We therefore believe that assessing vitamin D status in a cross-sectional manner from one region may not provide a true picture of the burden of vitamin D deficiency in patients with COPD. However, we agree with the conclusion reached by Janssens *et al*[1] that trials of vitamin D supplementation in COPD are required.

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β-agonist safety and the elephant in the room?

We read with interest the recent paper by Weatherall *et al* who presented data from a meta-analysis of the relative safety of long-acting β-agonists (LABAs).[1] In 2008 the FDA reported on the safety of LABAs and concluded that the nature and magnitude of risk needs to be confirmed. When adverse outcomes are reported relatively infrequently in clinical trials, it is difficult to interpret the value of such analysis and a more thorough examination of these index cases may yield more meaningful information about individual risks per se.

Table 1 Change in bronchial hyper-reactivity as a doubling dilution shift for formoterol and salmeterol in genotype-specific patients as change from placebo after chronic dosing

		Doubling dilution (dd) shift		
Drug	**Genotype**	**>1 dd (improvement)**	**±1 dd (no change)**	**>1 dd (worsening)**
Formoterol	Arg-Arg and Arg-Gly	17%	23%	60%
	Gly-Gly	27%	44%	29%
Salmeterol	Arg-Arg and Arg-Gly	35%	46%	18%
	Gly-Gly	50%	39%	11%

After data from Lee *et al*.[5]

Polymorphisms in the β_2-adrenoceptor have long been linked to differences in response to β_2-agonists after chronic dosing. In asthma, the prevalence of the genotype Arg-Arg-16 is approximately 15% and of Arg-Gly-16 is 45%.[2] In patients with asthma using frequent β-agonists, there is an increased risk of asthma exacerbation per copy of Arg16 allele (OR 1.64; 95% CI 1.22 to 2.20; p=0.001).[3] Could this be the elephant in the room for better understanding risk?

In a recent multicentre study assessing salmeterol as an add-on to inhaled corticosteroids in genotype-selected patients (the LARGE study), patients with the Gly-Gly-16 genotype had a 2.4-fold greater improvement in bronchial hyper-reactivity (BHR) with salmeterol than with placebo (p<0.0001), while patients with the Arg-Arg genotype had no such benefit (p=0.87).[4] Lee *et al* have previously shown similar differences in response to BHR for patients with the Gly-Gly genotype compared with individuals carrying either one or two copies of Arg16 (table 1).[5] Furthermore, this paper demonstrated differences in patients with Arg16 in their response to the full agonist formoterol compared with the partial agonist salmeterol. These findings are in keeping with the discussion by Weatherall *et al* which suggested that there may be different risks in different drugs from the same drug class.

It is common practice for respiratory physicians to measure levels of thiopurine methyltransferase before administration of the drug azathioprine in pulmonary fibrosis. This test identifies individuals with genetic polymorphisms which predispose to an adverse reaction to the drug. Perhaps the time has come to join up the dots and start assessing individual risk to β_2-agonists rather than continuing to count cases.

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Author's response

We thank the authors for their interest in our paper.[1] They raise an interesting and pertinent point about identifying patients at greater risk of β-agonist toxicity, a group in whom either the dose of β-agonist should be lowered, or in whom our point about co-prescription of inhaled corticosteroids is even more relevant.[2] Unfortunately, we feel that the question about whether these patients could be identified in the context of randomised controlled trials, in which mortality is very rare and important morbid outcomes are relatively uncommon, is that it would be impossible to demonstrate a difference in these rare outcomes stratified by genetic status. This of course amounts to a similar problem as experienced by subgroup analysis of randomised controlled trials, namely a lack of statistical power to detect important differences. Another way of examining whether genotype affects morbid outcomes related to medication use