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Is it possible to make a diagnosis of raw, heated and baked egg allergy in children using cut-offs? A systematic review

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Running title: Reviewing SPTs and IgEs cut-offs for egg allergy

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Accepted Article

Abstract

Is it possible to make a diagnosis of raw, heated and baked egg allergy in children using cut-offs? A systematic review

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Background. The diagnosis of IgE-mediated egg allergy lies both on a compatible clinical history and on the results of skin prick tests (SPTs) and IgEs levels. Both tests have good sensitivity but low specificity. For this reason, oral food challenge (OFC) is the ultimate gold standard for the diagnosis. The aim of the present paper is to systematically review the literature in order to identify, analyze and synthesize the predictive value of SPT and specific IgEs both to egg white and main egg allergens and to review the cut-offs suggested in the literature.

Methods. A total of 37 articles were included in this systematic review. Studies were grouped according to degree of cooking of the egg used for OFC, age and type of allergen used to perform the allergy work-up.

Results. In children < 2 years, raw egg allergy seems very likely when SPTs with egg white extract are ≥ 4 mm or specific IgEs are ≥ 1.7 kU_A/L. In children ≥ 2 years, OFC could be avoided when SPTs with egg white extract are ≥ 10 mm or Prick by Prick with egg white are ≥ 14 mm or specific IgE are ≥ 7.3 kU_A/L. Likewise, heated egg allergy can be diagnosed if SPTs with egg white extract are > 5 mm and > 11 mm in children < 2 years and ≥ 2 years, respectively.

Conclusions. Further and better-designed studies are needed to determine the remaining diagnostic cut-off of specific IgE and SPT for heated and baked egg allergy.

Key Words: egg, cut-off, skin prick test, specific IgE, oral food challenge

The Authors have no conflict of interest to declare for the present paper.

Introduction

Hen's egg is a vital source of proteins and lipids and is widely consumed worldwide in different ways. Egg allergy is one of the three main food allergies in pediatrics and its prevalence ranges between 1.6 and 8-9% (1-4).

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According to a European study, egg is the main cause of food allergy in children aged 5 months to 15 years, being highlighted in 35.7% of subjects (5). The importance of egg allergy is also underlined by two recent collaborative Italian studies: egg was the most frequently evaluated food in a cohort of 544 oral food challenge (OFC) (6) and it is the second allergen, besides cow's milk proteins, related to food anaphylaxis in pediatrics (7).

The diagnosis of IgE-mediated egg allergy lies on a compatible clinical history and on both the results of skin prick tests (SPTs) and the determination of serum specific Immunoglobulins E (sIgEs). Both tests have good sensitivity but low specificity, which means that they are often positive in non-allergic subjects (8). Therefore, if a diagnosis was based on the positivity of such tests only, a group of sensitized subjects would uselessly undergo an egg-free diet. For this reason, OFC is the ultimate gold standard for the diagnosis of egg allergy, despite the difficulties due to cost, commitment and, above all, risk for the patient to develop a potentially severe anaphylactic reaction during the test.

It is well known that the greater the SPTs wheal size or the sIgEs level, the greater the probability to show allergic symptoms (9, 10). For such a reason, many authors tried to determine a cut-off for wheal sizes or for sIgEs levels able to predict with the highest probability a positive egg challenge (11, 12).

The aim of the present paper was to systematically review the literature in order to identify, appraise and synthesize the predictive value of SPTs and specific IgEs both to egg white and to main egg allergens (ovoalbumin, OVA, and ovomucoid, OVM). We also tried to review the cut-offs suggested in the literature, in order to provide practical clinical indications for the diagnosis of egg allergy in children.

Several studies showed that cut-off values might vary with the degree of cooking of the egg used for the oral food challenge (13), with age (14, 15) and with the type of allergen used to perform SPTs (commercial extract, raw or heated egg) (6, 16). Thus, in the present review we grouped studies according to these three factors.

At the best of our knowledge, such a classification has never been taken into account in previous reviews (15,17), guidelines or international consensus (18, 22) published on this subject.

Methods

Search strategy

A comprehensive search was conducted on December 2014 on MEDLINE literature via PubMed and Scopus. Citations were identified on the electronic databases using the terms “SPT” or “skin prick test” or “specific IgE” and “egg allergy” or “egg hypersensitivity”.

To reduce the risk of losing relevant studies, searches were not restricted by publication type or study design. Relevant retrieved articles, reviews and clinical studies published on this topic were included as well, even though not highlighted by our initial search (20-25).

All these studies were assessed, discussed in details and evaluated for quality by the authors in a standardized independent way.

Inclusion and exclusion criteria

We included studies in which authors looked for a cut-off value for SPTs or sIgEs levels for the diagnosis of egg allergy. In most of the included study, diagnosis was based on OFC. We also included studies in which diagnosis, based on a clear relationship between egg exposure and allergic reaction, was recently highlighted with a positive test (SPTs and/or sIgE levels).

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Studies were excluded if information on food allergy was not specific for egg allergy only. Studies were also excluded whenever the results only pointed out the optimal cut-off (best criterion for sensitivity and specificity optimization), which is not sufficient to select children at high risk of allergic reactions during an OFC.

Methodological quality of the included studies

The methodological quality of the included studies was evaluated according to the criteria given by the QUADAS-2 tool (26). Five reviewers appraised studies to assess the risk of bias. Two different authors independently reviewed each article. Any discrepancies were resolved by consensus between all reviewers.

Results

The search run on the electronic databases produced 469 results in Pubmed and 348 in Scopus. Four hundred and seventeen studies found on Pubmed and 312 found on Scopus were immediately excluded because they tested for allergens other than egg or were oral immunotherapy trials or did not quantify the association between SPTs wheal size or specific IgE and the risk of egg allergy. The remaining 52 and 36 articles from each database respectively were assessed as to whether they met the inclusion criteria and 35 papers were finally included in this review. After a manual search of the references, a total of 37 articles were included in this systematic review (Figure 1).

These studies are hereby presented separately, grouping them on the basis of SPTs wheal size or sIgEs. Then they were further grouped according to the cooking degree of egg administered during OFC into three groups that are:

- a) raw: raw egg was administered for the OFC (or dehydrated egg, for which an allergenicity identical to raw egg was demonstrated) (27, 28);

b) heated: lightly boiled or scrambled (regular) egg was administered for the OFC ($\leq 100^{\circ}\text{C}$ or 212°F , usually for few minutes);

c) baked: extensively heated egg was administered for the OFC ($> 100^{\circ}\text{C}$ or 212°F , usually for many minutes).

Those studies proposing cut-offs, but not differentiating the results on the basis of different degrees of eggs cooking were excluded from the analysis (6, 29-34). Data from these studies are reported in supplementary tables.

Figure 2 summarizes the methodological quality of the 37 included articles. Most articles were judged to be at high risk of bias and applicability as for patients' selection. Many studies showed high or unclear risk of bias as for flow and timing and high or unclear risk of bias and applicability as for reference standards. All studies were judged to be at low risk as for the index test.

SPT predictive value

19 studies assessed the diagnostic efficacy of SPTs with egg white or egg allergens. 4 studies have proposed cut-offs without distinguishing the degree of eggs cooking (6, 29-31). They were therefore excluded from the analysis (Table s1). The remaining 15 studies were grouped according to the cooking degree of egg administered during the OFC. Two studies (16, 35) proposed cut-offs for different cooking degrees of egg, and are therefore included in each group.

a) Egg SPTs predictive value and cut-off for raw egg allergy diagnosis

6 studies evaluated the predictive value of SPTs using commercial extracts or Prick by Prick (PbP) with raw egg by OFC with raw egg (11, 12, 16, 35-37). Five (11,16, 35-37) out of six were prospective studies and three out six were DBPCFC (11, 12, 35). One (37) out six studies showed a low risk of bias according to QUADAS-2. Studies differ in allergy prevalence, statistic analysis, type

of cut-off, criteria to define a positive OFC, and type of allergen used to perform the SPTs (commercial extract or raw egg). All these factors could contribute to explain the difference between the proposed cut-off values, which range between 4 and 14 mm for egg white.

However, differences between the proposed cut-off values are notably reduced when differentiating the type of allergen used to perform the SPTs and the age of the included population (Table 1a and 1b).

Indeed, in children younger than 2 years, two studies showed quite similar cut-offs (4 mm and 5 mm) (16, 36) whereas in children aged 2 years or older the other two studies showed quite different cut-offs (6 mm and 10 mm), the greater in the study enrolling a population with an older mean age (35, 37). Moreover, one of these last two studies (37) used more conservative criteria to define a positive OFC. In fact, OFC was considered as positive when an immediate reaction involved at least two organs. Also, the type of selected cut-off was very different (100% PPV and 70% specificity vs. 80% PPV and 95% specificity).

When fresh hen's egg is used to perform PbP, two studies showed quite similar cut-off (13 and 14 mm) (11, 12). Even if one (12) of these studies was a prospective one, both were at high risk of bias according to QUADAS-2.

Only one study (35) proposed a 95% specificity cut-off for ovoalbumin and ovomucoid of 10 mm and 8.5 mm, respectively.

b) Egg SPTs predictive value and cut-off for heated egg allergy diagnosis

Two studies proposed a cut-off for heated egg allergy (35, 38). Both were prospective studies, and in one the authors run a DBPCFC. Both studies were judged at risk of bias (Table 2). Only one study

(38) proposed a 100% specificity cut off for egg white of 5 mm and 7 mm in children respectively younger and older than 2 years. The other study (35) proposed a 95% specificity cut off in children over two years for egg white, ovoalbumin and ovomucoid of 11 mm, 10.5 mm and 13 mm, respectively.

c) Egg SPTs predictive value and cut-off for baked (extensively heated) egg allergy diagnosis

9 studies were included in this group (16, 39-46). None of them was a DBPCFC study and only four were prospective studies (16, 39, 43, 45). All studies were judged at risk of bias in one or more domains. There were also differences between cooking time and temperature and the amount of egg used.

Six studies (16, 39, 41-44) evaluated the diagnostic efficacy of the commercial extracts; two (45, 46) of Prick by Prick (PbP) performed with muffin containing baked egg; and one study (40) assessed both commercial extract and PbP. The main features of the studies are shown in Table 3.

Among these 9 studies, four studies were able to find diagnostic cut-off values for egg white (16, 40, 41, 43) and only one study suggest a diagnostic cut-off for ovomucoid (45).

One study only enrolled children younger than 2 years (16). In this prospective study, Peters reported that “no SPT threshold had a 95% PPV for baked egg”; however, an 82% PPV was calculated at 11 mm. The area under the curve (AUC) was low (0.65), and therefore SPTs are poor predictors of baked egg allergy (16). The remaining studies (39-46) were conducted in children older than two years. They were all considered at high risk of bias and proposed different cut-offs. In the first study (40), Turner also demonstrated that children who reacted to baked egg had a larger SPT wheal to both commercial extract SPT (median 8 mm) and raw egg (median 12 mm) compared to baked-egg

tolerant children, median 5 mm and 10 mm, respectively ($p < 0.001$). However, the ROC curve analysis demonstrated poor predictive ability, with an AUC for commercial extract and raw egg SPTs equal to 0.71 and 0.63, respectively. In this study, the cut-off value of 12 mm for commercial extract and of 20 mm for raw egg demonstrated 98% and 95% specificity, respectively (40). In the second study (41), Bartnikas showed that SPT wheal size was significantly higher in children allergic to baked egg (median 13 mm) in comparison to those who tolerated it (median 9 mm). The cut-off value with a specificity of 95% for allergy to baked egg was 25 mm (41). Lemon-Mulè showed that a SPT wheal size of 15 mm of diameter only had a 60% PPV for heated egg allergy (43). Finally, in the study of Tan (45), a SPT wheal size with OVM of 11 mm represented the diagnostic cut-off value, with a PPV of 100%. No diagnostic cut-off for PbP containing baked egg were found in two studies (45,46).

Specific IgE predictive value

30 studies examined the diagnostic efficacy of specific IgE to egg white or egg allergens toward egg allergy diagnosis confirmed by OFC. Six studies proposed cut-offs without distinguishing the results of the OFC on the basis of different degrees of eggs cooking (29-34), as shown in Table S2. The remaining 24 studies were divided according to the cooking degree of the egg administered during the OFC.

a) Predictive value of specific IgEs to egg white, ovalbumin or ovomucoid and cut-offs for raw egg allergy diagnosis

14 out of 24 studies performed an OFC with raw or lyophilized egg (9, 12, 16, 35-37, 47-54). Eight out of 14 were prospective studies (12, 16, 35-37, 49, 52, 53) and 7 out of 14 were DBPCFC (9, 12, 35, 49, 50, 52, 53).

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According to QUADAS-2, three (37, 47, 51) out of 14 studies were at low risk of bias and four (9, 48, 50, 52) were at unclear risk of bias. The main features of these studies are shown in Table 4.

These studies are quite different for relevant variables, such as allergy prevalence, diagnostic methodology, statistical analysis, and type of proposed cut-off. All these factors could contribute to explain the differences between the proposed cut-off values.

Three studies enrolling children aged less than 2 years proposed very different cut-offs for egg white (16, 36, 48). Two were open prospective studies: the first (36) proposed a 100% specificity cut-off of > 99 kU_A/L, the second (16) a 95% PPV cut off of 1.7 kU_A/L. One (47) was a retrospective study and proposed a 100% PPV with a cut-off of 1.5 kU_A/L.

12 studies enrolled children aged more than 2 years (9, 12, 35, 37, 47-54). All these studies also were at risk of bias according to QUADAS-2. The proposed cut-offs proposed for egg white range between 1.3 kU_A/L and 75 kU_A/L. In this group, five were prospective DBPCFC studies (12, 35, 49, 52, 53), and proposed a cut-off ranging between 3.7 kU_A/L and 17.5 kU_A/L.

Two (50, 52) out of the total 14 studies reported the diagnostic efficacy of molecular allergens as well. Ott et al. demonstrated that specific IgEs to OVM, determined through ISAC®, have a PPV for a positive OFC with raw egg comparable to egg white IgEs and SPTs. The study did not propose any diagnostic cut-off value (50). Ando et al. identified a cut-off value of 9.8 kU_A/L for OVA and of 5.2 kU_A/L for OVM as predictive of an allergic reaction to raw egg, with a 95% PPV (52). This study was judged at unclear risk of bias only for flow and timing.

b) Predictive value of specific IgEs to egg white, ovoalbumin or ovomucoid and cut-offs for heated egg allergy diagnosis

Five (35, 52, 55-57) out of 24 studies performed an OFC with heated egg. Three (35, 52, 55) out five were prospective studies and two (35, 52) out five were DBPCFC studies. These studies are rather different as for age of the enrolled population, different time of heating, amount of administered egg, and different statistical analysis. They proposed different cut-offs for egg white, ranging from ≥ 24 kU_A/L to 61 kU_A/L (Table 5). All of these studies were judged at high or unclear risk of bias.

Only two (35, 52) out of the three prospective studies were able to provide a diagnostic cut-off. The first (35), conducted by Vazquez-Ortiz et al., proposed a 95% PPV cut-off for egg white, ovoalbumin and ovomucoid of 4.08 kU_A/L, 2.8 kU_A/L and 3.74 kU_A/L, respectively. The second (52), conducted by Ando et al., proposed a 96% specificity cut-off for egg white, ovoalbumin and ovomucoid of 30.7 kU_A/L, 29.3 kU_A/L and 10.8 kU_A/L, respectively.

c) Predictive value of specific IgEs to egg white or egg allergens and cut-offs for baked (extensively heated) egg allergy diagnosis

Seven studies evaluated the diagnostic efficacy of cut-off values for specific IgEs to egg white or to molecular allergens as compared to an OFC with baked egg (41-44, 58-60). Methodological value was quite low: only three (43, 59, 60) of these studies were prospective study, none used DBPCFC and all were judged to be at high risk of bias in several domains (Table 6).

Of the three prospective studies (43, 59, 60), only one (59) proposed a 95% PPV diagnostic cut-off for egg white and ovomucoid (10 kU_A/L and 6 kU_A/L, respectively).

The cut-offs proposed from prospective studies ranged from 10 kU_A/L to 26.2 kU_A/L and from 6 kU_A/L to 50 kU_A/L for egg white and ovomucoid, respectively. Only one study (60) proposed a cut-off for ovoalbumin (25.3 kU_A/L).

Discussion

Several authors, guidelines and international consensus have suggested the use of cut-off values to reach a diagnosis of egg allergy without performing an OFC (20-24). So far, more than thirty articles have addressed this issue and proposed diagnostic cut-offs for egg allergy.

To make these studies as homogeneous as possible, we have grouped them according to the age of the study population (< or ≥ 2 years) and to the type of allergen used to perform SPTs. OVA, the most abundant protein found in egg white, is quite sensitive to thermic denaturation, like other egg proteins, such as ovotransferrin and lysozyme (61). On the contrary, OVM is relatively resistant to heat and is considered to be the dominant allergen in egg white (62). Thermal treatment may be divided in two types: moist (such as boiling, frying, etc), and dry heat (such as baking, roasting, etc) (63). Moist heat has only a mild effect on egg allergen reactivity, since OVM and OVA can still be detected immunologically despite hard-boiling of egg white (100°C for 20 min). Dry heat seems to have a stronger effect on many allergens within egg white, with the exception of OVM, and therefore significantly reduces egg allergen reactivity (64), probably because such a cooking technique requires more time and higher temperatures. Thus, we grouped the studies into three groups: raw, heated (≤ 100°C or 212°F) and baked (extensively heated) egg (>100°C or 212°F).

To appraise the quality and validity of the included studies, we evaluated the design of the study (prospective vs retrospective), the type of OFC (open vs DBPCFC) and assessed studies according to the QUADAS-2 tool.

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Despite the division into groups based on the degree of cooking, age and the type of allergen used to perform the SPTs, with the exception of cut-offs for raw egg, the other proposed cut-offs showed a large variability, especially for sIgEs.

Several reasons might explain such variability:

- a) two different kinds of cut-off values were proposed in literature, both for SPT and for sIgEs: those based on a high positive predictive value (95% PPV) and those based on a high specificity (cut-off values with 95% of specificity). The first ones, being based on the predictive value, depend on the prevalence of allergy in the studied population and are applicable in allergy centres where it is assumed that the prevalence of food allergy is similar to the one found in the studies providing the values (65). On the contrary, the cut-off values based on 95% of specificity do not change with the prevalence of the disease in the population and give us the chance to better select the children to test with OFC, given the high risk of a positive challenge. These two kinds of cut-off values could provide different results even in the same study population.
- b) the proposed cut-offs may change dramatically, even within the same study population, for small variations in the chosen level of predictive value, especially for sIgEs. For instance, Celik Bilgili showed that egg cut-offs increase from 6 kU_A/L when considering a 90% PPV to 12.6 kU_A/L with a 95% PPV to 59.9 kU_A/L with a 99% PPV (48).
- c) other reasons may be related to patients' selection, criteria to define a positive OFC, SPT devices, etc (17).

Practical clinical indications

Given the large variability of the proposed cut-offs, we tried to highlight some practical clinical indications considering, above all, the methodologically best studies (prospective DBPCFC studies) and, whenever it was possible, those with the best QUADAS-2 results. As for raw-egg allergy, 95% or higher cut-offs for SPT with commercial extracts and with PbP and sIgE in children younger and older than 2 years were identified. As for heated egg allergy, only SPT cut-offs for commercial extract in children younger and older than 2 years were identified. On the contrary, a cut-off value for sIgE for heated egg allergy seems hard to suggest. In fact, the only two prospective studies for heated egg allergy in children older than 2 years suggested very different cut-offs (Table 7). Finally, no cut-off seems advisable for SPT and for sIgEs for baked egg allergy. In fact, the included studies proposed rather different cut-offs. However, it seems likely that children with baked egg allergy have higher SPT wheal sizes and sIgEs than children suffering from raw or heated egg allergy.

It is difficult to explain the greater difficulty in defining cut-offs for specific IgEs for heated egg than for SPTs. The greater range of sIgEs values (from 0.1 kU_A/L to over 100 kU_A/L) compared to SPTs values (from 1 mm to over 20 mm) could be a reason. As for baked egg allergy, the low quality of the included studies may be the cause: no study was prospective nor DBPCFC. Differences in other variables not considered in the studies, and further discrepancies in the degree of cooking, or the presence of other ingredients (matrix effect) may have influenced the results as well.

Conclusions

No cut-off value by itself may allow a firm diagnosis of raw, heated or baked egg allergy. However, as for raw egg allergy, when SPTs are ≥ 4 mm (in children < 2 years) and ≥ 10 mm (in children ≥ 2 years) for raw egg white extract, or when PbP with egg white are ≥ 14 mm, it is necessary to carefully assess the costs and benefits and to determine the necessity to reach a higher diagnostic certainty,

affordable only through an OFC. Slightly higher cut-offs for raw egg commercial extract (5 mm and 11 mm in children < 2 years and \geq 2 years, respectively) may be adopted for heated egg allergy.

As for specific IgEs, raw egg allergy seems very likely if sIgE are \geq 1.7 kU_A/L in children aged less than 2 years and, in order to choose a safer cut-off, \geq 7.3 kU_A/L in children \geq 2 years.

Further and better-designed studies are needed to determine the remaining diagnostic cut-offs of sIgEs and SPTs for heated and baked egg allergy.

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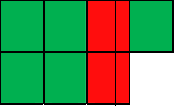
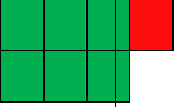
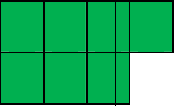
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Table 1 – Studies and suggested cut-offs for raw egg allergy diagnosis using egg white, ovalbumin and ovomucoid SPTs stratified by the type of allergen used to perform SPTs, design and age (< 2 years and ≥ 2 years)

a) Skin Prick Test (commercial extracts)

Age	Study	OF C Type (n)	Age Median (range) or Mean [± SD]	Allergy prevalence (%)	Egg administered	Design	Method	Egg white cut-off (mm)	Ovalbumin cut off (mm)	Ovomucoid cut off (mm)	Diagnostics	QUADAS-2			
												Domains 1	2	3	4
												Risk of Bias 1 2 3			
												Applicability			
< 2 yrs	Monti 2002 (36)	Open (107)	5 mos (1-19 mos)	67	Raw egg	Prospective	100% PPV 100% Sp NS	5	ND	ND	NEO-Abello				
	Peters 2013 (16)	Open (650)	12.6 mos [±0.7 mos]	68	Raw egg	Prospective	95% PPV 93% Sp LR	4	ND	ND	ALK-Abello				
≥ 2 yr	Tripodi 2009 (37)	Open (47)	6.2 yrs [±4.2 yrs]	43	Raw egg	Prospective	100% PPV 70% Sp ROC	6	ND	ND	Stallergenes				

s							<i>curve</i>					
	Vazquez-Ortiz 2014 (35)	DBPC (85)	8.2 yrs (5-18 yrs)	75	Raw egg	Prospective	95% PPV EW 94% PPV OVA 96% PPV OVM 95% Sp ROC curve	10	8.5	Alk-Abellò		

b) Prick by Prick (PbP)

Age	Study	OF C Type (n)	Age Median (range) or Mean [± SD]	Allergy prevalence (%)	Egg administered	Design	Method	PbP cut-off (mm)	Ovoalbumin cut off (mm)	Ovomucoid cut off (mm)	Diagnosics	QUADAS-2 Domains 1 2 3 4 Risk of Bias 1 2 3 Applicability
≥ 2 yrs	Verstege 2005 (11)	DBPC / Open (160)	22 mos (3-14.5 yrs)	63	Raw egg	Retrospective	95% PPV NS Sp RL	13	ND	ND	Fresh HE whisked white and yolk	
	Mehl 2006 (12)	DBPC / Open (193)	13 mos (3-14 yrs)	66	Raw egg	Prospective	95% PPV NS Sp RL	14	ND	ND	Fresh HE whisked white and yolk	

PPV: Positive Predictive Value; Sp: Specificity; ROC: Receiver Operating Characteristic (ROC) curve; RL: logistic regression; NS: not specified; ND not determined; EW: egg white, OVA: ovalbumin; OVM: ovomucoid.

Table 2 – Study and suggested cut-offs for heated egg allergy diagnosis using egg white, ovoalbumin and ovomucoid SPTs (commercial extracts), stratified by design and age (< 2 years and ≥ 2 years)

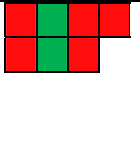
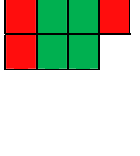
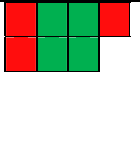
Age	Study	OF C Type (n)	Age Median (range) or Mean [± SD]	Allergy prevalence (%)	Egg administered	Design	Method	Egg white cut-off (mm)	Ovoalbumin cut off (mm)	Ovomucoid cut off (mm)	Diagnosics	QUADAS-Domains 1 2 Risk of Bias Applicability
< 2 yrs	Sporik 2000 (38)	Open (39)	< 2 yrs	74	Lightly heated egg white (approx 2 min)	Prospective	NS PPV 100% Sp ROC curve	5	ND	ND	Dome Hollister Stier	
	Sporik 2000 (38)	Open (82)	> 2 yrs (2-12.8 yrs)	78	Lightly heated egg white (approx 2 min)	Prospective	NS PPV 100% Sp ROC curve	7	ND	ND	Dome Hollister Stier	
≥ 2 yrs	Vazquez-Ortiz 2014 (35)	DB PCFC (85)	8.2 yrs (5-18 yrs)	59	One egg boiled for 10 min at 90°	Prospective	82% PPV EW 87% PPV OVA 75% PPV OVM 95% Sp ROC curve	11	10.5	13	Alk-Abellò	

PPV: Positive Predictive Value; Sp: Specificity; ROC: Receiver Operating Characteristic (ROC) curve; RL: logistic regression; NS: not specified; ND: not determined; EW: egg white, OVA: ovoalbumin; OVM: ovomucoid

Table 3 - Studies and suggested cut-offs for baked egg allergy diagnosis using egg white, ovalbumin and ovomucoid SPTs, stratified by the type of allergen used to perform SPTs, design and age (< 2 years and ≥ 2 years)

a) Skin Prick Test (commercial extracts)

Age	Study	OF C Type (n)	Age Median (range) or Mean [± SD]	Allergy prevalence (%)	Egg administered	Design	Method	Egg white cut-off (mm)	Ovalbumin Cut off (mm)	Ovomucoid cut off (mm)	Diagnostics	QUADAS-2 Domains 1 2 3 4 Risk of Bias 1 2 3 Applicability
< 2 yrs	Peters 2013 (16)	Open (185)	12.6 mos [±0.7 mos]	NS	OFC with a muffin	Prospective	82% PPV NS Sp RL	11	ND	ND	ALK-Abellò	
	Des Roches 2006 (39)	Open (60)	> 5 yrs	27	Cake (unspecified amount of egg)	Prospective	NS	ND	ND	ND	ND	
≥ 2 yrs	Turner 2014 (40)	Open (186)	5.3 yrs (3.3-9.8 yrs)	34	A muffin containing 3g of an egg and baked for 20' at 180° C	Retrospective	NS PPV 98% Sp ROC curve	12	ND	ND	Stallergenes	
	Bartnikas 2013 (41)	Open (169)	5.5 yrs (0.8-17 yrs)	16	OFC with muffin or cake (1/3 of egg)	Retrospective	90% PPV NS Sp ROC curve	25	ND	ND	Greer Laboratories	

Lieberman 2012 (42)	Open (100)	5.9 yrs (1.2-19.8 yrs)	31	OFC with muffin (1/3 of egg baked at 350°F for 30')	Retrospective	95%P PV NS Sp NS	NF	NF	NF	Greer Laboratories	
Lemon Mulè 2008 (43)	Open (117)	6.9 yrs (1.6-18.6 yrs)	23	OFC with muffin (1/3 of egg baked at 350°F for 30' or waffle at 500° F for 3')	Prospective	60% PPV NS Sp RL	15	ND	ND	Greer Laboratories	
Cortot 2012 (44)	Open (52)	7.2 yrs (2.2-18 yrs)	17 allergic to baked egg	OFC with muffin or cake (1/3 of egg baked at 375°F for 30')	Retrospective	95%P PV NS Sp ROC curve	NF	NF	NF	Greer Laboratories	

b) Prick by Prick (PbP)

Age	Study	OFC Type (n)	Age Median (range) or Mean [\pm SD]	Allergy prevalence (%)	Egg administered	Design	Method	PbP cut-off (mm)	Ovoalbumin Cut off (mm)	Ovomucoid cut off (mm)	Diagnostics	QUADAS-2 Domains 1 2 3 4 Risk of Bias 1 2 3 Applicability
≥ 2 yrs	Tan 2013 (45)	Open (143)	3.8 yrs (1.8-6.7 yrs)	37	OFC with muffin (1/6 of egg baked ad 180° C for 20')	Prospective	100%PPV NS Sp ROC curve	ND	ND	11	PbP with a muffin containing baked egg (Commercial extract ALK Abello Spain)	
	Faraj 2012 (46)	Open (40)	3.5 yrs (1.25-13 yrs)	7	OFC with muffin (1/3 of egg baked at 350° F for 30')	Retrospective	NS	ND	ND	ND	PbP with a muffin containing baked egg	
	Turner 2014 (40)	Open (186)	5.3 yrs (3.3-9.8 yrs)	34	A muffin containing 3g of an egg and baked for 20' at 180°	Retrospective	NS PPV 95% Sp ROC curve	20	ND	ND	PbP with raw egg	

PPV: Positive Predictive Value; Sp: Specificity, ROC: Receiver Operating Characteristic (ROC) curve; RL: logistic regression; NS: not specified; ND: not determined; NF: not found
EW: egg white, OVA: ovoalbumin; OVM: ovomucoid

Table 4 – Studies and proposed cut-offs for raw egg allergy diagnosis with specific IgEs for egg white, ovalbumin and ovomucoid listed according to study design and patients’ age (< 2 years and ≥ 2 years)

Age	Study	OFC Type (n)	Age Median (range) or Mean [±SD]	Allergy prevalence (%)	Egg administered	Design	Method	Egg white cut-off (kU _A /L)	Ovalbumin Cut off (mm)	Ovomucoid cut off (mm)	Diagnostics	QUADAS-2 Domains 1 2 3 4 Risk of Bias 1 2 3 Applicability
< 2 yrs	Monti 2002 (36)	Open (107)	5 mos (1-19 mos)	67	Raw egg	Prospective	NS PPV 100% Sp NS	> 99	ND	ND	CAP system	
	Peters 2013 (16)	Open (652)	12.6 mos [±0.7 mos]	68	Raw egg white	Prospective	95% PPV 98% Sp LR	1.7	ND	ND	CAP system	
	Osterballe 2003 (47)	Open (28)	1.1 yrs (0.5-2 yrs)	(64)*	Raw egg	Retrospective	100% PPV 100% Sp ROC curve	1.5	ND	ND	CAP system and Magic Lite (Alk-Abellò)	

≥ 2 yrs	Osterballe 2003 (47)	Open (28)	3.3 yrs (2–4.9 yrs)	(64)*	Raw egg	Retrospective	100% PPV 100% Sp <i>ROC curve</i>	1.3	ND	ND	CAP system and Magic Lite (Alk- Abellò)	
	Celik-Bilgili 2005 (48)	Open (178)	13 mos (1 mos- 16.1 yrs)	67	Raw egg	Retrospective	90% PPV NS Sp 95% PPV NS Sp 99%PPV NS Sp <i>LR</i>	6 12.6 59.2	ND	ND	CAP system	
	Mehl 2006 (12)	DBPCFC/ Open (437)	13 mos (3 mos-14 yrs)	29	Raw egg	Prospective	95% PPV NS Sp 99% PPV NS Sp <i>LR</i>	15.9 75.5	ND	ND	CAP system	
	Roehr 2001 (49)	DBPCFC (42)	13 mos (2 mos- 11.2 yrs)	51	Raw egg	Prospective	100% PPV 100% Sp <i>NS</i>	17.5	ND	ND	CAP system	

Ott 2008 (50)	DBPCFC/ Open (60)	14 mos (5-150 mos)	75	Raw egg	Retrospective	90% PPV NS Sp 95% PPV NS Sp 99% PPV NS Sp <i>RL</i>	7.72 10.1 15.62	ND	ND	CAP system	
Crespo 1994 (51)	Open (40)	2.91 yrs [±0.44] OFC + 4.67 yrs [±1.02] OFC -	62	Raw egg white	Retrospective	92% PPV 99% Sp <i>NS</i>	1.20	ND	ND	CAP system	
Ando 2008 (52)	DBPCFC (108)	34.5 mos (14 mos - 13 yr)	62	Raw egg white	Prospective	95% PPV 95% Sp <i>ROC curve</i>	7.38	9.8	5.2	CAP system	
Sampson 2001 (53)	DBPCFC (25)	3.8 yrs (3 mos-14 yrs)	80	Dehydrated egg	Prospective	96% PPV 90% Sp <i>ROC curve</i>	6	ND	ND	CAP system	

Sampson 1997 (9)	DBPCFC (126)	5.2 yrs (0.6-17.9 yrs)	73	Dehydrated egg	Retrospective	90%PPV NS Sp 95% PPV NS Sp <i>ROC curve</i>	2 6	ND	ND	CAP system	
Tripodi 2009 (37)	Open (31)	6.2 yrs [±4.2]	42	Raw egg	Prospective	100% PPV 100% Sp <i>ROC curve</i>	7.4	ND	ND	CARLA (Radim)	
Vazquez- Ortiz 2014 (35)	DBPCFC (85)	8.2 yrs (5-18 yrs)	75	Raw egg	Prospective	95%PPV 95% Sp <i>ROC curve</i>	3.69	ND	ND	CAP system	
Benhamou 2015 (54)	Open (80)	2.1 yrs (0.8-11.7 yrs)	84	Pasteurized raw egg	Retrospective	NS PPV 100% Sp <i>ROC curve</i>	1.6	ND	ND	CAP system	

* Overall prevalence of allergy in the two age groups; PPV: Positive Predictive Value; Sp: Specificity, ROC: Receiver Operating Characteristic (ROC) curve; RL: logistic regression; NS: not specified; ND: not determined; EW: egg white, OVA: ovalbumin; OVM: ovomucoid.

Table 5 – Studies and proposed cut-offs for heated egg allergy diagnosis with specific IgEs for egg white, ovalbumin and ovomucoid, listed according to study design and patients' age (< 2 years and ≥ 2 years)

Age	Study	OFC Type (n)	Age Median (range)	Allergy prevalence (%)	Egg administered	Design	Method	Egg white Cut-off (kU _A /L)	Ovalbumin Cut-off (kU _A /L)	Ovomucoid Cut-off (kU _A /L)	Diagnostics	QUADAS-2 Domains 1 2 3 4 Risk of Bias 1 2 3 Applicability
< 2 yrs	Min 2013 (55)	Open (41)	16 mos (3-23 mos)	61	Egg white boiled for 15 min	Prospective	71% PPV 62% Sp NS	≥ 2	ND	ND	CAP system	
	Haneda 2012 (57)	Open (100)	17 mos (12-23 mos)	33	Egg boiled for >20 min (1/2 egg)	Retrospective	95% PPV NS Sp LR	61.8	ND	26.6	CAP system	
	Komata 2007 (56)	Open (764) ^o	<2 yrs	(49) *	Heated egg	Retrospective	95% PPV 48% Sp ROC curve	13 (<1 yr) 23 (1-2 yrs)	ND	ND	CAP system	
≥ 2	Komata 2007 (56)	Open (764) ^o	15 mos (0.2-14.6 yrs)	(49) *	Heated egg	Retrospective	95% PPV 48% Sp ROC curve	30 (>2 yrs)	ND	ND	CAP system	

yrs	Ando 2008 (52)	DBPCFC (108)	34.5 mos (14 mos– 13 yrs)	35	1 egg boiled for 60 min at 90°C (195°F) Patients who did not react to heated egg were then challenged with raw egg white	Prospective	84% PPV 96% Sp EW 86% PPV 96% Sp OVA 88% PPV 96% Sp OVM <i>ROC curve</i>	30.7	29.3	10.8	CAP system	
	Vazquez -Ortiz 2014 (35)	DBPCFC (85)	8.2 yrs (5-18 yrs)	59	One egg boiled for 10 min at 90°	Prospective	95%PPV 95% Sp <i>ROC curve</i>	4.08	2.8	3.74	CAP system	

° Overall number of allergy in the two age groups; * Overall prevalence of allergy in the two age groups; PPV: Positive Predictive Value; Sp: Specificity, ROC: Receiver Operating Characteristic (ROC) curve; RL: logistic regression; NS: not specified; ND: not determined; EW: egg white, OVA: ovalbumin; OVM: ovomucoid

Table 6 – Studies and proposed cut-offs for extensively heated (baked) egg allergy diagnosis with specific IgEs for egg white, ovalbumin and ovomucoid, listed according to the increasing age of the population

Age	Study	OFC Type (n)	Age Median (range) or Mean [\pm SD]	Allergy prevalence (%)	Egg administered	Design	Method	Egg white Cut-off (kU _A /L)	Ovalbumin Cut-off (kU _A /L)	Ovomucoid Cut-off (kU _A /L)	Diagnostics	QUADAS-2 Domains 1 2 3 4 Risk of Bias 1 2 3 Applicability
≥ 2 yrs	Kostantinou 2008 (58)	Open (94)	2.5 mos (12-48 mos)	7 baked egg allergy 5 raw egg allergy	A cake containing 1 egg (not specified time and temperature used)	Retrospective	95% PPV Sp NS NS	6	ND	ND	CAP system	
	Marriage 2012 (59)	NS (47)	4.6 yrs (2-16 yrs)	51	Extensively heated egg (not specified time and temperature used)	Prospective	95% PPV Sp 70% EW Sp 78% OVM ROC curve	10	ND	6	CAP system	
	Bartnikas 2013 (41)	Open (169)	5.5 yrs (0.84 – 17.07 yrs)	16 baked egg allergy	A muffin or cupcake containing 1/3 of an egg and baked for 30' at 350°F	Retrospective	59% PPV EW 42% PPV OVM 95% Sp ROC curve	9.65	ND	3.38	CAP system	

	Lieberman 2012 (42)	Open (100)	5.9 yrs (1.2-19.8 yrs)	31 baked egg allergy	A muffin (1/3 of an egg baked at 350°F for 30')	Retrospective	60% PPV 94% Sp NS	10	NF	NF	CAP system	
	Lemon Mulé 2008 (43)	Open (117)	6.9 yrs (1.6-18.6 yrs)	23 baked egg allergy 33 raw egg allergy	A muffin (1/3 of an egg baked at 350°F for 30') or a waffle (baked at 500°F for 3')	Prospective	>90% PPV NS Sp LR	NS	NS	50	CAP system	
	Caubet 2012 (60)	Open (117)	6.9 yrs (1.6-18.6 yrs)	23 baked egg allergy 56 raw egg allergy	A muffin (1/3 of an egg baked at 350°F for 30') or a waffle (baked at 500°F for 3')	Prospective	43% PPV EW 33% PPV OVA 64% PPV OVM 95% Sp ROC curve	26.2	25.3	12.8	CAP system	
≥ 2 yrs	Cortot 2012 (44)	Open (52)	7.2 yrs (2.2-18 yrs)	17 baked egg allergy	A muffin or cupcake (1/3 of an egg baked for 30' at >375°F)	Retrospective	95% PPV NS Sp ROC curve	NF	NF	NF	CAP system	

PPV: Predictive Positive Value; Sp: Specificity; LR: Logistic Regression; NS: Not Specified; NF: not founded; EW: egg white, OVA: ovoalbumin; OVM: ovomucoid

Table 7 - Practical clinical indications. Cut-offs proposed by the methodologically best studies

A: Raw egg

Raw egg (Skin Prick Test)	< 2 years	Ref	> 2 years	Ref
Raw egg (Commercial extract)	SPT = 4 mm wheal (95% PPV)	Peters 2013 (16)	SPT = 10 mm wheal (95% Sp)	Vazquez- Ortiz 2014 (35)
Raw egg (PbP)	-	-	PbP = 14 mm wheal (95% PPV)	Mehl 2006 (12)
Ovoalbumin (Commercial extract)	-	-	SPT = 10 mm wheal (95% Sp)	Vazquez- Ortiz 2014 (35)
Ovomucoid (Commercial extract)	-	-	SPT = 8.5 mm (95% Sp)	Vazquez- Ortiz 2014 (35)

Raw Egg (sIgE)	< 2 years	Ref	> 2 years	Ref
Raw egg	sIgE = 1.7 kU _A /L (95% PPV)	Peters 2013 (16)	sIgE = 3.6 kU _A /L (95% PPV)	Vazquez- Ortiz 2014 (35)
			sIgE = 6 kU _A /L (95% PPV)	Sampson 2001 (53)
			sIgE = 7.3 kU _A /L (95% PPV)	Ando 2001 (52)

B: Heated egg:

Heated egg (Skin Prick Test)	< 2 years	Ref	> 2 years	Ref
Raw egg (Commercial extract)	SPT = 5 mm wheal (100% Spec)	Sporik 2000 (38)	SPT = 11 mm wheal (95% Sp)	Vazquez- Ortiz 2014 (35)
Ovoalbumin (SPT commercial extract)	-		SPT = 10.5 mm wheal (95% Sp)	Vazquez- Ortiz 2014 (35)
Ovomucoid (SPT commercial extract)	-		SPT = 13 mm wheal (95% Sp)	Vazquez- Ortiz 2014 (35)

PPV: Predictive Positive Value; Sp: Specificity.

Figure 1 – Flow chart of the search run to obtain the studies included in the present review

(SPT: Skin Prick Tests; IgEs: specific serum IgEs)

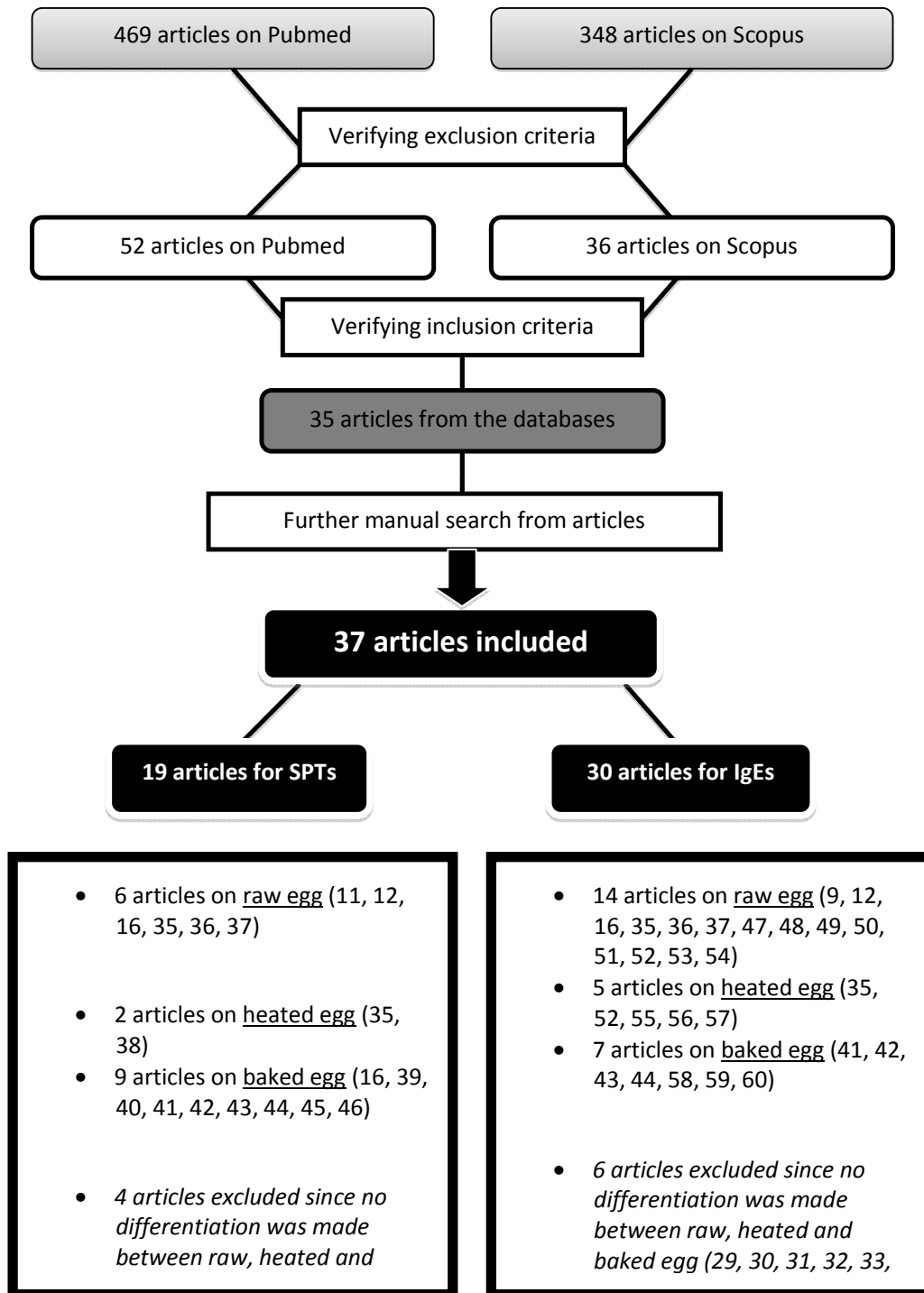
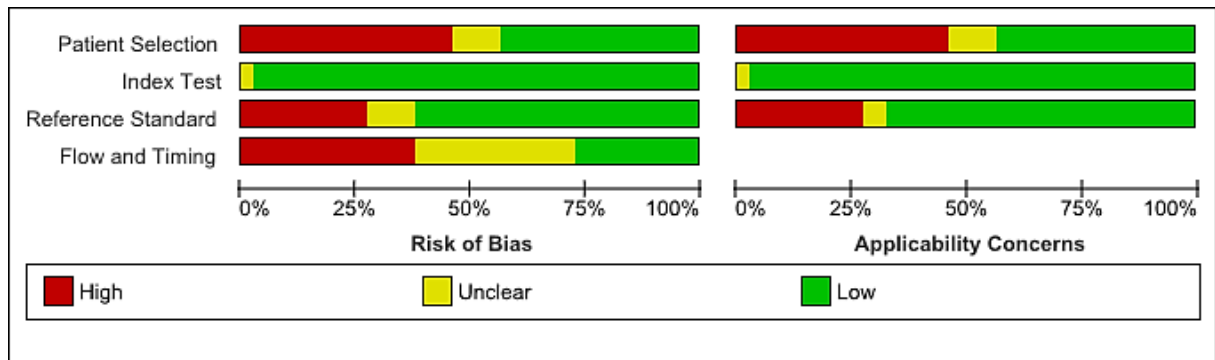


Figure 2 – Risk of bias and applicability concerns graph: authors' judgments about each domain presented as percentages in included studies.



Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.