Evaluation of Skin Prick Test Reading Time at 10 versus 15 min in Young Infants

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Keywords
Allergic sensitization · Infant · Mean wheal diameter · PreventADALL · Skin prick test

Abstract

Introduction: The optimal time point for reading the mean wheal diameter (MWD) of a skin prick test (SPT) in infants is not established. We aimed to assess if either of two reading time points of the SPT, 10 or 15 min, was superior to detect allergic sensitization (AS) in 6-month-old infants. Methods: In 1,431 6-month-old infants from the population-based Preventing Atopic Dermatitis and Allergies in children (PreventADALL) mother-child cohort, the SPT was performed with standard solutions for egg, cow’s milk, peanut, wheat, soy, birch, timothy, dog, and cat. The MWD was measured after 10 and 15 min. AS was defined as a positive SPT with MWD ≥2 mm larger than the negative control. Results: Overall, 149 (10.4%) infants were sensitized to at least one allergen at 10 and/or 15 min, while 138 (9.6%) had a positive SPT at 10 min and 141 (9.9%) at 15 min. A total of 12,873 allergen pricks were performed with 212 (1.6%) being positive at any time point, 194 (1.5%) positive at 10 min, and 196 (1.5%) positive at 15 min. The mean (95% CI) histamine MWD of 3.8 (3.8, 3.9) mm at 10 min was significantly larger than the 3.6 (3.6, 3.7) mm at 15 min. Discussion/Conclusions: Reading the SPT after both 10 and 15 min increased the number of 6-month-old infants with documented AS compared to reading after one time point only. As neither 10 nor 15 min...
reading time was superior to the other in detecting AS, our results indicate that readings at both time points should be considered. However, the histamine MWD was significantly larger at 10 min compared to 15 min. Reappraisal of SPT reading in infancy may be warranted.

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Introduction

Allergic diseases are common and often start in infancy [1, 2]. Allergic sensitization (AS) represents the presence of specific immunoglobulin E (IgE) antibodies to allergens [3], is associated with allergic diseases such as food allergy and allergic rhinitis, and may manifest from early infancy [1]. The skin prick test (SPT) is an indirect method for detecting IgE antibodies [3], commonly used in clinical practice and epidemiologic studies [1, 4], and has been used to screen infants before initiating interventions for primary prevention of food allergy [5, 6]. The SPT wheal size is measured after 15–20 min in the standard procedure [3] and is considered positive with a mean wheel diameter (MWD) of ≥3 mm larger than the negative control [3].

Infants have a decreased skin reactivity to skin prick testing compared to adults [3, 7, 8]. Therefore, to avoid underdiagnosis of AS in infants, several studies [4, 9, 10] report AS defined as MWD ≥2 mm, rather than the standard ≥3 mm. The histamine wheal has been shown to taper after 10 min [8, 11, 12], while it is not clear if this may also be the case for allergen-specific wheals in infants. Apart from the recent publication of Beken et al. [8] indicating that the SPT should be read at 10 min in children below 2 years of age, we are not aware of other studies assessing the optimal time to read the allergen wheal size during the SPT in infants. Our objective was to explore if reading the SPT wheal size earlier than standard 15–20 min would impact the detection of AS in 6-month-old infants. The primary aim was to assess if either time point of 10 or 15 min was superior to detect AS. Secondly, we aimed to explore differences in MWD (in mm) of specific allergen and histamine at 10 versus 15 min.

Methods

Study Design and Setting

The study used data from 1,431 infants in the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) study, a multicentre, cluster-randomized controlled trial and prospective observational population-based mother-child birth cohort described in detail elsewhere [13]. Briefly, PreventADALL enrolled 2,697 pregnant women in Norway (Oslo University Hospital and Østfold Hospital Trust) and Sweden (Karolinska Institutet) between December 2014 and October 2016, and 2,397 babies were included at birth, resulting in 2,394 mother-child pairs (three withdrew their consent after newborn inclusion) [13]. Exclusion criteria were insufficient skills in Nordic languages, more than two foetuses, foetuses or infants with severe disease or malformation, and birth before 35 gestational weeks. The children were followed with clinical visits at 3, 6, 12, 24, and 36 months of age, and the mothers filled out electronic questionnaires in pregnancy week 18 and 34, weekly the first 26 weeks after giving birth and then every 3–6 months. The present study reports results of routine SPT measurements at the 6-month follow-up visit.

Ethics

The PreventADALL study was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (2014/518) and in Sweden (2014/2242–31/4) and registered at ClinicalTrials.gov (number NCT02449850). Written informed consent was obtained from the mothers at inclusion in pregnancy and from both parents at inclusion of the newborn baby.

Subjects

The present study included 1,431 infants with histamine and at least one allergen-specific skin prick performed, read, and reported after both 10 and 15 min at the 6-month follow-up. We excluded 553 infants with readings after 10 min only (as was the procedure during the first 6 months of the trial), 5 with reading after 15 min only and 5 children with missing results for all allergens or histamine at both time points.

Skin Prick Test

The SPT was performed by trained study personnel. Nine standard solutions (egg, cow’s milk, peanut, wheat, soy, birch, Timothy, dog, and cat), histamine, and negative (saline) control (all from Soluprick ALK-Abelló, Hørsholm, Denmark) were applied on the volar side of the forearms in 1994 of the 2021 attending infants and pricked with a metal lancet (ALK-Abelló). The MWD was derived as the sum of the longest diameter and the diameter perpendicular to this divided by 2 and reported in mm without decimals. An MWD of 10 mm or more was assigned 10+ mm.

Outcomes and Definitions

The main outcome was number/percentage of infants detected to be sensitized by MWD of at least 2 mm to any of the pre-specified specific allergens at 10 min, 15 min, and either of the two time points (the largest MWD at either time point was used). The secondary outcomes were the changes in allergen-specific and histamine MWD (mm) between 10 and 15 min. Sensitivity outcomes correspond to the main outcome but defining a positive wheal as an MWD of ≥1 mm.

Definitions

A positive allergen wheal was defined as MWD ≥2 mm larger than the negative control, in line with recent studies [6, 10]. AS was defined as at least one positive allergen wheal towards the pre-specified allergens.

Any sensitization: AS to at least one allergen.
Polysensitization: AS to more than one allergen.

Reading time: minutes passed from pricking the allergen into the skin until measuring the MWD. Ten minutes, 15 min, or both reading time points (10 and 15 min).

Age: calculated from date of birth and date of the 6-month clinical visit.

Parental education and allergic diseases: information collected in antenatal electronic questionnaires.

Statistical Analysis
Categorical variables are presented in numbers and percentages and continuous variables as mean with minimum and maximum ranges or standard deviation. Complete case analysis and only a few single allergen results are missing (see Table 2b “Infants” per allergen for details). Histamine MWD difference was analysed using a paired t test. Agreement of allergen and histamine MWD at 10 and 15 min was analysed with test-retest intraclass correlation coefficients (ICCs) using 2-way mixed-effects model with absolute numbers and reporting absolute agreement. A sample size of at least 30 was considered representative, and absolute agreement ICC >0.9 was considered as excellent agreement, 0.75–0.9 as good, 0.5–0.75 as moderate, and <0.5 as poor agreement [14]. Due to small numbers and/or non-independency, no further comparative analyses were performed, and only descriptive data are presented. The significance level was set to 0.05. All analyses were performed using StataSE 16 (64 bit).

Table 1. Background characteristics

| Characteristics                        | Included infants, n=1,423 | Study population, n=1,431 | Non-included infants, n=963 |
|----------------------------------------|---------------------------|---------------------------|----------------------------|
| Age, months                            | 6.29 (±0.46)              | 6.11 (±0.36)              |
| Sex, n (%)                             |                           |                           |
| Boy                                    | 751 (52.5)                | 504 (52.3)                |
| Girl                                   | 680 (47.5)                | 459 (47.7)                |
| Study location, n (%)                  |                           |                           |
| Oslo, Norway                           | 876 (61.2)                | 433 (73.3)                |
| Østfold, Norway                        | 156 (10.9)                | 116 (19.7)                |
| Stockholm, Sweden                      | 399 (27.9)                | 41 (7.0)                  |
| Parental education, n (%)              |                           |                           |
| Preliminary school only                | 8 (0.6)                   | 8 (1.0)                   |
| High school only                       | 126 (9.6)                 | 97 (11.5)                 |
| Higher education <4 years              | 393 (29.9)                | 297 (35.1)                |
| Higher education ≥4 years              | 1,316                     | 421 (49.8)                |
| PhD                                    | 38 (2.9)                  | 22 (2.6)                  |
| Other                                  | 1 (0.1)                   | 1 (0.1)                   |
| Parent                                |                           |                           |
| Preliminary school only                | 16 (1.3)                  | 10 (1.2)                  |
| High school only                       | 230 (18.1)                | 163 (20.0)                |
| Higher education <4 years              | 365 (28.7)                | 264 (32.3)                |
| Higher education ≥4 years              | 1,270                     | 343 (42.0)                |
| PhD                                    | 42 (3.3)                  | 28 (3.4)                  |
| Other                                  | 13 (1.0)                  | 9 (1.1)                   |
| Parental allergic diseases, n (%)      |                           |                           |
| Mother                                 |                           |                           |
| Any atopy                              | 540 (40.9)                | 361 (42.5)                |
| Asthma                                 | 221 (16.7)                | 150 (17.7)                |
| Allergic rhinitis                      | 1,321                     | 189 (22.2)                |
| Atopic dermatitis                      | 270 (20.4)                | 161 (18.9)                |
| Food allergy                           | 173 (13.1)                | 108 (12.7)                |
| Father                                 |                           |                           |
| Any atopy                              | 468 (35.3)                | 283 (34.1)                |
| Asthma                                 | 176 (13.3)                | 103 (12.4)                |
| Allergic rhinitis                      | 1,326                     | 195 (23.5)                |
| Atopic dermatitis                      | 143 (10.8)                | 77 (9.3)                  |
| Food allergy                           | 121 (9.1)                 | 76 (9.2)                  |

Data are presented as n (%) or mean (±SD).
Results

The mean age of the 1,431 participants was 6.3 months (range 4.8–8.3), and background characteristics were similar for the included and the non-included infants shown in Table 1.

### Table 2. Results of the SPT read at 10 min, 15 min, and 10 and 15 min (10/15 min)

|                  | Infants | Main outcome (SPT-positive ≥2 mm) | Sensitivity outcome (SPT-positive ≥1 mm) |
|------------------|---------|-----------------------------------|----------------------------------------|
|                  |         | 10 min | 15 min | 10/15 min | 10 min | 15 min | 10/15 min |
| Any allergen     | 1,431   | 138 (9.6) | 141 (9.9) | 149 (10.4) | 181 (12.7) | 188 (13.1) | 196 (13.7) |
| Food allergen    | 1,431   | 126 (8.8) | 129 (9.0) | 135 (9.4) | 156 (10.9) | 166 (11.6) | 169 (11.8) |
| Inhalation allergen | 1,431 | 27 (1.9) | 26 (1.8) | 30 (2.1) | 50 (3.5) | 47 (3.3) | 53 (3.7) |
| Polysensitization | 1,431 | 37 (2.6) | 38 (2.7) | 43 (3.0) | 53 (3.7) | 55 (3.8) | 58 (4.1) |

**b** Allergen-specific SPT reactions

Positive wheals, n (%) mean MWD (min–max)

| Allergen | Infants | Main outcome (SPT-positive ≥2 mm) | Sensitivity outcome (SPT-positive ≥1 mm) |
|----------|---------|-----------------------------------|----------------------------------------|
|          |         | 10 min | 15 min | 10/15 min | 10 min | 15 min | 10/15 min |
| Egg      | 1,430   | 94 (6.6) | 93 (6.5) | 98 (6.9) | 110 (7.7) | 117 (8.2) | 120 (8.4) |
|          |         | 3.0 (2–6) | 3.2 (2–8) | 7 (2–9) | 2 (2–4) | 3 (2–4) | 2 (2–4) |
| Cow’s milk | 1,429 | 24 (1.7) | 27 (1.9) | 27 (1.9) | 33 (2.3) | 34 (2.4) | 36 (2.5) |
|          |         | 3.5 (2–7) | 3.6 (2–7) | 3.6 (2–7) | 2.8 (1–7) | 3 (0–7) | 3 (0–7) |
| Peanut   | 1,430   | 31 (2.2) | 34 (2.4) | 36 (2.5) | 44 (3.1) | 43 (3.0) | 46 (3.2) |
|          |         | 3.5 (2–9) | 3.8 (2–10) | 3.8 (2–10) | 2.8 (1–9) | 3.2 (1–10) | 3.2 (1–10) |
| Wheat    | 1,430   | 7 (0.5) | 6 (0.4) | 8 (0.6) | 12 (0.8) | 14 (1.0) | 16 (1.1) |
|          |         | 2.9 (2–4) | 3.3 (2–4) | 3.3 (2–4) | 2.1 (1–4) | 2 (1–4) | 2 (1–4) |
| Soy      | 1,431   | 6 (0.4) | 6 (0.4) | 7 (0.5) | 10 (0.7) | 8 (0.6) | 10 (0.7) |
|          |         | 2.1 (2–3) | 2.2 (2–3) | 2.2 (2–3) | 1.7 (1–3) | 1.9 (1–3) | 1.9 (1–3) |
| Birch    | 1,431   | 3 (0.2) | 4 (0.3) | 4 (0.3) | 11 (0.8) | 7 (0.5) | 11 (0.8) |
|          |         | 2.7 (2–3) | 2.5 (2–3) | 2.5 (2–3) | 1.5 (1–3) | 1.9 (1–3) | 1.9 (1–3) |
| Timothy | 1,430   | 3 (0.2) | 2 (0.1) | 3 (0.2) | 5 (0.4) | 4 (0.3) | 5 (0.4) |
|          |         | 2.3 (2–3) | 2.5 (2–3) | 2.5 (2–3) | 1.8 (1–3) | 1.8 (1–3) | 1.8 (1–3) |
| Dog      | 1,431   | 12 (0.8) | 11 (0.8) | 14 (1.0) | 22 (1.5) | 21 (1.5) | 24 (1.7) |
|          |         | 2.4 (2–4) | 2.4 (2–4) | 2.4 (2–4) | 1.8 (1–4) | 1.7 (1–4) | 1.7 (1–4) |
| Cat      | 1,431   | 14 (1.0) | 13 (0.9) | 15 (1.1) | 21 (1.5) | 22 (1.5) | 24 (1.7) |
|          |         | 2.6 (2–4) | 2.7 (2–4) | 2.7 (2–4) | 2.1 (1–4) | 2 (1–4) | 2 (1–4) |

Total positive wheals (% of 12,873 allergen pricks) | 194 (1.5) | 196 (1.5) | 212 (1.7) | 268 (2.1) | 270 (2.1) | 292 (2.3) |

"10/15 min" displays the number of tests that are positive when accounting the largest mean MWD at either of the two reading time points. The main outcome with positive SPT was defined as MWD ≥2 mm larger that the negative control, to the left, and the sensitivity outcome with positive SPT was defined as MWD ≥1 mm larger than the negative control, to the right. a) Number (percent) of the 1,431 infants of infants with positive SPT to at least one allergen (any sensitization), any food allergen (food allergen), any inhalation allergen (inhalation allergen), or at least two allergens (polysensitization). b) Number (percent) of infants with positive SPT to specific allergens and below the mean MWD (min–max) including only the wheals defined as positive in the respective outcome. MWD, mean wheal diameter.

AS at 10 and/or 15 min Reading Time

AS (MWD ≥2 mm larger than the negative control) was observed in 138 (9.6%) infants at 10 min and 141 (9.9%) at 15 min (Table 2a). As 8 (0.6%) infants were sensitized at 10 min only and 11 (0.8%) at 15 min only, the highest number of sensitized infants (n = 149, 10.4%) was
observed using both reading time points and accounting for the largest MWD (Table 2a; Fig. 1a). Similar observations were found for sensitization towards most of the specific allergens (Table 2b; Fig. 1b). While 9.4% of all infants had an MWD ≥2 mm to any food allergen at 10 and/or 15 min, the corresponding percentage was 2.1% for inhalation allergens. Three percent of the infants were sensitized to more than one allergen, constituting 29% of the sensitized infants.

Fig. 1. Any AS (MWD ≥2 mm larger than the negative control) and positive wheals (MWD ≥2 mm larger than the negative control) per allergen illustrated at each reading time point (10 and 15 min) and when read after both time points (10 and/or 15 min). The white part of the bars is the cases remaining unchanged positive at both 10 and 15 min. a Number of infants sensitized to any allergen and positive wheals at 10, 15, and 10 and/or 15 min. Numbers marked in brown are positive at one time point only. Reading after both time points will include all positive tests, marked in blue. b Number of positive wheals at each time point per allergen. Numbers marked in brown are positive at one time point only. Reading after both time points will include all positive tests, marked in blue. Note: different y-axis scale in inhalant allergens.
Fig. 2. Distribution of MWD subtracted the negative control, for all nine allergens at 10 and 15 min, respectively. Note: different y-axis scales in inhalant allergens.
A further 47 infants had at least one allergen wheal of 1 mm larger than the negative control at 10 and/or 15 min, and the total fraction with MWD ≥1 mm was 12.7% at 10 min, 13.1% at 15 min, and 13.7% using any time point (Table 2a). While 11.8% of all infants had an MWD ≥1 mm to food allergens at 10 and/or 15 min, the corresponding percentage was 3.7% for inhalation allergens and 4.1% for more than one allergen.

**Positive Allergen Wheals at 10 and/or 15 min Reading Time**

A total of 12,873 allergen pricks, evenly distributed across the nine allergens, were performed. An MWD of ≥2 mm larger than the negative control (positive wheal) was observed in 194 (1.5%) allergen pricks at 10 min and in 196 (1.5%) at 15 min. Overall, 212 (1.7%) positive wheals were identified after 10 and/or 15 min (Table 2b), with 34 (16%) being positive at one of the time points only. A positive SPT at 10 and/or 15 min was most frequently observed for egg (6.9%) and least frequently for timothy (0.2%).

An MWD of ≥1 mm was observed in 292 (2.3%) of the 12,873 allergen skin pricks at 10 and/or 15 min, with similar proportions at each time point (Table 2b).

The largest MWDs were observed for peanut (10 mm) and egg (8 mm), while neither wheat, soy, nor any of the inhalation allergens displayed MWDs of >4 mm (Table 2b). The distribution of MWDs for all nine allergens at 10 and 15 min, respectively, is illustrated in Figure 2.

**Changes in Allergen Wheal Size from 10 to 15 min**

Among the 292 wheals with an MWD ≥1 mm on at least one of the two time points, 77 (26.4%) increased and 42 (14.4%) decreased in size from 10 to 15 min, while 173 (59.3%) remained unchanged. The changes are shown (in mm) in Figure 3. Overall, there was a tendency towards increased MWD from 10 to 15 min (Fig. 3). The ICCs demonstrated good to excellent agreement of the MWD at 10 and 15 min, with absolute ICC (95% CI) being 0.82 (0.75, 0.88) for egg, 0.90 (0.80, 0.95) for milk, and 0.91 (0.83, 0.95) for peanut, the 3 allergens to which at least 30 infants were sensitized.

**Histamine Wheal Sizes after 10 and 15 min**

The histamine MWD (n = 1,431) was significantly larger at 10 compared to 15 min, with a mean (95% CI) of 3.8 mm (3.75, 3.86) at 10 min and 3.6 mm (3.58, 3.70) at 15 min (p < 0.001). The changes in histamine MWD are shown in Figure 4, with a total of 317 (22.2%) wheals decreasing and 142 (9.9%) increasing in MWD from 10 to 15 min. The absolute ICC (95% CI) for histamine was...
0.79 (0.76, 0.82), indicating good to moderate agreement. Two negative control wheals were 1 mm in diameter at 10 min, with 1 remaining at 1 mm while the other was 0 mm at 15 min.

**Discussion**

AS (MWD ≥2 mm) to at least one allergen was most commonly diagnosed in 6-month-old infants from a general population by reading the SPT at both 10 and 15 min, with 9.6% being sensitized at 10 min, 9.9% at 15 min, and 10.4% using any time point. Overall, 3% of all infants were sensitized to more than one allergen (polysensitized). Within the 12,873 SPT allergen pricks performed, 1.5% were positive at 10 min, 1.5% at 15 min, and 1.7% were positive at any time, most often to the egg and least frequently to timothy. Among all wheals of at least 1 mm above the negative control, 59% remained unchanged in size between 10 and 15 min, 26% increased, while 14% decreased in size from 10 to 15 min. The mean histamine MWD was significantly larger at 10 compared to 15 min.

The higher number of infants with any AS observed when including a positive SPT result read at either 10 or 15 min, compared to reading the MWD at one of the time points only, is to the best of our knowledge novel results. We were unable to demonstrate that either time point alone was more often associated with a positive SPT. The similar number of children sensitized based on reading at either time point alone and the good agreement observed in the ICC for the egg, milk, and peanut is in line with Beken at al [8], who also found similar MWD for allergens read after 10 and 15 min, respectively, in children below 2 years of age.

The prevalence of AS at 6 months of age was higher in our study at around 10% compared to the observed 6.8% among 389 infants born to mothers with asthma in Copenhagen Prospective Study on Asthma in Childhood (COPSAC2000) study [15] and 5% among 482 infants in the Danish Allergy Research Centre (DARC) birth cohort study [16]. However, the AS prevalence was similar to ours in the COPSAC2000 study (11.5%) when the latter combined SPT and s-IgE (≥0.35 kU/L) [17]. All three studies defined AS as an MWD of ≥2 mm to common food and inhalant allergens, while the SPT was read at 15 min in the COPSAC study [15, 17] and at 10 min in the DARC cohort [16]. The prevalence of AS in our cohort is in line with the whole PreventADALL cohort of 1,994 children published previously (any sensitization 9.9%, food 8.9%, and inhalation 1.9%) [18]. The infants in our study were born almost 20 years after the two Danish infant populations [15–17]. The largest discrepancies appears to be within sensitization to foods, reported in 9.0% at 15 min in the present study, compared to 5.3% by the SPT and 7.8% by s-IgE in the COPSAC2000 study [15], and 4.8% in the DARC cohort [16], while sensitization to
Thus, the SPT in infants may optimally be read at both 10
varying size and persistence of the skin wheal in infancy.
stable skin reactivity within this time period, resulting in
relevant AS in infants [9].
dicating that an MWD below 3 mm may represent a rel-
infants with the SPT 1–2 mm had s-IgE ≥0.35 kU/L, in-
LEAP study with a mean age of 7.8 months, 46% of the
ported that 4% reacted to egg within a week despite the
mains unclear, although Wei-Liang Tan et al. [23] re-
wards peanut at 60 months of age.
4–10 months of age had a positive oral food challenge to-
the avoidance group with SPT 1–2 mm towards peanut at
About Peanut Allergy (LEAP) study [21] where 37.5% in
infants, in line with the findings in the Learning Early
[3] to define a positive SPT in the clinic, also in infants.
A threshold of 2-mm MWD or more for AS is widely
used in research [4, 15, 16] despite the standard MWD ≥3
mm proposed by the World Allergy Organization (WAO)
[3] to define a positive SPT in the clinic, also in infants.
An MWD ≥2 mm is likely to be of clinical relevance in
infants, in line with the findings in the Learning Early
About Peanut Allergy (LEAP) study [21] where 37.5% in
the avoidance group with SPT 1–2 mm towards peanut at
4–10 months of age had a positive oral food challenge to-
wards peanut at 60 months of age.
Using an allergen MWD of at least 1 mm to indicate
AS in sensitivity analyses increased the prevalence of any
sensitization from 10.4% to 13.7% with an SPT reading
at 10 and/or 15 min. Although not commonly used in
clinical investigations, ≥1 mm has been used as cut-off
value in randomized controlled trials on prevention of
atopic diseases [5, 6, 22], including the PreventADALL
study, to screen for possible allergy prior to oral food
challenges. The clinical relevance of the 1 mm cut-off re-
mains unclear, although Wei-Liang Tan et al. [23] re-
ported that 4% reacted to egg within a week despite the
SPT being <2 mm to egg at 4 months of age. Also, in the
LEAP study with a mean age of 7.8 months, 46% of the
infants with the SPT 1–2 mm had s-IgE ≥0.35 kU/L, in-
dicating that an MWD below 3 mm may represent a rel-
evant AS in infants [9].
Our finding that 16% of the wheals were positive at one
time point only, as well as changes in MWD between 10 and
15 min in around 40% of the wheals, may indicate an un-
stable skin reactivity within this time period, resulting in
varying size and persistence of the skin wheal in infancy.
Thus, the SPT in infants may optimally be read at both 10
and 15 min to be in line with the suggestions of the WAO
[3] that SPTs should be read at the peak of their reaction.
The overall larger histamine MWD at 10 compared to
15 min is in line with previous findings [8, 11, 12]. Our
findings do not support that a single reading of the SPT
earlier than the standard 15 min [3] could compensate for
the decreased infant skin reactivity [3, 7]. But, our results
do support that in early infancy, allergen wheal measure-
ments may be relevant earlier than the recommended
reading after 15–20 min [3]. Likely due to the larger his-
tamine MWD after 10 min compared to 15 min, Beken et
al. [8] overall suggest that SPT reading after 10 min is
more accurate in children below 24 months of age. As we
find an almost equal number of sensitized infants using
either 10 or 15 min reading time point and 13% were clas-
sified as sensitized at one of the time points only, we pro-
pose that using both reading time points would improve
the likelihood of detecting AS in infants.
Strengths and Limitations
A strength of this study is the recruitment of a high num-
ber of infants from the general population, however with a
modest overrepresentation of parental atopy and higher pa-
rental education compared to the general population. Nev-
ertheless, this potential skewness towards higher risk of at-
opy is unlikely to affect the validity of our results. We there-
fore believe that the results are widely applicable. During
registration, an MWD of 10 mm or more was registered as
“10+ mm,” but with only one allergen wheal being regist-
ered as “10+ mm,” the effect of this theoretical method-
ological weakness seems negligible. To be able to draw
around and measure the wheal the exact same way, one skin
prick should optimally be performed per reading time for
all allergens and histamine. As the SPT was one of many as-
sessments performed in the large, epidemiologic Preven-
tADALL study, it seemed unethical to double-prick. Addi-
tionally, the limited skin surface available on the tiny fore-
arms of such young infants would have made double-
pricking problematic with that many allergens.
Conclusion
In conclusion, AS was documented by the SPT more
often when including readings after both 10 and 15 min,
compared to either time point alone, in 6-month-old in-
fants. As neither 10 nor 15 min reading time was superior
to the other in detecting AS, our results indicate that read-
ings at both time points should be considered for optimal
test sensitivity. However, the histamine MWD was sig-
nificantly larger at 10 min compared to 15 min. Reap-
praisal of SPT readings in infancy may be warranted.
Acknowledgments

We sincerely thank all the study participants and the healthcare personnel contributing in planning of the study, recruitment, clinical and biological sampling, and expert panel decisions. We would like to thank all the individuals involved in facilitating as well as running the study and especially: Oslo University Hospital: Karen Eline Stensby Bains, Kim Advocaat Endre, Ingvild Essen, Thea A. Fatnes, Berit Granum, Malen Gudbrandsgard, Hrefna Katrin Gudmundsdottir, Guttorm Haugen, Mari Kjendsløkken, Ina Kreyberg, Live Nordhagen, and Carina Saunders; Østfold Hospital Trust: Line Kvenshagen, Jon Terje Lunde, Sigríður Sjelmo, Magdalena Værnesbranden, and Johanna Wiik; Karolinska University Hospital/Karolinska Institutet: Anna Asarnoj, Ann Berglind, Sandra Ganrud-Tedner, Sandra Götberg, Gunilla Hedlin, Caroline-Aleksi Olsson-Mägi, Päivi Südeman, Ellen Tegnerud, and Lovisa Tolan-
der. All the authors have completed the ICMJE disclosure form and have no conflicts of interest to disclose. However, Eva Maria Rehbinde has received honoraria for lecture from Sanofi-Genzyme, Novartis, Leo-Pharma, Perrigo, and the Norwegian Asthma and Allergy Association. Marissa LeBlanc reports speaking fees from Novartis, Leo-Pharma, Perrigo, and the Norwegian Asthma and Allergy Association. Marissa LeBlanc reports speaking fees from MSD, unrelated to the contents of this work. Karin C. Lodrup Carlsen has received lecture honorarium to the institution from Thermo Fisher Scientific.

Statement of Ethics

The PreventADALL study was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (2014/518) and in Sweden (2014/2242–31/4) and was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the mothers at inclusion during pregnancy and from both parents at inclusion of the newborn baby. The PreventADALL study is registered at ClinicalTrials.gov (number NCT02449850).

Conflict of Interest Statement

All the authors have completed the ICMJE disclosure form and have no conflicts of interest to disclose. However, Eva Maria Rehbinde has received honoraria for lecture from Sanofi-Genzyme, Novartis, Leo-Pharma, Perrigo, and the Norwegian Asthma and Allergy Association. Marissa LeBlanc reports speaking fees from MSD, unrelated to the contents of this work. Karin C. Lodrup Carlsen has received lecture honorarium to the institution from Thermo Fisher Scientific.

Funding Sources

This study is part of a PhD project within the University of Oslo, Norway. The PreventADALL trial was supported by a number of public and private funding bodies with no influence on the design, conduct, or analysis of the trial. The PreventADALL study has received funding from the following sources: South-Eastern Norway Regional Health Authority, the Research council of Norway, Oslo University Hospital, the University of Oslo, Health and Rehabilitation Norway, the Foundation for Healthcare and Allergy Research in Sweden – Vårdalstiftelsen, the Swedish Asthma and Allergy Association’s Research Foundation, the Swedish Research Council – the Initiative for Clinical Therapy Research, the Swedish Heart-Lung Foundation, SFO-V Karolinska Institutet, Østfold Hospital Trust, the European Union (MeDALL project), by unrestricted grants from the Norwegian Association of Asthma and Allergy, the Kloster foundation, Thermo Fisher, Uppsala, Sweden (through supplying allergen reagents) and Fürst Medical Laboratory, Oslo, Norway (through performing IgE analyses), the Norwegian Society of Dermatology and Venerology, Arne Ingel’s legat, Region Stockholm (ALF project and individual grants), Forte, Swedish Order of Freemasons Foundation Barnhuset, the Sven Jerring Foundation, the Hesselman Foundation, the Magnus Bergwall Foundation, the Konsul Th. C. Bergh’s Foundation, the Swedish Society of Medicine, the King Gustaf V 80th Birthday Foundation, Karolinska Institutet grants, the Cancer and Allergy Foundation, the Pediatric Research Foundation at Astrid Lindgren Children’s Hospital, the Samaritan Foundation for Pediatric research, the Children’s Foundation at Oslo University Hospital, and the Nansen Foundation, Roche Norway. The authors have no financial relationships relevant to this article to disclose.

Author Contributions

All the authors have contributed to the design and/or clinical follow-up of the PreventADALL study, as well as have contributed to drafting and/or critically revising the paper. All the authors approved the last version before submission. A.L., I.S., E.M.R., A.C.S., C.S., K.C.L.C., H.O.S., and B.N. participated in the conception and design of the study. A.L., S.W.G., E.M.R., A.A., H.A., K.C.L.C., H.O.S., and B.N. participated in running of the study and/or data collection. A.L., S.W.G., R.V., M.L., K.C.L.C., H.O.S., and B.N. participated in the data analysis.

Data Availability Statement

The data that support the findings of this study are not publicly available as identification of individuals by study code is not permitted to be stored in public databases according to Norwegian legislation. Data may be available from the study PI (K.C.L.C.) upon reasonable request, in line with the participant consent.

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