

Letter to the Editor

Bitter perception is altered in asthma and predicts its severity*To the Editor:*

Despite a broad range of available treatment options, 5% to 10% of patients with asthma cannot achieve optimal disease control. Taste receptors (TAS2Rs) in human airway smooth muscle cells have been shown to cause bronchodilatation upon activation.^{1,2} The expression of leukocyte TAS2Rs correlates positively with asthma severity in both children and adults.³ This overexpression could be a compensation for the diminished functionality of TAS2Rs. Association between TAS2R polymorphisms and severe asthma outcomes was also demonstrated.⁴ In this clinical prospective study, we evaluated whether bitter taste or n-propylthiouracil (PROP) sensitivity is altered in patients with asthma, and whether this correlates with disease characteristics.

A total of 127 adult participants were included: 65 patients with asthma, confirmed through a pulmonologist, and 62 age- and sex-matched volunteers without asthma. Exclusion criteria were age less than 18 years and more than 60 years, presence of chronic obstructive pulmonary disease, smoking history of more than 10 pack-years, and other conditions associated with taste loss, which was defined as a diminished sensitivity to primary taste qualities: bitter, sweet, salty, sour, and umami. Decrease in general taste sense due to olfactory loss was not an exclusion criterion, because the latter is associated with chronic rhinosinusitis, which is frequent in the population with asthma. Participants rated their smelling and tasting abilities on 10-cm visual analogue scales, an asthma-specific questionnaire was completed to evaluate the

asthma control status (see p29, Box2-2A at ginasthma.org/ginareports),⁵ and the medication profile was assessed. Asthma therapy step 1 to 5 was determined (see p44, Box 3-5 at ginasthma.org/ginareports).⁵ To account for broad distribution of asthma control (43.1%, well controlled; 41.5%, partly controlled; 15.4%, uncontrolled asthma), asthma severity was evaluated, with light and moderate asthma being well controlled with treatment step 1/2 or 3/4, respectively, and severe asthma needing treatment step 5 or being less than well controlled when treated with step 4 or stepping down to 3.⁶ Latest percent predicted value of FEV₁, ratio FEV₁/forced vital capacity, and presence of a diagnosed allergy, exercise-induced asthma, or Samter triad were noted.

The gustatory sensitivity was assessed with the suprathreshold “Taste Sprays” test⁷ (perceived/not perceived) and the quasi-threshold “Taste Strips” test (TST)^{8,9} for sweet, sour, bitter, salty, and umami (0-4-point score per tastant; cumulative score, 0-20). In addition, each patient and control subject was offered a paper taste strip impregnated with PROP (Sensonics International, Haddon Heights, NJ). Depending on whether PROP was perceived as bitter or not, the participants were labeled as “tasters” or “nontasters.” Study population characteristics, taste test scores, and asthma characteristics are summarized in [Tables E1 and E2](#) in this article’s Online Depository at www.jacionline.org.

Patients with asthma had significantly lower sensitivity for bitter, salty, and umami tastes and for PROP than healthy volunteers (Mann-Whitney *U* test $P = .026$, $P = .035$, $P < .001$; χ^2 [1, $n = 127$] = 11.53, $P = .001$, respectively). About 3.1% of patients with asthma scored 0 in bitter TST (vs 0% by controls),

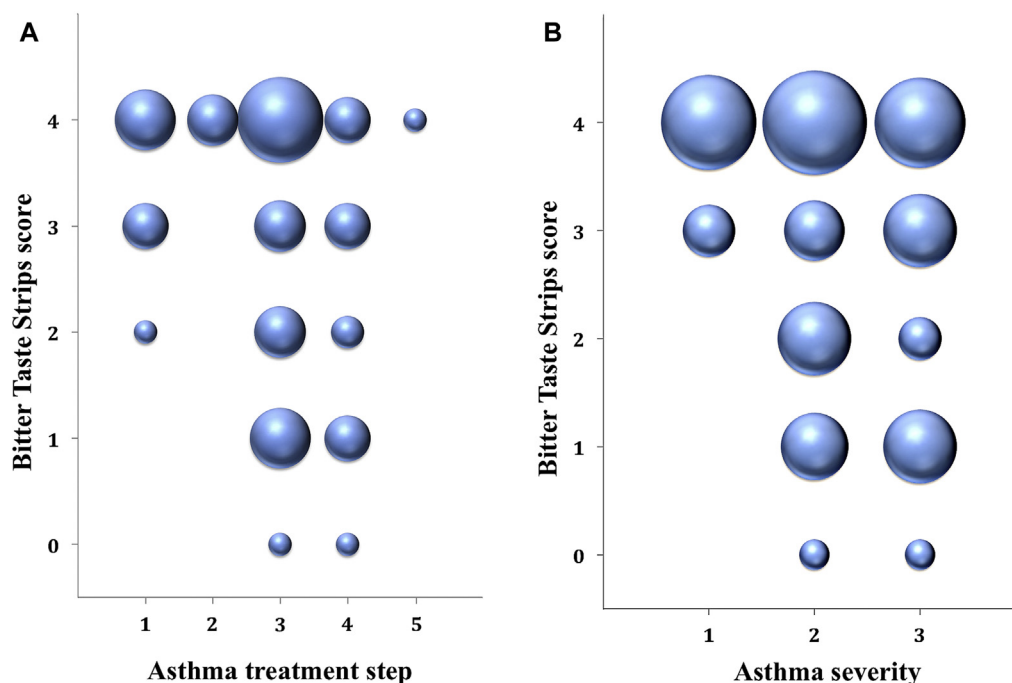


FIG 1. Bubble plots for the significant correlations between the bitter Taste Strips test score and the asthma treatment step (A) and the severity of the asthma (B; 1, mild; 2, moderate; 3, severe). The larger the bubble the more data points are clustering on this coordinate.

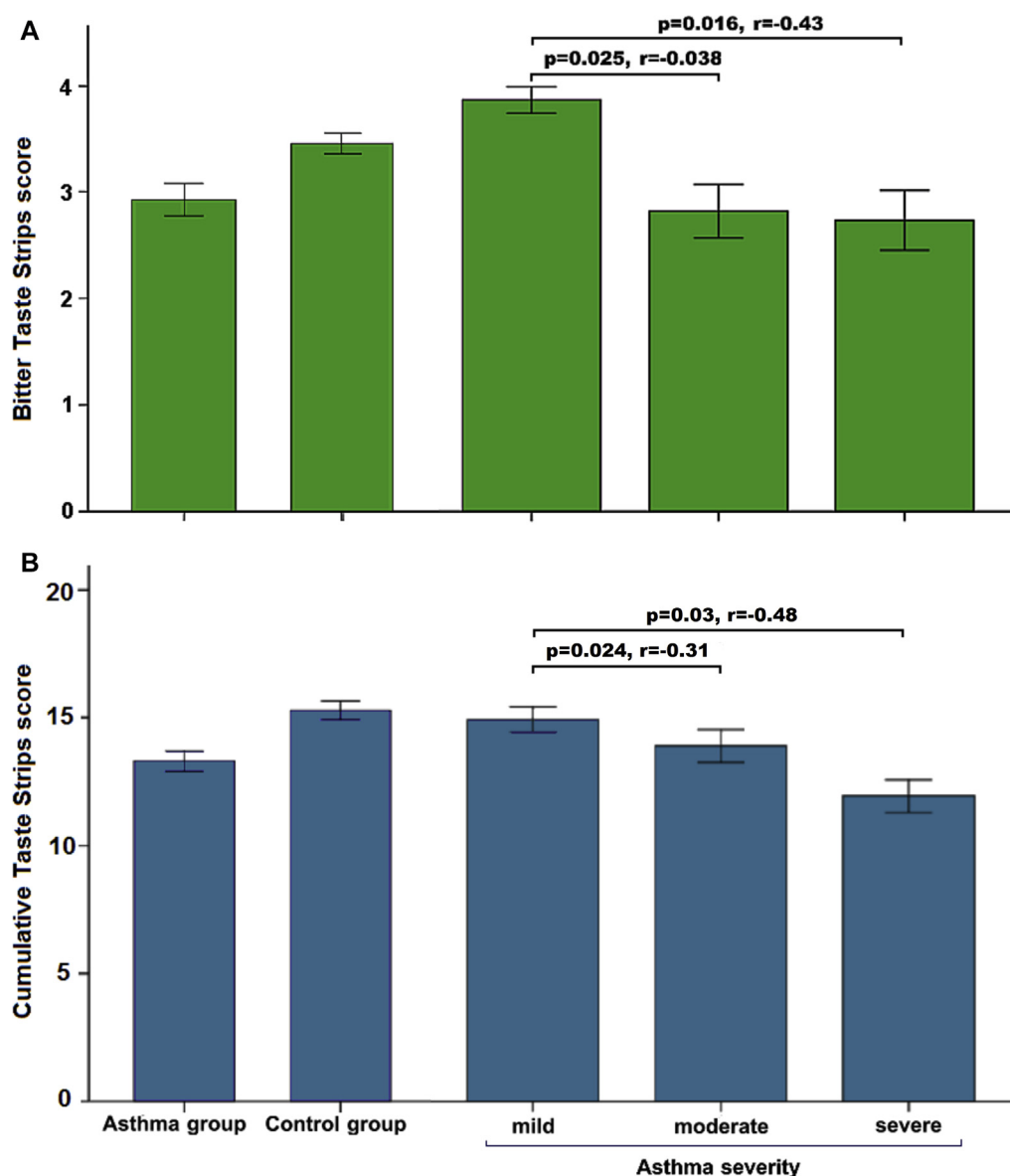


FIG 2. The patients with a higher asthma severity had a lower score of the bitter (A) and the cumulative (B) Taste Strips test (mean $\pm$ SD). Mean scores of asthma and control groups are also shown.

16.9% scored 1 (vs 0%), 12.3% scored 2 (vs 16.1%), 20% scored 3 (vs 22.6%), and 47.7% scored 4 (vs 61.3%). About 12.3% and 14.5% of patients in asthma and control groups, respectively, took general medications with possible gustatory side effects (MwPGSEs, eg, ramipril or sertraline). An additional 38.5% of patients with asthma took asthma-specific MwPGSEs (eg, cetirizine or formoterol). Taking the MwPGSEs had no influence on the TST results in the asthma group (Mann-Whitney U test $P \geq .28$ in all TSTs). To further investigate this relationship, the patients with asthma were divided into 3 groups: (1) no MwPGSEs, (2) asthma-specific MwPGSEs, and (3) other MwPGSEs. The Kruskal-Wallis test revealed no significant difference in rated and measured taste scores between the 3 groups in this scenario ($P > .35$). In the control group, however, taking the MwPGSEs had a significant impact with a moderate effect size on the results of salty TST (Mann-Whitney $U = 60.5$, $Z = -3.79$, $P < .001$,

$r = -0.48$) and cumulative TST ($U = 111.5$, $Z = -2.56$, $P = .01$, $r = -0.33$). Hence, there should be another, more potent factor in the patients with asthma that levels out the gustatory influence of drug side effects.

Spearman correlations between the results of taste tests and other patients' or control subjects' parameters are presented in Table E3 in this article's Online Depository at www.jacionline.org. The asthma treatment step (1-5 according to the Global Initiative for Asthma classification, with 5 being the maximal therapy) showed a negative correlation with the cumulative TST score ($\rho = -0.26$, $P = .036$) and with the bitter TST score ($\rho = -0.3$, $P = .015$, Fig 1, A). The asthma severity graded with 1 for mild, 2 for moderate, and 3 for severe asthma showed a negative correlation with the bitter TST score ($\rho = -0.28$, $P = .026$, Fig 1, B) and with the cumulative TST score ($\rho = -0.37$, $P = .003$). There was no significant correlation

between the results of the tests for other taste modalities and the asthma treatment step or asthma severity. Mann-Whitney *U* test revealed a significant association of medium effect size between the bitter and cumulative TST scores and the asthma severity (see Table E4 in this article's Online Depository at www.jacionline.org). Fig 2 shows how bitter and overall taste sensitivity decreases with increasing asthma severity. Chances of patients with asthma with the cumulative TST score of 14 or less ($n = 36$) to have severe asthma were more than 5 times higher than of those whose score was 15 or more (odds ratio, 5.36; 95% CI, 1.67-17.19; $P = .005$). Presence of allergy ($n = 55$), Samter triad ($n = 3$), or exercise-induced asthma ($n = 4$) had no significant effect on taste sensitivity (Mann-Whitney *U* test, $P > .24$, $P > .52$, $P > .19$, respectively, for all TST scores).

The "Tasters" among the patients with asthma showed significantly better results for sweet, salty, bitter, and cumulative TST (Mann-Whitney $P < .04$, $r = -0.26$; $P < .001$, $r = -0.41$; $P = .001$, $r = -0.44$; $P < .001$, $r = -0.44$, respectively) and had a significantly lower asthma severity (Mann-Whitney $P = .036$, $r = -0.26$) compared with "nontasters."

The negative correlation of asthma severity and bitter taste sensitivity is consistent with the work of Yoon et al,⁴ who observed that genetic variations in TAS2Rs may be predictors of therapy response in asthma. Similar correlation with PROP sensitivity suggests that the corresponding haplotype (Alanin-Valin-Isoleucin [AVI]/Prolin-Alanin-Valin [PAV]) may stand in linkage disequilibrium with the single nucleotide polymorphisms of the bitter taste receptors, which may play a role in the course of asthma. This would be consistent with the hypothesis for the role of TAS2R in the upper respiratory tract.¹ Accordingly, the ability to register the pathogenic bitter substances and thus to trigger bronchodilation would be reduced in nontasters.

Relatively low number of participants, heterogeneity of the groups, insufficient differentiation of patients into different asthma phenotypes, as well as subjective nature of the psychophysical tests and limited possibility to extrapolate the results on the total population are limitations of this study. However, to our knowledge, for the first time, this study has demonstrated a diminished gustatory sensitivity to bitter taste and to PROP in patients with asthma and its relationship with asthma severity with a validated test battery.

Further genomic studies will be required to localize the haplotype or the single nucleotide polymorphism underlying the altered taste sensitivity in asthma. In addition, longitudinal studies with larger populations are needed to define the role of the taste

tests in the prognosis of asthma severity or therapeutic response. If our results are confirmed, a simple PROP or quinine taste test may be an appropriate prognostic test to predict severe asthma.

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TABLE E1. The summary of patients' data and taste tests for both groups

Parameter	Asthma group	Control group
Age (y), median (first/third quartile)	46 (33/53.5)	42 (31/53)
BMI, median (first/third quartile)	25.7(22.7/29.7)	23.9(21.4/28.1)
Pack-years, median (first/third quartile)	0 (0/2)	0 (0/0.4)
Olfactory disorder subjectively present, n (%) of cases	16 (24.6)	2 (3.2)
Taste disorder subjectively present, n (%) of cases	9 (13.8)	1 (1.6)
VAS for smell, median (first/third quartile)	7.9 (6.9/9.9)	8.5 (7.6/9.2)
VAS for taste, median (first/third quartile)	7.9 (7.2/9.8)	8.7 (7.7/9.2)
Taste Strips scores, median (first/third quartile)		
Sweet	4 (3/4)	4 (3/4)
Sour	3 (2/3)	3 (2/3)
Bitter	3 (2/4)*	3 (3/4)*
Salty	3 (2/4)*	3 (2.75/4)*
Umami	2 (1/3)*	3 (2/4)*
Cumulative score	14 (11/16)*	16 (13.75/18)*
Taste Spray identified, n (%) of cases		
Sweet	61 (93.8)	62 (100)
Sour	57 (87.7)	59 (95.2)
Bitter	59 (90.8)	58 (93.5)
Salty	57 (87.7)	51 (82.3)
Umami	39 (60)*	56 (90.3)*
Cumulative score, median (first/third quartile)	4 (4/5)*	5 (4/5)*
FEV ₁ , median (first/third quartile)†	92.8 (81/106.8)	—
FEV ₁ /FVC (FEV ₁ /VC MAX)†	82.35 ± 8.65	—
Presence of diagnosed allergy, n (%) of cases	55 (84.6%)	—
Exertion asthma, n (%) of cases	4 (6.2)	—
Samter Triad, n (%) of cases	3 (4.6)	—
Medicaments with gustatory side effects taken, n (%) of cases	33 (50.8)	9 (14.5)
Taster (perceived PROP), n (%) of cases	46 (70.8)*	59 (95.2)*

FVC, Forced vital capacity; VAS, visual analogue scale; VC MAX, maximum vital capacity.

*Difference statistically significant with $P < .05$.†For 1 of 65 patients, the FEV₁ value and for 13 patients the FVC value were not available; in the latter case, the VC MAX was used instead.

TABLE E2. Distribution of the asthma features in the asthma group

No. of asthma medications					
0	1	2	3	4	5
2 (3.1)	22 (33.8)	25 (38.5)	11 (16.9)	4 (6.2)	1 (1.5)
Asthma symptom control					
Well controlled	Partly controlled				Uncontrolled
28 (43.1)	27 (41.5)				10 (15.4)
Asthma treatment step					
1	2	3	4	5	
12 (18.5)	5 (7.7)	32 (49.2)	15 (23.1)	1 (1.5)	
Asthma severity					
Light	Moderate				Severe
13 (20)	28 (43.1)				24 (36.9)

Values are n (%) of cases.

TABLE E3. Correlations between the results of taste tests and other patients' or control subjects' parameters

Taste test		Age	BMI	Pack-years	VAS for smell	VAS for taste	FEV ₁	FEV ₁ /FVC (or VC MAX)	No. of asthma medications	Treatment step	Asthma symptom control	Asthma severity	PROP
Spray sweet	ρ	-0.056*	0.014*	-0.01*	0.127*	0.340*†	-0.014‡	0.101‡	0.047*	0.061*	0.173*	0.081*	-0.024*
	<i>P</i> (2-sided)	.656	.914	.94	.314	.006	.913	.426	.711	.631	.169	.522	.851
Spray sour	ρ	0.02*	-0.022*	0.028*	-0.01*	0.188*	-0.013‡	0.041‡	0.007*	-0.001*	0.178*	0.034*	-0.035*
	<i>P</i> (2-sided)	.874	.859	.825	.937	.133	.92	.748	.959	.992	.156	.79	.783
Spray bitter	ρ	-0.162*	-0.201*	-0.092*	-0.095*	-0.194*	0.09‡	0.041‡	-0.093*	0.073*	0.031*	0.084*	-0.088*
	<i>P</i> (2-sided)	.198	.108	.467	.45	.122	.48	.75	.463	.562	.807	.506	.485
Spray salty	ρ	-0.02*	0.092*	-0.011*	0.04*	-0.009*	0.172‡	0.186‡	-0.122*	-0.118*	-0.272*†	-0.106*	0.171*
	<i>P</i> (2-sided)	.874	.464	.93	.751	.945	.174	.142	.331	.348	.029	.4	.173
Spray umami	ρ	-0.119*	-0.294*†	0.031*	0.106*	0.107*	-0.084‡	-0.031‡	-0.221*	-0.183	0.074*	-0.11*	0.166*
	<i>P</i> (2-sided)	.345	.018	.807	.401	.397	.507	.808	.076	.145	.559	.383	.187
Spray cumulative	ρ	-0.222†§	-0.183†§	0.029*	0.081§	0.197†§	0.006‡	0.084‡	-0.229*	-0.121*	0.037*	-0.046*	0.182†§
	<i>P</i> (2-sided)	.012	.04	.819	.368	.027	.963	.507	.066	.339	.77	.714	.041
Strips sweet	ρ	-0.026§	-0.141§	-0.026*	0.194†§	0.175†§	0.017‡	0.055‡	-0.038*	-0.064*	-0.014*	-0.146	0.200†§
	<i>P</i> (2-sided)	.769	.115	.84	.029	.049	.893	.668	.764	.612	.909	.244	.024
Strips sour	ρ	-0.179†§	-0.018§	-0.002*	0.088§	0.025§	-0.043‡	0.131‡	-0.1*	0.02*	-0.107*	-0.114*	-0.083§
	<i>P</i> (2-sided)	.044	.839	.985	.326	.783	.734	.302	.429	.877	.397	.367	.352
Strips bitter	ρ	-0.088§	-0.179†§	-0.159*	0.151§	0.188†§	0.121‡	0.156‡	-0.243	-0.301*†	-0.03*	-0.277*†	0.339†§
	<i>P</i> (2-sided)	.323	.045	.205	.091	.035	.339	.218	.052	.015	.815	.026	<.001
Strips salty	ρ	-0.197†§	-0.168§	-0.135*	0.209†§	0.187†§	0.067‡	0.094‡	-0.178*	-0.133*	-0.155*	-0.215*	0.345†§
	<i>P</i> (2-sided)	.026	.059	.284	.018	.035	.601	.458	.157	.29	.216	.085	<.001
Strips umami	ρ	-0.180†§	-0.029§	-0.083*	0.191†§	0.226†§	0.21‡	0.121‡	-0.319*†	-0.161*	-0.14*	-0.206*	0.196†§
	<i>P</i> (2-sided)	.043	.745	.513	.032	.011	.096	.341	.009	.201	.266	.099	.027
Strips cumulative	ρ	-0.223†§	-0.187†§	-0.184*	0.288†§	0.292†§	0.142‡	0.189‡	-0.378*†	-0.260*†	-0.178*	-0.369*†	.370†§
	<i>P</i> (2-sided)	.012	.035	.142	.001	.001	.262	.136	.002	.036	.156	.003	<.001
PROP	ρ	-0.036§	-0.157§	-0.246*†	0.197†§	0.234†§	0.195‡	0.066‡	-0.077*	-0.197*	-0.121*	-0.262*†	—
	<i>P</i> (2-sided)	.68	.079	.048	.027	.008	.122	.606	.542	.116	.339	.035	—

BMI, Body mass index; FVC, forced vital capacity; VAS, visual analogue scale; VC MAX, maximum vital capacity.

The FEV₁ score was missing for 1 patient. *P* < .05 is in boldface.

**N* = 65.

†Significant correlation with *P* < .05 (2-sided).

‡*N* = 64.

§*N* = 127.

TABLE E4. Differences in the cumulative and bitter Taste Strips test score as a function of the severity of asthma investigated with the Mann-Whitney *U* test

Taste test		<i>U</i>	<i>Z</i>	<i>P</i> value	<i>r</i>
Bitter Taste Strips score	Mild and moderate asthma	102	−2.45	.025	−0.38
	Mild and severe asthma	81	−2.59	.016	−0.43
	Moderate and severe asthma	321.5	−0.28	.781	−0.04
Cumulative Taste Strips score	Mild and moderate asthma	163	−0.54	.609	−0.08
	Mild and severe asthma	65.5	−2.9	.003	−0.48
	Moderate and severe asthma	213.5	−2.26	.024	−0.31

P < .05 is in boldface.