



Do asthma patients with panic disorder really have worse asthma? A comparison of physiological and psychological responses to a methacholine challenge



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ABSTRACT

Background: Panic disorder (PD) has been linked to worse asthma outcomes. Some suggest that asthmatics with PD have worse underlying asthma; others argue that worse outcomes are a result of their tendency to over-report symptoms. This study aimed to measure physiological and psychological responses to a simulated asthma attack (methacholine challenge test: MCT) in asthmatics with and without PD.

Methods: Asthmatics with ($n = 19$) and without ($n = 20$) PD were recruited to undergo a MCT. Patients completed subjective symptom questionnaires (Panic Symptom Scale, Borg Scale) before and after a MCT. Physiological measures including heart rate (HR), and systolic and diastolic blood pressure (SBP/DBP) were also recorded.

Results: Analyses, adjusting for age and sex, revealed no difference in methacholine concentration required to induce a 20% drop in forced expiratory volume in one second (FEV_1 : $F = 0.21$, $p = .652$). However, PD patients reported worse subjective symptoms, including greater ratings of dyspnea ($F = 8.81$, $p = .006$) and anxiety ($F = 9.44$, $p = .004$), although they exhibited lower levels of physiological arousal (i.e., HR, SBP/DBP). An interaction effect also indicated that PD, relative to non-PD, patients reported more panic symptoms post-MCT ($F = 5.05$, $p = .031$).

Conclusions: Asthmatics with PD report higher levels of subjective distress, despite exhibiting lower levels of physiological arousal, with no evidence of greater airway responsiveness. Results suggest that worse outcomes in PD patients may be more likely due to a catastrophization of bodily symptoms, rather than worse underlying asthma. Interventions designed to educate patients on how to distinguish and manage anxiety in the context of asthma are needed.

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Abbreviations: ACQ, Asthma Control Questionnaire; ADIS-IV, Anxiety Disorders Interview Schedule for DSM-IV; BMI, Body Mass Index; DBP, Diastolic Blood Pressure; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised; ED, Emergency Department visits; FEV_1 , Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GLM, General Linear Model; HSCM, Hôpital du Sacré-Cœur de Montréal; HR, Heart Rate; MCT, Methacholine Challenge Test; PC_{20} , Provocative Concentration; PD, Panic Disorder; PSS, Panic Symptom Scale; SBP, Systolic Blood Pressure; SD-VAS, Subjective Distress Visual Analogue Scale.

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1. Introduction

Asthma is characterized by chronic airway inflammation in response to a variety of stimuli [1,2] causing respiratory symptoms such as shortness of breath [1]. The high economic and quality of life-related burden of asthma has led to the evaluation of potential risk factors for asthma morbidity [3,4]. Over the last 20 years, research has linked chronic negative mood states to worse objective measures of asthma [5–7]. Panic disorder (PD) affects between 6 and 24% of asthmatics [8–10], which is 3–10 times more prevalent than the general population [11]. PD is

characterized by sudden, recurrent panic attacks, which are episodes of intense fear or discomfort associated with cognitive (e.g., fear of losing control) and physiological (e.g., shortness of breath) symptoms [12]. Studies have also shown that comorbid PD and asthma tends to be associated with worse outcomes, e.g., excessive use of bronchodilators and more emergency department (ED) visits [13–16].

Two potential pathways have been proposed to explain the PD-worse asthma outcomes association: one postulates a direct physiological pathway where panic leads to physiological changes (e.g., increased cardiorespiratory reactivity such as heart rate, carbon dioxide partial pressure, and respiratory rate) [17,18] via increased autonomic nervous activation that may be causally linked to asthma [5–7]. The other proposes that PD patients' tendency to catastrophize bodily sensations is associated with increased symptom reporting, resulting in greater treatment-seeking, independent of worse asthma [16,19–23]. Previous evidence supports both hypotheses, but has suffered from methodological weaknesses: a failure to objectively diagnose asthma [22,24], often relying upon self-reported diagnoses which are subject to bias [25]; a failure to use a validated psychiatric interview to diagnose PD [22,26], over-relying on questionnaire measures of panic-like anxiety which are insufficient to confirm PD diagnoses; and the use of resting spirometry as the sole objective measures of asthma [23,27], which may appear normal when asthma is well controlled [28]. In order to test the extent to which asthmatics with PD have physiologically worse asthma, bronchial provocation tests are needed. Based on the American Thoracic Society (ATS) recommendations [29], the methacholine challenge test (MCT) would be a good alternative since this standardized challenge permits to assess several objective measures of asthma such as bronchial hyperresponsiveness, which to our knowledge has not been done in asthmatics with and without PD.

This study aimed to determine whether asthmatics with (versus without) PD had greater non-specific bronchial responsiveness and if they simply report more symptoms and subjective distress in response to a MCT. It was hypothesized that asthmatics with, versus without, PD would exhibit greater airway responsiveness; report greater subjective distress; and experience exaggerated physiological arousal during a MCT.

2. Methods

2.1. Participants

Patients were recruited from the asthma clinics of Hôpital du Sacré-Coeur de Montréal (HSCM) from September 2011 to December 2013. To be included, patients had to have a primary diagnosis of asthma (chart evidence of previous positive MCT and/or bronchodilator reversibility), be non-smoking, and be between the ages of 18–70. Eligible patients underwent spirometry, and only patients with a forced expiratory volume in one second [FEV₁] >70% (predicted) and >1.5 L participated. PD patients had to meet current Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revised (DSM-IV-TR) criteria for a primary psychiatric diagnosis of PD. Patients in the control group could not meet DSM-IV-TR criteria for any current or past Axis I disorder. Patients were excluded for chart evidence of a medical condition that was more severe than asthma and evidence of cognitive or language deficit that would have impaired providing informed consent. A total of 228 patients were screened for inclusion (see Fig. 1). Of the 122 initially eligible patients, 83 patients refused participation or were subsequently ineligible, resulting in a final sample of 39 patients.

2.2. Study procedure

The Ethics Committee of HSCM approved this study (#2003-10-198; 2010-95) and written consent was obtained from all participants. Consenting patients completed an initial screening interview (including demographic, medical, and psychological measures) performed routinely at the asthma clinics with the consent of the attending patients. Patients meeting initial eligibility criteria completed the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) on the phone to confirm all psychiatric diagnoses. A supervised, trained, clinical psychology PhD student conducted the interviews. Patients were then scheduled to undergo the MCT. At the laboratory, patients were asked to complete the Asthma Control Questionnaire (ACQ) and, prior to starting the MCT and following the final methacholine dose, patients were administered the Panic Symptom Scale (PSS) to assess panic symptoms. After each concentration of methacholine, the Borg Scale and the Subjective Distress Visual Analogue Scale (SD-VAS) were administered, assessing perceived breathlessness and anxiety symptoms. Physiological measures were recorded throughout the MCT, including heart rate (HR), and systolic and diastolic blood pressure (SBP/DPB) (Datascope Accutorr Plus, New Jersey, USA).

2.3. Methacholine challenge test protocol

As per the ATS recommendations [29], patients inhaled incremental two-fold concentrations of methacholine chloride from 0.03 to 16 mg/ml through a Wright nebulizer (output of 9.3 L/min) following a diluent (0.9% sodium chloride) [30]. When FEV₁ fell by at least 20%, the test was stopped and the technician, who was blind to the patient's psychiatric status, administered inhaled albuterol.

3. Measures

3.1. Baseline measures

3.1.1. Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV)

The ADIS-IV [31] was used to confirm the diagnosis of PD. It is a widely used semi-structured interview for the diagnosis of mood, anxiety, substance abuse, and somatoform disorders. Good to excellent inter-rater reliability (e.g., PD, $k = 0.72$) has been reported for the various dimensional ratings [32].

3.1.2. Anxiety Sensitivity Index (ASI)

In order to assess trait anxiety sensitivity, patients completed the ASI [33], a 16-item self-report questionnaire measuring the extent to which individuals are fearful of anxiety-related symptoms. It yields scores from 0 to 64, with higher scores indicating higher anxiety sensitivity [34]. The ASI has high internal consistency ($\alpha = 0.83$) and test-retest reliability [35], and is highly correlated with diagnoses of PD [36].

3.1.3. Asthma Control Questionnaire (ACQ)

In order to assess asthma control levels in the week prior to the MCT, patients completed the ACQ [37], a 7-item questionnaire that measures asthma symptoms and bronchodilator use. Each item is ranked on a 7-point scale (0 = good control, 6 = poor control), with lower scoring indicating better asthma control. The ACQ has demonstrated high intraclass coefficient (ICC = 0.90) and good cross-sectional validity ($r = 0.76$) [37,38].

3.2. Experimental measures

3.2.1. Borg Scale

The Borg Scale [39] is a self-report questionnaire that was used

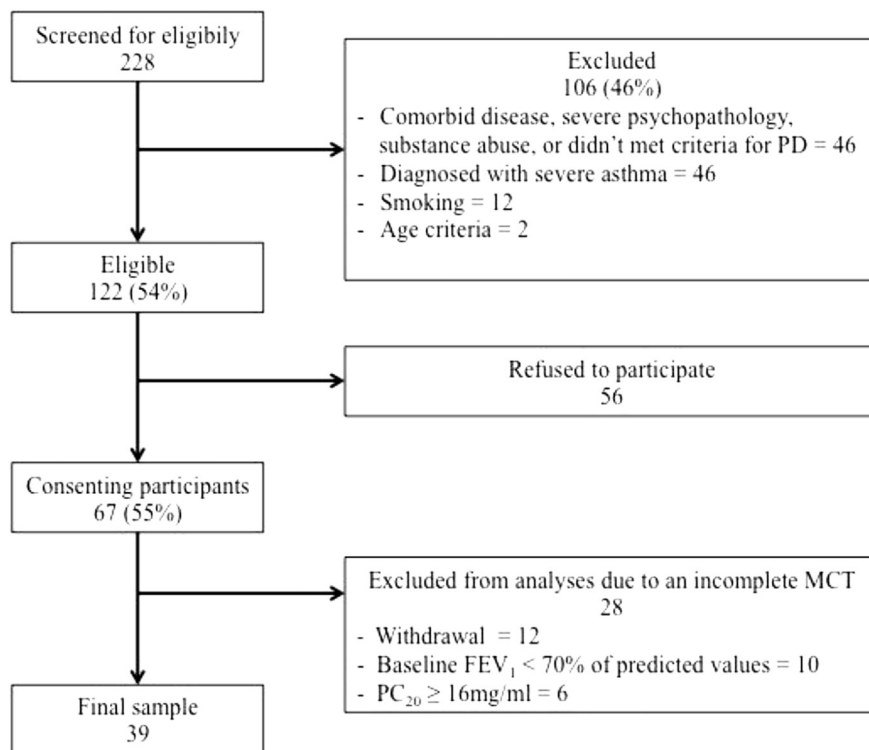


Fig. 1. Flow chart of patient screening, eligibility, and participation.

to assess current perceived dyspnea. It consists of a 12-point vertical scale, ranging from 0 to 10, with a point beyond a maximal rating of 10 indicating maximal intensity of breathlessness. It has good reliability, intra-class coefficient (ICC = 0.97) [40], and validity in adult respiratory patients [41].

3.2.2. Panic Symptom Scale (PSS)

The PSS [42] is a 13-item checklist comprised of the physical and psychological symptoms of panic attacks derived from the DSM-III-R [43]. For each item, the patient ranks their current symptoms on a 5-point Likert-like scale from 0 (absent) to 4 (extremely severe). Scores reflect the total number of panic symptoms reported (0–13) and also a sum intensity score (0–65).

3.2.3. Subjective Distress Visual Analogue Scale (SD-VAS)

The SD-VAS [44] is a self-report questionnaire used to measure a variety of current subjective mood states [45]. Participants were asked to report their anxiety, discomfort, and worry level by indicating a position along a continuous line between two end-points (from 0 = not at all to 100 = extremely), with higher scores indicating higher mood intensity. The SD-VAS has shown good reliability and criterion-related validity ($r = 0.42$ – 0.91) [44].

3.3. Statistical analyses

Baseline differences in a variety of characteristics between those with and without PD were assessed using general linear models (GLM). A similar two-group GLM was used to analyze the relationship between PD and methacholine provocative concentration (PC_{20}), as well as between PD and the total % drop in FEV_1 at the last dose of methacholine. A series of group (PD vs. non-PD) $\times$ time (baseline and post-MCT) repeated-measures mixed model analyses were conducted to test for main and interaction effects on subjective and physiological responses. Age, sex, and PC_{20} (with the

number of methacholine doses added to the % drop in FEV_1 analysis) were included as a-priori covariates [46]. In addition, as requested as part of the review process, a supplemental analysis was conducted to include absolute FEV_1 as an additional covariate (see Supplement). All analyses were performed using SAS v9.3 (SAS Institute, Cary NC).

4. Results

4.1. Group characteristics

Table 1 shows the sample characteristics of the participants as a function of PD diagnosis. Compared to the non-PD group, PD patients had significantly more ED visits during the last year, a longer asthma diagnosis, and a higher prevalence of antidepressant and anxiolytic use. Unsurprisingly, PD patients also had significantly higher scores on the ASI, which validates the PD diagnoses.

4.2. Association between PD status and objective airway responsiveness

Adjusted analyses showed that PD and non-PD patients had similar PC_{20} levels (geometric M [95%CI]: PD = 0.58 [0.22–1.50]; non-PD = 0.79 [0.32–2.04], $F = 0.21$, $p = .652$), reflecting moderate bronchial hyperreactivity (see Fig. 2). However, adjusted analyses revealed a trend indicating greater % drop in FEV_1 at the last dose of methacholine in PD compared to non-PD patients (M [SD]: PD = 28.3 [1.9]; non-PD = 23.6 [1.8], $F = 3.11$, $p = .087$).

4.3. Association between PD status and subjective measures

Table 2 shows the results of the adjusted subjective responses and revealed a number of group main effects, with PD patients reporting higher levels of dyspnea, panic, general anxiety,

Table 1

Participant sociodemographic, medical, asthma, and psychological characteristics.

	PD (n = 19)	No PD (n = 20)	F	p
Sociodemographics				
Age (years)	44 ± 14	51 ± 14	2.48	.124
Sex (% female)	84 (16)	70 (14)	1.08	.305
Ethnicity (% white)	84 (16)	100 (20)	3.56	.067
Cohabiting (% yes)	63 (12)	60 (12)	0.04	.845
Education (years)	15.26 ± 3.18	15.25 ± 3.57	0.00	.990
Employed (% yes)	74 (14)	65 (13)	0.33	.569
Medical and asthma characteristics				
Measured BMI (kg/m ²)	26.90 ± 5.66	28.29 ± 5.19	0.63	.431
Past smoker (%)	47 (9)	45 (9)	0.02	.886
Emergency visits (%) in the last year	21 (4)	0 (0)	5.06	.031 ^a
Asthma duration (years)	23.89 ± 17.07	13.95 ± 9.32	5.17	.029 ^a
FEV ₁ (absolute value) at baseline	2.75 ± 0.46	2.63 ± 0.70	0.37	.548
FEV ₁ (% predicted)	94.44 ± 14.88	88.48 ± 15.01	1.51	.227
FVC (% predicted)	105.39 ± 15.76	99.58 ± 11.42	1.70	.201
FEV ₁ /FVC (% predicted)	83.12 ± 2.08	82.50 ± 2.69	.65	.426
ICS (%)	100 (19)	95 (19)	0.95	.337
ICS dose (µg)	616.88 ± 554.58	433.33 ± 22.93	1.43	.242
LABA (%)	56 (11)	58 (12)	0.02	.890
Combined LABA (%)	47 (9)	55 (11)	0.22	.644
Beta-2 short action (%)	84 (16)	85 (17)	0.00	.947
ACQ score	1.17 ± 1.07	1.08 ± 0.80	0.09	.769
Psychological characteristics				
ASI score	31.50 ± 20.65	17.19 ± 13.29	6.25	.017 ^a
Any antidepressants (%)	47 (9)	5 (1)	11.38	.002 ^a
Any anxiolytics (%)	21 (4)	0 (0)	5.06	.031 ^a

Note. Data are presented as M ± SD or percent (n). BMI = Body Mass Index; ICS = Inhaled Corticosteroids; ACQ = Asthma Control Questionnaire; ASI = Anxiety Sensitivity Index.

^a Significant difference between the groups set at 0.05.

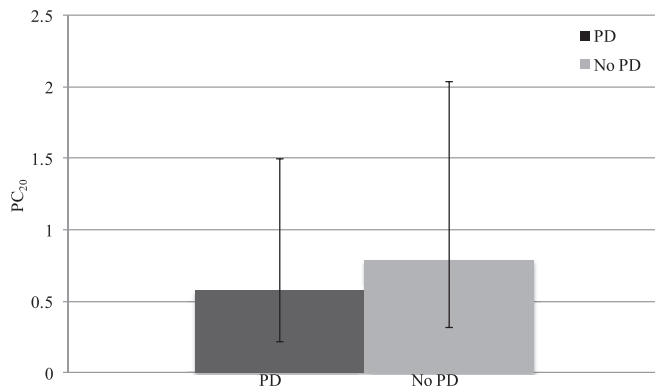


Fig. 2. Main effect of PD on objective airway responsiveness during a Methacholine Challenge Test.

discomfort, and worry compared to non-PD patients during the MCT. Analyses also showed a main effect of time, for dyspnea, panic, and discomfort following the MCT. There was also one

PD × time interaction for the total number of panic symptoms, showing that patients with PD reported greater increases in panic symptoms after the MCT compared to those without PD (see Fig. 3). This pattern of results remained when FEV₁ was included as an additional covariate, though the effect was reduced, suggesting some potential moderation (see Supplement).

4.4. Association between PD status and physiological arousal

Table 3 shows the results of the adjusted physiological responses analyses which revealed main effects of group and time showing that having PD was associated with significantly lower HR, SBP and DBP responses to the MCT, in comparison to the non-PD group, and both SBP and DBP were reduced in response to the MCT, irrespective of group.

5. Discussion

The purpose of this study was to help understand the nature of the relationship between PD and worse asthma outcomes by concurrently investigating physiological and psychological

Table 2

Effect of PD status and time on subjective distress during a Methacholine Challenge Test.

	PD		No PD		PD status		Time		PD x time	
	Pre-test M ± SD	Post-test M ± SD	Pre-test M ± SD	Post-test M ± SD	F	p	F	p	F	p
Borg Scale	1.34 ± 1.46	4.08 ± 2.25	0.43 ± 0.73	2.68 ± 1.59	8.81	.006 ^a	73.66	<.001 ^a	0.70	.407
PSS – Total number of symptoms	2.21 ± 2.42	5.00 ± 3.32	0.75 ± 1.07	2.25 ± 1.89	8.48	.006 ^a	55.91	<.001 ^a	5.05	.031 ^a
PSS – Total score ^b	2.84 ± 4.62	8.26 ± 8.26	0.68 ± 0.91	2.89 ± 2.92	0.47	.497	0.66	.422	0.72	.402
SD-VAS – Anxiety	16.68 ± 22.27	22.79 ± 27.90	2.10 ± 2.86	5.20 ± 10.32	9.44	.004 ^a	3.38	.074	0.36	.554
SD-VAS – Discomfort	15.47 ± 19.79	30.53 ± 31.26	2.40 ± 2.76	18.70 ± 21.08	5.77	.022 ^a	14.39	<.001 ^a	0.02	.882
SD-VAS – Worry	15.21 ± 21.57	20.68 ± 26.64	2.70 ± 5.46	4.20 ± 7.67	8.92	.005 ^a	2.57	.117	0.84	.366

Note. PSS = Panic Symptom Scale; SD-VAS = Subjective Distress Visual Analogue Scale. Results are adjusted for age, sex, and PC₂₀.

^a Significant difference between the groups set at 0.05.

^b Also adjusted for the total number of panic symptoms on the PSS.

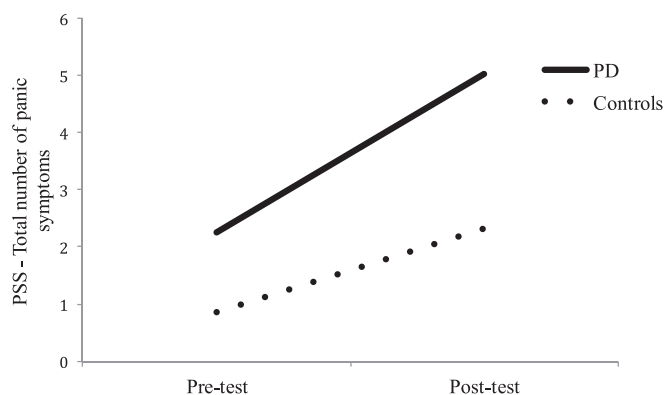


Fig. 3. Interaction effect of PD and time on the total number of panic symptoms of PSS during a Methacholine Challenge Test.

responses to a simulated asthma attack. Our hypotheses were partially supported: while PD patients did report more subjective symptoms than non-PD patients they did not show more severe airway responsiveness to the MCT. Though PD patients exhibited larger % drops in FEV₁ at the last dose of methacholine relative to non-PD patients, this difference did not reach statistical significance. To our knowledge, our study is the first to show, in a single study, that greater subjective distress for a similar level of airflow obstruction is associated with PD during a MCT in adult asthmatics. Of note, this pattern of result stood when looking at the mid-point MCT dose (see Supplement).

Our findings revealing no significant difference between PD and non-PD patients on measures of airway hyperresponsiveness are consistent with similar studies demonstrating no correlation between general anxiety levels and other objective measures of asthma, such as pulmonary function and peak flow variability [16,47–49]. Our findings are also consistent with reports showing increases in subjective responses during stress tasks among anxious asthmatics, despite the absence of changes in airway obstruction [50]. Others have shown that various subjective measures of distress, such as the perceived danger associated with asthma, were important predictors of increased healthcare use in anxious asthmatics [15,51,52]. Such findings could suggest a classical conditioning model of asthma-induced panic. Asthma attacks can be severe and life-threatening, and experiencing one such event could be sufficient to produce hypersensitivity to sensations of dyspnea, where these sensations serve as potent triggers or conditioned stimuli of anxiety-induced hyperventilation and panic [20,24,53]. Indeed, PD is characterized by catastrophization of bodily sensations [54] that could lead to a vicious cycle with an exaggerated reaction to normal variations in bodily sensations stimulating an increase in somatic symptoms [55], and lead to increased healthcare seeking [52]. The results of this study suggest that the associations between PD and worse asthma outcomes demonstrated in other studies could be driven by fears rather than

increased non-specific bronchial responsiveness [27,56].

Findings of decreased physiological responses after the MCT were unexpected, and may have been driven by the pharmacokinetics of methacholine. Methacholine is known to produce bronchoconstriction of the airways [57], which is thought to be driven by parasympathetic activation [58,59]. Methacholine has also been shown to lower blood pressure [60], so it is plausible that a methacholine-induced imbalance between parasympathetic and sympathetic tone could explain our results of diminished physiological responses in reaction to the MCT.

Findings should be interpreted with caution due to some limitations. It is possible that our results may not generalize to asthmatics treated in primary care due to the inclusion of patients treated in tertiary care, and the relatively low participation rate may also limit generalizability. It is possible that those who chose not to participate may have had more severe PD symptoms. However, if these individuals were included, this would likely have increased our effect size, thus the non-significant trend for FEV₁ levels at the last methacholine dose may have reached significance. In addition, it could be possible that, with the use of the ADIS-IV, PD patients who are on an effective treatment regime and thus do not exhibit current characteristic symptoms of PD may have been excluded. This would further limit the generalizability of the findings, likely by the exclusion of mild PD cases. The research assistant assessing panic symptoms was not blind to the psychiatric status of patients. However, the PSS was administered as a structured interview, where only patients' responses to each symptom were recorded, which minimizes subjective bias. Finally, the total number of patients in this study was relatively small, which potentially limited statistical power. However, the absolute mean group differences in PC₂₀ were minimal, which suggests that even with a larger sample size, it is unlikely that there would be a difference between groups.

Despite its limitations, this study has several important strengths. First, patients with physician-diagnosed, objectively confirmed, asthma were recruited, ensuring a valid asthma diagnoses, which can be over self-reported among anxious individuals [20,24]. Second, a validated psychiatric interview to assess PD and a validated questionnaire to assess panic attacks were used. Finally, the use of a common asthma challenge strengthens this study by allowing standardization of the stimulus and greater experimental control.

In conclusion, our results indicate that asthmatics with PD generally report higher levels of subjective distress, despite exhibiting lower levels of physiological arousal, and that in response to a MCT they have exaggerated panic symptoms compared to non-PD asthmatics. There was no evidence of greater airway responsiveness among PD patients. This suggests that worse outcomes among asthmatics with PD are likely not due to greater bronchial responsiveness but rather to increased subjective distress in response to asthma symptoms. It stresses the need for objective evidence of asthma by assessing airway caliber and bronchial responsiveness as recommended in current asthma guidelines.

Table 3
Effect of PD status and time on physiological arousal during a Methacholine Challenge Test.

	PD		No PD		PD status		Time		PD x time	
	Pre-test M ± SD	Post-test M ± SD	Pre-test M ± SD	Post-test M ± SD	F	p	F	p	F	p
HR	75.58 ± 12.28	75.89 ± 13.38	79.15 ± 9.54	79.05 ± 10.36	4.58	.040 ^a	0.02	.902	0.06	.805
SBP	113.95 ± 8.90	109.05 ± 9.40	125.25 ± 11.13	118.30 ± 9.71	12.82	.001 ^a	15.99	<.001 ^a	0.49	.487
DBP	71.47 ± 8.78	68.58 ± 8.46	76.45 ± 7.16	73.75 ± 10.28	4.15	.050 ^a	4.37	.043 ^a	0.01	.942
SpO ₂	97.37 ± 2.14	96.94 ± 2.51	97.15 ± 2.18	96.35 ± 2.54	0.01	.935	2.65	.112	0.27	.607

Note. HR = Heart rate; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; SpO₂ = Oxygen saturation. Results are adjusted for age, sex, and PC₂₀.

^a Significant difference between the groups set at 0.05.

Physicians may also consider systematic screening for PD, followed by referral to a mental health professional for appropriate treatment of PD (e.g., cognitive-behavioral therapy, pharmacotherapy).

Contributions

Conception and design: MB, KLL, AC, BT, AM, CL, SLB; Analysis and interpretation: SLB, MB; Drafting the manuscript for important intellectual content: MB, KLL, AC, BT, AM, CL, SLB.

Conflict of interest

All authors had no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2015.09.002>.

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Do asthma patients with panic disorder really have worse asthma? A comparison of physiological and psychological responses to a methacholine challenge

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SUPPLEMENTAL MATERIAL

Secondary analysis

Our main analyses revealed that asthmatics with PD reported more panic symptoms post-MCT than non-PD patients. To further investigate the pattern of distress reported among PD patients, a supplemental analysis was performed. In order to determine whether asthmatics with PD experienced subjective symptoms earlier in response to MCT than non-PD patients, a series of group (PD vs. non-PD) x time (pre-test vs. midpoint of the MCT) repeated-measures mixed model analyses were conducted. The midpoint of the MCT was calculated as the total number of doses of methacholine experienced by each patients divided by two, which reflects an approximate drop of 10% in FEV₁. When the calculation of the mid dose fell between two doses of methacholine (e.g., 2.5), an average of the lower and higher dose was measured (e.g., mean of dose 2 and 3). Age, sex, PC₂₀, and last concentration of methacholine were included as a-priori covariates (1). Significance was set at 0.05 and data analysis were performed using SAS v9.3 (SAS Institute, Cary NC).

e-Table 1 shows the results of subjective distress responses at the halfway point of the MCT which revealed a main effect of group, with PD patients reporting higher ratings of dyspnea, general anxiety, discomfort, and worry compared to the non-PD group. It also shows a main

effect of time, with patients reporting higher levels of dyspnea and discomfort, irrespective of group. There were no significant interaction effects. Of note, the data from the PSS was not included in this additional analysis since it was not used during the test but only pre and post MCT.

e-Table 2 shows the results of subjective distress responses during the MCT with FEV₁ added as a covariate to adjust for the tendency of PD patients to achieve a greater % drop in FEV₁ at the last methacholine dose. Consistent with the original analyses, these additional analyses revealed main effects of group, with PD patients reporting higher ratings of dyspnea, more panic symptoms, general anxiety, discomfort, and worry compared to the non-PD group. It also showed the same main effect of time for dyspnea. The main effects of time for the number of panic symptoms and discomfort were no longer significant. Finally, there was a trend of an interaction effect between PD status, time and the number of panic symptoms, where PD patients tended to have greater increases in the number of panic symptoms in response to the MCT compared to the no PD patients, which is consistent with the original analyses.

These additional findings are consistent with the main findings suggesting that PD patients report more subjective symptoms than non-PD patients and this seems to be consistent across the whole test (i.e., pre, mid, and post MCT) and even after adjustment for FEV₁ changes in response to each methacholine dose. This lends further support to the classical conditioning model of asthma-induced panic. As explained in the article, PD is characterized by persistent catastrophization (e.g., “I am going to suffocate”) of bodily sensations such as dyspnea (2), which could lead to a vicious cycle with an exaggerated reaction to normal variations in bodily sensations stimulating an increase in somatic symptoms, which may confirm their original fears.

e-Table 1: Effect of PD status and time on subjective distress at the midpoint of the Methacholine Challenge Test.

	PD		No PD		PD status		Time		PD x time	
	Pre-test	Midpoint	Pre-test	Midpoint						
	M ± SD	M ± SD	M ± SD	M ± SD	F	p	F	p	F	p
Borg Scale	1.51 ± 0.29	2.83 ± 0.35	0.72 ± 0.19	1.52 ± 0.24	10.16	.003*	38.39	<.001*	0.91	.408
SD-VAS - Anxiety	15.32 ± 3.96	17.56 ± 4.87	3.39 ± 1.70	4.06 ± 2.01	9.07	.005*	2.20	.118	0.18	.835
SD-VAS - Discomfort	16.66 ± 5.17	20.50 ± 4.25	4.18 ± 1.58	9.36 ± 2.61	6.88	.013*	7.26	.001*	0.04	.965
SD-VAS - Worry	14.13 ± 3.69	17.52 ± 4.40	4.27 ± 1.93	5.72 ± 2.50	8.63	.006*	1.30	.279	0.48	.622

Note. SD-VAS = Subjective Distress Visual Analogue Scale. Results are adjusted for age, sex, PC₂₀, and last concentration of methacholine.

* Significant difference between the groups set at 0.05.

e-Table 2: Effect of PD status and time on subjective distress during the Methacholine Challenge Test (adding FEV₁ as a covariate).

	PD		No PD		PD status		Time		PD x time	
	Pre-test	Post-test	Pre-test	Post-test						
	M ± SD	M ± SD	M ± SD	M ± SD	F	p	F	p	F	p
Borg Scale	1.83 ± 0.40	3.97 ± 0.38	1.08 ± 0.34	2.85 ± 0.36	7.70	.009*	18.18	<.001*	0.50	.484
PSS - Total number of symptoms	3.35 ± 0.80	4.01 ± 0.63	2.14 ± 0.51	1.92 ± 0.44	6.05	.019*	0.14	.713	3.20	.082
PSS - Total score †	3.41 ± 0.51	3.35 ± 0.55	4.10 ± 0.63	3.33 ± 0.23	0.42	.520	0.60	.443	0.76	.388
SD-VAS - Anxiety	23.15 ± 7.01	14.39 ± 4.44	12.48 ± 5.58	3.52 ± 2.89	5.90	.021*	2.00	.166	0.00	.961
SD-VAS - Discomfort	24.03 ± 6.15	25.84 ± 5.31	12.45 ± 3.64	18.00 ± 4.67	4.57	.040*	0.42	.520	0.23	.636
SD-VAS - Worry	20.93 ± 6.67	13.59 ± 4.09	12.13 ± 5.84	3.24 ± 2.82	6.28	.017*	1.47	.233	0.28	.602

Note. PSS = Panic Symptom Scale; SD-VAS = Subjective Distress Visual Analogue Scale.

Results are adjusted for age, sex, PC₂₀, and FEV₁.

† Also adjusted for the total number of panic symptoms on the PSS.

* Significant difference between the groups set at 0.05.

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