5.3 days for non-users. This bias unques-
tionably explains the phenomenal 92% reduction in mortality associated with short acting β agonists as over 95% of subjects used the agents and the magnitude of the bias is directly proportional to the frequency of exposure. Second, bias was introduced if β blockers are less likely to be used in the fatal hospitalisation of a patient with COPD who is in the final stages of the disease. Indeed, if these drugs are withheld in the context of palliative care, the rate of death in patients exposed to β blockers will be underestimated, which will make β blockers appear protective. Thirdly, selection bias was likely intro-
duced by the way the cohort was defined. The cohort of 825 subjects was formed using the last hospitalisation for a COPD exacer-
bation that occurred during the period 1999–
2006. There were, however, approximately 2,100 hospitalisations that occurred during this period (calculated from table 1 of the paper). By selecting the last hospitalisation, the cohort necessarily overrepresented the hospitalisations resulting in death. Basic tenets of epidemiology propose instead to use either the first hospitalisation to define the cohort, or to use all hospitalisations, albeit with a data analysis complicated by the correlated nature of hospitalisations occurring in an individual patient. Selection bias is amplified if β blockers are likely to be withheld in fatal hospitalisations.

Another important source of selection bias was introduced by identifying study subjects according to death summaries citing COPD as the probable cause of death. As death from cardiovascular causes is frequent in patients with COPD, and as patients prescribed a β blocker, and therefore with cardiovascular disease, are less likely to have COPD listed as the cause of death, subjects with COPD receiving a β blocker who died were systematically less likely to be included. As a result, a significant number of deaths exposed to β blockers was likely left out, leaving only eight such subjects in the study, thus leading to the appearance of a protective effect of β blockers. The presence of this bias is further suggested by the trend towards a protective effect of calcium channel blockers (odds ratio 0.76).

Observational studies are essential to complement information from randomised controlled trials. However, when such studies suggest astounding benefits that are inconsistent with trial data and use methods that are known to introduce well recognised biases, their results regretfully must be considered unfounded.

S Suissa, P Ernst
Center for Clinical Epidemiology and McGill Pharmacoepidemiology Research Unit, Jewish General Hospital, and Departments of Epidemiology and Biostatistics and of Medicine, McGill University, Montreal, QC Canada

Correspondence to: Dr S Suissa, Center for Clinical Epidemiology, Jewish General Hospital, 3755 Côte-Sainte-Catherine Road, Montréal, Québec, Canada H3T 1E2; sanny.suissa@mcgill.ca

Competing interests: None declared.

Accepted 29 June 2008

REFERENCES


Authors’ response

We thank Suissa and Ernst for their important comments regarding our paper and the design of observational studies. They raise several methodological concerns that call into question the validity of the results and highlight the many limitations of observational studies, including ours. It is certainly possible that immortal time bias and selection bias may have confounded our results and inflated the mortality benefit we observed with β blocker use; however, we strongly disagree that the results are inconsistent with clinical trial data as no randomised studies examining the effect of β blockers on COPD exacerbations or mortality exist. In fact, our results are entirely consistent with the few randomised studies of combination beta-blocker use in COPD patients which suggest no harmful effects on lung function, and with the majority of observational studies of β blocker use in patients with COPD which suggest benefit.

Our study included a number of controls to appropriately account for confounding. Principally among them was the finding that in contrast with β blockers, calcium channel blockers were not associated with a beneficial effect on mortality, arguing against a healthy user bias. Drs Suissa and Ernst point out that there was a trend towards a protective benefit with calcium channel blockers but this was not significant and the effect size was far smaller than that observed with β blockers. We should point out that the pharmacy billing dataset did not include the date patients were charged for the agents and the magnitude of the reduction in mortality associated with short acting β agonists as over 95% of subjects used the agents and the magnitude of the bias is directly proportional to the frequency of exposure. 

Importantly, it is highly unlikely that β blocker use among patients with COPD with cardiovascular disease whose lung disease was not severe enough to warrant inclusion in the discharge summary as a primary or secondary diagnosis would be harmful.

Suissa and Ernst are correct to highlight the limitations of our observational study. However, the systematic withholding of β blockers from patients with COPD is not supported by published data, and we found no evidence of harm even among this inpatient population. Our results highlight the need for a randomised trial in the outpatient setting to definitively examine this issue.

M T Dransfield, SM Rowe, J Johnson, W Bailey, L Gerald
University at Alabama at Birmingham and the Birmingham VA Medical Centre, Birmingham, Alabama, USA

Correspondence to: Dr M T Dransfield, University at Alabama at Birmingham and the Birmingham VA Medical Centre, 215 THT 1900 University Blvd, Birmingham, AL 35294, USA; mdransfield@bham.emory.edu

Competing interests: None declared.

REFERENCES


Predicting development and progression of COPD

Albers and colleagues recently concluded that “Lung function below the normal range and early respiratory signs predict the development and progression of COPD”. We have some concerns about the data. Table 2 in their article lists 151 subjects
Table 1 Mean FEV₁%/FVC and FEV₁ values from 28 authors and from the study of Albers and colleagues

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Mean 43</th>
<th>Mean 48</th>
<th>Decline</th>
<th>Mean 43</th>
<th>Mean 48</th>
<th>Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>80.2</td>
<td>79.2</td>
<td>1.0</td>
<td>3.486</td>
<td>3.350</td>
<td>0.135</td>
</tr>
<tr>
<td>48</td>
<td>73.8</td>
<td>84.1</td>
<td>10.4</td>
<td>3.10–3.82</td>
<td>2.95–3.66</td>
<td>0.11–0.16</td>
</tr>
<tr>
<td>5</td>
<td>84.5</td>
<td>79.3</td>
<td>5.2</td>
<td>3.532</td>
<td>3.335</td>
<td>0.197</td>
</tr>
<tr>
<td>SD</td>
<td>9.8</td>
<td>8.8</td>
<td>–</td>
<td>0.833</td>
<td>0.806</td>
<td>–</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

without baseline abnormalities. In 5 years, forced expiratory volume in 1 s (FEV₁) fell by 200 ml and FEV₁%/vital capacity (VC) by 5.2%, remarkably large declines for such subjects. We computed predicted values at ages 43 and 48 years according to 28 authors who had published predicted values for FEV₁%/forced vital capacity (FVC) for Caucasians, and 50 who had done so for FEV₁. The results are shown in Table 1; the values reported by Albers and colleagues are in the bottom two rows.

The decline in FEV₁/FVC during the study period was more than five times the expected average drop; the fall in FEV₁ was larger than expected. If the non-smokers declined at an expected rate (153 ml in 5 years) and we attribute the excess decline to smokers, the decline in smokers must have been 340 ml; as a minority of smokers exhibit an accelerated decline in FEV₁, leading to COPD, a limited number of smokers must have had a decline in FEV₁ far in excess of this. In that case, one would expect an increase in the scatter, but the SD of FEV₁ did not increase. The decreased scatter in FEV₁/VC over the 5 year period suggests that the group became more homogeneous, which makes it unlikely that the excess decline was caused by a subgroup. In any study, the ratio of average FEV₁ and average VC is not exactly equal to the average FEV₁/VC ratio; however, in 4557 observations from a random sample of a Dutch population, the difference was very small: 0.7623 vs 0.7655. Thus if we reconstruct the VC in the study of Albers and colleagues, we would increase the FEV₁/VC. VC at baseline was about 4.18 l, and 5 years later 4.21 l, so there was at best a trivial change.

One wonders whether these unusual findings are caused by problems with data collection which would invalidate the conclusions of this study. The authors state that variation in spirometer performance was assessed and accounted for; this merits a more detailed account. Measurements were performed according to the American Thoracic Society standards, but the study started prior to that report; were measurements recalculated?

P H Quanjer,1 I Steenbruggen,2 G Ruppel,2 M P Swanney2

1 Erasmus University, Rotterdam, The Netherlands; 2 Isala Klinieken, Zwolle, The Netherlands; 4 St Louis University Hospital, St Louis, Missouri, USA; 5 Respiratory Physiology Laboratory, Christchurch Hospital, New Zealand

Correspondence to: Dr P H Quanjer, Erasmus University, Rotterdam, The Netherlands; pquanjer@xs4all.nl

Competing interests: None declared.

Accepted 26 June 2008

REFERENCES


2. www.spirxpert.com/download/download1x.htm


Authors’ response

We thank Quanjer et al for their detailed comments on our study. The decline in lung function is a key aspect of COPD. The DIMCA study has been one of the first that focused on patients in the early stage of COPD and collected data covering a period of 10 years. It is therefore important to review the quality and reliability of our data.

In response to the comments raised by Quanjer et al we would like to stress the following. Our paper reported on the first 5 years of follow-up of our study population. For the baseline and year 10 measurements, the same spirometer (Microspiro HI-298 spirometer; Chest Corporation, Japan) was used. Because a different spirometer was used at year 5 (Fukuda Sangyo spirometer), equipment performance was assessed before as well as after lung function measurements in all participants had been completed. As we observed a systematic linear deviation in the lung function indices compared with the original spirometer, we considered it necessary to account for this. Further support for the reliability of our data was found in the follow-up of our study subjects. After 10 years, lung function was reassessed using the same spirometer that was used at baseline, and all assessments at year 10 were performed by the same lung function technician who performed the baseline assessments. We have now analysed the 10 year follow-up data and observed a further lung function decline that was fully in line with the pattern presented at year 5.

Although the 10 year data have not been published to date (Mieke Albers thesis: COPD in primary care. Aspects of secondary prevention; chapters 6 and 7), the group of subjects without baseline abnormalities showed a decline in forced expiratory volume in 1 s (FEV₁) amounting to 348 ml over the 10 year observation period. Over the 5 year period, this decline amounted to 197 ml. The decline in FEV₁/vital capacity (VC) was 10.8% after 10 years of follow-up and 5.2% after 5 years of follow-up.

Given the quality of the measurements and consistency of the pattern over time, we do not think there are reasons to doubt our findings. Quanjer et al point to the use of FEV₁/FVC. It is to be expected that our findings would have been arithmetically different had we used this ratio instead of the FEV₁/VC ratio. But the systematic difference still leaves the prediction in decline intact. For that reason, we do not believe there were fundamental flaws in our study, although we agree that the decline is relatively high compared with findings in previous population cohorts. We have have no explanation for this.

Quanjer et al are correct in that it would have been more appropriate to refer to the 1987 update of the American Thoracic Society statement on the standardisation of spirometry. At the time, this guideline served as the basis of procedures in the lung function laboratory of the University Lung Centre Dekkerswal, where all of our study subjects were measured.

M Albers, T Schermer, Y Heijdra, J Molema, R Akkermans, C van Weel

1 Department of General Practice, Radboud University Nijmegen Medical Centre, The Netherlands; 2 Department of Pulmonology, Radboud University Nijmegen Medical Centre, The Netherlands

Correspondence to: Professor C van Weel, Department of General Practice, 117-HAG, PO Box 9101, Nijmegen, The Netherlands; c.vanweel@hag.umcn.nl

Competing interests: None declared.

REFERENCE


No role for routine CT scans in paediatric empyemas

In the paper by Jaffe et al, the authors describe the CT findings of 51 patients with thoracic empyema who had three investigations (chest radiography, CT scan and ultrasound scan).1 They correctly conclude that routine CT scanning has no role for children with empyema treated with urokinase and percutaneous chest drainage. It is interesting to note that CT scanning is becoming popular as nearly half the subjects

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