5.3 days for non-users. This bias unquestionably 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.[3]

Secondly, 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 introduced by the way the cohort was defined. The cohort of 825 subjects was formed using the last hospitalisation for a COPD exacerbation that occurred during the period 1999–2006. There were, however, approximately 2120 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,[4] and as patients prescribed a β blocker, and therefore with cardiovascular disease, are less likely to have COPD listed as the cause of death,[5] 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 regrettably must be considered unfounded.

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REFERENCES

1. **Dransfield MT,** Rowe SM, Johnson JE, *et al*. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008;**63**:301–5.
2. **Suissa S.** Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf* 2007;**16**:241–9.
3. **Suissa S.** Immortal time bias in pharmacoepidemiology. *Am J Epidemiol* 2008;**167**:492–9.
4. **Anthonisen NR,** Connett JE, Enright PL, *et al*. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002;**166**:333–9.
5. **Camilli AE,** Robbins DR, Lebowitz MD. Death certificate reporting of confirmed airways obstructive disease. *Am J Epidemiol* 1991;**133**:795–800.

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 cardioselective β blocker use in COPD patients which suggest no harmful effects on lung function,[1] and with the majority of observational studies of β blocker use in patients with COPD which suggest benefit.[2–5]

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 β blockers and thus we could not eliminate immortal time bias. However, because β blockers are much more likely to be instituted during the chronic care of the patient with COPD, rather than during the hospitalisation itself, this effect is likely reduced.

As suggested, we did examine the data using the first hospitalisation as the index event and found similar results to those we report. This approach supports the conclusions in the manuscript but does not allow for the inclusion of exacerbation frequency as a measure of disease severity which we viewed as critical to the analysis. Although our methodology for subject selection is not immune to bias, we did not select patients for inclusion based on a death summary citing COPD as the cause of death, as is suggested. We included all patients admitted with a primary diagnosis of COPD or a secondary diagnosis of COPD with a primary diagnosis of respiratory failure regardless of their hospital outcomes. 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.

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REFERENCES

1. **Salpeter S,** Omiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;**4**:CD003566.
2. **Au DH,** Bryson CL, Fan VS, *et al*. Beta-blockers as single-agent therapy for hypertension and the risk of mortality among patients with chronic obstructive pulmonary disease. *Am J Med* 2004;**117**:925–31.
3. **Andrus MR,** Holloway KP, Clark DB. Use of beta-blockers in patients with COPD. *Ann Pharmacother* 2004;**38**:142–5.
4. **Chen J,** Radford MJ, Wang Y, *et al*. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol* 2001;**37**:1950–6.
5. **Gottlieb SS,** McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;**339**:489–97.

Predicting development and progression of COPD

Albers and colleagues[1] 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 FEV_1%/FVC and FEV_1 values from 28 authors and from the study of Albers and colleagues[1]

	FEV_1/FVC (%)			FEV1 (l)		
Age (year)	43	48	Decline	43	48	Decline
Mean	80.2	79.2	1.0	3.486	3.350	0.135
Range	73.8–84.1	72.4–83.5	0.4–1.6	3.10–3.82	2.95–3.66	0.11–0.16
Mean[1]	84.5	79.3	5.2	3.532	3.335	0.197
SD[1]	9.8	8.8	–	0.833	0.806	–

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

without baseline abnormalities. In 5 years, forced expiratory volume in 1 s (FEV_1) fell by 200 ml and FEV_1%/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 FEV_1%/forced vital capacity (FVC) for Caucasians, and 30 who had done so for FEV_1.[2] The results are shown in table 1; the values reported by Albers and colleagues[1] are in the bottom two rows.

The decline in FEV_1/FVC during the study period was more than five times the expected average drop; the fall in FEV_1 was larger than expected. If the non-smokers declined at an expected rate (135 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 FEV_1 leading to COPD,[3] a limited number of smokers must have had a decline in FEV_1 far in excess of this. In that case, one would expect an increase in the scatter, but the SD of FEV_1 did not increase. The decreased scatter in FEV_1/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 FEV_1 and average VC is not exactly equal to the average FEV_1/VC ratio; however, in 4557 observations from a random sample of a Dutch population, the difference was very small: 0.7623 vs 0.7635. Thus if we reconstruct the VC in the study of Albers and colleagues[1] from FEV_1 and FEV_1/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,[4] but the study started prior to that report; were measurements recalculated?

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REFERENCES

1. **Albers M,** Schermer T, Heijdra Y, *et al*. Predictive value of lung function below the normal range and respiratory symptoms for progression of chronic obstructive pulmonary disease. *Thorax* 2008;**63**:201–7.
2. www.spirxpert.com/download/download1x.htm (accessed 11 September 2008).
3. **Mannino DM.** COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest* 2002;**121**:121S–6.
4. **American Thoracic Society**. Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995;**152**:1107–1116.

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[1] 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 spiro analyzer ST-250, Japan), 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 (FEV_1) amounting to 348 ml over the 10 year observation period. Over the 5 year period, this decline amounted to 197 ml. The decline in FEV_1/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 FEV_1/FVC. It is to be expected that our findings would have been arithmetically different had we used this ratio instead of the FEV_1/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 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 Dekkerswald, where all of our study subjects were measured.

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REFERENCE

1. **Albers M,** Schermer T, Heijdra Y, *et al*. Predictive value of lung function below the normal range and respiratory symptoms for progression of chronic obstructive pulmonary disease. *Thorax* 2008;**63**:201–7.

No role for routine CT scans in paediatric empyemas

In the paper by Jaffe *et al*, the authors describe the CT findings of 31 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