of exposure to active and passive tobacco smoke on urinary eicosanoids in relevant asthma populations. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Thomson

From the Authors:

We thank Dr. Thomson for raising the important issue of the effects of smoking status upon observed urinary eicosanoid metabolite levels. In our recent publication reporting the utility of certain urinary eicosanoids in identifying type 2 (T2) inflammation in the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) study (1), we examined the effects of a number of potential confounders; however, we did not report on the influence of current smoking. To mimic real-life conditions, the U-BIOPRED study indeed recruited one group of individuals ($n = 109$) that included past (>5 pack-years) and current smokers. As reported in Table 3 of our paper, the majority of the measured eicosanoid metabolites exhibited no significant differences between the smoking and nonsmoking ($n = 302$) group of participants with severe asthma using this dual inclusion criteria for the smokers. Although there were small differences in the 2,3-dinor thromboxane B_2 metabolite and the isoprostane 8-iso-prostaglandin (PG)$F_{2\alpha}$, the most pronounced difference related to the main metabolite of prostaglandin E_2 (PGE_2), which was higher in both men and women in the smoking group, in line with published data (2). In contrast, the T2-associated metabolites of cysteinyl leukotrienes and PGD_2 were the same in the smoking and nonsmoking patients with severe asthma.

In response to Dr. Thomson's inquiry, we have now extracted data for the subgroup of current smokers ($n = 42$) and compared the T2-associated urinary eicosanoids in question with those in the larger group of nonsmoking patients with severe asthma (Table 1). Neither leukotriene E_4 (LTE_4) excretion nor recovery of the two main PGD_2 metabolites, 2,3-dinor-11β-$PGF_{2\alpha}$ and tetranor-PGDM, were significantly different between the current smokers and the larger group of nonsmokers. Interestingly, in the same subgroup analysis, fractional exhaled nitric oxide was 41% lower in current smokers ($P < 0.001$), validating that one established effect of smoking (3) was replicated in the U-BIOPRED study. In terms of other T2 markers, serum periostin was slightly (14%) lower in the smokers ($P = 0.013$), whereas blood eosinophil counts were the same in both groups ($P = 0.482$).

With respect to passive smoking, urinary cotinine was in fact measured in spot samples of 509 of the participants with asthma but was only found present in 33 of the those with severe asthma belonging to the smokers/ex-smokers group. This unfortunately does not permit analysis of a potential influence of passive smoking because cotinine-positive cases most likely reflect active smoking at the time of the study visit.

Dr. Thomson also raised the question concerning the possible confounding effect of smoking status upon our data supporting the ability of urinary PGD_2 and LTE_4 to identify T2 asthma. To further examine this important point, we performed a focused analysis of the reported extreme groups in Figure 6 of our paper. Based upon quartile concentrations of the PGD_2 metabolites (*c*-PGD_2) and LTE_4, the groups contained less than 12% and 7% current smokers in the 75th quartile for *c*-PGD_2 and LTE_4, respectively. In those subgroups of participants, their quartile median values did not contribute to any different extent to the total 75th quartile median. Consequently, the contribution from active smoking participants to define concentration-based quartiles of urinary concentration of *c*-PGD_2 and LTE_4 could not be considered to be confounded by current smokers.

In summary, the herein reported new analysis of data for the current smoking group of U-BIOPRED participants does not lend support to the concept that smoking may induce high levels of urinary LTE_4 or metabolites of PGD_2. However, because only 42 subjects were current smokers, we believe that the data should be interpreted with caution. Clearly, as referred to in Dr. Thomson's letter, there are reports that suggest such effects, in particular his own work (4). The latter study is well designed and conducted; however, at that time T2 markers in blood were not assessed, so it is difficult to directly compare the findings with ours. In addition, earlier work has reported an increase in urinary LTE_4 in children with asthma exposed to environmental tobacco smoke assessed by urinary cotinine levels

Supported by the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No. 115010 (U-BIOPRED [Unbiased Biomarkers for the Prediction of Respiratory Diseases Outcomes]) and 831434 for Taxonomy, Targets, Treatment, and Remission. The JU receives support from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associates. C.E.W. was supported by the Swedish Heart–Lung Foundation (20180290).

Originally Published in Press as DOI: 10.1164/rccm.202101-0208LE on February 23, 2021

Table 1. Urinary Concentration of T2 Inflammation–associated Urinary Eicosanoids and Common T2 Inflammatory Markers in the U-BIOPRED Participants with Severe Asthma

	Nonsmoker with Severe Asthma (*n* = *302*)	Current Smoker with Severe Asthma (*n* = *42*)*	*P* Value†
2,3-Dinor-11β-$PGF_{2\alpha}$	58 (39–80)	67 (48–86)	0.115
Tetranor-PGDM	268 (191–368)	252 (198–364)	0.696
LTE_4	6.3 (3.9–11.0)	7.0 (4.5–12.7)	0.571
FE_{NO}, ppb	27 (16–48) (*n* = 281)	16 (10–32) (*n* = 41)	**<0.001**
Blood eosinophils, counts/μl	200 (100–400) (*n* = 294)	210 (130–413) (*n* =42)	0.482
Serum periostin, ng/ml	50 (42–60) (*n* = 250)	43 (37–53) (*n* = 33)	**0.013**

Definition of abbreviations: 2,3-Dinor-11β-$PGF_{2\alpha}$ = 2,3 dinor-11β-prostaglandin $F_{2\alpha}$; FE_{NO} = fractional exhaled nitric oxide; LTE_4 = cysteinyl leukotriene E_4; T2 = type 2; TetranorPGDM = tetranor prostaglandin D_2 metabolite.
Values are presented as median (interquartile range). Urinary eicosanoids are expressed in ng/mmol creatinine.
*In the U-BIOPRED study, there were *n* = 109 current or ex-smokers. Of these individuals, *n* = 42 were defined as current smokers and are included in the current analysis.
†Statistical comparisons were performed with a Mann-Whitney test, and bold values indicate $P < 0.05$.

(5). There are subsequently indications in the literature of an interaction between both active and passive smoking with urinary eicosanoid levels. We believe future studies specifically designed to address active and passive smoking influences on not only T2 markers but also the whole panel of urinary eicosanoids are warranted. We thank Dr. Thompson for this opportunity to reanalyze part of our own data and agree very much that all proposed biomarkers should be rigorously tested for confounding factors. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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