Table 1. Medications Administered to Patients at Baseline

	No Previous CVD (*n* = 1,381)	Previous CVD (*n* = 320)	*P* Value
β-Blockers	161 (11.7)	194 (60.6)	<0.001*
Calcium antagonists	122 (8.83)	81 (25.3)	<0.001*
Angiotensin II receptor antagonists	181 (13.1)	65 (20.3)	0.001*
Angiotensin converting enzyme inhibitors	247 (17.9)	144 (45.0)	<0.001*
Diuretics drug	193 (14.0)	79 (24.7)	<0.001*
Antihypertensive drug	567 (41.1)	287 (89.7)	<0.001*

Definition of abbreviation: CVD = cardiovascular disease.
Data are *n* (%).
*Significant *P* values ($P < 0.05$).

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Exposure to Active and Passive Tobacco Smoke on Urinary Eicosanoid Metabolites in Type 2 Asthma

To the Editor:

Data from the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) study reported by Kolmert and colleagues (1) have highlighted the potential value of urinary eicosanoids in identifying type 2 inflammation in asthma. Urinary metabolites of prostaglandin D_2 (PGD_2), tetranor PGD_2 (PGDM) and 2,3-dinor-11β-PGF2α, were elevated in severe asthma compared with mild to moderate asthma, and urinary cysteinyl leukotriene E_4 (LTE_4) concentrations were elevated in mild to severe asthma compared with healthy nonsmoking control subjects. Importantly, high concentrations of urinary PGD_2 and LTE_4 metabolites were associated with markers of type 2 high inflammation in the UBIOPRED cohort and in validation populations of severe asthma and adolescents with asthma. Although metabolite concentrations were unrelated to several demographic factors, the study does not report on the effects of current smoking status or exposure to passive smoke on urinary metabolite eicosanoid concentrations.

Previous studies have found that PGD_2 urinary metabolite PGDM concentrations are increased in current smokers with asthma compared with never-smokers with asthma (2) and that LTE_4 urinary metabolite concentrations are elevated in healthy smokers (2, 3), current smokers with asthma compared with never-smokers (2, 4), and children with asthma exposed to passive smoke and at risk of severe exacerbations (5). Collectively, these findings indicate that exposure to tobacco smoke is an important variable to consider when interpreting urinary PGDM and LTE_4 concentrations as a biomarker of type 2 inflammatory status. Interestingly, urinary LTE_4 (2, 4) and PGDM concentrations (2) are directly associated with sputum eosinophils among current smokers with asthma, suggesting a potential link between urinary eicosanoids and type 2 eosinophilic inflammation, at least in a proportion of this subgroup of smokers. Although the UBIOPRED study included a "smoking" group of 109 current and former smokers with severe asthma, in whom urinary eicosanoid concentration did not differ from the nonsmokers with severe asthma, urinary biomarker results are not reported in the subgroup of current smokers with asthma. It would also be helpful to know whether exposure to passive smoke altered urinary eicosanoid concentrations in the UBIOPRED and validation populations.

Type 2 inflammation occurs in adults with severe asthma and a smoking history (6), although non–type 2 inflammation is a more frequently found phenotype. Current cigarette smoking can alter several biomarkers of type 2 inflammation, for example, by reducing fractional exhaled nitric oxide and serum periostin concentrations, which may hinder stratification of current smokers with asthma for targeted treatments. Further assessment of the role of urinary eicosanoids in identifying and monitoring type 2 inflammation in adults and adolescents with asthma should include data on the effects

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

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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

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