



ABSTRACT

Background: The degree to which allergy symptoms experienced upon pollen exposure in a pollen chamber correlate with those experienced in the natural season is unknown.

Purpose: To determine whether allergy symptoms to short ragweed in a pollen chamber predict symptomatology in the giant ragweed natural season.

Methods: Thirty-one ragweed sensitive subjects recorded symptoms during the natural ragweed season in San Antonio, TX. Ragweed pollen in grains/m³ was counted daily. Twenty-six of these subjects were challenged to short ragweed pollen in a chamber outside the natural season for 3 hours/day for up to 4 days. Symptoms and pollen counts were recorded at 30 minute intervals. Symptomatology in the chamber and natural season was compared in the 26 subjects who completed both studies.

Results: Twenty-six/31 subjects recorded reflective total nasal symptom scores (TNSS) and reflective total ocular symptom scores (TOSS) at significant levels during the natural season with mean pollen counts of 774/m³. There was no association between the pollen count and symptoms. During chamber runs, 17/26 subjects recorded significant instantaneous TNSS and 16/26 recorded significant instantaneous TOSS at mean pollen count of 3450/m³. Hierarchical clustering identified three clusters of individuals: clusters 1 and 2 were those who had concordantly high (n=14) versus low (n=7) total symptom scores (TSS) in both the natural season and the chamber, and accordingly, the correlation between the TSS recorded in the natural season and chamber for these 21 subjects was very high (r=0.90; P<0.0001). Although persons in cluster 3 (n=5) had much greater TSS in the natural season than in the chamber, the degree of correlation in the TSS recorded remained high (r=0.98; p=0.003). Persons with a high TSS in the chamber were nearly 12-fold more likely to have also had a high TSS in the natural season (OR=12.38; 95% CI=1.69-90.58; P=0.021). No serious adverse events occurred.

Conclusions: The degree of symptoms experienced upon exposure to short ragweed pollen in a chamber and giant ragweed in the natural season correlates highly. Additionally, we identified three specific allergic endophenotypes. These data suggest that pollen chamber studies may help elucidate mechanisms underlying pathogenesis of allergies and provide insight into biological effects, mechanisms of action and dose-response characteristics of therapies directed against allergens.

INTRODUCTION

Pollen challenge chambers have been utilized for several years to study certain characteristics of drugs by stimulating symptoms in a controlled environment.

Correlation of symptoms between those induced in a chamber and those of a natural seasonal exposure is unknown.

METHODS

Natural Season

- Thirty-one subjects, males and females, 18-65 years of age, with a ≥2 years history of seasonal allergic rhinitis to ragweed pollen and a ≥5 mm positive response over a saline control by prick skin testing to ragweed mix, were selected for the study.
- Upon obtaining written consent, the following procedures were performed.
- Review inclusion/exclusion criteria. Obtain demographic information, medical history, and concomitant medication use.
- Vital Signs were obtained and physical examination performed.
- A standard prick skin test was done.
- Urine pregnancy test performed on all female subjects.
- Subjects were instructed to discontinue any disallowed medication.
- A Medical Events Calendar and Subject Daily Diary were dispensed.
- Symptoms were self-scored with a Likert scale with the values of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe) during the peak of the natural ragweed season.
- After collection of diary data, an out-of-season chamber exposure was scheduled.

Chamber Exposures

- Twenty-six of the 31 natural seasonal subjects, meeting entry criteria, were exposed to 3500 grains/m³ of defatted short ragweed (*Ambrosia artemisiifolia*) pollen during a series of priming chamber runs of 3 hours duration on sequential days.
- Symptoms were self-scored on a Likert scale of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe).
- Symptoms that were scored included nasal congestion, sneezing, rhinorrhea, and itching. Ocular symptoms included redness, tearing, and itching.
- The pollen delivery and dispersal system was activated at pre-set levels to deliver 3500 pollen grains/m³.
- Pollen was monitored utilizing Allergenco Cassettes at 30 minute intervals.
- Subjects recorded signs, symptoms, and adverse responses at baseline and 30 minute intervals on a manual chamber diary card.
- 4 chamber runs were conducted that were of 3 hour durations.
- TNSS and TOSS were computed as was the composite TSS.
- Subjects were considered primed if meeting priming criteria (TNSS>6).

Statistical Analysis

- Pearson correlation coefficient was used to determine the correlations of TSS between chamber and natural season.
- The effects of (i) increasing duration of exposure time in the chamber, and (ii) each additional day of a chamber run on TSS was assessed using linear generalized estimating equations (linear GEE) models.
- The maximum value that was within two standard deviations from the mean TSS was considered as the maximum chamber or natural season TSS value abbreviated as cTSSmax and nTSSmax, respectively.
- Linear regression was used to examine the relationship between cTSSmax and nTSSmax in both concordant and discordant group.
- Hierarchical clustering was used by taking into account of both cTSSmax and nTSSmax.

RESULTS

Fig. 1. Study design and participants

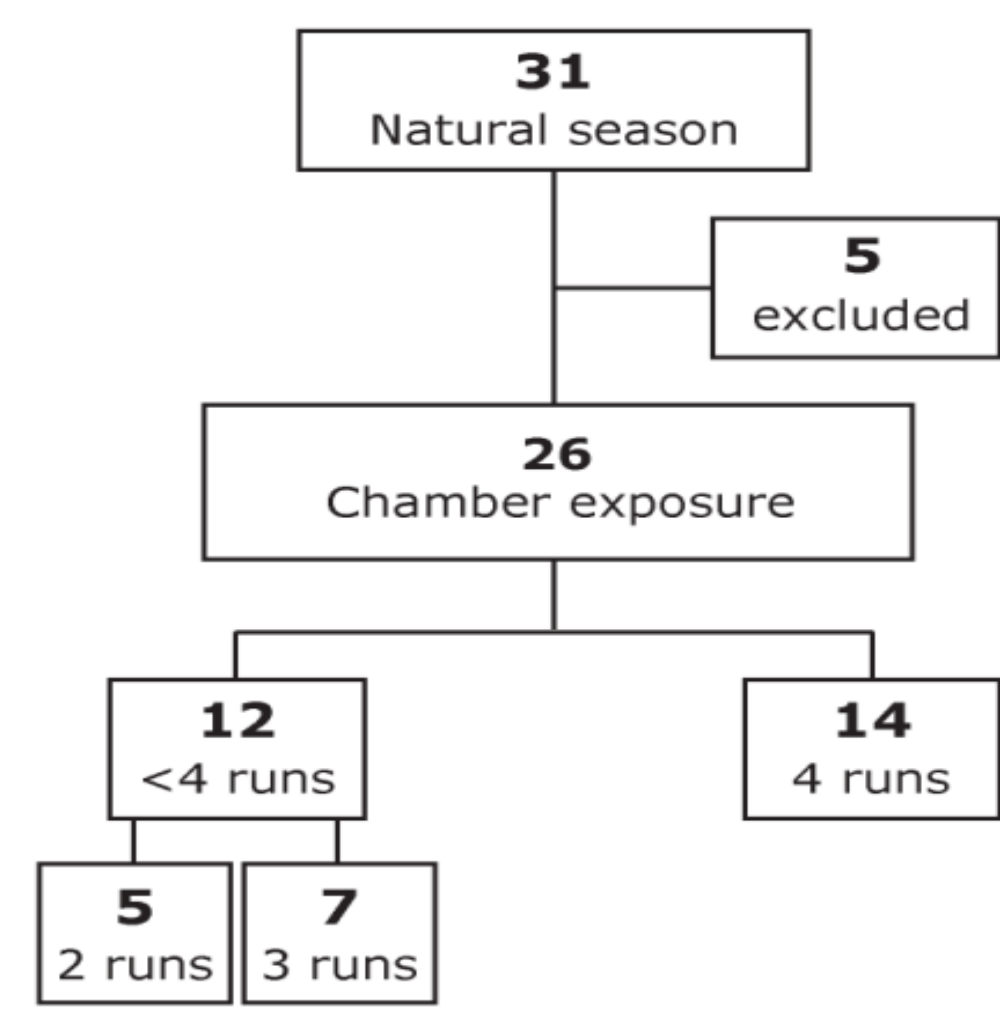
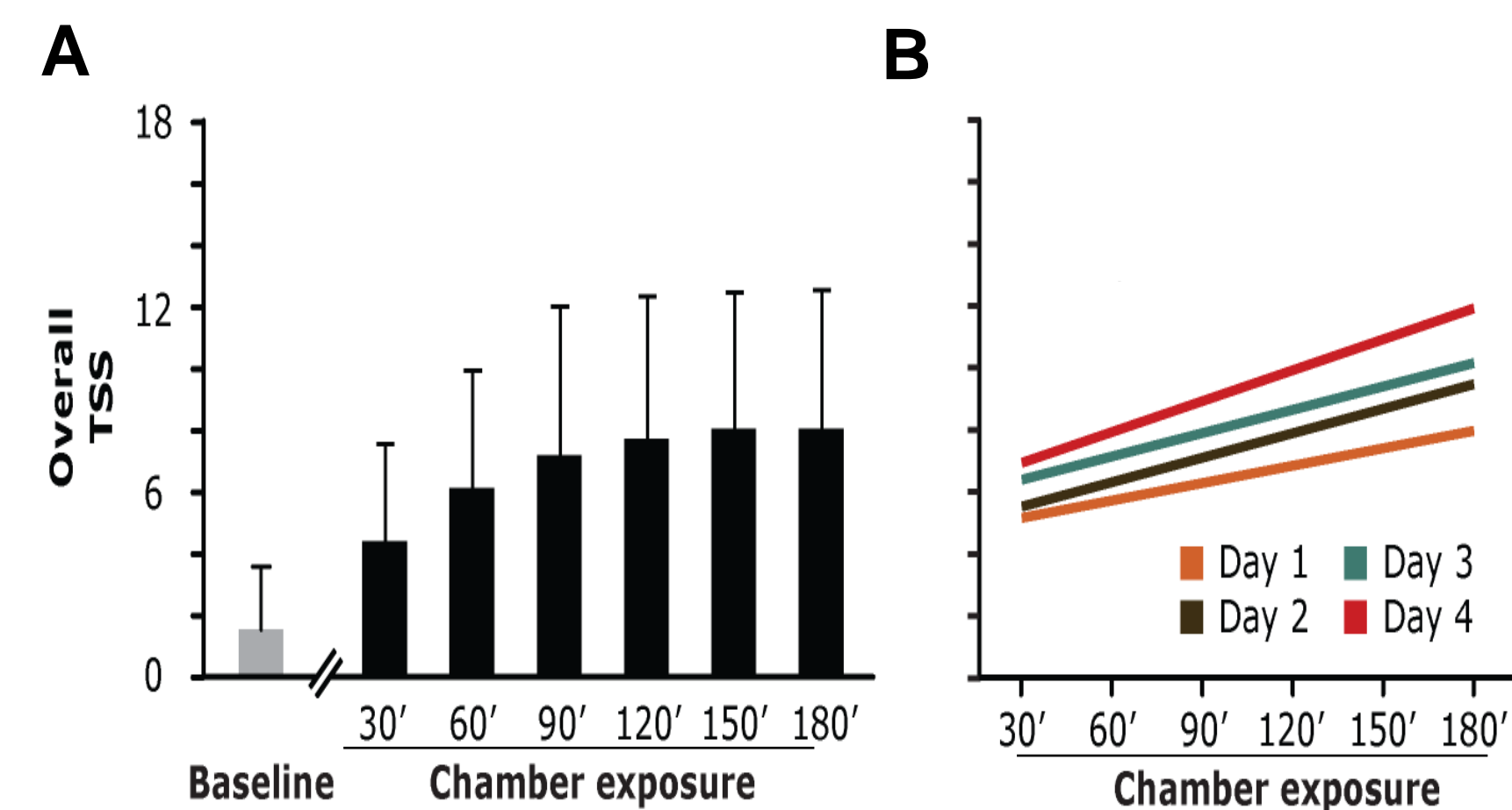
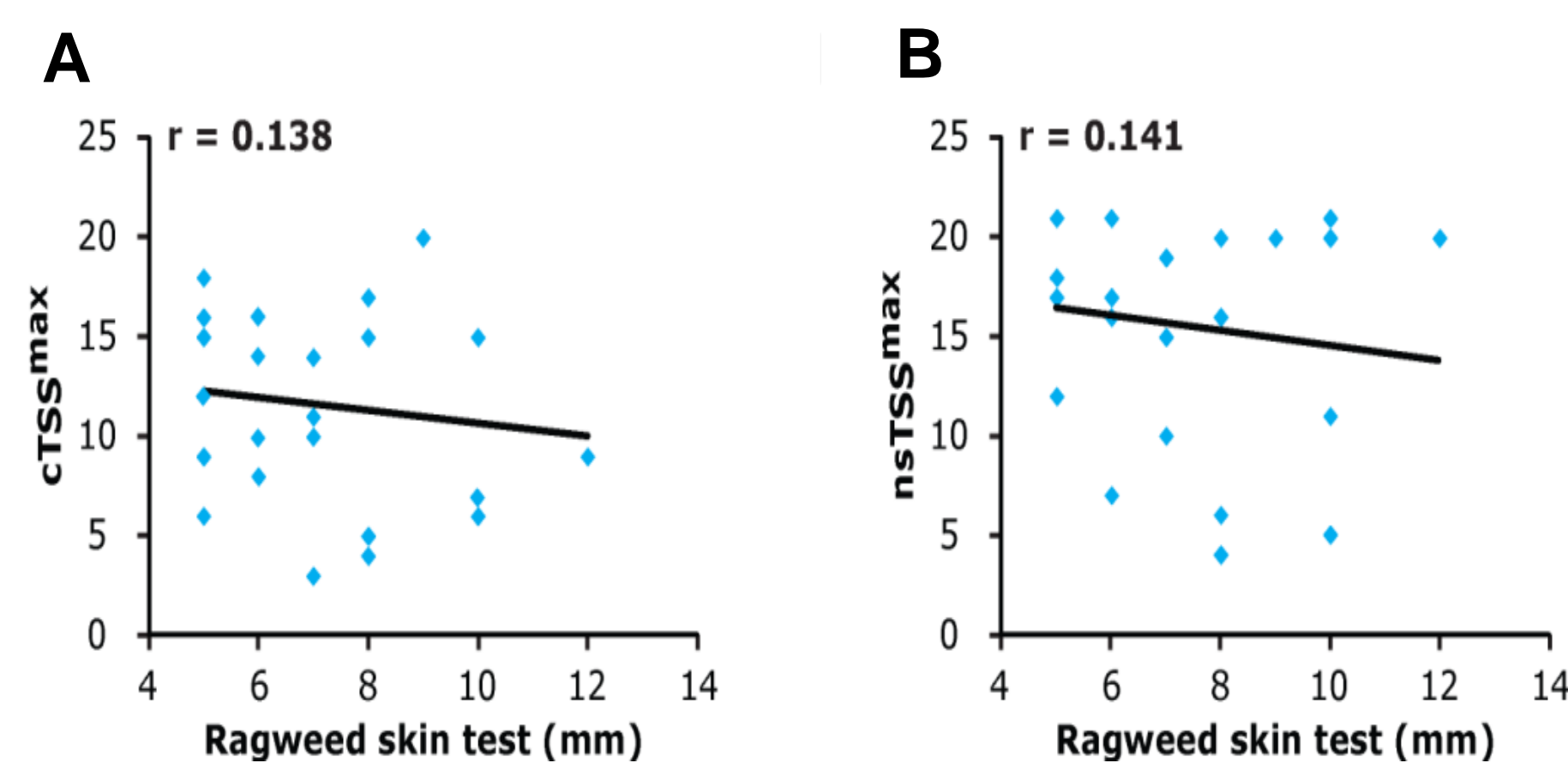


Fig. 3 Chamber exposure induced symptoms within 30 min.



(A) Baseline TSS (mean ± SD) was derived by 9 pre-challenge measurements, and also depicted are the mean TSS (± SD) for measurements at the indicated time-points recorded on all 4 days of the chamber runs. (B) Linear GEE depicts changes in TSS on each of the given chamber runs.

Fig. 5 Lack of correlation between ragweed skin test and TSS



RESULTS (cont.)

Fig. 2 Lack of correlations between TSS and pollen count during the natural season

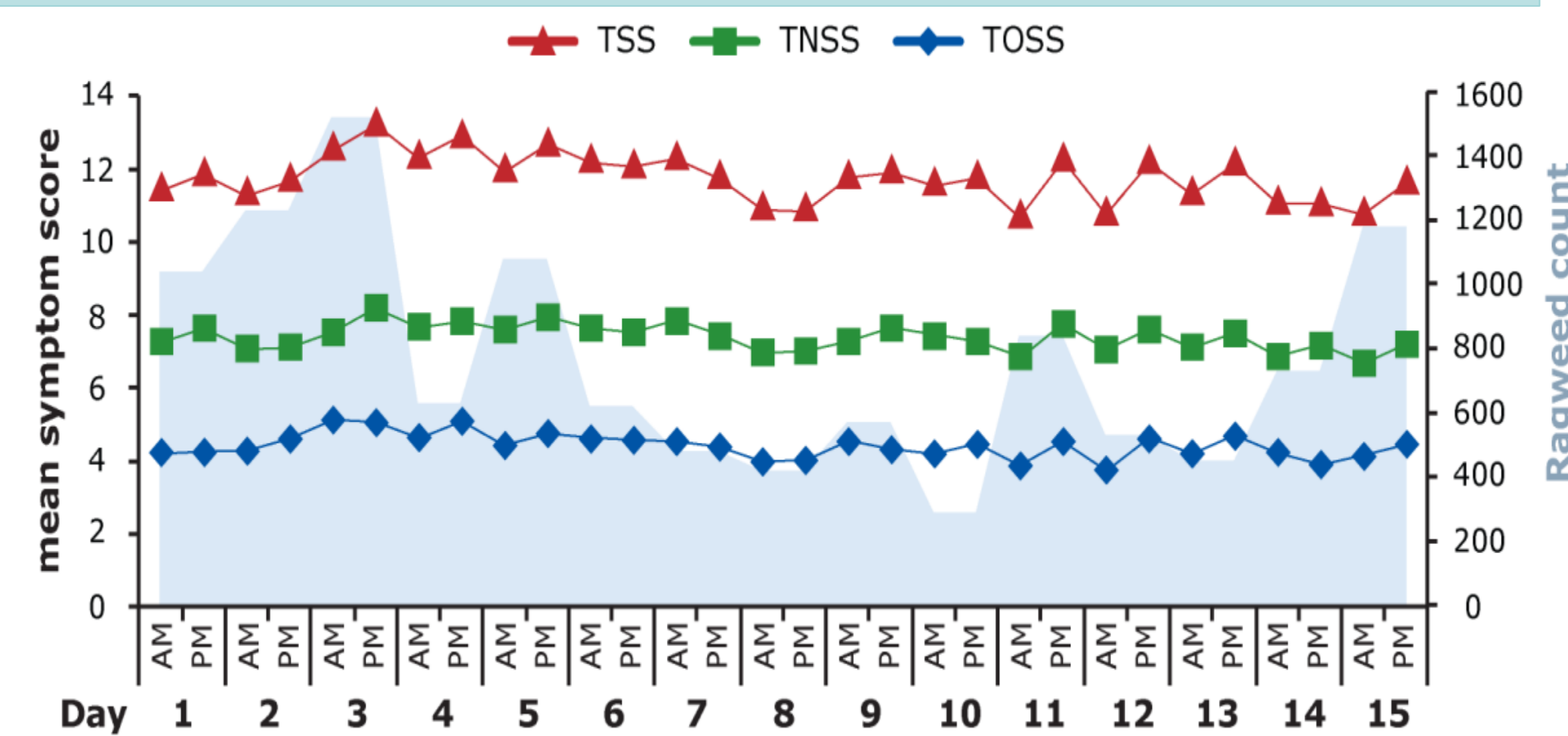
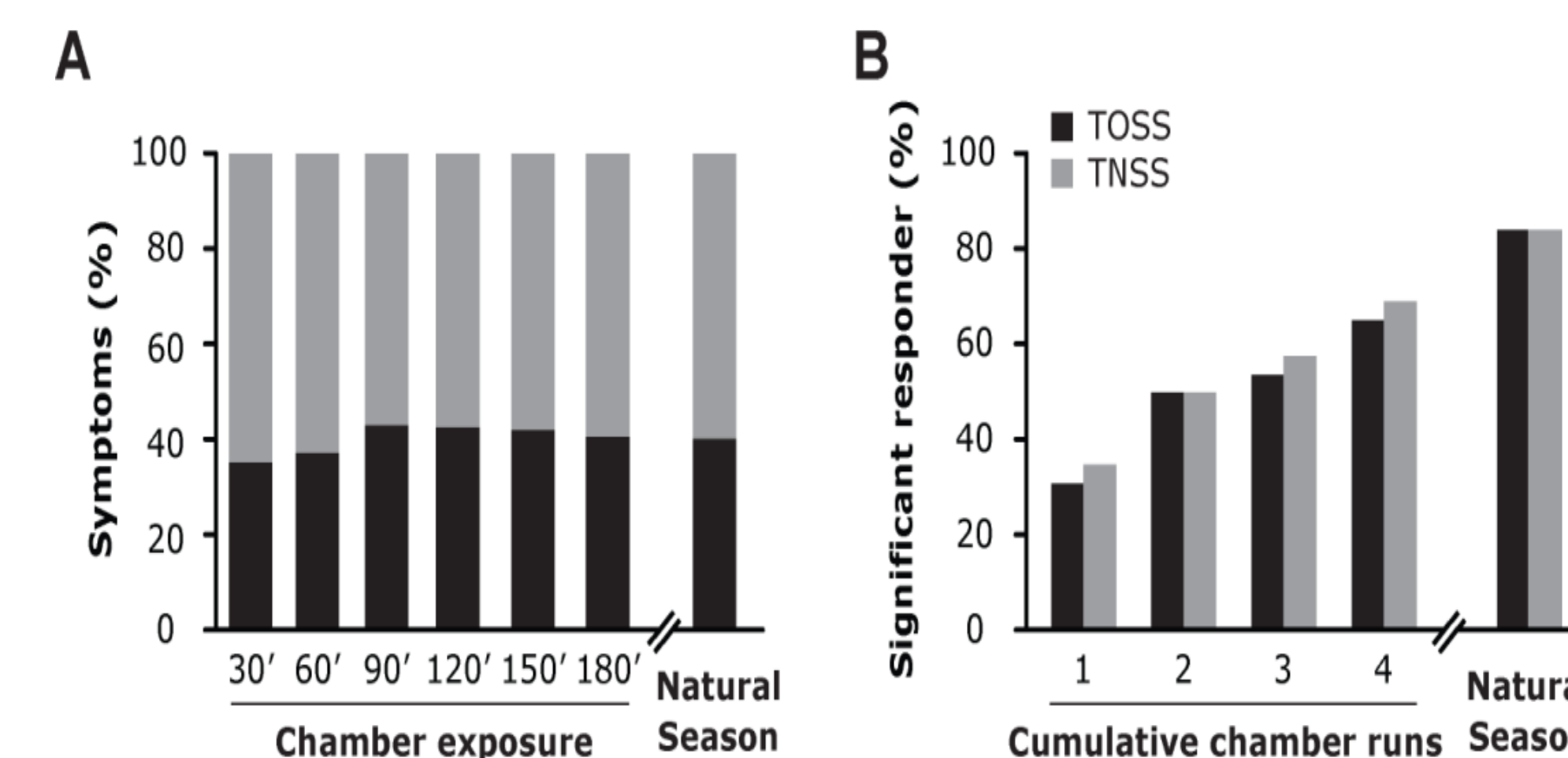


Fig. 4 Comparable TOSS and TNSS in chamber and natural season



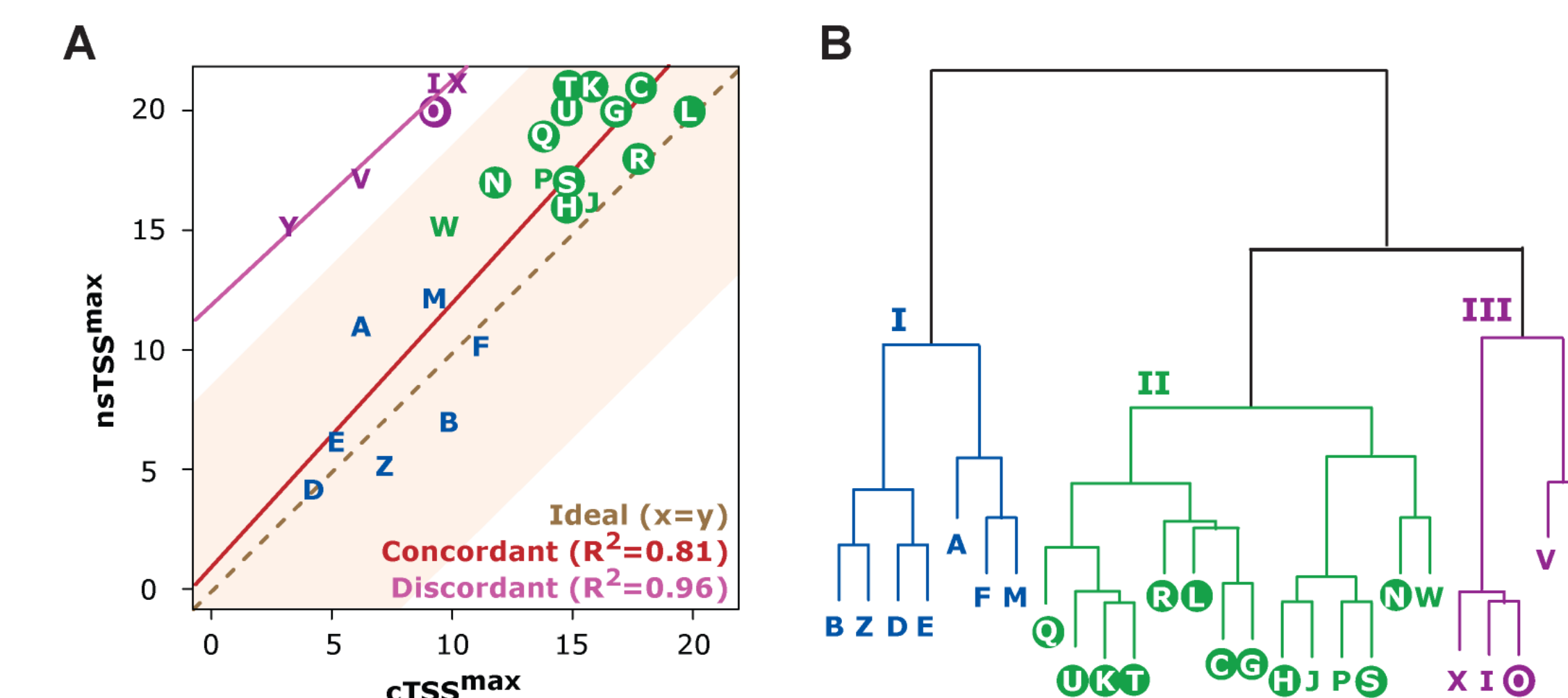
(A). Contribution of TOSS and TNSS to TSS in chamber and natural season. (B) Proportion of significant responder by TOSS (score ≥5) and TNSS (score ≥7) in chamber runs and in natural season. The number of subjects that classified as responders increased progressively, and represented as cumulative chamber runs.

Table. 1 High correlation of symptoms between natural season and chamber

Symptom Score comparison	correlation R	P value
TOSS components		
Eye itch	0.49	0.010
Tears	0.56	0.003
Redness	0.54	0.004
TNSS components		
Congestion	0.58	0.001
Sneezing	0.21	0.298
Runny Nose	0.17	0.397
Nasal Itch	0.63	3.59E-04
TSS Components		
TOSS	0.57	0.002
TNSS	0.56	0.002
TSS	0.65	1.95E-04

RESULTS(cont.)

Fig. 6 High correlation between TSS in natural season and chamber runs



(A) Correlation of maximum TSS in natural seasons (nTSS^{max}) and chamber (cTSS^{max}). Two major clusters of subjects (letter- and color-coded) were identified (purple vs. green/blue letters). Purple color-coded participants represents those in whom nTSS^{max} is greater than cTSS^{max}, i.e., discordant group. Green- and blue- color-coded participants respectively represent those with concordantly high vs. concordantly low TSS in both chamber and natural season, i.e., concordant group. The purple and red lines represent the correlation lines for the discordant and concordant groups, respectively and R² values for the correlation are shown. The dashed line represents the ideal correlation (Y=X), and the band (light brown) represents ± 2SD of the ideal line. (B) Cluster analysis based on both nTSS^{max} and cTSS^{max}. Subjects were color- and letter-coded as described in panel A. Shaded letters represent subjects who exited the study before completion of 4 chamber runs. Cluster I and II are those with concordantly low vs. high symptoms scores, respectively in both chamber and natural season. Cluster III represent those who have higher symptom scores in the natural season compared with chamber.

These data suggests that both the concordant group and the discordant group have similar relationships between the maximum chamber TSS and the maximum natural season TSS. The greatest difference is that the discordant group does not obtain a similar level of maximum TSS in the chamber run as that observed in the natural season. In both groups, the maximum chamber TSS does predict the maximum natural season TSS with high accuracy.

CONCLUSIONS

- The degree of symptoms experienced upon exposure to short ragweed pollen in a chamber and giant ragweed in the natural season correlates highly.
- Ragweed sensitive subjects in South Texas responded to common, or short, ragweed pollen in a pollen challenge chamber similar to responses reported from geographic areas where short ragweed is the dominant species.
- There was also significant correlation between individual symptom scores between the natural season and the chamber exposure.
- There was no correlation between level of skin test reactivity and symptoms scores during the natural season as well as the chamber exposure. Natural season non-responders failed to prime in the chamber.
- These data suggest that pollen chamber studies may help elucidate mechanisms underlying pathogenesis of allergies and provide insight into biological effects, mechanisms of action, and dose-response characteristics of therapies directed against allergens