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Title:

Reclassification of bronchodilator reversibility in the U-BIOPRED adult asthma cohort using z-scores

Running title:

bronchodilator reversibility using z-scores

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None

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To the Editor:

Bronchodilator reversibility (BDR) is a hallmark feature of asthma. In a recent publication Quanjer et al.,[1] raise two valuable points to consider in the interpretation of BDR:

i. the current ERS/ATS criteria for BDR[2], i.e., >12% and >200 ml increase in FEV_1 and/or FVC, leads to a bias in that the likelihood of BDR increases with deteriorating pulmonary function. Consequently, the authors propose new criteria for BDR that is based on z-scores, which eliminates this artefact; $\Delta zFEV_1 > 0.78$ or $\Delta zFVC > 0.64$.
ii. FVC BDR, unlike FEV_1 BDR, increases with asthma severity and hence FVC BDR should be interpreted independently to FEV_1 BDR.

We applied the newly proposed BDR criteria to the U-BIOPRED adult asthma cohort[3] to; i) determine the influence of these new criteria on the prevalence of BDR and, ii) explore the difference in clinical characteristics between individuals with FEV_1 BDR and FVC BDR. Four-hundred and ninety-nine asthmatics underwent BDR testing. GLI-2012 reference equations were used to calculate z-scores[4]. Full methodology is presented elsewhere[3].

Using the ERS/ATS BDR criteria[2], 55% of the asthma cohort displayed BDR. The re-evaluation of BDR using $\Delta zFEV_1 > 0.78$ or $\Delta zFVC > 0.64$, resulted in the reclassification of 12% of the population; 9% no longer having BDR and 3% now fulfilling BDR criteria. A further 10% with BDR changed classification on the type of BDR they displayed (Figure).

We compared the clinical characteristics between the new BDR classifications. Individuals with FVC BDR only and both FEV_1 and FVC BDR had worse lung function, higher BMI and poorer asthma control and quality of life compared to individuals with FEV_1 BDR only (Table).

Conclusion

The z-score represents how many standard deviations the measured value is away from the mean predicted value, and in spirometry it is used to adjust for age, gender, ethnicity and height[4]. Recently, new criteria for the classification of BDR based on z-scores were proposed, which overcome bias from baseline pulmonary function values[1]. These new criteria influenced the BDR classification in nearly one quarter of the U-BIOPRED adult asthma cohort. Given that we observed

significant differences in clinical characteristics between BDR classifications, our results substantiate the proposal that FVC BDR and FEV_1 BDR should be considered independently. We strongly believe that the important work of Quanjer et al.,[1] should be taken into account when reviewing the guidelines on BDR interpretation.

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Guarantor
Andrew Simpson PhD takes responsibility for the content of the manuscript, including the data and analysis.

Author contribution
AJS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AJS and SJF contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript

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Collaborators
This paper is presented on behalf of the U-BIOPRED Study Group with input from the U-BIOPRED Patient Input Platform, Ethics Board and Safety Management Board. For a full list of members of the U-BIOPRED Study Group, please refer to the online supplement or U-BIOPRED project website; http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/home

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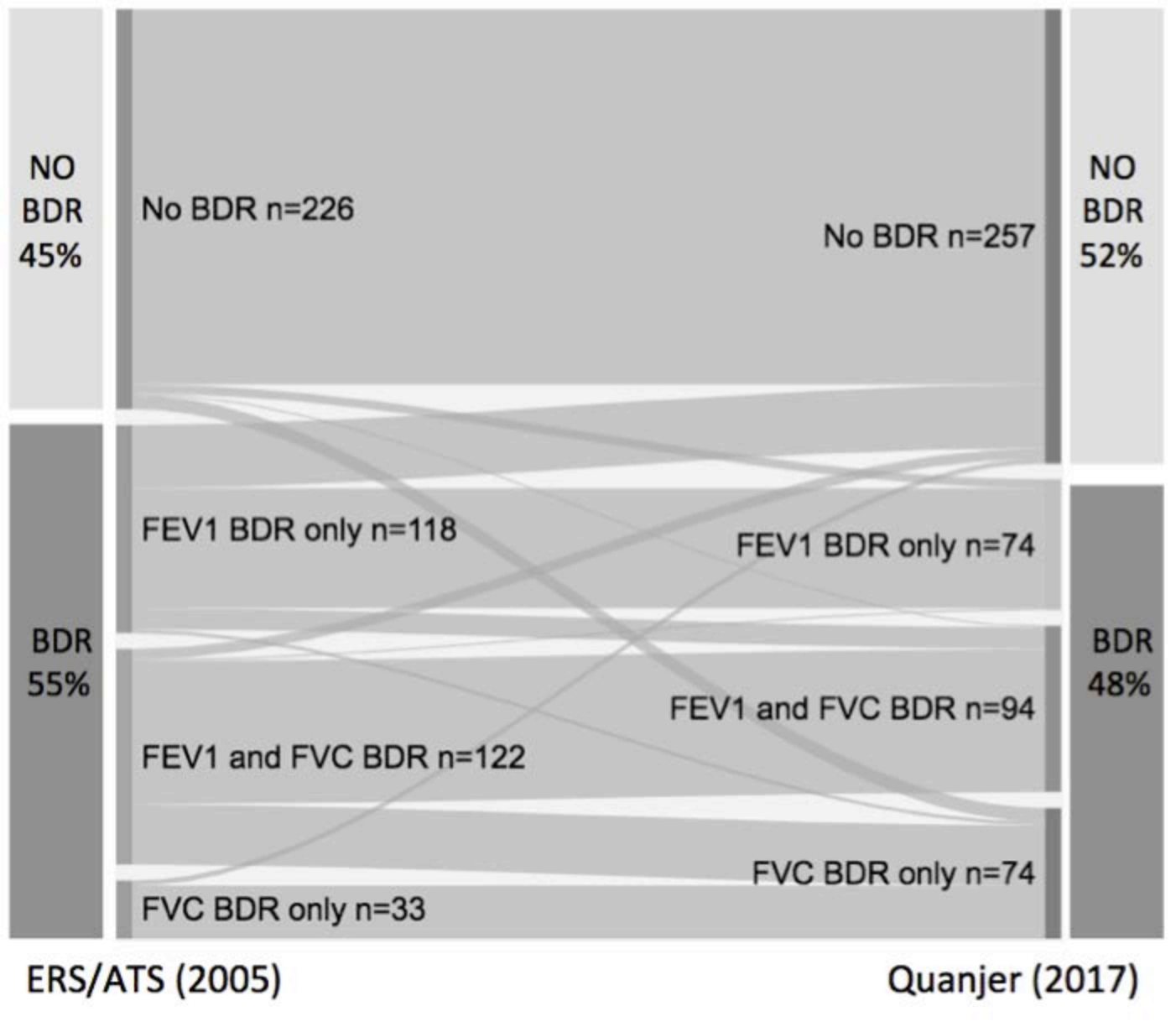
NO BDR 45%
BDR 55%
No BDR n=226
FEV1 BDR only n=118
FEV1 and FVC BDR n=122
FVC BDR only n=33
No BDR n=257
FEV1 BDR only n=74
FEV1 and FVC BDR n=94
FVC BDR only n=74
NO BDR 52%
BDR 48%
ERS/ATS (2005)
Quanjer (2017)

Figure Legend

Figure. Sankey diagram demonstrating the reclassification of bronchodilator reversibility (BDR) in the U-BIOPRED adult asthma cohort using the ERS/ATS (2005) criteria[2] and the z score criteria proposed by Quanjer et al., (2017)[1].

Table. Clinical characteristics of individuals with and without bronchodilator reversibility (BDR) in the U-BIOPRED adult asthma cohort.

	No BDR [a]	FEV_1 BDR only [b]	FVC BDR only [c]	FEV_1 & FVC BDR [d]	Sig
n	257	74	74	94	
Females	149 (58%)	44 (60%)	48 (65%)	60 (64%)	P=0.63
Age, years	52 (41-62) [b,c]	45 (30-57) [a,c]	57 (49-64) [a,b,d]	52 (43-58) [c]	P<0.001
Age of asthma onset/diagnosis, years	22 (7-40)	21 (8-38)	26 (10-45)	26 (7-42)	P=0.53
BMI	29 ± 6 [b]	26 ± 5 [a,c,d]	29 ± 7 [b]	30 ± 6 [b]	P<0.001
FEV_1 % pred. (pre -BD)	71 ± 22 [c,d]	73 ± 15 [c,d]	53 ± 19 [a,b]	58 ± 16 [a,b]	P<0.001
FEV_1 z-score (pre -BD)	-1.95 ± 1.48 [c,d]	-1.97 ± 1.10 [c,d]	-3.13 ± 1.20 [a,b]	-2.96 ± 1.10 [a,b]	P<0.001
FVC % pred. (pre-BD)	85 ± 17 [b,c,d]	93 ± 15 [a,c,d]	71 ± 16 [a,b]	75 ± 17 [a,b]	P<0.001
FVC z-score (pre-BD)	-1.07 ± 1.27 [b,c,d]	-0.52 ± 1.13 [a,c,d]	-2.05 ± 1.17 [a,b]	-1.86 ± 1.27 [a,b]	P<0.001
FEV_1/FVC % (pre-BD)	66 ± 14 [c]	64 ± 10	58 ± 14 [a]	63 ± 13	P<0.001
FeNO	22 (15-37) [b,d]	32 (21-91) [a]	26 (14-39)	33 (17-60) [a]	P<0.001
Exacerbations over the previous year	2 (1-4)	2 (2-3)	2 (2-3)	2 (1-4)	P=0.997
IgE $IU \cdot mL^{-1}$	125 (51-351)	125 (58-412)	102 (43-266)	113 (45-307)	P=0.85
Regular oral steroid Rx	90 (37%)	19 (27%)	38 (53%)	30 (33%)	P=0.010
AQLQ, average score	4.9 ± 1.2 [c]	4.9 ± 1.3 [c]	4.2 ± 1.3 [a,b]	4.6 ± 1.3	P<0.001
ACQ 5, average score	1.8 ± 1.1 [c,d]	1.7 ± 1.3 [c,d]	2.4 ± 1.3 [a,b]	2.3 ± 1.3 [a,b]	P<0.001

Data are expressed as mean ± SD, median (interquartile range) or n (%); Differences between groups explored using ANOVA, Kruskal-Wallis Test and Chi Square tests and post-hoc analysis with Bonferonni correction as appropriate; BDR: bronchodilator reversibility; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FeNO: Fraction of exhaled Nitric Oxide; IgE: immunoglobulin E; AQLQ: Asthma Quality of Life Questionnaire; ACQ: Asthma Control Questionnaire; [a]: different to NO BDR; [b]: different to FEV_1 BDR only; [c]: different to FVC BDR only; [d]: different to FEV_1 and FVC BDR.