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A systematic review of quality and consistency of clinical practice guidelines on the primary prevention of food allergy and atopic dermatitis

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ABSTRACT

Background and aims: With an increasing number of Clinical Practice Guidelines (CPGs) addressing primary prevention of food allergy and atopic dermatitis, it is timely to undertake a comprehensive assessment of the quality and consistency of recommendations and evaluation of their implementability in different geographical settings.

Methods: We systematically reviewed CPGs from 8 international databases and extensive website searches. Seven reviewers screened records in any language and then used the AGREE II and AGREE REX instruments to critically appraise CPGs published between January 2011 and April 2022.

Results: Our search identified 2138 relevant articles, of which 30 CPGs were eventually included. Eight (27%) CPGs were shortlisted based on our predefined quality criteria of achieving scores >70% in the "Scope and Purpose" and "Rigour of Development" domains of the AGREE II instrument. Among the shortlisted CPGs, scores on the "Applicability" domain were generally low, and only 3 CPGs rated highly in the "Implementability" domain of AGREE-REX, suggesting that the majority of CPGs fared poorly on global applicability. Recommendations on maternal diet and complementary feeding in infants were mostly consistent, but recommendations on use of hydrolysed formula and supplements varied considerably.

Conclusion: The overall quality of a CPG for Food Allergy and Atopic Dermatitis prevention did not correlate well with its global applicability. It is imperative that CPG developers consider stakeholders' preferences, local applicability, and adapt existing recommendations to each

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individual population and healthcare system to ensure successful implementation. There is a need for development of high-quality CPGs for allergy prevention outside of North America and Europe.

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Keywords: Allergy prevention, Food allergy, Atopic dermatitis, Eczema, Clinical practice guideline, Quality, Applicability, Consistency, AGREE II, AGREE-REX, Systematic review

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin condition affecting up to 30% of children worldwide,[1,2] and there is a strong association between AD and food allergy (FA).[3,4] A significant proportion of children with FA and AD also go on to develop chronic allergic respiratory diseases such as asthma and allergic rhinitis (AR), in what is termed the "atopic march".[3,4] Management of allergic diseases is mainly directed at symptom control and trigger avoidance. The high socioeconomic burden of managing chronic allergic diseases drives interest in allergy prevention.

In the past decade, randomized controlled clinical trials (RCTs) have investigated the utility of interventions such as early allergenic food introduction, prophylactic emollients, other dietary interventions in both mothers and high-risk infants for allergy prevention with varying degrees of benefit.[5–9] Many allergy organizations and scientific societies have issued evidence-based clinical practice guideline (CPG) recommendations for allergy prevention. CPGs are intended to be "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".[10] They are typically designed to be relevant to a specific population under the jurisdiction of an organization developing the guidelines and often vary in clinical focus, quality and intended end-users.

The large number of published CPGs addressing allergic disease prevention highlights the need to comprehensively assess the quality and generalizability of such CPGs. A global perspective is required to inform end-users of the international applicability of recommendations. No systematic review, however, has critically appraised FA and AD prevention CPGs. We, the Allergy Prevention Committee of the World Allergy Organization (WAO), aimed to assess the quality, consistency, and wider applicability of global CPGs addressing FA and AD. The Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument was employed to assess CPG quality in this systematic review because it is the most comprehensively validated instrument for appraisal of CPGs[11] and complements the Appraisal of Guidelines Research and Evaluation–Recommendations Excellence (AGREE-REX) tool that was used to assess CPG implementability. Areas covered by AGREE II overlap with those covered by the Institute of Medicine's (IOM) set of standards,[12] while providing additional context on the applicability of a CPG.[10]

METHODS

Aims

We sought to: explore the scope of CPGs pertaining to clinical purpose, presentation, and intended end-users; assess the consistency of recommendations on the primary prevention of FA and AD across CPGs; evaluate the implementability of CPGs in different geographical settings; and present synthesized recommendations of guidelines rated to be of the highest quality in terms of CPG development methodology.

MATERIALS AND METHODS

The separately published protocol details, search terms, and filters; databases searched; eligibility criteria; and data extraction and quality assessment strategies have been previously reported.[13] This review was also registered *a priori* with the International Prospective Register of

Systematic Reviews (PROSPERO): CRD42021 265689.

Identification of guidelines

We used controlled vocabulary search terms (MeSH Terms), combined using Boolean operators with a wide-range of free-text, to systematically searched eight international databases: MEDLINE & MEDLINE IN-Process, EMBASE, CINAHL, ISI Web of Science, PAHO, Science Citation Index, and Social Sciences Citation Index, TRIP, World Health Organization (Supplementary Material) for articles published from January 2011 to February 2023 with no restriction on geographical location or language. To identify additional relevant CPGs, we scrutinized references of published studies and hand searched all professional allergy society websites, details of which are described in the study protocol. We excluded randomized controlled trials, nonrandomized controlled prospective clinical trials, long-term follow-up studies, prospective observation studies and systematic reviews, and documents that were not available in full-text format. For CPGs with more than 1 version, only the most recent version was included.

Population

Clinical Practice Guidelines (CPGs), endorsed by national or international scientific societies, that referred to the prevention of FA and AD in children (<18 years of age) of any gender and ethnicity.

Interventions and comparators

The review focused on any guidelines providing recommendations with regards to interventions to prevent the development of FA and AD compared with no intervention, placebo, or any active comparator.

Outcomes

Our outcomes of interest were: 1) scope of CPGs for FA and AD prevention (clinical orientation and purpose, complexity of presentation, and intended end-users); 2) consistency of CPG recommendations across guidelines; 3) methodological quality of CPGs using the AGREE II instrument;[14] 4) implementability of CPGs in different geographical settings using the AGREE-REX instrument;[15] and 5) synthesized recommendations of guidelines rated as being of highest quality in terms of methodological design.

Selection of guidelines

Two researchers screened titles and abstracts of studies independently and in duplicate, after calibration, according to the predetermined inclusion and exclusion criteria as outlined in our study protocol.[13] Similarly, the same paired reviewers evaluated full-text copies of all CPGs identified as potentially relevant independently and in duplicate. Any discrepancies were resolved by consensus, and if necessary, arbitration by a third reviewer.

Evaluation of guidelines

We assessed methodological quality of guideline development using AGREE-II[14] and evaluated applicability using AGREE-REX.[15] AGREE II is a widely validated international assessment tool that enables assessment of the methodological and reporting quality of CPGs. The AGREE-REX instrument assesses how closely the recommendations align with implementation goals, anticipates impact of the recommendations on individuals and considers its suitability for the population and healthcare systems in which they are being implemented. Seven trained appraisers, each representing a different geographical region (South Asia, East Asia, North America, South America, South-Eastern Europe, North-Western Europe, and Africa), performed independent assessments. Total domain scores were calculated after completion of independent appraisals.

Data analysis and synthesis

Two authors independently extracted data from all shortlisted CPGs onto a customized data extraction sheet in Excel and any discrepancies were resolved by discussion. As per our predetermined protocol, the 7 appraisers separately scored each CPG independently according to the list of items in each of the AGREE II and AGREE-REX instruments. If the range of appraiser scores for a particular item in the AGREE II and AGREE-REX instruments exceeded 2 points, all 7

appraisers clarified their interpretations of the item through discussion and were allowed to re-score their responses until consensus was achieved (within 2 points). The individual scores of each domain were then averaged according to the prescribed formula and reported as percentages. We shortlisted highest scoring guidelines if they scored >70% in the "Scope and Purpose" as well as "Rigour of development" domains in the AGREE II instrument. Each appraiser also scored each CPG according to their overall recommendation for the guideline to be used in their own local context ("Overall" item in the AGREE-REX tool) – an assessment of the global applicability of each CPG. Consensus was not required for this item. We assigned the answer "Yes" a score of 1; "Yes with modifications" was scored 2; and "No" was scored 3. These scores were categorical and non-overlapping; however, the scores were treated as continuous and a mean score was calculated for each CPG in order to demonstrate smaller differences between the scores awarded by appraisers. We then summarized the scope of CPGs and consistency of CPG recommendations across guidelines.

RESULTS

Literature search

Our searches identified 2319 potentially relevant records and a total of 30 were eventually eligible[16–45] (Fig. 1).

Supplementary Table 1 summarizes the characteristics of the 30 selected CPGs. Of these, 8 were developed by regional or international organizations or developed by multidisciplinary teams involving more than one country. The remaining CPGs were from Australia, Canada, Finland, Germany, Hong Kong, Italy, Japan, Malaysia, Netherlands, Philippines, Russia, Singapore, Thailand, United Kingdom and the United States. Six CPGs were reported as being updated versions: 3 of which were second versions (EAACI, Thailand, AAP)[18,28,45] and 3 were third versions (German S3, ASCIA,

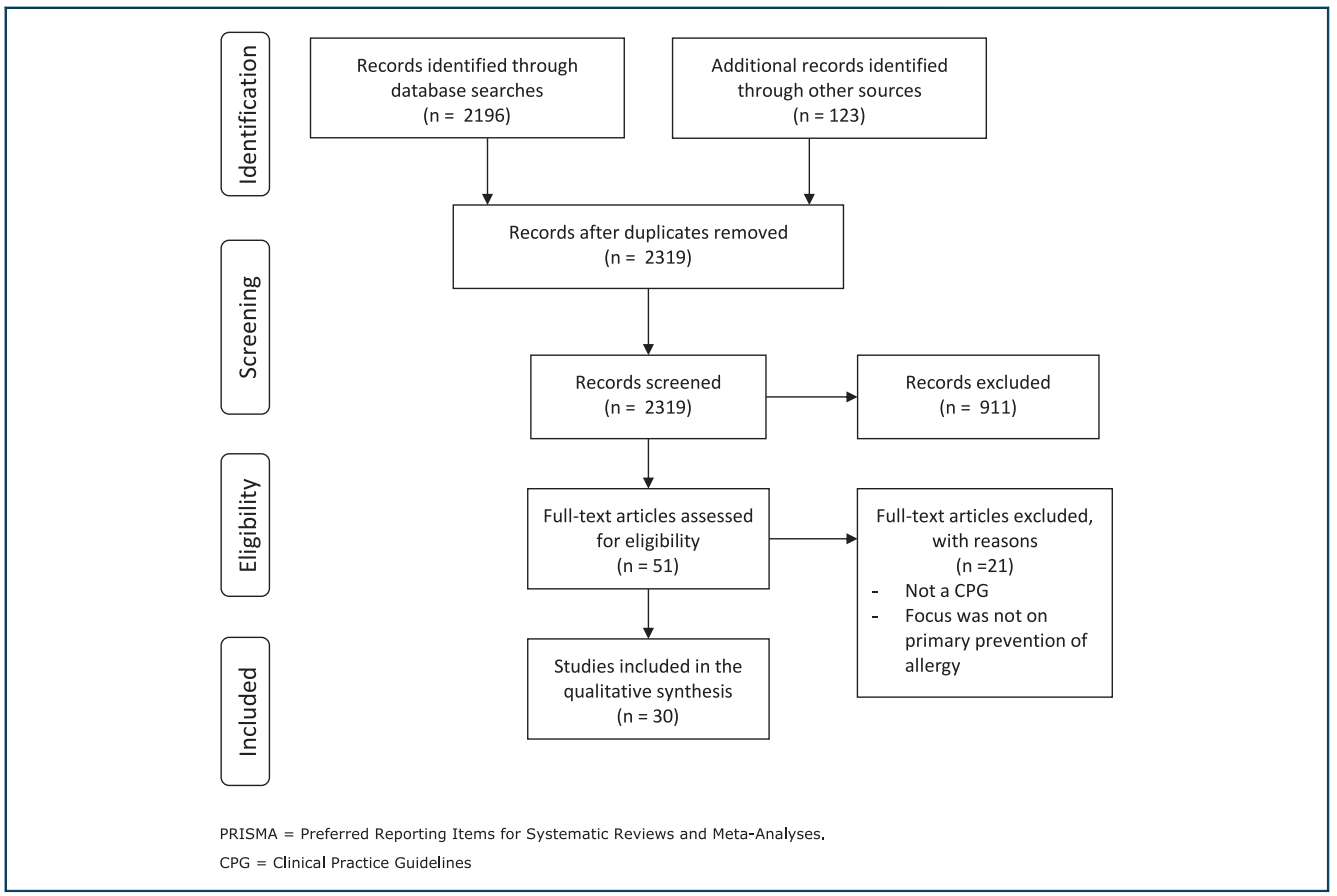


Fig. 1 PRISMA Flow Diagram of CPG selection.

	AGREE II						AGREE-REX			Overall recommendations	
	1.Scope and purpose (%)	2.Stake-holder involvement (%)	3.Rigor development (%)	4.Clarity of presentation (%)	5.Applica-bility (%)	6.Editorial indepen-dence (%)	1. Clinical applicability (%)	2. Values & preference (%)	3.Implemen-tability (%)	In the appropriate context	In my context
NIAID, 2017[15]	90.48	93.65	82.74	95.24	50.60	92.86	84.92	64.88	73.81	1.00	1.43
WAO-Probiotics, 2015[17]	97.62	94.44	92.26	88.89	55.36	97.62	91.27	79.76	77.38	1.14	1.43
WAO-Vitamin D, 2016[19]	96.03	94.44	95.54	92.86	48.81	97.62	88.89	82.74	85.71	1.00	1.00
WAO-Prebiotics, 2016[21]	95.24	93.65	93.75	82.54	63.10	97.62	90.48	83.33	82.14	1.14	1.29
NAS, 2016[24]	84.13	72.22	84.23	68.25	56.55	59.52	82.54	61.90	60.71	1.14	1.14
German S3, 2022[25]	88.89	86.51	76.19	80.95	57.74	46.43	84.92	44.05	70.24	1.29	1.57
EAACI, 2021[26]	90.48	92.06	90.18	92.06	88.69	97.62	92.86	88.69	89.29	1.00	1.00
US/Canada, 2021[29]	93.65	86.51	87.50	86.51	63.69	73.81	53.17	47.62	58.33	2.43	2.71

Table 1. AGREE II and AGREE-REX scores for the final shortlisted CPGs

JSA)[27,29,36] of recommendations. The remaining CPGs did not explicitly state version numbers and as no superseding CPGs were found during the search, these were assumed to be the first or most up-to-date versions. Of the 244 recommendations, 136 (56%) targeted exclusively infants, 70 (29%) targeted pregnant and lactating mothers, 31 (13%) targeted mothers & infants simultaneously, and 7 (3%) targeted childhood. Most guidelines included prevention strategies on more than 1 allergic disease (47%); 9 guidelines focused on the prevention of food allergy (30%), 2 on atopic dermatitis (7%), 4 on peanut allergy (13%), and 1 on cow's milk protein allergy (3%).

Quality assessment of guidelines

Supplementary Tables 2 and 3 presents scores in each domain of AGREE-II and AGREE-REX for each appraised CPG. A total of 8 CPGs which scored >70% in the "Scope and Purpose" as well as the "Rigour of Development" domains in AGREE II were shortlisted as those likely to be highest in methodological quality (Table 1). Four CPGs were developed by international organizations such as World Allergy Organization (WAO)[19,21,23] and the European Academy of Allergy and Clinical Immunology (EAACI).[28] The remaining CPGs were developed by national scientific organizations representing specific populations, such as the United States and Canada (NIAID, NAS, US/Canada)[17,26,31] and Germany (German S3).[27]

Across AGREE II domains, these 8 CPGs all scored highly (>70%) in the first 4 domains: Scope and Purpose, Stakeholder involvement, Rigour of Development and Clarity of Presentation (Fig. 2A). However, scores in the other domains were more variable. The EAACI 2020[28] CPG was the only document which scored >70% in the Applicability domain of the AGREE II instrument, which measures whether the CPG provides advice on how recommendations can be put into practice, describes facilitators and barriers to application, considers resource limitations and monitoring/auditing criteria.

It was notable that although the 8 shortlisted CPGs met the criteria for high reporting quality on AGREE II, only the WAO Vitamin D guidelines, WAO Prebiotics guidelines, and the EAACI 2020

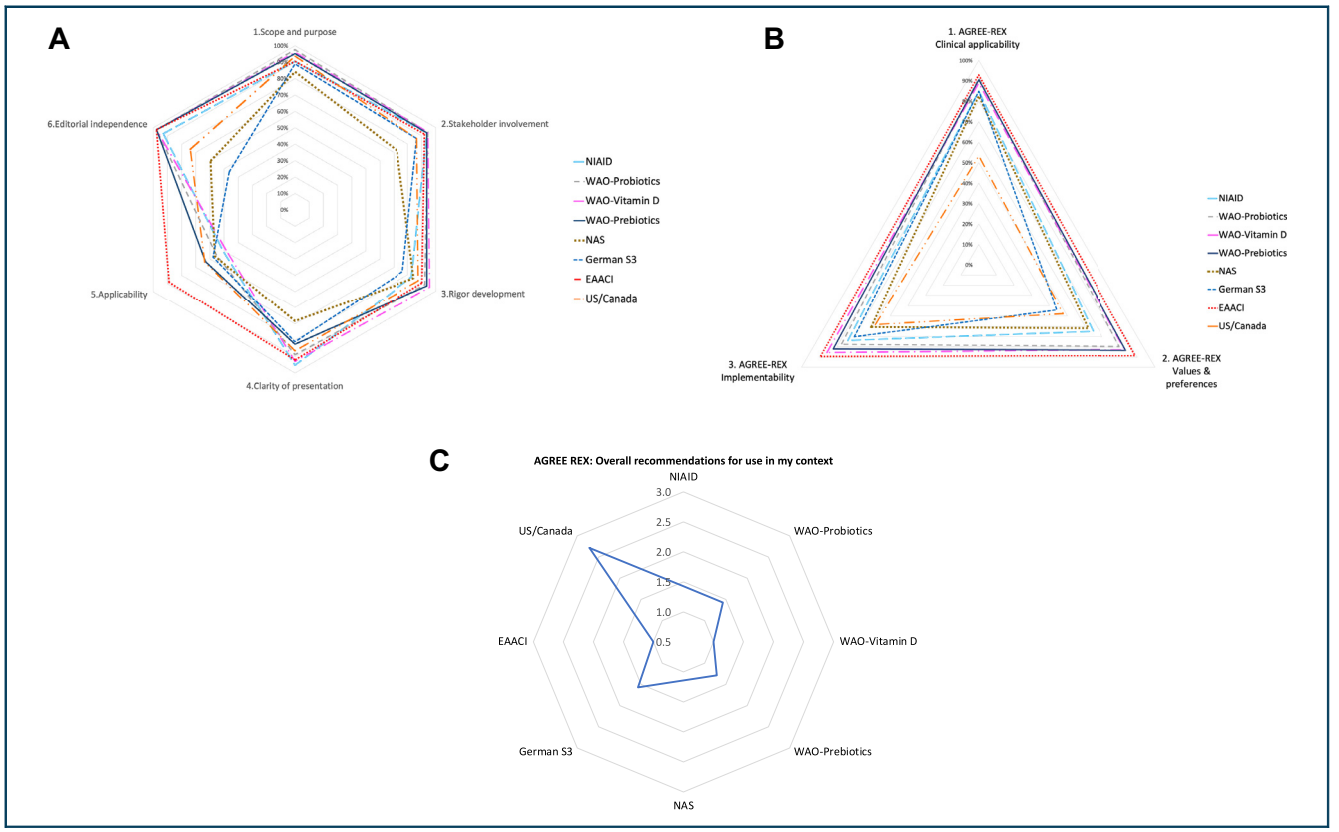


Fig. 2 A) AGREE II scores for shortlisted CPGs. B) AGREE-REX scores for the shortlisted CPGs. C) AGREE-REX assessment of global applicability of CPGs.

updated guideline[21,23,28] scored >70% in the Implementability domain of AGREE-REX (Fig. 2B). The WAO Vitamin D guidelines[21] and EAACI 2020[28] guideline unanimously scored highest in global applicability (mean score 1.0 out of 3.0 where 1.0 indicates the highest possible score and 3.0 the lowest possible score) (Fig. 2C). The US/Canada CPG,[31] in contrast, scored lowest in global applicability (mean score 2.71), indicating that the majority of appraisers felt that this CPG would not be applicable in their own local context (score of 3) or would require modifications (score of 2).

AGREE II scores varied by geographic region of CPG development. Those developed by mainly North American or European organizations scored highly, and none of the Asia-Pacific, Middle Eastern, or Australasian CPGs met the cut-off scores (>70% in the Scope and Purpose and Rigour of Development domains). CPGs which did not fulfil the prespecified quality criteria in the 2 selected domains also tended to score lower on other domains (Table 2), failing to demonstrate engagement of stakeholders and consideration of end-user values and preferences; practical implications of applicability on the ground and a clear declaration of editorial independence or conflicts of interests. They likewise scored lower on AGREE-REX domains including global applicability.

CPG recommendations across shortlisted guidelines

Among the 8 shortlisted CPGs, four CPGs (WAO-Probiotics, WAO-Vitamin D, WAO-Prebiotics and German S3 guidelines)[19,21,23,27] focused broadly on the prevention of allergic diseases, 2 CPGs (NAS, EAACI)[26,28] discussed primary prevention strategies against food allergy while the remaining 2 CPGs (NIAID, US/Canada)[17,31] focused specifically on peanut allergy. All of these shortlisted CPGs were targeted at children, with 2 specifically focused on infants[13] and toddlers younger than 5 years old.[24] Healthcare providers were the intended end-users of all of these guidelines, with the

addition of policy makers,[15,17,19,22,24] the public including food-allergic patients and families[22] and food industry[22] in some CPGs. CPG recommendations evolved with time and were primarily determined by timing of publication of practice-changing interventional RCTs (Table 3).[6-8,46-51]

Dietary recommendations during pregnancy or lactation

Recommendations against the restriction of maternal diet, including potentially allergens, remained fairly consistent because of the lack of new evidence relevant to this practice in the recent 5 years.[26-28,31] This likely reflects the ethical issues associated with conducting randomised trials of breastfeeding for prevention of allergy. CPGs gave no recommendations on breastfeeding,[26,28,31] and one recommended exclusive breastfeeding for the first 4–6 months of life.[27]

Complementary food introduction in infants

After publication of the LEAP[8] trial in 2015, 4 CPGs recommended the introduction of peanuts in an age-appropriate form as part of complementary feeding for infants at high-risk of developing allergy,[17,26-28] 2 of which recommended evaluation of peanut allergy by physician-guided allergy testing before the introduction of peanuts.[17,27] Since findings on the early introduction of peanuts and eggs were released,[7,47-49,52] 4 CPGs recommended no delay in the timing of introduction of allergenic solids[17,26,27,31] and specifically encouraged the introduction of peanuts, eggs, cow's milk, and wheat before infants' first birthday. Specific age windows for introduction of solid food,[27,31] well-cooked

	8 shortlisted CPGs Mean Score (SD) (%)	Other CPGs Mean Score (SD) (%)
AGREE II Domains		
Scope and Purpose	92.07 (4.43)	58.41 (22.15)
Stakeholder involvement	89.19 (7.61)	41.81 (18.76)
Rigour of Development	87.80 (6.48)	31.85 (19.68)
Clarity and presentation	85.91 (8.70)	72.98 (10.88)
Applicability	60.57 (12.51)	23.75 (9.62)
Editorial Independence	82.89 (20.44)	43.18 (27.94)
AGREE-REX Domains		
Clinical applicability	88.20 (3.64)	50.36 (15.42)
Values & Preferences	72.69 (14.78)	23.11 (9.45)
Implementability	78.57 (10.04)	42.86 (15.20)
AGREE-REX Overall scores		
Overall recommendations for use in the appropriate context	1.11 (0.10)	2.19 (0.50)
Overall recommendations for use in my context	1.29 (0.22)	2.27 (0.43)

Table 2. Comparison of AGREE II and AGREE-REX scores between highest quality CPGs and other CPGs

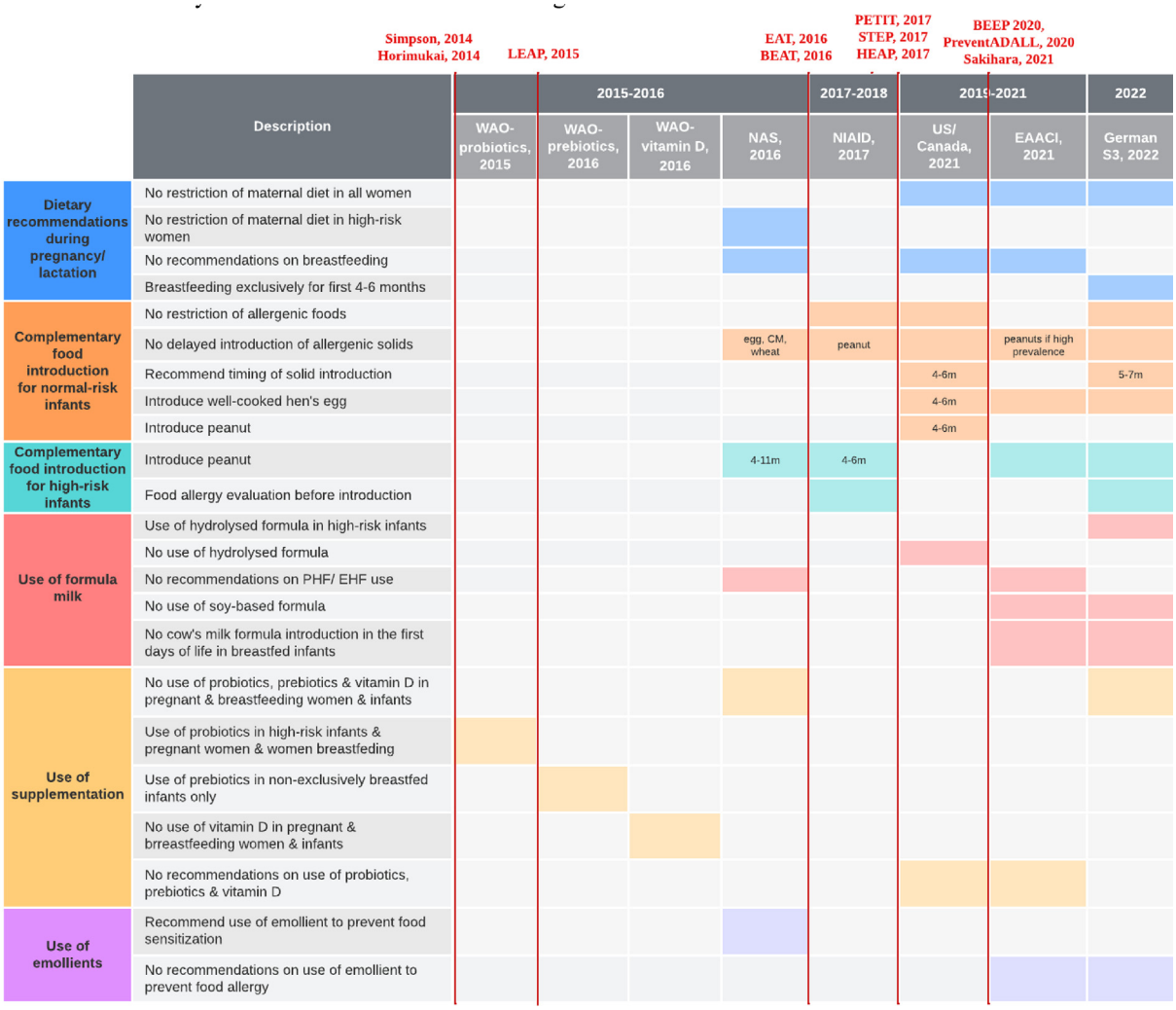
eggs,[27,28,31] and peanut[31] were recommended by 2, 3, and 1 CPGs, respectively.

Use of formula milk

There was a lack of new evidence around the use of formula milk and supplementation on the primary prevention of allergy in the past few years; thus recommendations on this area were considerably more diverse with 1 CPG recommending the use of hydrolysed formula in children at risk of developing allergy,[27] 1 recommending against the use of hydrolysed formula,[31] and 2 providing no recommendations on the use of hydrolysed formula in infants.[26,28] No use of cow's milk formula supplementation in the first days of life in breastfed infants were recommended by 2 CPGs updated in 2021–2022[27,28] after release of findings from a RCT regarding cow's milk supplementation on the subsequent development of cow's milk protein allergy.[51,53]

Use of supplementation & emollients

A lack of consistent evidence from high quality RCTs was reflected in the heterogenous recommendations on probiotics, prebiotics, and vitamin D supplementation in pregnant, lactating, and infants. No definitive recommendations on the use of emollients for prevention of AD and food



*In exclusively breastfed infants
Abbrev: m: month

Table 3. Consistency of CPG recommendations across guidelines

sensitization/allergy have yet been made, likely because of conflicting evidence from various studies.[5,6,9,46,50,54,55]

DISCUSSION

The rising prevalence of allergic diseases has stimulated interest in allergy prevention strategies. A recent systematic review evaluated recommendations and quality of CPGs on food allergy prevention using the AGREE II tool, but did not address AD prevention nor the global applicability of the CPGs.[56] The EAACI 2020[28] CPG was also not included in that systematic review as it was not yet published at the time of writing. In this study we reviewed all published CPGs on the primary prevention of FA and AD and identified the highest quality CPGs and their global applicability. Of the 30 CPGs identified through systematic search conducted in this review, 8 CPGs met the predetermined quality criteria for relevant scope and purpose and rigour of development. The highest scoring CPGs were developed mainly by North American and European organizations, and CPGs from the Asia-Pacific and Middle Eastern regions scored lower across most domains. There were very few CPGs on allergy prevention originating from regions of low allergy prevalence such as South Africa and the Indian subcontinent.

AGREE II scores of CPGs did not correlate well with global applicability overall. We also observed that the "Clinical Applicability" component of the AGREE-REX instrument had the best correlation with the global applicability item. CPGs that focused narrowly on one outcome, such as prevention of peanut allergy or cow's milk allergy alone, were less applicable globally compared to CPGs that addressed a variety of measures for FA and AD prevention. CPGs that were developed within a single country were also less globally applicable compared to those developed by multinational workgroups – this is likely attributable to the fact that they were designed for use only in that population. Early peanut introduction consensus guidelines[17] have been the focus of much international interest, yet our study found that it scored lowly on the AGREE-REX global applicability items "use in appropriate context" and "use in my context".

The evidence base for most other recommendations is heterogenous, with some recommendations being specific only to certain populations, or are still evolving as more data emerge from ongoing RCTs. The clinical implication is that healthcare providers who seek to utilize existing CPGs to guide their clinical practice should constantly stay abreast of the latest evidence as new RCT findings in this rapidly advancing field often reverse or challenge previous recommendations, and there is usually a long delay before CPGs are updated.

Some CPGs were published prior to the publication of influential RCTs and thus would not have addressed that particular intervention in their recommendations. One example of this pertains to the timing of cow's milk introduction for cow's milk allergy prevention. The Urashima et al RCT published in 2019 found that avoidance of cow's milk was associated with cow's milk protein allergy development at 6 months.[57] This prompted the inclusion of this recommendation into the German S3[27] and EAACI 2020 updated guidelines,[28] albeit with clarifications that it had a low evidence base. The majority of other CPGs, having been published prior to 2019, did not address this recommendation at all. Since then, RCT publications from Sakihara et al in 2021 and 2022 reported that daily ingestion of cow's milk formula between 1 and 2 months of age was protective against cow's milk allergy,[51] and that early discontinuation after initial introduction, particularly in the first month of life, was instead associated with increased risk of cow's milk allergy.[53]

Early studies, particularly from the German Infant Nutritional Intervention (GINI) study,[58–60] had suggested that partially hydrolysed infant formulas were beneficial for allergy prevention, prompting the inclusion of this recommendation in guidelines published prior to 2015.[18,61,62] However, as later trials and a Boyle et al meta-analysis in 2016[63] demonstrated a lack of evidence to support this recommendation, CPGs published after this period generally removed this recommendation with the exception of the latest German S3 CPG.[27] The latter qualified its recommendation by stating that the hydrolysed formulas which had been tested in previous studies (eg, German Infant Nutritional

Gaps in current CPGs for AD and FA prevention	Best practices & Future direction in CPG development
Quality of CPGs	
Few CPGs adopted validated systems for evidence grading such as the GRADE framework	Evidence base should be presented based on validated grading systems eg GRADE approach
Lack of a clear explanation of the relationship between preventive measures and associated health outcomes, and review of the evidence base behind recommendations	Development of CPGs should follow rigorous methodologies and based on systematic review of existing evidence
Failure to demonstrate editorial independence or conflicts of interest	Evidence should be founded on a clear and open approach. The funding body should not influence the content of the guideline and competing interests of CPG development group members should be clearly stated and addressed
Implementability of CPGs	
Failure to demonstrate engagement of stakeholders and end-users	To take into consideration of all relevant users' resources, workflow adjustments, and infrastructures for CPG deployment
Failure to assess practical aspects of CPG rollout	Identify facilitators and barriers to implementation, as well as engaging clinical stakeholders in the implementation process
Few CPGs are globally applicable, and intended end-users are not clearly stated	A statement of intended end-users or population of relevance should be made
Few studies are done post-CPG implementation to assess impact	Following the introduction of CPGs, follow-up studies should be conducted to assess end-user knowledge, uptake, and impact as well as any potential downstream effects on other aspects of child health
Specific to CPGs on primary FA & AD prevention	
Lack of timely updates of CPGs	Evidence on primary FA & AD prevention are rapidly evolving, and timely revisions with new evidence of existing CPGs should be performed regularly
Early peanut introduction has limited global application	Recommendations on primary FA & AD prevention should be adapted to the local context. Perspectives from the Asia-Pacific, Middle Eastern, African, and Indian subcontinent areas are lacking (areas with lower peanut allergy prevalence)
Lack of advice based on newly emerging knowledge on the risk of cow's milk protein allergy and early discontinuation of cow's milk after initial introduction	Replication of results in different populations and settings, and to assess the effect post-implementation

(continued)

Gaps in current CPGs for AD and FA prevention	Best practices & Future direction in CPG development
Lack of consistent data from high quality RCTs on probiotics, prebiotics, and vitamin D supplementation in mothers and infants	High quality RCTs with attention to strain-specific effect for probiotic, dosage, duration of use and targeted users are needed
Inconsistent evidence on the preemptive use of emollient for prevention of AD±FA	Successful allergy prevention outcomes can be affected by the population's risk, age at outcome assessment, and treatment length, which needs to be researched further

Table 4. (Continued) Gaps in research & future direction

Intervention, GINI, study) are no longer available on the market, or no longer available in the original composition which had demonstrated effectiveness against allergy prevention, suggesting that the observed allergy prevention benefits may be formula-specific. They thus recommended that for children with an increased risk of atopic disease and in whom breastfeeding is not possible, "*it should be checked whether an infant formula with proven effectiveness, demonstrated in allergy prevention studies, is available until complementary food is introduced*."[27]

One of the first measures widely studied was the use of probiotics, prebiotics, and vitamin D in the primary prevention of FA and AD. One of the first RCTs involved 159 pregnant mothers with a high atopic risk who were given either 2 placebo capsules or 1×10^{10} colony-forming units of *Lactobacillus rhamnosus* strain GG (ATCC 53103) daily for 4 weeks before expected delivery and for 6 months after delivery to their infants. During 2-year follow-up, the prevalence of atopic eczema in the probiotic group was half that of the placebo group (23 vs 46%; $p = 0.008$), although there was no significant difference in rates of food sensitisation.[64] The preventive effect of *Lactobacillus GG* on AD was later shown to extend beyond infancy and up to 7 years.[65,66] Trials have, however, found no benefit of probiotic supplementation on the prevention of AD or allergen sensitization.[67-69]

Early findings suggesting a putative link between food allergy and vitamin D deficiency stemmed from the observation that there appeared to be a direct relationship between increasing latitude and incidence of anaphylaxis.[70] In several prospective cohort studies, higher maternal vitamin D intake or maternal blood vitamin D levels were shown to be inversely associated with risk of food sensitization,[71] food allergy,[72,73] eczema,[74] and recurrent wheeze in early childhood.[75] However, no significant reduction in food sensitization at 12 months was noted in the vitamin D supplementation group in a RCT.[76] As a result, heterogeneous recommendations were provided by CPGs published after this period due to a lack of consistent high quality data from RCTs on these supplements for allergy prevention.

Emollient application for AD prevention has also been the focus of intense interest in the past 5 years. Preliminary evidence has shown that preemptive application of topical emollients may prevent the onset of atopic dermatitis (AD),[6,46] but 2 subsequent large randomized controlled trials conducted in Norway/Sweden (PreventADALL) and the United Kingdom (BEEP) reported negative results.[5,50] A Cochrane systematic review published in 2021 concluded that prophylactic skin interventions did not prevent AD development from age 1–3 years, and that regular emollient applications may increase risk of skin infections in healthy infants in the first year of life.[54] A separate meta-analysis published in 2021, however, demonstrated that this intervention might be efficacious in specific subpopulations, such as high-risk infants only or those in whom emollients were continued up to the point of AD assessment instead of an interval of cessation.[55] Only the EAACI 2020 CPG addressed this intervention (stating a lack of evidence to suggest a recommendation) but CPGs published prior to this would not have addressed this intervention. With recently published results from PreventADALL[9] with regards to food allergy

prevention, national and international CPGs may face new changes. Regular updates of existing CPGs should be performed to ensure that end-users are aware of changes in guidelines with emergence of new evidence.

This systematic review also highlights several gaps in CPG development (Table 4). Many scientific organizations focused mainly on evaluating evidence bases and generating statements on allergy prevention interventions (ie, Scope and Purpose and Clarity of Presentation). Several CPGs used the GRADE approach, but many others did not consistently follow validated grading systems for assessment of the evidence base behind recommendations. CPGs which scored low in the quality measures also generally failed to demonstrate engagement of stakeholders such as patients and families as well as general and specialty healthcare professionals on the ground: consideration of end-users' values and preferences; practical implications of guideline implementation and editorial independence or conflicts of interests, which are crucial aspects of successful CPG implementation that future CPG developers should be aware of. The Institute of Medicine also proposed a set of criteria by which CPGs could be assessed to be trustworthy (summarized briefly here):[12,77] 1) To be based on a systematic review of existing evidence; 2) Developed by an expert multidisciplinary panel and key stakeholders; 3) Consideration of end-user preferences and based on an explicit and transparent process; 4) Clear explanations of clinical translatability of recommendations, assessment of quality of evidence, and strength of recommendations; 5) Appropriate timely revisions with new evidence warranting updates in recommendations.

A limitation of this study is the use of just 2 instruments under the same framework (AGREE II and AGREE-REX) for assessment of quality and applicability. While the AGREE II and AGREE-REX are two of many possible tools for evaluation of CPGs, some may view its use as a reporting checklist and it may not fully capture other important aspects of trustworthy guideline development.[77] AGREE II, however, is the most comprehensively validated instrument and the items covered overlap with many other frameworks used for guideline evaluation.[11] AGREE-REX is also one of very few instruments available which assess global applicability. As the EAACI 2020 CPG explicitly used the AGREE II instrument to guide its development, its high score in this study is unsurprising but provides an illustration of the essential components in CPG development. Second, the main focus of this study was the appraisal of methodological aspects on allergy prevention in a CPGs' development and applicability but not to evaluate the evidence base underlying the CPGs themselves. Third, assessments of international CPGs were dependent on our panel of appraisers, one representing each geographical region of the world. Our selected appraisers were nominated and trained by members of WAO to perform quality appraisals of the selected CPGs, and the WAO Allergy Prevention Committee also regularly met to review the methodology and results, which supports the robustness of findings. Fourth, we intended to present recommendations from guidelines rated as being of highest methodological quality and global applicability, but due to the variability in prevalence of food allergy as well as region-specific culture and practices, there were eventually only a few recommendations that could be universally applicable.

CONCLUSION

Across all CPGs, the only universally applicable recommendations to most populations are: "No maternal allergenic food restrictions during pregnancy or lactation", "No restriction on the variety of allergenic foods in infants", and "No delayed introduction of allergenic solids into the diet of normal-risk infants".

This study outlines best practices for CPG development and recommends that scientific readers and CPG end-users should always carefully evaluate each CPG's intended scope and target population, stakeholder's views and preferences, and practical aspects of implementation before adopting recommendations from a particular CPG for clinical practice. Individual countries seeking to issue allergy prevention guidelines might benefit from this review to identify guidelines that can be adapted to their local context. After CPGs are released, follow up studies should

also be planned to evaluate end-user awareness, uptake and effectiveness for its intended outcome as well as potentially secondary impacts on other aspects of child health.[78,79] In light of rapidly expanding research in this space, allergy prevention CPGs should also be updated regularly to ensure that end users are kept informed on recommendations based on the latest evidence base.

Abbreviations
AAP, American Academy of Pediatrics; AD, Atopic dermatitis; AGREE-II, Appraisal of Guidelines for Research and Evaluation - II; AGREE-REX, Appraisal of Guidelines for Research and Evaluation–Recommendations Excellence (AGREE-REX); ASCIA, Australasian Society of Clinical Immunology and Allergy; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CPG, Clinical Practice Guideline; EAACI, European Academy of Allergy and Clinical Immunology; EMBASE, Excerpta Medica data-BASE; FA, Food allergy; ISAAC, International Study of Asthma and Allergies in Childhood; ISI, International Science Indexing; JSA, Japanese Society of Allergology; LEAP, Learning Early About Peanut Allergy; NAS, National Academy of Sciences; NIAID, National Institute of Allergy and Infectious Diseases; PAHO, Pan American Health Organization; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, Prospective Register of Systematic Reviews; RCT, Randomized controlled trial; SR, Systematic Review; TRIP, Turning Research Into Practice; US, United States; WAO, World Allergy Organization; WHO, World Health Organization.

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Author contributions
ASYL & EHT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ASYL and EHT contributed to the study concept, data collection, data analysis and interpretation, all aspects of the study, and manuscript preparation and revision; KYH, LD, TT, VVW, MN, EN and DL contributed as appraisers of the CPGs and GWKW, JS, MLKT, DM and DKC contributed to the study design and critical review. All authors made substantial contributions for important intellectual and approved the final manuscript.

Authors' consent for publication
All authors have given their consent for publication.

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The authors declare that they have no competing interests.

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Additional information
The e-Tables can be found in the Supplemental Materials section of the online article.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100770.

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