Q&A Document
The Global Burden of COPD
Vancouver, Canada, October 21-22, 2004

This document summarizes the question and answer discussions related to the proceedings of a scientific workshop entitled The Global Burden of COPD, held in Vancouver, Canada, October 21-22, 2004. The proceedings of this workshop appear published in four consecutive issues of the European Respiratory Journal, available to subscribers or license holders at http://www.erj.ersjournals.com/ . We thank the European Respiratory Society for posting this additional educational material in their external website.

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Paper 1 of 4:

Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, Connell C, Jemal A, Lee TA, Miravitlles M, Aldington S, Beasley R.
The Global Burden of COPD: Epidemiology and costs of COPD.
Eur Respir J 2005 (in press).

Worldwide Epidemiology of COPD and BOLD - Sonia Buist

GULSVIK: If we are going to move forward in this field, we have to agree to approach our studies the same way, otherwise we'll be where our ancestors were 50 years ago. It's interesting that we have been doing spirometry and respiratory symptom studies for more than 50 years, however, there is very little value placed on the predictive value of reports on respiratory symptoms.

MANNINO: The definition for COPD that we are using now requires a post-bronchodilator measurement of lung function. A lot of longitudinal studies never looked at bronchodilator response and you find a direct relationship between lung function impairment and various outcomes. If you look at the Copenhagen data from Hansen et al in well-defined clinical populations, there did not seem to be a whole lot of difference in responsiveness between clinically diagnosed COPD and asthma. How important is it?

BUIST: I would argue that the important point is to get the information in a standardized way in order to properly evaluate its relevance. I don't think any of us believe that a bronchodilator response is a good way of deciding if someone has asthma or COPD. It is not a good discriminator. There have not been large population-based surveys that have done a bronchodilator response in everyone. This is information that we need to obtain.

GULSVIK: Using post-bronchodilation data, the prevalence rate of COPD is reduced by 30%. Risk factors like smoking and socioeconomic status appear to have a greater effect on the post-bronchodilator results.

VIEGI: An important question is when do we start doing spirometry? The age limit for BOLD and PLATINO is 40. But, we have seen recently in the literature data from the ECRHS that 12% of people in the age range of 20-44 have GOLD Stage 0 and 2-4% have GOLD Grade 1 or more. Unlike lung cancer, where the gold standard diagnostic is clear, COPD diagnosis by definition should be based on spirometry. But, if we look at the natural history of the disease, we know that people go to the doctor with symptoms. So, perhaps, we should see what happens in the reverse way. Rather than using symptoms as predictive of lung function criteria perhaps we should use lung function criteria to predict symptoms.

MENEZES: I agree with your comments on symptoms and spirometry. It depends upon what the gold standards are. If you look at the specificity and sensitivity comparing symptoms with GOLD criteria for spirometry, it is higher than comparing with fixed ratio criteria. The patients will look for the doctor when they have symptoms, not because they know that they have low lung function.

BUIST: The issue of age is very important. We took a very pragmatic approach to try to develop methods that used relatively small sample sizes with an age cut-off of 40. We encouraged but did not require investigators to look at ages under 40. There's no question that the majority of COPD is going to be manifest above the age of 40. If you want to do efficient surveys, it may be a good idea to focus on the age group in which you're going to find it. But, it would be more informative to do the whole population over the age of 18.

MIRAVITLLES: Perhaps, some of the differences we see are not between countries but are between socioeconomic areas. In the IBERPOC Spanish study, we found 2-fold differences in prevalence in some areas. In the areas with highest prevalence, it was due to women non-smokers who were working in textile industries but they had what we call epidemiologically-defined COPD, not clinical COPD. They had very mild obstruction without respiratory symptoms, had not been previously diagnosed, and they will probably not die from this disease, if it is indeed a disease. It seems to me that it would be very difficult to develop severe COPD from occupational exposure if a patient does not also smoke.

WATT: It is interesting that in this study the prevalence of moderate COPD was higher than the prevalence of mild COPD. That is different from the distributions of risk associated with such factors as blood pressure and cholesterol, where the opposite is true. When "cases" are defined simply in terms of quantitative shifts from normality, within a normal distribution, one expects a higher prevalence of mild compared to moderate cases. Does this suggest that COPD "cases" represent a qualitative, rather than a quantitative difference from normality?"

GULSVIK: That may have something to do with the arbitrarily cut-off points of $FEV_1/FVC < 0.7$, greater than 80% of predicted FEV_1 for mild severity, and 50-79% of predicted FEV_1 for moderate severity. Using local reference values, this gives a smaller fraction with mild disease compared with severe disease.

VOLLMER: These discussions raise some important methodological issues. For example, which prediction equations should we be using to define COPD? Peter Burney has argued within the BOLD executive committee that we should use a single prediction equation across all sites, rather than developing local equations for each site. His concern is that local country-specific or population-specific equations may mask some environmental or other factor that we're not otherwise measuring. So by using a common prediction equation, you get to see variation across sites which you can then try to explain on the basis of other factors. I noticed that the data in the PLATINO analyses were all using NHANES as a uniform prediction. We are still debating this issue within the BOLD group.

SORIANO: How successful is BOLD in recruiting African centers and other developing countries in Asia?

BUIST: South Africa is about to start up. Korea is very interested and is looking for funding. Japan is interested with the hope that BOLD would validate the NICE survey. There are some centers in India that are also interested.

Surveillance of COPD: Lessons from Cancer - Michael Thun, Cary Connell, Ahmedin Jemal

CHAPMAN: COPD can be a primary cause of mortality in many people but also a significant cofactor in other potentially lethal diseases such as cardiovascular disease. Is there a corollary to this in cancer?

THUN: Irrespective if there's one for cancer, the influence of COPD on mortality/morbidity from more common conditions like heart disease would be important to quantify. The issue of the effects of cancer on comorbid conditions is complex and is getting a lot of attention. With respect to mortality, the whole registration of underlying cause of death is entirely dependent on coding rules. But the relationship across these diseases has not been given enough attention. Heart disease and cancer have many common risk factors. There's still a huge amount to be learned about the commonality of causal pathways across these diseases and how one disease affects another.

BUIST: What proportion of cancer patients in cancer registries in the US have a tissue diagnosis as opposed to a clinical diagnosis? COPD has a lung function definition, which is a huge barrier towards establishing any type of registry.

THUN: About 50% have tissue diagnoses. You can get into a cancer registry with just a clinical diagnosis, but this has changed over time due to better diagnostic methods (i.e., thin needle aspiration). In the state registries, one measure of the quality of the registry is how many cases are first identified from death certificates only. If this number exceeds a certain percentage, it is perceived as a lower quality registry.

MANNINO: One of the challenges in COPD epidemiology, particularly using administrative data, is underestimation. If lung cancer appears as the diagnosis on a death certificate, it will be listed as the underlying cause of death 95% of the time. However, COPD will be listed as the underlying cause of death only 40-45% of the time. COPD is listed as the cause of death in only 20% of patients with GOLD Stage 3 or 4.

THUN: When discussing the surveillance of COPD, this group must consider which questions are the most important questions to be answered. Do we need complete counts? Or do we need to look at survival in a population-based sample? Or do we need to do comparisons across 2-3 populations that have some commonality?

GULSVIK: Perhaps it would be helpful to classify the quality of the data and compare the trends in those registers with high quality versus those with low quality registers.

THUN: I agree that comparability of data quality is essential to make comparisons. The quality of the data in the National Cancer Institutes' registries is well standardized. That was why I showed you temporal trend data that are based either on mortality statistics or data from the SEER program. However, the much larger collection of registries on the national level has more variability across states and also over time and does not lend itself to assessment of long-term trends. Although the National Association of Cancer Registries has a structure in place to standardize data definitions and data collection processes, regional differences still exist.

CHAPMAN: COPD is a heterogeneous group of disorders and there is a confusing clinical overlap of COPD with asthma. We know a great deal more about asthma prevalence than COPD prevalence. Not only do we need to have a good definition of COPD but we need to reconcile it with the definition for asthma. We are talking about the global burden of COPD here but we have missed step one, which gets back to the clinician's dilemma of diagnosing a patient who wheezes and coughs and who might have either of these common obstructive lung diseases. If the patient belongs to a higher social class, he is more likely to be labeled asthmatic.

KNOBIL: Death certificates may not fully reflect actual cause of death, especially if COPD exacerbations may have led to some other cause of death. In our ongoing mortality trials, cause of death is defined by the investigator as well as by a clinical endpoints committee. This committee evaluates all the data (including medical records, etc) at the end of study. It will be interesting to see how these two correlate. We have probably vastly underestimated the rates of death from COPD just based on death certificates.

THUN: Misclassification of disease on death certificates is a long-standing problem. However, mortality data have proven extremely informative, despite the misclassification.

VOLLMER: Even under an ideal situation where we could get good lung function data on everyone, we still don't have a single definition of COPD that we all agree on. Even if we did, we all know that any threshold is arbitrary. For the purpose of looking at trends and understanding shifting patterns of disease and risk factors over time, I wonder if the lessons of cancer epidemiology would suggest that having the "right" definition is less important than having a consistent definition that we all apply uniformly?

THUN: For surveillance, consistency is essential, "rightness" is good. Coming up with a consistent definition should be one of the immediate goals in this process.

VESTBO: As a clinician, I think that the main lesson from cancer registration is that this would never work for chronic disease management. We need to go for consistency rather than correct diagnostics.

Global Economic Costs and Modeling in COPD - Todd A Lee, Marc Miravitlles

GULSVIK: These differences in costs in Sweden may be a result of the differences in population-based data versus physician registers. Using the more complete population-based data increases the costs by a factor of two.

VIEGI: These are important data. But, what does this mean, in general? How can we reduce the overall costs? With interventions like vaccinations? Or implementing a more correct diagnosis on the source of infection? How can the two parts of this presentation be linked together?

MIRAVITLLES: In Spain, we found that patients with severe disease had a shorter life span, but spent more money than patients with milder disease who had a longer life span. Based on this information, the best cost savings could be achieved by early diagnosis of the disease. Then we would have the opportunity to help people to quit smoking and stop the evolution of the disease. Once the patient is diagnosed, the most important driver of cost is hospitalization. Then, all the strategies directed at reducing the exacerbation rate would be cost-effective, particularly in severe patients.

CHAPMAN: I was intrigued by your treatment failure data. One of the subtle but profound shifts that occur when we make the diagnosis of COPD is the difference in strategy on the part of primary care physicians (PCPs). At least in Canada and the US where PCPs are told to be somewhat reserved about the use of antibiotics, patients with COPD that is unrecognized may get late intervention for exacerbations. Once we have made the diagnosis, the intervention with antibiotics and prednisone occurs earlier. It is one of the subtle but important shifts that I have not seen documented elsewhere but may account for some cost savings, once we make the diagnosis.

MIRAVITLLES: There is at least one recent paper that shows that delay in treatment for an exacerbation results in prolonged time with symptoms. I'm not aware that this may also result in an increased rate of hospitalizations, but this may be the case. I think that once the patient is diagnosed, patients should have an action plan for exacerbations, similar to that for asthma patients, so that treatment can be started as early as possible.

BUIST: Has anyone looked at the cost of COPD in non-smokers? This may be important to help identify whether or not this is a different disease or whether it is the same disease caused by different risk factors.

LEE: Smoking status has not been a differentiating factor in the economic studies that I have seen.

MIRAVITLLES: Approximately 20% of COPD occurred in non-smokers. We analyzed smokers versus non-smokers in terms of risk factors, symptoms, and evolution of the disease. We did not perform an analysis of costs but I assume that the costs would be very low because those were mainly mild cases.

VOLLMER: A lot of morbidity associated with COPD is related to comorbidities. People with COPD are more likely to end up in the hospital with CHF, pneumonia, or IHD. Is this part of the model? Are you looking at total costs or COPD costs?

LEE: The model runs on both sets: COPD-specific costs defined as hospitalizations for COPD exacerbations and total costs that look at some of these other issues. We use public domain estimates for a lot of these cost estimates in developing the models.

VOLLMER: You noted that you hope to have the economic model on the BOLD website soon. You also mentioned that it won't be a totally static model, but rather that it will grow and evolve as new sites are added. I wonder if you could talk a bit about the richness of the model and how it will evolve.

LEE: As more BOLD sites come onto the project, their data are entered into the model, and the model is able to estimate site-specific healthcare resources according to their COPD patients. It also helps to inform the overall model as a whole so we can start to look at total disease burden. We learn more as we get more sites and can build on developing those estimates. It's going to continue to grow and will, we hope, become a usable tool in the near future.

THUN: In this presentation, while increasing the emphasis on factors other than smoking, it is essential not to de-emphasize the impact of smoking and all the diseases for which smoking has an important influence. Any opportunity to deflect attention away from smoking is seized on by the tobacco industry. COPD in rich countries remains extremely uncommon in the absence of smoking. It is the interaction of smoking with those risk factors that will determine who will or will not develop COPD. Also, in analyses of population-attributable risk, it is important to consider the percentage of the population that has been seriously smoking for a substantial length of time. This is much more important, particularly for lung cancer, than how much is being smoked.

BEASLEY: I think that we can explore the science of these other factors without interfering with the public health initiatives, which clearly are so important and have led to such gains over the last 20 years. However, if we turn a blind eye to these other factors, I don't think we are serving our patients properly either. I think that we must consider these other factors within the framework of the whole picture and this can be done without too much difficulty.

SORIANO: We need to remember that the population-attributable risk depends on two factors: the absolute risk and the prevalence of the given condition or risk factor in that population. For example, in countries like New Zealand where marijuana use may be higher than anywhere else in the world, that risk factor would probably be more important than others in that country.

BEASLEY: We looked at many studies to determine the population-attributable risk due to smoking. The numbers that we got seemed to be entirely consistent in different communities and populations. Unfortunately, there are not a lot of studies out there from which data can be pulled for these calculations. In particular, there are few studies that have post-bronchodilator values, which I think is now the standard that we must use since it has been established in GOLD.

HANSELL: My concern is about the heterogeneity and phenotypes within COPD and their effect on gene environment. If you look at the English data, you see a much closer relationship with smoking for emphysema mortality than for chronic bronchitis mortality. Using COPD as a group diagnosis may not be specific enough when we start to look at gene environment interactions.

BEASLEY: I think the GOLD criteria have been inclusive rather than exclusive. I'm sure the definition now includes a substantial proportion of people who we would have excluded previously because they had a prior diagnosis of asthma. I think there is general acceptance that we're talking about a syndrome of many different disorders.

MANNINO: I think that the public health community has been asleep at the wheel with regard to COPD and lung cancer. Today we saw data showing that if everyone stopped smoking today, we would not see an appreciable dip in COPD-related mortality. If we look at former smokers in the US, there is just as much COPD amongst former smokers as amongst current smokers. My clinic is full of patients who stopped smoking 10-15 years ago and who are living now with problems that are related to their previous smoking, including lung cancer and the development of COPD. I agree that we must continue to move forward with campaigns of non-initiation and smoking cessation. But, we really need to pay attention to these other risk factors in order to make advances in this field.

Paper 2 of 4:

Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V.
The Global Burden of COPD: Future COPD projections.
Eur Respir J 2005 (in press).

Estimating the Burden of Chronic Obstructive Pulmonary Disease: Methods and Results from the Global Burden of Disease Study - Alan D. Lopez, K. Shibuya, C. Rao, and C.D. Mathers

SULLIVAN: Were the predictive models for the unregistered populations based on registered population models or were some imputations made based on what you knew about the unregistered populations?

LOPEZ: We modeled the epidemiological transition in rich countries and came up with 3 broad mortality causes: communicable, non-communicable, and injuries. We looked at how the proportionate mortality of those three causes of death changes as overall mortality declines. It changes in a relatively predictive way. In countries that did not have cause of death data, we estimated with demographers the overall level of mortality. In terms of data, demography is much richer than epidemiology. We used these CODMOD models at different levels of mortality to determine what the Group 1, 2, and 3 distribution would be. Then we applied those distributions across what is observed to the unobserved population.

Now that's somewhat hazardous, because you're allowing for the Group 1, 2, and 3 difference between registered and non-registered. However, within the non-registered, you're assuming the same proportionate distribution across specific causes and that's a concern.

So, we've gone back and looked at other evidence (e.g., autopsy and community studies) to see if we can tweak it. The WHO has several disease programs in infectious disease, which we used to tweak the specific distribution.

GORECKA: We still don't have the ICD code for the disease. For example, we have codes for asthma, emphysema, and chronic bronchitis. Why does the WHO not have the specific term of COPD? If we want to raise awareness of the disease, we should use the name of the disease for coding, rather than using emphysema or chronic bronchitis as a surrogate for COPD or using COPD as a descriptive definition.

LOPEZ: The way to change that is to lobby the WHO when they come to ICD-11 to make sure that the name change is what we want it to be.

VOLLMER: With the focus on smoking as the primary risk factor, it is possible that we have overlooked the importance of other factors contributing to the smoking burden. Have you included these other risk factors into your models?

LOPEZ: The Global Burden of Disease 2000 does include estimates of regional prevalence of biomass exposure for men and women. The new relative risk model that we have includes smoking and biomass.

Projecting the future Burden of Chronic Obstructive Pulmonary Disease (COPD) - Anna L Hansell, Leonhard S Held, Volker Schmid

THUN: If one of the major goals of the COPD research community is to motivate more interest and support of COPD as a problem, the issues that may be important levers include disability at younger ages (not in the very old) and costs. Also, the fact that women live to be older would affect the number of people who would be diagnosed, so you really would not want to cancel age out of the equation. Have you thought about modeling aspects of the issue that would be persuasive to policy makers?

HANSELL: It would be difficult, but not impossible, with routine data. One would need to set up a special cohort study where one would have access to the medical records as well as the death certificate data.

LOPEZ: This issue of projections is extraordinarily important. An age-period cohort can be elaborated into an age-period cohort "plus". We have gone back for the UK, US, Canada, and Australia data and remodeled the past lung cancer epidemic by replacing the period variable with a Tau-weighted consumption variable and projected lung cancer. They could be applied just as well to COPD.

HANSELL: We did look at the effect of replacing the period factor by smoking prevalence within the projections model and found that it was actually a much worse model when we tested it.

VIEGI: What about looking at the combination of causes on the death certificate?

SORIANO: The natural history of COPD is very confusing in the end stages. We have problems identifying the cause of death even in apparently well-characterized and monitored individuals recruited in randomized controlled trials. As we discussed earlier, COPD may be a group of diseases, particularly at the time of death, and is therefore very difficult to diagnose the cause of death.

Paper 3 of 4:

Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, Davey Smith G, Upton M Hawthorne V, Sin DD, Man SFP, Van Eeden S, Mapel DW, Vestbo J.
The Global Burden of COPD: The Natural History of COPD.
Eur Respir J 2005 (in press).

The Natural History of Chronic Obstructive Pulmonary Disease: The Decline of Lung Function and the Contributory Role of Exacerbations - David Mannino

BUIST: Do we know if obesity is a complicating factor? We know they were symptomatic, but what more have you done to tease out what was going on in the restrictive group?

MANNINO: Within NHANES-I, the strongest predictor of restriction was cardiomegaly on chest X-ray suggesting either diagnosed or undiagnosed CHF. The presence of diabetes and obesity is also predictive. Surprisingly, things that you think would predict it, e.g., interstitial lung disease and cracked ribs, were not predictive risk factors. Granted, this was only about 6-7% of the population, but I think that it's an important group to which we need to pay more attention.

BUIST: In a small study that I conducted many years ago looking at restrictive patterns using PFTs and X-rays, we also found that the strongest relationship was with cardiomegaly. Have you looked at the quality control of the spirometry of the restricted group? Particularly, FVC? We know that FVC is a huge problem.

MANNINO: These were NHANES I data that met reliability criteria. Reproducible criteria were diminished in the restrictive group but were also diminished in the obstructive group. However, they still predict an increased risk of mortality. We are in the process now of looking at data from a large managed care organization. The biggest problem there relates to people not having a long enough exhalation time. I think you get a disproportionately higher number of people who meet restrictive criteria than you would expect. We acknowledge this issue and recognize the need to deal with it.

THUN: The people who have lung function impairment are much more likely to develop lung cancer. I was thinking that there might be two hypotheses for this: 1) The people who develop both are likely to have been more intensive smokers for a longer period of time and 2) There are common unidentified host susceptibility factors.

Finally, to what extent have people looked at markers of chronic inflammatory response as a prognostic indicator of these diseases?

MANNINO: The presence of impaired lung function is related to higher levels of inflammatory measures such as fibrinogen, CRP, and other factors. I would add a third explanation to your hypotheses. That is, people with COPD have structurally altered lungs. It may be that toxins that get into the lung are less likely to get out when you have some degree of lung function impairment. But, it may well be a common pathway phenomenon, too. In Kentucky, we will be collecting biomarkers to see if we can find common factors that predict both. We have been trying to make the case that the presence of COPD is a biomarker for the susceptibility of developing lung cancer.

MAPEL: When you do high-resolution computer tomographies (HRCT) scans on a group of patients labeled with COPD, you see some really remarkable things. Even in patients with COPD who have never smoked, you find things like bronchiectasis and post-inflammatory fibrosis. As a consequence of that, you discover that some patients are misdiagnosed with COPD, but even amongst those who have emphysema and chronic bronchitis, you can subtype them even better. As we build these BOLD populations for research purposes, what do you think about including high resolution HRCT scans and phenotyping your population?

MANNINO: In Kentucky, we will use low-dose spiral HRCTs (not maximal resolution quality), but not in normal patients or in those with mild COPD. Yes, that would be a great study to do.

The Epidemiology of Respiratory Impairment and Disease in Two Generations of the Renfrew and Paisley (MIDSPAN) Study - Graham Watt, David Hole, Charles Gillis, Carole Hart, Alex McConnachie, George Davey Smith, Mark Upton, Victor Hawthorne

SORIANO: In the Framingham study, the best single surrogate marker that explained total mortality was not cholesterol or hypertension, but was FEV1. You corroborate this in your study.

WATT: Rather than measuring infant mortality as a measure of general population health, I think that there is an argument for measuring respiratory function in the general population in early adulthood, which would be a more informative public health monitoring variable.

VIEGI: I was impressed by the difference in asthma diagnosis and wheezing between the parents and the sons. It seems that asthma went up and wheezing went down. Secondly, how do you feel about the quality control of lung function measurements in this study?

WATT: The previously published study on the trends in asthma between the two generations has a rigorous discussion section explaining what you can and cannot conclude in terms of wheeze and asthma. As for the issue of quality of the respiratory measurements, I feel quite comfortable with the quality of measurements in the second generation. However, I don't have that level of comfort with the more historical data from the 1970's.

GULSVIK: Out of 4000 couples, what percentage of offspring was followed?

WATT: The response rate of offspring was about 70%, representing about 80% of the original families. Although the data are ripe for all sorts of selection bias, there don't seem to be huge selection biases operating here because the fathers and mothers in the population seem quite similar to the general adult population of 30 years ago. We don't know about the offspring that left the area and live in other parts of the world. That's why peer-reviewers were so concerned about us making claims to show trends in the population prevalence of asthma.

Chronic Obstructive Pulmonary Disease (COPD), Systemic Inflammation, and Its Relevance To Cardiovascular Disease - Don D. Sin, S.F. Paul Man, Stephan Van Eeden

LEONARD: Think about reversing this idea: that atherosclerosis may drive emphysema. If, as you stated, you get increases in CRP and it leads to activation of endothelium, then endothelium damage in the lung can produce emphysematous-like lesions, so it may be that cardiovascular disease is actually driving emphysema. The development of pulmonary hypertension, which would aggravate cardiovascular disease, worsens this vicious cycle. Which is the chicken and which is the egg?

SIN: We need to explore testable hypotheses. More work must be done to explore these cytokines and pathways. More importantly, by turning off airway inflammation, can we affect the endpoints of relevance, in this particular case, atherosclerosis? We need both animal and human studies to test this hypothesis.

MIRAVITLLES: You showed an association between COPD and systemic inflammation but it's not so clear to me that this is a cause-effect relationship. The animal model you presented showed a relationship between inhalation of particles and atherosclerosis but not between atherosclerosis and COPD, in particular. Could it be that COPD is a pulmonary manifestation of a systemic disease which is smoking and smoking is the cause of the inflammation in cardiac and lung disease?

SIN: Animal models of COPD are extremely difficult to produce. The human condition of COPD is very different from the animal condition of COPD. That's why you don't see the typical COPD model in rats and mice. I don't buy that notion of cigarette smoking causing both. Even among those who quit smoking, there is clear evidence years afterwards of persistent airway inflammation. So the animal model in this particular case is helpful to show that airway inflammation can lead to systemic inflammation, which then contributes to atherosclerosis. To extend the concept beyond that would be stretching the point.

HOGG: The evidence of cardiovascular events after acute episodes of air pollution in humans is very strong. It is highly relevant to COPD in the sense that inflammation is produced in the lung with those particles. Clearly there is chronic inflammation in COPD that never goes away. In the study that we just finished in people who had stopped smoking, up to 9 years afterwards we were still measuring an increase in inflammatory reactions. It seems that once it gets going, it never stops.

VESTBO: My worry with what you present is that some of the associations could be FEV1 serving as a significant comorbidity to already existing heart disease. You presented the Copenhagen City Heart study to show a relationship between FEV_1 and myocardial infarction. In that study, FEV_1 was a predictor of a fatal MI but not of a non-fatal MI. Once you look at mortality, you run the risk that the death is a result of comorbidity. There is this discrepancy between fatal and non-fatal MI. There was no association when they adjusted for smoking between FEV_1 and a non-fatal MI.

Characteristics of the Perfect COPD Natural History- Jorgen Vestbo

BUIST: I don't think we understand the socioeconomic status (SES) and early childhood piece of this puzzle. I agree that starting a 50-year study from before birth will not work. We need to break it into segments and ask specific questions of specific age groups. We need to look across countries, like the BOLD and PLATINO models. What is SES telling us about the phenotype? It is puzzling to ponder the role of nutrition or infection and if these and other factors are the same across countries.

VESTBO: I agree. We looked at SES in the Copenhagen City Heart study because the difference between rich and poor was not that big. But, we showed a large difference in FEV_1 between the lowest and highest education groups (300mL). It was surprising that these data were similar in the young adult age group and the old adult age group after adjusting for smoking. It had nothing to do with occupation and was something that happened very early. One of the segments that we have not explored is what determines lung function at birth and the subsequent growth of lung function. We can study that cohort and then we don't need the decline cohort.

WATT: What does SES really mean in this discussion? It shows us premature mortality where the key point is the age of death, not the cause of death. Possibly, respiratory function is a good marker of that process.

VIEGI: Theoretically, we should already have the "perfect study". Look at the Tucson experience in 1972. If the NIH had funded this study further, data could have been collected for 30-35 years. With regard to the issue of whether or not to continue studying FEV_1 decline, I think we need to update reference values for spirometry. We keep saying that these reference values need to be updated because people of today are different than people of 10 years ago. So if it is valid for reference values, should it also be valid for FEV_1 decline?

VESTBO: No I don't think so. I'm not really sure that NIH should have put more money in the Tucson study and I'm not sure that we should continue doing the Copenhagen City heart study. We have just done the 25-year follow up. What we are learning now is not really different from what we learned after the first 10 years because we don't have more detailed data. It's not really telling us anything new. If we want to start taking steps forward, we need to do something different.

HOGG: The value of FEV_1 is that it reflects time and the time constant of lung emptying, which reflects both the resistance and the compliance. It is multivalent and picks up both the emphysema and the airways disease. Would it be possible to hook on to these many studies that are going on all over the place (many of which have included FEV_1), screen for lung nodules, and follow those people? You may have an opportunity to say what proportion of the FEV_1 is due to the emphysema. There is no good way to measure the small airways with HRCTs because the target is too small. But, at least you could get at the relative proportionality that way. Could you do that from an epidemiological viewpoint or would you get too biased of a sample because of heavy smokers who are worried about whether they have lung cancer or not?

VESTBO: If you just took those who came themselves for a screening program, it would not be a good population. But many places set up screening trials and if they involved respiratory

epidemiologists, we could put together a sample which would be of interest to follow over time. That's what I mean by multiple studies, to link in with people who get the information otherwise. This is a wonderful suggestion.

Paper 4 of 4:

Zielinski J, Bednarek M, Górecka D, Viegi G, Hurd SS, Fukuchi Y, Lai CKW, Ran PX, Ko FWS, Liu SM, Zheng JP, Zhong NS, Ip MSM.
The Global Burden of COPD: Increasing COPD awareness.
Eur Respir J 2005 (in press).

Implementing Population Spirometry- Jan Zielinski, M Bednarek, Dorota Górecka

VERMEIRE: What kind of anti-smoking advice did you give to the subjects?

GORECKA: We found that it was very important to show the patients their numbers on the graph. When they were shown the probability of the rate of decline, it was a motivational factor for them to try to quit.

VERMEIRE: Did you refer patients to more specialized smoking cessation centers?

GORECKA: We did it in Warsaw. The experience was not very good. After 1 year, we screened our patients a second time. Those who did not stop smoking were invited to a smoking cessation clinic. Only 20% of those who were invited (and were offered free treatment) came to the clinic.

BUIST: I'm interested in the proportion of those who had a restrictive pattern. Our experience with BOLD is that the most common mistake is to end exhalation early. It takes a lot of time to train technicians and watch them carefully. In large population studies like this where technician performance is likely to be inconsistent or suboptimal, use of FEV_1/FEV_6 rather than FEV_1/FVC may be more useful.

HANSELL: Is population screening for COPD something that we should be recommending? There are clear guidelines from the WHO to consider before starting such a programme and these are broadly related to the disease, the test proposed, the treatment, and the programme.

Are we happy that we know enough about the natural history of the disease, particularly of GOLD Stage 0 or 1? How likely are they to progress to a more serious disease and how important is it to pick them up at that stage? In terms of treatment, our main intervention is to get them to quit smoking, but this intervention is desirable in any patient. Is the program sustainable with ongoing funding within the health care systems?

GORECKA: The program was designed to raise awareness of COPD. A recent opinion poll showed that this goal was obtained. The other goal was to motivate smokers to stop smoking. We gave this advice to both those with normal lung function and those with newly detected airway limitation. We found that 6% of patients had FEV_1% predicted less than 50%. Those were patients who should be treated. For those with milder forms of the disease, the smoking intervention motivated them to stop smoking. Smokers with moderate and severe COPD stopped smoking after 1 year at the rate of 16.7%. Those who did not want to stop smoking had mild disease and quit at a rate of only 6%.

MIRAVITLLES: With our experience in Spain, we sent letters to GPs telling them about their patients with newly diagnosed airway limitation, but most patients did not follow up with their GPs for further examination. Did you have this same experience and did you give any further instructions to GPs for these newly detected patients?

GORECKA: If patients had a severe form of the disease, a letter was sent to their GPs asking them to send a letter of referral to a test clinic for further evaluation. We don't have the data on how many patients actually came back to the test clinics.

CHAPMAN: With regard to the restrictive pattern of the disease that you showed, do we know what this restriction is about (for example, obesity)?

GORECKA: We did not look into this because we did not have enough data. But, these patients were sent for further evaluations in chest clinics through their GPs because we did not want to leave them with an unexplained abnormal spirometry. Obesity could be a factor.

MAPEL: With regard to the public health implications of COPD screening, let's compare what we do in cholesterol screening to what's being done in COPD. The public has been overly indoctrinated on the importance of cholesterol, so awareness has been good. But, to find an effect on treatment, you have to collect thousands of patients and follow them for many years to see any effect on mortality. Compare that to the Lung Health study. We put people through these intensive smoking cessation programs and only an additional 15% managed to have sustained smoking cessation. But, in that relatively smaller study with only 5 years of follow up and with only marginally successful smoking cessation programs, it did have a significant effect on mortality. These programs clearly have an important effect on overall survival, not just in lung health but also in cardiovascular and cancer health. It's easy to be cynical about smoking cessation, but when you look at studies such as this one, the impact is truly phenomenal.

COPD in Women- Giovanni Viegi

THUN: Understanding gender differences is an important topic with respect to lung cancer as well as COPD. It's really important to try to look critically at the data and to report them accurately. In your presentation you showed that the relative risks or odds ratios were higher in women than in men. However, I think that it is important to not confuse relative risk with absolute risk. Relative risk is the risk in the exposed versus the risk in the unexposed and it is completely dependent on where the baseline is in the unexposed. In the case of lung cancer, there have been quite a few case-control studies that have reported higher relative risk of lung cancer from smoking in women than in men. These studies reported that women are more susceptible and that their risk is higher. But there have now been seven large prospective studies that show that the actual risk is not higher in women than men and the risk is actually slightly lower. I think there's a political incentive to make the case that women are at even higher risk than men because smoking prevalence in women has equaled or exceeded that of men in many countries.

VIEGI: When we went to medical school, there was a perception that COPD was a male disease. That's why it is important to raise awareness that this is no longer a male-specific disease. Rather, in terms of absolute numbers, it can be even worse for women.

SIN: Histologically, at least in lung cancer, women appear to have a slightly different type of lung cancer than do men. Do you think that airway disease or inflammation is any different in women than in men?

VIEGI: There seems to be more obstruction in men than in women, at least in the Italian population. The pattern of the change in Western society is probably driven by countries like Denmark, the US, or the UK. Perhaps our experience in the Mediterranean area is lagging.

MANNINO: If you look at the US data, the absolute number of women dying from COPD has surpassed men although the rates are still lower. The linkage between COPD and development of cardiovascular disease is important. One of the hypotheses is that men with COPD are more likely to die from cardiovascular disease than women.

VIEGI: I agree that we need more detailed population studies that will take into account the possible influence of diet, body mass index, hormones, and these other factors.

CHAPMAN: There are clinical differences in COPD between men and women. In the Canadian report that you mentioned, the authors reported that there are more physician-diagnosed cases of COPD in women than in men. Also, women tended to develop the disease at a younger age than men. Women seem to be less likely to quit smoking than men. I suspect that there are differences at many levels.

VIEGI: We know that the ratio of FEV_1/FVC is higher in women than in men. On the other hand, we have confirmation from the Canadian report that women have more bronchial hyperresponsiveness than men.

WATT: In our study, we found that maternal smoking was an independent risk factor for respiratory impairment in offspring, whether or not offspring were smokers themselves. Knowing this adverse

effect of maternal smoking might be a more motivating factor for women to stop smoking than their personal risk of respiratory impairment.

VESTBO: If you want to compare men and women, you have to conduct a study with extremely detailed smoking information because there is no way you can compare a female smoker with a male smoker. In all categories of smoking history, men and women will differ. If you don't adjust for that, you can get completely skewed results. We were able to do that with the Copenhagen data and found some interesting differences. In cancer, it is more problematic, in that the case studies are not very conclusive. In our study, we saw no gender differences in lung cancer.

VIEGI: Again, to get away from this image of COPD being a male-oriented disease, I think that if we see a small difference, even if it's not significant, it is a signal that we need to do more studies.

Raising Awareness of COPD- Suzanne Hurd

VERMEIRE: You were rather critical about using educational materials.

HURD: I found this Cochrane review interesting because everyone thinks that just by putting this information in the literature, in workshop reports, or on websites that people are going to read it. But, study after study shows that unless you actually do something with it, and tell people that it's there and work with it in a more interactive way, the documents are useless. I think we can learn from the drug companies; if you have a message, you must market it.

BUIST: I think the point of Cochrane review was the importance of behavior change. Educational programs provide information only. The only way behavior changes is if the person becomes engaged in an interactive way and understands what he or she must do.

MAPEL: You often hear rumors that CMS, the organization that monitors quality of care for Medicare patients in the U.S., is going to start looking at COPD management as one of their quality measures. Do you know if there has been any progress on this?

HURD: That is one of the steps that the US COPD Coalition is working on. The letters have been sent to the directors of CMS through the congressional caucus to try to get CMS to pay attention to the reimbursement and payment for rehabilitation and to re-examine the whole issue of chronic care management.

VIEGI: The questionnaire, "Breathing for Life" focuses only on smoking. Why are there no questions about environmental factors such as indoor pollution or occupation?

HURD: There is a place at the bottom of the survey where any given country can add a question like that, if it is desired.

VOLLMER: With the advent of electronic medical records, some organizations are using technology to get information (i.e., guidelines) to clinicians in a way that they can use it at the time they need it. For example, some health care organizations have programmed pop-up reminders in their electronic medical records for clinicians at the time of ordering prescriptions or procedures for certain diagnoses.

MENEZES: Before PLATINO, most people in Latin America did not know about COPD. We had medical diagnoses of just 1.6% in Chile, the highest percentage. After the PLATINO survey, it was good to see that the awareness of COPD was much higher.

The Japanese COPD Experiences through NICE 1- Yoshinosuke Fukuchi

MENEZES: What was the design effect for cluster? We are using the same sampling for the PLATINO study and we are finding that the design effect for cluster is just around 1, meaning that we don't have to increase the sample size.

FUKUCHI: Yes, cluster effect was taken into consideration and was around 1. From the first stage of recruitment, we intended to have a cohort that was very similar with regard to gender and age to the total population of Japan. But, because of a low response rate, the data set was not fully validated.

MIRAVITLLES: I was surprised by the large percentage of underdiagnosed cases of COPD in your country (90%). Does it have any relationship with the severity of disease?

FUKUCHI: The majority of cases are Stage 1 or 2 COPD. More than 90% have milder COPD.

BUIST: I like to use this study as an example of the importance of doing good prevalence surveys. Do you have any idea if this has made any impact with the Japanese Ministry of Health?

FUKUCHI: The Japanese Respiratory Society has the interest and support of the ministry to promote the awareness of the importance of chronic respiratory disease. These data have had an impact on increasing the awareness of COPD and will help with policy-making.

SIN: My experience in Asia has been that doctors have a difficult time explaining COPD to their patients because of limited nomenclature. I wonder if that's a problem in Japan?

FUKUCHI: Three years ago, I was invited to talk about chronic respiratory illness on national TV, but the TV network would not let me use the term COPD. But, when I gave the same talk 3 years later, I did use the term COPD without a problem. So in 3 years' time, the mass media's acceptance of this disease has changed dramatically.

TAN: I'm in a roundtable for the Asian Pacific region and we meet about twice a year. The term used for COPD is a problem that we face. In many of the Asian countries, the word for COPD is asthma. The other term is breathlessness. They don't really have a word for COPD. It is translated literally and is not very easy for patients to understand. In the Southeast Asian countries, we do not have field studies. We used a mathematical model projection, the results of which were published in Respirology last year. Although they were projected prevalences for each country, we used a standardized method. These projected data were actually embraced by each of the governments and they have made policy based on those projected values. So, I think it has an impact. Of course, it must be followed up with proper field studies.

LAI: The terms that are commonly used in Asia are emphysema and chronic bronchitis. It is only in the last few years that we have been using the term COPD with patients, so it will take a few years to catch on.

GULSVIK: We did a survey on the recognition of the term “COPD” in Norway. In the beginning, only 20% recognized this term. After 3 years, this percentage of awareness of COPD was raised to 65%.

The Chinese COPD Experience- Christopher KW Lai, PX Ran, FWS Ko, SM Liu, JP Zheng, Nanshan Zhong, MSM Ip

SIN: Which reference values did you use in your spirometric calculations? Should measurements in airflow obstruction in Orientals be modified?

LAI: It will be very difficult to compare time trend data, especially with regard to severity of COPD, if we just base it on spirometric data alone. The reference lung function varies amongst populations. Even within the same populations, if you do your study at different times, you will probably see a change as well. In the Hong Kong study, we know that our predicted lung function values have increased by more than 10% from what we gathered 10 years ago. The most well-known Chinese reference lung function data were published by da Costa from Singapore. For ages below 40, the da Costa's lung function would be much higher than what we found in the last 2 years. But, in the older age group, the predicted values that we found in Hong Kong are much higher than the da Costa's reference values. In this study data set, we used the da Costa's lung function reference values. If anything, the Hong Kong dataset has underestimated the prevalence of COPD. On the other hand, because we used pre-bronchodilator values, this may overestimate the prevalence.

VOLLMER: Part of the problem that we face with BOLD is in determining which prediction equations to use for each site. We are actually planning to calculate two sets of spirometry measures. One based on the NHANES prediction equations and one using prediction equations derived from each site's data. Calculating the latter can be problematic for some sites due to the high prevalence of smoking. For example, in China, we wound up with relatively few non-smoking men but lots of non-smoking women to build our local prediction equations. It may be that we would be better off using the da Costa equations, but that is not our currently planned approach.

BEASLEY: In New Zealand, our lung function in the normal population is about 15% higher than the equations. I would be interested to know if these other reference values may not actually apply to our current populations.

VIEGI: The ERS equation was derived in the 70s and revised in 1983 and 1993. We have been discussing this issue of reference equations within the ERS/ATS Task Force. Our American colleagues were in favor of suggesting one overall equation as they are doing with NHANES. In Europe, we are not convinced of that. If you apply this older equation to the population of today, of course you will get 15% higher on the average.

TAN: The da Costa value was done in the late 1970s. We actually have an updated version of it.

LAI: One of the difficult issues I have with GOLD is defining the disease just by lung function. How are you going to compare data, especially with regard to severity of the disease, between different populations if you don't know what the reference lung function values are? That is particularly true for developing countries.

SORIANO: As asthma prevalence is higher in Hong Kong than in mainland China, and if we believe in the Dutch hypothesis, do you think that the asthma epidemic will produce a lot of COPD in men and women in mainland China?

LAI: The prevalence of asthma is actually decreasing in Hong Kong, but in mainland China, time-trend data have been showing an increase in asthma. If the elderly data that I showed you from Hong Kong hold true for mainland China then you may see a significant increase in the number of people with COPD.

Willingness to Pay for a COPD Life - Sean Sullivan

CHAPMAN: In looking at the Australian data or NICE data, I wonder if we could multiply the QALYs by the prevalence of the disease. That has to be a big factor for the payer, not just how much per QALY but how many QALYs.

SULLIVAN: If you were considering the budget impact of the decision you would make, you would have to do that because you would want to know what your expenditures were going to be.

LOPEZ: QALYs and DALYs are the converse of each other. The Australian government is using QALYs in terms of cost-effectiveness of DALYs, so that it uses both the burden of disease and the cost-effectiveness of interventions. That's the advantage of DALYs over QALYs.

Overall Workshop Discussion: A call to the COPD Research Community

MANNINO: In the latest ATS/ERS recommendations, a statement in the opening paragraph reads, "COPD is a treatable and preventable disease." I think this is a mantra that we should all take forward. A few take-home points include: better phenotyping of disease with regard to prognosis and progressions, and more data regarding the natural history of COPD and how that influences outcomes.

CHAPMAN: I am impressed with the general over-emphasis we have placed on cigarette smoking as the culprit in this disease. I have come away with the impression that there is a great deal more to learn about the causes of COPD. In terms of management, we're probably overlooking the importance of occupational, household, and environmental exposure. One of the difficulties that we have with COPD and heightening awareness is the sense that COPD sufferers brought it upon themselves by smoking. But it is important to remember that many people have this disease for reasons well beyond their control.

VIEGI: We need to use other lung function tests, not only spirometry. In future studies, it would be helpful to further study those patients who have abnormal FEV1/FVC ratios.

BUIST: I have been impressed over the last few days that there are very important methodological issues that can be addressed from the existing datasets and from the ones that are being developed right now. Discussions about the methodological issues are not necessarily going to happen spontaneously. This is something that pharmaceutical companies can help sustain. If we can come up with a more uniform definition or approach to diagnosis as a result of these discussions, we will all be able to progress much better in our research.