FOOD ALLERGENS IN MATERNAL DIET DURING BREASTFEEDING AND OUTCOME OF ELIMINATION DIET ON INFANT ALLERGY DEVELOPMENT: A SYSTEMATIC REVIEW

NUR ALYA HANNANI MAT TENA'AIN
DEPARTMENT OF NUTRITION SCIENCES, KULLIYYAH OF ALLIED HEALTH SCIENCES, INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA, JALAN SULTAN AHMAD SHAH, BANDAR INDERA MAHKOTA 25200 KUANTAN, PAHANG, MALAYSIA
nuralyahannani@gmail.com

NOR AZWANI MOHD SHUKRI, PhD (CORRESPONDING AUTHOR)
DEPARTMENT OF NUTRITION SCIENCES, KULLIYYAH OF ALLIED HEALTH SCIENCES, INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA, JALAN SULTAN AHMAD SHAH, BANDAR INDERA MAHKOTA 25200 KUANTAN, PAHANG, MALAYSIA
norazwani@iium.edu.my

ABSTRACT

Introduction: Breastfeeding is recommended to provide sufficient nutrition source to infants. Although adverse reactions to allergenic food in exclusively breastfed infants have been identified yet the assessment among lactation mothers is still lacking. Hence, this study aims to review the effects of food allergens manipulation in maternal diet towards infant allergy reaction. **Methods:** A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified through five electronic databases using 15 keywords and were included if they met the following criteria: published in English, assessed mothers free from chronic diseases and included full term infants aged less than 24 months who were exclusively breastfed for at least four months. **Results:** A total of 1,094 relevant abstracts were screened and 8 full text articles, describing observational studies were reviewed and summarized. All studies reported responsible foods that trigger allergy reaction in infants. Nine food allergens were recognized in the maternal diet such as fish, shellfish, peanut, soy, cow's milk, tree nuts (chocolate and coffee beans), fermented foods (cheese, yogurt, bread, soy sauce, miso soup and fermented soy beans), egg and pork. All but one study presented significant association between maternal dietary intake and allergy outcome. Nevertheless, only one study recommended maternal dietary elimination during breastfeeding, two agreed but with a few conditions, two rejected the recommendation and the remaining did not give any comment. **Conclusion:** Food allergens in maternal diet can indeed be transferred through breastmilk. However, maternal elimination diet is not recommended for

breastfeeding mothers as some foods are good sources of important nutrients unless the relationship is established. Even then the maternal elimination diet practice must be guided by clinicians so as not to jeopardize the growth and development of infants.

Keywords: Food allergen, maternal dietary intake, breastfeeding, infant, food allergy

INTRODUCTION

Since the past few decades, the prevalence of children suffering from allergic reaction has been increasing including among breastfed infants (Yadav & Naidu, 2015). The cause of the allergy is reported to be due to maternal dietary intake which indirectly results in breastmilk – containing allergens and causes adverse reaction in infants. There is a long list of allergenic foods that can trigger allergy reaction yet the foods containing potential allergens among breastfeeding mothers are still unclear.

Some food taboos for lactating mothers such as cow's milk is discouraged to be consumed to prevent allergy reaction in their infants. Furthermore, some lactating mothers may obtain an unverified information regarding proteins that they consume which may be transmitted to their babies through breastmilk. They learn that by eliminating allergenic food from their diet, it can preserve the health of their babies. However, the omission of those foods may disrupt the mother's nutritional quality which is important for their infants' development (Jeong et al, 2017; Jeurink et al, 2018). Some studies have verified that the omission of allergy – causing food from maternal diet is pointless and ineffective to reduce the allergy risk (Jeurink et al, 2018). In fact, it is encouraged for infants to have human milk as the milk contains dietary proteins that can increase immunological response towards allergens. Due to the conflicting results from studies mentioned, the roles of maternal factors on development of infant allergy are poorly understood.

To lower the risk for allergy, many interventions or preventive actions have been established. However, to date, food allergens assessment among lactating mothers is still lacking. Most of the studies were done in European countries where the allergenic foods identified might not give the same effects to other countries. This study aimed to provide a map of available evidences on food allergens in maternal diet and infant allergy. The outcome of maternal diet manipulation among breastfeeding mothers on infant allergy was determined. The findings would have the potential to be used in planning future intervention studies to prevent allergy development.

METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (Appendix A)

Eligibility Criteria

Inclusion and exclusion criteria were constructed to filter the studies. Articles that met the exclusion criteria were rejected with justification. As we are interested in studies related to allergenic foods and infant allergy in exclusively breastfed infants, as described above, we chose to focus on mothers and infants with the following characteristics: (1) infants are exclusively breastfed for at least four months, (2) infants' age less than 24 months, (3) full term birth infants and (4) mothers free from chronic diseases. The studies were limited to English publication and all study designs except review article, use of animals as subjects, book chapters, editorial and conference abstract. The studies chosen were published in the last two decades as the relevance of findings beyond that could be questioned for their inaptness. The participant/intervention/control/outcome/setting (PICOS) for this systematic review are described in Table 1.

Information sources and search strategies

A search strategy was developed using Boolean Operators to identify articles related to the study interest. The sources of this study were from five online databases which could be accessed through International Islamic University Malaysia (IIUM) Library such as;- Springer Link, Scopus, PubMed, ProQuest and Wiley Online Library. Given the abroad range of food allergy, the keywords were narrowed which were: ("food allergen*" OR "food antigen*") AND ("diet*" OR "nutrition*" OR "food intake" OR "meal*") AND ("breastfeeding*" OR "lactating*") AND ("infant*" OR "child*" OR "new-born*" OR "baby") AND ("food allergy" OR "food hypersensitivity" OR "food aversion").

Table 1 Population, Intervention, Comparison, Outcome, Study design (PICOS)

Element of Study Question	Description	Search Term
Population	Infant	Child OR new-born OR baby
Intervention	Food allergens	Food allergens OR food antigens
Comparison	No intervention/ Control group	-
Outcome	Food allergy	Food allergy OR food hypersensitivity OR food aversion
Study Design	All except study review and meta-analyses.	-

Study selection

A reference management tool, Mendeley software® - was used to screen the exported articles. Duplicates were removed and the number of articles left to be screened again was recorded. Then, the titles and abstracts of articles were screened and articles that are not related to review questions were excluded. The total number of excluded articles was recorded. Full-text articles that fulfilled the inclusion criteria were downloaded. Subsequently, studies that did not match the eligibility criteria were removed with specific reasons.

Data extraction and analysis

Tabulation of findings summary was done to identify, analyse and interpret the patterns of the data. The table was adopted from Cochrane Handbook and was modified according to study objectives (Higgins et al, 2019). The elements extracted from data were author, year of publication, country, study design, article title, food allergens, infant age, infant feeding method, study description and result.

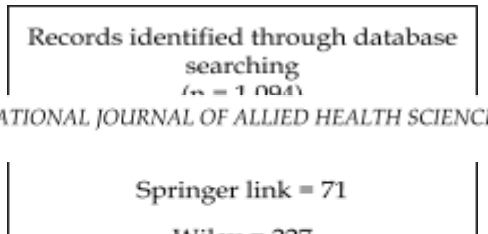
Study quality assessment

The methodological quality of included studies was examined using the Case Report (CARE) Guidelines Checklist (2013) for case report and National Institutes of Health (NIH) Quality Assessment Tool for cross-sectional, cohort studies and Before-After (Pre-Post) Studies with No Control Group. The CARE Checklist 2013 was developed as a guideline that appraise the quality of case report (Riley et al, 2017; Dragnev & Wong, 2018). Meanwhile, The NIH tools can accommodate a range of study designs and a final quality rating of good, fair, or poor for each included study. One reviewer critically assessed study quality and assessment verification done by the second reviewer.

RESULTS

Study selection

The initial hits identified a total of 1094 articles: ProQuest (n = 752), Springerlink (n = 71), Wiley Online Library (n = 227), Scopus (n = 33) and PubMed (n = 11). Another 14 more articles were found through citation searching. Then, duplicates of articles were removed using Mendeley software resulting in 1038 articles. A total of 959 were removed and 93 relevant articles were screened for full text after screening the title and abstracts. After examining the full-text articles according to the inclusion and exclusion criteria of this review, eight studies were included in the review while another 85 articles were removed due to a few reasons (refer Figure 1).



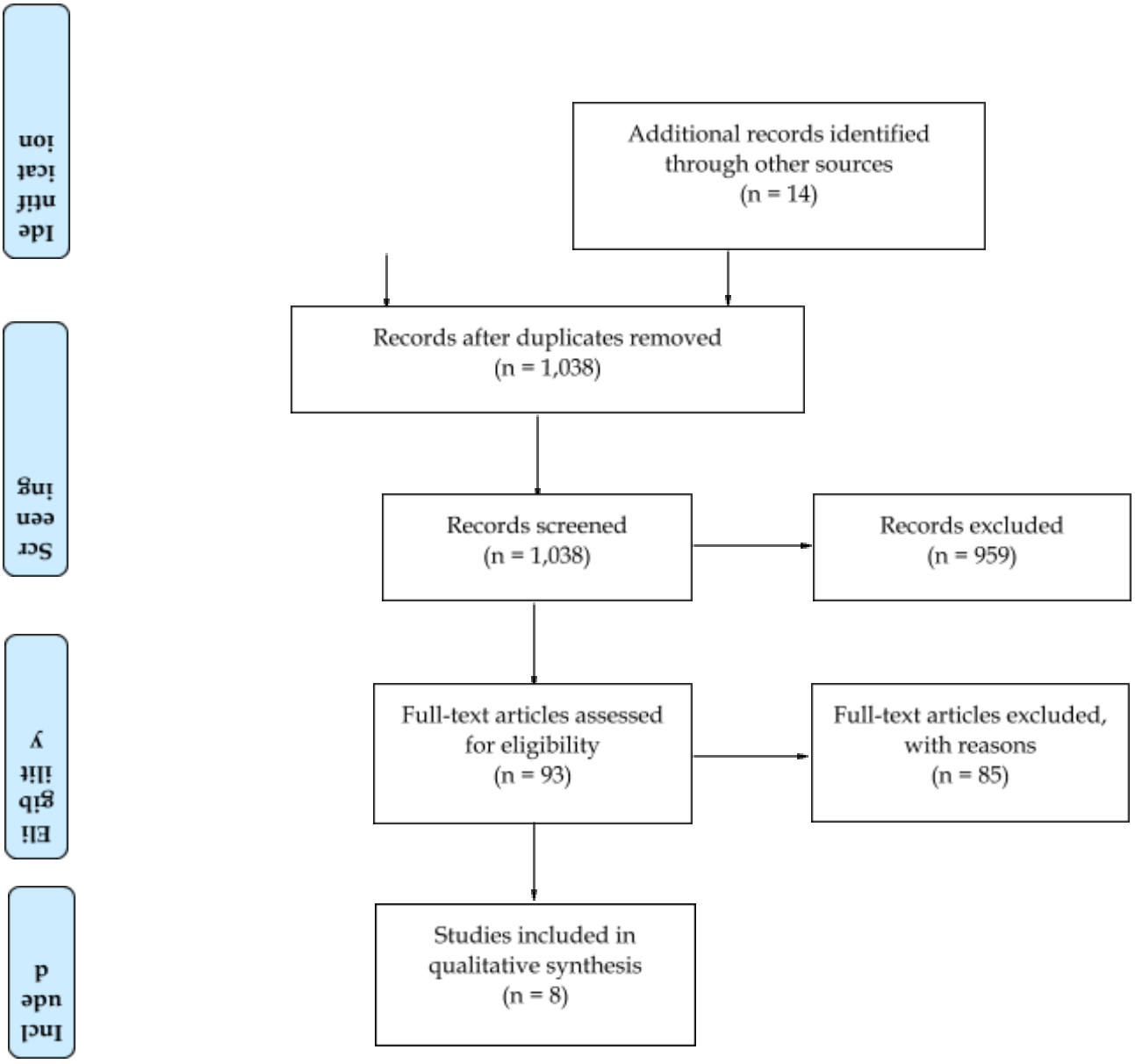


Figure 1. PRISMA 2009: Flow Guideline: Number of studies found, sourced from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009).

Study Characteristics

Of the eight studies included, four were case reports, and one each of case series, pre- and post-test, cross-sectional and cohort studies. All were published between 2005 and 2017. Two studies were conducted in Japan and Italy while the remaining were diverse in geographical locations, representing Australia, Canada, Spain and United State of America. A total of 289 participants were involved in these studies with age ranging from two weeks to 19 months. However, one cross-sectional study did not specify the age of their participants. The details of

studies that identified food allergens in diet of breastfeeding mothers are summarized in Table 2.

Table 2 Summary of findings on food allergens in maternal diet of breastfeeding mothers and outcome of elimination diet on infant allergy.

Study	Author, Year	Study Design	Infant Age	Food Allergens	Allergy Outcome	Maternal Elimination Diet Outcome
1	Arima et al, 2016	Case report	5 months	Fish	**Positive** Urticaria developed 1 hour following breastfeeding after maternal fish ingestion. Skin prick test to some fish species was positive.	**Positive**
2	Des Roches et al, 2005	Case report	2 weeks	Peanut	**Positive** Frothy, unformed stools while breastfeeding. SPT at 10 weeks was negative for milk, soy, egg and wheat. No reaction in commercial peanut but in fresh peanut.	**Positive** No improvement with maternal elimination of milk and soy products but became normalized after stop eating peanut butter.
3	Monti et al, 2006	Case report	4 months	Fish	**Positive** Severe anaphylactic reaction (urticaria, vomiting, wheezing and coughing) after breastfeeding; mother had eaten fish several hours before lactating. Positive IgE to two fish species.	**Positive**
4	Tan et al, 2012	Case report	5 months	Soy	**Positive** Symptoms appeared in infant hours after soy-based formula feeding. Acute food protein-induced enterocolitis syndrome symptoms were observed subsequent breastfeeding	-

					following previous large amount maternal ingestion of soy-based ice cream at 6 months. SPT result to soy was negative.	
5	Miceli Sopo et al, 2014	Case series	3 months & 2 months	Cow's milk	**Positive** **Infant 1:** chronic GI symptoms (episodes of colic, diarrhea and mild lethargy, viral gastroenteritis, persistent hypotonia, pallor and bloody diarrhea). **Infant 2:** chronic symptoms with the first two exposures to CM formula.	**Positive** **Infant 1:** Symptoms disappeared after mother eliminate both cow's milk (CM) and egg. Chronic food protein-induced enterocolitis syndrome occurred after mother accidentally ingest CM subsequent breastfeeding.
6	Bovey, 2017	Cross-sectional	Not specified	Peanut, tree nuts, milk, egg, shellfish & pork	**Negative** 2 out of 37 (5.4%) exclusively breastfed infants had at least one reported food allergy which is not significant (p = 0.26). Four children diagnosed with allergy.	**Negative** No significant differences (p = 0.91) in maternal elimination (spicy, acidic and dairy) in 46% of breastfeeding mothers.
7	Martin-Munoz et al, 2016	Cohort	1-19 months	Peanut & egg	**Positive** **Infant 1:** Peanut identification in serum IgE of patient. **Infant 2:** Hen's egg was identified in patients' IgE serum. Skin prick-by-prick test in all infants were positive.	**Positive** Symptoms in both infants resolved after maternal elimination diet. Infant 1 developed tolerance to other allergen (egg).
8	Uenishi et al, 2011	Pre- & post- test without control group	3 to 8 months	Tree nuts and fermented foods	**Positive** Predominant offending foods were chocolate, yogurt, soy sauce and miso soup.	**Positive** 67 of 92 had positive maternal exclusion test. 61 of them were followed up and

						54 of 61 had progressive improvement while 7 had mild/moderate exacerbation. Among 25 infants, 19 were followed up and 11 of them had slight improvement while another 8 showed no improvement.

Quality of bias assessment of included studies

Among the four case reports, only one study (Arima et al, 2016) had high quality rating which was (19/30) while the remaining studies (Des Roches, 2005; Monti el al, 2006; Tan et al, 2012) were moderate (16/30 and 17/30 and 12/30). High quality rating indicates low risk of bias. While the quality of included studies for case series, cross-sectional, cohort and pre- and post- test were 'good', 'poor', 'fair' and 'poor' according to the NIH quality assessment tool.

DISCUSSION

Food allergens in the diet of exclusively breastfeeding mothers

The findings from all eight studies have identified and confirmed the presence of food allergens in the diet of exclusively breastfeeding mothers. A total of nine food allergens were recognized from these studies which either induced allergy reaction or aggravated allergy symptoms. These included fish, shellfish, peanut, soy, cow's milk, tree nuts (chocolate and coffee beans), fermented foods (cheese, yogurt, bread, soy sauce, miso soup and fermented soybeans), egg and pork. Among the food allergens, peanut (n=3) was the most reported allergen in the studies while the fewest were pork (n=1), soy (n=1), shellfish (n=1) and fermented foods (n=1). The countries which identified these food allergens were Japan (n=2), Canada (n=1), Italy (n=2), Australia (n=1), United States (n=1) and Spain (n=1). When categorization of these countries was done according to geographical region (eastern and western), the result showed that fermented foods were commonly studied in eastern country which is Japan while peanut, egg, cow's milk, shellfish, pork and soy were frequently studied in the western countries (Canada, United States, Spain, Italy and Australia). Nevertheless, these eastern and western countries also shared a similar finding on identification of tree nut and fish allergens.

Outcome of maternal elimination diet on infant allergy development

This review has identified eight studies that fulfilled the inclusion criteria, only seven (Arima et al, 2016; Des Roches et al, 2005; Monti et al, 2006; Miceli Sopo et al, 2014; Bovey, 2017; Martin-Munoz et al, 2016; Uenishi et al, 2011) of which had investigated the association of maternal suspected foods elimination and food allergy development in infants and all the findings were positive except one (Bovey, 2017). These findings prove the role of maternal ingestion of allergenic foods in provoking allergy symptoms in which the maternal and genetic factors could increase the susceptibility of infants to allergies (Arshad, 2001).

Interestingly, among these seven studies, two had yielded different results in which one did not observe significant association of maternal elimination diet and infant allergy development (Bovey, 2017) while another showed tolerance towards different allergens tested (Martin-Munoz et al, 2016) yet each of studies' quality was either poor or fair. No significant association was found which might be due to the influence of maternal diet on the specific IgA composition of breastmilk and providing protection against infant allergy development (Jarvinen et al, 2019). In general, there was a clear pattern that as majority of studies had provided evidence suggesting that the maternal elimination diet of allergenic food was associated with resolution of symptoms while allergens exposure through breastmilk or direct consumption could cause relapse of symptoms.

Differences in recommendation of maternal diet elimination during lactation as a treatment for infant allergy

Despite positive association between maternal elimination diet and resolution of symptoms, one study (Des Roches et al, 2005) recommended maternal elimination diet during breastfeeding, two studies agreed with recommendation but with few conditions (Tan, Campbell & Mehr, 2012; Martin-Munoz et al, 2016), two studies did not suggest (Miceli Sopo et al, 2014; Bovey, 2017) and while the rest (Arima et al, 2016; Monti et al, 2006; Uenishi et al, 2011) did not give comments regarding this association. Des Roches et al (2005) had suggested to remove maternal peanut consumption during lactation and reintroduce only when infant's gut barrier is fully developed and become matured. In contrast, other studies were pro to unrestricted maternal diet. Tan, Campbell, and Mehr (2012) and Martin-Munoz et al (2016) suggested removal of trigger food in maternal diet if supporting evidence on breast-milk-triggering reaction and infant food allergy is confirmed.

However, these studies have moderate risk of bias. Martin-Munoz et al (2106) also proposed tolerance development by breastmilk-containing food allergens. In contrast, Bovey (2017) and Miceli Sopo et al (2014) did not recommend maternal elimination of allergenic foods as there was no adverse reaction in FPIES acute reports. In the meantime, the three remaining studies (Arima et al, 2016; Monti et al,

2006; Uenishi et al, 2011) did not provide any comments regarding maternal elimination diet. However, Arima et al (2016) was seen to support maternal ingestion of suspected food during breastfeeding as more evidence supported reduced risk of infant allergy along with trigger food consumption. Overall, maternal elimination diet was not recommended unless there was a history of allergic reaction and diagnosis of suspected food was confirmed. Otherwise, the breastfeeding mothers could proceed with normal diet.

Differences in study designs and clinical implications

It is essential to emphasize the level of certainty of the included studies for future practice. The level of certainty for descriptive and observational design studies are at the level of IV and V evidence which includes historical cohort, studies with no control, case-control study or systematic review of these studies, case series and expert opinion, case report or clinical example. In this review, all studies were from case report, case series, cross-sectional, retrospective cohort and pre- and post-test without control group (Burns, Rohrich & Chung, 2011). All studies other than case reports and case series did not report sample size justification therefore estimation for statistical power cannot analysed. For the cross-sectional study, the procedure used to collect data on maternal elimination diet relied on retrospectively collected dietary recall questionnaires which have flaws than dietary data obtained in prospective.

Other than that, some infants were reported with medical and family history of allergy and the adjustment were not reported. This makes comparison and possible masked association difficult to establish on infants with high risk of food allergy. Despite these methodological errors, the allergy diagnosis mentioned in the studies was performed and certified by clinicians using validated methods such as skin prick test and specific IgE serum. Therefore, all the studies were classified as level IV of evidence rating and level V for case reports. As the levels of evidence are IV and V and the findings were not inconsistent, the studies are graded as grade C where the implications for practice are opened for option. This also suggests that healthcare professionals need to be flexible in making decision regarding appropriate practice.

This study has used PRISMA Statement as reference for methodology and was conducted accordingly. This was also among the first review to identify responsible allergens in diet of breastfeeding mothers which cause allergy reaction and association between maternal diet manipulation and infant allergy outcome. The studies were also selected thoroughly according to the criteria and the risk of bias for each study was also addressed. This study would be the first systematic review identifying and listing the allergens in breastmilk which trigger allergy reaction in infants and addressing the outcome of maternal suspected food elimination for resolution of symptoms. However, this review also has its limitations. First, only

eight studies were included in this review as a result of the inclusion criteria applied. On the other hand, vast studies included in this review have high risk of bias which represent low quality of evidence with significant clinical results across studies. Lastly, this review only included English-published articles which may increase the selection bias risk.

CONCLUSION

The findings in this review identified nine food allergens in maternal diet transferred through breastmilk which produce adverse reaction in exclusively breastfed infants. The removal of food proteins in maternal diet could lead to progressive improvement of allergic symptoms. However, maternal elimination diet is not recommended for breastfeeding mothers as some foods are good sources of important nutrients. The elimination of allergenic food is only necessary if the relationship between maternal suspected food ingestion and development of infant allergy in exclusively breastfed infants is proven and allergy diagnosis is confirmed, so as not to compromise infants' growth and development. In addition, future research could investigate the specific number of allergens that could elicit reaction and peak concentration that produce the infant's reaction threshold. This would be useful in determining the upper tolerable consumption of allergenic food for mothers during breastfeeding.

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