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The predictive value of the skin prick test weal size for the outcome of oral food challenges

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Summary

Background The skin prick test (SPT) is regarded as an important diagnostic measure in the diagnostic work-up of food allergy.

Objective To evaluate the diagnostic capacity of the SPT in predicting the outcome of oral food challenges, and to determine decision points for the weal size and the skin index (SI) that could render double-blind, placebo-controlled food challenges unnecessary.

Methods In 385 children (median age 22 months), 735 controlled oral challenges were performed with cow's milk (CM), hen's egg (HE), wheat and soy. Three hundred and thirty-six of 385 (87%) children suffered from atopic dermatitis. SPT was performed in all children. Diagnostic capacity, receiver–operator characteristics (ROC) curves and predictive decision points were calculated for the mean weal size and the calculated SI.

Results Three hundred and twelve of 735 (43%) oral food challenges were assessed to be positive. Calculation of 95% and 99% predicted probabilities using logistic regression revealed predictive decision points of 13.0 and 17.8 mm for HE, and 12.5 and 17.3 mm for CM, respectively. However, using the SI, the corresponding cut-off levels were 2.6 and 3.7, respectively, for HE, and 2.7 and 3.7 for CM. For wheat, 95% and 99% decision points of 2.2 and 3.0 were found in children below 1 year of age.

Conclusion Predictive decision points for a positive outcome of food challenges can be calculated for HE and CM using weal size and SI. They may help to avoid oral food challenges.

Keywords children, DBPCFC, food allergy, oral challenge, skin prick test, specific IgE, SPT
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Introduction

Food allergies can strongly affect children's health, and their prevalence is increasing [1–3]. Patients with food allergy are always at risk of inadvertent ingestion of offending foods, which can lead to symptoms like urticaria, worsening of eczema, gastrointestinal or respiratory reactions or even anaphylactic shock [5]. The most common foods with allergenic potential in childhood are cow's milk (CM), hen's egg (HE), wheat, soy and peanut [4, 5]. The early and reliable diagnosis of food allergy is of major importance for initiation of the appropriate diet on the one hand and for the avoidance of unnecessary dietary restrictions on the other.

Several methods are commonly used in the diagnostic work-up for suspected food allergy including skin prick tests (SPTs), the measurement of food-specific IgE antibodies in serum, atopy patch tests and double-blind, placebo-controlled food challenges (DBPCFC). While oral food challenges are still regarded as the gold standard [6–8], they are time consuming, expensive and may cause severe clinical reactions including life-threatening anaphylactic reactions [8]. It would be desirable to have a simple diagnostic test that could render resource-consuming oral food challenges unnecessary.

As the SPT is easy to perform, rapid and inexpensive, it appears to be a valuable first-line procedure for the evaluation of food allergy. However, despite a high sensitivity, its specificity is rather low [9–12]. Therefore, simply considering the reaction as positive or negative, the SPT alone may not provide sufficient proof of a clinically relevant food allergy. Investigating graduated skin test responses and establishing predicted probability decision points might improve specificity. Moreover, it seems interesting to relate the absolute weal size of the specific allergen and the reaction induced by histamine by calculating skin indices (SI) as the ratio of allergen weal size to histamine weal size.

The aim of this study was therefore to analyse retrospectively the diagnostic value of the absolute weal size and the SI of SPT in comparison with the outcome of DBPCFCs in a large number of children who also underwent controlled oral food challenges with CM, HE, wheat and/or soy.

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Materials and Methods

Patients

Our retrospective study included 385 children consecutively referred to the Department of Pediatric Pneumology and Immunology at the Children's Hospital Charité with suspected food-dependent symptoms to CM, HE, wheat and/or soy. The most common symptoms reported by parents were worsening of eczema, urticaria and vomiting. In addition, all children underwent skin prick testing and controlled oral food challenges.

Patients were between 3 months and $14\frac{1}{2}$ years of age (median 22 months); 225 were boys (58%) and 160 were girls (42%). Three hundred and thirty-five of the children (87%) presented with atopic dermatitis (AD) as defined by the criteria of Sampson [13] and Seymour et al. [14], modified from Hanifin and Rajka [15]. One hundred and sixty-eight of these children had mild AD (severity scoring of atopic dermatitis (SCORAD) $\leqslant$ 25 points), 87 had moderate AD (26–50 points) and 41 had severe AD ($\geqslant$ 51 points). At the time of the oral food challenge, 40 children had no clinical symptoms of AD. In addition, 43 (11%) patients had an underlying condition of asthma, 24 (6%) of recurrent wheezing and 26 (27%) of rhinoconjunctivitis. We assessed the severity of eczema according to the SCORAD score as described previously [16].

Skin prick test

One drop of each fresh food [17] was applied to the patients' forearm: fresh CM containing 3.5% fat; native HE (whisked white of egg and yolk); gluten powder (Kröner, Ibbenbüren, Germany) dissolved in water (1 g/10 mL); and soy milk. SPTs were performed with 1 mm single-peak lancets (ALK, Copenhagen, Denmark). We used 10 mg/mL histamine dihydrochloride (ALK) as a positive control and saline solution as a negative control. SPTs were read after 15 min. All tests with a weal diameter below 3 mm elicited by histamine or with a weal of $\geqslant$ 2 mm by the negative control were excluded [18].

The mean diameters of food allergen weals were calculated from the sum of the largest measurement across the weal and the largest weal measurement perpendicular to this divided by two. In addition, we calculated the SI as the ratio of allergen weal diameter divided by the histamine weal size. The SPT result for each allergen was defined as positive if the mean weal diameter was 3 mm or larger [19], and if the SI was greater than 0.6.

Oral food challenges

Oral challenges were performed in all children using the four most common food allergens in our population (CM, HE, wheat and soy), and placebo [7]. Children being treated with an antihistamine (predominantly Cetirizine) were advised to avoid it for 72 h before provocation. Topical glucocorticosteroids were allowed twice daily at a maximum concentration of 1% hydrocortisone or 0.01% betamethasone.

A total of 735 controlled oral food challenges were performed: 552 (75%) challenges were carried out in a double-blind, placebo-controlled manner, and 183 (25%) challenges were performed in an open manner. Open challenges were allowed if children were younger than 1 year and had a history of immediate-type reactions; otherwise, challenges were performed as DBPCFC. In more detail, 303/735 (41%) challenges were performed with CM, 160/735 (22%) with HE, 122/735 (17%) with wheat and 150/735 (20%) with soy. In addition, 280 oral challenges were performed with placebo.

Usually, blocks of two allergens and one placebo were administered, as described previously [20]. Briefly, the clinical dietician performed randomization and preparation of the challenges. Every 48 h, a maximum of seven successive cumulative doses of either 150 mL fresh pasteurized CM containing 3.5% fat, or of one fresh whisked HE, or of 150 mL soy milk, or of 4 g gluten powder (Kröner, Ibbenbüren, Germany) or of a placebo (Neocate®, SHS, Liverpool, UK) were administered. All open challenges were performed using titration steps identical to those of the double-blind ones. The time interval between doses was 30 min. Full emergency equipment was at hand.

The provocation was stopped if clinical symptoms occured or the highest dose was reached. The children were observed for 48 h after each challenge on an in-patient basis in order to detect late clinical reactions. The food challenges were considered positive if objective cutaneous symptoms (urticaria, worsening of eczema), or respiratory (wheezing) or gastrointestinal symptoms (vomiting, diarrhoea, abdominal pain) or even shock developed after ingestion of the food. We distinguished early reactions with symptoms occurring within 2 h after food ingestion and late reactions with clinical symptoms $\geqslant$ 2 h after administering the highest dose.

Statistical analyses

For statistical analyses we used SPSS for Windows (version 11.5, SPSS, Chicago, IL, USA). Two-by-two tables were used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and efficiency. Test sensitivity was defined as the proportion of true positives detected, and specificity as the proportion of true negatives detected. The PPV describes the proportion of symptomatic individuals among test positives, and the NPV describes the proportion of non-symptomatic individuals among test negatives. Efficiency was defined as the fraction of tested individuals correctly classified by the test. Moreover, we calculated predictive probabilities of the outcome of oral food challenges by means of SPT weal size and SI. We used the logistic regression calculated with the following formula described previously [8, 20, 21]:

$$P = \frac{1}{e^{-\alpha-\beta x} + 1}$$

In addition, we plotted receiver–operator characteristics (ROC) curves for skin weal diameter and the SI. Area under the curve (AUC) was calculated to quantify the accuracy of the single test and to compare the diagnostic value of the weal size with that of the SI.

Results

A total of 735 controlled oral challenges with CM, HE, wheat and soy in 385 children were analysed. Three hundred and twelve of 735 (43%) serum challenges were assessed as positive, and 10/280 (4%) placebo challenges as positive. One hundred and one (63%) egg challenges were positive, and 149 (49%) milk challenges, as well as 34 (28%) of wheat challenges and 28 (19%) of soy challenges were positive. Of the 312 positive challenges, 208 (67%) were immediate-type clinical reactions (e.g. urticaria, gastro-intestinal reactions), 45 (14%) were late-phase reactions (e.g. exacerbation of eczema) and 59 (19%) were combined early- plus late-phase reactions. One child developed anaphylaxis to egg.

The weal diameters ranged from 0 to 25.0 mm (median 7.0 mm) for HE, from 0 to 15.5 mm (median 4.1 mm) for CM, from 0 to 10.5 mm (median 2.0 mm) for wheat and from 0 to 10.0 mm (median 1.0 mm) for soy. The SI ranged from 0 to 5.7 (median 1.3) for HE, from 0 to 5.0 (median 0.8) for CM, from 0 to 3.0 (median 0.2) for wheat, and from 0 to 2.5 (median 0.2) for soy.

Results for sensitivity, specificity, PPVs, NPVs and efficiency are shown in Table 1. While sensitivity values ranged from 21% to 93%, specificity values were between 59% and 88%.

A graphic presentation of the correlation between sensitivity and specificity can be obtained by calculating ROC curves as shown in Fig. 1. AUC for weal sizes showed acceptable values for CM (0.82), HE (0.83) and wheat (0.75). The values for the SI were comparable: 0.83 for CM, 0.85 for HE and 0.74 for wheat. For soy, the relationship between sensitivity and specificity in the ROC curves was poor and the AUC (0.56) was not statistically significant ($P = 0.56$ for weal size, $P = 0.57$ for SI).

Logistic regression proposed by Sampson was used to calculate predicted probabilities illustrating the likelihood of patients with a given weal size to generate a positive oral food challenge [8, 21]. Choosing a 95% predicted probability resulted in a decision point for the weal diameter of 13.0 mm for HE and 12.5 mm for CM (Fig. 2). The criterion was fulfilled by 14/160 positive challenges with HE (9%) and by seven of 303 with CM (2%) for the weal size of SPT.

Choosing 99% predicted probability resulted in a cut-off point of 17.8 mm absolute weal size for HE, which was fulfilled by five of 160 (3%) positive challenges. The calculated 99% cut-off point for CM was 17.3 mm (which was not fulfilled by any patient). No 95% or 99% predicted probabilities could be calculated for wheat and soy considering all children. Corresponding figures for the SI are shown in Table 3.

Subdividing our children in those below or above 1 year of age provided different predicted probabilities for HE and CM for the absolute weal size (Table 2) and the SI (Table 3). In contrast to the absolute weal size, use of the SI resulted in 95% and 99% cut-off points for wheat of 2.2, and 3.0, respectively.

Table 1. Diagnostic capacity of skin prick test (SPT) for oral food challenges

	HE (%)	CM (%)	Wheat (%)	Soy (%)
Sensitivity	93	85	65	21
Specificity	59	75	77	88
PPV	80	76	52	29
NPV	83	83	85	83
Efficiency	83	78	74	81

HE, hen's egg; CM, cow's milk; PPV, positive predictive value; NPV, negative predictive value.
Cross tables were calculated on the basis of positive or negative oral food challenges and positive or negative SPT.

Discussion

In the diagnostic work-up of suspected food allergies in children, there is a great demand for straightforward diagnostic procedures. While a positive SPT indicates sensitization, it does not necessarily prove a clinically relevant food allergy [22]. Thus, the specificity of the SPT for the outcome of oral food challenges is limited [9–12].

Several studies have revealed a close relationship between the specific serum IgE levels and symptomatic food allergy by defining cut-off points indicative of a positive reaction during oral challenges [8, 20, 21, 23, 24]. However, these diagnostic decision points vary for different allergens: while values for CM and HE are usually quite satisfying, the predictive capacity for wheat – and especially for soy – does not fulfill the criteria to be useful *in vitro* diagnostic [20]. Furthermore, the influence of the study population seems to be remarkable [22].

The SPT can be performed both with commercial allergen extracts and fresh foods. In many countries, commercial extracts are used; however, there may be differences in terms of sensitivity and specificity from extract to extract. We preferred fresh, native foods, because we aimed at reflecting the reality of the patients' life as much as possible, and because we used identical material for oral provocations. Furthermore, in a French study it was shown that fresh foods were superior compared with commercial extracts [17].

As the SPT is easy to perform, inexpensive and its results are immediately available, it is widely used in the diagnosis of food allergy. Despite these facts, few studies have defined cut-off levels for the weal size diameters with regard to the clinical outcome of oral food challenges. In the present retrospective study of 385 children, we correlated the outcome of 735 controlled oral challenges with SPTs. We demonstrated that 95% and 99% predicted probabilities could be calculated for CM and HE for the mean weal diameter and the SI. In contrast, no such levels were found for wheat and soy.

In a previous study, Sporik investigated prospectively the results of SPT and 555 oral food challenges performed in 467 children (median age 3.0 years) over a 9-year period. He defined SPT weal diameters as '100% diagnostic' by using 100% specificity for CM ($\geqslant$8 mm), HE ($\geqslant$7 mm) and peanut ($\geqslant$8 mm) [25, 26]. Therefore, he suggested that all children exceeding these limits should be considered allergic to this specific food without further investigation. In contrast to the present study, all oral food challenges were performed openly, and delayed reactions were judged by parents at home. Furthermore, variations between the study populations may account for some of the differences of cut-off levels.

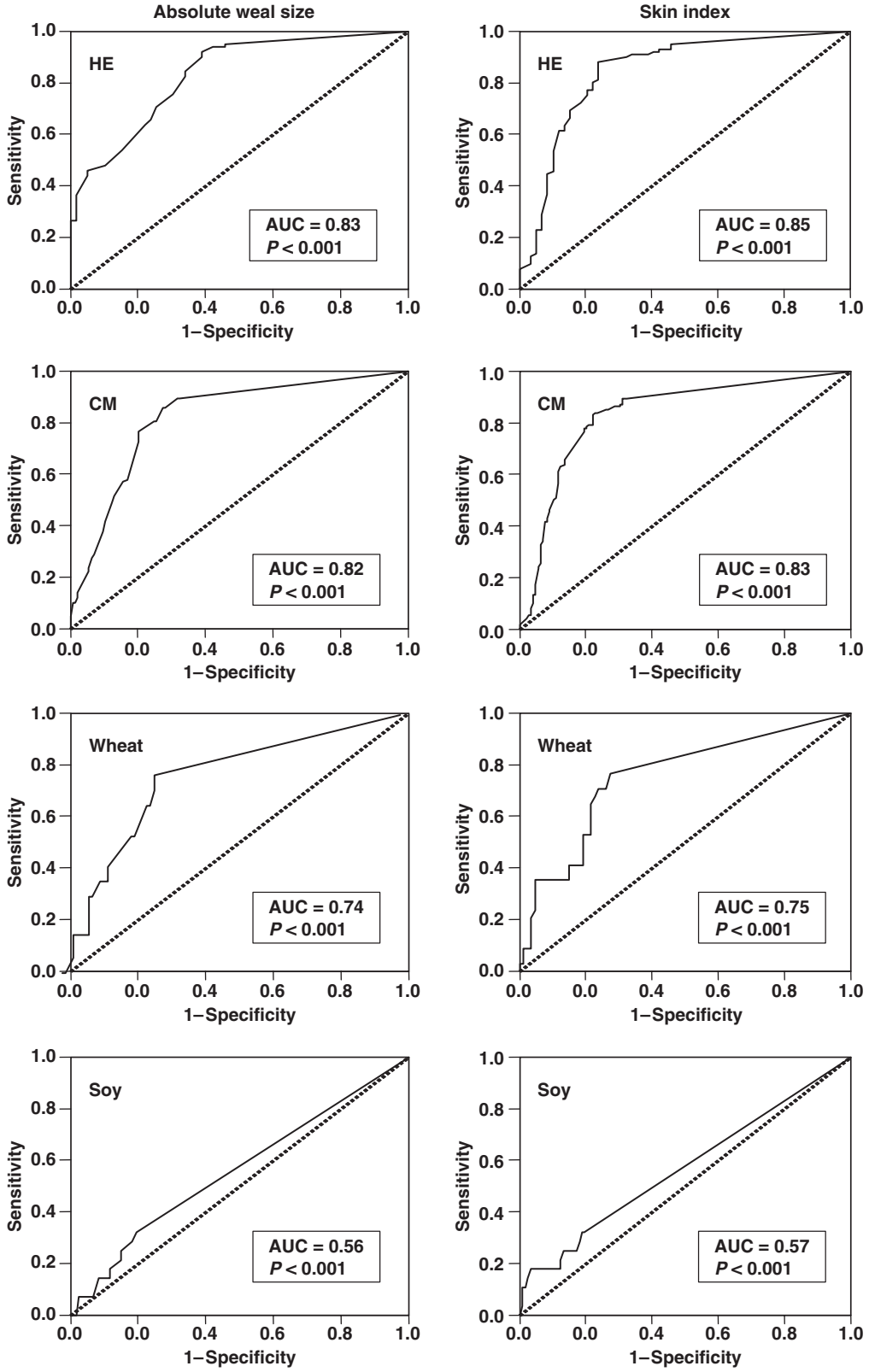

Fig. 1. Receiver–operator characteristics (ROC) curves for cow's milk (CM), hen's egg (HE), wheat and soy for the weal size of the skin prick test and the skin index.

In our study, subdividing children into those of below and above 1 year of age resulted in different cut-off levels, with a tendency towards lower values in the younger children (Tables 2 and 3). This is in accordance with the results of Sporik showing lower cut-off levels in children below 2 years of age [25].

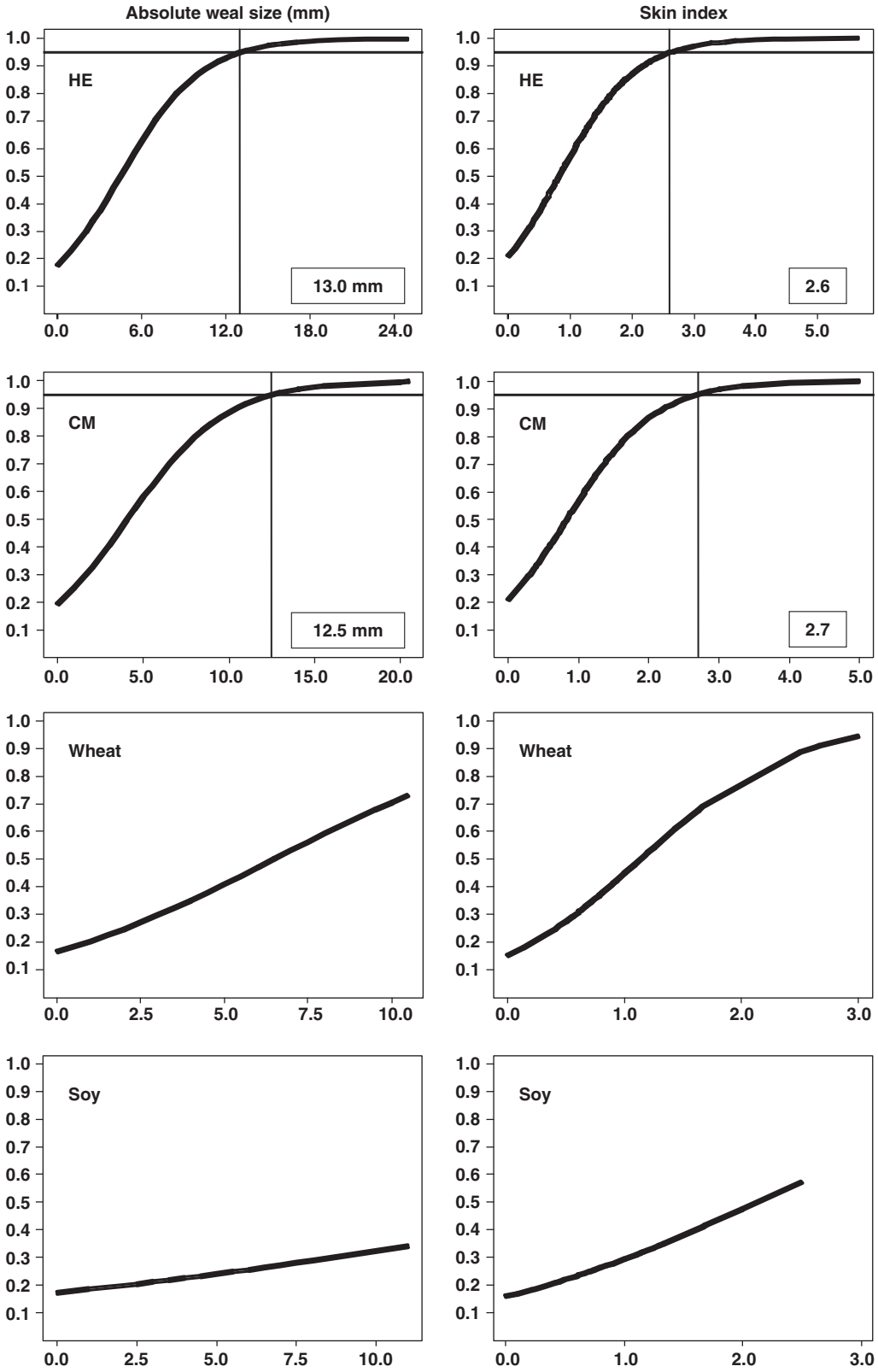

Fig. 2. Predictive probabilities for cow's milk (CM), hen's egg (HE), wheat and soy for a positive food challenge in relation to the weal size of the skin prick test (mm) and the skin index.Thin lines and inserted numbers represent 95% predicted probabilities.

The findings of Sporik were in agreement with a previous study of Eigenmann and Sampson reporting similar low cut-off levels for HE (4 mm), CM (5 mm), wheat (3 mm) and peanut (6 mm) [25, 27]. Cut-off point weal sizes were used at the upper 95% confidence interval. Importantly, children with clear evidence (convincing history) of food allergy were

Table 2. Predicted probabilities of the absolute weal size (mm) for children below and above 1 year of age

	Cut-off (%)	<1 year	⩾1 year	All children
HE	90	9.3	11.1	10.8
	95	11.2	13.3	13.0
	99	15.4	18.3	17.8
		$n = 26$	$n = 134$	$n = 160$
CM	90	7.9	13.2	10.4
	95	9.7	15.7	12.5
	99	13.5	*	17.3
		$n = 154$	$n = 149$	$n = 303$
Wheat	90	*	*	*
	95	*	*	*
	99	*	*	*
		$n = 57$	$n = 65$	$n = 122$
Soy	90	*	*	*
	95	*	*	*
	99	*	*	*
		$n = 74$	$n = 76$	$n = 150$

*90%, 95% and/or 99% predictive values could not be calculated.
HE, hen's egg; CM, cow's milk.

Table 3. Predicted probabilities of the skin index for children below and above 1 year of age

	Cut-off (%)	<1 year	⩾1 year	All children
HE	90	2.9	2.0	2.2
	95	3.8	2.5	2.6
	99	5.7	3.3	3.7
		$n = 26$	$n = 134$	$n = 160$
CM	90	1.6	3.0	2.2
	95	2.0	3.6	2.7
	99	2.8	4.9	3.7
		$n = 154$	$n = 149$	$n = 303$
Wheat	90	1.8	*	2.2
	95	2.2	*	*
	99	3.0	*	*
		$n = 57$	$n = 65$	$n = 122$
Soy	90	*	*	*
	95	*	*	*
	99	*	*	*
		$n = 74$	$n = 76$	$n = 150$

*90%, 95% and/or 99% predictive values could not be calculated.
HE, hen's egg; CM, cow's milk.

not challenged. In contrast, every child referred to our unit with suspected food allergy underwent a controlled oral food challenge that was mostly double-blind, placebo-controlled. Transferring the previously determined lower decision points [25] to our study population would lead to the false diagnosis of 15/303 (5%) children (oral food challenge negative) as CM allergic and 15/160 (9%) as HE allergic.

It should be considered whether positive predictive values of 99% should be preferred to 95% in order to avoid unnecessary diets in one out of 20 children. In our population, the 99% predictive cut-off value of 17.8 mm for HE was reached by only five of 160 positive challenges with HE (3%); however, no patient reached or exceeded the 99% cut-off level for CM. Even the 95% predictive cut-off value was only fulfilled by 9% for HE and 2% for CM. These numbers are quite low, but every single oral challenge was rendered superfluous in the children with the highest SPT weal sizes by using the 99% predicted probabilities eliminates the risk of severe side-effects.

Besides the absolute weal sizes in mm of the SPT, we calculated the SI as the ratio of the allergen weal to the histamine control. This approach may consider differences in the individual dermal reactivity [18]. In general, the AUC values of the ROC curves for the SI were comparable with those of the absolute weal diameters for all four allergens tested (Fig. 2). We therefore conclude that calculating the SI does not add any information for the daily routine diagnostic work-up for CM, HE and soy. Surprisingly, we found cut-off levels for the SI for wheat in children younger than 1 year (Table 3); however, no such cut-off levels were observed using the weal size. One other study investigated the SI of the SPT with CM [28]. The authors proposed that patients with a weal diameter for CM twice the size of the histamine weal (corresponds to SI 2.0) should be regarded as having a food allergy.

Comparing the predictive capacity of the SPT with that of specific serum IgE [9, 20], we found that the sensitivity of specific IgE is slightly higher than that of the SPT. Conversely, the SPT has a remarkably high specificity (Table 1). Concerning predicted probabilities, 95% and 99% cut-off levels could be defined for HE for SPT and specific serum IgE [20]. Interestingly, we were able to define cut-off levels for CM by using the SPT, which was not possible using the specific serum IgE. Thus, our findings indicate that the SPT provides additional diagnostic information compared with specific serum IgE for some allergens.

Our data point out that foods seem to be of a different character in terms of their diagnostic accessibility. For wheat and soy, the correlation of the IgE methods (SPT, specific serum IgE) and the outcome of oral food challenges were not satisfying [20]. The reasons for this phenomenon are unknown; one hypothesis may be that the animal-protein foods CM and HE are reflected by IgE sensitization [20, 21, 23], while this may be less be valid for the plant-protein foods wheat – and especially soy [20]. This view is supported by the fact that there were a higher proportion of non-IgE-mediated clinical reactions upon challenge with the plant proteins [29].

We aimed at validating the predictive capacity of the SPT on the basis of controlled oral food challenges. Although DBPCFCs reflect the gold standard in the diagnostic work-up of food allergy, even these tests have limitations. A standardized clinical setting may not consider e.g. augmentation factors (such as physical exercise, fever and anti-inflammatory drugs), which may occur in the daily life of the children. However, use of this gold standard should be preferred over the comparison of tests among each other.

In conclusion, predictive decision points for the SPT can be calculated for HE and CM. Predicted probabilities exceeding 99% may render oral food challenges superfluous and indicate a therapeutic elimination diet. Smaller weal sizes, however, do not prove the absence of a food allergy with acceptable confidence. Furthermore, our data show that the SPT offers advantages over the determination of specific serum IgE for the diagnostic work-up of suspected CM allergy. Decision points need to be ascertained for each

allergen separately. The calculated decision points differ widely in comparison with other studies. Therefore, a generally accepted cut-off level should be based on an international approach including a large study population undergoing controlled food challenges. At present, in the majority of cases, controlled oral challenges still remain the gold standard to verify clinically relevant food allergy.

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