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RESEARCH LETTER

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Test-guided dietary exclusions for treating established atopic dermatitis in children: A systematic review

To the Editor,

Atopic dermatitis (AD), synonymous with atopic eczema, is a chronic inflammatory skin disease, characterized by acute flares of pruritic lesions. It affects around 20% of children in the UK. While immediate, IgE-mediated food allergy, is more common in AD, non-IgE-mediated food allergies causing eczema symptoms are more controversial, and literature on the use of exclusion diets for treating AD is mixed.[1] The most recent Cochrane systematic review, published in 2008 and including randomized controlled trials (RCTs) up to March 2006, found that most studies were of poor quality and generally did not support dietary exclusion for treating established eczema.[1] Since this review, landmark trials have demonstrated the risk of delayed food introduction,[2] and dietary exclusions, which may cause loss of oral tolerance as well as nutritional deficiencies. Despite this, parents often seek food allergy testing, and/or exclude foods to help manage their child's eczema, and healthcare professionals' practice varies.[3] We sought to provide an up-to-date review of the literature to answer the research question, "What is the value of test-guided dietary exclusions for treating established AD in children under 12 years of age?" We searched MEDLINE and EMBASE databases from January 2006 to June 2021, using the search strategies employed by Bath-Hextall et al.[1] Eligibility criteria were: RCT; participants under 12 years with established AD; intervention of dietary exclusions informed by allergen-specific IgE blood or skin prick test; eczema severity collected as the outcome; comparator was children with AD with no test-guided dietary exclusions. The primary outcome measure of interest was changes in parent or participant-rated eczema symptoms. Studies using only history-based or serial dietary exclusions for treating established AD, or indirect exclusion via the breastfeeding mother's diet, were excluded. KR completed title/abstract screening, with AG and SD each independently screening a random sample of 50 titles and abstracts. The nine RCTs from the 2008 Cochrane Systematic review were also screened and included if relevant.[1] Studies that met the inclusion criteria on title/abstract screening were read in full by KR and reasons for exclusion were noted (see supplementary material). Queries were discussed and resolved between KR, AG and MJR. Data were extracted from the included trials by KR. Risk of bias for the included studies was assessed using the ROB2 Cochrane tool,[4] by KR, AG, SD and MJR. Discrepancies were resolved by discussion.

From the databases searched, a total of 1416 records were identified for title/abstract screening. After removing 171 duplicates, 1245 records were screened for eligibility and 24 full-text papers were identified. Three of the 24 papers (trial results, protocol and findings from the nested qualitative study) related to the one study that met the inclusion criteria, "Trial of Eczema allergy Screening Tests, 'TEST.'".[5,6] Additionally, of the nine studies identified by Bath-Hextall et al,[1] only one met our inclusion criteria (see supplementary material). A total of two trials were therefore included. The TEST trial was judged to be at low risk of bias, whereas there were some concerns in 3 of the risk of bias 2 (ROB2) tool domains for the study by Lever et al (see supplementary material). Judgement had to be exercised when assessing the effect of assignment in domain 2 (bias due to deviations from the intended interventions) because participants in both trials were aware of their assigned group. The characteristics and results of both trials are recorded in Tables 1 and 2. It was not possible to synthesize the results from the two included studies, so their findings are presented narratively.

Both studies were UK based. The first study was published in 1998, involving 62 participants aged 11–17 months.[7] All participants in this trial had "raised IgE to eggs" (threshold not specified). Those allocated to the intervention group underwent an egg exclusion diet for four weeks, while the control group received no dietary exclusion advice. The primary outcome was not prespecified. Eczema severity was assessed at study entry and after week four by percentage of skin surface area affected by AD and

No protocol was registered prior to conducting this review.

composite severity score (possible range 0–48), both unvalidated outcomes. Based on statistically significant changes in these outcomes (see Table 2) between the two groups, the authors concluded that children with AD and egg sensitivity may benefit from an egg exclusion diet.

The second study ("TEST") was conducted in 2019, with 84 children aged 3 months to 5 years. Participants were randomized to either dietary advice based on allergy history and skin prick testing of six common allergens (cow's milk, hen's eggs, peanut, cashew, codfish and wheat), or usual care.[6] Eczema severity was measured at baseline and 24 weeks using Patient-Oriented Eczema Measure (POEM) and Eczema Area and Severity Index (EASI), both Harmonising Outcome Measures for Eczema (HOME) recommended core outcomes.[8] The primary focus of this trial was to assess the feasibility of a definitive study, so there was no statistical analysis of eczema outcome measures. However, mean differences in POEM and EASI were small and did not approach their established Minimally Clinically Important Difference (MCID) of 3 and 6.6, respectively.[9]

The effect of dietary exclusion was attenuated in TEST because most participants were not advised to make any dietary changes. This, and the absence of validated outcome measures in the earlier trial, makes the studies difficult to compare. In addition, children in TEST had milder eczema, which limits its relevance to populations with more severe disease. Future RCTs need to use validated outcome measures and be adequately powered to detect clinically meaningful differences. The Lever et al study lacked clear reporting and was conducted before the HOME guidance on core outcomes.[8] In contrast, while the Ridd et al study had many strengths (prospectively registered, published protocol, inclusion of three of the four HOME recommended outcomes and better reported), its findings were limited for the purposes of this review because it was a small, feasibility trial. Furthermore, adherence to the exclusion diet was mixed, measured as 81%.

Key Messages

- Food allergy tests are sometimes used to guide dietary exclusions for eczema symptoms.
- Dietary exclusion of egg may benefit infants with eczema and positive specific IgE to eggs.
- Better research into the benefits and risks of test-guided dietary exclusions for children with eczema is needed.

In conclusion, new research answering our research question since the last relevant systematic review is lacking. Arguably, the focus of our review was too narrow, hence the small number of eligible studies. However, it is directly relevant to clinical practice, since some clinicians advise dietary exclusions for the management of eczema symptoms based on food allergy tests which is not evidence based. Dietary exclusions are burdensome, may discourage breastfeeding and can cause long-term harm, through malnutrition or loss of oral tolerance. The restricted nature of our review (searching only two databases and exclusion of papers not in English) is a further limitation, although we think it is unlikely that any significant trials were missed. Dietary exclusions informed by tests may benefit some children with AD but further adequately powered trials of test-guided dietary exclusions for established AD in children are needed to make robust conclusions. Meanwhile, as per NICE guidance, food allergy tests should be interpreted in the context of childen's symptoms where IgE-mediated allergy is suspected and allergy-focused clinical

TABLE 1 Study Characteristics

Author	Study Design and Setting	Patient population	Baseline characteristics		Lost to follow-up (by group)	Intervention	Comparator	Compliance	Eczema outcome measure
			Intervention group	Comparator group					
Lever et al (1998)	Randomized controlled trial. Secondary care dermatology clinic in Glasgow, Scotland.	62 children (55 evaluable) with clinically diagnosed AD aged 11–17 months with raised IgE to eggs[a], 7 of which had a history suggestive of egg allergy.	Mean age (SD) at presentation: 11.3 months (1.4)[b] Eczema severity at study entry: Mean % surface area (SD): 19.6 (12.8) Severity score, mean (SD): 33.9 (15.3)	Mean age (months) at presentation (SD): 17.2 (2.2)[b] Eczema severity at study entry: Mean % surface area (SD): 21.9 (14.8) Severity score, mean (SD): 36.7 (19.0)	7 (4 from intervention group, 3 from comparator group)	"General advice regarding AD," unchanged topical treatment and specific advice delivered by dietician for a 4-week trial of egg exclusion diet.	"General advice regarding AD," unchanged topical treatment and no dietary advice.	Not reported	Eczema severity assessed by estimate of total skin area affected (%) and using an unvalidated composite severity score. Participants scored by same blinded observer on initial presentation, at study entry and at the end of 4-week dietary phase.
Ridd et al (2021)	Single-centre, two-group, individually randomized feasibility randomized controlled trial Primary care (GP surgeries) in West of England	84 children with clinical diagnosis of AD (70% meeting UK diagnostic criteria), mild or worse (POEM>2), aged 3 months to 5 years with no medically diagnosed food allergy or possibility of food allergy (awaiting referral/previous investigations).	Mean age (SD): 33.5 months (15.2) Mean Patient-Oriented Eczema Measure (POEM) (SD): 9.0 (5.2) Median EASI (IQR): 1.7 (0.7, 4.8)	Mean age (SD): 31.4 months (12.7) Mean POEM (SD): 8.4 (4.5) Median EASI (IQR): 2.1 (1.1, 4.0)	4 (1 from intervention group, 3 from comparator group)	Usual AD care plus skin prick testing for cow's milk, hen's eggs, peanut, cashew, codfish and wheat, performed by researcher, with dietary exclusion advice based on results for 2–4 weeks.	Usual AD care, no skin prick testing or dietary advice given, but treating clinician could independently request additional tests if indicated during 24-week follow-up).	Mixed adherence to exclusion diet by 6 "test positive" participants in the intervention group. 81% adherence to exclusion diet (29/36 person-weeks of available data). 2 from comparator group saw allergy specialist during trial.	Eczema severity assessed using POEM, for symptoms and EASI (Eczema Area Severity Index), for clinical signs). Participants were followed up for 24 weeks. Parents completed questionnaires every 4 weeks and participants had skin assessment by researcher at baseline and week 24.

[a]"Raised" value not specified. Assumed to be above the normal range for blood IgE for their hospital.

[b]Mean time from presentation to study entry was 3.5 months.

TABLE 2 Effect of interventions on eczema severity

		Baseline		Follow-up		Change		Statistical tests
		Control	Intervention	Control	Intervention	Control	Intervention	Difference in mean differences (95% CI)	
Lever et al, 1998	Mean % Surface area (SD)	21.9 (14.8)	19.6 (12.8)	18.7 (15.3)	10.9 (10.8)	3.2	8.7	(0.1, 10.9)	T-test: $t = 2.08$, $p = .04$
	Mean severity score (SD)	36.7 (19.0)	33.9 (15.3)	33.4 (21.6)	24.0 (16.6)	3.3	9.4*	(−0.1, 12.3)	T-test: $t = 1.99$, $p = .05$
Ridd et al, 2021	Mean POEM (SD)	8.4 (4.5)	9.0 (5.2)	7.5 (5.7)	7.9 (6.0)	−0.9	−1.1	−0.2 (NR)	
	Median EASI (IQR)	2.1 (1.1, 4.0)	1.7 (0.7, 4.8)	2.7 (0.6, 4.25)	1.4 (0.2, 3.1)	0.6	−0.3	−0.9 (NR)	

Abbreviations: NR, Not Reported.
*All figures in Table 2 are as reported by Lever et al. Lever et al may have used complete cases only in their calculations, using individual scores rather than aggregate.
†Adjusted for baseline score.

history should guide dietary exclusion and reintroduction advice in suspected non-IgE food allergy.

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CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

MJR conceived the review. KR led the search, screening process and data extraction. AG and SD assisted in the screening process and in assessing risk of bias. MJR and AG assisted with data extraction and interpretation. NT assisted with data reporting. KR wrote the first draft of the research letter and all authors reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for established atopic eczema. *Cochrane Database Syst Rev*. 2008;1:CD005203.
2. Krawiec M, Fisher HR, Du Toit G, Bahnson HT, Lack G. Overview of oral tolerance induction for prevention of food allergy—Where are we now? *Allergy*. 2021;76:2684-2698. 10.1111/all.14758
3. Gilbertson A, Boyle RJ, MacNeill S, Ridd MJ. Healthcare professionals' beliefs and practices regarding food allergy testing for children with eczema. *Clin Exp Allergy*. 2021;51(5):735-739.
4. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;28(366):l4898.
5. Ridd MJ, Edwards L, Santer M, et al. TEST (Trial of Eczema allergy Screening Tests): protocol for feasibility randomised controlled trial

of allergy tests in children with eczema, including economic scoping and nested qualitative study. *BMJ Open*. 2019;9(5):e028428.
6. Ridd MJ, Webb D, Roberts K, et al. Test-guided dietary management of eczema in children: a randomized controlled feasibility trial (TEST). *Clin Exp Allergy*. 2021;51(3):452-462.
7. Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol*. 1998;9(1):13-19.
8. Schmitt J, Spuls P, Boers M, et al. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. *Allergy*. 2012;67(9):1111-1117.
9. Gaunt DM, Metcalfe C, Ridd M. The Patient-Oriented Eczema Measure in young children: responsiveness and minimal clinically important difference. *Allergy*. 2016;71(11):1620-1625.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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