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LETTER TO THE EDITOR

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Discordant use of short-acting β_2 agonists in children and adults with severe, uncontrolled asthma from the U-BIOPRED cohort

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To the Editor,

Poor perception of asthma symptoms by the children themselves or their parents may result in inadequate medication use and poor asthma control. It is known that in pediatric asthmatics, parents can misperceive their child's daily symptoms.[1–3] The aim was to investigate child–parent concordance in reporting daily asthma symptoms and its relationship with reliever use and compare this pattern to the adult with severe, uncontrolled asthma. Furthermore, we assessed changes of daily symptoms and β_2 mimetic use over time in the group of children and adults.

Longitudinal data on children (aged 6–17) and adults (aged 28–73) with severe, uncontrolled asthma at 12-week telemonitoring was obtained from the prospective Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort.[4] The study was approved by local ethical committees. All participants and guardians gave their written, informed consent. The study design is illustrated in Figure S1.

Telemonitoring assessment included daily recoding in Asthma Diaries (Supporting Information Material). The Pediatric Asthma Diaries (PAD) for children and the Pediatric Asthma Caregiver Diary (PACD) for their parents contained 12 questions (four child-completed and eight parent-completed). Adults recorded in the Adult Asthma Diaries (AAD) which consists of eight items similar to the PACD. The primary outcome measures included a full version of PAD and a shortened version of PACD and AAD from domains related to asthma symptoms (asthma bother, activity limitation, cough frequency, and night-time wake) recorded by children, their parents,

and adults, respectively, and the daily number of β-agonist inhaler puffs not related to physical activity (Table S1). Response level varies from 0—no asthma symptoms to 3—the most severe and frequent asthma symptoms. We calculated the daily composite asthma symptom score as a sum of selected responses (sum score) with a range from 0 to 12. To compare discordant use of β-agonist inhalers, we also classified days under observation into four groups: (1) days without any asthma bother symptoms and without any inhaler use; (2) days with asthma bother and inhaler use; (3) days without any asthma bother symptoms, but with inhaler use; (4) days with asthma bother symptoms, but without inhaler use. The first two groups were considered as days with concordant inhaler use; the second two groups were classified as days with discordant inhaler use.

We evaluated the daily changes in asthma symptoms with daily changes in the use of β-agonist inhalers using a nonparametric Spearman rank correlation test. Agreement between child- and parent-reported scores was assessed using kappa statistics. We calculated the number of days with discordant and concordant uses of β-agonist inhalers per each subject (e.g., number of days with concordant/discordant use of inhalers divided by the total number of days under observation). We applied the nonparametric Wilcoxon's rank sum test to compare medication concordance between children and their parents. Analyses were performed using Stata version 15 and R (version 3.2.1) software.

Fourteen children and their parents, each with 21–88 observed days, completed 897 diaries and 18 adults, with 72–97 observed days, completed 1,549 diaries. Population characteristics are described in Table S2.

There were significant moderate-to-high correlations in symptom scores between children and their parents (Figure 1A). A high correlation was found between child- and parent-reported cough scores ($\rho = 0.79$, $p < .0001$) and total sum scores ($\rho = 0.80$, $p < .0001$). Agreement between PAD and PACD was moderate with the highest agreement between cough scores (κ coefficient 0.65). Children reported higher asthma symptoms scores than their parents over the entire study period (Figure S2). The pattern of change in average asthma sum scores among children and their parents was similar and correlated with the average reliever use.

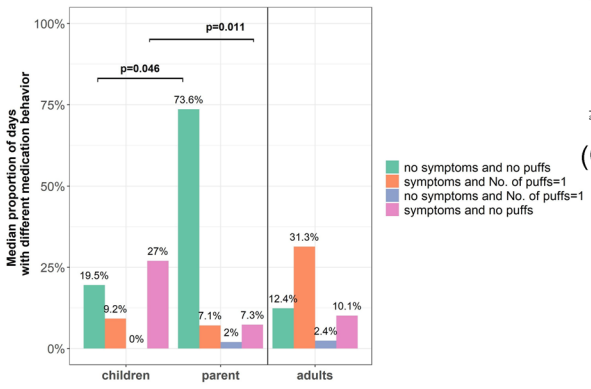
Comparisons of the prevalence of days with discordant behavior demonstrated that the children had a significantly higher prevalence of days with asthma bother symptoms, but without inhaler use than reported by their parents (27% vs. 7.3%, $p = .011$; Figure 1C). Parents tended to underestimate the asthma symptoms of their children (prevalence of days without symptoms and using relievers 73.6% and 19.5% between parent- and child-reported diaries, $p = .046$).

Considering the symptom diaries filled by the patients themselves, it was striking that the prevalence of days when the adult patients used a reliever and had asthma bother symptoms was higher than in the child population (31.3% vs. 9.2%, respectively).

Our findings are consistent with published results that parents underreport asthma symptoms and its severity in children,[1–3] especially in children with severe asthma,[5] and extend previous literature by demonstrating that pediatric severe asthmatics do not take their quick-relief medication for asthma despite experiencing asthma symptoms (discordant behavior). However, the reasons for child–parent difference in reporting symptoms are still unclear. It may be that parents are unaware of the asthma symptoms and their severity, especially during school time. If both children and parents have no appropriate training, this could lead to difficulties in the understanding and interpretation of questions in the diaries. Interestingly, the highest agreement was observed between parent- and child-reported cough suggesting that parents better recognize the presence and frequency of a cough.

Although the U-BIOPRED cohort is now the largest cohort with a subset of children with severe, uncontrolled asthma, the sample size is limited such that did not allow us to perform the multivariable analysis and findings must be interpreted with caution. However, the

(A) **The median proportion of days with different asthma bother symptoms and inhaler use. P-value was obtained using Wilcoxon's rank sum test.**



(B) **Kappa agreement and correlation between child and parent reported diaries**

Questions:	Kappa	p-value	Spearman correlation	p-value
Q1 asthma bother	0.37	<0.0001	0.63	<0.0001
Q2 activity	0.43	<0.0001	0.60	<0.0001
Q3 cough	**0.65**	<0.0001	**0.79**	<0.0001
Q4 night awake	0.61	<0.0001	0.67	<0.0001
Average symptom score:				
Sum score[a]	0.31	<0.0001	0.80	<0.0001

[a] weekly sum of Q1, Q2, Q3, and Q4

(C) **Subject-specific average of diary questions and their scores for the whole study period**

Question No./Score	Children: child reported mean (sd)	Children: parent reported mean (sd)	p-value for difference[c]	Adults mean (sd)
Questions:				
Q1 asthma bother	0.83 (0.4)	0.50 (0.5)	0.001	0.83 (0.6)
Q2 activity	0.61 (0.4)	0.41 (0.4)	0.007	0.73 (0.6)
Q3 cough	0.63 (0.4)	0.54 (0.3)	0.069	0.91 (0.4)
Q4 night awake	0.24 (0.3)	0.23 (0.3)	0.850	0.50 (0.6)
Average symptom score:				
Sum score[a]	2.30 (1.3)	1.69 (1.3)	0.005	3.00 (1.9)
Average of inhaler puffs per day		0.58 (0.7)		1.10 (1.2)

[a] daily sum of Q1, Q2, Q3, and Q4
[b] p-value for difference between child and parent reported items was calculated using paired Wilcoxon signed-rank test

FIGURE 1 (A) The median proportion of days with different asthma bother symptoms and inhaler use. A p value was obtained using Wilcoxon's rank sum test. (B) Kappa agreement and correlation between child- and parent-reported diaries. (C) Subject-specific average of diary questions and their scores for the whole study period [Color figure can be viewed at wileyonlinelibrary.com]

long follow-up resulting to 897 completed diaries allowed us to detect a significant difference of discordant behavior and different perception of asthma symptoms. Since this is a multicenter pan-European study, it is possible that centers recruited patients differently into each cohort, leading to selection bias.

Our data suggest that better consideration of a child's symptom perception may improve disconcordant medication use. Indeed, discordance detected by telemonitoring might be a candidate-treatable trait in asthma as identification of disagreement might prevent future exacerbations. Our data suggest that effective strategies to improve asthma control should include such aspects of symptom perception and disconcordant medication behavior, especially for younger populations, to prevent exacerbation and progression of the disease.

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CONFLICT OF INTERESTS

Mohib Uddin is an employee of AstraZeneca and holds shares in the company. Florian Singer reports personal fees from Vertex, personal fees from Novartis, grants from Swiss Society of Cystic Fibrosis (CFCH), grants from LUNGENLIGA BERN, outside the submitted work. Peter J. Sterk reports grants from public-private funding to his institute by the Innovative Medicines Initiative covered by the European Union (EU) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), during the conduct of the study. Ian M. received grants from EU-IMI, during the conduct of the study. The other authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conception and design: Olga Gorlanova, Eveline Tischhauser, and Urs Frey. *Acquisition of data, analysis, and interpretation*: Olga Gorlanova, Eveline Tischhauser, Delphine Meier, and Urs Frey. *Drafting the manuscript for important intellectual content and final approval of the manuscript*: All authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.