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Asthma and odors: The role of risk perception in asthma exacerbation

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Abstract

Objective—Fragrances and strong odors have been characterized as putative triggers that may exacerbate asthma symptoms and many asthmatics readily avoid odors and fragranced products. However, the mechanism by which exposure to pure, non-irritating odorants can elicit an adverse reaction in asthmatic patients is still unclear and may involve both physiological and psychological processes. The aim of this study was to investigate how beliefs about an odors relationship to asthmatic symptoms could affect the physiological and psychological ‘responses of asthmatics.

Methods—Asthmatics classified as ‘moderate-persistent’, according to NIH criteria, were exposed for 15 mi to a fragrance which was described either as eliciting or alleviating asthma symptoms. During exposure, participants were asked to rate odor intensity, perceived irritation and subjective annoyance while physiological parameters such as electrocardiogram, respiratory rate, and end tidal carbon dioxide (etCO₂) were recorded. Before, immediately after, and at 2 and 24 h post-exposure, participants were required to subjectively assess their asthma symptom status using a standardized questionnaire. We also measured asthma status at each of those time points using objective parameters of broncho-constriction (spirometry) and measures of airway inflammation (exhaled nitric oxide, FeNO).

Results—Predictably, manipulations of perceived risk altered both the quality ratings of the fragrance as well as the reported levels of asthma symptoms. Perceived risk also modulated the inflammatory airway response.

Conclusions—Expectations elicited by smelling a perceived harmful odor may affect airway physiology and impact asthma exacerbations.

Keywords

Asthma; Odors; Fragrances; Risk perception; Exhaled nitric oxide; Nocebo effect

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Conflict of interest

All authors have completed the Unified Competing Interest form and declare that all authors have no competing interest to report.

Introduction

Asthma, a chronic inflammatory disorder of the respiratory tract, affects approximately 17 million Americans. Asthma poses significant challenges to an individual's quality of life, results in lost productivity due to work or school absences and imposes significant financial burdens from chronic medical care. Epidemiologic studies frequently associate exposures to airborne chemicals with asthma exacerbations [1], yet, controlled studies to determine the doses that may trigger symptoms or the mechanisms underlying those symptoms often fail to support the epidemiology [2]. Based on a paucity of data, guidelines for residential and occupational exposures to airborne chemicals are often set or adjusted even though little scientific evidence is available to determine whether such adjustments are adequately protective or necessary.

Many asthmatics report airway symptoms upon exposure to fragrances and odorants, however, the mechanisms underlying these adverse responses are likely to be varied and may involve both physiological and psychological processes. Interestingly, many odor-averse asthmatics identify a subset of odors which do not cause them to perceive symptoms or concern (unpublished data from focus groups & [3]). Because the airways are under the control of the autonomic nervous system (ANS), activation of the ANS or variation in autonomic regulation may contribute to or amplify the bronchoconstriction that asthmatics experience when an attack is triggered [4]. This may in part be due to the fact that people with asthma commonly express concerns about the possible impact of airborne chemical exposures on their health, and these concerns escalate when airborne emissions are odorous.

Most odorants at sufficiently high concentrations can activate two different sensory systems in the nose: the olfactory system (via Cranial Nerve I) and the trigeminal system (via Cranial Nerve V) [5]. Cranial nerve I is the olfactory nerve that provides neural information from odorant receptors. Cranial nerve V is the trigeminal nerve, an unmyelinated free nerve distributed throughout the nasal, ocular and oral mucosa that responds to irritant vapors and leads to chemesthetic irritant sensations such as burning, tingling, prickling, and cooling. Trigeminal stimulation from volatile chemicals can give rise to the release of neuropeptide mediators such as substance P (SP) and calcitonin-gene-related peptides. The release of these neuropeptides can affect a variety of physiological functions including respiration, vasodilation and glandular secretions in the airways and can potentially trigger the onset of asthma symptoms [6]. For this reason, when studying the role of fragrance perception among asthmatics, it is critically important to evaluate whether the stimulus is capable of activating trigeminal fibers in the respiratory system in order to separate trigeminally-induced adverse responses from those induced merely by the perception of an odor.

Chen and Miller [7] have formally considered the role of psychological variables such as health beliefs or expectations in their model of stress induced asthma exacerbation (Fig. 1). The model posits that perception of an odor deemed potentially harmful can initiate cognitive and emotional events which, for an asthmatic, can culminate in the interpretation and appraisal of an uncontrolled health threat. The emotional state induced by threat perception can affect biological pathways initiating a cascade of events, which can lead to changes in smooth muscle tone (bronchoconstriction), airway inflammation and increases in

airway sensitivity to inhaled agents. In short, a threat can stimulate both arms of the autonomic nervous system (ANS): the sympathetic and the parasympathetic branches. It will also stimulate the hypothalamic–pituitary–adrenal (HPA) cortex and the sympathetic–adrenal–medullary axes (SAM). Bronchoconstriction may occur by the activation of the parasympathetic system [8,9], while inflammation will be regulated among other things through the interplay of the different hormones such as cortisol, epinephrine, norepinephrine and their effects in the immune system [7,9–11].

Despite numerous claims to the contrary, many experimental chamber studies to evaluate odorous asthma triggers fail to substantiate the epidemiological or anecdotal evidence [2]. In addition, the number and quality of the studies investigating the role of odorous chemicals in triggering respiratory symptoms in asthmatics are often low. Shim and Williams [12] examined the effect of cologne and a saline placebo challenge on the expiratory volume of four patients with self-reported sensitivity to cologne. They reported an approximate decline from base-line in Forced Expiratory Volume in one second (FEV₁) of 18–58% during the 10-minute challenge period, but during the next 20 min, the FEV₁ gradually increased. The authors could not discard a psychological component involved in the response to the cologne, since the study was not blinded to the participants. Kumar et al. [13] studied the effects of exposure to commercial perfume-scented strips on 29 asthmatic and 13 non-asthmatic control adults. They reported significant declines of FEV₁ in asthmatic subjects when compared to controls, but no significant decline was observed after the saline (placebo) challenge in the asthmatic subjects. The percent decline in FEV₁ was greatest in severe asthmatics (15–20%) as compared to those with moderate (~11%) and mild asthma (~3–6%). In 1996, a study by Millqvist and Lowhagen [14] examined 9 non-smoking patients reporting respiratory symptoms following exposure to stimuli such as cigarette smoke, house paint, flower scents and perfumes. Each patient underwent a single-blind 30-minute provocation test with a musk-like perfume or saline (placebo) in a special exposure chamber and was asked to record respiratory and sensory symptoms. In almost all cases, patients evaluated the total strength of reaction to the perfume stronger than the saline. This was true whether or not a carbon filter face mask was worn. Participants wore a nasal clamp to eliminate odor cues, and breathed through the mouth and through a facial mask, which sometimes contained a carbon filter.

Furthermore, the mean symptom score in the perfume condition increased throughout the 30-minute provocation period. The authors concluded that symptoms suggestive of respiratory hyperreactivity and asthma could be provoked by perfume in the absence of bronchial obstruction. The authors reasoned that odor cues did not contribute as the subjects wore nasal clips throughout the exposure.

Following a review of these studies, the Institute of Medicine (2000) [15] concluded that it is difficult to draw conclusions regarding the direct role of chemical odors/fragrances in eliciting respiratory symptoms or asthma because many studies fail to control for the possible influence of odor perception among individuals reporting odor sensitivity. Those studies that did attempt to control for odor provide limited or only suggestive evidence of an association between exposure to certain fragrances and the manifestation of respiratory symptoms in asthmatics reportedly sensitive to such exposures. Moreover, the use of nose

clips as a control for odor cues, forces subjects to breathe orally and expose their lungs in ways that normal oro-nasal breathing would not. It should also be noted that none of the studies to date have evaluated whether any exposure fragrances were at levels capable of eliciting airway irritation via stimulation of trigeminal free-nerve endings. For example, many commercial perfumes are ethanol-based, so any inflammatory effects in the respiratory system could be subsequent to trigeminal activation from ethanol.

Thus, the pathophysiologic mechanisms of odor-induced asthma remain to be elucidated, but may include some or all of the following: (1) immunological reactions with a secondary chemical mediator release or neural reflex, (2) direct irritant effects on the trigeminal somatosensory system, mediated by transient receptor potential channels (TRP) [16], in the upper or lower airways, or (3) psychologically-mediated reactions stemming from prior beliefs, expectations or conditioned responses.

It is now generally accepted that asthma is a chronic multifactorial disease with acute episodes that may be precipitated by a complex interplay of psychological, immunological and physiological factors [9]. In parallel with the increased prevalence of asthma, research in the last two decades has continued to support the existence of significant interactions between the behavioral, neural endocrine and immune systems that allow psychosocial stressors to influence the expression of inflammatory disease [17,18]. Asthmatics often appear to be more worried or anxious than non-asthmatic subjects [19], perhaps due to concerns about triggers in their environment. It is well known that stress tends to exacerbate asthma episodes [20,21], and although the mechanisms by which this happens are still not clear, stress could exacerbate asthma episodes not only by modulation of the immune response of the host, but also through modulation of microbial pathogens [11]. A recent report found that high levels of anxiety measured via personality questionnaires were present in 70% of the 195 asthmatic subjects surveyed, and were associated with worse subjective asthma outcomes [22].

To test the hypothesis that harmful/negative expectations could amplify asthmatic symptoms, we utilized the Chen and Miller model to evaluate whether airway symptoms following exposure to a pure odorant (i.e., one stimulating the olfactory system via Cranial Nerve I) but not the trigeminal system (via Cranial Nerve V) [5] could be modified through the manipulation of health beliefs. We hypothesized that exposing asthmatics to a pure olfactory stimulus when the odor was perceived as potentially 'harmful' would exacerbate symptoms relative to a condition when it was perceived as benign or even therapeutic (i.e., a 'nocebo' effect [23]). Accordingly, we exposed two groups of asthmatics to a non-irritating compound (phenylethyl alcohol) which was either characterized as 'therapeutic' (healthy condition) or 'asthmogenic', (harmful condition). This odorant was specifically chosen because it is one of the few pure olfactory stimuli that do not activate the trigeminal system at airborne concentrations. Thus, we reasoned that any symptoms or physiological changes observed that were associated with the perception of hazard or health from an odor would not be confounded by co-activation of the trigeminal system.

Methods

The study reported here was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants provided informed consent using a form that was approved by the University of Pennsylvania Institutional Review Board.

Participants

Participants were recruited through advertisements in the Philadelphia area and through referrals from asthma clinics. Exclusion criteria included a history of heart/cardiovascular disease, anosmia, respiratory problems except for asthma, and a FEV₁ that fell outside of the predicted value for moderate asthmatics according to the NIH classification of asthma. Moderate asthmatic subjects' lung function, as measured by FEV₁, is roughly between 60–80% of normal function.

We recruited and screened a total of 34 potential participants, however, only 17 (50%) of them were characterized as moderate asthmatics and therefore included in our study. From our excluded subjects, eleven (32%) were classified as mild asthmatics with an FEV₁ higher than 80%, and six (18%) were classified as severe asthmatics with an FEV₁ lower than 60%.

Nine subjects were assigned to the “therapeutic” group (age range 39.11 ± 11.85 , 4 females) and eight subjects to the “asthmogenic” group (age range 37.88 ± 13.26 , 4 females). We assigned participants to each group attempting to match the groups on relevant variables such as gender, age and duration of asthma. Some demographic information about our study participants, including their smoking status, medication history and fragrance use is shown in Table 1.

Odor stimulus

Many odorants used in olfactory research at high concentrations also elicit responses through the trigeminal system, producing an irritant sensation and affecting the response of the respiratory system. Phenyl ethyl alcohol (PEA), considered a ‘pure odorant’ in that it does not activate the trigeminal system in airborne concentrations [24], was either labeled as “therapeutic” or “asthmogenic” and presented to all participants. PEA is characterized as a “rose odor”, and is normatively considered to be pleasant. Air was odorized by passing it over the surface of a vessel containing undiluted liquid (neat) PEA. The odor stimuli were delivered via an olfactometer into one nostril through a Teflon nosepiece coupled to a nasal cannula. The flow rate of the odorized air was at 0.5 L/m and the odorant was presented for 10 s per minute over a period of 15 min. The intermittent exposure was intended to reduce the potential for odor adaptation.

Sensory measures

During each odor presentation interval (15 × 1 min intervals) participants were asked to rate the odor on multiple dimensions, including the perceived intensity, irritancy and annoyance using the general Labeled Magnitude Scale (gLMS) scale [25].

Physiological measures

End-tidal carbon-dioxide and respiratory rate—End-tidal CO₂ (etCO₂) and respiratory rate data were acquired with the Ohmeda 5200 CO₂ monitor (ACE Medical Equipment, Largo, Florida, US) and analyzed with WinDaqPro software (DATAQ Instruments, Akron, Ohio, US) continuously throughout the baseline and odor exposure (see Fig. 2). By measuring etCO₂ in exhaled breath via one nostril using a cannula, we were able to obtain an objective measure of hyper-ventilation, stress and anxiety levels [26,27] in addition to the more traditional subjective reports obtained via questionnaire.

Heart rate variability (HRV)—HRV refers to the beat-to-beat alterations in heart rate which when quantified, provide a useful and non-invasive tool for assessing autonomic, and especially vagal function, in different physiological and pathophysiological conditions. Cardiodynamic activity was continuously recorded during baseline and odor exposure (see Fig. 2) using an electrocardiogram (ECG) via a MP36 BIOPAC physiological monitoring system (Biopac Systems Inc., Goleta, California, US) set to collect frequencies between 0.5 and 35 Hz. The ECG leads were sampled at a continuous 180 samples per second (digitizing rate). All recordings were visually examined and manually over-edited to verify beat classification. HRV analysis was performed using the Kubios HRV Version 2.0 software (University of Kuopio, Kuopio, Finland) in accordance with the standards of measurement, physiological interpretation, and clinical use of HRV [28].

Measurement of pulmonary function—Pulmonary function changes were evaluated at baseline and at multiple time points post-stress using a KoKo Legend Spirometer (nSpire Health, Inc, Longmont, CO, US), which complies with the American Thoracic Society (ATS) performance status guidelines 1994 [29]. Spirometry, particularly decreases in FEV₁, remains the gold standard for indexing changes in pulmonary function that signal bronchoconstriction. Spirometric reference values were obtained from the third National Health and Nutrition Examination Survey (NHANES III) [30].

Measurement of airway inflammation—Airway inflammation was determined by the fraction of exhaled nitric oxide (FeNO) measured at baseline and at multiple time points post-stress using the Analyzer CLD 88 series in combination with the DENOX 88 module (Eco Medics AG, Duernten, Switzerland), a chemiluminescence NO-analyzer system. FeNO measurements were performed in accordance with the ATS and the European Society Executive Committee (ERS) established consensus guidelines for measurement of exhaled NO online [31].

Due to technical problems with the NO analyzer, a complete set of data for two participants could not be obtained. Data for the rest of the participants (8 subjects in the therapeutic group and 7 subjects in the asthmogenic group) was obtained. However, one data point was missing for two participants (one for the FeNO post and the other for a FeNO 2 h after), so in both cases each value was substituted with the mean value of the group for that data point.

Subjective measures

Personality and mood scales questionnaire—In order to document any interactions between personality and asthma responsiveness, subjects completed the Positive and Negative Affect Schedule (PANAS) questionnaire [32] prior to the exposure. The PANAS allowed us to assess the trait characteristics of Negative Affectivity (NA: a broad range of aversive mood states, such as anger, disgust, guilt and fearfulness) and Positive Affectivity (PA), which may differentially affect stress and subjective symptoms reporting [33].

Asthma symptoms checklist questionnaire—The asthma symptom checklist (ASC) is a 36-item questionnaire developed to measure the subjective symptomatology of asthma [34]. This questionnaire is composed of 5 symptom clusters associated with asthma attacks: hyperventilation, bronchoconstriction, panic-fear, irritability, and fatigue. For our study we used 5 symptoms per cluster: hyperventilation (tingling sensation, headache, nausea, dizzy, itchy lungs); bronchoconstriction (mucous congestion, hard to breathe, chest congestion, short of breath, chest filling up); panic-fear (scared, worried, panicky, afraid of dying, worried about attack); irritability (irritable, short tempered, anxious, frustrated, cranky); fatigue (fatigued, worn out, weak, tired, no energy), and we added 5 sham symptoms grouped into the sham category (stomachache, toothache, back pain, joint pain, leg cramps).

Each symptom was rated on a 5-point intensity scale that ranged from not at all to extremely. The participant rated how she/he felt at that moment and completed the checklist at baseline and immediately, 2 h and 24 h after exposure.

Procedure

Participants arrived at the center and were explained the purpose of the study and the requirements needed for inclusion. After their questions were answered and they signed the consent form, spirometry was performed in order to ensure they met the inclusion criteria. If they passed the spirometry test, they filled out a general health questionnaire, the asthma symptom checklist, and the PANAS. Airway inflammation using the NO analyzer was also measured at this time. The qualified subjects were then taken to the test chamber where electrodes and the nasal cannula were applied and five minutes of baseline recordings of etCO₂, respiratory rate and heart rate were obtained. After that, the experimenter entered the test room and informed the participant which odor was going to be used that day. In the asthmogenic condition, participants were told they would be “exposed to an odor that some people have reported produces some mild respiratory problems”. In the therapeutic condition, participants were told they would be “exposed to an odor that some people have reported helps them breathe better”. The participant was then exposed to PEA, using 10-second pulses every minute for 15 min, while collecting odor quality ratings on the gLMS and continually recording etCO₂, respiratory rate and heart rate. Immediately after exposure, then again 2 h after, participants refilled out the asthma symptoms checklist, FeNO was collected and spirometry was performed. Participants were then scheduled to come in the next day so that asthma symptoms, FeNO and spirometry data could be collected at the 24 hour post-exposure time point. Fig. 2 indicates the timeline of events as well as the different tests performed at each point in time.

Statistical analysis

Analyses of Variance (ANOVAs) and repeated measure ANOVAs were used to analyze the data. Treatment (Asthmogenic vs. Therapeutic) was used as the between group factor, and the within group factor depended on the time interval being compared (e.g., measures like etCO_2 , respiratory rate and HRV parameters, were compared 'baseline' vs. 'exposure'; whereas endpoints like FeNO, $\text{FEV}_{1\text{L}}$, and subjective ASC ratings were compared 'immediately post-exposure' vs. '2 hours post-exposure' vs. '24 hours post exposure').

Some data needed to be processed before analysis. For example, FeNO data did not differ significantly between groups at baseline ($p = 0.25$), but due to individual variation in baseline values, post-exposure FeNO values were normalized to each individual's baseline and are presented as percentage change from that baseline. Further, subjective ratings of odor perception (intensity, irritation and annoyance), had to be collapsed, via their mean, over 15 separate ratings to compare overall exposure ratings between groups. P values for multiple comparisons were adjusted using the Holm–Bonferroni correction. Statistica 10 software package was used to perform the analysis.

Results

Population characteristics

Based on the PANAS questionnaire, the asthmogenic and therapeutic groups did not differ significantly on either the positive or negative affect dimension: PA traits: $F(1,15) = 1.34$, $p = 0.26$; NA traits: $F(1,15) = 2.53$, $p = 0.13$. The two groups were also similar in the reported intensity of their perceived asthma symptoms and sham symptoms during normal life (data not shown). Both groups also did not differ significantly on respiratory frequency (cycles/min) ($F(1,15) = 0.0034$, $p = 0.954531$) and etCO_2 (mm Hg) levels ($F(1,15) = 2.21$, $p = 0.15$) at baseline, nor did they differ significantly on spirometric values ($F(1,15) = 0.467$, $p = 0.50$) or FeNO levels ($F(1,13) = 1.40821$, $p = 0.25$) at baseline.

Odor qualities

Manipulation of the perceived risk of exposure affected the rated qualities of the odor. When the odor was perceived as harmful it was described as significantly more irritating ($F(1,15) = 8.1351$ $p < 0.02$) and annoying ($F(1,15) = 7.44$ $p < 0.02$) (see Fig. 3).

Subjective symptoms

Participants completed the Asthma Symptom Checklist before and at three time-points post-exposure (immediately, 2 and 24 h). Even though neither group's symptom ratings changed significantly from time point to time point, there was a tendency among the 'asthmogenic' group to report higher levels of bronchoconstriction, hyperventilation and panic immediately after exposure to a perceived harmful odor than the 'therapeutic' group. This subjective increase in asthma symptoms (bronchoconstriction, hyperventilation) as well as panic-fear symptoms was short-lived because the self-reported values for those symptoms obtained two hours after the odor exposure were similar to the ones obtained at baseline (see Fig. 4). No such trend was observed for the sham symptoms.

Objective physiological symptoms

Risk perception did not affect objective bronchoconstriction and hyperventilation status, as measured by changes in FEV₁, etCO₂ and respiratory rate. Nor did it significantly enhance the autonomic nervous system response as measured by the heart rate or the sympathetic/parasympathetic drive as measured by the LF/HF ratio using HRV measurements (see Table 2).

In contrast, measures of exhaled FeNO taken at multiple time points revealed that perception of a perceived harmful odor significantly and persistently increased airway inflammation. A repeated-measures ANOVA revealed a group effect ($F(1,13) = 9.93$, $p < 0.007$) such that the asthmogenic group FeNO measures were significantly higher than the therapeutic group. FeNO was observed to be significantly higher immediately after ($p = 0.0001$), at 2 h after exposure ($p < 0.042$), and at 24 h after exposure ($p < 0.041$) in the asthmogenic group (see Fig. 5).

Discussion

To our knowledge this is the first study that has evaluated the effect of a common fragrance component on an inflammatory airway response in which the effect was likely mediated through the cognitive bias produced from perceived risk of exposure toward a benign non-irritant odorant.

Consistent with previous studies, we found that an odorant that is characterized as ‘harmful’ (i.e., asthmogenic to asthmatics) is described as more irritating and annoying when compared with the same odor characterized as ‘healthful’ (i.e. ‘therapeutic’) [35] and [36]. More surprisingly, however, we also found that this same odorant characterization significantly and persistently increased airway inflammation among individuals who were led to believe that it could induce asthma symptoms.

Increased exhaled nitric oxide levels after an acute laboratory stressor in both asthmatics and healthy controls have recently been reported. Asthmatic participants subjected to the Trier Social Stress Test (TSST) had an increase on FeNO after stress exposure [37]. Even though we did not find evidence that our manipulation elicited a stress response, our results indicate that just characterizing an odor as asthmogenic, and changing participants’ expectations, was sufficient to alter their perceptual response to the odor and indirectly increase exhaled nitric oxide levels. There were no significant increases in symptom reports or nitric oxide levels when the odor was characterized as ‘therapeutic’, even among asthmatics who reported sensitivity to perfumes and other odors. These data suggest that some fragrance effects on asthma exacerbation are not caused by the chemical properties of the odor and its effect on the respiratory system but are instead mediated through a cognitive mechanism such as the belief or expectation of harm from exposure.

Although the subjects in the ‘asthmogenic’ group reported increased ‘hyperventilation’ following the exposure, no objective evidence of hyperventilation was observed in either group, consistent with responses previously found to the TSST [38]. Although there were no significant differences in subjective symptoms between the two groups, a slight increase in

subjective bronchoconstriction and hyperventilation was reported by the group exposed to the asthmogenic odor. Increases in subjective asthma exacerbation have been reported in all the studies that used a fragrance challenge and asked for subjective symptoms independently of a measurable bronchoconstrictive response or hyperventilation [12,13,39,40]. It is possible that in our study we did not reach significance level in regard to the magnitude of subjective symptoms because our participants were recruited based on the severity of their asthma, not specifically on sensitivity to odor exposure. Interestingly, as can be seen in Table 1, although some participants reported that they always or often got sick from exposure to perfume, many of those individuals also reported using perfume on a frequent basis. Among the ‘asthmogenic’ group, the trend toward reports of increased symptoms in the panic-fear, bronchoconstriction and hyperventilation endpoints compared with the flat response in the “sham symptoms” cluster, indicates that the manipulation was effective. In particular, the increased reports of worry among the ‘asthmogenic’ group suggest a change in anxiety level introduced by the odor characterization. The failure to reach significance for these endpoints, however, may have been due to the assurance provided by the consent process regarding safety of the procedures. It is likely that these responses shown in the confines of the laboratory underestimate the potential for increased symptom responses in everyday situations.

Given the difficulty in recruiting eligible participants (50% screen failure), our sample size was necessarily limited, and may have prevented us from seeing significant differences on the subjective symptom reports or even ratings of stress. Nevertheless, we observed a significant effect of our manipulation in the hypothesized direction on odor irritation and annoyance as well as on FeNO levels. The subjective symptom responses and ratings of stress did not differ significantly, perhaps due to the limited sample we tested. Although additional studies are needed to better understand this and other potential mechanisms of odor-induced asthma exacerbation, the current study demonstrated that characterizing an odorant as potentially harmful to asthmatics was sufficient to alter perception of the odor, slightly increase subjective asthmatic symptoms and induce rapid and persistent airway inflammation. Our study supports the current view that airway nitric oxide may be linked to changes in psychological states in asthmatic subjects. The mechanisms by which psychological processes may increase the levels of NO could be diverse, such as increased NO released from the neurons of the non-adrenergic–non-cholinergic (NANC) system, or catecholamine release by the adrenal gland among other pathways, with different mechanisms and sources contributing NO release at different timepoints. What is interesting about our findings is that the increase in NO was not transient; it persisted for at least 24 h.

Our finding also has therapeutic implications, as it has been suggested that excessive airway nitric oxide can amplify asthmatic airway response to allergens or airborne volatiles and exacerbate asthma pathogenesis from increased respiratory infections. Among asthmatics, pre-existing concerns about fragrances coupled with avoidance warnings from respected health groups (i.e., the NIH and the American Lung Association) could lead individuals to mount a stress response upon exposure and provoke symptoms that then become further conditioned to odorous triggers.

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Fig. 1.

Biophysical model of stress-induced asthma exacerbation. Perception of an odor deemed potentially harmful can start cognitive and emotional events which, for an asthmatic, can culminate in the interpretation and appraisal of an uncontrolled health threat. This threat can affect biological pathways initiating a cascade of events, which can lead to changes in smooth muscle tone (bronchoconstriction), airway inflammation and increases in airway sensitivity to inhaled agents. The Central Nervous System (CNS), the Autonomic Nervous System (ANS), and the Hypothalamic–Pituitary–Adrenal (HPA) axis are involved in the muscle tone control and airways inflammation. Solid arrows indicate the interactions among the different components; broken line hexagonal boxes indicate the end-points measured in this study.

Adapted from Chen and Miller [7].

Fig. 2.
Time line of events.

Fig. 3.

Quality ratings of the odor. Risk perception affects the subjective qualities of the odor. Participants rated on a Labeled Magnitude Scale (LMS) scale the perceived quality of the odor in regard of its intensity, irritancy and annoyance, once a minute over 15 min (each rating is a mean of 15 ratings). White bar corresponds to the “therapeutic” odor (n = 9); gray bar is from the “asthmogenic” odor (n = 8). Asterisk (*) indicates a significance level $p < 0.05$ using ANOVA test. Error bars indicate SEM.

Fig. 4.

Subjective symptoms are influenced by odor risk perception. Subjective symptoms were measured at different points in time before, immediately after, 2 h after and 24 h after odor exposure using a validated asthma symptoms questionnaire that clusters all the symptoms into several categories. Each symptom uses a 5 point scale that goes from “not at all” to “extremely”. The three post exposure values are expressed as percentage change from the baseline value obtained before odor exposure. Therapeutic odor group is depicted by light gray circle ($n = 9$) and the asthmogenic group is represented with dark gray squares ($n = 8$). Error bars indicate SEM.

Fig. 5.

Risk perception affects airways inflammation. Fraction of Exhaled Nitric Oxide (FeNO), an indicator of airways inflammation, was measured at different points in time before, immediately after, 2 h after and 24 h after odor exposure. Therapeutic odor group is depicted by light gray circle ($n = 8$) and the asthmogenic group is represented with dark gray squares ($n = 7$). The values are expressed as percentage change from the baseline value obtained before odor exposure. Asterisk (*) indicates a significance level $p < 0.05$ using ANOVA test. Error bars indicate SEM.

Table 1

Demographic information.

Information about our sample population in regard to gender (F = female, M = male), age, race (A = African-American, C = Caucasian), smoking status (cgt = cigarettes), education achieved, length of asthma diagnosed, medications taken (IC = inhaled corticosteroids, SABAs = short-acting beta agonists, LM = leukotriene modifier, LABA = long-acting beta agonists) as well as perfume usage and history of aversive reactions to it.

Gender	Age	Race	Smoking status	Education	Asthma	Medications	Perfume usage	Perfume-induced sickness
<i>Therapeutic group</i>								
F	54	A	Quit 20 y ago	High school degree	3+ years	IC, SABA	1 time/day	Never
M	39	A	Never smoked	Technical school	3+ years	IC, SABA, LM	1 time/week	Never
F	39	A	Never smoked	Some college	3+ years	IC, SABA	1 time/day	Often
F	37	A	Never smoked	College degree	3+ years	IC, SABA, LM, LABA	1 time/day	Often
M	46	A	8 cgt/day	Some college	3+ years	IC, SABA	2 or 3 times/week	Rarely
F	27	A	Never smoked	Some college	0–1 year	IC, SABA	1 time/week	Never
M	18	C	Never smoked	Some college	3+ years	IC, SABA	Less than once/month	Never
M	37	A	Quit 1 y ago	High school degree	3+ years	SABAs	1 time/day	Never
M	55	C	Never smoked	Graduate degree	3+ years	SABA	Less than once/month	Never
<i>Asthmogenic group</i>								
M	47	A	Quit 2 y ago	High school degree	3+ years	IC	1 time/day	Never
M	31	A	Half a pack/day	High school degree	3+ years	SABAs	2 or 3 times/week	Often
F	55	A	Quit 20 y ago	College degree	3+ years	SABA	1 time/day	Always
M	45	A	Never smoked	High school degree	1–3 years	IC, SABAs	Never	Often
F	31	A	4 cgt/day	High school degree	3+ years	IC, SABA, LM	Never	Never
M	22	A	4 cgt/day	College degree	3+ years	IC, SABA	1 time/day	Never
F	21	A	Never smoked	Some college	3+ years	SABAs	1 time/week	Never
F	51	A	Quit 3 y ago	Some college	3+ years	IC, SABA	Never	Often

Table 2

Raw data from objective outcome measurements. Expressed as mean (SD).

	Therapeutic		Asthmogenic			
	Baseline	Test	Baseline	Test	Before	After
etCO ₂ (mm Hg)	37.91 (2.73)	36.32 (3.35)	39.98 (3.03)	36.96 (4.2)		
Respiratory rate (cycles/min)	16.6 (4.82)	18.85 (4.36)	16.73 (4.34)	17.59 (3.25)		
Heart rate (1/min)	75.26 (15.6)	75.59 (14.4)	86.05 (11.88)	84.42 (12.01)		
Mean R to R beat (ms)	834.44 (188.34)	826.01 (170.86)	712.14 (94.47)	726.05 (95.45)		
Low frequency power (ms ²)	879 (1152.92)	1112 (1156.8)	401.43 (397.11)	570.1 (388.8)		
High frequency power (ms ²)	730.56 (797.64)	860.22 (757.04)	362.57 (431.82)	396.88 (273.6)		
LF/HF	1.8 (2.49)	2.52 (4.17)	3.9 (4.01)	2.16 (1.39)		
	Before	After	Before	After	After 2 h	After 24 h
FEV1 (% predicted)	71.89 (7.72)	73.22 (7.76)	69.5 (6.55)	71.13 (11.85)	71.38 (9.64)	71 (10.61)
FeNO ppb	31.41 (27.09)	27.62 (23.48)	18.38 (10.96)	21.87 (12.57)	25.57 (14.37)	27.97 (21.52)