Protocol

The Effectiveness of Early Food Introduction in Preventing Childhood Allergic Diseases: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Allergic diseases affect around 40% of the pediatric population worldwide. The coexistence of asthma, allergic rhinitis, eczema, and food allergy renders allergy treatment and prevention challenging. Infant feeding strategies recommend avoiding allergenic foods to prevent allergy development and anaphylaxis. However, recent evidence suggests that early consumption of food allergens during weaning in infants aged 4-6 months could result in food tolerance, thus reducing the risk of developing allergies.

Objective: The aim of this study is to systematically review and carry out a meta-analysis of evidence on the outcome of early food introduction for preventing childhood allergic diseases.

Methods: We will conduct a systematic review of interventions through a comprehensive search of various databases including PubMed, Embase, Scopus, CENTRAL, PsycINFO, CINAHL, and Google Scholar to identify potential studies. The search will be performed for any eligible articles from the earliest published articles up to the latest available studies in 2023. We will include randomized controlled trials (RCTs), cluster RCTs, non-RCTs, and other observational studies that assess the effect of early food introduction to prevent childhood allergic diseases.

Results: Primary outcomes will include measures related to the effect of childhood allergic diseases (ie, asthma, allergic rhinitis, eczema, and food allergy). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines will be followed for study selection. All data will be extracted using a standardized data extraction form and the quality of the studies will be assessed using the Cochrane Risk of Bias tool. A *summary of findings* table will be generated for the following outcomes: (1) total number of allergic diseases, (2) rate of sensitization, (3) total number of adverse events, (4) improvement of health-related quality of life, and (5) all-cause mortality. Descriptive and meta-analyses will be performed using a random-effects model in Review Manager (Cochrane). Heterogeneity among selected studies will be assessed using the I^2 statistic and explored through meta-regression and subgroup analyses. Data collection is expected to start in June 2023.

Conclusions: The results acquired from this study will contribute to the existing literature and harmonize recommendations for infant feeding with regard to the prevention of childhood allergic diseases.

Introduction

Background

There has been a steep increase in the reported prevalence of common childhood allergic diseases (namely asthma, allergic rhinitis, eczema, and food allergy) in the last few decades [1-3]. According to Asher and Pearce [1], the International Study of Asthma and Allergies in Childhood concluded in the early 2000s reported that the prevalence of asthma, allergic rhinitis, and eczema had risen to over 30% in most industrialized countries. In addition, asthma is prevalent among approximately 300 million people worldwide, and by 2025, a further 100 million will likely be affected [4]. It is therefore crucial to evaluate the effectiveness of early life prevention techniques in order to lower the burden of childhood allergic diseases.

Infant feeding guidelines recommend early initiation of breastfeeding, including exclusive breastfeeding for the first 6 months of life and continued breastfeeding up to and after 2 years of age. Additionally, weaning or complementary feeding—defined as the provision of nutrition in the form of liquid or solid other than breast milk or infant milk formula—is introduced to neonates by 6 months of age, depending on the achievement of developmental milestones and the availability of safe complementary foods [5,6]. Besides providing essential nutrients to the growing infants, weaning exposes the developing gut microbiome to different antigens, thus influencing immune system development [7]. Food sensitization frequently occurs early in life and is often the first sign of future allergic disease; this is because the infant's immune system has yet to develop, if at all, an allergic phenotype [8]. Food items with allergenic properties may resist digestion and enhance allergenicity. Hence, susceptible infants who did not develop tolerance will manifest an allergic phenotype. Additionally, the preservation of "beneficial" gut microbiota in the neonate prevents immunity alteration that subsequently predisposes him/her from developing an allergy [9]. As a result, many researchers propose nutritional allergy interventions during this period, such as prolonged breastfeeding, early introduction of foods, maternal avoidance diets during pregnancy and lactation, use of hypoallergenic formulas, and early allergen avoidance, albeit with varying degrees of success [8,10,11].

The landmark study, Learning Early About Peanut Allergy, was one of the first to suggest early introduction of peanuts to reduce the development of peanut allergies [12]. In 2016, the Enquiring about Tolerance study expanded to multiple allergenic food items (ie, peanuts, cooked eggs, cow's milk, sesame, whitefish, and wheat) and observed a significant reduction in the prevalence of food allergies in the studied population [13]. These studies, along with others, appear to offer an effective and robust strategy to minimize the burden of allergy in the general population [10,14].

Living with allergic disease affects the quality of life of both patients and their guardians, considering the increasing health care costs. The determinants of health-related quality of life (HRQoL) in children with allergies traverse beyond biophysiological parameters and the symptom status of the child (such as physical limitations and emotional stress) and may include family dynamics and socioeconomic status, the community in which they live (ie, restrictions on participation in activities and social interaction), and organizational and policy-related factors (eg, inadequate food labelling and public information on allergies) [15-17]. Thus, effective allergy management strategy, including allergy prevention is imperative to avert allergic episodes that can be life-threatening.

Current recommendations for infant feeding require more consensus in the area of early life nutrition, specifically for prevention of childhood allergic diseases [18]. Moreover, an increasing number of studies have been examining the effect of early food introduction on reducing allergic sensitization, thus promoting allergy tolerance in these children [19-21]. We acknowledge earlier reports; however, most reviews have focused on the development of food allergies as well as having a diverse methodological approach [22-25]. In addition, there are diverse dietary patterns that may influence the development and progression of allergic diseases and their phenotypic expression in Asian populations. Although the published studies might have promising findings, less is understood about the potential harm that might result from the population-based guidelines and public health programs [26]. Thus, the aim of this systematic review is to identify evidence regarding the effect of early food introduction in preventing childhood allergic diseases.

Objective

This study aims to systematically review and carry out a meta-analysis of the effectiveness of early food introduction in preventing childhood allergic diseases.

Methods

This systematic review and meta-analysis will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [27]

(Multimedia Appendix 1) and the Cochrane Handbook for Systematic Reviews of Interventions [28].

Study Population and Selection Criteria

Inclusion Criteria

Our inclusion criteria will be based on the PICOS framework where the population of interest ("P") is defined as comprising healthy infants who were introduced to early feeding, the intervention ("I") is early introduction of complementary food (allergenic and nonallergenic) as a method of weaning when an infant approaches 4 months of age (ie, before turning 6 months old)—complementary food introduction is defined by the provision of nutrition other than breast milk or infants' milk formula [29]. Weaning may involve liquid food, as in formula feeding, or solid food that provides essential nutrients to an infant and the developing gut microbiome while influencing immune development [30]. We will accept other interventions that were not specified in this study and were defined by individual authors if they do not involve any pharmacological agent. We will compare ("C") our study cohort with infants who have been initiated on complementary feeding (ie, weaning) in accordance with the standard infant feeding guidelines as described by the studies included in this meta-analysis. The World Health Organization and United Nations International Children's Emergency Fund recommend early initiation of breastfeeding, including exclusive breastfeeding for the first 6 months of life followed by continued breastfeeding for up to 2 years and beyond [31]. Additionally, adequate complementary foods are recommended from the beginning of 4 months to latest 6 months of age to all neonates [32]. The outcomes ("O") are categorized as (1) primary outcomes including the total number of cases presented with asthma, allergic rhinitis, eczema, and food allergy (a reproducible hypersensitivity reaction to certain food items) and (2) secondary outcomes such as allergic sensitization (ie, the presence of elevated total and specific immunoglobulin E (IgE) levels to an allergen [33]) and total number of adverse events from allergen exposure. We will also evaluate studies reporting improvement in HRQoL, measured using validated scales (eg, Pediatric Allergic Disease Quality of Life Questionnaire, Food Allergy Quality of Life Questionnaires, and Pediatric Quality of Life Inventory) as well as all-cause mortality. We will include studies ("S") that are randomized controlled trials (RCTs) or cluster-RCTs, non-RCTs, and other observational studies that evaluate the effectiveness of early food introduction for preventing childhood allergic diseases. All published reports from inception up to October 2023 will be included.

Exclusion Criteria

Excluded studies are those that enrolled infants older than 6 months, those that involved food interventions among infants with congenital abnormalities (eg, dysmorphism), those not published in English, all unpublished trials and abstracts, and those describing multicomponent management (studies including the use of drugs). We will also exclude studies where infants initiated on supplementary feeding before the age of 4 months and those in which infants were initiated on certain immune suppressors (eg, steroids). We will exclude cross-over studies due to concerns about the carryover effects. We will also exclude all observational studies, any short communication, case report, and guidelines. Table 1 summarizes the PICOS search strategies, and sources of review for this study.

Table 1. PICO[a] search strategies and sources of review.

	Sources based on the PRISMA[b] checklist
Population	Healthy infants at recruitment as outlined by study authors.
Intervention	Early food introduction or early weaning when an infant approaches 4 months of age and before turning 6 months old.
Comparison	Infants initiated on complementary feeding (weaning) in accordance with standard infant feeding guidelines as described by the author.
Outcome	Primary outcome: total number of events of allergic disease (including asthma, allergic rhinitis, eczema, and food allergy). Secondary outcomes: rate of sensitization (level of total and specific immunoglobulin E), total number of adverse events, improvement of health-related quality of life measured using validated scales, and all-cause mortality.

[a]PICOS: population, intervention, compare, outcomes, and studies.

[b]PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Search Strategy

A systematic and comprehensive literature search will be conducted in various databases including PubMed, CENTRAL, Embase, Scopus, PsycINFO, CINAHL, and Google Scholar from inception to October 2023. A search strategy will be developed for PubMed and adapted for use with other electronic databases (Multimedia Appendix 2). The search will include MeSH terms and keywords relating to the study population ("childhood" OR "children" OR "paediatric" OR "pediatrics" OR "infants"), intervention ("early food introduction" OR "weaning" OR "complementary feeding" OR "supplementary feeding"), and outcomes ("allergies" OR "allergy" OR "allergic diseases" OR "asthma" OR "allergic rhinitis" OR "eczema" OR "dermatitis" OR "food allergy" OR "sensitization").

Data Collection

Standard Cochrane methods will be used, as described in the Cochrane Handbook for Systematic Reviews of Interventions [34]. Two authors will independently screen all the titles and abstracts to examine all the potential studies. We will code them as "retrieve" (eligible, or potentially eligible or unclear) or "do not retrieve." We will retrieve full-text reports or publications, and 2 other review authors will independently screen the full

text to identify studies for inclusion and will identify and record the reasons for exclusion of the ineligible studies. We will use a standardized data extraction form in accordance with the Cochrane Handbook for Systematic Reviews of Intervention [28]. Data will be independently extracted in accordance with general information (author, source, date of publication, country, and language), study (type of study, study duration, sample size, and control group selection), participants (age, sex, and type of allergy), types of intervention (food avoidance upon diagnosis and food challenge), and, lastly, outcomes (allergic episodes, admissions or emergency visits, duration of illness, and quality of life measured using validated scales) [28].

We will resolve any disagreement through discussion or consult a third review author if necessary. We will identify and exclude duplicates, and if multiple or overlapped reports of the same study are found, we will group them under a single study ID, and assign the report with the most amount of relevant information as the primary publication. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and construct a table describing the characteristics of the excluded studies [35]. We will resolve any discrepancies through discussion and by involving a third author.

Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for reporting studies.
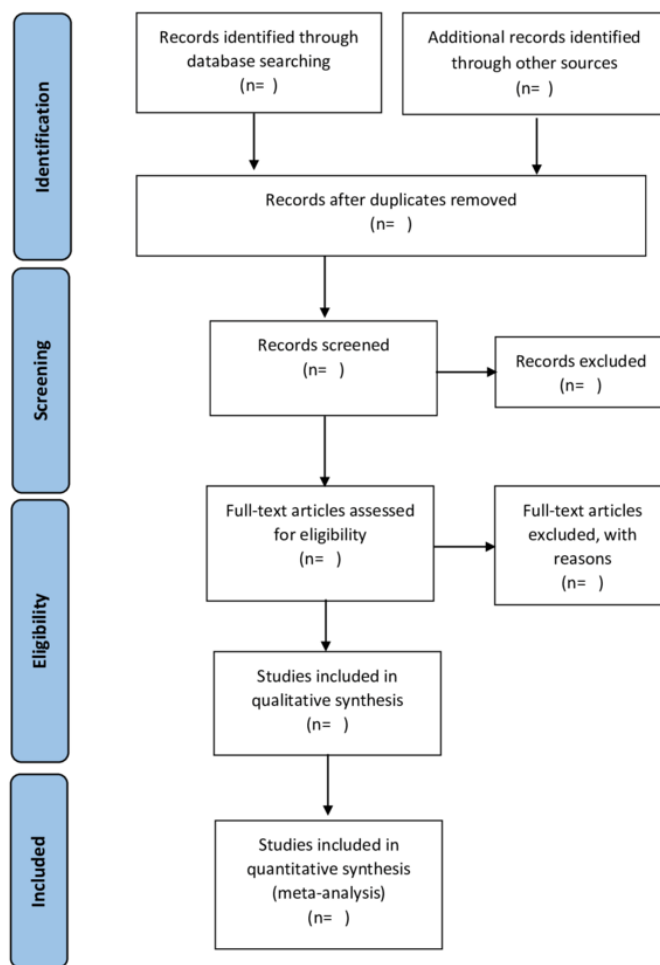
Quality Assessment of the Included Studies

Two reviewers will independently assess the quality of the included studies. The methodological quality of selected studies will be assessed using the Cochrane Risk of Bias Tool [36] for RCTs and cluster-RCTs, which includes the following domains: allocation concealment of random sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. We will use ACROBAT-NRSi (A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies), which evaluates the risk of bias in the results of non-RCTs studies that compare the health effects of 2 or more interventions [37]. We will use Newcastle-Ottawa scale for observational studies and evaluate the quality parameters (selection, comparability, and outcome)

of the selected studies [38]. We will make judgments on each of the abovementioned criteria regarding whether the study has a high, low, or unclear risk of bias. We will summarize the risk-of-bias judgements with justification for each of the domains listed in the *Risk of bias* table. Any disagreement among the review authors will be resolved by discussion to achieve a consensus.

Summary of Findings Table

We will create a *summary of findings* table by tabulating the following outcomes: (1) total number of allergic diseases (asthma, allergic rhinitis, eczema, and food allergy), (2) rate of sensitization (level of total and specific IgE), (3) total number of adverse events, (4) improvement of HRQoL measured using validated questionnaires, and (5) all-cause mortality [39]. We

will use the following 5 GRADE (Grading of Recommendations Assessment, Development and Evaluation) elements to assess the quality of the body of evidence as it relates to the prespecified outcomes: quality of evidence, consistency of effect, imprecision, indirectness, and publication bias. We will assess the quality of evidence for all outcomes using the GRADE methodology [40].

Data Analysis

Statistical Analysis

A meta-analysis will be conducted if there are at least 2 similar studies with broadly similar populations, interventions, and outcome measures using a random-effects model in Review Manager (Cochrane) [41]. A random-effects model will be used if studies are statistically heterogeneous; otherwise, we will use a fixed-effects model. For the random-effects model, we will conduct a sensitivity check by using the fixed-effects model to reveal differences in the results. We will include a 95% CI for all estimates. We will report skewed data as medians and IQRs. Studies will be considered as being sufficiently similar if the relevant outcome data are available in the group originally allocated or if the intervention, such as early food introduction in the allocated group, belongs to the same category—for example, the same amount of food (eg, frequency or total daily intake)—and if only frequencies are reported, we will include binary comparisons; for example, weekly versus never and daily versus never. The primary data analysis will include proportions or the frequency of childhood allergic diseases and types of food (allergenic and nonallergenic).

Assessment of Heterogeneity

The clinical heterogeneity of the results of the included studies will be assessed on the basis of the similarity of their populations, interventions, outcomes, and follow-up if we can pool sufficient studies together. We will consider populations as similar when they are in the same categories of age with outcomes measured in similar ways as stated in the eligibility criteria. We will consider interventions as similar if they fall into the same category as indicated in the abovementioned types of interventions. The outcomes will be considered as similar when they are measured at similar events as stated in the eligibility criteria. We will estimate the treatment effects of individual RCTs and examine heterogeneity among RCTs by inspecting forest plots and quantifying the impact of heterogeneity using the I^2 statistic [42].

Assessment of Reporting Biases

We will generate and examine a funnel plot to explore possible small biases in studies if we can pool more than 5 RCTs in a single meta-analysis.

Ethics and Dissemination

This systematic review is registered with the National Medical Research Register, Ministry of Health Malaysia (ID: NMRR ID-22-01049-HQ4). This protocol registered in PROSPERO (CRD42021256776). We will present the findings of this review in National and international conferences and continuous medical education initiatives, and we will disseminate our findings to policy makers and top managements (stakeholders) of Ministry of Health Malaysia.

Results

The protocol has been registered in PROSPERO and we initiated the review on June 1, 2023, and the results are expected by October 1, 2023. This systematic review and meta-analysis shall contribute an update to the existing literature on infant feeding with emphasis on the risk of childhood allergic diseases.

Discussion

Anticipated Findings

This protocol outlines the methods for a systematic review of the literature to assess the effectiveness of early food introduction in the prevention of childhood allergic diseases. Figure 2 illustrates a flow diagram of the study process to be followed as a guide for this review in terms of literature search using keywords identified through discussion among authors, the screening of shortlisted studies following a standardized framework, and the process of full text retrieval. This will be followed by quality assessment with data extraction for evidence synthesis and finally publishing of the study results.

We take note of 2 similar systematic reviews and meta-analyses that are closely related to our study [23,43]. However, their methodology (in terms of population variability and age of weaning) and diverse outcomes are different from those based on our study objective. In our study, we aim specifically to evaluate the effectiveness of early food introduction in infants aged 4-6 months irrespective of risks, and to evaluate outcomes related to 4 common allergic diseases in children. We believe that our findings will provide a reasonable and robust update to the existing literature.

Figure 2. Flow diagram of the study process. PICOS: population, intervention, compare, outcomes, and studies.
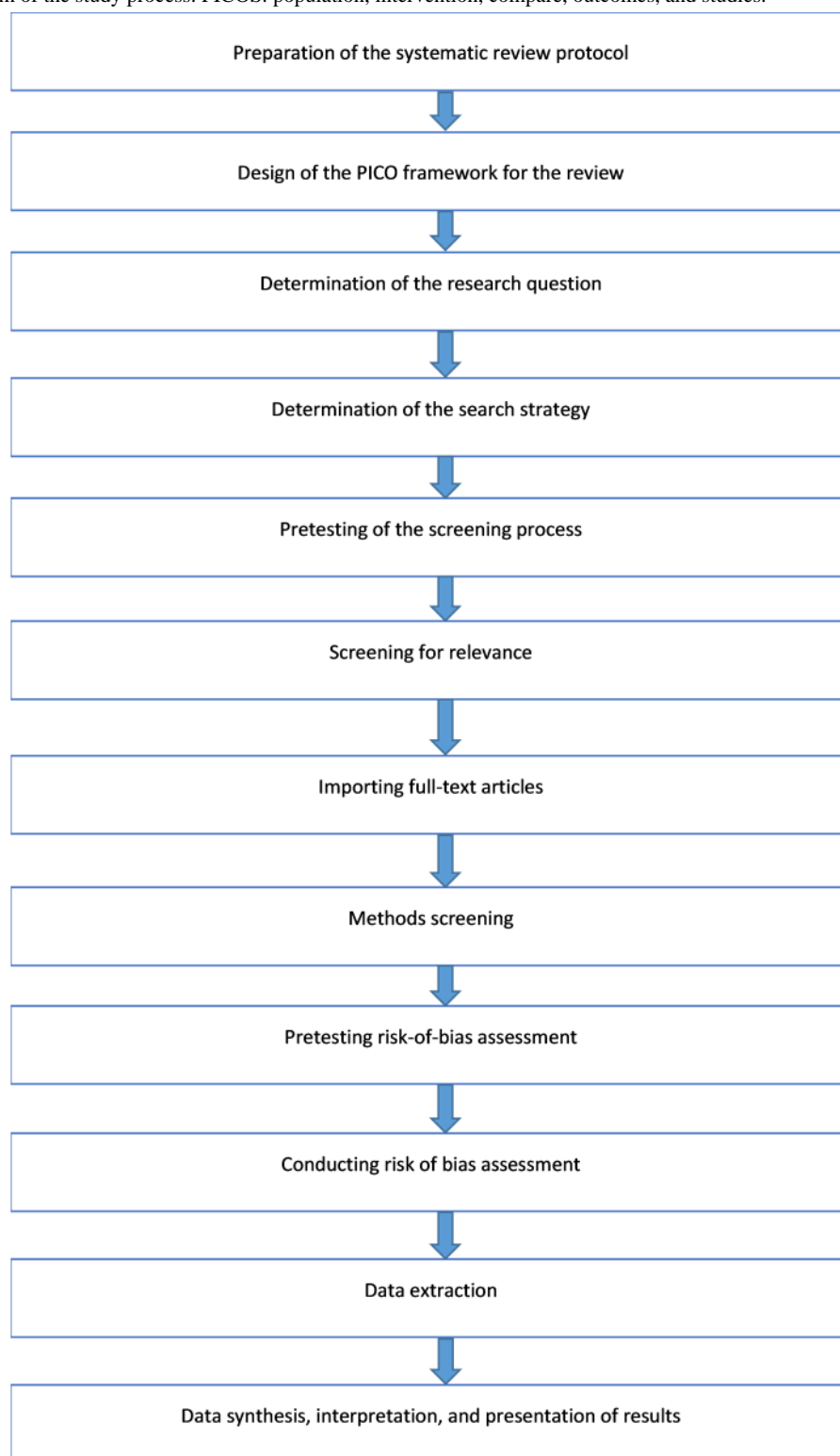
Reaching Conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of the studies included in this review. The conclusions can be used as guidelines for top managers and stakeholders for evidence-informed policy on infant feeding guidelines for the prevention of childhood allergic diseases. Our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

Data Availability

The original contributions shown in the study are contained within this systematic review and its multimedia appendices; further inquiries can be addressed to the corresponding author.

Authors' Contributions

All authors contributed to conceptualization and the development of the study plan. AFAA, C-LT, and NAM are responsible for title registration, development of the overall study methodology, and evidence rating schemes. AFAA and RMAG will conduct the literature searches, manage the references, and draft the intellectual content. NAM, SMS, and AFAA and will oversee the data extraction process and revision of the final manuscript with specific input from all other coauthors.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[PDF File (Adobe PDF File), 81 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Search strategy developed for PubMed.
[PDF File (Adobe PDF File), 115 KB-Multimedia Appendix 2]

References

1. Asher I, Pearce N. Global burden of asthma among children. Int J Tuberc Lung Dis 2014 Nov 01;18(11):1269-1278 [doi: 10.5588/ijtld.14.0170] [Medline: 25299857]
2. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011 Jul;128(1):e9-17 [doi: 10.1542/peds.2011-0204] [Medline: 21690110]
3. Lopez Carrera YI, Al Hammadi A, Huang Y, Llamado LJ, Mahgoub E, Tallman AM. Epidemiology, diagnosis, and treatment of atopic dermatitis in the developing countries of Asia, Africa, Latin America, and the Middle East: a review. Dermatol Ther (Heidelb) 2019 Dec 24;9(4):685-705 [FREE Full text] [doi: 10.1007/s13555-019-00332-3] [Medline: 31650504]
4. Custovic A. Epidemiology of Allergic Disease. In: Middleton's Allergy Essentials. Amsterdam: Elsevier; 2017:51-72
5. Halken S, Muraro A, de Silva D, Khaleva E, Angier E, Arasi S, European Academy of AllergyClinical Immunology Food AllergyAnaphylaxis Guidelines Group. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol 2021 Jul 29;32(5):843-858 [doi: 10.1111/pai.13496] [Medline: 33710678]
6. Bailey RL, Stang JS, Davis TA, Naimi TS, Schneeman BO, Dewey KG, et al. Dietary and complementary feeding practices of US infants, 6 to 12 Months: a narrative review of the Federal Nutrition Monitoring Data. J Acad Nutr Diet 2022 Dec;122(12):2337-2345.e1 [doi: 10.1016/j.jand.2021.10.017] [Medline: 34688966]
7. Santos A. Prevention of food allergy: can we stop the rise of IgE mediated food allergies? Curr Opin Allergy Clin Immunol 2021 Apr 01;21(2):195-201 [doi: 10.1097/ACI.0000000000000719] [Medline: 33394703]
8. Mavroudi A, Xinias I. Dietary interventions for primary allergy prevention in infants. Hippokratia 2011 Jul;15(3):216-222 [FREE Full text] [Medline: 22435018]
9. Hendaus M, Jomha F, Ehlayel M. Allergic diseases among children: nutritional prevention and intervention. TCRM 2016 Mar:361 [doi: 10.2147/tcrm.s98100]
10. Heine R. Food allergy prevention and treatment by targeted nutrition. Ann Nutr Metab 2018 Apr 9;72 Suppl 3(Suppl. 3):33-45 [FREE Full text] [doi: 10.1159/000487380] [Medline: 29631274]
11. Turner PJ, Feeney M, Meyer R, Perkin MR, Fox AT. Implementing primary prevention of food allergy in infants: New BSACI guidance published. Clin Exp Allergy 2018 Aug 30;48(8):912-915 [FREE Full text] [doi: 10.1111/cea.13218] [Medline: 30133860]
12. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015 Feb 26;372(9):803-813 [doi: 10.1056/nejmoa1414850]
13. Perkin M, Logan K, Craven J, Marrs T, Radulovic S, Flohr C, et al. Enquiring About Tolerance (EAT) study – feasibility of early introduction of allergenic foods and impact on breastfeeding. Clin Transl Allergy 2015 Mar 30;5(S3) [doi: 10.1186/2045-7022-5-s3-o6]
14. Chan ES, Abrams EM, Hildebrand KJ, Watson W. Early introduction of foods to prevent food allergy. Allergy Asthma Clin Immunol 2018 Sep 12;14(Suppl 2):57 [FREE Full text] [doi: 10.1186/s13223-018-0286-1] [Medline: 30275847]

15.   Dean BB, Calimlim BM, Kindermann SL, Khandker RK, Tinkelman D. The impact of uncontrolled asthma on absenteeism and health-related quality of life. J Asthma 2009 Nov 11;46(9):861-866 [doi: 10.3109/02770900903184237] [Medline: 19905909]

16.   Hossny E, Shousha G, Wassif G, Hana S. A study of health-related quality of life in pediatric atopic dermatitis. Egypt J Pediatr Allergy Immunol 2020 Oct 03;18(2):61-69 [doi: 10.21608/EJPA.2020.117838]

17.   Gupta RS, Kim JS, Barnathan JA, Amsden LB, Tummala LS, Holl JL. Food allergy knowledge, attitudes and beliefs: focus groups of parents, physicians and the general public. BMC Pediatr 2008 Sep 19;8(1):36 [FREE Full text] [doi: 10.1186/1471-2431-8-36] [Medline: 18803842]

18.   Ferrante G, Carta M, Montante C, Notarbartolo V, Corsello G, Giuffrè M. Current insights on early life nutrition and prevention of allergy. Front Pediatr 2020 Aug 6;8:448 [FREE Full text] [doi: 10.3389/fped.2020.00448] [Medline: 32850557]

19.   Zutavern A, Brockow I, Schaaf B, von Berg A, Diez U, Borte M, LISA Study Group. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. Pediatrics 2008 Jan;121(1):e44-e52 [doi: 10.1542/peds.2006-3553] [Medline: 18166543]

20.   Turcanu V, Brough HA, Du Toit G, Foong R, Marrs T, Santos AF, et al. Immune mechanisms of food allergy and its prevention by early intervention. Curr Opin Immunol 2017 Oct;48:92-98 [FREE Full text] [doi: 10.1016/j.coi.2017.08.009] [Medline: 28892729]

21.   Turati F, Bertuccio P, Galeone C, Pelucchi C, Naldi L, Bach J, HYGIENE Study Group. Early weaning is beneficial to prevent atopic dermatitis occurrence in young children. Allergy 2016 Jun 04;71(6):878-888 [doi: 10.1111/all.12864] [Medline: 26893011]

22.   de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, et al. Preventing immediate-onset food allergy in infants, children and adults: systematic review protocol. Pediatr Allergy Immunol 2020 Apr 13;31(3):243-249 [doi: 10.1111/pai.13177] [Medline: 31736128]

23.   Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. JAMA 2016 Sep 20;316(11):1181-1192 [FREE Full text] [doi: 10.1001/jama.2016.12623] [Medline: 27654604]

24.   Comberiati P, Costagliola G, D'Elios S, Peroni D. Prevention of food allergy: the significance of early introduction. Medicina (Kaunas) 2019 Jun 30;55(7):323 [FREE Full text] [doi: 10.3390/medicina55070323] [Medline: 31261990]

25.   Kakieu Djossi S, Khedr A, Neupane B, Proskuriakova E, Jada K, Mostafa J. Food allergy prevention: early versus late introduction of food allergens in children. Cureus 2022 Jan;14(1):e21046 [FREE Full text] [doi: 10.7759/cureus.21046] [Medline: 35155013]

26.   Turner PJ, Campbell DE, Boyle RJ, Levin ME. Primary prevention of food allergy: translating evidence from clinical trials to population-based recommendations. J Allergy Clin Immunol Pract 2018 Mar;6(2):367-375 [FREE Full text] [doi: 10.1016/j.jaip.2017.12.015] [Medline: 29524992]

27.   Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol 2021 Jun;134:103-112 [doi: 10.1016/j.jclinepi.2021.02.003] [Medline: 33577987]

28.   Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Chichester: John Wiley & Sons; 2021.

29.   Dipasquale V, Romano C. Complementary feeding: new styles versus old myths. Minerva Med 2020 Apr;111(2) [FREE Full text] [doi: 10.23736/s0026-4806.19.06320-1]

30.   McKeen S, Young W, Mullaney J, Fraser K, McNabb WC, Roy NC. Infant complementary feeding of prebiotics for the microbiome and immunity. Nutrients 2019 Feb 09;11(2):364 [FREE Full text] [doi: 10.3390/nu11020364] [Medline: 30744134]

31.   Infant and young child nutrition. World Health Organization. 2010. URL: https://apps.who.int/iris/handle/10665/3097 [accessed 2023-03-23]

32.   Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, et al. Complementary feeding: a position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. J Pediatr Gastroenterol Nutr 2017 Jan;64(1):119-132 [doi: 10.1097/MPG.0000000000001454] [Medline: 28027215]

33.   Chad Z. Allergies in children. Paediatr Child Health 2001 Oct;6(8):555-566 [FREE Full text] [doi: 10.1093/pch/6.8.555] [Medline: 20084126]

34.   Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M, Cochrane Information Retrieval Methods Group. Searching for and selecting studies. In: Cochrane Handbook for Systematic Reviews of Interventions, Second Edition. Hoboken, NJ: John Wiley & Sons; 2019:67-107

35.   Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;350(jan02 1):g7647-g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]

36.   Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343(oct18 2):d5928-d5928 [FREE Full text] [doi: 10.1136/bmj.d5928] [Medline: 22008217]

37.   Thomson H, Sterne J, Higgins J. ACROBAT-NRSi (A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions) for non-clinical community based studies: a participatory workshop using a worked example from public health. 2015 Presented at: 23rd Cochrane Colloquium; October 3-7, 2015; Vienna, Austria

38.   Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis. URL: http://www.evidencebasedpublichealth.de/download/Newcastle_Ottowa_Scale_Pope_Bruce.pdf [accessed 2023-06-13]

39.   Schünemann H, Higgins J, Vist G, Glasziou P, Akl E, Skoetz N, et al. Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Cochrane Handbook for Systematic Reviews of Interventions, Second Edition. Hoboken, NJ: John Wiley & Sons; 2019:375-402

40.   Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011 Apr;64(4):383-394 [doi: 10.1016/j.jclinepi.2010.04.026] [Medline: 21195583]

41.   Deeks J, Higgins J. Statistical algorithms in review manager 5. 2010. URL: https://www.researchgate.net/profile/Jonathan-Deeks/publication/252093205_Statistical_Algorithms_in_Review_Manager_5/links/54d159b70cf28370d0e07f9e/Statistical-Algorithms-in-Review-Manager-5.pdf [accessed 2023-03-23]

42.   Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 06;327(7414):557-560 [FREE Full text] [doi: 10.1136/bmj.327.7414.557] [Medline: 12958120]

43.   Burgess JA, Dharmage SC, Allen K, Koplin J, Garcia-Larsen V, Boyle R, et al. Age at introduction to complementary solid food and food allergy and sensitization: a systematic review and meta-analysis. Clin Exp Allergy 2019 Jun 03;49(6):754-769 [FREE Full text] [doi: 10.1111/cea.13383] [Medline: 30861244]

Abbreviations

ACROBAT-NRSi: A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HRQoL: health-related quality of life
IgE: immunoglobulin E
PICOS: population, intervention, compare, outcomes, and studies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial