Location, location, location: studying anatomically comparable airways is highly relevant to understanding COPD

We have read with interest Nakano and colleague's thoughtful comments[1] on Smith *et al*[2] and are pleased to offer the following observations.

We believe that a key strength of our paper is that it defines a rigorous sampling strategy to compare airways from matched hierarchical positions within the tracheobronchial tree with control for the known hierarchical gradient in airway dimensions.[3] Nakano *et al* are correct to point out that hierarchical sampling by generation number results in grouping of airways from multiple anatomic locations (eg, segmental and lobar airways); conversely, hierarchical sampling by anatomic location results in grouping of airways from multiple generations.[4] It is for this reason that we reported both sampling approaches (tables 2 and E6), consistently demonstrating smaller airway wall areas in COPD compared with controls. Importantly, analyses stratified by lobe demonstrated smaller segmental airway wall areas in COPD for each of the five lobes ($p<0.001$ for lobes). Therefore, the finding of thinner airway walls in COPD was not due to grouping measures from different lobes. Additionally, this lobar analysis demonstrates that the findings were not due to motion artefact in the lower lobes.

We reported adjusted analyses, in addition to unadjusted analyses, to assess differences in airway wall area by COPD status after accounting for other factors that affect airway wall dimensions including body size, lung volume and current smoking status. These adjustments in fact had little impact on the results: intermediate models that omitted smoking status, airway length, percent emphysema$_{-950HU}$, milliampere dose and lung volume, either individually or in combination, demonstrated consistently smaller airway wall areas in COPD compared with controls from generations 1 through 6 ($p<0.005$ for all models).

In the context of our paper, the term bias is used to mean that there may be—or actually will be—systematic differences in the results depending on how the airways are sampled. Thus, bias refers to systematic differences as a result of the sampling strategy, a fact and not a judgment. The objective was to determine if airway wall dimensions differed by COPD status—not to determine if proximal airway wall dimensions differed from distal airway wall dimensions. Fewer distal airways in COPD compared with controls, when sampled at random, result in more proximal airways in COPD being compared with more distal airways in controls. This bias is not specific to the central airways, and may be even more pronounced in the peripheral airway tree, where the difference in airway number by COPD status is large.[5]

Finally, we agree with Nakano *et al* that airway lumen size is important with respect to certain functional consequences of airway wall pathology (eg, airflow resistance). However, we believe that unbiased methods of studying airway wall properties, which ultimately define airway lumen size, are highly relevant toward understanding the pathobiology of COPD.

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Correction notice This article has been corrected since it was published Online First. The competing interests statement has been corrected.

Acknowledgements We thank Professor Ewald R Weibel for graciously providing advice on the ideas expressed in this response to Nakano *et al*.

Contributors All authors contributed to the discussion, formulation and revising of this letter. BMS also conducted additional analyses and drafted the original letter.

Funding US Department of Health and Human Services-National Institutes of Health (HHSN268200900013C-HHSN268200900020C, N01-HC95159-HC95169, R01-HL075476, R01-HL077612, R01-HL093081), Fonds de Recherche du Québec—Santé (Clinician-researcher training award)

Competing interests EAF is a founder and share holder of VIDA Diagnostics, a company that is commercialising pulmonary image analysis software developed, in part, at the University of Iowa.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite Smith BM, Hoffman EA, Rennard S, *et al*. *Thorax* 2014;**69**:1049–1050.

Received 19 August 2014
Accepted 20 August 2014
Published Online First 12 September 2014

Linked

- http://dx.doi.org/10.1136/thoraxjnl-2014-205160
- http://dx.doi.org/10.1136/thoraxjnl-2014-206118

Thorax 2014;**69**:1049–1050.
doi:10.1136/thoraxjnl-2014-206188

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