

ORIGINAL ARTICLE

Food Allergy & Anaphylaxis

The diagnostic value of APT for food allergy in children: a systematic review and meta-analysis

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Abstract

Background: The role of atopy patch test (APT) in the diagnosis of food allergy (FA) remains largely controversial. In our meta-analysis, we aimed to evaluate the accuracy of APT for diagnosing FA in children.

Methods: Pubmed, Embase and Cochrane Library were searched for studies regarding the diagnostic value of APT for FA in children compared to oral food challenge (double-blind placebo-controlled food challenge and/or open food challenge). The last search was conducted on November 11, 2017. Two reviewers independently screened relevant studies and assessed the quality by QUADAS-2. Meta-analysis was performed to calculate the pooled sensitivity, specificity, DOR (diagnostic odds ratio), PLR (positive likelihood ratio), NLR (negative likelihood ratio) with their 95% confidence intervals (CIs). Subgroup analyses were conducted according to different food allergens, atopic dermatitis, gastrointestinal symptoms, and age younger than 3 years.

Results: Forty-one studies were included in the meta-analysis. The pooled sensitivity, specificity, PLR, NLR and DOR were 50.30% (95% CI 48.40%-52.30%), 86.60% (95% CI 85.30%-87.80%), 3.405 (95% CI 2.594-4.470), 0.545 (95% CI 0.469-0.634) and 7.528 (95% CI 5.507-11.206), respectively. However, for children with FA-related gastrointestinal symptoms, the pooled sensitivity and specificity were 57.40% (95% CI 52.10%-62.50%) and 91.50% (95% CI 88.30%-94.10%) respectively.

Conclusions: Our findings suggest that APT is specific but not sensitive for diagnosing FA in children, especially in children with FA-related gastrointestinal symptoms.

KEYWORDS

atopy patch test, children, food allergy, gastrointestinal symptoms, oral food challenge

1 | INTRODUCTION

Food allergy (FA) refers to the abnormal immune response after ingestion of offending food which can affect multiple systems including skin, respiratory and digestive systems etc.¹ In recent years, the prevalence of FA has been increasing worldwide. In Europe, about one in twenty children are considered to have one or more FAs reported by their parents.² While in the US, FAs affect more than 1% or 2% but less than 10%.³ FA is also the commonest cause of anaphylaxis, which can be fatal. It was reported in a meta-analysis that

the incidence rate of fatal anaphylaxis due to FA was 3.25 per million ones per year in food-allergic people aged 0-19 years.⁴

Nowadays, the diagnostic procedures for FA include detailed medical history and diagnostic tests. The medical history is indispensable which will help identify the cause of symptoms and determine appropriate tests for diagnosing FA. However, medical history is not enough to diagnose alone.⁵ It is well-known that double-blind placebo-controlled food challenges (DBPCFCs) are the gold standard so far for the diagnosis of FA. However, they are time-consuming, costly and difficult to perform in the clinic, and may provoke

TABLE 1 Characteristic of studies included in the meta-analysis

Author (year)	Country	Sample size	Age	Characteristics of the population	Food evaluated	Index test	Reference standard
Mehl ¹³ (2006)	Germany	437	3 m-14 y	Children with suspected FA and 90% had history of AD	Fresh CM, HE (white and yolk), wheat, soy	Erythema together with infiltration or papules	OFC (n = 873)
Giusti ¹⁴ (2005)	Italy	85	6 m-14 y	All children with AD	HE	Erythema and edema	OFC (n = 85)
yang ¹⁵ (2014)	China	150	3-24 m	All children with suspected FA and AD	Fresh CM, HE (white and yolk), wheat, soy	Erythema and infiltration	OFC (n = 498)
Jarvinen ¹⁶ (2003)	USA	90	2.5-36 m	All had a CM elimination and positive challenge, residual symptoms on egg and CM elimination diet	Cereals (rye, wheat, oats barley)	Oedema and eczema	OFC (n = 90)
Osterballe ¹⁷ (2004)	Denmark	486	3 y	Children	Fresh whole egg and CM	Erythema and slight infiltration	OFC (n = 21)
Breuer ¹⁸ (2004)	Germany	64	1-10 y	Children with suspected food-related worsening of AD or immediate-type reactions	Fresh CM, HE, wheat, soy	Erythema together with an infiltration	OFC (n = 66)
Mowszet ¹⁹ (2014)	Poland	61	3-36 m	Children with food-related GI symptoms	CM, wheat	Redness and infiltration	OFC (n = 80)
Kalach ²⁰ (2013)	France	25	1-18 m	Children with GI and/or extra-GI suggesting CM allergy	CM	/	OFC (n = 25)
Visitsunthorn ²¹ (2016)	Thailand	53	5 m-13 y	Children with AD	Lyophilized CM, HE (white and yolk), wheat, soybean, shrimp	Erythema together with infiltration	OFC (n = 238)
Stromberg ⁹ (2002)	Sweden	141	2 m-4 y	Children with AEDS	Fresh CM, egg white, wheat, rye	Redness and palpable infiltration	OFC (n = 564)
Boissieu ²² (2003)	France	35	2-57 m	Children referred for diagnosis of non specific persistent digestive symptoms	CM	Clear redness and palpable infiltration or eczema	OFC (n = 35)
Alves ²³ (2015)	Brazil	31	mean age: 97 d	All children with small and fresh rectal bleeding	Fresh CM	/	OFC (n = 31)
Zapatero ²⁴ (2005)	Spain	14	9-12 m	All children with FPIES due to dietary fish protein	Fish	Eczema and infiltration	OFC (n = 6)
Kokkonen ²⁵ (2001)	Finland	84	1.6-15 y	All children had recurrent abdominal pains lasting for at least 3 months during 1 year	CM, HE, soy, gliadin, wheat, barley, rye, oats	Significant erythema	OFC (n = 84)
Kalach ²⁶ (2005)	France	49	5-78 m	All children exhibited at least one symptom of FA	CM	Clear redness with palpable infiltration or eczema	OFC (n = 41)
Costa ⁷ (2011)	Brazil	192	1-5 y	All children with a diagnostic hypothesis of FA	CM	A hyperemic reaction with palpable edema	OFC (n = 116)
Nocerino ²⁷ (2013)	Italy	172	2-12 m	Children with CM allergy-related GI symptoms	CM	Erythema and slight infiltration	OFC (n = 172)
Seidenari ²⁸ (2003)	Italy	132	3-12 y	All children with AD	Peanuts	Erythema, edema, and few papules	OFC (n = 82)

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Sample size	Age	Characteristics of the population	Food evaluated	Index test	Reference standard
Yukselen ²⁹ (2016)	Turkey	151	3-60 m	Children with persistent vomiting and refractory GERD	CM	Redness and palpable infiltration with papules	OFC (n = 151)
Keskin ³⁰ (2005)	Turkey	37	1.5-84 m	Children with suspected CM allergy	CM	Redness and induration	OFC (n = 36)
Canani ³¹ (2007)	Italy	60	3-48 m	Children with suspected FA-related GI symptoms	Fresh CM, HE, wheat	Erythema and slight infiltration	OFC (n = 89)
Fogg ³² (2006)	USA	19	5-30 m	All children with suspected FPIES	CM, soy, HE, wheat, rice, oat	Erythema	OFC (n = 33)
Roehr ³³ (2001)	Germany	98	2 m-11.2 y	All children had AD and with suspected FA	Fresh CM, HE, wheat, soy	Erythema with infiltration	OFC (n = 173)
Boonyaviwat ³⁴ (2015)	Thailand	39	2 m-1 y	Children was suspected FA-related GI symptoms	Lyophilized CM, HE (white and yolk), wheat, soybean	Erythema, infiltration	OFC (n = 41)
Majamaa ³⁵ (1999)	Finland	39	<2 y	Children with suspected wheat allergy	Wheat	Clear redness with palpable infiltration	OFC (n = 39)
Niggemann ³⁶ (2000)	Germany	75	4 m-12.5 y	Children with suspected FA and 69/75 had AD	Fresh CM, HE, wheat, soybean	Erythema and slight infiltration	OFC (n = 133)
Cudowska ³⁷ (2008)	Poland	34	5 m-16 y	Children with suspicion of milk-related AEDS	Fresh CM	Redness and palpable infiltration with papules	OFC (n = 34)
Heine ³⁸ (2006)	Germany	87	0.5-13.5 y	Children with AD and suspected FA	Fresh CM, soy, HE, wheat	Moderate erythema plus any induration	OFC (n = 165)
Hansen ³⁹ (2004)	Denmark	30	10 m-11 y	10 clinically egg-allergic children with AD/10 egg-tolerant children having AD/10 egg-tolerant children without AD	Fresh HE (25%concentration)	At least erythema and slight infiltration	OFC (n = 24)
Cudowska ⁴⁰ (2010)	Poland	28	6-144 m	Children suspected of FA-related GI symptoms	CM	Redness and palpable infiltration with papules	OFC (n = 28)
Peron ⁴¹ (2011)	Italy	20	7 m-6 y	Children had AD and suspected food-related symptoms	Commercial extracts of CM, casein, HE (white and yolk)	Erythema and mild infiltration	OFC (n = 40)
Niggemann ⁴² (2002)	Germany	30	3-58 m	All children had AD	Fresh CM, soy, HE (white and yolk), wheat	Erythema together with infiltration	OFC (n = 55)
Majamaa ⁴³ (1999)	Finland	143	<2 y	Children with suspected allergy to CM	CM	Clear redness with palpable infiltration	OFC (n = 132)
Isolauri ⁴⁴ (1996)	Finland	183	2-36 m	Children had AD	Humidified skimmed CM	Erythema with edema or eczema	OFC (n = 183)
Vanto ⁴⁵ (1999)	Finland	301	2-11 m	Children with suspected hypersensitivity to CM	CM	Redness with induration	OFC (n = 245)
Rasanen ⁴⁶ (1992)	Finland	34	0.6-14.5 y	Children had skin problems and/or suspicion of FA	α 1-casein, β -lactoglobulin	Significant erythema	OFC (n = 29)

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Sample size	Age	Characteristics of the population	Food evaluated	Index test	Reference standard
Saarinen ⁴⁷ (2001)	Finland	239	6.3-7.5 m	All children had symptoms suggestive of CM allergy	CM, bovine serum albumin, crystallized bovine β -lactoglobulin and bovine casein	Erythema with induration	OFC (n = 204)
Sozmen ⁴⁸ (2015)	Turkey	243	12 m-16 y	Children with a suspicion of CM or egg allergies	Lyophilized HE, casein, CM	Erythema, infiltration	OFC (n = 243)
Cudowska ⁴⁹ (2005)	Poland	27	5-36 m	Children with suspected milk-related skin and digestive symptoms	CM	Erythema, infiltration/single nodules	OFC (n = 27)
Kekez ⁵⁰ (2010)	/	61	3 w-4 y	Children with suggestive of CM allergy	CM	Erythema with infiltration	OFC (n = 61)
Perackis ⁵¹ (2003)	Germany	255	3-148 m	All children had AD	Fresh CM, HE, soy, wheat	/	OFC (n = 335)

AD = atopic dermatitis; GI = gastrointestinal; FA = food allergy; CM = cow's milk; HE = hen's egg; AEDS = atopic eczema/dermatitis syndrome; OFC = double-blind placebo-control food challenge and/or open food challenge; FPIES = food protein-induced enterocolitis syndrome; GERD = refractory gastroesophageal reflux disease; m = months; y = years; w = weeks; d = days;

fatal anaphylactic reactions. In a study of 178 positive oral food challenges with four allergens, it was shown that 120 subjects need medical intervention.⁶ Therefore, a lot of work has been done to find proper tests to minimize the use of oral food challenge. Currently, skin prick test (SPT) and specific IgE (sIgE) determinations are the first line for diagnosing FA. However, they are mainly used to investigate immediate reactions rather than the non-IgE-mediated ones.⁷ In a meta-analysis, it was suggested that SPT and sIgE had good sensitivities (SPT: 55%-95%; sIgE: 83%-96%) but poor specificities (SPT: 58%-73%; sIgE: 38%-59%) for the diagnosis of IgE-mediated FA with five different food allergens.⁸ However, as for non-IgE-mediated FA, it is difficult to make a diagnosis because the allergic reactions often occur a long time after ingesting food which makes the involved food allergens hard to find. Currently, oral food challenge is the only available test for diagnosing non-IgE-mediated FA.

Early in 2002, APT had been found to be a useful diagnostic test with high specificity and sensitivity when investigating IgE-independent FA.⁹ However, the use of APT for diagnosing FA is still controversial in the clinic because of its variable reproducibility and lack of standardization. To date, no meta-analysis has summarized the diagnostic value of APT for FA in children. Therefore, we conducted a systematic review and meta-analysis to evaluate the diagnostic value of APT for FA in children.

2 | METHODS

2.1 | Search strategy

A comprehensive systematic search was conducted in three electronic databases including PubMed, Cochrane Library and Embase, to identify all relevant studies evaluating the diagnostic value of APT for FA in children. We used the following key words: "food allergy",

"food hypersensitivity", "gastrointestinal symptoms", "atopic dermatitis", and "atopy patch test". No language restriction was imposed. The last search was conducted on November 11, 2017. The detailed search strategy is shown in Table S1. Reference lists of related articles were also checked to identify additional eligible studies. Two investigators (Y-L and G-QZ) independently conducted the initial search, removed duplicate records, screened the titles and abstracts for relevance, checked the reference lists of all related articles and identified as excluded or requiring further assessment. Finally, we screened the full-text of articles.

2.2 | Inclusion and exclusion criteria

We developed a PICOS (Patient, Intervention, Comparators, Outcome, and Study design) approach as the eligibility criteria. All included studies should meet the following criteria: (a) the participants were children (≤ 18 years old); (b) FA was confirmed by oral food challenge; (c) APT was performed as the evaluated test; (d) the data including the true positive (TP), false positive (FP), false negative (FN) and true negative (TN) of APT compared to oral food challenge could be found or calculated from the provided data in all included studies. The exclusion criteria were as follows: (a) articles with non-English full text and abstracts; (b) articles from which we could not extract data to form the 2×2 table. When studies used duplicate samples, the study with the largest sample size was included in the meta-analysis. Disagreements regarding screening and study inclusion were solved through discussion with a third reviewer (Z-YL), as required.

2.3 | Data extraction

Data extraction was performed independently by Y-L and confirmed by G-QZ. The following important information of all included studies

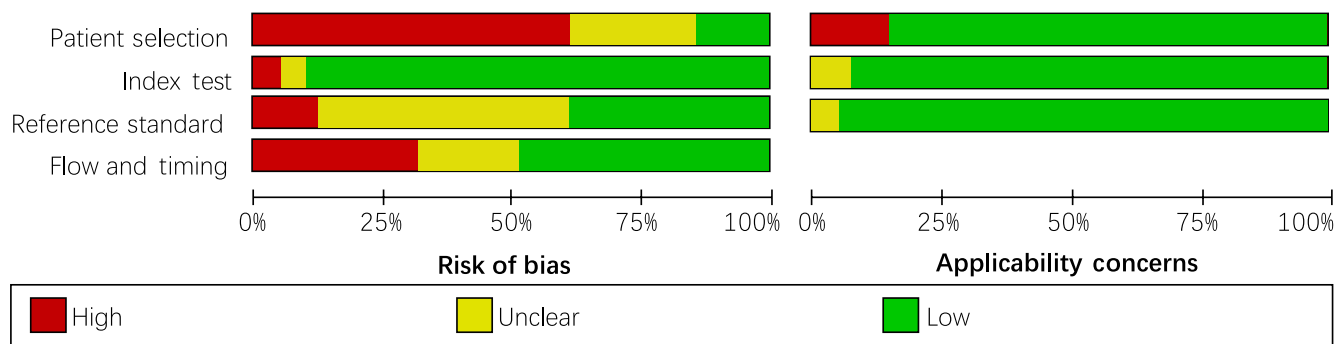


FIGURE 1 QUADAS-2 results [Colour figure can be viewed at wileyonlinelibrary.com]

was recorded: the first author, published year, nationality, sample size, ages, characteristics of the participants, involved food allergens and the positive threshold of APT. The key data including TP, FP, FN and TN of APT were also extracted. Extracted data were entered into a standardized Excel file. We checked the original articles to get consensus if there were discrepancies regarding the data extraction.

2.4 | Quality assessment

For each study, the quality assessment was completed separately by two researchers with QUADAS-2 in the Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). QUADAS-2 includes 4 domains: patient selection, index test, reference standard, flow and timing. Each domain concludes signaling questions answering “yes”, “no” or “unclear” to judge the risk of bias (low/high/unclear). In particular, the “unclear” could be answered only when the provided information is insufficient. When all “yes” correspond to the “low risk of bias”, any “no” means to be “high risk of bias”. However, the applicability sections are only involved in the first three domains and structured in a way similar to that of the bias sections. It is rated as “low concern”, “high concern” and “unclear concern” by answering questions as well. Similarly, we judge it to be “high concern” if any answer is “no”.¹⁰

2.5 | Statistical analysis

All data analyses were performed in Meta-disc version 1.4 to evaluate the diagnostic accuracy of APT. Different metrics were calculated by random effects model including the pooled sensitivity,

specificity, PLR (positive likelihood ratio), NLR (negative likelihood ratio) and DOR (diagnostic odds ratio) with their 95% confidence intervals (CIs). The AUC (area under the curve) of SROC (summary receiver operating characteristic curve) was also calculated. When the sensitivity and specificity refer to the conditional hit rate of the evaluated test, the ROC is used to synthesize the above indexes and better reflect the diagnostic accuracy. The value of DOR is not influenced by the prevalence of the target disease. In particular, there is a mathematical connection between the DOR and the AUC. The higher DOR corresponds to the better value of the AUC. The DOR takes value of 0 to infinity whereas the AUC ranges from 0 to 1. The closer it is to 1, the better diagnostic accuracy it shows.¹¹ The AUC with 0.7 to 0.9 means to be a certain accuracy, while the 0.5-0.7 indicates a low accuracy. Subgroup analyses were conducted according to different food allergens, atopic dermatitis (AD), gastrointestinal symptoms, and age younger than 3 years. The I^2 statistic was used to measure the heterogeneity between studies in the meta-analysis. A I^2 value greater than 50% was considered to have significant heterogeneity.¹² The diagnostic threshold effect was judged by the spearman correlation coefficient test.

3 | RESULTS

3.1 | Literature search

A total of 41 eligible studies^{7,9,13-51} were included in our meta-analysis. Firstly, 578 studies were identified by the initial search and supplemented by 7 additional studies^{35,43-47,52} which were searched

TABLE 2 The diagnostic value of APT for food allergy in children

	NO.of studies	Sample size	Cases	Pooling model	Pooled (95%CI)
Sensitivity	41	4534	5607	REM	0.503 (0.484-0.523)
Specificity	41	4534	5607	REM	0.866 (0.853-0.878)
PLR	41	4534	5607	REM	3.405 (2.594-4.470)
NLR	41	4534	5607	REM	0.545 (0.469-0.634)
DOR	41	4534	5607	REM	7.528 (5.057-11.206)

CI = confidence interval; PLR = positive likelihood ratio; NLR = negative likelihood ratio
DOR = diagnostic odds rate; REM = random-effects model

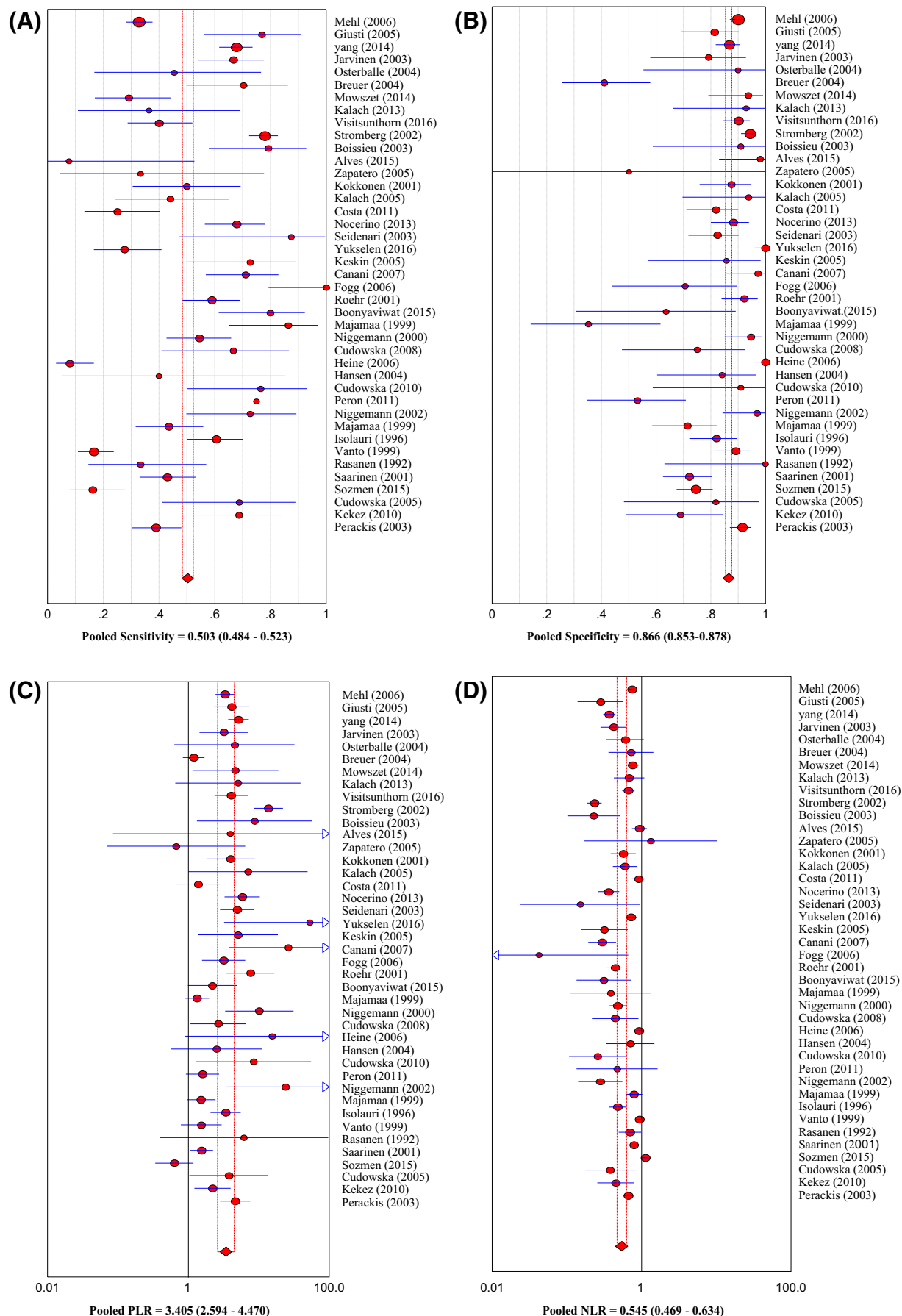


FIGURE 2 Forest plots of pooled results of APT in the diagnosis of food allergy [Colour figure can be viewed at wileyonlinelibrary.com]

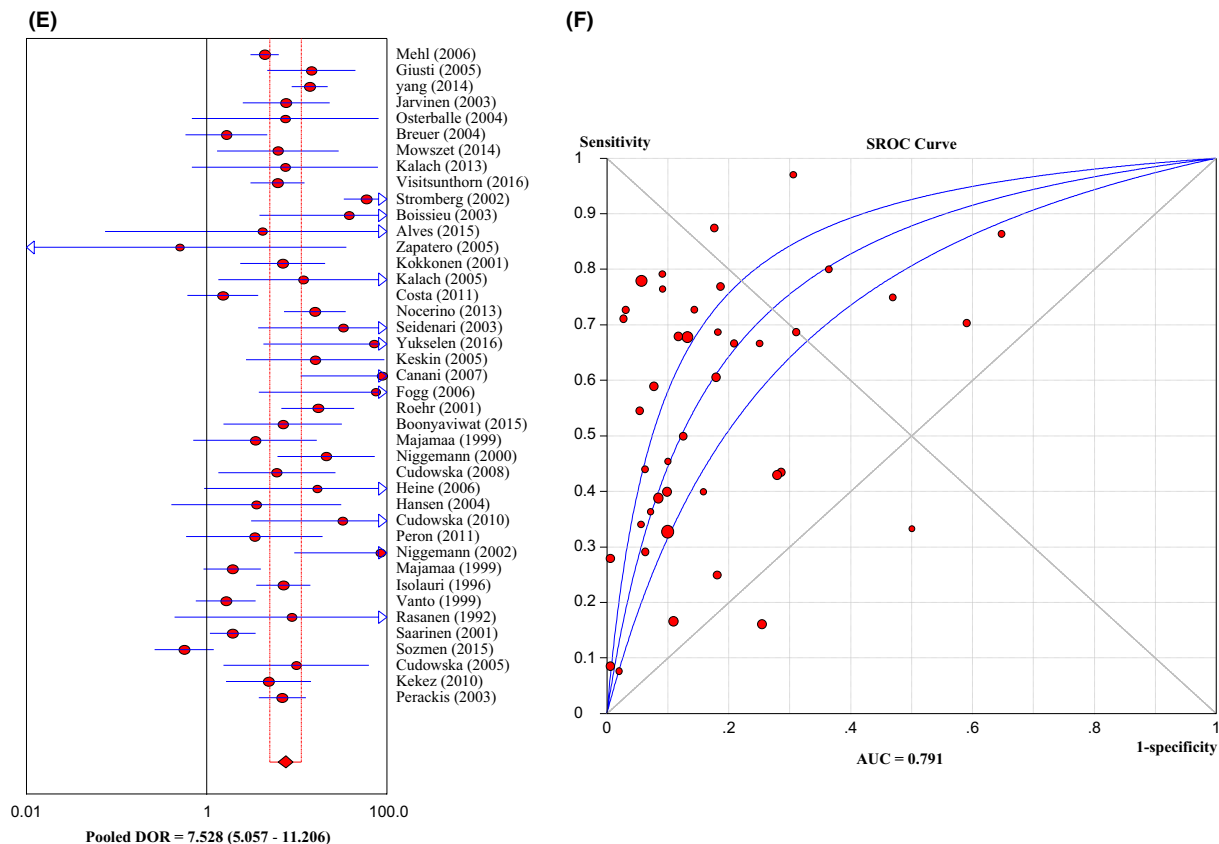


FIGURE 2 (Continued)

manually. Then, 166 articles were removed for duplications, whereas 334 records were excluded due to unrelated titles and abstracts. After reviewing the full-text, 40 articles were removed including 4 studies of which we were unable to find the full-text. Finally, of the remaining 45 candidate articles, 4 studies⁵²⁻⁵⁵ were removed because the data we calculated based on the provided data were inconsistent with the information mentioned in the articles. We contacted the authors and no response was received. Finally, a total of 41 studies including 5,607 cases between 1992 and 2016 were included in our study. The detailed flowchart of screening articles is shown in Figure S1. Table 1 summarizes the characteristics of the included studies.

3.2 | Quality assessment

QUADAS-2 results are shown in Figure 1. Most studies were judged to be high or unclear risk of bias in all domains except the index test. In the patient selection domain: (a) high risk of bias: 25 studies;^{9,14,16,18,22,24,25,27-30,32,36,38-47,49,51} (b) unclear risk of bias: 10 studies;^{7,15,17,19,21,23,26,35,37,50} (c) low risk of bias: 6 studies.^{13,20,31,33,34,48} In the index test domain: (a) high risk of bias: 2 studies;^{39,46} (b) unclear risk of bias: 2 studies;^{23,50} (c) low risk of bias: 37 studies. In the reference standard domain: (a) high risk of bias: 5 studies;^{15,17,21,32,34} (b) unclear risk of bias: 20 studies;^{7,14,16,19,22-25,27-29,35,39,41,43,44,47-50} (c) low risk of bias: 16 studies. In the flow and timing domain: (a) high risk of bias: 13 studies;^{7,17,18,21,24,26,30,39,43,45-48} (b) unclear risk

of bias: 8 studies;^{25,27,33,36,38,42,50,51} (c) low risk of bias: 20 studies. However, the applicability concerns were considered to be low concern in most studies, except 6 studies^{16,25,27,32,39,46} to be high concern in the patient selection domain, 3 studies^{23,39,50} to be unclear in the index test domain, and 2 studies^{27,50} to be unclear in the reference standard domain. Detailed information of QUADAS-2 assessment is represented in Table S2. As for the threshold effect, the spearman correlation coefficient of sensitivity and 1-specificity is 0.348 ($P = 0.026$) which indicates that it is not the source of heterogeneity in the meta-analysis. Increase size of Figure 1 to cover the whole width of the page. Readability!!!

3.3 | Meta-analysis results

A total of 5,607 cases were obtained in 41 included studies. In general, the overall pooled sensitivity, specificity, PLR, NLR with their 95% CIs were 50.30% (95% CI: 48.40%-52.30%), 86.60% (95% CI: 85.30%-87.80%), 3.405 (95% CI: 2.594-4.470), and 0.545 (95% CI: 0.469-0.634) respectively. The DOR was 7.528 (95% CI: 5.507-11.206) and the AUC was 0.791. The overall results of diagnostic accuracy of APT are shown in Table 2. The forest plots of the pooled sensitivity, specificity, PLR, NLR, DOR and SROC are shown in Figure 2.

3.4 | Subgroup analyses

Summary results of the subgroup analyses are shown in Table 3.

TABLE 3 Subgroup analyses for APT in the diagnosis of food allergy in children

Subgroup analysis	Studies	Cases	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC	Refs.
Patient selection	AD	16	3279	0.536 (0.511-0.560)	0.886 (0.871-0.900)	4.229 (2.921-6.326)	0.475 (0.363-0.622)	10.297 (6.171-17.180)	0.803
	GI	11	750	0.574 (0.521-0.625)	0.915 (0.883-0.941)	4.575 (2.782-7.524)	0.473 (0.333-0.671)	14.370 (7.611-27.129)	0.857
Different foods	CM	30	2623	0.442 (0.415-0.470)	0.869 (0.850-0.887)	3.420 (2.491-4.696)	0.618 (0.534-0.714)	6.823 (4.327-10.759)	0.804
	HE	13	1026	0.543 (0.499-0.586)	0.845 (0.810-0.876)	3.654 (2.144-6.229)	0.498 (0.375-0.663)	8.089 (3.696-17.702)	0.788
	Soy	7	484	0.538 (0.444-0.630)	0.860 (0.820-0.894)	3.326 (2.233-4.954)	0.512 (0.302-0.869)	7.194 (3.013-17.181)	0.886
	Wheat	11	672	0.640 (0.579-0.698)	0.890 (0.855-0.918)	5.002 (2.371-10.553)	0.364 (0.215-0.614)	15.893 (5.606-45.059)	0.885
	Age ≤3 yrs	17	2030	0.519 (0.489-0.550)	0.837 (0.812-0.859)	2.770 (1.981-3.873)	0.587 (0.464-0.744)	5.536 (3.322-9.224)	0.785

AD = atopic dermatitis; GI = gastrointestinal symptoms; CM = cow's milk; HE = hen's egg

3.4.1 | Atopic dermatitis

In children with AD, the pooled sensitivity, specificity, PLR and NLR were 53.60% (95%CI: 51.10%-56.00%), 88.60% (95% CI: 87.10%-90.00%), 4.229 (95% CI: 2.921-6.326) and 0.475 (95% CI: 0.363-0.622) respectively. As for the DOR, it showed 10.297 (95% CI: 6.171-17.180). The AUC was 0.803.

3.4.2 | FA-related gastrointestinal symptoms

In children with FA-related gastrointestinal symptoms, the pooled sensitivity was 57.40% (95% CI: 52.10%-62.50%) and specificity was 91.50% (95% CI: 88.30%-94.10%). As for the likelihood ratio, the PLR and NLR were 4.575 (95% CI: 2.782-7.524), and 0.473 (95% CI: 0.333-0.671) respectively. The DOR was 14.370 (95% CI: 7.611-27.129) and the AUC was 0.857.

3.4.3 | Age under 3 years old

In participants aged under 3 years old, the pooled sensitivity and specificity were 51.90% (95%CI: 48.90%-55.00%) and 83.70% (95% CI: 81.20%-85.90%) respectively. The PLR was 2.770 (95% CI: 1.981-3.873) and NLR was 0.587 (95% CI: 0.464-0.744). The DOR was 5.536 (95% CI: 3.322-9.224). As for the AUC, it was 0.785.

3.4.4 | Different foods

The pooled results for specific FA were as follows: (a) cow's milk allergy: sensitivity 44.20% (95% CI: 41.50%-47.00%), specificity 86.90% (95% CI: 85.00%-88.70%); (b) egg allergy: sensitivity 54.30% (95% CI: 49.90%-58.60%), specificity 84.50% (95% CI: 81.00%-87.60%); (c) soy allergy: sensitivity 53.80% (95% CI: 44.40%-63.00%), specificity 86.00% (95% CI: 82.00%-89.40%); (d) wheat allergy: sensitivity 64.00% (95% CI: 57.90%-69.80%), specificity 89.00% (95% CI: 85.50%-91.80%).

4 | DISCUSSION

APT was first described as the skin reactions by applying inhalants allergens in patients with AD in 1982 by Mtichell et al.⁵⁶ Its value for diagnosing FA was later investigated in 1989.⁵⁷ In a study that investigated specific immunological parameters in AD patients with different results of APT, it was indicated that the CD69⁺ which is thought to be the early marker of the activation of T cell was higher on peripheral blood mononuclear cells (PBMCs) stimulated with allergens leading to positive APT reactions. The higher number of ICAM-1 (CD54⁺) and CD30⁺ allergen-stimulated T cells was also found in patients with positive APT reactions than negative ones.⁵⁸ In addition, it was indicated that cutaneous exposure to food allergens could reprogram gut-homing effectors T cells in lymph nodes to express skin-homing receptors and elicit skin lesions upon food allergen contact,⁵⁹

and T cell-mediated processes predominated in non-IgE-mediated FA.⁵ In all, current evidence suggests that APT is associated with non-IgE-mediated FA.

To our knowledge, no meta-analysis has investigated the diagnostic value of APT for diagnosing FA in children. In our study, we found that APT had good specificity (86.60%) but poor sensitivity (50.30%). Low sensitivity indicates that the negative result of APT cannot rule out FA and the oral food challenge is still needed in this condition. In contrast, good specificity means it is possible to omit oral food challenge because the risk of FA in that case is high enough. The pooled PLR and NLR were also calculated in order to evaluate the diagnostic accuracy in clinical level. The PLR of 3.405 (95% CI: 2.594-4.470) shows that children with FA could have 3.405 times chance of being APT positive than that of healthy ones. Moreover, the NLR of 0.545 (95% CI: 0.469-0.634) indicates that the possibility of being APT negative in the children with FA is 0.545 times than that in the healthy ones. As for the AUC, it (0.791) indicates that APT is an accurate tool for diagnosing FA regardless of prevalence. Furthermore, with the high sensitivity (but low specificity) of SPT/sIgE,⁸ several studies found that the combination of SPT with APT could significantly improve the sensitivity and/or NPV for diagnosing FA,^{16,30,31,41,44} while other studies indicated that their combination improved the specificity and/or PPV.^{13,21,28,34} It was also reported that APT together with sIgE enhanced the PPV for the diagnosis of FA.^{13,33} Hence, we suggest that APT can be added into the diagnostic workup of FA in children.

FA-related gastrointestinal symptoms play an important role in FAs and often occur several hours after ingestion of related food allergens. GI allergies mainly include food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE) and eosinophilic gastrointestinal disorders (EGID). Most of them are thought to be non-IgE-mediated reactions.⁶⁰ Morita et al⁶¹ mentioned T cells could produce different inflammatory cytokines antigen-specifically like TNF- α in GI allergies. In contrast, B cells did not produce any food-related IgE in this condition by which mechanism is still unclear. Similarly, another study found the food-allergen special suppressor of CD8 + T cell in FPE and increased TNF- α /IFN- γ released by active T cell in FPIES.⁶² In all, SPT/sIgE may be useless in patients with FA-related GI symptoms and oral food challenge is still needed. We found that APT had high specificity (0.915) and low sensitivity (0.574) for children with FA-related gastrointestinal symptoms.

There are some limitations in our systematic review. Firstly, four studies with non-English full text and abstracts were removed. However, due to its limited number, we believe that it cannot influence the overall results. Secondly, the varied standard of positive APT and variable reproducibility might be limitations in our review (e.g. different allergen concentration, vehicles, preparation of related allergens, occlusion time, size of the chamber). The quality of the included studies also varies. But overall, APT shows a good diagnostic value for FA in children. Additional work

is needed on the standardization of APT. Thirdly, FA was confirmed by oral food challenge rather than only the DBPCFCs in some of the included studies. However, it has been shown that open oral challenges could be performed in children up to 3 years for diagnosing FA according to the European Academy of Allergy and Clinical Immunology.⁶³

5 | CONCLUSION

Our findings suggest that APT is specific but not sensitive for diagnosing FA in children. APT would be a useful supplementary diagnostic test, especially in children with FA-related gastrointestinal symptoms.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Figure S1 Selection process for the studies included in the meta-analysis

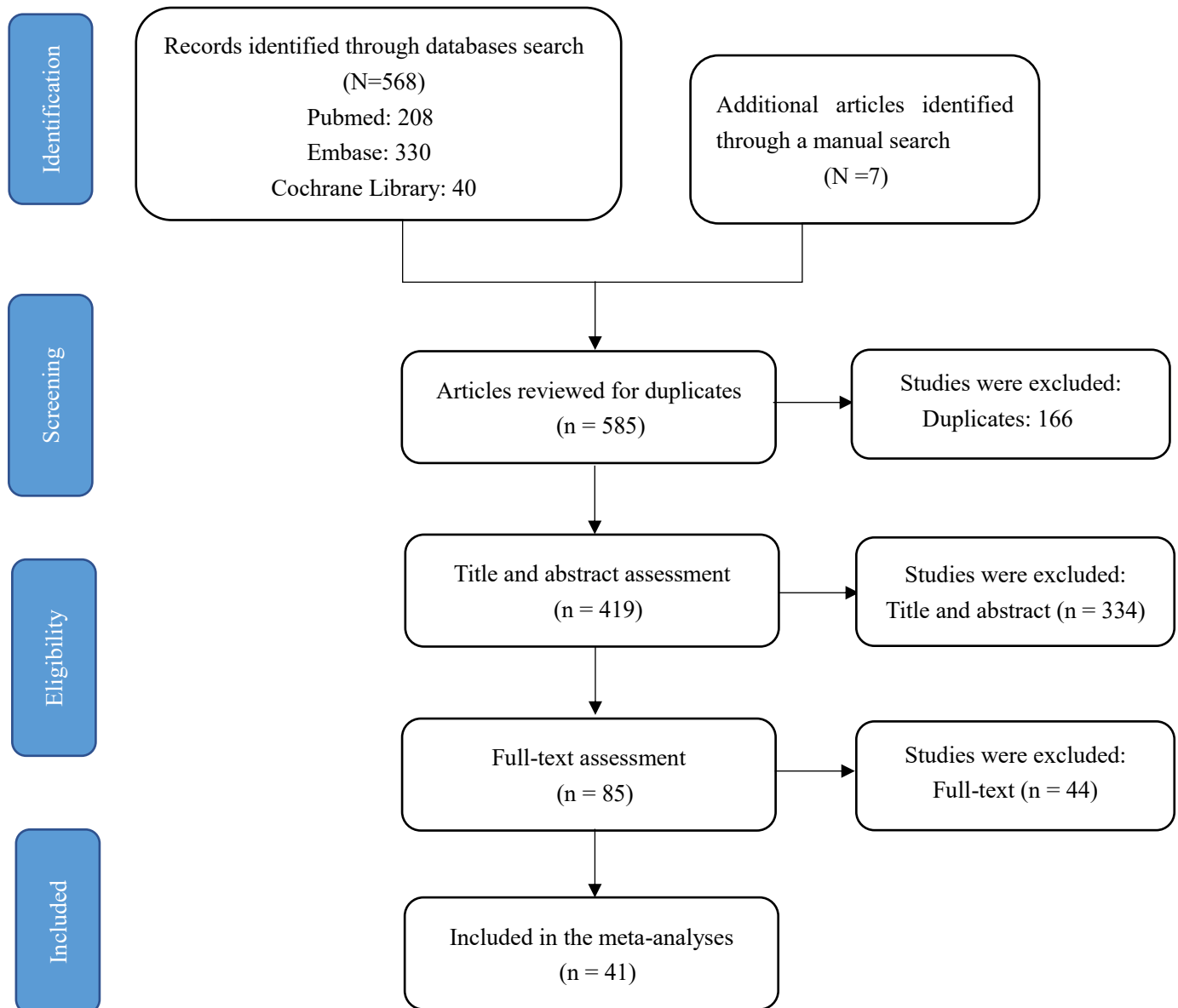


Table S1. Search Strategy

Search terms

1. atopy patch test, OR APT
 2. food allergy OR food hypersensitivity OR gastrointestinal symptoms OR atopic dermatitis
 3. child: birth-18 years
 4. 1, 2, AND 3
-

Table S2 Detailed information of quality assessments

Study	Risk of Bias				Applicability concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Mehl (2006)	😊	😊	😊	😊	😊	😊	😊
Giusti (2005)	😞	😊	?	😊	😊	😊	😊
yang (2014)	?	😊	😞	😊	😊	😊	😊
Jarvinen (2003)	😞	😊	?	😊	😞	😊	😊
Osterballe (2004)	?	😊	😞	😞	😊	😊	😊
Breuer (2004)	😞	😊	😊	😞	😊	😊	😊
Mowszet (2014)	?	😊	?	😊	😊	😊	😊
Kalach (2013)	😊	😊	😊	😊	😊	😊	😊
Visitsunthorn (2016)	?	😊	😞	😞	😊	😊	😊
Stromberg (2002)	😞	😊	😊	😊	😊	😊	😊
Boissieu (2003)	😞	😊	?	😊	😊	😊	😊
Alves (2015)	?	?	?	😊	😊	?	😊
Zapatero (2005)	😞	😊	?	😞	😊	😊	😊
Kokkonen (2001)	😞	😊	?	?	😞	😊	😊
Kalach (2005)	?	😊	😊	😞	😊	😊	😊
Costa (2011)	?	😊	?	😞	😊	😊	😊
Nocerino (2013)	😞	😊	?	?	😞	😊	?
Seidenari (2003)	😞	😊	?	😊	😊	😊	😊
Yukselen (2016)	😞	😊	?	😊	😊	😊	😊

Study	Risk of Bias				Applicability concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Keskin (2005)	☹	😊	😊	☹	😊	😊	😊
Canani (2007)	😊	😊	😊	😊	😊	😊	😊
Fogg (2006)	☹	😊	☹	😊	☹	😊	😊
Roehr (2001)	😊	😊	😊	?	😊	😊	😊
Boonyaviwat (2015)	😊	😊	☹	😊	😊	😊	😊
Majamaa (1999)	?	😊	?	😊	😊	😊	😊
Niggemann (2000)	☹	😊	😊	?	😊	😊	😊
Cudowska (2008)	?	😊	😊	😊	😊	😊	😊
Heine (2006)	☹	😊	😊	?	😊	😊	😊
Hansen (2004)	☹	☹	?	☹	☹	?	😊
Cudowska (2010)	☹	😊	😊	😊	😊	😊	😊
Peron (2011)	☹	😊	?	😊	😊	😊	😊
Niggemann (2002)	☹	😊	😊	?	😊	😊	😊
Majamaa (1999)	☹	😊	?	☹	😊	😊	😊
Isolauri (1996)	☹	😊	?	😊	😊	😊	😊
Vanto (1999)	☹	😊	😊	☹	😊	😊	😊
Rasanen (1992)	☹	☹	😊	☹	☹	😊	😊
Saarinen (2001)	☹	😊	?	☹	😊	😊	😊
Sozmen (2015)	😊	😊	?	☹	😊	😊	😊
Cudowska (2005)	☹	😊	?	😊	😊	😊	😊
Kekez (2010)	?	?	?	?	😊	?	?
Perackis (2003)	☹	😊	😊	?	😊	😊	😊

😊 = Low; ☹ = High; ? = Unclear