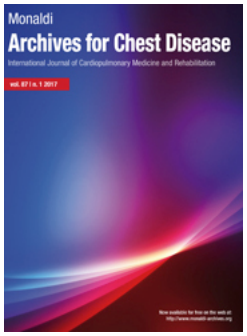

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Skin prick test wheal size: a potential predictor of respiratory allergies?

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CC for the manuscript re-editing process; GL, CM, FDB, AP, DG, AP, MLS, FM, AS, skin prick tests and data collection. All the authors critically revised and approved the manuscript.

Conflict of interest: all the authors declare that they have no conflict of interest.

Ethics approval and consent to participate: our study did not require the approval of the Ethics Committee because the procedures were part of the routine diagnostic allergy tests (Skin Prick Test). Usually, these tests are preceded by a verbal informed consent obtained after full explanations about the procedures and the related possible (very rare) side effects. Patients' data were anonymized for recording purposes.

Informed consent: verbal informed consent (as per clinical practice).

Patient consent for publication: not applicable.

Availability of data and materials: the materials related to this study (medical records and original statistical processing) are available on demand and are stored at UO University Hospital "O.O.R.R. San Giovanni di Dio and Ruggi d'Aragona", Salerno, Italy.

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Dear Editor,

The skin prick test (SPT) is the most commonly used method for diagnosing IgE-mediated sensitizations in conditions like bronchial asthma, allergic rhinitis, and food allergies. This is due to its cost-effectiveness, rapidity, non-invasiveness, and high diagnostic accuracy.

In clinical practice, the wheal is typically used to assess the positivity of the skin test, while erythema is generally not considered essential. Only wheal diameters ≥ 3 mm are regarded as positive in SPTs, as diameters < 3 mm are not deemed clinically significant. Some authors suggest that skin test results to allergens should always be correlated with the size of the histamine-induced reaction. However, others argue that histamine reactivity in the skin can vary among individuals, regardless of their skin test reactivity to allergens. In fact, studies have shown that the size of the wheal is not solely attributed to histamine release. For instance, some patients with positive SPT reactions do not exhibit significant histamine release to allergens when assessed using microdialysis techniques.

Another controversial issue is whether the degree of the allergen-induced skin response is correlated with the onset or severity of clinical symptoms. While some authors believe that larger reactions do not necessarily indicate more severe disease, others have shown significant correlations. For example, Nur Husna et al. demonstrated a significant correlation between wheal sizes in response to *Dermatophagoides farinae* sensitization and the severity of both nasal and non-nasal symptoms [1]. Similarly, Madani et al. found that a wheal size >6 mm was associated with more severe allergic rhinitis symptoms, particularly in patients sensitive to Alternaria, weed pollens, and tree pollens [2]. Haahtela et al. also reported that the risk of allergic nasal/bronchial symptoms increased significantly with larger wheal sizes for almost all common allergens tested [3].

Building on this background, the aim of this study was to investigate the correlation between skin responses to SPTs (conducted using a standardized methodology) and the key clinical and anamnestic parameters of patients sensitized to at least one common allergen in the Campania region (Southern Italy). Six allergy units or centers affiliated with the Italian Association of Hospital and Territorial Allergologists (AAIITO, Campania region), uniformly distributed across the region, participated in this cross-sectional study. A shared protocol was implemented across all participating centers, which collected data from consecutive outpatients aged 6-75 years referred for suspected or current respiratory allergies (asthma and/or rhinitis). Patient enrollment started on January 1 and concluded on June 30, 2019.

A case report form (CRF), specifically designed for this study, was completed during the screening consultation for each patient. The standardized form included demographic data, type and duration of respiratory symptoms, pet ownership, SPT results, and age of onset of respiratory symptoms. Diagnosis of respiratory allergy was made according to international guidelines. Commercial allergen extracts used for SPTs were provided by ALK-Abellò Group (Milan, Italy). A standard panel of allergens, covering the main causative agents of respiratory allergies in the Campania region, was used. This panel included *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog dander, *Parietaria*, grass pollen mix, *Artemisia vulgaris*, *Olea europaea*, *Betula pendula*, *Cupressus sempervirens*, and *Corylus avellana*. Positive (10 mg/ml histamine HCl) and negative (saline solution in glycerine-phenol solution) controls were also used. SPTs were performed and interpreted following international guidelines; results were read after 15 minutes and recorded as the mean of the major wheal diameter plus its orthogonal. A skin reaction of 3 mm or greater was considered positive. Wheal profiles were outlined using a fine-point marking pen and transferred by adhesive tape onto the patient's CRF. Patients with chronic or metabolic diseases, severe cutaneous disorders, negative skin reactions to histamine, or those on medications affecting skin responses were excluded from the study.

A total of 454 patients were examined (230 females, 51%). For the purposes of this study, we selected only those patients with positive SPTs to at least one allergen, all of whom had been diagnosed with respiratory allergy (Table 1).

In Figure 1, we report wheal diameters (from 0 to 3) and the percentages of allergic sensitizations for the most common allergens tested.

The main finding of our study was that asthma was more frequently associated with wheals larger than 10 mm for *D. farinae*. Specifically, 46.7% of patients with a >10 mm wheal had asthma, compared to 18.4% and 32.3% of patients with >5-10 mm and 3-5 mm wheals, respectively ($p = 0.002$) (Table 2). Similar trends were observed for *D. pteronyssinus* in allergic rhinitis, with 95.2% of patients having a >10 mm wheal compared to 89.8% and 81.1% of patients with 5-10 mm and ± 3-5 mm diameters, respectively ($p = 0.055$). Larger wheals were also associated with early onset of respiratory nasal/bronchial symptoms (<10 years) ($p = 0.021$), male gender ($p = 0.011$), younger age at the time of skin testing ($p = 0.005$), no association was found between wheal size and other age groups. As regard older patients this last finding is in contrast with what is reported by Scichilone et al. [4], and also by Liccardi et

al. [5], which seem to support the decline of allergen sensitization with age. This discrepancy is probably due to differences in the objectives of the studies. No correlation was found between allergen wheal diameters and histamine wheal diameters as well as there is no difference in histamine wheal diameters in various age groups.

We believe our findings have significant clinical relevance and align with the natural history of allergic bronchial asthma. Dust mites are the most common cause of allergic sensitization in the early years of life, and constitute a relevant risk factor for the onset of nasal and later, in susceptible individuals, bronchial symptoms. It is also well established that these conditions are more common in males, at least until adolescence.

In conclusion, our study underscores the importance of properly executing SPT, with particular attention to accurately measuring wheal diameters, especially in younger patients. In fact, we have found an association between the wheal diameters and presence of respiratory symptoms in individuals sensitized to dust mites.

Prospective longitudinal studies are needed to confirm these findings and also to explore the possibility that the degree of wheal diameters could be associated with the severity of nasal and, above all, of bronchial symptoms in sensitized individuals.

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Table 1. Baseline demographic characteristics (n=454).

Total N°	454	
Median age [IQR]	30 [21,42]	
Gender M/F n (%)	224/230 (49/51)	
Family history of atopy		
No	140	31%
Yes	219	48%
Smoking		
No	262	58%
Yes	61	13%
Former	31	7%
Exposure to pets		
No	255	56%
Yes	96	21%

IQR, interquartile range; M, males; F, females.

Table 2. Frequency of clinical manifestations according to wheal diameters of Dermatophagoides farinae and Dermatophagoides pteronissinus.

D. farinae				
Wheal (mm)	3-5	>5-10	>10	Total
No asthma	65 (67.71%)	200 (81.63%)	8 (53.33%)	273 (76.69%)
Asthma	31 (32.29%)	45 (18.37%)	7 (46.67%)	83 (23.31%)
Total	96 (100.00%)	245 (100.00%)	15 (100.00%)	356 (100.00%)
p=0.002				
D. pteronissinus				
Wheal (mm)	3-5	>5-10	>10	Total
No rhinitis	17 (18.89%)	26 (10.24%)	1 (4.76%)	44 (12.05%)
Rhinitis	73 (81.11%)	228 (89.76%)	20 (95.24%)	321 (87.95%)
Total	90 (100.00%)	254 (100.00%)	21 (100.00%)	365 (100.00%)
p=0.055				

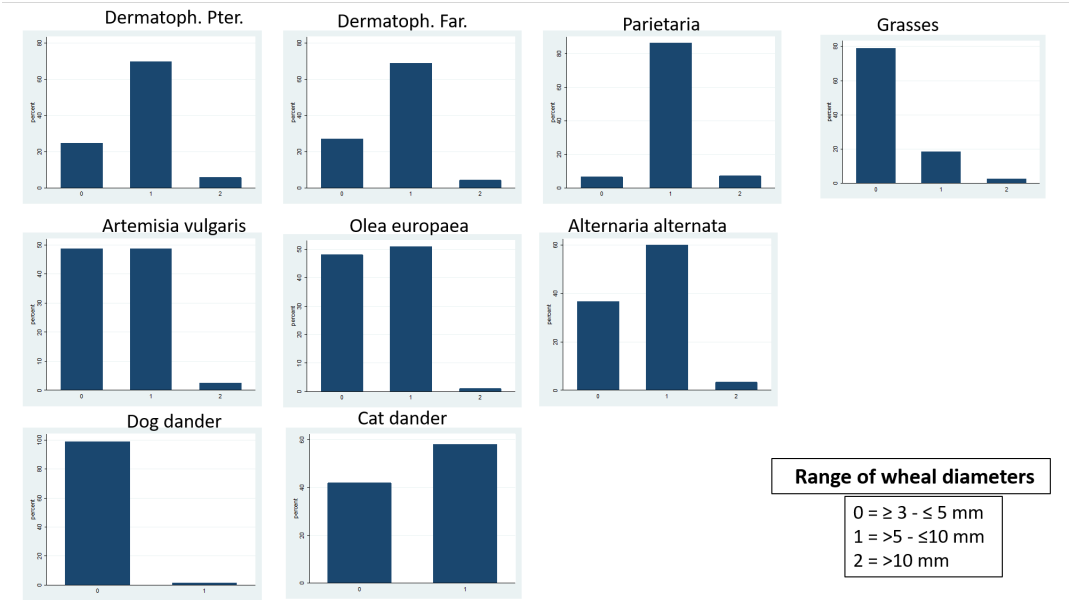

Figure 1. Frequency of allergic sensitizations for the most common allergens tested, grouped per wheal diameters.