac episodes was eliminated by controlling for NO_2, strongly suggesting confounding.[14] Effect modification is suggested by a study in which greater effects of NO_2 on mortality occurred in cities with higher PM_{10} concentrations,[15] and by another that has shown a stronger effect of particles (measured as black smoke, a metric roughly equivalent to $PM_{4.5}$) on respiratory admissions when NO_2 concentrations were simultaneously raised.[16]

This issue of confounding and/or effect modification is important. If a demonstrated association is a consequence of confounding by some other toxic substance, the effect of one may be ignored in terms of standard setting, whereas if the association is explained by effect modification, both toxic substances require regulation. Of course, if both come from a common source, regulation of one may regulate the other, but this cannot be guaranteed as changes in technology may increase one by reducing the other. Is it conceivable that these confusing associations are the consequence of confounding of all the above mentioned apparently toxic substances by one as yet unmeasured substance? We think that they may be, the confounder being the number of particles and thus the surface area presented to the lung.

PARTICLE NUMBERS AND NITROGEN DIOXIDE

The particulate aerosol we inhale comprises particles of all sizes ranging from organic matter like pollen grains some 10 μm or more in diameter to primary combustion particles of 10 nm diameter. The smallest tend to aggregate rapidly into what are still submicron particles. When we measure particles as mass—for example, PM_{10}, $PM_{2.5}$ or black smoke—the greatest contribution comes from the largest particles, but the greatest number of particles by far are the submicron ones. These ultrafine particles are generated, as is NO, by the combustion process, and therefore the two pollutants (and NO_2) are likely to correlate closely. We have carried out two separate investigations during which we have measured simultaneously particle number counts (by TSI 3934 scanning mobility particle sizer) and nitrogen oxides (by ML9841A chemoluminescent analyser). The first of these was in an unventilated laboratory during a study of the effects of electric and gas cooking on indoor pollution, the pollution source being a gas cooker.[7] Figure 1 shows the close relationship between the two pollutants when derived from a common source. The second was a study of the effects of exposures to particles on the health of individuals with chronic lung disease over the course of 6 months, the measurements being made at a background site in Aberdeen city. Here we found a very striking association between concentrations of nitrogen oxides and the number of particles of <100 nm aerodynamic diameter measured simultaneously (fig 2); this association was stronger than the corresponding associations with particles measured as mass (table 1). These associations are so close that it would be impossible to distinguish their effects in epidemiological studies. Thus, if NO_2 in these environments is measured as an index of pollution and is shown to be associated with health effects, these effects could equally be due to the numbers of particles.

IS PARTICLE NUMBER THE VILLAIN?

The number of particles is an important and usually unmeasured confounder in studies in which both particle mass and NO_2 are associated with health effects.

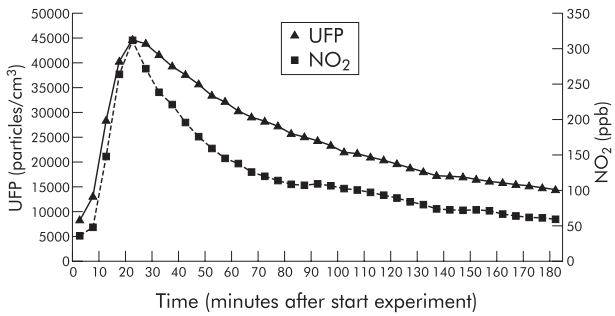

Figure 1 Indoor ultrafine particle number (UFP) and nitrogen dioxide (NO_2) concentrations in an unventilated laboratory over 3 hours during and after burning of one gas ring for 15 minutes (r=0.97).

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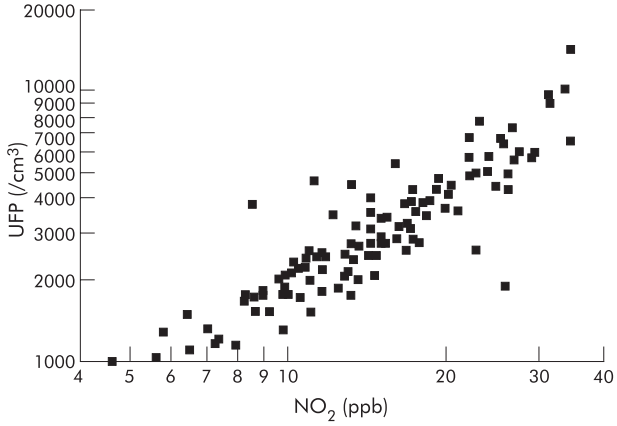

Figure 2 Relationship between mean outdoor air 24 hour counts of particles <100 nm in diameter (UFP) and nitrogen dioxide (NO_2) concentrations in parts per billion. Data represent 6 months of continuous side by side measurement.

We are left to argue, from toxicological considerations, which of these is likely—at the known concentrations to which individuals are exposed—to cause the observed effects. At the moment there is evidence for toxic effects of ultrafine particles at quite low concentrations in animals.[17] Relatively few studies have related particle numbers to cardiorespiratory illness, the most detailed being those of Wichmann's group in Erfurt, Germany. They have shown a somewhat weaker correlation between gases and particle numbers than us, but they have shown associations between numbers, NO_2, SO_2, CO and cardiorespiratory deaths.[18 19] It should be noted that, in contrast to most UK cities, domestic heating in Erfurt makes an important contribution to particulate pollution in the winter and SO_2 concentrations are higher. Wichmann and colleagues concluded that the apparent effects of the gases were likely to be a result of confounding.

PARTICLES AS MICROBES – AN HYPOTHESIS

A plausible explanation for this toxicity is as follows. We hypothesise that the lung reacts to particle numbers rather than mass, since its primary defensive role is to counter invasion by microorganisms which may be inhaled in large numbers but never in high mass. The first requirement of the lung is to kill organisms in situ and/or to transfer them to lymph nodes where immune responses may be concentrated, and ingestion by macrophages is central to this mechanism. Ultrafine particles, however, may evade this and pass directly through the alveolar wall, thus being able directly to influence endothelial cell structures. Both macrophages and endothelium release mediators that have local and more general influences, one of which is to signal that bloodstream invasion may be imminent; a systemic reaction—the acute phase response—is a consequence. If we assume that the lung treats small particles as microorganisms, it is reasonable to propose that its response relates to numbers rather than mass. By altering blood coagulability and possibly by destabilising atheromatous plaques, this systemic response may be responsible for the acute cardiac effects seen in vulnerable individuals. It seems far more plausible that these effects are a response to the number of particles rather than to NO_2, for which no comparable hypothetical explanation of effects at such low concentrations has yet been proposed.

Table 1 Pearson correlation coefficients for the logged daily outdoor concentrations of NO_2, NO, particle numbers, $PM_{2.5}$ and PM_{10} in Aberdeen

	Particle numbers	$PM_{2.5}$	PM_{10}
No of particles <200 nm diameter		0.56 (n=124)	0.40 (n=121)
Nitric oxide (NO)	0.86 (n=115)	0.45 (n=121)	0.39 (n=117)
Nitrogen dioxide (NO_2)	0.89 (n=115)	0.55 (n=121)	0.45 (n=117)

Each box gives correlation coefficient and number of daily observations. All correlations were significant at $p<0.001$.

The toxicity of microorganisms does not, of course, depend entirely on the numbers inhaled; their inherent ability to initiate cell damaging reactions or to resist defences is critically important. Similarly, not all inhaled particles would be expected to be equally toxic—for example, quartz and titanium dioxide. Thus, something other than particle numbers needs to be invoked to explain their effects, and this is likely to be the nature of the surfaces they present to the lung's defences.[12 17] A further step in explaining toxicity therefore requires consideration of surface properties. However, in urban air the very smallest particles make an overwhelming contribution to the total surface area, so measurement of one represents the other.

We propose that the observed associations between ill health and NO_2 at low concentrations in the ambient air are the result of confounding by particle numbers. We have earlier hypothesised that a systemic response to particle inhalation is responsible for the acute cardiorespiratory effects,[10] a suggestion for which there is now considerable support.[20] This hypothesis also explains the association between air pollution and long term risk of heart disease,[21] since it proposes that particles cause inflammation and thus an increase in the blood of markers such as C reactive protein and fibrinogen that have been associated with increased cardiac risk. Here we propose that this is a consequence of the lung's evolutionary system of defence against microorganisms. From a practical point of view, we now need to explore relations between particle numbers and illness in order to obtain evidence upon which a number standard might be considered. For the moment, however, it seems likely that in situations such as those in most UK cities where motor vehicles are the main source of pollution, measurement of NO_2 is the simplest means of assessing exposures to particle numbers and, conveniently for epidemiologists, this can be done on a personal basis.

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Annual report

Annual report October 2002 to September 2003

J A Wedzicha, S L Johnston, D M Mitchell

In January 2003 the Editorship of *Thorax* changed and it is with great privilege and considerable awe and trepidation that we took over as Editors.[1] Under the editorship of John Britton and Alan Knox *Thorax* has achieved high standards and increased its impact factor, which now stands at 4.078 (fig 1). *Thorax* is currently the most successful European respiratory journal and the third among all respiratory journals (behind the two American Thoracic Society publications). The readership of *Thorax*, together with the whole respiratory community, owes an enormous debt of gratitude to John and Alan and the previous editorial team for their outstanding achievement.

With the advent of the new editorial team, *Thorax* changed to an on-line submission system using Bench>Press.[5] Although there were some initial difficulties with the change over from a paper based system to complete online submission, this is now running very well and authors, reviewers, and all our editors seem to have adapted very well to the change. The number of submissions to *Thorax* has increased, particularly from March 2003, with a total of 1260 submissions for the 12 months from October 2002 to 30 September 2003, representing an overall increase of around 33% on the previous year (tables 1 and 2). The number of original research articles submitted to the journal has increased by a similar amount. We have also seen an increase in submissions from outside the UK, especially from North America and Canada (from 74 in 2001–2 to 126 for the past year) and a doubling in the number of submissions from Asia (table 3). The median time to the first decision on a paper is 38 days. However, the increased number of submissions means that our acceptance rate for original research papers now stands at only 12.4%.

This year we have published some important original papers and useful management guidelines for common conditions including the new BTS/SIGN (British Thoracic Society/Scottish Intercollegiate Guidelines Network) guidelines for the management of asthma in February 2003,[6 7] BTS guidelines for the management of pulmonary embolism,[8 9] BTS guidelines for the management of pleural disease,[10] and BTS guidelines on respiratory aspects of fitness for diving.[11] We have also published the *Year in Review 2002*,[12] and have completed the review series on the pulmonary physician in critical care,[13–17] continued the series on important aspects of COPD,[18–28] and started a series on lung cancer.[29–37]

A number of new features have started in *Thorax*, primarily aimed at increasing the educational value of the journal. Every month we now produce our Airwaves section at the front of the journal with short paragraphs highlighting the key messages of some of

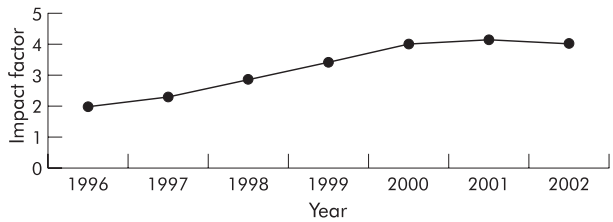

Figure 1 *Thorax* impact factor 1996–2002.

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Table 1 Submissions to *Thorax* by article type

	1998	1999	2000	2001	2002	2003
Original research						
Full papers	398	453	505	573	592	860
Short papers	31	36	34	36	44	N/A
Rapid communications	7	3	6	9	6	0
Case reports	211	149	165	186	146	211
Editorials/reviews	81	57	56	55	33	77
Review series	13	19	14	15	40	26
Supplement articles	17	16	46	5	16	N/A
Case report commentaries	7	0	0	0	0	0
Letters	72	9	96	95	70	82
Images in *Thorax*	0	0	0	0	0	4
Total	837	812	922	974	947	1260

Table 2 *Thorax* submissions by month, October 2002 to September 2003

October	65
November	86
December	90
January	90
February	87
March	140
April	118
May	108
June	112
July	140
August	106
September	118

the papers in the journal. We have also started the ''Lung Alerts'' feature as, at a time of ever increasing numbers of medical publications and a vast range of journals publishing papers of interest to practitioners in respiratory medicine, we do not have the time to scan all the general and specialist journals for papers on respiratory topics.[38] A number of very important papers are published in general medical or scientific journals or in specialist journals. We have therefore started to publish short reviews and alerts of papers that we have selected from these journals. We have had an excellent response to our call to younger *Thorax* readers for help with this feature, and we are very grateful to all the contributors who have made this series such a success this year. In November 2003 we launched a new educational series called ''Images in *Thorax*'' in which we will publish an image or a pathological section with a short explanatory and educational note.[39] The *Thorax* website (www.thoraxjnl.com) has proved very popular and our 10 most frequently read articles on line between December 2001 to December 2002 had a total of nearly 65 000 accesses as either full text, PDF versions, or abstracts.[40–49]

We would like to thank all the authors who have sent us such high quality papers for review in the journal, and the many reviewers who have given up their valuable time to assess papers for *Thorax* and who have contributed to the success of the journal (a full list of reviewers is available on the *Thorax* website at www.thoraxjnl.com/supplemental). We would like to thank the Associate Editors for their invaluable help in selecting the best papers for publication and the International Advisory Board for their support of the journal. We thank Angshu Bhowmik and Terry Seemungal for organising Lung Alerts each month and Mark Fitzgerald for organising the new Images series. Ed Howard, our editorial assistant, has performed a superb job in running the journal and managing so expertly the change over to the online manuscript submission system and the office moves at the start of the year; thanks also to Julia Cresswell, our part time assistant. Finally, we would like to thank Sue King, the managing editor, for all her support in our first year and Liz Stockman, the technical editor, for ensuring that the monthly issues of *Thorax* are always produced to the highest standard.

This has been the first year that *Thorax* has operated from its permanent home in the British Thoracic Society offices in London. As our submission and peer review system is now entirely online, there is less need for the *Thorax* office to follow the Editors geographically and a permanent base will allow us to employ permanent editorial staff to ensure the future continuity of the journal.

Our first year as Editors of *Thorax* has been busy, challenging, and exciting. We are committed to ensuring that the journal continues its success and increases its impact internationally, while at the same time maintaining its educational value for the global respiratory community.

A full list of reviewers used between 1 October 2002 and 30 September 2003 is available at the *Thorax* website www.thoraxjnl.com/supplemental.

Thorax 2003;**58**:1015–1017

Table 3 Geographical distribution of submissions

	1998	1999	2000	2001	2002	2003
UK	265	326	348	323	325	378
Europe excluding UK	274	259	310	386	329	437
USA and Canada	76	81	87	68	74	126
Japan	46	54	56	69	74	99
Australasia	48	38	60	57	45	67
Asia	35	30	39	26	41	85
South America	3	1	5	7	6	21
Africa	3	3	4	5	1	6
Middle East	15	20	13	24	21	21

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