



Review article

Effects of acute psychological stress induced in laboratory on physiological responses in asthma populations: A systematic review



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ABSTRACT

Background: Psychological stress has long been suspected to have a deleterious effect on asthma, with acute psychological stress being associated with physiological responses in asthma patients.

Objectives: The purpose of this systematic review was to provide a narrative synthesis of the impact of acute laboratory psychological stress on physiological responses among asthma patients.

Methods: An extensive search was conducted by two independent authors using Pubmed, PsycINFO, PsyArticles and the Cochrane Library electronic databases (up to September 2016). English and French articles which assessed physiological responses during or post-stress and compare them to baseline or pre-stress values were included.

Results: Thirty-two studies met the inclusion criteria. Studies indicated that exposure to active stressors (e.g., arithmetic tasks) was associated with an increase in sympathetic nervous system (SNS) responses, cortisol, and inflammatory responses, but had little effect on the caliber of the bronchi. Exposure to passive stressors (e.g., watching stressful movies or pictures) was also associated with an increase in SNS responses and with mild bronchoconstriction. However, a paucity of data for passive stressors limited conclusions on other measures.

Conclusions: In patients with asthma, both active and passive stressors seem to be associated with an increased activation of the SNS. Passive stressors seem to have a more immediate, deleterious impact on the airways than active stressors, but the latter may be associated with delayed inflammatory driven an asthma exacerbation. Further studies are needed to understand the impact of acute stressors on the physiological mechanisms associated with asthma, particularly HPA and immune markers.

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ABBREVIATIONS: ANS, Autonomic nervous system; FeNO, Fraction of exhaled nitric oxide; FEV₁, Forced expiratory volume in 1 s; % FEV₁, Percent predicted FEV₁; HPA, Hypothalamic-pituitary-adrenocortical; M, Mean; MeSH, Medical subject headings; PNS, Parasympathetic nervous system; RSA, Respiratory sinus arrhythmia; SD, Standard deviation; SES, Socioeconomic status; SNS, Sympathetic nervous system; TSST, Trier Social Stress Test.

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1. Introduction

Asthma is a chronic respiratory disease characterized by airway hyper-responsiveness, inflammation, and airflow obstruction [1], and is one of the world's most common chronic diseases in adults [2]. Despite the availability of effective treatments, over 50% of asthma patients remain poorly controlled [3], accounting for a significant proportion of health care costs [4,5]. Optimal asthma control depends on several behavioral (e.g., managing environmental triggers, and adherence to controller medication) [1] and physiological (e.g., bronchial and immune responses to allergens) [6] factors, both of which may be influenced by psychological stress. Psychological stress occurs when an individual perceives that their environmental demands exceed their abilities to cope with them [7]. The psychological stress - asthma link is not new [8], with asthma being referred to as a “neurotic affection” as far back as the 19th century [9]. Interestingly, some asthma patients report psychological stress as an asthma trigger [1], and both chronic (e.g., presence of psychiatric disorders [10,11]) and acute (e.g., public speaking) psychological stress have been associated with increased asthma exacerbations [12,13].

Several laboratory studies have been conducted to better understand the impact of psychological stress on asthma [14–16]. Physiological responses to stress (e.g., respiratory, immune, autonomic, hypothalamic-pituitary-adrenocortical [HPA], and cardiovascular) seem to vary as a function of stressor type, *i.e.*, passive vs. active stressors [17–19]. Passive psychological stressors are defined as the presentation of stimuli during which participants do not have control over and cannot use active coping efforts to resolve the stressful situation [20], e.g., watching stressful movies or pictures [14,16,21–28]. Active psychological stressors are defined as stimuli that participants feel they have a certain degree of control over and can use psychological or behavioral coping efforts to deal with [29], e.g., public speaking and video games [15,30–38].

Though there have been several narrative reviews [17–19,39], to our knowledge, no systematic reviews have summarized the impact of different laboratory-based acute psychological stress tasks on physiological responses in asthmatics. The purpose of this systematic review was to provide a synthesis of the physiological

responses to different acute laboratory psychological stress tasks, specifically, active and passive.

2. Methods

The present systematic review was conducted in accordance with the Preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA-P) guidelines [40]. The protocol was registered in Prospero (registration number: CRD42015026431).

2.1. Literature search

A comprehensive search was performed using the following electronic bibliographic databases: PubMed, PsycINFO, PsyArticles, and The Cochrane Library (publication dates: up to the 15th of September 2016). Medical subject headings (MeSH) were used as search terms when available, or key words when appropriate, see [Supplement A](#) for details. We complemented this by reviewing the reference sections of eligible articles and review articles.

2.2. Study selection and data extraction

Two reviewers independently screened the titles and abstracts of potentially eligible articles retrieved. Study inclusion criteria were: (1) English or French language peer-reviewed articles; (2) pediatric or adult asthma populations; (3) experimental studies assessing the impact of an acute laboratory psychological stress task on physiological responses; and (4) physiological responses assessed during or post-stress and compared to baseline or pre-stress values.

In this review, an “acute psychological stressor” was defined as a stimulus that triggered immediate/short term mental or psychological stress (*i.e.*, negative emotional responses) in a controlled laboratory setting. Stress induced by physical challenges were not included (e.g., exercise, pain tasks or inhalation of carbon dioxide) considering that they have been found to have a different impact on physiological responses [41,42]. Stress tasks could be active (e.g., mental arithmetic tasks, Trier Social Stress Test [TSST], etc.) or

passive (e.g., watching stressful movies or pictures, recalling a stressful experience, etc.).

After the first screening, all selected articles underwent full-text reading by two reviewers. Any disagreement between the two reviewers over eligibility was resolved through discussion with a third reviewer. Data extraction was performed on a standardized Excel form created for this study. When information was not available in the original article, efforts were made to contact the authors by email.

The quality of selected studies was also rated using an adapted version of the Downs and Black Checklist [43]. Only questions relevant to prospective studies were retained (i.e., 13 items). This method of assessment has been successfully used in the previous studies [44,45].

3. Results

A total of 6784 records were retrieved (Fig. 1). After removal of duplicates and exclusions based on titles and abstracts, 59 full text articles were evaluated for eligibility. A total of 27 articles were eliminated (details in Supplement B). Thus, 32 studies met inclusion criteria and were retained [14–16,21–28,30–38,46–57].

3.1. Study characteristics

Table 1 describes the characteristics of the selected studies. The overall percentage of women was 48%. The studies included a wide range of age groups; with mean age ranging from 9.8 [48] to 40.1 [28]. Seventeen studies recruited participants who had physician-diagnosed asthma [14,21–23,25,26,30–32,34,35,37,38,48,51,56,57], two studies relied on methacholine challenge [15,53], five studies used self-reported asthma [24,27,33,47,54], and seven studies did not report how asthma was diagnosed [16,28,36,49,50,52,55]. For the remaining article [46], which reported two separate experiments, one of them did not mention how asthma was assessed, and the other one included participants with a positive methacholine challenge test. The most commonly used active stressors were mental arithmetic tasks (8 studies, 32% [14–16,21,32,49,50,52]) and the TSST (8 studies, 32% [30,33,36–38,54,56,57]), whereas exposure to emotional films was the most frequently used passive stressor (8 studies, 67% [14,16,21,23–26,28]).

3.2. Physiological stress responses

A summary of all physiological responses patterns are provided in Fig. 2.

3.2.1. Respiratory responses

Twenty-six studies assessed respiratory responses (Table 2) [14–16,21–28,31,32,34–37,46,48–53,55,56].

3.2.1.1. Passive stressors. Overall, passive stressors seemed to induce mild bronchoconstriction, according to observed increases in respiratory rate [14,16] and resistance [16,24,27,28], though two studies observed no changes in respiratory resistance [24,25]. Forced expiratory volume in 1 s (FEV₁), seemed to remain unchanged across studies [22,25].

3.2.1.2. Active stressors. There was a great deal of inconsistency in respiratory responses across active stressor studies. For example, one study exposing participants to a time-pressure puzzle task showed a decrease in FEV₁ [48] one study using the TSST showed an increase in FEV₁ [56] and three studies using different tasks showed no change in FEV₁ [31,35,55]. Respiratory rate increased in

3/5 studies [14,35,53] and remained unchanged in 2/5 studies [37,49]. Peak flow did not change in 2/4 studies [32,52], decreased in 1/4 studies [51], and decreased after an asthma attack recall interview, but not after a mental arithmetic tasks [15]. Taken together, active stressors seem to have little effect of the caliber of bronchi.

3.2.2. Immune responses

Among the seven studies [31,32,37,38,54–56] assessing immune responses to acute psychological stress, none examined the impact of a passive stressors. Thus, we will focus here on the impact of active stressors (Table 3).

3.2.2.1. Active stressors. Fraction of exhaled nitric oxide (FeNO) - an indicator of airway inflammation [58,59], and eosinophilic activation [55,56], were the only two markers assessed in more than one study. FeNO increased in 2/4 studies [37,54], but one study found a non-significant decrease of FeNO after asking children to take part of a conflict discussion with their parents [31]. However, SES may have moderated this relationship (low SES was associated with increased FeNO and high SES with decreased FeNO). Another study [56] found that participants reporting low levels of chronic stress during daily life had decreased FeNO, while those reporting high chronic stress had increased FeNO. With respect to eosinophilic activation, one study found no changes in eosinophil count when exposing participants to an imaging task [55], while another found that TSST induced increase [56]. Furthermore, total leukocyte, lymphocytes, cystatin S, light chain IgA, and glutathione S-transferase were also found to increase in response to active stressors [32,38]. Overall, these findings seem to link active stressors with an upregulation of immune responses.

3.2.3. Autonomic responses

Eleven studies [14–16,23,25,27,32,34,49,50,56] assessed autonomic responses to acute psychological stress (Table 4).

3.2.3.1. Passive stressors. Passive stressors seem to activate the sympathetic nervous system (SNS), as suggested by observed increases in electrodermal activity [14,16,23], though there seemed to be no effect on parasympathetic nervous system (PNS) activity, as measured by respiratory sinus arrhythmia (RSA) [14,23,27].

3.2.3.2. Active stressors. For active stressors, skin conductance [14,16,23,49], catecholamine levels [32], and alpha amylase [56] were found to increase, which suggests an activation of the SNS. As for RSA, results were mixed, with no changes seen in response to an asthma attack recall interview and a reaction time task [15,23], but decreases in response to mental arithmetic [14,15]. Taken together, active stressors seem to activate the SNS and, depending on the type of stressor, to decrease RSA.

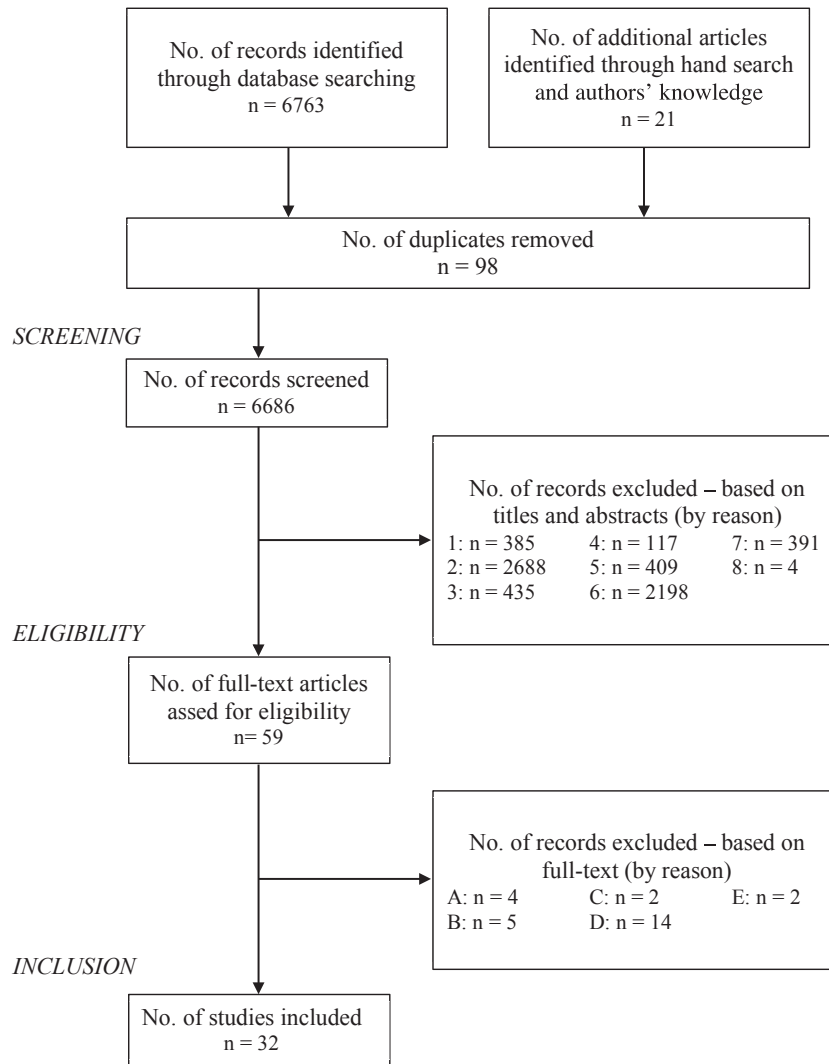
3.2.4. Hypothalamic-pituitary-adrenocortical responses

Seven studies [30,32,33,37,47,56,57] assessed HPA responses to active stressors. However, no studies assessed HPA responses to passive stressors (Table 5).

3.2.4.1. Active stressors. Cortisol, an HPA hormone, can be assessed by various means. In this review, salivary cortisol was assessed in six studies [30,33,37,47,56,57] and plasma cortisol was assessed in one [32]. Even though salivary and plasma cortisol is correlated [60], we have decided to present results as a function of sample type due to differences in the responses patterns observed.

In the one plasma cortisol study, a TSST-like stressor did not change cortisol levels [32]. For salivary cortisol, 4/6 studies [30,33,37,56] observed increases, 1/6 observed no changes, and the

IDENTIFICATION



Note: Reasons of exclusion during the screening: 1 = Non English or French; 2 = Animal study; 3 = Review; 4 = Intervention; 5 = Not an experimental study; 6 = Non-asthma population; 7 = No acute psychological stress induced in laboratory; 8 = No physiological responses measured. Reasons of exclusion during eligibility assessment: A = Not an experimental study; B = Non-asthma population; C = No acute psychological stress induced in laboratory; D = The comparator is not physiological measure at baseline or during pre-task period; E = The study did not assess physiological responses to acute stress in asthmatics.

Fig. 1. Flow of information through the different phases of the systematic review.

final study found that depressive mood moderated cortisol responses [57], with low depression being associated with no changes and high depression being associated with increases. Of note, all studies used the TSST.

3.2.5. Cardiovascular responses

Fourteen studies [14–16,21,23,24,30,34,35,48–50,52,53] assessed cardiovascular responses to psychological stress tasks in asthmatics (Table 6).

3.2.5.1. Passive stressors. Heart rate (HR) responses to passive stressors were found to remain unchanged [14,16,23]. The one study that assessed blood pressure (BP) found that systolic (SBP) and diastolic (DBP) were increased when the task induced negative

valence emotions [16].

3.2.5.2. Active stressors. As for active stressors, cardiovascular responses were quite consistent, as most studies reported an increase in HR and BP reactivity [14–16,23,30,35,48–50,52,53].

3.3. Risk of bias assessment

The Downs and Black score [43] ranged from 6 to 12 (mean [M] ± standard deviation [SD] = 8.9 ± 1.6, median = 9) (Table 1). Eleven of the 28 studies received a high score (≥10/13) [16,23,25,27,28,32,33,36,48,51,54]. Studies were generally well rated on the reporting (M ± SD = 6.2 ± 1.2, maximum = 8) and internal validity (M ± SD = 2.6 ± 0.6, maximum = 3) subscales.

Table 1
Characteristics of the studies.

First author (year)	Location	N of asthmatics	Age M(SD)	% Women	Asthma assessment	% Atopy	Type of stress tasks	D&B score
Aboussafy (2005) [15]	Canada	31	35.0 (2.8)	71.0	Methacholine Test		Active	8
Buske-Kirschbaum (2003) [30]	Germany	17	11.8 (1.9)	47.0	Physician Diagnosis	100.0	Active	8
Carr (1996) [21]	USA	61	24.9 (6.5)	51.0	Physician Diagnosis		Active & Passive	9
Chen (2010) [31]	Canada	38	15.0 (2.8)	32.0	Physician Diagnosis	55.0	Active	9
Clarke (1970) [22]	Australia	3			Physician Diagnosis		Passive	6
Clarke (1980) [46]	Australia	12		0.0	Not mentioned		Passive	9
		4			Methacholine Test		Passive	8
Eddington (2012) [47]	USA	30	20.0 (1.4)	60.0	Self-reported		Active	9
Feldman (2002) [23]	USA	88	25.9 (6.7)	60.2	Physician Diagnosis		Active & Passive	10
Florin (1985) [48]	Germany	18	9.8 (1.5)	38.9	Physician Diagnosis	83.3	Active	10
Hahn (1966) [49]	USA	20	10.5	0.0	Not mentioned		Active	8
Hahn (1967) [50]	USA	18	12.5	0.0	Not mentioned		Active & Passive	6
Hollaender (1983) [51]	Germany	14	10.3	35.7	Physician Diagnosis	78.6	Active	10
Kang (2000) [32]	USA	20	21.7 (2.8)	65.0	Physician Diagnosis		Active	11
Kelsay (2013) [33]	USA	48	18.0	54.0	Self-reported		Active	12
Lehrer (1996) [14]	USA	51	26.9 (6.6)	39.2	Physician Diagnosis		Active & Passive	9
Levenson (1979) [24]	USA	29		62.1	Self-reported		Passive	8
McQuaid (2000) [34]	USA	114	11.8	51.0	Physician Diagnosis		Active	9
Miklich (1973) [52]	USA	17	13.7	0.0	Not mentioned		Active	7
Miller (2009) [25]	USA	90	11.8 (2.7)	46.7	Physician Diagnosis		Passive	11
Rietveld (1998) [26]	Netherlands	40	12.2 (3.5)		Physician Diagnosis		Passive	9
Rietveld (1999) [35]	Netherlands	30	16.6 (1.5)	56.7	Physician Diagnosis		Active	9
Ringsberg (1999) [53]	Sweden	10		100.0	Methacholine Test		Active	6
Ritz (2000) [16]	UK	24	30.0	66.7	Not mentioned	87.5	Active & Passive	10
Ritz (2001) [27]	Germany	20	26.6 (3.9)	65.0	Self-reported	100.0	Passive	11
Ritz (2011) [28]	USA	15	40.1	73.3	Not mentioned	93.3	Passive	11
Ritz (2011) [37]	USA	20	20.6	55.0	Physician Diagnosis		Active	8
Ritz (2011) [36]	USA	20	20.6	55.0	Not mentioned		Active	11
Ritz (2014) [54]	USA	39	24.6 (10.1)	59.0	Self-reported		Active	10
Rosenkranz (2005) [55]	USA	6		50.0	History of asthma	100.0	Active	7
Rosenkranz (2016) [56]	USA	30	26.2 (6.0)	40.0	Physician Diagnosis	100.0	Active	9
Trueba (2012) [38]	USA	12	30.6 (13.7)	66.7	Physician Diagnosis		Active	9
Trueba (2016) [57]	USA	39	24.6 (10.1)	59.0	Physician Diagnosis		Active	6

Note: D&B, Downs and Black [43] (Maximal total score = 13).

However, external validity was generally poor ($M \pm SD = 0.1 \pm 0.3$, maximum = 2). Notably, information regarding the representativeness of the sample was not available in most of the studies (29/32).

4. Discussion

The purpose of this systematic review was to provide a synthesis of the impact of acute laboratory psychological stress on physiological responses in asthmatics. As hypothesised, this review of 32 studies found that active and passive stressors have a differential and specific impact on various physiological responses.

4.1. Physiological stress responses in asthmatics

4.1.1. Impact of active stressors

Findings suggest that active stressors activate the SNS and lead to withdrawal of PNS. The increase in HR and BP [14–16,23,30,35,48–50,52,53], skin conductance [14,16,49], catecholamines [32], and alpha amylase [56], and decrease in finger pulse amplitude [52], provide evidence for SNS activation. Active stressors, such as mental arithmetic task, are associated with a withdrawal of PNS, as suggested by the decreases in RSA [14,15].

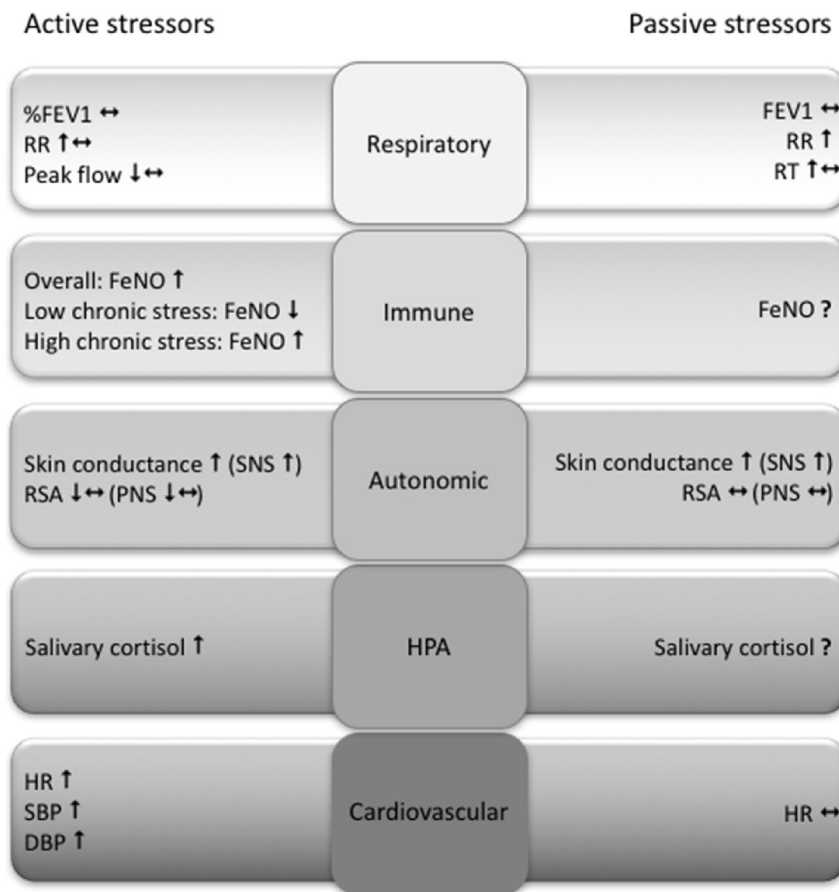
Although active stressors were associated with sympathetic activation, they did not seem to be associated with the expected concomitant bronchodilation, considering the little or no effect on peak flow [15,32,51,52], FEV₁, [48,55] or %FEV₁. [31,35] Active stressors were also found to have mixed effects on respiratory rate, with some studies showing an increase [14,35,53] and others showing no changes [37,49].

This review also indicates that active stressors seem to increase inflammation, with those living with high chronic stress having worse responses. Consistent increases in FeNO [37,54,56] were observed along with increases in other immune markers (i.e., leukocytes, cystatin S, light chain IgA, glutathione s-transferase, and eosinophils) [32,38]. However, this response may be modulated by chronic stress [31,56], such as low SES, due to its association with negative environmental and social conditions, e.g., crowding, crime, distress, etc. [61] Chen et al.'s study [31] found that low SES individuals had increased stress-induced inflammation compared to high SES individuals, a result similar to Rosenkranz et al.'s study [56].

Finally, the HPA-axis seems to be activated in response to active stressors. Four studies [30,33,37,56] reported increases in cortisol in response to the TSST and one study [57] found increases in cortisol only in depressive asthmatics, suggesting potential moderation by depression. Furthermore, Eddington et al. [47] reported no changes in cortisol level after a helplessness task, suggesting that cortisol maybe specifically influenced by social-evaluative threat [62].

4.1.2. Impact of passive stressors

Exposure to passive stressors was associated with SNS activation, as evidenced by changes in electrodermal activity [14–16,48]. However, no changes were found in cardiovascular responses, except for one study [16] reporting increased BP during the presentation of graphic medical slides. Furthermore, no changes were observed in parasympathetic responses [14,23,27]. In contrast, passive stressors seemed to induce mild bronchoconstriction (based on global increases in respiratory resistance [16,24,27,28] and in respiratory rate [14,16]).



Note: This summary of the physiological responses to active and passive stress tasks is based on the findings of at least two consistent studies. ↑, Increase; ↓, Decrease; ↔, No change; ?, not enough studies to infer the direction of the response; DBP, Diastolic blood pressure; FeNO, Fraction of exhaled nitric oxide; FEV₁, Forced expiratory volume in 1 second; %FEV₁, FEV₁ percent predicted; HPA, Hypothalamic-pituitary-adrenocortical; HR, Heart rate; PNS, Parasympathetic nervous system; RR, Respiratory rate; RSA, Respiratory sinus arrhythmia; RT, Respiratory resistance; SBP, Systolic blood pressure; SNS, Sympathetic nervous system.

Fig. 2. Summary of the main physiological responses to active and passive stressors.

Compared to active stressors, there were fewer studies assessing physiological responses to passive stressors. In addition, no data were found for immune and HPA responses to passive stressors, which underlines the importance of future studies on these physiological responses among asthmatics.

4.1.3. Summary and clinical implications

In sum, active and passive stressors seem to be associated with an increase in sympathetic activity. However, during active stressors, PNS activity seems to decrease; whereas, during passive stressors, it seems to remain unchanged. As for respiratory responses, active stressors seem to have very little effect, but passive stressors seem to induce mild bronchoconstriction. This suggests that active and passive stressors may lead to asthma exacerbations, but through different pathways. When confronted with an active stressor, changes in SNS and PNS activation may counterbalance each other and result in little immediate effects on airway caliber.

However, active stressors seem to increase immune activation (*i.e.*, leukocytes, inflammatory cells, and cortisol) which can make the airways more prone to swell (alone and in the presence of known triggers), and make asthmatics more vulnerable to exacerbations several hours after exposure active stress. Regarding passive stressors, they seem to trigger an immediate bronchoconstriction response, as evidenced by the various respiratory changes observed. However, it is still difficult to predict how this type of stressor affects asthmatics' airways during the secondary, inflammatory-driven phase of an exacerbation, because of the relatively little information we have on immune and HPA responses.

4.2. Methodological implications and recommendations

Although many studies have assessed the impact of laboratory acute stress on physiological responses in asthmatics,

Table 2
Respiratory responses.

First author (year)	Measurements	Active stressors	Active stressor findings	Passive stressors	Passive stressor findings
Aboussafy (2005) [15]	pre/post	Mental arithmetic Asthma crisis recall interview	Peak flow $\leftrightarrow^a$ Peak flow $\downarrow^a$		
Carr (1996) [21]	pre/during	Mental arithmetic Reaction time task	RR ^c , Respiratory amplitude ^c , Accident film Airway impedance ^c RR ^c , Respiratory amplitude ^c , Thoracic surgery film Airway impedance ^c		RR ^c , Respiratory amplitude ^c , Airway impedance ^c RR ^c , Respiratory amplitude ^c , Airway impedance ^c
Chen (2010) [31]	pre/post	Conflict discussion task	%FEV1 $\leftrightarrow$		
Clarke (1970) [22]	pre/post			Under hypnosis: Voluntary cough Under hypnosis: Asthma alone Under hypnosis: Fear and anger alone Under hypnosis: Fear, anger, cough and asthma	FEV1 $\leftrightarrow^a$ FEV1 $\downarrow^a$ FEV1 $\leftrightarrow^a$ FEV1 $\downarrow^a$
Clarke (1980) [46]	pre/during			Recall of an asthma attack Anger (under hypnosis /conscious) Fear (under hypnosis /conscious) Excitement (under hypnosis /conscious) Asthma (under hypnosis /conscious) Accident film	EV $\uparrow^a$ EV $\uparrow$ EV $\uparrow$ EV $\uparrow$ EV $\uparrow$ EV $\uparrow$ %FEV1 $\uparrow$, FVC $\uparrow$
Feldman (2002) [23]	pre/post	Reaction time task	%FEV1 $\uparrow$, FVC $\uparrow$		
Florin (1985) [48]	pre/post	Puzzle under time pressure	FEV1 $\downarrow$		
Hahn (1966) [49]	pre/post	Mental arithmetic, Mental arithmetic with presentation of numbers	RR $\leftrightarrow^a$		
Hahn (1967) [50]	pre/post	Mental arithmetic with neutral/positive comments Mental arithmetic with negative comments	RR ^{ae} RR ^{ae}	Tones	RR ^{ae}
Hollaender (1983) [51]	pre/during	Puzzle under time pressure and negative criticism	Peak flow $\downarrow^b$		
Kang (2000) [32]	pre/during	Speech task, Mental arithmetic	Peak flow $\leftrightarrow^a$		
Lehrer (1996) [14]	pre/during	Mental arithmetic, Reaction time task	RR $\uparrow$, Respiratory amplitude*, Airway impedance $\downarrow$	Accident film, Thoracic surgery film	RR $\uparrow$, Respiratory amplitude $\leftrightarrow$, Airway impedance $\leftrightarrow$
Levenson (1979) [24]	pre/during			Asthmatic children film, Industrial accident film Adoption film	RT $\uparrow$, Inspiratory and expiratory time?, I-E ration? RT $\leftrightarrow$, Inspiratory and expiratory time?, I-E ration?
McQuaid (2000) [34]	pre/during	Talk about a stressful incident	RT $\leftrightarrow^a$		
Miklich (1973) [52]	pre/post	Mental arithmetic	Peak flow $\leftrightarrow^a$, Duration of expiration $\downarrow^a$		
Miller (2009) [25]	pre/post			E.T. film (scary, sad, happy scenes)	FEV1 $\leftrightarrow^a$, RT $\leftrightarrow^a$
Rietveld (1998) [26]	pre/post			Emotional film (negative emotions)	%FEV1 $\leftrightarrow$
Rietveld (1999) [35]	RR, End tidal CO2: pre/during %FEV1, %FVC: pre/post	Computer task	RR $\uparrow$, End tidal CO2 $\leftrightarrow$, %FEV1 $\leftrightarrow$, %FVC $\leftrightarrow$		
Ringsberg (1999) [53]	pre/during	Word color conflict	RR $\uparrow^a$, PETCO ₂ ^{ab}		
Ritz (2000) [16]	pre/during	Mental arithmetic	RT $\uparrow^a$, RR?, Vt?		
Ritz (2001) [27]	pre/post			Emotional films (anxiety, anger, sadness, happiness, contentment) Medical slides Depressing pictures Depressing statements Happy pictures Happy statements Emotional films (unpleasant, neutral, pleasant, surgery, asthma)	RR $\uparrow$ (only for anger & elation) ^{ad} , RT $\uparrow$ (for all emotions) ^{ad} , Vt? RT $\uparrow^a$, RR?, Vt? RT $\uparrow$, Ventilation ^a RT $\uparrow$, Ventilation ^a RT $\leftrightarrow$, Ventilation ^a RT $\leftrightarrow$, Ventilation ^a RT $\uparrow$ (from baseline to neutral film) RT $\uparrow^d$ (surgery), RR $\uparrow^d$ (pleasant), Vt ^{cd} , End-tial PCO ₂ ^{cd} , Minute ventilation ^{cd}
Ritz (2011) [28]	RT: pre/during neutral condition All measures: during				
Ritz (2011) [37]	pre/post	Trier Social Stress Test	RR $\leftrightarrow^a$, EV $\leftrightarrow^a$, Inspiratory flow $\leftrightarrow^a$		
Ritz (2011) [36]	pre/post	Trier Social Stress Test	Minute ventilation $\uparrow$, Total respiratory		

(continued on next page)

Table 2 (continued)

First author (year)	Measurements	Active stressors	Active stressor findings	Passive stressors	Passive stressor findings
Rosenkranz (2005) [55] pre/post		Imaging task	cycle time ↑, Inspiratory time ↓, Expiratory time ↑, Vt ↑, Expiratory volume variability ↑ FEV1 ↔ ^a		
Rosenkranz (2016) [56] pre/post		Trier Social Stress Test	FEV1 ↑ ^a		

Note: EV, Expiratory volume; FEV1, Forced expiratory volume in 1 s; %FEV1, Forced expiratory volume in 1 s percent predicted; FVC, Forced vital capacity; %FVC, Forced vital capacity percent predicted; I-E ration, Ratio of inspiratory to expiratory period; PETCO₂, End tidal PCO₂; RR, Respiratory rate; RT, Respiratory resistance; Vt, Tidal volume. ↑, Increase; ↓, Decrease; ↔, No change; ?, Noted as a measure in the procedure, but no results were reported for stress tasks; **a**, No mean and/or standard deviation were reported in the Results section; **b**, No comparative statistics were reported in the Results section (are not mentioning if significant or not); **c**, Significant main effect for tasks, but no information regarding the significance of the specific effects and/or the direction of the effects of acute stress tasks compared to baseline; **d**, Comparator is not the baseline or a pre-task period; **e**, No information regarding the specific effects of acute stress tasks compared to baseline; *, Results are mixed, subanalyses are presented in the paper.

inconsistencies remain. Methodological factors, such as the timing the assessments, the choice of comparison group or assessment point, the variety of acute stress tasks used, the reliability of the asthma diagnoses, and the variable withdrawal of asthma medication prior to testing, may all have potentially influenced the findings. This section aims to address these factors and make recommendations for future studies.

4.2.1. Timing of the stress response assessments and the use of comparators

Large discrepancies were observed in the timing of the assessment of stress responses across studies. Studies assessed responses pre, during, and/or post (duration range: 0–60-min) stress task. For the pre assessment period, some studies took baseline assessments, whilst others assessed “pre-test” responses just prior to the stress task without letting participants get habituated to their environment. Finally, some compared stress responses to a neutral task rather than resting values. Determining the best time to assess physiological responses to stress in asthmatics can be quite challenging considering the bimodal nature of the asthma response, *i.e.*, immediate bronchoconstriction followed by longer-term airway inflammation [1]. In order to assess the more immediate response to stressors, continuous measures throughout stress tasks should be prioritized for autonomic, catecholamine, respiratory, and cardiovascular responses. If this is not possible, measurements should

be taken as soon as possible after the end of the task. In fact, studies looking at airway recovery responses have shown that in the first minute following the end of the task, airway constriction levels are already much less than they were during the task [28,63]. As for immune and HPA responses, they are believed to have impact on airways several minutes to hours after stress exposure [64]. For such markers, assessments should be conducted to coincide with their peak time [65], *e.g.*, for cortisol, the peak response generally occurs 30–60 min after stress exposure [66] which should be used as the window for measurement. Also, to measure the true impact of acute stress on physiological responses, an appropriate duration of “resting” baseline measures should be assessed. These measures should be taken in a temperature and noise controlled environment [67] after the removal of all or most external stimuli, *e.g.*, no music, book, films, pictured presented to them [67]. This should also allow participants to adjust to the task environment and apparatus.

4.2.2. Acute stress tasks and manipulation checks

The large variety of stress tasks used in the literature is advantageous as it helps us understand similarities and differences in the physiological responses across different stressors. However, some studies have used stress tasks that have both passive and active components. This makes it difficult to disentangle what responses are due to their respective active and passive components. In addition, the valence and intensity of emotions elicited varied

Table 3
Immune responses.

First author (year)	Measurements	Active stressors	Active stressor findings	Passive stressors	Passive stressor findings
Chen (2010) [31]	pre/post	Conflict discussion task	Overall: FeNO ↓ ^b Low family SES: FeNO ↑ ^{ab} High family SES: FeNO ↓ ^{ab}		
Kang (2000) [32]	pre/post	Speech task, Mental arithmetic	Total leukocytes ↑ ^a , Lymphocytes (no ↑ ^a & % ↑ ^a), Neutrophils (no ^c & % ^c), IgE?		
Ritz (2011) [37]	pre/post	Trier Social Stress Test	FeNO ↑ ^a		
Ritz (2014) [54]	pre/post	Trier Social Stress Test	FeNO ↑		
Rosenkranz (2005) [55]	TNF-α: pre/during EOS: pre/post	Imaging task	TNF-α ↓ ^{ab} EOS ↔ ^a		
Rosenkranz (2016) [56]	pre/post	Trier Social Stress Test	Low chronic stress: FeNO ↓ ^a High chronic stress: FeNO ↑ ^a EOS ↑ ^a		
Trueba (2012) [38]	pre/post	Trier Social Stress Test	Cystatin S ↑ ^a , Light chain IgA ↑ ^a , Glutathione S-Transferase ↑ ^a , FeNO?		

Note: EOS, Eosinophil; IgE, Immunoglobulin E; FeNO, Fraction of exhaled nitric oxide; no, Number; %, Percentage; SES, socioeconomic status; TNF-α, tumor necrosis factor alpha.

↑, Increase; ↓, Decrease; ↔, No change; ?, Noted as a measure in the procedure, but no results were reported for stress tasks; **a**, No mean and/or standard deviation were reported in the Results section; **b**, No comparative statistics were reported in the Results section (are not mentioning if significant or not); **c**, Significant time effect, but no information regarding the specific effects of acute stress tasks compared to baseline.

Table 4
Autonomic responses.

First author (year)	Measurements	Active stressors	Active stressor findings	Passive stressors	Passive stressor findings
Aboussafy (2005) [15]	pre/during	Mental arithmetic Asthma crisis recall interview	RSA ↓ ^a , Skin conductance ? RSA ↔ ^a , Skin conductance ?		
Feldman (2002) [23]	pre/during	Reaction time task	Skin conductance ↑, RSA ↔ ^a	Accident film	Skin conductance ↑, RSA ↔ ^a
Hahn (1966) [49]	pre/post	Mental arithmetic, Mental arithmetic with presentation of numbers	Skin conductance ↑ ^b		
Hahn (1967) [50]	Skin temperature: pre/post Skin conduction: pre/during	Mental arithmetic with neutral/positive comments Mental arithmetic with negative comments	Skin resistance ^{af} , Skin temperature ^{af} , Skin resistance ^{af} , Skin temperature ^{af}	Tones	Skin resistance ^{af} , Skin temperature ^{af}
Kang (2000) [32]	pre/post	Speech task, Mental arithmetic	EPI ↑ ^a , NE ↑		
Lehrer (1996) [14]	pre/during	Mental arithmetic, Reaction time task	Skin conductance ↑, RSA ↓ ^a	Accident film, Thoracic surgery film	Skin conductance ↑, RSA ↔ ^a
McQuaid (2000) [34]	pre/during	Talk about a stressful incident	Skin conductance ^{ae} , Skin temperature ^{ae}		
Miller (2009) [25]	during			E.T. film (scary, sad, happy scenes)	RSA ^f , PEP ^f
Ritz (2000) [16]	pre/during	Mental arithmetic	Skin conductance ↑ ^a	Emotional films (anxiety, anger, sadness, happiness, contentment) Medical slides Depressing pictures Depressing statements Happy pictures Happy statements	Skin conductance ↑ ^{acd} Skin conductance ↑ ^a RSA ↔ ^a RSA ↔ ^a RSA ↔ ^a RSA ↔ ^a
Ritz (2001) [27]	pre/post				
Rosenkranz (2016) [56]	pre/during	Trier Social Stress Test	Alpha amylase ↑ ^{ab}		

Note: EPI, Epinephrine; NE, Norepinephrine; PEP, Pre-ejection period; RSA, Respiratory sinus arrhythmia.

↑, Increase; ↓, Decrease; ↔, No change; ?, Noted as a measure in the procedure, but no results reported stress tasks; **a**, No mean and/or standard deviation were reported in the Results section; **b**, No comparative statistics reported in the Results section (are not mentioning if significant or not); **c**, Significant main effect for tasks, but no information regarding the specific effects of acute stress tasks compared to baseline; **d**, Comparator is not the baseline or a pre-task period; **e**, No information regarding the specific effects of acute stress tasks compared to baseline in asthmatics; **f**, No information regarding the specific effects of acute stress tasks compared to baseline.

Table 5
Hypothalamic-pituitary-adrenocortical responses.

First author (year)	Measurements	Active stressors	Active stressor findings	Passive stressors	Passive stressor findings
Buske-Kirschbaum (2003) [30]	pre/post	Trier Social Stress Test - Children	Saliva cortisol ↑ ^a		
Eddington (2012) [47]	pre/post	Helplessness task	Saliva cortisol ↔ ^a		
Kang (2000) [32]	pre/post	Speech task, Mental arithmetic	Plasma cortisol ↔ ^a		
Kelsay (2013) [33]	pre/post	Trier Social Stress Test-children	Saliva cortisol ↑		
Ritz (2011) [37]	pre/post	Trier Social Stress Test	Saliva cortisol ↑ ^a		
Rosenkranz (2016) [56]	pre/during & pre/post	Trier Social Stress Test	Saliva cortisol ↑ ^a		
Trueba (2016) [57]	pre/post	Trier Social Stress Test	Low depressive: ↔ ^a High depressive: ↑ ^a		

Note: ↑, Increase; ↔, No change; **a**, No mean and/or standard deviation were reported in the Results section.

greatly across stress tasks, which may have effect physiological responses. For example, some stress tasks induced disgust, anger, or fear [14,16,25,27,28], and others induced helplessness [47] and social anxiety [32,36,37]. In order to better understand these relationships, participants' emotional states should be systematically assessed (which was not the case in this review, where only 18/32 studies reported such data). The Self-Assessment Manikin [68], which is a non-verbal pictorial assessment technique that measures the person's affective level of pleasure, arousal, and dominance associated to a stimuli, or a Visual Analogue Scale are some quick tools that can effectively evaluate emotional states.

4.2.3. Asthma assessment

There was great variability in asthma diagnoses criteria, with studies tending to rely on one of the following: positive

methacholine challenge, physician confirmed diagnosis, reported history of asthma, or self-reported current asthma. It is recommended that researchers use the American Thoracic Society guidelines [69], or equivalent national guidelines, to determine the presence of asthma. Failing to use such guidelines is likely to generate selection bias with a high probability of including patients without asthma [70]. In addition, asthma control should be reported using standard tools, e.g., the Asthma Control Questionnaire [71], since poorly controlled asthma is associated with poorly controlled inflammation, symptom exacerbations, impaired pulmonary function, and increased bronchodilator use [1], all of which may confound stress response measures.

4.2.4. Medication cessation prior to testing

Only 50% of the included studies reported the details of

Table 6
Cardiovascular measures.

First author (year)	Measurements	Active stressors	Active stressor findings	Passive stressors	Passive stressor findings
Aboussafy (2005) [15]	pre/during	Mental arithmetic	HR ↑ ^{ab} , DBP ↑ ^{ab}		
Buske-Kirschbaum (2003) [30]	pre/during	Asthma crisis recall interview Trier Social Stress Test - Children	HR ↑ ^a , DBP ↑ ^a HR ↑ ^a		
Carr (1996) [21]	pre/during	Mental arithmetic Reaction time task	HR ^c HR ^c	Accident film Thoracic surgery film	HR ^c HR ^c
Feldman (2002) [23]	pre/during	Reaction time task	HR ↑	Accident film	HR ↔
Florin (1985) [48]	pre/during	Puzzle under time pressure	HR ↑		
Hahn (1966) [49]	pre/during	Mental arithmetic, Mental arithmetic with presentation of numbers	HR ↑ ^{ab}		
Hahn (1967) [50]	pre/during	Mental arithmetic with neutral/positive comments Mental arithmetic with negative comments	HR ^{ae} HR ↑ ^a	Tones	HR ^{ae}
Lehrer (1996) [14]	pre/during	Mental arithmetic, Reaction time task	HR ↑	Accident film, Thoracic surgery film	HR ↔
Levenson (1979) [24]	pre/during			Asthmatic children film, Industrial accident film, Adoption film	IBI ↔
McQuaid (2000) [34]	pre/during	Talk about a stressful incident	HR ↔ ^a		
Miklich (1973) [52]	pre/during	Mental arithmetic	HR ↑, FPA ↓		
Rietveld (1999) [35]	pre/during	Computer task	HR ↑, SBP ↑, DBP ↑		
Ringsberg (1999) [53]	pre/during	Word color conflict test	HR ↑ ^a , SBP ↑ ^a , DBP ↑ ^a		
Ritz (2000) [16]	pre/during	Mental arithmetic	HR ↑ ^a , SBP ↑ ^a , DBP ↑ ^a , BRSd ↓ ^a , BRSu ↓ ^a	Emotional films (anxiety, anger, sadness, happiness, contentment) Medical slides	HR ^{acd} , SBP?, DBP?, BRSd?, BRSu? HR ↔ ^a , SBP ↑ ^a , DBP ↑ ^a , BRSd ↔ ^a , BRSu ↔ ^a

Note: BRSd, Baroreflex sensitivity down sequence; BRSu, Baroreflex sensitivity up sequence; DBP, Diastolic blood pressure; FPA, Finger pulse amplitude; HR, Heart rate; IBI, Interbeat interval; SBP, Systolic blood pressure.

↑, Increase; ↓, Decrease; ↔, No change; ?, Noted as a measure in the procedure, but no results were reported for stress tasks; **a**, No mean and/or standard deviation were reported in the Results section; **b**, No comparative statistics were reported in the Results section (are not mentioning if significant or not); **c**, Significant main effect for tasks, but no information regarding the specific effects of acute stress task compared to baseline; **d**, Comparator is not the baseline or a pre-task period; **e**, No information regarding the specific effects of acute stress tasks compared to baseline.

medication cessation prior to testing, with an additional 4/32 mentioning that participants were asked not to take medication on the day of the testing, but failed to indicate the duration of cessation. The decision to temporarily withdraw medication needs to reflect the goals of the study. If the aim is to understand the physiological mechanisms by which acute stress may influence asthmatics, then it is important to have a standard and safe medication cessation protocol. For example, the minimal time interval from last dose to study should be 8 h for short-acting inhaled bronchodilators and 48 h for long active bronchodilators [72]. In contrast, if the aim of the study is to assess the impact of stress responses on asthma in everyday life, letting participants follow their regular asthma medication regimen would be appropriate and have more external validity since findings should be more generalizable to daily life. Either way, monitoring and reporting of medication taking (and withdrawal) prior to testing is critically important.

4.3. Limitations and strengths of the present review

There are several limitations that warrant consideration. First, although the number of studies in this review was relatively high, the external validity of the studies was quite poor, primarily due to the variability in asthma diagnoses. In contrast, the internal validity and reporting of general participant characteristics were generally good. Second, research protocols were not always well described. It is therefore possible that some excluded studies were inaccurately

identified as ineligible. Finally, some authors were unable to be contacted. As such, there was some missing details for certain studies, which limited our ability to interpret the data. Despite these limitations, this review has a number of important strengths. First, to our knowledge, this is the first systematic review to specifically examine the impact of laboratory-based acute psychological stress on physiological responses in asthmatics. Second, this review examined a range of relevant physiological responses to stress including respiratory, cardiovascular, immune, autonomic, and HPA responses, to both active and passive stressors which allows to draw conclusions about the distinct pathways by which stress might affect asthma.

5. Conclusion

To conclude, considering the wide variety in stress tasks used and the notable methodological issues, further studies are needed to better understand the impact of acute psychological stress on the physiological mechanisms associated with asthma.

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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.2017.03.024>.

Competing interests

Dr Lavoie has served on the advisory board for Schering-Plough, Takeda, AbbVie, Almirall, Janssen, and Boehringer Ingelheim (BI), and received sponsorship for investigator-generated research grants from GlaxoSmithKline (GSK) and AbbVie, lecture fees from GSK, Astra-Zeneca, Novartis, Takeda, AbbVie, Merck, AstraZeneca, BI, Bayer, Pfizer and Air Liquide, and support for educational materials from Merck and Kataka Medical Communication. Dr Bacon has received consultancy fees from Kataka Medical Communication and Merck for the development of behaviour change continuing education modules and speaker fees from Novartis.

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Supplement A

Data search strategies presented by database

PubMed

asthma[MeSH Terms] **AND** stress, psychological[MeSH Terms] **OR** acute stress[Title/Abstract]
OR coping stress*[Title/Abstract]

PsycINFO and PsycArticles

Write down “asthma” as the first keyword and choose “abstract”. Write down “stress*” as the second keyword and choose “abstract”.

The Cochrane Library

Choose “Title, Abstracts, Keywords” and write down “asthma” as the first keyword. Choose “Title, Abstracts, Keywords” and write down “stress*” as the second keyword.

Supplement B

A total of 27 articles were eliminated for the following reasons: four were not laboratory experimental studies [1–4]; four did not include asthmatics [5–8]; one only included bronchial asthmatics in remission [9]; two assessed the impact of non-laboratory (ambulatory) acute stress [10,11]; 14 did not assess physiological responses at baseline or pre-task [12–25]; and the two remaining articles did not assess physiological responses to acute stress in asthmatics (one study assessed the impact of psychological stress combined with exposure to allergen – so we were unable to isolate the effect of psychological stress from the allergen [26], and one study evaluated the concordance of two self-report methods of operationalizing repressive-defensive style in children with asthma during a stress task [27]).

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Supplement C

Description of the active and passive stress tasks

Task	Description and examples
Active tasks	
Mental arithmetic	Perform a series of additions or subtractions. <i>Examples:</i> • Presentation of one- and two-digit addition and subtraction problems on a computer screen at an increasingly rapid pace. Answers are given on a piece of paper. • Additions of as many one- and two-digit numbers as possible during a 3-minute period. • Solving arithmetic problems mentally while random numbers are presented.
Reaction time	Respond as quickly as possible to a particular stimulus when it is presented. <i>Examples:</i> • Forty fixed-foreperiod trials of 6-second duration, with 10-second interstimulus intervals are presented. The foreperiod stimulus is a numerical countdown from 6, by seconds, displayed on a computer screen. In place of "0," a series of asterisks are presented, signaling the participant to press a button with the dominant hand as quickly as possible.
Puzzle under pressure time	Put together a puzzle under time pressure while a playmate is given negative criticisms. The puzzle is placed behind a screen so it can only be seen in a mirror.
Speech task	Prepare a speech in a relatively short amount of time. The speech is recorded and evaluated by judges or evaluated live by a judges. <i>Examples of speech themes:</i> Job interview, being falsely accused of shoplifting, etc.
Talk about a stressful or asthma-related incident	Talk into a tape recorder about a stressful or embarrassing incident, in the presence of an experimenter. Prompts are given if the story finishes before the time is up. <i>Note:</i> Although the Aboussafy et al.'s [1] task called "Asthma crisis recall interview" was considered by the authors as a passive stressor, it was considered an active task in the present review. Since participants had to recall an upsetting asthma-related incident while breathing through a drinking straw, and then describe the incident, we believe that participants were able in this task to use coping strategies.
Conflict discussion task	Discuss a disagreement topic with family members for a predetermined period of time and try to reach a resolution.
Computer task	Undergo a computer game designed to be extremely difficult and stressful.
World color conflict test and Imaging task	Four color words (red, blue, green, yellow) are printed in different colors, the combination of word and color being incongruous. The goal is to name the color of the print as fast and accurately as possible. Similarly, in the imaging task, words of various category (<i>e.g.</i> asthma related, negative, neutral words) are presented in different colors. The goal is to identify the color of each word, while reaction time and accuracy are recorded.
Trier Social Stress Test	Includes a free speech and a mental arithmetic task, both under evaluative threat. A predetermined time is given to prepare the speech. The mental arithmetic task consists of continuous subtraction problems.
Helplessness task	Resolve problems on a computer. One group receives positive feedback from the computer screen in order to successfully complete the task (control condition), and the other group receives random, negative feedback, which prevent successful completion of the task (experimental condition). From the beginning, both groups are led to believe that the task is solvable. After the computer task, research assistants verbally comment participant's performance with similar positive feedback or random, negative feedback (depending on the experimental condition).

Passive tasks	
Emotional films	Presentations of films or sequences of a film to induce various emotions. <i>Examples:</i> Shop accident film, thoracic surgery film, scary and sad scenes from E.T. movie, film that portrays asthmatic children in a hospital setting, etc.
Emotional pictures	Presentations of series of pictures to induce various emotions. <i>Examples:</i> • Medical slides from the International Affective Picture System showing injuries, mutilation, and corpses or other unpleasant pictures • Sometimes, participants are asked to imagine the pictures after their offset for a certain period of time.
Emotional statements	Read statements presented on a screen for the whole duration of presentation, and after stimulus offset, to imagine being in a situation using the self-referent statement for a certain period of time.
Emotions induced under hypnosis	Inducing suggested emotional states under hypnosis. <i>Example:</i> Suggested emotional states (anger, fear, excitement, having an asthma attack) last two minutes, with a 5 min of suggested relaxation between each suggested emotion.
Tones	Presentations of auditory stimuli tones at 1000 centipoises and approximately 65 decibels
Recalling an asthma attack	Recall an asthma attack for a certain period of time. Suggestions of actual asthma symptoms sensations are given during that time.

Reference: 1. Aboussafy D, Campbell TS, Lavoie K, *et al.* Airflow and autonomic responses to stress and relaxation in asthma: The impact of stressor type. *Int J Psychophysiol* 2005;**57**:195–201. doi:10.1016/j.ijpsycho.2005.02.004