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Reactions to peanut at first introduction in infancy are associated with age ≥ 8 months and severity of eczema

Dirk H. J. Verhoeven^{1,2}  | Irene C. E. M. Herpertz³ | Jeroen Hol⁴ | Ted Klok⁵ | Suzanne P. M. Fleuren⁶ | Tom Hendriks⁷ | Roy Gerth van Wijk² | Hans de Groot¹

¹Department of Pediatrics, Reinier de Graaf Hospital, Delft, The Netherlands

²Section of Allergology and Clinical Immunology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

³Department of Pediatrics, Martini Hospital, Groningen, The Netherlands

⁴Department of Pediatrics, NoordWest Hospital Group, Alkmaar, The Netherlands

⁵Pediatrics Allergy Treatment Centre, Deventer Hospital, Deventer, The Netherlands

⁶Department of Pediatrics, Elkerliek Hospital, Helmond, The Netherlands

⁷Department of Pediatrics, Catharina Hospital, Eindhoven, The Netherlands

Correspondence

Dirk H. J. Verhoeven, Department of Pediatrics, Reinier de Graaf Hospital, PO Box 5011, 2600 GA Delft, The Netherlands.

Email: dirk.verhoeven@rdgg.nl

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Abstract

Background: Previous studies have shown the efficacy of the early introduction of peanut to prevent peanut allergy. Due to the exclusion of infants with sensitization to peanut, it remains unclear what the optimal timing of introduction is.

Methods: The PeanutNL study was performed in 6 pediatric allergology centers in the Netherlands. Infants referred for the clinical early introduction of peanut to prevent peanut allergy underwent skin prick tests for peanut and an oral peanut challenge at a median age of 6 months.

Results: One hundred sixty two of 707 infants (23%) who had never eaten peanut before were sensitized to peanut, of which 80 (49%) had wheals of >4 mm. Sixty seven of 707 infants (9.5%) had a positive oral challenge to peanut at first introduction. Multivariate analysis revealed that age ($p < .001$) and SCORAD eczema severity scores ($p = .001$) were significant risk factors. Introduction of peanut at ≥ 8 months in infants with moderate and severe eczema resulted in an increased risk (odds ratio 5.24 ($p = .013$) and 3.61 ($p = .019$), respectively) of having reactions to peanut as compared to introduction before 8 months. A family history of peanut allergy and previous reactions to egg were not identified as independent risk factors.

Conclusion: These results suggest that peanut should be introduced before the age of 8 months to reduce the risk of reactions at first exposure in infants with moderate and severe eczema. Furthermore, since children with severe eczema have the highest risk of reactions, the clinical introduction of peanut should be considered, at the latest at the age of 7 months.

KEYWORDS

age, early introduction, eczema, peanut allergy, prevention

1 | INTRODUCTION

Since the Learning Early About Peanut allergy (LEAP) study,¹ the concept of cutaneous sensitization and gastrointestinal tolerance has been postulated to explain the occurrence of peanut allergies

and the development of tolerance to peanut when introducing at an early age.² The LEAP study demonstrated a clear effect on the reduction of peanut allergies when peanut was introduced between 4 and 11 months of age versus avoidance for 5 years. However, since the LEAP study protocol excluded 76 infants with >4 -mm wheal to

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peanut in skin prick tests, the optimal timing of introduction and the risk of introducing peanut in highly sensitized patients remains unresolved.

In the current study, the first results of the PeanutNL cohort are described: a cohort of infants from atopic families, aged 4–12 months, referred for clinical first introduction of peanut in 6 pediatric allergology centers in the Netherlands. The primary goal of this study was to determine risk factors for having a peanut allergy at first introduction, without excluding infants with strong sensitization to peanut and to identify the optimal timing of early introduction of peanut.

2 | PATIENTS, MATERIALS, AND METHODS

2.1 | Patients

Patients were referred by primary care physicians, pediatricians, and dermatologists according to the Early Introduction Advice to Prevent Peanut and Egg Allergy (2017) issued by the Dutch Society for Pediatrics.³ This advice promotes early introduction of peanut at home and referral of high-risk infants for clinical introduction. They were screened by pediatricians for inclusion at one of the 6 participating pediatric allergology centers in nonacademic general hospitals (Reinier de Graaf, Delft $n=520$; Martini Ziekenhuis, Groningen $n=135$; NoordWest Ziekenhuisgroep, Alkmaar $n=122$; Deventer Ziekenhuis, Deventer $n=76$; Elkerliek Ziekenhuis, Helmond $n=25$; Catharina Ziekenhuis, Eindhoven $n=17$) between 1 February 2018 and 1 January 2021. Inclusion criteria were an age between 4 and 12 months and either: moderate-to-severe eczema (SCORAD ≥ 15), previous immediate reactions to another food than peanut, or a first-degree family member with systemic reactions to peanut. Infants (4–12 months) with immediate reactions to peanut at first introduction at home were also included in the study but not used in the current analysis.

Severity of eczema was classified using the SCORAD classification.⁴ Since atopic dermatitis disease activity varies over time, SCORAD was scored based on the average severity of atopic dermatitis in the months prior to inclusion as provided by the parents.

The study protocol was judged by the Medical Ethical Committee, which concluded that this study did not fall under the scope of the Medical Research Involving Human Subjects Act in the Netherlands. The study was conducted according to the Declaration of Helsinki. All parents or custodians provided written informed consent for participation in the study. Patient data were collected in a GCP-certified database (CASTOR EDC).

2.2 | Materials and methods

Skin prick tests were performed with in-house produced peanut extracts (10% in Phosphate Buffered Saline) as previously

Key Message

International guidelines about the prevention of food or peanut allergy are conflicting in the timing of the introduction of highly allergenic food. This cohort study suggests that the most optimal timing of the introduction of peanut in infancy is before the age of 8 months and that clinical introduction should be considered in infants with severe eczema.

described,⁵ or commercial whole-peanut extract (ALK-Abelló). Dilution buffer (ALK-Abelló (no. 002)) was used as a negative control. Mean values of two histamine dihydrochloride 10 mg/mL (ALK-Abelló (no. 001))-induced wheal sizes were used as a positive control. The skin prick tests were performed according to EAACI guideline standards.⁶ Wheal size was defined as the average of two 180°-angled diameters in the case of nonsymmetrical wheal shapes.

Food challenges were performed in the food challenge units of the 6 participating pediatric allergology centers under the supervision of a pediatric allergologist, pediatrician, or specialized nurse practitioner. Either commercially available peanut butter or defatted peanut powder (Golden Peanut Company or Sukrin) was blended through mashed fruit or vegetables. The following dose-escalation schedules were used, based on peanut skin prick tests: 0-mm wheal to peanut: 2-step challenge (200 and 2000 mg of peanut protein); 1- to 4-mm wheal to peanut: four-step challenge (100, 300, 1000, and 2000 mg of peanut protein); >4-mm wheal to peanut: eight-step challenge (1, 3, 10, 30, 100, 300, 1000, and 3000 mg of peanut protein). All doses were given at 30-min intervals with at least 60-min observation after the final step. Allergic reactions were treated according to the Dutch guideline Anaphylaxis in Children⁷ and classified as described previously.⁸ As rescue medication, oral antihistamine (desloratadine or cetirizine), intramuscular adrenaline, intravenous saline solution, ondansetron, and inhaled salbutamol were available. The primary outcome of the study was a negative peanut challenge.

After a negative challenge, parents were advised to introduce peanut at home and to administer at least 2000 mg peanut protein cumulatively every week for at least 6 months, and to eat peanut regularly thereafter. After a positive challenge, parents were instructed to avoid peanut. Follow-up evaluation was scheduled 4 weeks and 6 months after the challenge.

Statistical analysis was performed using SPSS (version 25, IBM). The following tests were used: the Pearson's Chi-square test for the univariable analysis of categorical data; the Mann-Whitney *U* test was used for the univariable analysis of nonequally distributed continuous data; binary logistic regression analysis for multivariable analysis of parameters with *p*-values $< .10$ in univariate analysis and for analysis of stratified data in > 2 groups.

3 | RESULTS

3.1 | The PeanutNL cohort: inclusion and characteristics

Between February 2018 and January 2021, 952 infants were referred to the participating pediatric allergology centers. Sixty infants (6.3%) were excluded for several reasons: already eating peanut ($n=17$), no written informed consent provided ($n=14$), no show after referral ($n=13$), did not meet inclusion criteria ($n=12$), refused challenge ($n=4$).

Eight hundred ninety two infants were included in the cohort. 707/892 were referred for the first introduction of peanut and had never eaten peanut before. 185/892 were referred because of reactions to peanut at home.

Since the primary goal of the study was to assess risk factors for reactions at the first introduction of peanut, only infants who never ingested peanut before were analyzed. The characteristics of this primary prevention cohort of 707 infants are displayed in Table 1. These infants had a median age of 26 weeks at inclusion and a median SCORAD eczema score of 30. Almost half of the infants ($n=346$) had parents or siblings with primary (pea)nut allergies.

Eighty seven infants (12%) were included with no visible eczema. None of those was treated with topical corticosteroids. Mild eczema (SCORAD 1–14) was seen in 85 infants (12%). Two hundred eighty nine infants (41%) were included based on moderate eczema (SCORAD 15–39) and 246 infants (35%) had severe eczema (SCORAD >40). Four hundred thirty six children (62%) received prior treatment with topical corticosteroids (Table 1). One hundred thirty two infants (19%) had previous immediate reactions to food,

TABLE 1 Characteristics of the PeanutNL primary prevention cohort, $n=707$.

		Additional remarks
Gender	60% male	
Median age at inclusion	26 weeks	IQR: 21.5–30.5 weeks
Eczema	88% (620/707)	
Median SCORAD	30	IQR: 15–45 SCORAD
Prior topical corticosteroid treatment	62% (436/707)	
SCORAD 0: prior steroid treatment	0% (0/87)	
SCORAD 1–14: prior steroid treatment	9% (8/85)	
SCORAD 15–39: prior steroid treatment	77% (193/287)	
SCORAD ≥ 40 : prior steroid treatment	96% (235/246)	
First degree relative with (pea)nut allergy	49% (346/707)	
History of wheezing	8.9% (63/707)	
History of immediate reactions to food	19% (132/707)	
Egg	8.2% (58/707)	42/58 (72%) Sampson II–IV ^a
Cow's milk	9.5% (67/707)	35/67 (52%) Sampson II–IV ^a
Exclusively or partially breastfed	76% (536/707)	
First-degree family member with atopic disease	94% (662/707)	
Mean number of family members	3.7	SD=0.91
Mean number of family members with atopic disease	1.9	SD=1.1
Pets at home	28% (197/700)	
Smoking at home	16% (113/707)	
Consumption of peanut at home	76% (537/707)	92% (333/361) ^b
Consumption of hazelnut at home	70% (497/707)	81% (291/361) ^b
Consumption of cashewnut at home	63% (444/707)	76% (273/361) ^b

Abbreviations: IQR, interquartile range; SD, standard deviation.

^aAllergic reactions were graded according to Sampson.⁸

^bConsumption of (pea)nuts in families without a family member with a primary (pea)nut allergy. Consumption was defined as eating the product at least once a month.

most noticeably to cow's milk ($n=67$) and egg ($n=58$). Six hundred sixty two included infants (94%) had one or more first-degree family members with atopic disease (either rhinoconjunctivitis, eczema, asthma, or food allergy).

3.2 | Skin prick tests and challenges in the primary prevention cohort

All 707 children underwent skin prick tests for peanut at inclusion and a clinical oral peanut challenge (Figure 1). One hundred sixty two infants (22.9%) had a positive skin prick test for peanut. 80/162 infants (49.4%) had a skin prick test >4 mm.

Twenty three children (3.3%) had an inconclusive first challenge; they were all rechallenged. After a second challenge, two children (0.3%) with sensitization to peanut still had an inconclusive result (in both cases because of refusal to eat a sufficient amount of peanut).

In 67/705 (9.5%) evaluable infants, a peanut allergy was diagnosed. In two cases (3%) adrenalin was required as rescue medication. In 6/67 (9%) patients, the reaction was classified as $\geq$ grade III according to Sampson.⁸ A phenotype of delayed and severe vomiting to peanut, compatible with the diagnostic criteria of food

protein-induced enterocolitis syndrome (FPIES) allergy⁹ with a negative skin prick test was observed in three infants with a positive challenge. Therefore, the analytical sample contained data of 702 infants, excluding three with FPIES allergies and two with repeated inconclusive challenges. 16% ($n=13/82$) of the infants with 1- to 4-mm skin prick tests had positive challenges. A skin prick test of 5–9 mm resulted in 45% positive challenges ($n=26/58$). If the skin prick test to peanut was ≥ 10 mm, 19/21 infants reacted during the peanut challenge (91%). The median skin prick test in infants with sensitization to peanut was: 4 mm (interquartile range (IQR): 2.5–5.5) in peanut-tolerant infants and 8 mm (IQR: 5.5–10.5) in peanut-allergic infants.

3.3 | Risk factors for a peanut allergy at first introduction

To determine risk factors for having a peanut allergy in this high-risk atopic cohort, first, a univariable analysis was performed. The following variables had a significance with a p -value $<.10$ (Table 2): age (higher age at risk), severity of eczema (higher SCORAD at risk), a first-degree relative with systemic reactions to (pea)nut (protective),

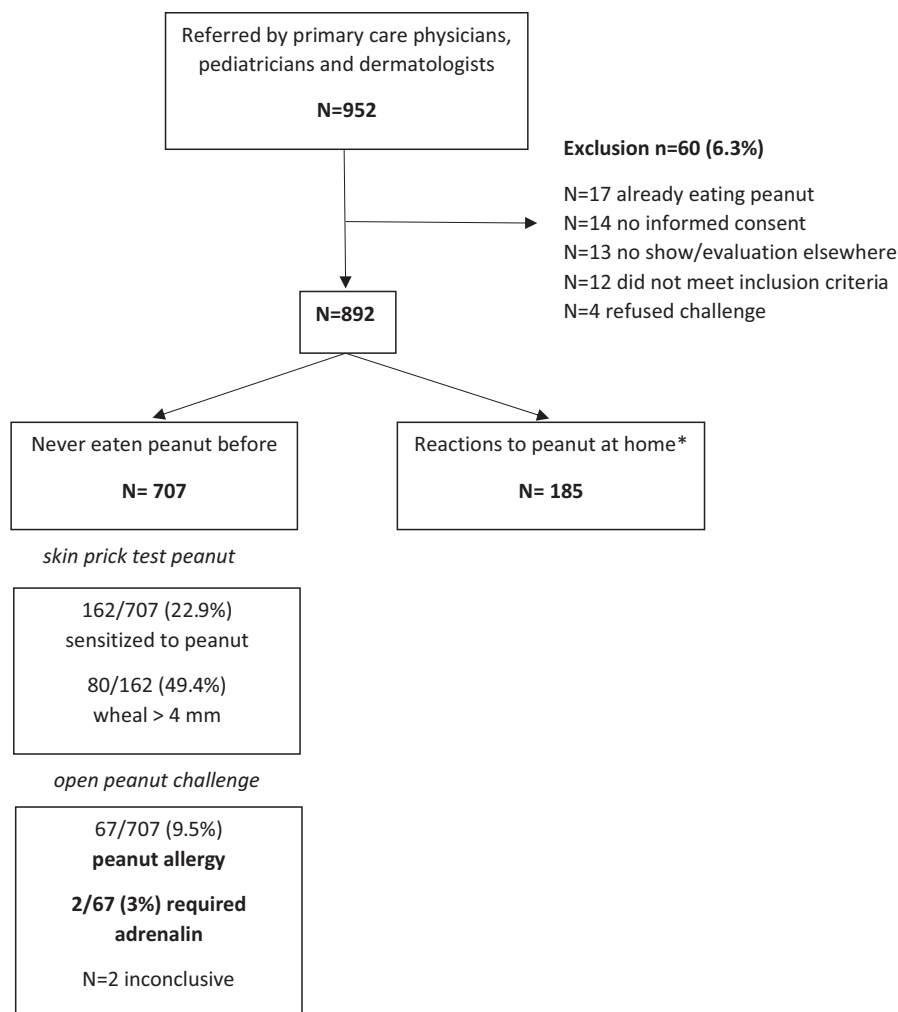


FIGURE 1 Overview of the PeanutNL cohort. Infants (4–12 months) with a high risk of food allergy were referred according to the Early Introduction Advice to prevent Peanut and Egg Allergy (2017) issued by the Dutch Society for Pediatrics.³ *Children with previous reactions to peanut at home were not included in the analysis of this manuscript.

TABLE 2 Uni- and multivariable analysis of risk factors for having a peanut allergy at first exposure.

Risk factor	Negative peanut challenge	Positive peanut challenge	Univariable significance (p)	Multivariable significance ^a	
				p-Value	Odds ratio (95% CI)
Age (median in months)	6.0 months	7.0 months	<.001 ^b	<.001	1.30 per month (1.13–1.50)
Severity eczema (median)	SCORAD 30	SCORAD 41	<.001 ^b	.001	1.27 per 10 SCORAD (1.10–1.45)
First degree relative with systemic reactions to (pea)nut	51%	37%	.037 ^c	.74	0.90 (0.49–1.66)
History of immediate reaction to food	18%	28%	.039 ^c	.78	1.13 (0.49–2.63)
History of immediate reaction to egg	7.5%	16%	.025 ^c	.58	0.74 (0.25–2.18)
Consumption of peanut at home	75%	88%	.025 ^c	.22	0.60 (0.26–1.35)

Note: Six risk factors with univariate significance of $p < 0.10$ were included in a multivariate binary logistic regression model, with the result of the peanut challenge as an outcome. $N = 702$ infants; 2 children with repeated inconclusive challenges and 3 children with food protein-induced enterocolitis syndrome (FPIES) to peanut were excluded from this analysis.

Abbreviation: CI, confidence interval.

^aBinary logistic regression.

^bMann–Whitney U .

^cPearson Chi-square.

previous immediate reactions to food, in particular to egg (increased risk) and consumption of peanut at home by other family members (increased risk).

The following factors were not significantly associated with the risk of reactions to peanut: gender ($p = .41$), the duration of exacerbations of eczema ($p = .12$), the number of family members with atopic disease ($p = .78$), the type of atopic disease ($p = .10$ – 0.63), wheezing ($p = .66$), previous reactions to cow's milk ($p = .97$) and (partial) breastfeeding ($p = .15$).

Multivariate analysis using binary logistic regression revealed that only age and severity of eczema were independent risk factors for having a peanut allergy at first introduction. The odds ratio was 1.30 ($p < .001$) for each additional month of age and 1.28 ($p = .001$) for each additional 10 SCORAD points (Table 2).

An increased incidence of reactions to peanut starting at 7 and reaching a plateau after 9 months of age was observed in this cohort (Figure 2A). In Figure 2B, the relationship between severity of eczema and peanut allergy is displayed. In 52 infants with a SCORAD > 60 , the chance of having a peanut allergy was 25%. In the Dutch Primary Care guideline "Food and Eating Behavior"¹⁰ advises introducing complementary food at 4 months. The WHO guideline breastfeeding¹¹ advises exclusive breastfeeding until the age of 6 months. Therefore, infants were stratified in the following age groups for first introduction of peanut: 4–5, 6–7, and ≥ 8 months to assess the risk of age and reactions to peanut at first introduction. The results for moderate and severe eczema are depicted in Figure 3. In both moderate and severe eczema, a significant effect of age was observed: an introduction ≥ 8 months significantly increased the risk of having a peanut allergy at first introduction (Odds ratio (OR) 5.24, $p = .013$ and OR 3.61, $p = .019$, respectively, binary logistic regression).

In 85 children with mild eczema (SCORAD 1–14) no reactions to peanut were observed at first introduction. However, in 6 out of 86 infants (7%) with no history of eczema, a peanut allergy was diagnosed. Five out of six had a first-degree relative with peanut allergy and one out of six had a previous reaction to egg.

4 | DISCUSSION

The results of the PeanutNL cohort study show that age and severity of eczema are two major risk factors for having a peanut allergy at the first introduction of peanut. An introduction of peanut at ≥ 8 months of age results in a significantly increased risk of having reactions to peanut. Using an approach with stepped challenges based on the wheal size of the skin prick test, only 3% required adrenalin as rescue medication, indicating it is safe to perform challenges, even in those with skin prick tests > 4 mm.

In the analysis of the LEAP study and additional publications of that dataset,¹² very early introduction did not appear to be beneficial. The analysis by Greenhawt included a multivariate analysis of the tolerance to peanut at 60 months, which demonstrated the superiority of the introduction of peanut between 6 and 11 months as compared to 4 and 6 months. That analysis, however, is hampered by the exclusion criteria of the LEAP study: 76 infants (10.6%) were excluded because of a skin prick test > 4 mm. Those infants were older and had a higher severity and duration of eczema and more frequently had an egg allergy.¹³ The exclusion of older children may lead to a bias in the analysis for optimal timing of early introduction of peanut. In the PeanutNL cohort, results of the peanut skin prick test were not an exclusion criterion, and a significant benefit of introducing peanut before the age of 8 months was observed.

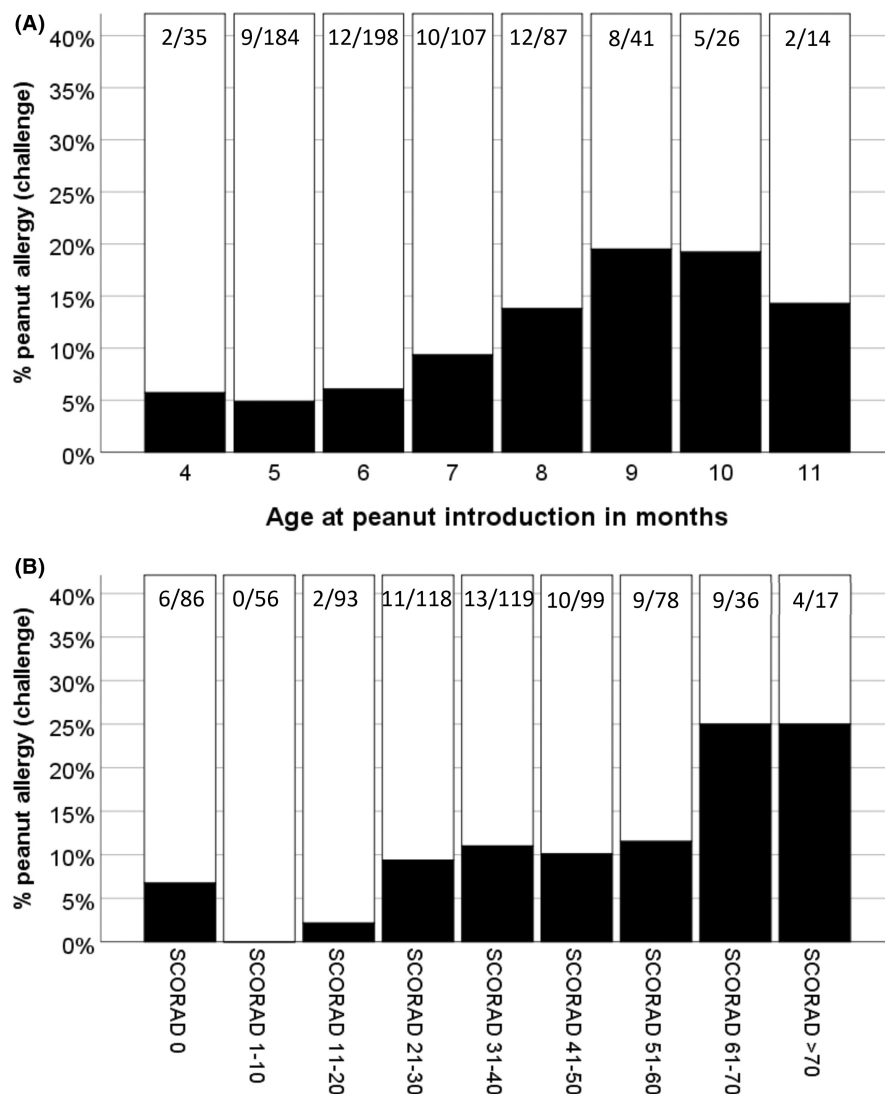


FIGURE 2 The prevalence of peanut allergy according to age at introduction (A) or severity of eczema (B). $N = 702$ infants; 2 children with repeated inconclusive challenges and 3 children with food protein-induced enterocolitis syndrome (FPIES) to peanut were excluded from this analysis.

Recently, the data of an American cohort of 321 infants at risk of peanut allergy were published.¹⁴ That study identified age (OR 1.3 for each increased month of age) and severity of eczema (OR 1.19 for each five-point increase in SCORAD) as major risk factors of peanut allergy in the first year of life. The current study confirms their main findings in a much larger European cohort and allows for a more detailed analysis of subgroups.

The PeanutNL cohort is a high-risk cohort consisting of infants with eczema, previous reactions to food and families with first-degree relatives with (pea)nut allergy. This is also reflected in the fact that 88 infants (12.4%) were diagnosed with an egg allergy in infancy in this cohort (data not shown). Since 49% of the included children were from families with a primary (pea)nut allergy, this subgroup may introduce specific confounders. Particularly, peanut was significantly less consumed in families with (pea)nut allergies (92% vs. 59% household peanut consumption, $p < .001$ Pearson's Chi-square). The reduced environmental exposure to peanut might explain why a first-degree relative with a peanut allergy is protective against a peanut allergy in univariable analysis (Table 2). It is important to notice that, in line with the US cohort study,¹⁴ a family history of (pea)nut allergy

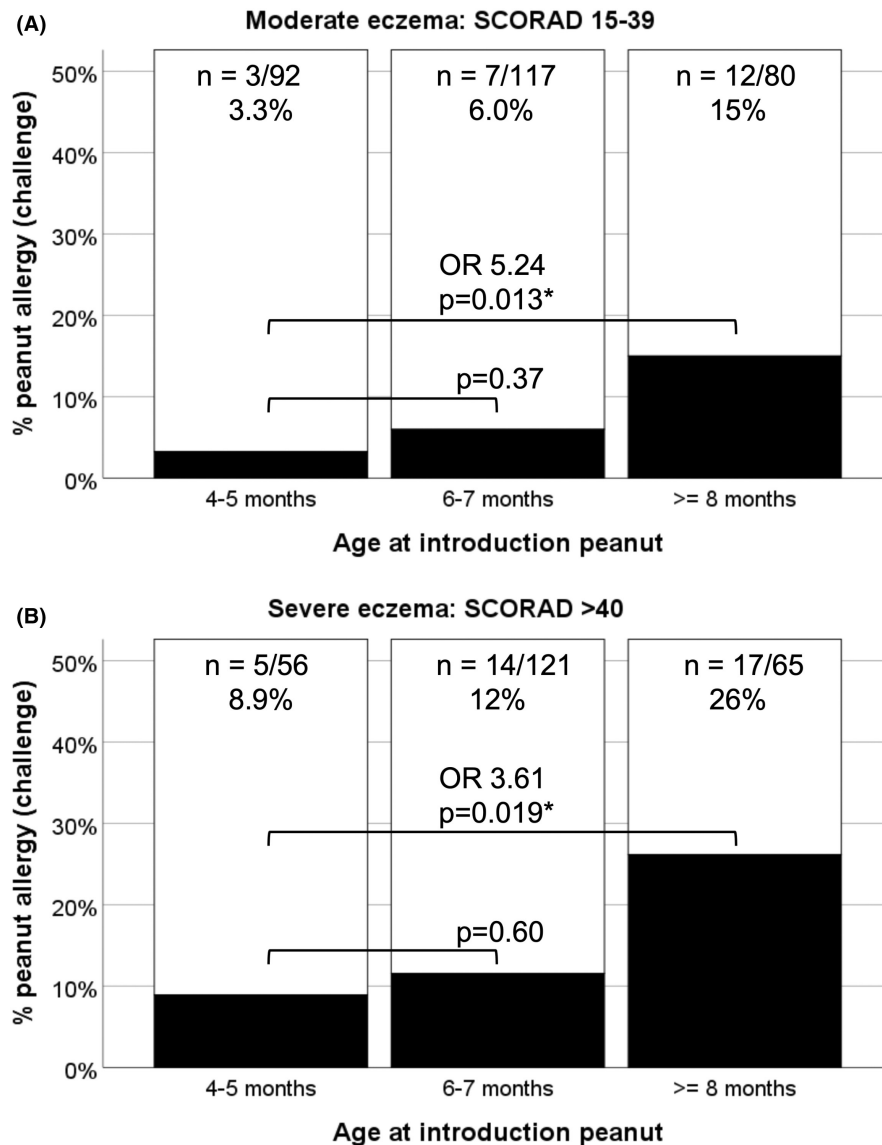
is not an independent risk factor for having a reaction to peanut. Many of those parents report fear of introducing peanut at home, so additional counseling and guidance are justified in those cases. However, clinical introduction of peanut is not indicated in those cases, if the age is < 8 months and eczema is mild (SCORAD < 15).

There were 6 infants with peanut allergy at first introduction without having eczema. Therefore, other risk factors may be involved besides age and severity of eczema in a minority of cases. These may include impaired skin barrier without inflammation, genetic factors (since five out of six had family members with (pea)nut allergies), or gastrointestinal barrier impairments.

4.1 | Generalizability

The Netherlands is a country with a high peanut consumption: the current study shows that peanut is being eaten in 92% of all families (Table 1) and previous studies have shown that children aged 1–3 years consume 1000g of peanut(butter) per year in the Netherlands.¹⁵ Furthermore, the incidence of atopic dermatitis, as

FIGURE 3 The prevalence of peanut allergy in infants with moderate (A) and severe eczema (B), stratified for the age of introduction A and B: Peanut allergies in 289 infants with moderate (A) and 242 infants with severe eczema (B), stratified for introduction at 4–5, 6–7, and ≥ 8 months and statistical analysis using binary logistic regression (reference = 4–5 months).



recorded by the NIVEL primary care survey, was 106/1.000 males and 97/1.000 females aged 0–4 years.¹⁶

International and national guidelines give conflicting advice about the timing of complementary food and the introduction of highly allergenic food. Many guidelines, such as the WHO breastfeeding guideline, European Food Safety Authority, and the Australian Consensus on Infant Feeding Guidelines to Prevent Food Allergy, advise introducing complementary food around the age of 6 months.^{11,17,18} In contrast, in high peanut-consuming countries such as the United States, United Kingdom, and The Netherlands, guidelines advise introducing pureed complementary food from the age of 4–5 months.^{10,19,20} This allows for the introduction of peanut around the age of 6 months, as also has been advised in the recent guideline from the European Academy of Allergy and Clinical Immunology.²¹ The data from this study with a large Dutch cohort of high-risk infants suggests that timely introduction of peanut, at the latest at the age of 7 months, is justified advice in children with atopic dermatitis living in countries with high peanut consumption.

The benefits of early peanut introduction will vary from country to country, depending on the consumption of peanut and the prevalence of peanut allergy. Therefore, it will be hard to define a universal guideline for the introduction of complementary food and preventing specific food allergies. And, in reverse, current universal guidelines may not be beneficial to certain subgroups (infants with eczema).

In conclusion, this study shows that age ≥ 8 months and severe eczema are independent major risk factors for having reactions to peanut at first introduction. Infants with atopic dermatitis in high peanut consumption countries may therefore benefit from the introduction of peanut.

AUTHOR CONTRIBUTIONS

Dirk H. J. Verhoeven: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; project administration; data curation. **Irene C. E. M. Herperetz:** Investigation; writing

– review and editing; validation; project administration. **Jeroen Hol:** Investigation; validation; writing – review and editing; project administration. **Ted Klok:** Investigation; validation; writing – review and editing; project administration. **Suzanne P. M. Fleuren:** Investigation; validation; writing – review and editing; project administration. **Tom Hendriks:** Investigation; validation; writing – review and editing; project administration. **Roy Gerth van Wijk:** Conceptualization; writing – review and editing; supervision; methodology. **Hans de Groot:** Conceptualization; investigation; funding acquisition; methodology; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicting interests to disclose.

PEER REVIEW

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ORCID

Dirk H. J. Verhoeven  <https://orcid.org/0009-0004-3599-6888>

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