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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Competing interests None.

Ethics approval This study was conducted with the approval of the Norfolk research ethics committee.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 28 January 2010
Published Online First 26 June 2010

Thorax 2011;**66**:541–542. doi:10.1136/thx.2009.134338

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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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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 9 March 2010
Published Online First 7 June 2010

Thorax 2011;**66**:542. doi:10.1136/thx.2010.137182

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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

may be to use this as a covariate in case–control studies and examine whether risk is modified. This would require that cases and controls had appropriate genetic material available for analysis and would probably require a prospective study.

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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 24 August 2010
Published Online First 14 October 2010

Thorax 2011;**66**:542–543.
doi:10.1136/thx.2010.149765

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Transbronchial needle aspiration in the diagnosis of mediastinal amyloidosis

We read with interest the pulmonary puzzle by Khor *et al*[1] on mediastinal lymph node amyloidosis diagnosed by direct real-time endobronchial ultrasound-guided (EBUS) transbronchial needle aspiration (TBNA). The development of EBUS-TBNA is improving the diagnostic yield of mediastinal lymphadenopathy.[2] However, we offer some comments about the diagnostic approach used in the case described.

First, in our opinion, conventional TBNA continues to have a significant value in diagnosing mediastinal node involvement, especially in cases of lymph nodes with a short axis >1 cm that are readily accessible.[3] The potential advantages of TBNA over EBUS-TBNA are the lower cost, routine availability, ease of mastery, reduced need for patient sedation and the possibility of using histology needles that allow acquisition of a core of tissue, improving diagnostic sensitivity for other lesions such as tuberculosis, lymphoma and sarcoidosis.[3] Our group reported the first case of mediastinal amyloidosis diagnosed by TBNA using a histology TBNA needle.[4] In our opinion, according to the characteristics of the patient described and CT chest images, the safest and most cost-effective probe that was indicated in this case was TBNA using a histology needle. Second, there is a previous report in the literature of mediastinal amyloidosis diagnosis made with EBUS-TBNA[5] so the report was not, as the authors stated, the first published case. Finally, we agree with the authors that, although mediastinoscopy is still considered the 'gold standard' diagnostic approach for mediastinal nodal amyloidosis, conventional TBNA sampling has value and should be considered as a less costly alternative that is universal and accessible to any bronchoscopist compared with EBUS-TBNA. In fact, it should be considered the first step in the diagnostic sequence. The debate over the role of conventional TBNA in the era of EBUS remains unresolved.

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Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 6 May 2010
Published Online First 17 August 2010

Thorax 2011;**66**:543. doi:10.1136/thx.2010.138628

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Implementing the change in National Institute for Health and Clinical Excellence guidance on airflow obstruction grading in chronic obstructive pulmonary disease

The updated National Institute for Health and Clinical Excellence (NICE) chronic obstructive pulmonary disease (COPD) guidelines[1] and the draft national strategy for COPD[2] have recommended a change in the classification of airflow obstruction severity to align them with international classifications. NICE's 2004 guidelines recognised that disease severity is not the same as the severity of airflow obstruction and has recommended using other measures such as the Medical Research Council (MRC) dyspnoea scale, exacerbation frequency and multicomponent indices.[3] However, UK primary care has been encouraged to code disease severity into mild, moderate and severe COPD based on lung function alone in line with NICE's 2004 guidance on airflow obstruction.

The code for COPD is thus H3; H36 is mild COPD; H37 is moderate COPD and H38 is severe COPD.

A person with COPD and an forced expiratory volume in 1 s of 42% of predicted has until now been coded as having moderate COPD; according to NICE 2010 they should now be coded as severe airflow obstruction. However, codes do not exist for mild, moderate, severe and very severe airflow obstruction. Therefore, for both patients and primary clinicians we have a communication problem and a coding problem. Clear guidance is needed on how the disease/airflow obstruction severity should be coded on primary care records without any conflicting or confusing advice.

Perhaps the answer is to abolish the codes for mild moderate and severe COPD and for new codes for airflow obstruction based on GOLD stages 1–4 to be generated. For practical purposes of classifying COPD severity, for example, for deciding the frequency of reviews, the MRC dyspnoea scale could replace H36–8 as markers of disease severity. The MRC scale is already being recorded in primary care. In future, COPD severity codes should be based on multicomponent indices, at present a suitable index for primary care has not been chosen. The NICE guidelines recommend the use of the BODE index when its component items are available, the need for the six minute walking test will make this impractical for routine use in primary care and there is insufficient evidence to approve newer indices such as the ADO[4] and DOSE.[5]

Action is required now to address both the coding and communication issues so that the sensible advice from NICE can be implemented without causing confusion in primary care and distress to patients.

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Competing interests None to declare.