



Cortisol response to acute stress in asthma: Moderation by depressive mood



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HIGHLIGHTS

- Cortisol responses to acute stress depended on depressive mood and asthma.
- Cortisol responses to acute stress were moderated by depressive mood in asthma.
- Cortisol response to acute stress was greater in asthmatics with depressive mood.

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ABSTRACT

Both individuals with asthma and depression show signs of a dysregulated hypothalamus-pituitary-adrenal axis. However, little is known about the cortisol response to stress in the context of co-occurring asthma and depressive mood. Thirty-nine individuals with asthma and 41 healthy controls underwent a combined speech and mental arithmetic stressor. During the course of the laboratory session, salivary cortisol was collected 5 times, with 1 sample at 0 min before the stressor and 4 samples at 0, 15, 30 and 45 min after the stressor. Depressive mood in the past week was assessed with the Hospital Anxiety and Depression Scale at the beginning of the session. Depressive symptoms moderated cortisol response to the acute stressor, but only among asthmatic patients. Higher depressive mood was associated with a significant increase in cortisol, whereas low depressive mood was associated with no cortisol response. In healthy participants, depressive mood had no substantial effect on cortisol response to the stressor. These findings suggest that depressive mood and chronic inflammatory diseases such as asthma can interact to augment cortisol response to stress.

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1. Introduction

Research suggests that the hypothalamus-pituitary-adrenal (HPA) axis can be dysregulated in mental disorders and medical conditions. Adverse effects of elevated cortisol levels in depression have been linked to a range of conditions, including abdominal obesity, loss of bone density, hypertension, peptic ulcers, and diabetes [6]. Depression can also be associated with asthma, as studies have shown an elevated comorbidity of both conditions (e.g., [31,36,57]). However, the potential contribution of the HPA axis to this comorbidity has not been explored well. Given that airway inflammation is the hallmark of asthma and that corticosteroids are still the first line of treatment [22,41], knowledge

about HPA axis activity in stress and depression could serve asthma management efforts well.

Hypoactivity of the HPA axis has been identified in several allergic disorders including asthma. Asthmatic children have been shown to have lower basal endogenous cortisol levels compared to healthy controls [4,35]. One study found that children with allergic asthma display a blunted cortisol response to an acute laboratory stressor (Trier Social Stress Test, a combination of free speech and mental arithmetics under evaluative pressure) compared to healthy controls [15]. Children and adults with allergic conditions other than asthma have also shown blunted cortisol responses exposed to this laboratory stressor [9,11–14, 63]. It can be speculated that the use of corticosteroid medication in this population could explain the hypoactivity of the HPA axis, however, there is evidence that indicates that alterations in HPA axis are independent of medication use [15]. However, most of the studies involving asthma samples have focused on children and adolescents,

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and there is evidence that hypoactivity is more pronounced in allergic patients with more severe symptoms of allergy and acute exacerbations [9].

In contrast, evidence suggests that hyperactivity of the HPA axis is a central feature of depression [68]. This may be manifested in overall elevations of cortisol levels and flatter diurnal slopes [43]. For cortisol responses, studies have found a stronger cortisol response to acute stressors among women with chronic depression compared to healthy controls [28,69]. Similarly, women with remitted depression had heightened cortisol response to a laboratory stress challenge [30]. A number of reports with child and adolescent samples have also provided evidence for stronger cortisol elevations following psychological stress [19,26,39,40,49]. In addition, a stronger cortisol response to stress was also found in women with an elevated risk of developing depression (indicated by a short allele of the 5-HTTLPR gene; [23]). Other aspects of HPA-axis reactivity also indicate a tendency towards hyperactivity in depression. Men with current depression and a history of early life abuse showed stronger cortisol responses to dexamethasone [70]. A meta-analysis of 17 studies with children and adolescents with depression also found robust evidence for elevated cortisol responses to dexamethasone [38]. Interestingly, there is some evidence that elevated cortisol responses to dexamethasone can also predict the development of depression [67]. Another study found that participants with subclinical depressive personality traits had a greater cortisol response when exposed to reboxetine (a selective norepinephrine reuptake inhibitor; [29]).

However, findings on stress-responsiveness of the HPA axis are not fully consistent, with some studies showing similar unresponsiveness in depressed and non-depressed individuals [50], similar responses [65], or even hyporesponsiveness in depressed samples [17,40]. A meta-analysis including these earlier studies found some evidence for hyperresponsiveness, with studies that take place in the morning, involve older participants, and include more severe cases of depression being more likely to show hyporesponsiveness [7]. The severity-dependence was confirmed in a study with adolescents ([26], in interaction with childhood maltreatment) but age-dependence was reversed in a study with dysphoric children and adolescents (hyperresponsiveness in the latter group; [24]). It is important to note that the type of depression can also alter results, for example melancholic depression is related to hyperactive HPA axis and atypical depression is related to hypoactive HPA functioning [21]. Individuals with atypical depression unlike melancholic depression can experience positive affect when they experience a positive event [46].

The mechanism and consequences of a potential dysregulation of the HPA axis in depression or asthma have been subject to speculation. Exaggerated and prolonged secretion of cortisol to stress in depression may be due to a defective negative feedback to the HPA axis that normally guides recovery to normal cortisol levels after a stressor [68]. Dexamethasone usually leads to a decrease in cortisol release by activating the negative feedback to the anterior pituitary gland that results in reduced secretion of ACTH and ultimately diminished cortisol secretion [71]. Individuals with depression have also shown HPA axis hyperactivity in the form of elevations in corticotropin releasing hormone (CRH) levels in the cerebrospinal fluid and also display heightened CRH levels in the limbic region of the brain [20]. The same study also provided evidence that the administration of dexamethasone in patients did not result in the usual reduction in cortisol. It is possible that the chronic elevation in cortisol leads to a resistance to the anti-inflammatory effects of glucocorticoids and as such it has been associated with more pronounced immune activation or inflammation, specifically of cytokines IL-1 β and IL-6, which in turn are related to neurodegeneration [68]. Another cytokine involved in inflammatory responses, interferon alpha (IFN- α), can contribute to glucocorticoid resistance by impairing glucocorticoid receptor function [42] and is related to symptoms of sickness such as fatigue [16] in individuals with depression. Additionally, in-

vitro studies have linked higher glucocorticoid levels to elevations in asthma-related cytokines [2,55]. Thus, higher stress-induced levels of cortisol could pose a risk factor for exacerbation in systemic and/or airway inflammation in asthma.

Although a relationship has been observed between allergy, asthma, and depression in the literature, links between these conditions have not been well elucidated [62]. To the best of our knowledge cortisol responses to acute stressors in individuals with comorbid asthma and depressive mood have not been previously examined. In addition, we sought to focus on cortisol responses to acute stressors in individuals with subclinical depressive mood. Understanding how smaller fluctuations in depressive mood are related to HPA functioning is important because such fluctuations may occur more frequently during the course of a life with asthma and are more common in the population in general. The literature cited above points to an importance of subclinical variations in depressive symptoms for HPA-axis reactivity to stress (e.g., [17,24,29]). We have also found that smaller variations in depressive mood are associated with stress-related changes in fraction of exhaled nitric oxide (FeNO) in asthma, a measure of airway inflammation [52,60].

The specific aim of the current study was to examine the moderating effect of depressive mood on cortisol responses to an acute laboratory stressor, the Trier Social Stress Test, in asthma. Based on the available literature the prediction of cortisol responses to stress for those who suffer from asthma and depression is not necessarily straightforward. We expected, on balance, that individuals with subclinical depressive mood would have greater elevations in cortisol following the stressor than those low in depressive mood. This may counteract possible hypoactivation of the HPA axis in asthma and make those patients appear more normal in responding. However, in mixed samples of allergic and nonallergic asthma patients that are well controlled, allergy-induced hypoactivation may be missing, which, in combination with depression, would then translate into the exaggerated cortisol secretion typically observed in nonasthmatic individuals.

2. Method

The data were collected as part of a larger study on stress reactivity in asthma. Here we analyze salivary cortisol in response to the laboratory stress protocol and examine the moderating effects of depressive mood. Approximately one half of the cortisol data analyzed here had been included in a previous publication that focused on the changes of exhaled nitric oxide to acute stress [51]. Analysis of moderation by depressive mood was not attempted in this earlier paper because of the difference in focus and the smaller sample size. Nitric oxide and depressive mood data from the expanded sample were subsequently analyzed and published [53], but cortisol data were dropped in response to suggestions of the reviewers that they would distract from the main theme of the paper.

2.1. Participants

Eighty participants, healthy controls ($n = 41$) and asthmatics ($n = 39$) were recruited from a private university in the Southwest of the US and its surrounding community through advertising by posters, flyers and internet sites. Participants in the asthma and healthy control groups were matched for gender and age. Asthmatic participants had a diagnosis of asthma from a physician, while healthy individuals had no asthma diagnosis. Exclusion criteria included current smoking (smoking in the past 6 months), severe psychopathology (including substance dependence, depression, and schizophrenia) assessed using screening questions from the Structured Clinical Interview for DSM-IV, health problems (cardiovascular conditions, lung disease, or chronic inflammatory conditions other than asthma), and corticosteroids in oral or injected form in the past 3 months. Oral or injected corticosteroids have systemic effects whereas inhaled corticosteroids have more of a

localized effect in the airways (although they can also be absorbed systemically at high doses). Systemic corticosteroids have a greater impact on HPA-axis measurements, which is not necessarily the case for inhaled corticosteroids (see, [37]). The local Institutional Review Board approved the study and all participants gave written informed consent.

Instructions were given to all participants with asthma that they should continue their use of maintenance medication during the course of the study as usual. They were also instructed to refrain from using their bronchodilators, short- and long-acting beta-agonists, for 6 h and 12 h, respectively, prior to the study. We asked patients taking leukotriene modifiers to refrain from their use for three days prior to the study.

2.2. Instruments and assessments

2.2.1. Asthma assessment

Asthma control and severity were determined through symptom frequency, daily functioning, night time symptoms, bronchodilator use, and spirometric lung function [22]. The evaluation of severity was restricted to individuals that were not taking maintenance medication [41]. See Table 1 for further information on asthma severity and control.

2.2.2. Negative affect assessment

To assess negative affect we used the subscale of the Positive Affect Negative Affect Schedule (PANAS-NA) which consists of 10 items [64].

2.2.3. Depressive mood assessment

The Hospital Anxiety and Depression Scale, depressive mood subscale (HADS-D; [66]) was used to measure depressive mood in the past week. This measure has the advantage of avoiding references to physical symptoms, which could inflate values when used in medical populations. The HADS-D subscale consists of seven items rated on 0–3 scales, resulting in an overall score range of 0 to 21. Scores indicating possible clinically relevant depression range from 8 to 10 and for probable clinical depression between 11 and 21. The HADS anxiety subscale (HADS-A) was also assessed but not included as part of the main analysis. The depressive mood variable was not used to dichotomize the sample into low and high depressive mood participants, rather, the complete sample is used to calculate slopes (based on regression analysis that uses interaction terms) of what would be the cortisol response for those with high and low depressive mood scores [1].

2.2.4. Salivary cortisol

Saliva samples were obtained using sterile cotton balls collected in salivettes (Sarstedt, Inc., Newton, NC, USA). Cortisol concentration was determined by radioimmunoassay, specifically a Coat-A-Count cortisol

kit TKCO2 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Samples were collected 6 times during the session at 15 min intervals (2 pre-stress and 4 post-stress time points). The first assessment point was omitted from the analyses due to concerns about the contamination with anticipatory anxiety and events prior to the session.

2.3. Laboratory protocol

All participants came to the laboratory at either 12 pm or 3 pm, to prevent major interferences by the cortisol diurnal rhythm. Self-report instruments evaluating demographics, asthma symptoms, stress, anxiety, and depressive mood were administered at the start of the laboratory session. The acute stressor was the Trier Social Stress Test [32]. The task consists of a free uninterrupted speech followed by mental arithmetic. Prior to the start of the stressor task, the exact details and components of the task were not disclosed to participants. The task has been shown to reliably elicit a cortisol response (e.g., [32,54]), with the threatening social evaluation as one of its key components [18]. The stress protocol is separated into three distinct segments: the first 5-min is dedicated to speech preparation, followed by 5 min of speech performance and 5 min of an unexpected mental arithmetic task (subtracting 13 from 2633 continuously). Two confederates acting as speech and math evaluators and a video recording of the participants' performance constituted the element of evaluative threat.

2.4. Data analysis

Mixed effect analysis of variance models in IBM SPSS was used for data analysis. The advantage of this statistical approach is that it allows the inclusion of all participants, including those with missing data points. This increases the power and generalizability of the analyses. In addition, this method also allows for a modeling of the error covariance matrix of the repeated measures, as it offers several options for the choice of structure of the covariance matrix (e.g., unstructured, AR(1), Toeplitz, compound symmetry (the assumption of a typical repeated measures ANOVA), scaled identity, etc.). Salivary cortisol concentration values (in nmol/ml) were log transformed in order to reduce skewness.

The main statistical model tested the effect of asthma diagnosis and depressive mood on changes in cortisol across the 5 time points. In this model the dependent variable was cortisol. The independent variables included time (5 levels representing cortisol collection time points), group (asthma, control), and depressive mood subscale (HADS-D). The triple interaction of Time $\times$ Group $\times$ Depressive mood was included as an independent variable. Additional independent variables included were: Group $\times$ Time, Depressive mood $\times$ Time, and Depressive mood $\times$ Group. These interaction terms allowed us to test whether the relationship between cortisol and time was influenced by depressive mood or group. Gender and inhaled corticosteroid use were included as covariates. The Corticosteroid use $\times$ Time interaction was included as a covariate in order to control for potential moderator effects that corticosteroid use could have on the cortisol change across time. The Gender by Time interaction was also tested as a covariate. All non-significant interactions were subsequently dropped from the final model [5,27]. Changes in negative affect (PANAS) across time were tested using a similar model, in which time was the main independent variable, group (asthma/control), age and gender were included as control variables.

In order to test the effect of depressive mood on cortisol response we did not dichotomize the sample into extreme low and high depressive mood groups, rather we used the simple slope [1] approach to compute model-predicted "simple slopes" for low and high depressive moods. This method treats the depressive mood variable as a continuous measure and allowed us to use the entire sample. In the interaction high and low depressive moods were set at 1 SD above and below the mean scores of the samples. For high depressive mood the variable

Table 1
Characteristics of asthmatic participants.

Characteristics	Asthmatic participants
FEV1, % of predicted, mean (SD)	91.6 (13.8)
FeNO, mean (SD)	39.4 (36.6)
Family history of asthma	26
Symptoms season-specific	29
Asthma onset, years, mean (SD)	8.7 (9.9)
<i>Medication</i>	
Short-acting bronchodilators, <i>n</i>	25
Long-acting bronchodilators, <i>n</i>	13
Inhaled corticosteroids, <i>n</i>	18
Leukotriene modifiers, <i>n</i>	8
<i>Asthma control</i>	
Well controlled, <i>n</i>	21
Not well controlled, <i>n</i>	12
Very poorly controlled, <i>n</i>	6

was centered at HADS-D ≥ 5.07 and low depressive mood was centered at HADS-D ≤ 1 . This was done for the illustration of the interaction effect only, as the simple slope method includes all participants in order to test the association between low and high depressive moods and salivary cortisol changes across time. The mixed effect analysis of variance model can only provide an overall effect of time, therefore in order to determine specific time points at which cortisol showed a significant change from pre- to post-stress we used dummy coded variables for each time point. With this method we contrasted pre-stress cortisol with the 4 post-stress assessments.

We selected the best fit error covariance matrix for each analysis by comparing deviance statistic ($-2 \log$ likelihood) to the unstructured covariance matrix. The covariance structure whose deviance statistic was not significantly different from the unstructured covariance matrix and that used the fewest parameters was selected [58]. The best fit covariance structure for our model was unstructured as all other covariance matrices had deviance statistics that were significantly different.

3. Results

3.1. Baseline participant characteristics

Our final participant sample consisted of 39 asthmatics (23 females, 16 males) and 41 healthy controls (25 females, 16 males). Sixty-four of the participants reported their race as white (80%). Four participants (5%) in total reported that their ethnicity was Hispanic, 68 participants reported non-Hispanic (85%), and 8 participants (10%) did not report ethnicity. Eighteen participants (22.5%) reported having at least some level of college education. Overall asthmatics and healthy controls did not significantly differ in age, gender, race/ethnicity, and education ($p > 0.40$). The mean age for individuals with asthma was $M = 24.6$ ($SD = 10.1$) and for healthy controls $M = 25.4$ ($SD = 11.6$). The mean HADS-D for asthmatics was $M = 2.6$ ($SD = 3.4$) and for healthy control $M = 3.1$ ($SD = 2.7$). There were no differences between asthmatics and healthy controls in HADS-D. The range of HADS-D score was from 0 to 19, indicating that some of the participants reached clinical levels of depression, however the vast majority did not. Out of 80 participants, 5 (6.25%) had a HADS-D score of 8 or above indicating at least possible clinical level of depression (2 participants scored 8, 1 participant scored 10, 1 participant scored 11 and 1 participant scored 19). For anxious mood, HADS-A scores were not significantly different between individuals with asthma ($M = 6.8$, $SD = 3.2$) and healthy controls ($M = 6.2$, $SD = 3.6$; $p = 0.45$).

In our sample, 16 individuals with asthma used inhaled corticosteroids. Classification of participants with asthma not taking controller medication indicated that 9 participants had intermittent, 2 mild persistent, 4 moderate persistent, and 2 severe persistent asthma (see Table 1 for variables characterizing participants' asthma). Participants overall experienced an increase in negative affect (PANAS) pre- to post-stress $F(4,78) = 18.02$, $p < 0.001$.

3.2. Missing data

Missing data in our study were in an acceptable range. From the self-report data, only 1 HADS-D score (1.3%) was missing. For cortisol samples we were missing 3 at the first time point (prior to the stressor, 3.8%), 5 at the second time point +0 min post-stress (6.3%), 6 at 15 min post-stress (7.5%), and then 3 samples at 30 and 45 min post-stress (3.8%). In total, 20 cortisol samples were missing out of 400 samples (5%).

3.3. Cortisol response to the acute stressor: associations with asthma and depressive mood

Depressive mood was not significantly associated with cortisol levels across all participants (main effect of depressive mood,

$p > 0.40$). Overall, there was a significant increase in cortisol across time, $F(4, 73) = 2.67$, $p < 0.05$. When examining individual time points, a significant increase was seen from 0 min pre-stress to 15 min post-stress across groups, $\beta = 0.38$, $t(77) = 2.71$, $p < 0.01$. There was a significant main effect of group on cortisol, such as overall participants with asthma had lower cortisol levels than healthy controls, $\beta = -0.55$, $t(75) = -2.09$, $p < 0.001$ (Fig. 1). The triple interaction of Time $\times$ Group $\times$ Depressive mood was significant, $F(4,71) = 3.09$, $p < 0.05$. Examining the components of this interaction we found that depressive mood moderated cortisol response, $F(4, 72) = 5.24$, $p < 0.001$, but only among individuals with asthma. Specifically, individuals with asthma and high depressive mood showed a significant increase in cortisol from 0 min pre- to post-stress time points, $F(4,73) = 13.49$, $p < 0.001$. Analysis using dummy coded time points showed that this increase in cortisol was only significant at 15 min post stress, $\beta = 1.34$, $t(100) = 6.82$, $p < 0.001$ (Fig. 1). For individuals with asthma and low depressive mood no significant change in cortisol from pre to post-stress was observed ($p = 0.86$), whereas for healthy controls the overall increase in cortisol was suggestive in its direction but not significant ($p = 0.12$). Depressive mood did not moderate the effect of time on cortisol for healthy controls ($p = 0.94$).

3.4. Effects of gender, time of day, inhaled corticosteroids, and antidepressant medication

No significant effects of gender were found across analyses ($ps > 0.30$), regardless of whether gender was included as a covariate or moderator variable. Similarly, no significant effects of inhaled corticosteroid use in asthma were found ($ps = 0.20$), regardless of whether this variable was used as a covariate or a moderator. We also tested time of day as a covariate in order to determine whether there was an effect at the beginning of the assessment at noon versus 3 pm. No significant main effect of time of day emerged, $p = 0.72$, and the results remained essentially unchanged. Similarly, when adding antidepressant medication as a covariate we found that it was not significant, $p = 0.06$, and did not change the results substantially.

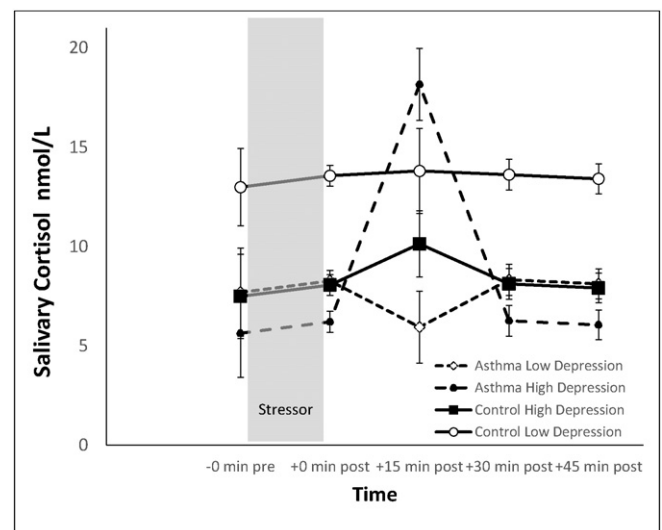


Fig. 1. Patterns of cortisol response to the Trier Social Stress Test in healthy and asthmatic participants with high (HADS-D ≥ 5.07) and low depressive moods (HADS-D ≤ 1). The error bars represent standard errors. This figure shows the fictive subgroup values (based on ± 1 SD) separately in the only for illustration of the results.

4. Discussion

This study sought to examine the effects of acute stress on cortisol release in individuals with asthma and healthy controls and its moderation by depressive mood. We found that individuals with higher depressive mood had a stronger cortisol response to acute stress than individuals with lower depressive mood, but this was only observed among asthmatic participants. To our knowledge this is the first study to examine the association of subclinical depressive mood with the cortisol response to an acute stressor in individuals with asthma. The findings could indicate that depressed asthma patients are at a particular risk of hypercortisolism under conditions of stress. In contrast to past studies of asthma and allergy we did not find a significant overall blunting of the cortisol response to the acute stressor (e.g., [15,63]). Differences in sample characteristics could be responsible for that, given that our sample was composed of well-controlled adults with asthma, which was not exclusively allergic. Similarly, our non-asthmatic group with higher depressive mood did also not display a significantly elevated cortisol response to the laboratory stressor, which may be due to the milder, on average subclinical levels of depressive symptoms.

The observed HPA axis hyperactivity for asthma patients with depressive mood could have problematic health consequences. Recent research suggests that combined effects of asthma and depression exacerbate inflammation [72]. Immune pathways activated by excess glucocorticoids in depression overlap with those involved in asthma pathology, thus possibly leading to exacerbations in inflammatory processes. Individuals with asthma and depression both display elevations in inflammatory cytokines, specifically interleukin (IL) 1 beta (IL-1 β) and tumor necrosis factor alpha (TNF- α), and mediators such as prostaglandins and neuropeptides (i.e. tachykinins; [62]). The similarities in the immune profiles (elevated IL-1 β and TNF- α) found in people with depression and asthma may be linked to abnormal glucocorticoid release. In addition, glucocorticoids can increase activity of cytokines that are central to atopic airway inflammation, such as type-2 T helper cell (Th2) cytokines including IL-4, IL-10 and IL-13 [2,47]. The combination of catecholamines and glucocorticoids appears to be a particular risk factor for increases in Th2 cytokines [55]. Observations of an elevated comorbidity of asthma and depression could also be the reflection of such an overlap in underlying immune pathways. The relationship between asthma and depression is most likely bidirectional in that depression increases the likelihood of asthma and asthma symptoms can increase depressive mood. Individuals with stronger asthma symptoms are more likely to develop depressive symptoms [48,59] and earlier psychopathology, including major depression, has been shown to be associated with later onset of asthma in longitudinal epidemiological studies [3,25].

In our study, the cortisol response to the stressor in non-asthmatic controls only was somewhat weaker than in prior studies. However, it should be noted that we found a significant cortisol response when we examined all groups together. Most TSST studies have observed significant responding with a sufficiently heterogeneous sample. It is possible that such studies also included subclinical elevations in depressive mood that might exist among a sample of individuals without clinical depression. In addition, many similar studies have not explicitly excluded asthmatic participants [8,10,73]. It is also possible that our sample with a strong representation of undergraduate students did not feel overly threatened by the task. Undergraduate students in the United States may be more used to oral self-presentation than European students due to an education that puts greater emphasis on public speech. It should also be noted that the effects of acute laboratory stressors on cortisol in younger populations have also been variable in other studies (e.g., [38]). Another consideration could be that the timing of our sampling did not allow us to capture elevations in cortisol, because we collected samples every 15 min and possible cortisol peaks at 20–25 min following stress may have been detected. However, other studies have found that the cortisol response peaks around 10 min following the

acute stressor [32,33], which should have been captured sufficiently well with our protocol. Finally, given that the cortisol elevation in healthy controls after stress was at least suggestive in direction ($p = 0.12$), it could be speculated that our study was not sufficiently powered to show the expected significant cortisol elevation in this subpopulation. The difference between the significant effect with the complete sample of $N = 80$ and the nonsignificant effect with the subsample of $n = 40$ could be indicative of that. However, it should be noted that with our design only a sample of $n = 32$ would have been needed to detect effect of a medium-size with 0.95 power.

Previous research indicates that the relationship between asthma and the HPA axis is complex, and individuals with asthma may show manifestations of HPA axis dysfunction in different ways. In our study, individuals with asthma had lower overall cortisol levels consistent with prior research [45]. However, this was paired with more pronounced cortisol reactivity in response to stress. The use of corticosteroids to control asthma could potentially alter HPA axis functioning, because patients are receiving exogenous glucocorticoids. However, exploring inhaled corticosteroid use as a covariate or moderator in our study did not alter the pattern of results. Other studies also found that blunted cortisol release in response to acute stressors is not associated with corticosteroid use in asthma [15]. It is possible that cytokines involved in allergic inflammation attenuate adrenal responses [45]. Moreover, there is evidence that correct corticosteroid use should not decrease the cortisol responses in asthma and longitudinal data suggest that adrenal function is actually improved with corticosteroid treatment [44].

In examining the relationship between asthma and depressive mood it is important to consider whether depression is conceptualized as a categorical diagnosis or a dimensional characteristic. This study followed a dimensional approach of biological system analysis that may be more appropriate in the study of psychopathology [56]. Participants showed a range of levels of depressive mood, including clinically significant ones, but they were not formally diagnosed. More studies are needed that examine subclinical manifestations linked to psychopathology and HPA axis functioning [61] in asthma.

Our study has a number of limitations that should be considered when interpreting the findings. Only a small number of our participants were in the clinically depressed range so these results are not representative for a clinical population. There are suggestions that responsiveness of the HPA axis may change with greater severity of depression from a hyper- to a hypoactivity in response to stress [7]. More severely depressed populations also tend to have more marked blunted cortisol responses than those less depressed [34]. Our study would have been significantly strengthened by the inclusion of clinical and non-clinical depression participant samples in order to determine if cortisol responses among asthmatics depend on depression severity. However, our sample had the benefit of covering the lower range of depressive states that is often neglected in depression studies and thus can significantly add to knowledge in that area. Our study also did not capture the prospective relationship between asthma, depression and HPA axis functioning. Therefore, we cannot draw conclusions about any causal relationship. We also did not control for contraceptive use or menstrual cycle phase in women, which may be related to HPA axis function. However, controlling for gender effects did not alter any of the results on cortisol levels or reactivity. In addition, although we controlled for inhaled corticosteroid use in asthma, we cannot completely rule out a potential effect of medication use. The effect of chronic corticosteroid medication among asthmatic individuals on cortisol response may be more prolonged and not necessarily be reflected in the more recent usage we captured here. The same may apply to effects of antidepressant medication. Although we tested its effect as a covariate and it did not change the results, we cannot rule out that it had an influence, given the notorious problems with self-report of medication data and medication adherence in asthma.

Despite these limitations our findings indicate that the combination of asthmatic and subclinical depressive mood can be associated with a particular risk for HPA axis hyperactivity in stress. Concerns about the elevated comorbidity of asthma and psychopathology underscore the importance for more studies that examine the additive effects of asthma and depression on HPA axis functioning.

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