

## ORIGINAL ARTICLE

# Systematic review: Early infant feeding practices and the risk of wheat allergy

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**Aim:** Wheat is a common allergen. Early feeding practices (breastfeeding, potentially allergenic foods) might affect the risk of allergy. To systematically evaluate the association between early feeding practices and the risk of wheat allergy and sensitisation.

**Methods:** Five databases were searched for studies of any design up to July 2015.

**Results:** We included seven studies (five observational, low to moderate quality, two randomised controlled trials (RCTs), high quality). The results come from observational studies unless stated otherwise. Longer breastfeeding was associated with wheat allergy (two studies,  $n = 1847$ ) and sensitisation (one study,  $n = 3781$ ). Evidence for exclusive breastfeeding was contradictory; longer exclusive breastfeeding was associated with either lower (one study,  $n = 408$ ) or higher (one study,  $n = 3781$ ) risk of wheat sensitisation. Breastfeeding at gluten introduction did not affect the risk of wheat allergy (two studies,  $n = 2581$ ). Introducing cereal  $\geq 7$  months of age increased the risk of wheat allergy (one study,  $n = 1612$ ), but results from an RCT ( $n = 1303$ ) showed no effect. Early introduction of gluten was associated with a reduced risk of wheat sensitisation up to 5 years in one observational study ( $n = 3781$ ) but not in RCTs ( $n = 1303$ ).

**Conclusions:** Based on limited evidence, the influence of breastfeeding and an early exposure to gluten on the risk of wheat allergy remain uncertain. There is no evidence supporting breastfeeding at gluten introduction as modifying the risk. Early introduction of gluten might reduce the risk of sensitisation, but currently, no evidence exists that it affects the risk of wheat allergy.

**Key words:** allergens; breastfeeding; child; glutens; infant; wheat hypersensitivity.

## What is already known on this topic

- 1 Wheat allergy is one of the most common food allergies.
- 2 Both genetic background and environmental factors have been claimed to affect the risk of allergy.
- 3 Breastfeeding and early exposition to allergens have been associated to the risk.

## What this paper adds

- 1 Current evidence comes mainly from observational studies.
- 2 Breastfeeding at the time of wheat/gluten introduction does not modify the risk of wheat allergy.
- 3 Timing of wheat/gluten introduction into infant's diet do not seem to decrease the risk of wheat allergy.

Wheat is the most widely consumed grain in the world, and it is one of the most common food allergens.<sup>1</sup> The prevalence of wheat allergy in general reaches 3.6% by self-reported symptoms, and the prevalence of food challenge-defined allergy to wheat is estimated to be 0.3%.<sup>2</sup> Atopic sensitisation is an important predictor of later onset of atopic symptoms and asthma. While the risk of developing an allergy is clearly influenced by the existing genetic background, a number of environmental factors, including feeding practices in early life, have been claimed to influence the risk of allergy.<sup>3</sup>

Exclusive breastfeeding for about 6 months is generally recommended due to positive health effects such as protection against infections, improved cognition and lower risk of

overweight and diabetes.<sup>4,5</sup> However, a 2016 meta-analysis of meta-analyses recently published by Victora *et al.* concluded that there is no evidence of an association between breastfeeding and food allergies (odds ratio (OR), 1.07, 95% confidence interval (CI), 0.90–1.26).<sup>6</sup> With regards to the introduction of gluten, previously, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended in 2009 that, based on observational data, one should avoid both early (less than 4 months) and late (7 or more months) introduction of gluten and to introduce gluten while the infant is still being breastfed as this may reduce not only the risk of coeliac disease but also type 1 diabetes mellitus and wheat allergy.<sup>4</sup>

Regarding coeliac disease, it has been recently shown in large interventional trials that infant feeding practices did not affect the risk of developing coeliac disease during childhood.<sup>7</sup> Therefore, ESPGHAN modified its recommendations with regards to gluten introduction and the risk of coeliac disease accordingly.<sup>8</sup> Although breastfeeding should be promoted for its other well-

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established health benefits, it cannot be recommended as a means to reduce the risk of coeliac disease, and introduction of gluten anytime between 4 and 12 completed months of age confers the same risk for developing coeliac disease.<sup>8</sup>

The recommended feeding practices for prevention of type 1 diabetes and wheat allergy have not been updated. Recently, we published a systematic review and meta-analysis with respect to type 1 diabetes and type 1 diabetes autoimmunity.<sup>9</sup> We concluded that current evidence, mainly from observational studies, does not support the claim that early infant feeding practices, such as breastfeeding at gluten introduction or the age of the infant at the time of gluten introduction, may decrease the risk of developing type 1 diabetes.

Here, we report the results of a systematic review that aimed to answer the questions of whether breastfeeding duration, exclusive or any breastfeeding and breastfeeding at the time of introducing wheat/gluten, as well as the timing of wheat/gluten introduction influence the risk of development of wheat allergy or wheat sensitisation.

## Methods

The protocol for this systematic review was registered with the PROSPERO database (registration number: CRD42015023574) before performing the searches. Five databases were searched up to July 2015: Cochrane Library, MEDLINE, EMBASE, Web of Science and CINAHL. We performed an additional search of MEDLINE and EMBASE in March 2016. No restrictions by either date or language were used in the search strategies. The results were imported into Endnote bibliographic software and de-duplicated, which resulted in a total number of 4491 records. These were screened and assessed for eligibility. The search strategies are provided in Table S1 (Supporting Information).

We attempted to obtain relevant unpublished data by contacting researchers in the field. Letters to the editor were excluded. Proceedings from scientific meetings were included if the results of interest were provided in the abstract. Authors were contacted by email and requested to provide additional data (e.g. if only a statement of no significant difference between study groups was given in the abstract, the authors were asked to provide the number of outcomes that occurred in each study group). Studies of any design were considered eligible for inclusion. Participants had to be infants at population risk or increased risk of developing a wheat allergy. Interventions eligible for assessment were those involving the consumption of wheat- or gluten-containing products of any type (cereals, flour or any other food items containing gluten). The comparators could be a placebo or no intervention/no exposure. The primary outcome measures were the development of wheat allergy (as defined by authors) or wheat sensitisation (increased titres of wheat-specific IgE antibodies and/or positive results on skin-prick tests). No other outcomes were pre-specified in the study protocol. No exclusion criteria were applied.

Two researchers (AC and MPL) independently screened titles and abstracts of the identified papers. Full texts of those papers that were potentially relevant were assessed. If disagreement occurred, the study team discussed these issues until a consensus was reached. Data were extracted with the use of standardised spreadsheets (Table S2, Supporting Information).

The risk of bias in the included studies was assessed independently by the reviewers. For interventional studies, the Cochrane Collaboration's tool for assessing risk of bias was used.<sup>10</sup> Observational studies were assessed with the Newcastle-Ottawa Scale (NOS),<sup>11</sup> in line with the recommendation by The Cochrane Handbook for Systematic Reviews of Interventions.<sup>10</sup> NOS is based on a 'star system' in which a study is assessed by taking into account the following aspects: representativeness of study group selection (four items, equal to four stars), comparability of groups (two items) and ascertainment of either the exposure or outcome (three items). Overall, the NOS scores vary between 0 and 9 (the highest level of quality).

We planned to analyse data with Review Manager (RevMan) software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical heterogeneity was to be quantified by  $I^2$  (the higher the value above 0%, the more heterogeneity between studies). Dichotomous outcomes for individual studies were reported as the risk ratio (RR), the OR or the hazard ratio (HR), as in the original publication, all with 95% CI. Means with standard deviations (SDs) or the medians with ranges were given for continuous outcomes. For meta-analyses of observational studies, we aimed to pool adjusted odds ratios from the included studies. In cases where authors did not provide these, we planned to use raw outcome data to yield unadjusted odds ratios. The following subgroup analyses were planned: population/increased risk of allergy, gender and wheat allergy/wheat sensitisation. However, pooling results was not possible (see 'Results' section), and the results are presented in a narrative form.

## Results

Out of the total number of 4491 potentially eligible studies identified by the search strategy, 7 studies (8853 participants) were included.<sup>12–18</sup> Two of them were randomised controlled trials (RCTs),<sup>17,18</sup> one was a case-control study,<sup>12</sup> and the remaining four were cohort studies.<sup>13–16</sup> The flowchart (Fig. S1, Supporting Information) shows the study identification process in detail. Four of the seven studies included were conference proceedings with limited data provided.<sup>12,15–17</sup> Three authors shared more detailed data when requested.<sup>15–17</sup> Characteristics of the included studies and a summary of results are presented in Table 1. The excluded studies together with the reasons for exclusion are listed in Table S3 (Supporting Information). Included studies were highly heterogeneous in terms of methodology, outcome definitions, time points of assessment and quality of evidence. The Newcastle-Ottawa methodology scores for the observational studies (Table S4, Supporting Information) ranged from 2 points (one study) through 5 points (one study), 6 points (one study), 8 points (one study) and 9 points (one study). Thus, the quality differed significantly between the studies. Overall, the quality of observational studies was weak to moderate. The lowest scores were due to the lack of information provided in the conference proceedings. Limited information on subject's selection<sup>12,15</sup> and comparability<sup>15,16</sup> as well as undefined exposures and outcomes<sup>12,15,16</sup> contributed mostly to low scores. The cohort studies with published results and complete information on methodology<sup>13,14</sup> received the highest possible scoring (Table S4, Supporting Information). The risk of bias assessment of the two included RCTs is

**Table 1** Characteristics of included individual studies and summary of results presented as odds ratios (OR)

| Reference                                                | Cases                                                                                                                                               | Controls                       | Age                            | Exposure measurement                                                                        | Confounding factors considered                                                                                                                                                                                                                                                         | Results and conclusions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Case-control study</b>                                |                                                                                                                                                     |                                |                                |                                                                                             |                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Sirivimonpan et al. <sup>12</sup> (conference abstract)  | n = 47<br>With IgE-mediated WA                                                                                                                      | n = 188 gender and age matched | Infants                        | Not described                                                                               | Not specified (personal histories and associated factors)                                                                                                                                                                                                                              | BF > 6 months vs. <6 months: adjOR 2.3 (1.1–4.8)<br>Longer BF associated with WA<br>Timing of gluten introduction >6 months vs. < 6 months: NS (no data)<br>No effect of timing of gluten introduction on WA                                                                                                                                                                                                                                                                                                                                            |
| <b>Cohort studies</b>                                    |                                                                                                                                                     |                                |                                |                                                                                             |                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Nwaru et al. <sup>13</sup>                               | n = 3781<br>Finish DIPP (Type 1 Diabetes Prediction and Prevention) birth cohort at risk of t1DM (HLA-confirmed); 5% developed WS                   |                                | Wheat sIgE measured at 5 years | Age-specific questionnaire filled out by parents at 3, 6 and 12 months                      | Gender, number of siblings, parental asthma and rhinitis, maternal smoking during pregnancy, season of birth, gestational week, maternal age and education, mode of delivery, birthweight, pets at home by 1 year. The results for outcomes of interest were unadjusted for the above. | All ORs are unadjusted.<br>Duration of BF:<br><5 months vs. >9.5 months: OR 0.5 (0.25–0.75);<br>5–9.5 months vs. >9.5 months: NS<br>Shorter BF associated with lower risk of WS<br>Duration of exBF:<br><0.5 months vs. >3 months: OR 0.37 (0.25–0.9);<br>0.5–3 months vs. >3 months: OR 0.5 (0.37–0.8)<br>Shorter exBF associated with lower risk of WS<br>Wheat introduction:<br><5.1 months vs. >6.5 months: OR 0.5 (0.37–0.75);<br>5.1–6.5 months vs. >6.5 months: OR 0.75 (0.5–0.9)<br>Earlier wheat introduction associated with lower risk of WS |
| Besednjak-Kocijancic <sup>15</sup> (conference abstract) | n = 408<br>Term infants of parents with confirmed allergy; levels of sIgE measured at 1 and 5 years                                                 |                                | Until 5 years                  | Not described                                                                               | Not described                                                                                                                                                                                                                                                                          | Duration of exBF (6 months vs. 4 months): WS at 1 year: 9.4% vs. 20.4% (P < 0.01)<br>WS at 5 years: 13.6% vs. 22.9% (NS)<br>Longer exBF associated with lower risk of WS at 1 year but not at 5 years                                                                                                                                                                                                                                                                                                                                                   |
| Venter et al. <sup>16</sup> (conference abstract)        | n = 969<br>Infants at population risk of allergy (n = 5 developed wheat hypersensitivity (food challenge or sensitisation + good clinical history)) |                                | Until 3 years                  | Standardised questionnaire by phone at 3, 6 and 9 months + 1, 2 and 3 years                 | Gender, family history of allergy, prenatal smoke exposure                                                                                                                                                                                                                             | BF at gluten introduction:<br>2/? BF vs. 3/? not BF: NS<br>No effect of BF at gluten introduction on WA                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Poole et al. <sup>14</sup>                               | n = 1612<br>DAISY cohort study (at risk for t1DM); n = 16 developed wheat allergy (symptoms +/- sensitisation)                                      |                                | 5–48 months at diagnosis       | Telephone or face-to-face interviews at 3, 6, 9, 12 and 15 months and every year thereafter | Breastfeeding duration, introduction of rice cereal, family history of allergy,                                                                                                                                                                                                        | ORs are unadjusted unless stated otherwise.<br>Duration of BF:<br>10.3 months (8.9) vs. 6.5 months (6.69); OR 1.11 (95% CI: 1.01–1.1)                                                                                                                                                                                                                                                                                                                                                                                                                   |

(Continues)

**Table 1** (Continued)

| Reference                                                                   | Cases                                                                                                                                                                  | Controls                                                                                                                                                                                                                                                                 | Age | Exposure measurement             | Confounding factors considered                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Results and conclusions                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population                                                                  |                                                                                                                                                                        |                                                                                                                                                                                                                                                                          |     |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                             |                                                                                                                                                                        |                                                                                                                                                                                                                                                                          |     |                                  | history of food allergy before 6 months of age                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Longer BF associated with higher risk of WA (note borderline significance)<br>BF at the time of cereal introduction (wheat, barley, rye, oats):<br>OR 2.0 (95% CI: 0.71–5.4)<br>No effect of BF at gluten introduction on WA<br>Cereal introduction. $\geq 7$ months vs. $< 6$ months:<br>OR 4.77 (95% CI: 1.33–17.09); adjOR 3.8 (1.18–12.28)<br>Late introduction of cereals associated with higher risk of WA (note broad confidence interval) |
| Reference                                                                   | Population                                                                                                                                                             | Intervention                                                                                                                                                                                                                                                             |     | Comparison                       | Outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Wong <i>et al.</i> <sup>17</sup><br>(conference abstract)                   | $n = 545$<br>Infants at risk of allergy ( $\geq$ first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases) <sup>†</sup> | Modified diet, life-style and environment with<br>• encouragement of BF (at least 4 months) and supplementation with a partially hydrolysed formula<br>• delayed introduction of solids ( $> 6$ months), avoidance of house dust mites, pet allergens, and tobacco smoke |     | No intervention                  | WS at 15 years:<br>OR 2.57 (95% CI: 0.26–24.94)<br>No effect of encouraging BF or delayed solids (as part of a multifaceted intervention) on WS at 15 years<br>BF vs. formula-fed: NS (data not given)<br>BF compared to formula feeding did not affect risk of WS at 15 years<br>WA at 3 years: 1/572 vs. 0/597 ( $P = 0.49$ )<br>No effect of early vs. late introduction of potentially allergenic foods on WA at 3 years<br>WS at 12 months: 7/550 vs. 19/601 ( $P = 0.03$ );<br>RR 0.4 (0.17–0.95);<br>WS at 36 months: 8/569 vs. 19/599 ( $P = 0.04$ );<br>RR 0.44 (0.2–1.00)<br>Early introduction lowered the risk of WS at 12 and 36 months |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Perkin <i>et al.</i> <sup>18</sup><br>EAT study (Enquiring About Tolerance) | $n = 1303$<br>exBF infants at population risk of allergy                                                                                                               | Early (3 months) introduction of six allergenic foods (cows milk, peanuts, cooked egg, sesame, whitefish and wheat)                                                                                                                                                      |     | Standard introduction (6 months) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

<sup>†</sup>Based on CAPPS study description: Chan-Young *et al.*<sup>20</sup> BF, breastfeeding; CAPPS, Canadian Asthma Primary Prevention Study; DAISY, Diabetes Autoimmunity Study in the Young; exBF, exclusively breastfeeding; HLA, human leukocyte antigen; NS, not significant; sigE, specific IgE; t1DM, type 1 diabetes mellitus; WA, wheat allergy; WS, wheat sensitisation.

presented in Table S5 (Supporting Information). They were both found to be of high quality in spite of the open-label design, which was due to the nature of intervention. High attrition in the study by Wong *et al.* was noted, but this is not unexpected in a study with a follow-up as long as 15 years.<sup>17</sup>

## Observational studies

The Finish DIPP (Type 1 Diabetes Prediction and Prevention) birth cohort included infants at risk of type 1 diabetes mellitus [Human leukocyte antigen (HLA)-conferred susceptibility].<sup>13</sup> Of these, 3781 children were invited to participate in the allergy study. Data on atopic sensitisation and dietary exposures were collected.

The study by Poole *et al.*<sup>14</sup> included 1612 children participating in the DAISY longitudinal birth cohort study (The Diabetes Autoimmunity Study in the Young, USA) investigating the natural history of islet autoimmunity in infants and children at risk of developing type 1 diabetes mellitus (defined by HLA status or having a first-degree relative with the condition).

The Slovenian cohort studied by Besednjak-Kocijancic consisted of 408 term infants with a positive history of parental allergy.<sup>15</sup> The conference proceeding for this study was identified. The results have not been published as a full paper; however, the author provided us with additional data.

The Food Allergy and Intolerance Research (FAIR) population-based cohort study included 969 infants in the UK who were followed up for allergy-related outcomes until the age of 10.<sup>16,19</sup> The outcomes of interest for this systematic review were identified as a conference abstract.<sup>16</sup>

The only case-control study included was performed in Thailand and included 47 infants with IgE-mediated wheat allergy and 188 controls.<sup>12</sup> A conference proceeding was only identified.

## Interventional studies

The study by Wong *et al.*<sup>17</sup> is a 15-year follow-up of The Canadian Asthma Primary Prevention Study (CAPPS).<sup>20</sup> It included 545 infants at risk of allergy and randomised them before birth into a multifaceted intervention (modified diet, life-style and environment); the latter part consisted of encouragement of breastfeeding for at least 4 months with partially hydrolysed formula supplementation when needed and the delayed introduction of solids until after 6 months of age. Only a conference proceeding was available for the results of the 15-years follow-up. Based on previous reports, rates of breastfeeding in the intervention and control groups were similar at birth (93% and 92%, respectively) and significantly higher in the intervention group at 8 months (61% vs. 50%,  $P = 0.02$ ). Significantly less children in the intervention group were given solid foods by the age of 4 months (19.5% vs. 49.8%,  $P < 0.001$ ).<sup>20</sup> According to the information provided by the authors of the previous reports (personal communication), total rates of children sensitised to wheat at follow-up were low (7/487 at 1 year, 3/474 at 2 years, 7/370 at 7 years and 4/325 at 15 years).

The Enquiring About Tolerance (EAT) study is a randomised open-label study in which 1303 breastfed infants from the general population were randomised to either early (3 months of

age) or standard (6 months) introduction of six potentially allergenic foods (cow's milk, cooked egg, whitefish, peanuts, sesame and wheat). Wheat in the experimental group was introduced last and not earlier than 4 months. The main outcome measure was a challenge-proven allergy to at least one food allergen at the age of 3.<sup>18</sup> There was one case of wheat allergy in the study.

A summary of the results is presented in Table 1.

## Breastfeeding

### Observational studies

A longer duration of breastfeeding was associated with wheat allergy in a case-control study (Sirivimonpan *et al.*)<sup>12</sup> and one of the cohort studies (Poole *et al.*;<sup>14</sup> borderline significance, Table 1). Similar findings for wheat sensitisation were reported by a large cohort study (Nwaru *et al.*)<sup>13</sup>; the risk was lower when duration of both breastfeeding and exclusive breastfeeding was shorter (Table 1). In contrast, Besednjak-Kocijancic<sup>15</sup> found that longer exclusive breastfeeding reduced rates of wheat sensitisation at 1 year but not at 5 years.

### Randomised controlled trials

Breastfeeding compared to formula feeding did not affect rates of wheat sensitisation at the age of 15.<sup>17</sup> As described above, in this trial (CAPPS study), breastfeeding encouragement was part of the intervention, and breastfeeding rates were higher in the intervention group at 8 months. However, it is not clear from the abstract if it was an intervention group versus control group comparison or if it was based on actual breastfeeding or formula feeding.

## Breastfeeding at the time of gluten introduction

### Observational studies

Two observational studies reported this outcome.<sup>14,16</sup> In both, breastfeeding at the time of gluten introduction had no effect on the risk of wheat allergy.

### Randomised controlled trials

None of the RCTs reported this outcome.

## Age of wheat/gluten introduction

### Observational studies

One study reported a higher risk of wheat allergy when gluten was introduced >7 months compared to earlier introduction (OR 4.77, 95% CI: 1.33–17.09).<sup>14</sup> Rates of wheat sensitisation measured at 5 years were lower if wheat/gluten was introduced early (Table 1).<sup>13</sup>

### Randomised controlled trials

The risk of wheat allergy at the age of 3 did not differ in children in whom potentially allergenic foods were introduced early (3 months) compared to standard introduction (6 months).<sup>18</sup> However, there was only one case of wheat allergy in the study (early introduction group), so drawing firm conclusions is not possible. In the same trial, early introduction of potentially allergenic foods resulted in lower rates of wheat sensitisation at 12 months (RR 0.4, 95% CI: 0.17–0.95) and at 36 months (RR 0.44, 95% CI: 0.2–1.0).<sup>18</sup> The timing of introduction of solids in general had no effect on the rates of wheat sensitisation at

15 years of age.<sup>17</sup> Of note, delaying the introduction of solid foods after 6 months of age was only one of the components of the multifaceted intervention in this study.

## Discussion

The main findings of our study suggest that neither breastfeeding at the time of wheat/gluten introduction nor the timing of wheat/gluten introduction into the infant's diet affect the risk of later wheat allergy. Limited data from observational studies suggest that longer duration of any breastfeeding and exclusive breastfeeding might be associated with an increased risk of wheat allergy and wheat sensitisation. Earlier introduction of wheat/gluten most likely lowers the risk of wheat sensitisation early in life, but it does not affect the risk of wheat allergy. These findings should be interpreted with caution as the number of included studies is low, the overall quality of evidence is low to moderate, and pooling data was not possible.

Allergy to wheat, with the estimated prevalence in children of 0.3–0.5%, is not as common as other food allergies.<sup>3,21</sup> Still, it is of major clinical importance. The associated risk of severe reactions, such as anaphylaxis and the restrictions imposed by an elimination diet, may have a negative effect on the quality of life of both patients and their families.<sup>22,23</sup> The primary prevention of food allergy has been of great research interest. Early feeding practices such as breastfeeding and potentially allergenic food introduction have been the main areas of focus.

Exclusive breastfeeding for at least 4–6 months is currently recommended for all infants.<sup>3</sup> However, there is no evidence of an association between breastfeeding and food allergies as shown by recent meta-analyses.<sup>24,25</sup> Our unexpected finding of an increased risk of wheat allergy in breastfed children might be explained by reverse causality as infants with an increased risk of food allergy may be breastfed longer in the hope of preventing the onset of allergy. This effect has been previously reported in the literature.<sup>26</sup>

With regards to the introduction of foods into an infant's diet, within the last 2 decades, there has been a shift from a 'better delay potentially allergenic foods' approach (American Academy of Pediatrics recommendation 2000)<sup>27</sup> to earlier introduction of solids, including potentially allergenic foods.<sup>3,4,28</sup> In this review, we found that early wheat/gluten introduction reduced rates of sensitisation early in life but not rates of wheat allergy at any time. This finding may be the consequence of the included studies being underpowered for the outcome of wheat allergy. Few subjects presented with the outcome in all of the studies. None of them were designed to look at wheat allergy as an individual outcome. The research is rather focused on the more common allergies. Results from observational studies suggest that early introduction of peanuts,<sup>29</sup> egg<sup>30</sup> or cows milk<sup>31</sup> may prevent allergy to these foods. Evidence from RCTs is mostly available for peanuts and eggs.<sup>32–34</sup> The Learning Early About Peanut Allergy (LEAP) study showed that early introduction of peanuts in high-risk infants reduced the risk of developing peanut allergy by 80% by 5 years of age.<sup>32</sup> With regards to egg, early (from 4 months of age) compared to late (from 8 months) exposure to egg powder in infants with eczema resulted in a lower (but not significant) proportion of infants given a diagnosis of IgE-mediated egg allergy.<sup>30</sup> However, such a protective effect was not shown in

breastfed infants at population risk, who were given six allergenic foods early (from 3 months) compared to standard introduction (from 6 months); the EAT study (included in this review) found no significant difference in rates of allergy to at least one allergen at 3 years of age.<sup>18</sup> This may suggest that the effect of early feeding interventions differs in children at high risk of allergy compared to those at population risk. However, authors of a recent meta-analysis found no clear difference in outcome among studies performed in populations at different risk levels (normal, high and very high).<sup>34</sup>

This systematic review has some strengths, the main one being the use of well-defined and widely recognised methodology developed by the Cochrane Collaboration. We attempted to reduce the risk of bias by applying an extensive comprehensive literature search, pre-specified criteria for methodological assessment, no restrictions by year and language of publication and efforts to identify unpublished trials.

There are, however, several important limitations to our study. Four of the seven included studies are conference proceedings. We approached all the authors by email but received limited feedback. Another very important limitation was that the numbers of subjects in whom outcomes of interest occurred were very low in all of the studies. This means that they were underpowered to draw conclusions on these outcomes. Unfortunately, we were not able to enlarge the power by means of performing a meta-analysis. Pooling results was not possible due to the heterogeneity of the included studies (observational studies and RCTs) and different definitions of outcomes used across the studies (e.g. exposure to wheat or all cereals in general, different time points of assessment). Another limitation was that only two RCTs were identified. Moreover, the intervention in one of them was of a complex nature, with breastfeeding promotion and recommendation to delay solid foods being some of the components. Thus, it was not possible to examine the effects of the timing of introduction of wheat or breastfeeding in this trial separately from other components of the intervention. Small number of RCTs in this review is an important limitation as a randomised trial is the methodology of choice to study the effects of treatment or prevention. The results of RCTs can be interpreted as causality, while observational studies report associations only. An example of the rejection of a hypothesis that had been based on results from observational studies was recently shown for gluten introduction and coeliac disease.<sup>35,36</sup>

## Conclusions

In summary, based on limited evidence mostly from observational studies, we can conclude that the influence of breastfeeding and early exposure to wheat/gluten on the subsequent development of wheat allergy remains uncertain. There is currently no evidence to support the role of breastfeeding at gluten introduction in modifying the risk of wheat allergy. Early introduction of wheat/gluten might reduce the risk of wheat sensitisation early in life but most likely does not affect the risk of wheat allergy. A longer duration of breastfeeding might be associated with higher rates of wheat allergy and wheat sensitisation, but this may be due to reverse causality.

More high-quality evidence is needed before any firm recommendation can be formulated. Trials randomising infants to different timings of wheat/gluten introduction would be the desired methodology. An important difficulty is that large sample sizes are required due to relatively low incidence of wheat allergy. This can be partly addressed by limiting study populations to at-risk children. Also, data from population-based and/or large cohort studies should be used to study the associations between early feeding practices and later risk of wheat allergy.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Fig. S1.** Flowchart of study identification process.

**Table S1.** Example of search strategies applied.

**Table S2.** Standardised spreadsheets used for data extraction.

**Table S3.** Excluded studies and reasons for exclusion.

**Table S4.** Assessment of methodology: observational studies, Newcastle-Ottawa Quality Assessment Scale.

**Table S5.** Assessment of methodology and potential risk of bias: randomised controlled studies.

# SYSTEMATIC REVIEW: EARLY INFANT FEEDING PRACTICES AND THE RISK OF WHEAT ALLERGY

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**Figure S1. Flowchart of study identification process**

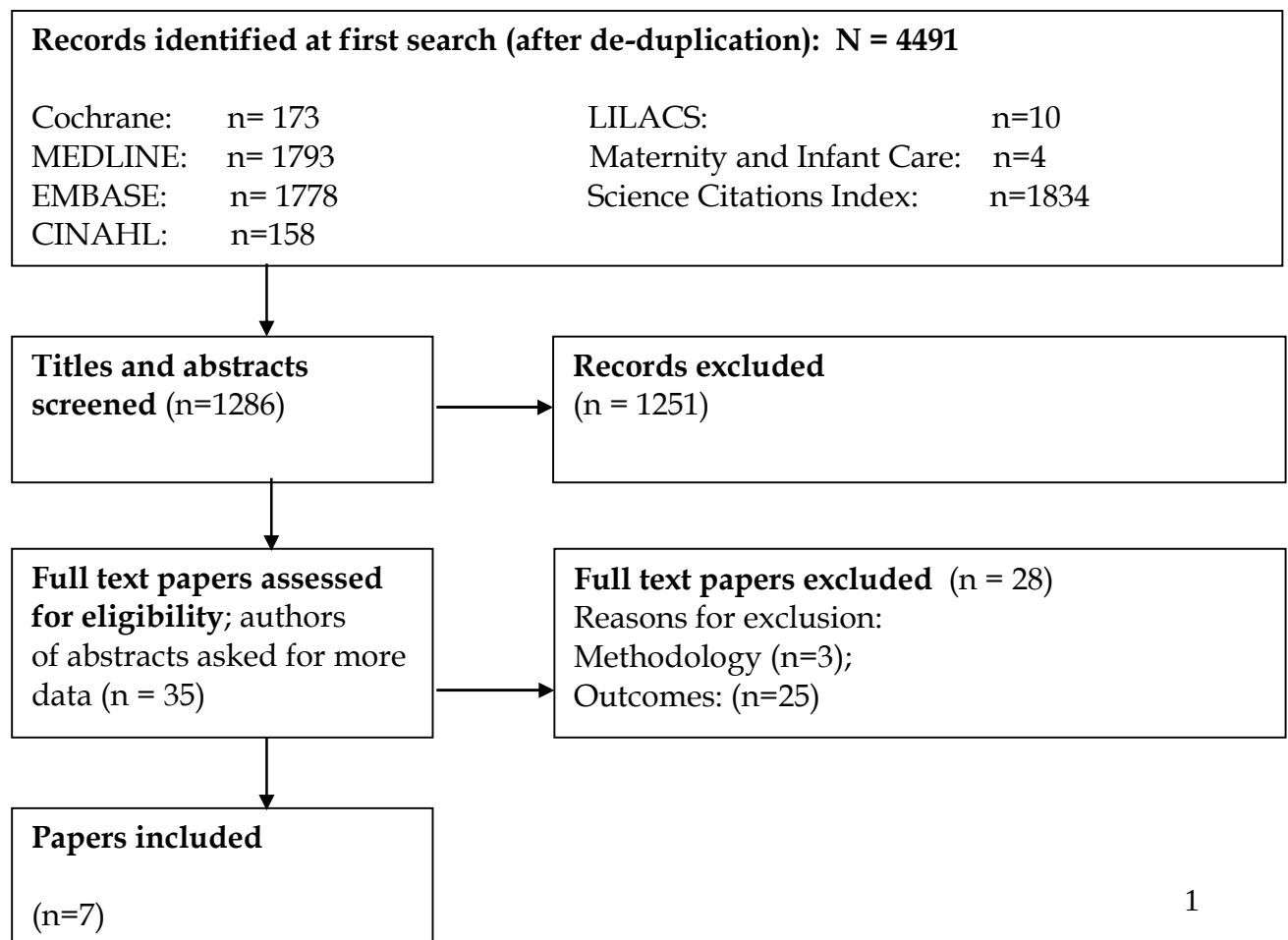


**Table S1. Examples of search strategy applied**

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**Embase <1974 to 2015 June 09> searched via OVID search date 10th June 2015, 937 records retrieved.**

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- 1 exp Breast Feeding/ (37751)
  - 2 (breastfeed\$ or breast-feed\$ or breastfed\$ or breast-fed\$).ti,ab. (36447)
  - 3 Lactation/ or Breast Milk/ (58533)
  - 4 (breastmilk\$ or lactat\$).ti,ab. (143408)
  - 5 1 or 2 or 3 or 4 (207255)
  - 6 Wheat Allergy/ (582)
  - 7 exp Cereal/ (65262)
  - 8 Gluten/ (6573)
  - 9 (wheat adj2 (hypersensitiv\$ or allerg\$)).ti,ab. (584)
  - 10 (cereal\$ adj2 (hypersensitiv\$ or allerg\$)).ti,ab. (102)
  - 11 (gluten\$ adj2 (hypersensitiv\$ or allerg\$)).ti,ab. (103)
  - 12 6 or 7 or 9 or 10 or 11 (65717)
  - 13 5 and 12 (1390)
  - 14 (mouse or mice or rat or rats or rabbit\$ or dog or dogs or cat or cats or cow or cows or cattle or bovine or sheep or ewe or ewes or ovine or goat or goats or horse or horses or pig or pigs or piglet\$ or ruminant\$ or ruminal\$).ti. (1911886)
  - 15 13 not 14 (937)
- 

**Medline: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search date 14<sup>th</sup> October 2015, 1793 records retrieved.**

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- 1 Hypersensitivity, Immediate/ (12037)
  - 2 Food Hypersensitivity/ (13182)
  - 3 Wheat Hypersensitivity/ (271)
  - 4 Allergens/ (33972)
  - 5 1 or 2 or 3 or 4 (52999)
  - 6 exp Infant Food/ (12294)
  - 7 exp Infant Nutritional Physiological Phenomena/ (45044)
  - 8 exp Cereals/ (80647)
  - 9 Triticum/ (21129)
  - 10 Diet/ (118607)
  - 11 wheat.ti,ab. (41213)
  - 12 glutens/ (5204)
  - 13 6 or 7 or 8 or 9 or 10 or 11 or 12 (266059)
  - 14 5 and 13 (3394)
  - 15 Cereals/ae [Adverse Effects] (347)
  - 16 14 or 15 (3656)
  - 17 infant/ (675159)
  - 18 (infant or infants or infancy or baby or babies).ti. (173336)
  - 19 child/ (1441648)
  - 20 (child or childhood or children or pediatric or paediatric).ti. (679539)
  - 21 17 or 18 or 19 or 20 (1946704)
  - 22 16 and 21 (1793)
-

**Table S2. Standardized spreadsheets used for data extraction: a) observational studies; b) interventional trials.**

**a.**

| Study ID (country) | Cases | Controls | Age | Exposure measurement | Confounding factors considered | Results |
|--------------------|-------|----------|-----|----------------------|--------------------------------|---------|
|                    |       |          |     |                      |                                |         |

**b.**

| Author /year | Randomisation | Allocation | Blinding | ITT | FU (n/N) | Patient characteristics | Intervention | Comparison | Length of follow up | Outcome measure | Effect size | P |
|--------------|---------------|------------|----------|-----|----------|-------------------------|--------------|------------|---------------------|-----------------|-------------|---|
|              |               |            |          |     |          |                         |              |            |                     |                 |             |   |

**Table S3. Excluded studies and reasons for exclusion**

| Reference                             | Reason for exclusion                                           |
|---------------------------------------|----------------------------------------------------------------|
| Astafyeva 2009 <sup>(1)</sup>         | Outcome of interest not reported                               |
| Armentia 2002 <sup>(2)</sup>          | Outcome of interest not reported                               |
| Banks 2012 <sup>(3)</sup>             | Outcome of interest not reported                               |
| Flohr 2011 <sup>(4)</sup>             | Outcome of interest not reported                               |
| Furuhjelm 2011 <sup>(5)</sup>         | Outcome of interest not reported                               |
| Fundora-Hernandez 2014 <sup>(6)</sup> | Outcome of interest not reported                               |
| Grandjean 2010 <sup>(7)</sup>         | Outcome of interest not reported                               |
| Hanson 1988 <sup>(8)</sup>            | Methodology: review                                            |
| Hanson 2003 <sup>(9)</sup>            | Outcome of interest not reported                               |
| Hofman 1998 <sup>(10)</sup>           | Outcome of interest not reported                               |
| Huang 2014 <sup>(11)</sup>            | Outcome of interest not reported                               |
| Kim 2009 <sup>(12)</sup>              | Outcome of interest not reported                               |
| Kull 2002 <sup>(13)</sup>             | Outcome of interest not reported                               |
| Lamb 2012 <sup>(14)</sup>             | Outcome of interest not reported                               |
| Logan 2011 <sup>(15)</sup>            | Methodology: study protocol, no results given                  |
| Luccioli 2014 <sup>(16)</sup>         | Outcome of interest not reported                               |
| Matheson 2007 <sup>(17)</sup>         | Outcome of interest not reported                               |
| McGowan 2013 <sup>(18)</sup>          | Methodology: comment on Nwaru 2013 <sup>(2)</sup>              |
| Miyake 2003 <sup>(19)</sup>           | Outcome of interest not reported                               |
| Nwaru 2013 <sup>(20)</sup>            | Outcome of interest not reported                               |
| Nwaru 2010 <sup>(21)</sup>            | Outcomes from the same population as Nwaru 2013 <sup>(2)</sup> |
| Perkin 2012 <sup>(22)</sup>           | Outcome of interest not reported                               |
| Pesonen 2006 <sup>(23)</sup>          | Outcome of interest not reported                               |
| Saarinen 1995 <sup>(24)</sup>         | Outcome of interest not reported                               |
| Saarinen 2000 <sup>(25)</sup>         | Outcome of interest not reported                               |
| Sears 2002 <sup>(26)</sup>            | Outcome of interest not reported                               |
| Snijders 2007 <sup>(27)</sup>         | Outcome of interest not reported                               |
| Stabell Benn 2004 <sup>(28)</sup>     | Outcome of interest not reported                               |

**Table S4. Assessment of methodology: observational studies, Newcastle-Ottawa Quality Assessment Scale**

| Quality Assessment Score                             |           |   |   |   |               |                      |   |   |  |
|------------------------------------------------------|-----------|---|---|---|---------------|----------------------|---|---|--|
| Study ID                                             | Selection |   |   |   | Comparability | Outcome/<br>Exposure |   |   |  |
| Case-control studies                                 |           |   |   |   |               |                      |   |   |  |
| Sirivimonpan 2014 <sup>(30)</sup> (abstract)         | ?         | ? | ★ | ? | ★             | ?                    | ? | ? |  |
| Cohort studies                                       |           |   |   |   |               |                      |   |   |  |
| Nwaru 2013 <sup>(31)</sup>                           | ★         | ★ | ★ | ★ | ★★            | ★                    | ★ | ★ |  |
| Poole 2006 <sup>(32)</sup>                           | ★         | ★ | ★ | ★ | ★             | ★                    | ★ | ★ |  |
| Besednjak-Kocijancic 2010 <sup>(33)</sup> (abstract) | ★         | ★ | ? | ★ | ?             | ★                    | ★ | ? |  |
| Venter 2010 <sup>(34)</sup> (abstract)               | ★         | ★ | ★ | ★ | ?             | ★                    | ★ | ? |  |

The Newcastle-Ottawa Scale (NOS)<sup>36</sup> is based on a 'star system'. Studies are judged on three domains: representativeness of study group selection (four items); comparability of groups (two items); and ascertainment of either the exposure or outcome (three items). This scale awards a maximum of four stars for the adequate selection of cases and controls, two stars for comparability of cases and controls on the basis of the design and analysis, and three stars for the adequate ascertainment of the exposure in both the case and control groups. Overall, the NOS scores vary between 0 and 9 (the highest level of quality). Question marks stand for 'no data given', mostly due to the fact that only abstracts were available.

**Table S5. Assessment of methodology and potential risk of bias: randomized controlled studies**

| Study ID                    | Sequence generation adequate | Allocation concealment adequate | Blinding of participants and personnel | Blinding of outcome assessors | Incomplete outcome data addressed | Selective outcome reporting | Other sources of bias |
|-----------------------------|------------------------------|---------------------------------|----------------------------------------|-------------------------------|-----------------------------------|-----------------------------|-----------------------|
| Wong 2012 <sup>(35)</sup>   | Yes                          | Yes                             | No                                     | No                            | Yes: 60% (at 15 ys)               | No                          | No                    |
| Perkin 2016 <sup>(36)</sup> | Yes                          | Unclear                         | No                                     | No                            | Yes: 91.3%                        | No                          | No                    |

\* Based on CAPPS study description: Chan-Yeung M et al. Arch Pediatr Adolesc Med. 2000;154:657-663.

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