Nasal hyperreactivity in allergic and non-allergic rhinitis: a potential risk factor for non-specific building-related illness

Abstract Self-reported non-allergic nasal symptom triggers in non-allergic ('vasomotor') rhinitis overlap with commonly identified environmental exposures in non-specific building-related illness. These include extremes of temperature and humidity, cleaning products, fragrances, and tobacco smoke. Some individuals with allergic rhinitis also report non-allergic triggers. We wished to explore the phenotypic overlap between allergic and non-allergic rhinitis by ascertaining self-reported non-allergic nasal symptom triggers among allergic rhinics. Sixty subjects without work-related respiratory exposures or symptoms, aged 19–68 years, stratified by age, gender and (skin test-proven) allergic rhinitis status, were queried with regard to self-reported non-allergic nasal symptom triggers (aggregate score 0–8). In this sample, the number of self-reported non-allergic triggers was bimodal, with peaks at 1 and 5. Forty-two percent of seasonal allergic rhinitic subjects reported more than three non-allergic triggers, compared with only 3% of non-allergic non-rhinics ($P < 0.01$). Subjects over 35 years were more likely to report one or more non-allergic triggers, particularly tobacco smoke ($P < 0.05$). Allergic rhinics reported more non-allergic symptom triggers than did non-allergic, non-rhinics. As indexed by self-reported reactivity to non-specific physical and chemical triggers, both non-allergic rhinics *and* a subset of allergic rhinics may constitute susceptible populations for non-specific building-related illness.

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Key words: Indoor air; Rhinitis; Nasal hyperreactivity; Volatile organic compounds; Temperature and humidity.

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Practical Implications

Judging by self-report, a substantial subset of individuals with allergic rhinitis – along with all individuals with nonallergic rhinitis (by definition) – are hyperreactive to non-allergic triggers. There is overlap between these triggers (elicited in the process of obtaining a clinical diagnosis) and environmental characteristics associated with "problem buildings." Since individuals with self-identified rhinitis report an excess of symptoms in most epidemiologic studies of problem buildings (even in the absence of unusual aeroallergen levels), rhintics may be acting as a "sentinel" subgroup when indoor air quality is suboptimal. Together, non-allergic rhinics plus allergic rhinics with prominent non-allergic triggers, are thought to constitute approximately one-sixth of the US population.

Introduction

Non-infectious, non-allergic building-related illness (also referred to as non-specific building-related illness) has been estimated to be responsible for some $40–200 billion in healthcare costs and lost productivity annually in the US (Fisk, 2000). Identified environmental factors in 'problem buildings' include extremes of temperature and humidity, combustion products (cigarette smoke, cooking and heating exhaust, and reintrained vehicular exhaust), and volatile organic compounds or 'VOCs' (from building materials, furnishings, cleaning products, fragrances, and microbial sources) (Hodgson et al., 1991; Nagda and Hodgson, 2001; Seppanen and Fisk, 2002). Despite numerous field studies, however, much unexplained variability in symptom reporting remains after accounting for building-related exposures.

Of interest, the above list of environmental stressors overlaps substantially with the environmental 'triggers' reported by patients with idiopathic non-allergic rhinitis (a.k.a., 'vasomotor' rhinitis or perennial non-allergic rhinitis) (Sanico and Togias, 1998). Typical nasal symptom triggers in this patient group include changes in air temperature and humidity, tobacco smoke, household cleaning products, and perfumes and colognes, in addition to the non-indoor air-related triggers of bright lights, spicy foods, exercise, and alcohol consumption (Dykewicz et al., 1998).

Heightened nasal responsiveness to non-specific physical and chemical triggers in inspired air has been termed 'nasal hyperreactivity,' and while a defining feature of idiopathic non-allergic rhinitis, is not confined to that patient group alone. A substantial subset of allergic rhinitics also report symptoms consistent with nasal hyperreactivity, giving rise to the label 'mixed' rhinitis. Together, individuals with non-allergic and mixed rhinitis are estimated to number some 45 million in the US (Mullarkey et al., 1980; Settipane and Lieberman, 2001). Thus, nearly a sixth of the US population reports heightened upper airway responsiveness to non-specific physical and chemical factors as a consequence of upper airway inflammation.

Consistent with this premise, epidemiologic investigations in 'problem buildings' have frequently identified pre-existing allergic rhinitis as a personal risk factor for reporting of building-related mucous membrane symptoms, even lacking substantial indoor allergen exposures (Brasche et al., 2001; Hall et al., 1993; Lundin, 1999; Mendell et al., 1993; Menzies et al., 1993, 1998; Runeson et al., 2006; Skyberg et al., 2003). Experimentally, individuals with allergic rhinitis have been found to have lower detection thresholds for nasal irritation from VOCs, and to nasally congest (obstruct) more markedly after irritant provocation than do non-allergic, non-rhinitic subjects (see Discussion, below). In principle then, individuals with pre-existing non-allergic *or* allergic rhinitis – a substantial fraction of the population – may constitute a susceptible subgroup with respect to potential building-related illness.

We were interested in exploring this phenotypic link between allergic and non-allergic rhinitis by studying the prevalence of specific self-reported non-allergic triggers in a population sample stratified by age, gender, and allergic rhinitis status. To do so, we analyzed questionnaire data from a study of nasal chemosensory function in which subjects aged 19–68 years without identified chronic irritant exposures were recruited to form a demographically counterbalanced sample (Shusterman et al., 2003a). Utilizing a separate 'non-allergic rhinitis scale,' we ascertained the number and types of self-reported non-allergic nasal symptom triggers as a function of age, gender, and seasonal allergic rhinitis (SAR) status, and report these findings in the present study.

Methods

Recruitment and screening

Subjects between 18–69 years of age were recruited through posters and on-line advertisements, with the goal of recruiting a balanced sample with regard to age, gender, and allergy status (Figure 1). Potential subjects
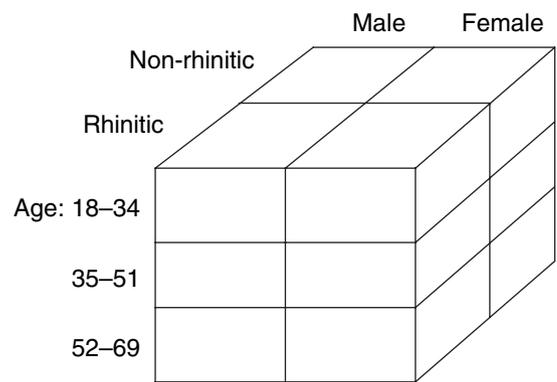

Fig. 1 Subject recruitment goals for parent study. The goal was to constitute a study group counter-balanced by age, gender, and allergic rhinitis status

with chronic cardiopulmonary diseases (including asthma), active smoking (within 6 months), who were pregnant or lactating, or receiving medications having anticholinergic or antihistaminic side effects were excluded, as were those who reported occupational exposure to irritant gases, vapors, smokes or fumes. Signed informed consent was obtained using documents approved by the Committee on Human Research at the University of California, San Francisco.

The questionnaire included basic demographics, pre-existing health conditions (both general and allergic/otolaryngologic), smoking and current occupational exposure histories, and current medications. Initial classification of allergic rhinitis status was based upon a positive answer to one (or both) of the following two questions:

- 'Have you been told by a physician that you have "hay fever" or "allergic rhinitis"?'
- 'Over the course of the year, do you experience episodes of sneezing, runny nose, or nasal itching or congestion not associated with colds?'

Positive answers to the second screening question were followed by prompts regarding season(s) in which nasal symptoms occur, as well as identified allergen triggers.

Subjects whose questionnaire responses were consistent with either SAR or no rhinitis (NR) underwent epicutaneous skin prick testing, including 16 common aeroallergens/mixes (Table 1), plus histamine (1.8 mg/ml; AllerMed Laboratories, San Diego, CA, USA) and saline controls. In addition, anterior rhinoscopy was performed. Significant skin test reactivity was defined by a wheal reaction ≥ the histamine control. Skin test and physical examination results were compared with questionnaire responses for consistency, and subjects were classified as SAR or NR when concordant information was present (discrepant cases being excluded from further testing). In this latter group were subjects with a positive history and negative skin test

Table 1 Skin test panel

Controls	Saline
	Histamine
Seasonal Antigens	Early tree mix
	Late tree mix
	Grass mix
	Bermuda grass
	Weed mix
Perennial Antigens	Mite (*Der p*)
	Mite (*Der f*)
	Mold mix
	Alternaria
	Cladisporium
	Cat (*Fel d* 1)
	Dog dander
	Rat
	Mouse
	Cockroach
	Feathers (mixed)

results, subjects with a negative history and positive skin test results, and individuals with reactivity solely to perennial allergens (e.g., dust-mites). Subjects with skin test reactivity to both seasonal and perennial allergens were included in the study if allergen control measures rendered them asymptomatic for at least a portion of a typical day. A total of 60 subjects were to be recruited with the goal of a balanced sample by gender, allergy status, and age stratum (18–34, 35–51, and 52–69 years).

Ascertainment of self-reported non-allergic triggers

In a separate portion of the questionnaire (and not considered during subject classification), was a series of questions pertaining to non-allergic nasal symptom triggers. Specifically, 'Do you experience a runny nose or nasal congestion when you:

- Eat hot or spicy foods?
- Are exposed to bright lights?
- Use household cleaning products?
- Smell strong perfumes, colognes, or after-shaves?
- Experience sudden changes in air temperature or humidity?
- Exercise?
- Consume alcohol?
- Enter a smoky room (cigarette smoke)?'

In the current analysis, each positive answer to one of the above questions was assigned a score of one point, and an aggregate 'non-allergic rhinitis' score of 0–8 was constructed. The distribution of scores was examined for normality prior to applying non-parametric statistics (Wilcoxon rank-sums test, chi-square likelihood ratios, and chi-square for trend) to compare aggregate score vs. allergic rhinitis status, gender, and age group (18–34, 35–51, 52–69 years). In addition, the relative reporting of individual trigger factors was

examined as a function of age, gender, and allergic rhinitis status. Statistical significance was defined as a $P < 0.05$. Analyses were performed on an Apple G4 computer (Apple Computers, Cupertino, CA, USA) using the JMP Statistics package (SAS Institute, Cary, NC, USA) and graphics produced with Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Results

The characteristics of the 60 subjects appear in Table 2. The sample was balanced with respect to gender, and quite nearly so by seasonal allergies (31 seasonal allergic rhinitics and 29 non-atopic, non-rhinitics). Subjects ranged from 19 to 68 years of age; there were more subjects in the middle age stratum (35–51 years old; $n = 24$) than in the younger or older strata ($n = 18$ each). The seasonal allergic rhinitic group did not differ significantly in age from the non-atopic, non-rhinitic group [40.7 vs. 43.1 years (mean); $P = 0.52$], nor did males differ significantly in their age distribution from females [41.6 vs. 42.1 years; $P = 0.89$]. Because of the balanced nature of the sample, univariate analyses were possible without concern for potential confounding.

The overall distribution of non-allergic rhinitis scores was bimodal, with the first peak at a score of 1 and a second peak at a score of 5 (Figure 2). As the distribution differed significantly from normal, non-parametric statistics (see above) were applied to all inter-group comparisons. No significant difference in overall non-allergic rhinitis score was apparent by gender (Figure 3). Although linear regression did not reveal a significant age effect, *post hoc* dichotomization of subjects as > or < age 35 years revealed that older subjects were more likely to report at least one non-allergic trigger (88% vs. 67%; $P < 0.05$ by Pearson chi-square; Figure 4). The prominent bimodal distribution in total scores largely reflected the responses of the allergic rhinitic subjects, 13 of 31 (42%) reported > 3 triggers, with only 1 of 29 non-atopic, non-rhinitic subjects (3%) yielding scores in this range (Figure 5).

Table 2 Characteristics of study subjects

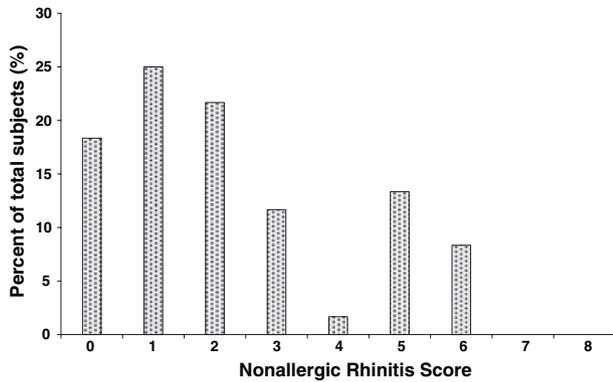| Age stratum	Rhinitis	Gender	*n*	Age (mean ± s.d.)
18–34 years	No	Male	4	23.3 ± 4.2
		Female	4	23.0 ± 4.2
	Yes	Male	5	24.0 ± 3.9
		Female	5	28.6 ± 2.5
35–51 years	No	Male	5	43.7 ± 8.6
		Female	6	43.8 ± 7.0
	Yes	Male	7	42.5 ± 5.1
		Female	6	39.4 ± 4.1
52–69 years	No	Male	5	56.6 ± 4.3
		Female	5	60.0 ± 5.6
	Yes	Male	4	59.5 ± 4.8
		Female	4	58.3 ± 5.3
Combined	–	–	60	41.9 ± 14.1

Fig. 2 Distribution of non-allergic rhinitis scores (0–8). A biphasic distribution was apparent, with peaks at 1 and 5. A single scoring point was allotted for each self-reported non-allergic trigger (as detailed in the text)
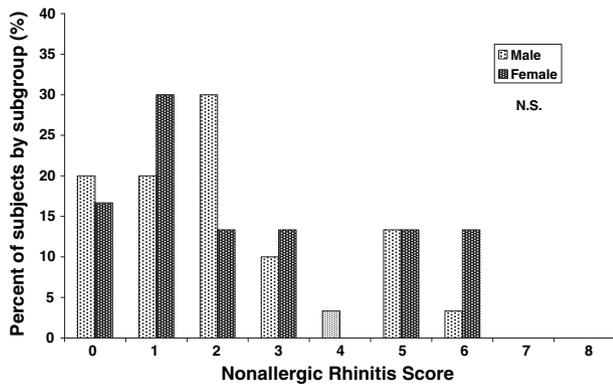

Fig. 3 Distribution of non-allergic rhinitis scores (0–8) by gender. Total number of subjects = 60, evenly divided between the sexes. No significant relationship was observed. A single scoring point was allotted for each self-reported non-allergic trigger (as detailed in the text)

Fig. 4 Distribution of non-allergic rhinitis scores (0–8) by age. Total number of subjects = 60, ranging from 19 to 68 years. No linear relationship was observed. However, dichotomizing for age < or > 35, older subjects were more likely to report at least one non-allergic trigger. A single scoring point was allotted for each self-reported non-allergic trigger (as detailed in the text)

Fig. 5 Distribution of non-allergic rhinitis scores (0–8) by allergic rhinitis status. Total number of subjects = 60, with 31 seasonal allergic rhinitics and 29 non-rhinitic controls. Seasonal allergic rhinitic subjects reported, on average, a significantly greater number of non-allergic triggers ($P < 0.01$). A single scoring point was allotted for each self-reported non-allergic trigger (as detailed in the text)

Fig. 6 Reporting of specific non-allergic triggers, by allergic rhinitis status. No inter-group difference was observed for gustatory rhinitis, but all other triggers reported more frequently by allergic rhinitics than by non-rhinitics (P values: * < 0.05, ** < 0.01)

Mean scores were 3.06 in seasonal allergic rhinitics and 1.41 in non-rhinitics. These distributions differed significantly ($P < 0.01$ by Wilcoxon signed-rank test).

With regard to specific non-allergic triggers, the relative order of reporting for both allergic rhinitics and non-rhinitics was identical: spicy foods > changes in temperature and humidity > environmental tobacco smoke ≅ exercise > household cleaning products ≅ perfumes and colognes > alcohol consumption > bright lights (Figure 6). With the exception of spicy foods (gustatory rhinitis) which was equally prevalent in both groups, triggers were reported more frequently by allergic rhinitics than non-atopic, non-rhinitics. The symptom reporting ratio varied from 2.4 times higher in allergic rhinitics (changes in temperature and humidity) to 6.6 higher (alcohol), with the few subjects reporting reactions to bright lights being confined to the allergic group. The majority of these reporting differences were significant at either the $P < 0.01$ level (changes in temperature or humidity; exposure to perfumes or colognes) or at the $P < 0.05$ level (all
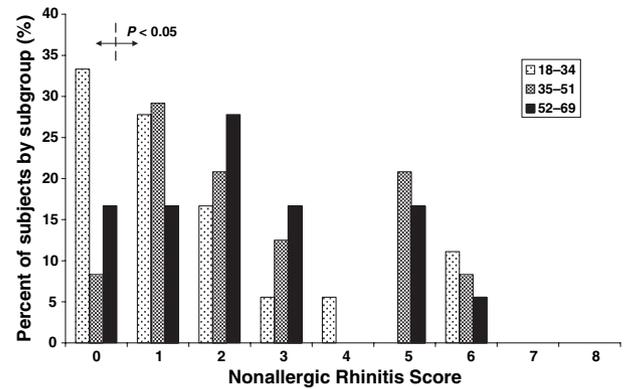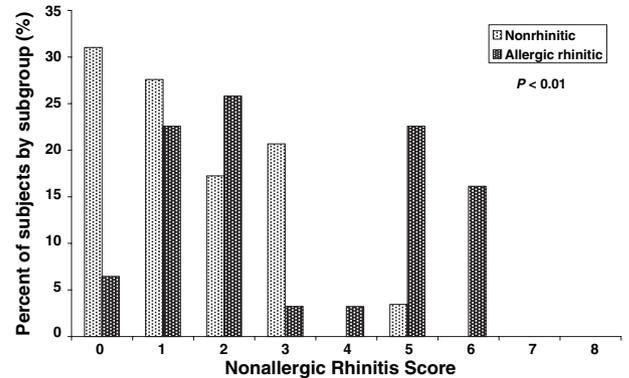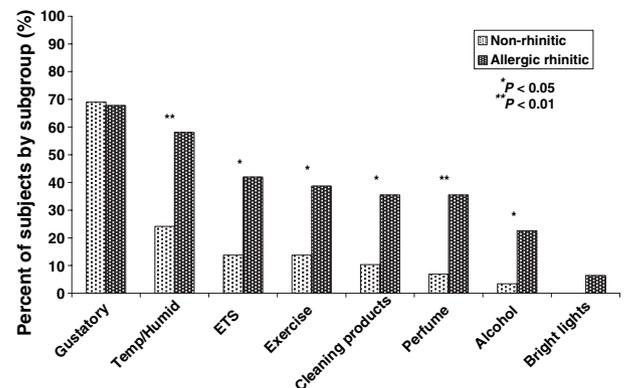
remaining triggers, excluding bright lights). There was also a significant age-related trend in identifying tobacco smoke as a rhinitis trigger (increasing reporting with increasing age; $P < 0.05$); otherwise, neither gender nor age predicted specific triggers.

Discussion

Taken at face value, our findings suggest that, compared with non-allergic, non-rhinitic individuals, seasonal allergic rhinitics report more non-allergic triggers for symptoms of rhinorrhea and/or nasal obstruction. Further, our findings suggest a bimodal distribution of self-reported reactivity within seasonal allergic rhinitics, with augmented reactivity confined to a subset of approximately 40% of the total group. We also found a consistent order of reporting for specific triggers, with all but gustatory rhinitis being reported more by allergic rhinitics than by non-rhinitic controls. Finally, we found that older subjects were more likely to report at least one non-allergic trigger and found tobacco smoke to be more troublesome with respect to nasal symptoms than did younger subjects.

In terms of limitations, the current study population was modest in size. However, potential confounding demographic factors were dealt with in design/sampling (counter-balanced sample) rather than in the analysis phase, thus maximizing statistical power. Further, the inclusion of objective allergy testing minimized the potential for subject misclassification. Another limitation is the non-inclusion of non-allergic rhinitics as a comparison group, as subjects who considered themselves to have rhinitis but had negative skin test results were screened out from further consideration.

Another potential critique of the present study is its reliance on self-reported symptom triggers. However, seasonal allergic rhinitics have been shown to have lower thresholds for detecting irritation from airborne VOCs nasally, and to objectively congest (obstruct) more in response to provocation with a variety of irritant gases (Shusterman et al., 1998, 2003a,b, 2005). In addition, older subjects have been found to show a stronger congestive response to irritant (chlorine gas) provocation (Shusterman et al., 2003b). Thus, the assumption that differential symptom reporting patterns by demographic or diagnostic subset derive solely from psychosocial factors appears to warrant some scrutiny (Hall et al., 1993; Lundin, 1999; Ryan and Morrow, 1992).

Limitations aside, the finding of a bimodal distribution of self-reported non-allergic reactivity among skin test-proven seasonal allergic rhinitic subjects corresponds well with the published literature on 'mixed' rhinitis. Our finding that 42% of seasonal allergic rhinitics report >3 non-allergic triggers is consistent with prior published estimates that between 44% and 46% of allergic rhinitics report physical triggers (Mullarkey et al., 1980; Settipane and Lieberman, 2001).

Expanding on these published data, however, ours is the first study to examine reporting pattern for *specific* triggers among skin test-proven allergic rhinitics.

In this last regard, a limited number of studies have examined non-allergic triggers. Montnemery et al. (2001), for example, carried out a large population-based survey and found that strong scents, followed by tobacco 'fumes,' cold or dry air, stress, spicy food, and red wine, were reported more frequently among respondents who *self-identified* as having allergic rhinitis, as compared with the sample at large. No objective allergy testing was carried out in that study, however. Ryden et al. (2004) interviewed groups of perennial allergic and perennial non-allergic rhinitic patients from an otolaryngology clinic, and noted that the two groups reported '…similar complaints and triggering irritants,' without offering further details. Sibbald and Rink (1991) queried seasonal, perennial, and mixed-pattern rhinitics regarding their (allergic and) non-allergic triggers, finding significant differences among the three groups. However, despite having skin test data, they did not compare allergic and non-allergic rhinitics, nor did they include non-rhinitic controls.

Underlying the 'hyperreactive' phenotypic response pattern is considerable uncertainty regarding biological mechanisms. Postulated non-allergic nasal response mechanisms include neurogenic responses (central autonomic or peripheral axon reflexes), osmotically induced mast cell degranulation, and epithelial cell activation (Baraniuk, 2001; Koskela et al., 2000; Togias et al., 1985). Alteration of airway nerve function by mediators of allergic inflammation (so-called 'neuromodulation') has been offered as a potential mechanism whereby allergic rhinitics might be rendered hyperresponsive to non-allergic stimuli (Togias, 2000; Undem et al., 2000). Further, 'model' airway stimuli (methacholine, histamine, and cold air) have been used to demonstrate augmented non-specific nasal physiologic reactivity among various rhinitis subgroups (Gerth van Wijk and Dieges, 1994). Given the heterogeneity of self-reported non-allergic triggers, however, more than one mechanism may be operative. Clearly, this is an area in need of further research attention.

Our data are consistent with the premise that, in addition to the subset of rhinitics who are *defined* by their self-reported reactivity to non-specific physical and chemical triggers (i.e., idiopathic non-allergic rhinitics, who are estimated to number some 19 million in the US), a substantial fraction of allergic rhinitics also *share this phenotypic response pattern*. If both non-allergic rhinitics and many allergic rhinitics – together constituting almost one-sixth of the US population – experience triggering of nasal symptoms by non-specific physical and chemical factors, then risk assessors, heating, ventilating and air-conditioning systems engineers, and building managers need to be cognizant of that fact. Careful regulation of indoor temperature,

humidity and air exchange rates, minimization of VOC off-gassing from building materials, furnishings and cleaning products, and avoidance of microbial growth are all preventive measures that can lessen the likelihood of symptom complaints among this large subset of workers. Viewed from a clinical perspective, physicians evaluating and treating individuals with non-specific building-related illness should also be attentive to the inflammatory state of their patients' upper airway/mucous membranes, and optimize medical therapy to help down-regulate their patients' mucosal reactivity to physical and chemical stimuli that might otherwise be innocuous. A balanced intervention involving both the host and environment holds the greatest promise of ameliorating this challenging (and often frustrating) problem.

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