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CORRESPONDENCE

Population-specific reference equations?

To the Editors:

The recent paper by CHINN *et al.* [1], published in the *European Respiratory Journal*, describing sources of variation of forced expiratory volume in one second (FEV1) and forced vital capacity in the large multicentre European Community Respiratory Health Survey trial, raises important issues in the ongoing debate over the misuse of reference equations in respiratory medicine. The authors demonstrate potentially important population differences, which call into question the application of ethnicity-specific reference equations.

However, we believe it is likely that much of the population heterogeneity in the study by CHINN *et al*. [1] arose from differences in methods, equipment and software. While the authors made some attempts to account for such differences, the level of ''noise'' and the limited site-specific details available (such as quality-control criteria and software versions) would make it hard to demonstrate statistically significant contributions from all sources.

Although the differences were not explained by the different equipment models, differences in equipment software version or measurement protocols could have led to systematic measurement errors. Since quality-control visits were conducted as part of the study protocol, it may have been reasonable to measure biological controls in each of the centres to assess the intra-subject variability between test centres [2]. As the authors suggest, a multicentre trial with a common protocol and identical equipment and quality-control techniques may be better able to tease apart methodological and equipment differences from true population differences.

Given the strong correlation between height and FEV1, it is remarkable that a quarter of the centres did not measure height. Self-reported height is known to be overestimated, especially in males [3–5], and this could have contributed significantly to the observed inter-centre variability.

Furthermore, while the ethnicity of the study population was stated to be ''almost exclusively White'', it is unclear whether, in countries with multi-ethnic populations, such as the UK or the USA, non-Caucasians were excluded or merely studied in small numbers. Inclusion of even a small number of non-White subjects could increase the variability of spirometry measurements. Also, the recruitment of an exclusively White sample may be unrepresentative of the overall population owing to other confounders.

The study by CHINN *et al*. [1] raises awareness of the misuse of reference equations, but offers no realistic alternative. In the meantime, individual laboratories should take every precaution to ensure the reference equations installed in their equipment are appropriate for the population being studied. The inter-centre differences in the European Community Respiratory Health Study cannot be ignored. Current reference equations cannot be guaranteed to give accurate norms of lung health and this study emphasises the need for more suitable reference equations and/or statistical models that can adjust for between-centre differences.

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From the authors:

We thank S. Stanojevic and co-workers for their letter and the opportunity it gives us to provide some clarification.

Although our paper [1] is recent, the data were collected in the European Community Respiratory Health Study (ECRHS) I, carried out from 1990–1992, by research teams who had not worked together previously and who came from diverse healthcare systems and different language groups, across four continents.

We are well aware of improvements and clarifications that could have been made to the written protocol and to training and quality-control procedures. Unfortunately, we do not have access to the ''in press'' paper [2] referred to in the letter from S. Stanojevic and co-workers. While biological controls may have some advantages for assessing between-centre variations, it is not at all clear to us how many would be needed and what the effects of training would be. However, almost certainly the number of biological controls that would have been needed to assess intra-subject variability between centres would not have been available.

It is not correct to say that ''a quarter of centres did not measure height''. We reported that: ''Out of 42 centres, it was measured in 31, self-reported in five and not recorded whether measured or asked in six.'' We were being scrupulously honest and in five of the latter it is likely that height was measured. However, study personnel have moved on and definitive information could not be retrieved once we had realised that some centres had not measured height directly. In three of the centres that we classed as ''self-reported height'', subjects were measured if any doubt was expressed, and gross errors are unlikely to have occurred. Although the over-estimation of height in the study by STEWART *et al.* [3] was nontrivial, that found by NIEDHAMMER *et al*. [4] was <0.5 cm on average. The other reference does not seem relevant.

There was exclusion for non-White ethnicity in only one centre: Melbourne (Australia). Ethnicity was not recorded in any of the other centres, which are listed in table 1 of our paper [1], but this was not raised as an issue.

It was our intention in writing the paper to engender debate and our conclusions are endorsed by S. Stanojevic and co-workers. We believe that current reference curves cannot be guaranteed to give accurate norms of lung health, and that multicentre studies must invest substantially in standardised equipment. However, ''statistical models which can adjust for between-centre differences'', as advocated by S. Stanojevic and co-workers, do not solve the problem, as differences may be due to genuine variation in health.

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Improvement of endothelial function with allopurinol may occur in selected patients with OSA: effect of age and sex

To the Editors:

In a recent issue of the *European Respiratory Journal*, EL SOLH *et al.* [1] demonstrated that allopurinol improves endothelial dysfunction in patients with moderate-to-severe obstructive sleep apnoea (OSA). Because xanthine oxidase inhibition with allopurinol prevents the formation of superoxide free radicals, which leads to better endothelial function, EL SOLH *et al.* [1] speculated that excess activity of xanthine oxidase contributes significantly to vasodilatory impairment in patients with OSA.

The study was a sophisticated prospective, randomised, crossover design, minimising the presence of confounding variables and eliminating inherent individual variations in terms of the generation of free radicals, hyperaemic vascular reactivity or response to treatment. However, a number of arguable assumptions were made in the article of EL SOLH *et al.* [1].

First, endothelial function assessment using hyperaemia-induced flow-mediated vasodilation (FMD) is not always suitable for the assessment of endotheloial function in female obese patients with sleep apnoea. There is a significant relationship between FMD and brachial artery size; therefore, as males have larger arterial diameters, smaller FMD is noted in males [2]. Thus, the changes in FMD in males before and after therapeutic intervention are usually larger than those in females. As the current study did not examine the FMD results of females and males separately, the sex difference may exist in the study. Inversely, the FMD improvement after allopurinol treatment may be clearly indicated, when the males' results were analysed separately from the females' results.

Secondly, FMD of the brachial artery diminished with age [2]. Thus, the age distribution of the study sample affects the results of the FMD alterations after intervention. Because the authors examined subjects aged 29–60 yrs, this wide range of the population may not represent the genuine effects of allopirinol on the FMD in association with oxidative stress due to sleep apnoea itself.

Thirdly, obesity without sleep apnoea also causes endothelial dysfunction [3]. The FMD results should be standardised by the body mass index (BMI) or metabolic variables, when the FMD results are properly assessed. In the study by EL SOLH *et al.* [1], BMI ranged 23–67. We speculate that the FMD results in patients with a normal BMI of 24 might be very different from the extraordinarily obese patients with a BMI of 67. It has also been reported that FMD is associated with systemic inflammation and glucose homeostasis in obese patients, independent of