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## Confounding Factors Affecting sRAGE as a Biomarker for Chronic Obstructive Pulmonary Disease

To the Editor:

In a review paper recently published in the *Journal*, Stockley and colleagues provide an excellent overview of the current literature and the necessity and limitations of currently available and future chronic obstructive pulmonary disease (COPD) biomarkers (1). In their review, Stockley and colleagues state that the circulating level of sRAGE (soluble receptor for advanced glycation end-products) is the best known biomarker for the COPD phenotype emphysema, yet some limitations prohibit the current use of sRAGE in the clinic, including large interindividual variation with overlap between healthy controls and patients with COPD and limited knowledge on confounding factors such as smoking behavior. Although Stockley and colleagues provide a thorough overview of the currently available data on sRAGE as a biomarker for COPD, they overlooked key publications by our group on the role of sRAGE as a COPD biomarker. Stockley and colleagues speculate about the potential effects of smoking on circulating sRAGE levels, and state that this needs to be investigated further. In fact, we have recently addressed these issues, as we have shown that smoking acutely and severely decreases serum sRAGE levels by up to 50% within 2 hours after smoking three cigarettes (2). We validated these results using two distinct quantitative sRAGE assays to exclude the possibility of a technical artifact. Furthermore, in a second study, we showed that this difference is not caused by chronic smoke exposure, as we did not find significant differences in serum sRAGE levels among age-, sex-, and body mass index-matched, young and old smokers and never smokers (3, 4). These data indicate that smoking acutely and temporarily decreases serum sRAGE levels, which may cause large interindividual variations in serum sRAGE levels, as reviewed by Stockley and colleagues. Therefore, we proposed that smoking cessation in the hours before blood sampling may decrease the variation in serum sRAGE levels and increase the discriminative value of sRAGE as a biomarker for COPD. Furthermore, Stockley and colleagues state that more studies are needed investigating the effect of COPD exacerbations on serum sRAGE levels. Indeed, we investigated this using serum

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Supported by the Netherlands Organization for Scientific Research NWO (Domain Applied and Engineering Sciences; Perspectief program P12-04; projects: 13541 and 13544) and the Lung Foundation Netherlands (project: 6.2.15.044JO).

Author Contributions: S.D.P., F.K., R.B., and N.H.T.t.H. provided the conception and design of the study; S.D.P. provided the drafting of the manuscript; and S.D.P., F.K., R.B., and N.H.T.t.H. provided revision of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201902-0356LE on March 19, 2019

samples of 14 patients with COPD that were in stable disease, and serum samples from the same patients when they were experiencing an exacerbation (5). Here, we showed that serum sRAGE levels are significantly decreased during an exacerbation, although there is no difference in the expression of the gene encoding RAGE in granulocytes. In summary, our results are in line with Stockley and colleagues, that more research on confounding factors is needed before sRAGE can be implemented as a clinically usable COPD biomarker. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## Reply to Pouwels et al.



From the Authors:

We welcome the letter from Pouwels and colleagues, who provide recent and historical evidence to amplify the issues related to the role of smoking and exacerbations in the interpretation of sRAGE (soluble receptor for advanced glycation end-products) data (and

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Author Contributions: R.A.S. wrote the initial response. D.H., B.R.C., and D.S. critically appraised and added to the content, and approved the final submission.

Originally Published in Press as DOI: 10.1164/rccm.201903-0573LE on March 19, 2019