The Influence of Sex, Allergic Rhinitis, and Test System on Nasal Sensitivity to Airborne Irritants: A Pilot Study

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"Nasal irritant sensitivity" is an important construct in environmental health science; functional measures, however, lack standardization. We performed duplicate measures of nasal irritant perceptual acuity on 16 subjects (evenly divided by sex and seasonal allergy status) using two different test compounds: carbon dioxide (CO_2) (detection) and *n*-propanol (localization). The *a priori* hypotheses included *a*) allergic rhinitics will display lower perceptual thresholds than nonrhinitics; *b*) females will display lower perceptual thresholds than males; and *c*) estimates of perceptual acuity using the two test systems will be positively correlated. We obtained CO_2 detection thresholds using an ascending concentration series, presenting 3-sec pulses of CO_2, paired with air in random order, by nasal cannula. We obtained localization thresholds by simultaneously presenting stimuli (ascending concentrations of *n*-propanol vapor in air) and blanks (saturated water vapor in air) to opposite nostrils, with laterality randomized. In terms of test–retest reliability, individual replicate measures for CO_2 detection thresholds correlated more closely than did the localization thresholds of volatile organic compounds (VOC) ($r = 0.65$ and $r = 0.60$, respectively). As an intertest comparison, log-transformed individual mean CO_2 and VOC measures were positively correlated with an r of 0.63 ($p < 0.01$). In univariate analyses, sex predicted both log-transformed CO_2 and VOC thresholds (females being more "sensitive"; $p < 0.05$ and 0.001, respectively). Nasal allergies predicted sensory testing results only in the multivariate analysis, and then only for VOC localization ($p < 0.05$). The question of population variation in nasal irritant sensitivity (as well as the generalizability of results across test compounds) deserves further attention. *Key words*: allergic rhinitis, carbon dioxide, chemoreception, sex, irritation, nose, sick building syndrome, trigeminal, upper airway, VOCs (volatile organic compounds). *Environ Health Perspect* 109:15–19 (2001). [Online 28 November 2000]
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Eye, nose, and throat irritation—all trigeminally mediated sensations—are the most common symptom complaints in many polluted environments, particularly in so-called "problem buildings" (*1–6*). Together with the symptoms of nasal congestion, rhinorrhea, postnasal drip, headache, and lethargy, these constitute the major components of a symptom complex labeled (epidemiologically) as either "sick building syndrome" (SBS) or "nonspecific building-related illness" (*7,8*). Whatever the terminology, according to one estimate, nonallergic, noninfectious indoor air quality problems are responsible for a 2% decrease in productivity among office workers in the United States, amounting to $50 billion in annual economic losses (*9*).

The etiology of SBS is, strictly speaking, unknown, although suspected causal agents include volatile organic compounds (VOCs—from building materials, furnishings, microbial overgrowth, and cleaning products), combustion products (environmental tobacco smoke; re-entrained vehicular exhaust; malfunctioning combustion appliances), and extremes in air temperature and humidity (*10–13*). Mechanically ventilated buildings with air conditioning systems appear to have an increased likelihood of being designated "problem buildings" (*14*). Within such environments, symptom reporting appears to be nonrandom, with females and individuals with pre-existing allergic conditions tending to be more symptomatic (*4,5,8*). However, aeroallergens are thought to be responsible for symptoms in relatively few building occupants, suggesting that rhinitis may confer nonspecific sensitivity to airborne irritants (*15*). Despite the consistency of these epidemiologic reporting patterns, there has been a historical tendency to ascribe subpopulation differences in symptom reporting to sociological—as distinct from biological—factors (*16*). This tendency reflects an implicit assumption that there is little interindividual variability in biological susceptibility to indoor air pollutants—an assumption that has not, by and large, been empirically tested.

Background: Sensory Testing

From a sensory standpoint, the prime target of SBS—the upper airway—is innervated by both the first cranial (olfactory) and fifth cranial (trigeminal) nerves, mediating the sensations of olfaction and mucous membrane irritation, respectively. At the border of the upper and lower airways, the glossopharyngeal nerve (Cr. N. IX) innervates the hypopharynx and the vagus (Cr. N. X) the larynx). Irritation from low-level chemical exposures appears to be due largely to sensory nerve activation in mucous membranes, as opposed to frank tissue damage (*17*). Because many air pollutants stimulate both the olfactory and trigeminal apparatus simultaneously, special care must be exercised in ascribing an individual's responses in a given testing protocol to olfaction or mucous membrane irritation alone.

Because for most compounds the threshold for olfaction is lower than that for sensory irritation, determination of olfactory thresholds can be relatively straightforward. Most commonly, stimuli are presented from squeeze bottles with the test compound precisely diluted in carrier (water or mineral oil) to produce a target series of headspace vapor concentrations. Subjects are presented with two bottles—one the test compound and the other a blank (carrier) stimulus—as blinded pairs, allowed to sniff a measured "puff" from each, and asked which contains the odorant. Most commonly, this is performed as a forced-choice task, using an ascending concentration series. When the criterion number of correct choices occurs in a row, an odor detection threshold is generated (*18*).

Forced-choice discrimination theoretically could be used to derive nasal trigeminal (irritant) thresholds as well, were it not for the the phenomenon of odor cueing. Subjects with normal olfactory function (normosmics) can distinguish the stimulus-containing bottle from the "blank" by virtue of the test compound's odor before the stimulus concentration reaches the trigeminal irritant threshold. For those rare subjects with an absent sense of smell (anosmics), odor cueing is not a problem (and in fact, anosmics are sought out by sensory scientists for just this reason). An ideal trigeminal test

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compound, on the other hand, would be odorless, and hence could be used with any subject. This criterion is satisfied by carbon dioxide (CO_2), which dissolves in mucous membrane water to produce carbonic acid, an effective trigeminal stimulus. Carbon dioxide, in concentrations above 15% (vol/vol), can be used as brief pulses, paired with air, in a forced-choice, discrimination paradigm (*19–21*).

A relatively recent development has enabled researchers to obtain nasal (trigeminal) irritant thresholds using odorous volatile organic compounds (VOCs) among normosmic subjects. As summarized by Kobal and colleagues (*22*), a body of literature dating back to the 1920s has explored the ability of human subjects to localize the source of an odorant stimulus. Multiple studies have established that subjects can reliably identify the laterality of an applied olfactory stimulus (i.e., left vs. right nostril) only when trigeminal (irritant) stimulation occurs simultaneously (*22–24*). This phenomenon was exploited subsequently by Wysocki and colleagues (*25*), who devised a "localization threshold" procedure. In this procedure, stimuli (various dilutions of VOCs in air) and blanks (clean air) are presented simultaneously to the two nostrils, with laterality randomized. Gradually increasing stimulus concentrations are presented until the subject correctly identifies a criterion number of stimuli. The localization threshold so derived is taken as an indication of the lowest concentration at which the subject can reliably perceive the irritancy of a test compound. In a careful cross-comparison, Cometto-Muñiz and Cain found that the localization procedure produced equivalent results among normosmic and anosmic subjects, as well as results equivalent to forced-choice discrimination among the latter group (*26*).

Despite these advances in psychophysical testing, limited attention has been paid to systematic (population) determinants of nasal irritant perceptual acuity, nor to the degree to which individual variation in acuity generalizes across test compounds. Most of the work in this field has centered on variations in irritant potency among test compounds, with individual differences among subjects being treated as residual variance (*27*). Nevertheless, previous investigators have suggested that smokers have a blunted sense of nasal irritation (*21,28*), that females show a steeper psychophysical function (i.e., rate of increase in suprathreshold rating with increasing stimulus strength) than males (*29*), and that the effect of age varies with the test system (*30*).

Given the sparse nature of the literature regarding personal markers for nasal irritant sensitivity (perceptual acuity), our goals in this study were to explore two potential correlates of nasal irritant perceptual acuity, seasonal nasal allergies and sex; and to compare two different test systems, CO_2 detection and VOC localization. Our *a priori* hypotheses included *a*) seasonal allergic rhinitic (SAR) subjects will display lower irritant thresholds than nonrhinitics (NR); *b*) females will show lower thresholds than males; and *c*) compared across individuals, results of the two test systems will positively correlate.

Methods

Subject recruitment. Subjects were recruited at a local university through posters and newspaper advertisements. Inclusion criteria included age from 18 to 40 years and "general good health"; exclusion criteria were asthma, active smoking (within 6 months), and pregnancy or lactation. Informed consent was obtained per institutional guidelines. Questionnaire responses were reviewed for each applicant, who was provisionally classified as having seasonal allergic rhinitis (SAR), no rhinitis (NR), or "other" (perennial allergic or nonallergic rhinitis). Subjects whose questionnaire responses were consistent with one of the first two diagnoses were referred for allergy skin testing, including 13 common aeroallergens/mixes, plus histamine and saline controls. The threshold for "significant" skin test reactivity was taken as a wheal reaction greater than or equal to the diameter of the histamine control. Skin test results were compared with questionnaire responses for consistency, and subjects were classified as SAR or NR when concordant information was present. A total of 16 subjects—8 males and 8 females—were recruited, 4 of each sex being SAR and 4 being NR, allowing for a counterbalanced study design (see below).

Psychophysical testing. All testing took place in a 950 ft^3 custom-built climate-controlled chamber located at the University of California, Berkeley, Environmental Engineering and Health Sciences Laboratory. The air supply to the chamber is subjected to both high-efficiency particulate (HEPA) and charcoal filtering, with a supply temperature regulated to 22 ± 1°C, and relative humidity to 40 ± 3%. Airflow rates produced roughly 20 air exchanges per hour in a single-pass mode. At each session, subjects acclimated to the above atmosphere for at least 10 min before testing began. Replicate testing sessions were conducted for each of the two testing systems (CO_2 detection and VOC localization, as described below). Testing sessions were separated by at least 1 day, and alternated in the order of either CO_2-VOC-CO_2-VOC or VOC-CO_2-VOC-CO_2; the testing order was counterbalanced for each subgroup of subjects (rhinitic males, nonrhinitic males; rhinitic females, nonrhinitic females).

Carbon dioxide detection thresholds. The exposure apparatus consisted of two banks of electronically controlled solenoid valves connected to rotameters (flow meters) with individual metering valves (*20,21*). Medical grade compressed air (Nellcor Puritan-Bennett; Hayward, CA) was fed into one bank of valves, and CO_2 into the other. The rotameters were calibrated daily to deliver 0% and 15–45% CO_2 vol/vol (5% steps) at a total rate of 5 L/min; the flow rate for air and CO_2 for each pair of flow meters varied reciprocally to deliver a constant total volume at each concentration step. A solid-state timing device was used to control stimulus duration precisely; CO_2 stimulus levels were selected—and CO_2 pulses triggered—manually. No attempt was made to humidify the gaseous stream, since CO_2 is readily soluble in water, and would have been "scrubbed" from the exposure stream by use of a bubble humidifier. Subjects were instructed not to eat, drink (other than water), or exercise for 1 hr before testing; they were also asked not to wear perfumes, colognes, or aftershaves on the day of testing.

The output of each bank of rotameters was conveyed to the subject via a separate 7-ft length of respiratory tubing (Model 2002; Salter Labs, Arvin, CA); the two outputs were then combined using a polyethylene "Y" connector that rested on the subject's upper back. Mixed stimuli were delivered to both nostrils via a disposable, nonocclusive nasal cannula (Salter Model 1606). The right nostril of each cannula was equipped with a standard respiratory flow thermocouple (Model 1221; Pro-Tech Services, Inc., Woodinville, WA). The thermocouple, in turn, was connected to a thermocouple-to-analog converter (Model TAC-386-TF; Omega Engineering, Inc., Stamford, CT), the output of which fed one channel ("airflow") of a strip chart recorder (Omniscribe B117-5; Houston Instruments, Austin, TX) run at 20 cm/min. A second channel on the strip chart recorder ("event") registered a rectangular waveform corresponding to the electrical signal from the control unit to the solenoid valves (i.e., stimulus timing and duration). The thermocouple/recording apparatus allowed precise timing of stimulus pulses relative to subjects' breathing patterns. Nasal cannulae were replaced, and the airflow thermocouple disinfected, between research subjects.

On the day of testing the procedure was explained to the research subject, the nasal cannula fitted, and the subject was encouraged to breathe in a steady pattern while recording took place. Recording was stopped and the periodicity of breathing was determined from the strip chart record; the control unit was then adjusted to produce

pulses whose duration corresponded to approximately half of a breathing cycle plus 1 sec (3.0–3.5 sec). Recording was resumed and, while the subject was breathing steadily, a pulse of pure air (identified as such) was administered, beginning in late expiration. After initial recording, stimulus duration was adjusted further (as needed) to occupy the end of expiration and the succeeding inspiratory phase. Any stimulus-related disruption of breathing pattern was noted, and up to three training trials were employed to help subjects maintain a reasonably steady breathing pattern with "blank" (0% CO_2) stimuli.

Trials consisted of pairs of stimuli—one air and the other CO_2 diluted in air—with the two presented in random order and separated by an interstimulus interval of 12–15 sec. After each stimulus pair, recording was suspended and the subject was asked to state which stimulus—"A" or "B"—was more irritating in a forced-choice manner. Subjects were also asked to position the pointer on a computer-based visual analog scale (LabView; National Instruments, Austin, TX) calibrated with the words "none," "slight," "moderate," "strong," "very strong," and "overwhelming" to rate the more irritating of the two stimuli. (If the choice was based upon a "guess" and no definite nasal irritation was felt, the pointer could be left at "none.") Stimuli were presented in an ascending series, beginning at 0% CO_2, ("sham") with five trials being conducted at each level, and an intertrial interval of 60 sec. Subjects were blinded with regard to stimulus order and progression, and care was exercised not to provide auditory (or other) cues as to stimulus level. The "CO_2 detection threshold" was defined as the lowest concentration at which the subject correctly discriminated all five CO_2 stimuli from filtered air blanks.

VOC localization thresholds. The stimulus–delivery apparatus for this portion of the experiment consists of paired 240 mL polyethylene squeeze bottles (Gary Manufacturing, San Diego, CA) with "flip-top" closures, placed in an acrylic holder (enabling experimenter to compress the two bottles simultaneously). Stimuli and blanks (headspace from the squeeze bottles) were conveyed from bottles to nares via 6 in. lengths of flexible plastic tubing, 0.125 in. outside diameter, 0.0625 in. internal diameter, capped with modified (perforated) foam earplugs (Model QD-1; Howard Leight Hearing Protection, Santa Monica, CA), which anchored tubes in subjects' nostrils during trials. Stimuli were delivered over approximately 0.5 sec duration. The stimulus series consisted of a geometric progression of *n*-propanol dilutions in deionized water (see below); blanks were saturated water vapor in air.

Stimuli were prepared at the Chemosensory Perception Laboratory, University of California, San Diego Department of Otolaryngology, using certified grade *n*-propanol (Fischer Scientific, Fair Lawn, NJ). Stimulus concentrations were determined on three occasions: before commencing the study, at the midpoint of the study, and at the conclusion of the study. Headspace vapor concentrations were measured using a model 5890 gas chromatograph, equipped with a flame ionization detector and nonpolar megabore column (Hewlett Packard Corporation, Menlo Park, CA). Samples were obtained using a gas-sampling valve with 1.0 mL capacity, and using He carrier gas. Headspace concentrations were calculated as area-under-curve (AUC) utilizing the curve for headspace from undiluted *n*-propanol as the standard; predicted vapor pressure for the calibration were derived using the Antoine Equation (*31*). Mean headspace concentrations for the seven steps in the dilution series spanned the range of 4,060–23,700 ppm (Figure 1) and showed acceptable variation over the study period.

The exposure protocol consisted of a forced-choice lateralization procedure with an ascending concentration series. Subjects were seated at a modified slit lamp apparatus (optics removed), with the chin on an adjustable rest; the stimulus delivery apparatus was mounted on a fixed post in front of the subject. Each subject signaled his or her breathing pattern to the tester through hand movements, and at the end of expiration was instructed to sniff gently, at which time the stimulus and blank bottles were simultaneously compressed, delivering approximately 30 mL of headspace from each. After a brief interval, subjects were asked to indicate which side experienced the most "irritation" (defined as "burning, stinging, tingling, or simply a cooling sensation"). Subjects were asked specifically to focus on "irritation" rather than "odor." There were six trials per stimulus level, with an intertrial interval of 60 sec. The laterality of stimuli was subject to limited randomization (with the constraint that an equal number of stimuli and blanks were presented to each nostril). Subjects were blinded with regard to stimulus order and progression. The lowest stimulus concentration at which a subject correctly identified the laterality of all six stimuli was considered the "VOC localization threshold."

Data analysis. Data were entered and analyzed using a Macintosh-based statistical program (JMP; SAS Institute, Cary, NC). Data were examined for normality and log-transformed as indicated. Univariate and multivariate analyses were normally carried out using ANOVA methods. If significant non-normality remained after log-transformation of data, nonparametric data analyses were carried out.

Results

Subject panel. The characteristics of the 16 subjects appear in Table 1. By design, the sample was balanced with respect to sex and seasonal allergies. The seasonal allergic rhinitic group did not differ significantly in mean age from the nonrhinitic group (26.5 vs. 25.1 years), whereas male subjects were, on average, slightly older than female subjects (28.5 vs. 23.1 years).

Test–retest reproducibility: intertest comparison. Test–retest reproducibility was slightly greater for CO_2 ($r = 0.65$) than for *n*-propanol ($r = 0.60$). When individual mean CO_2 and VOC measures were compared with one another (Figure 2), the correlation coefficient (r) was 0.63 ($p < 0.01$).

Threshold variation by subject characteristics. For the univariate analyses, the distribution of (log-transformed) mean CO_2 detection thresholds by sex is plotted in Figure 3 and of VOC localization thresholds by sex in Figure 4. Female sex predicted lower thresholds in both test systems ($p < 0.05$ and 0.001, respectively). Also for the univariate analysis, the distribution of sensory thresholds with respect to rhinitis status appears in Figures 5 (CO_2 detection) and 6 (VOC localization). Rhinitis status did not significantly predict sensory thresholds, although for both measures the central tendency (mean) differed in the hypothesized

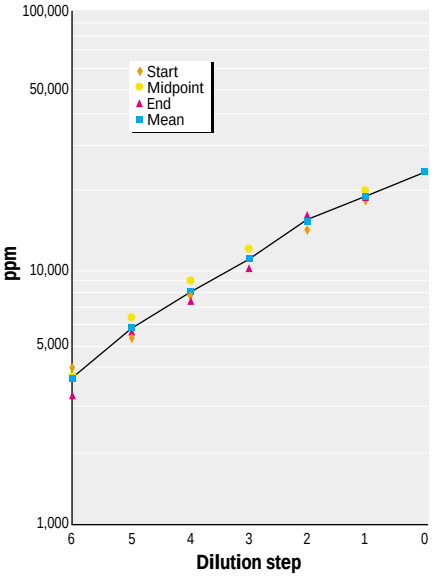

Figure 1. Mean (range) headspace *n*-propanol concentrations (in ppm, vol/vol) by dilution step. Gas chromatographic determinations were obtained at the beginning, midpoint, and conclusion of the study.

direction (i.e., rhinitics lower). In a multivariate ANOVA model (explanatory variables = rhinitis + sex), rhinitics did show lower (log-transformed) VOC localization thresholds (but not CO_2 detection thresholds) than did nonrhinitics ($p < 0.05$), and sex continued as a significant predictor for both sensory endpoints ($p < 0.001$ for VOC localization and $p < 0.05$ for CO_2 detection). We noted no significant interaction between the two explanatory variables.

Discussion

In this relatively limited-scale investigation (64 testing sessions total), both sensory tests—CO_2 detection and VOC localization—showed relatively modest stability over time ($r = 0.60–0.65$). Nevertheless, when replicate determinations were averaged for a given individual, results not only co-varied with those obtained using the complementary test system ($r = 0.63$; $p < 0.01$), but also differed by one (or both) imputed population marker of nasal irritant sensitivity (depending on the specific model and endpoint). In this analysis, although CO_2 detection appeared to be the more stable measure, VOC localization demonstrated more systematic variation by subgroup, in keeping with the *a priori* hypotheses.

With regard to stability of measures, several potential sources of variability may be operative. Mucous membrane irritation tends to be cumulative (*32*), and in each testing session the degree of stimulation prior to presenting at the "true" threshold concentration could conceivably affect observed results. To control for cumulative irritation, we tested for the full criterion number of trials at each concentration level before proceeding to the next higher level, even after an erroneous response was given. Beyond this factor, it is conceivable that variation in stimulus order within a given concentration step could affect outcome. However, the known advantage of stimulus order randomization—maintenance of subject blinding—was judged to outweigh its potential disadvantage (bias of results toward the null).

Beyond variability in testing procedures, individual factors could, indeed, have affected results. In general, such factors include attentiveness and mood (*33*), although in this study such airway-specific factors as consumption of hot or spicy foods, exposure to environmental pollutants, exercise (alters upper airway caliber), or allergic/ infectious processes could influence outcome. To avoid such potential confounders, smokers were excluded from the study, subjects were asked to avoid eating, exercise, or use of personal fragrance products before testing, allergic rhinitic subjects were tested outside of their identified allergy season, and any subject reporting "cold" symptoms was rescheduled after a 3-week symptom-free interval.

Despite the relatively small sample size, this study illustrates the potential utility of two different test systems for estimating nasal irritant sensitivity (perceptual acuity) in individual subjects. The resulting data may be used to explore both random and systematic variability in this trait. Our results suggest not only that there is significant interindividual variability in nasal trigeminal sensitivity (perceptual acuity) but also that *a*) variability may pertain across classes of chemical agents, and *b*) variability may be nonrandom in the

Table 1. Characteristics of study subjects.

Sex	Rhinitis	Number	Mean age (range)
Male	Yes	4	31.3 (26–37)
	No	4	25.8 (20–33)
	Combined	8	28.5 (20–37)
Female	Yes	4	21.8 (19–25)
	No	4	24.5 (19–36)
	Combined	8	23.1 (19–36)

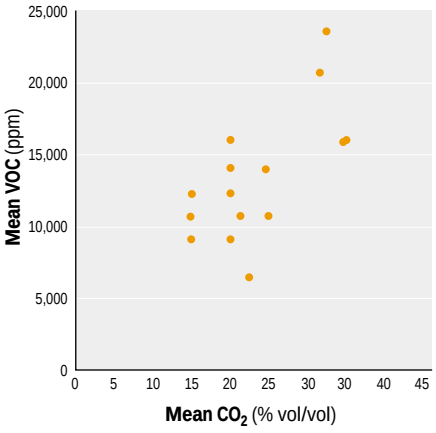

Figure 2. Intertest comparison: individual mean CO_2 detection vs. VOC localization thresholds ($r = 0.63$; $p < 0.01$). Number of observations exceeds number of data points due to identical observations.

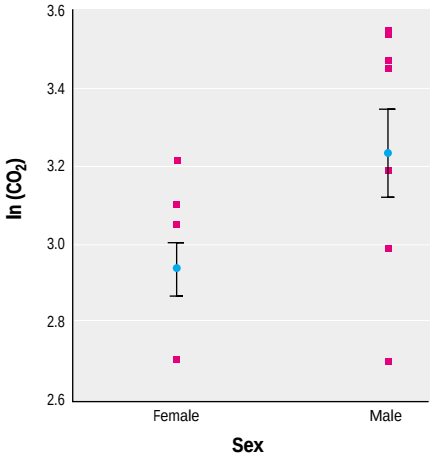

Figure 3. Log (individual mean) CO_2 detection threshold by sex ($f = 5.26$; $p < 0.05$). Number of observations exceeds number of data points due to identical observations.

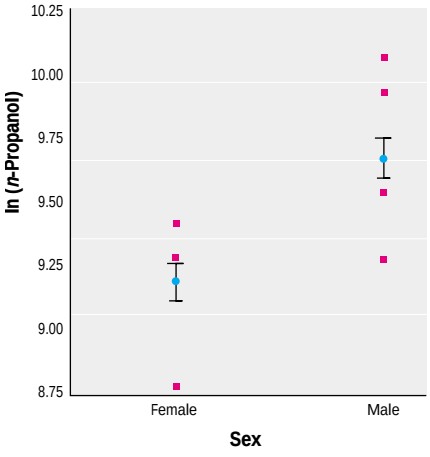

Figure 4. Log (individual mean) VOC localization threshold by sex ($f = 18.51$; $p < 0.001$). Number of observations exceeds number of data points due to identical observations.

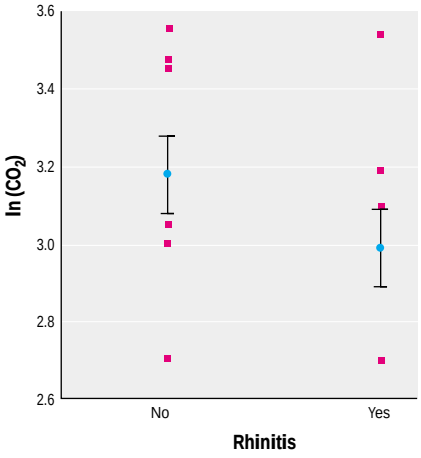

Figure 5. Log (individual mean) CO_2 detection threshold by allergic rhinitis status ($f = 1.61$; $p = 0.23$). Number of observations exceeds number of data points due to identical observations.

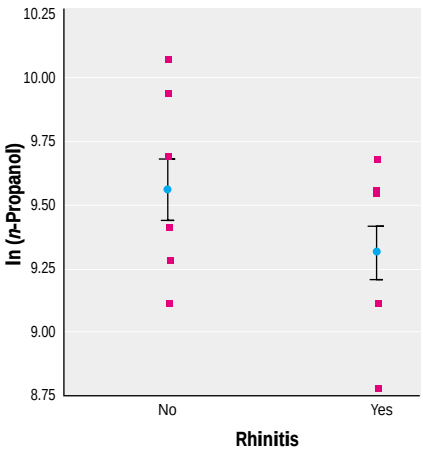

Figure 6. Log (individual mean) VOC localization threshold by allergic rhinitis status ($f = 2.42$; $p = 0.14$). Number of observations exceeds number of data points due to identical observations.

population, with sex—and possibly allergy status—predicting outcome.

Several refinements are planned for a larger-scale study that is about to commence based on the results of this pilot work. Age will be an additional focus of the study, with subjects being recruited through their late 60s. More precise control of stimulus concentration will be possible for the VOC localization task based upon regular (i.e., weekly) use of gas chromatography to document headspace concentrations. Finally, formal power calculations have ensured that the projected sample size (48) will be adequate to address the hypotheses posed: that female, allergic rhinitic, and younger subjects will show greater nasal perceptual acuity to irritants than will male, nonallergic, and older subjects.

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