



GERD AND FOOD ALLERGIES

H. JAVAHERIZADEH

PROF. OF PEDIATRIC GASTROENTEROLOGY AND HEPATOLOGY

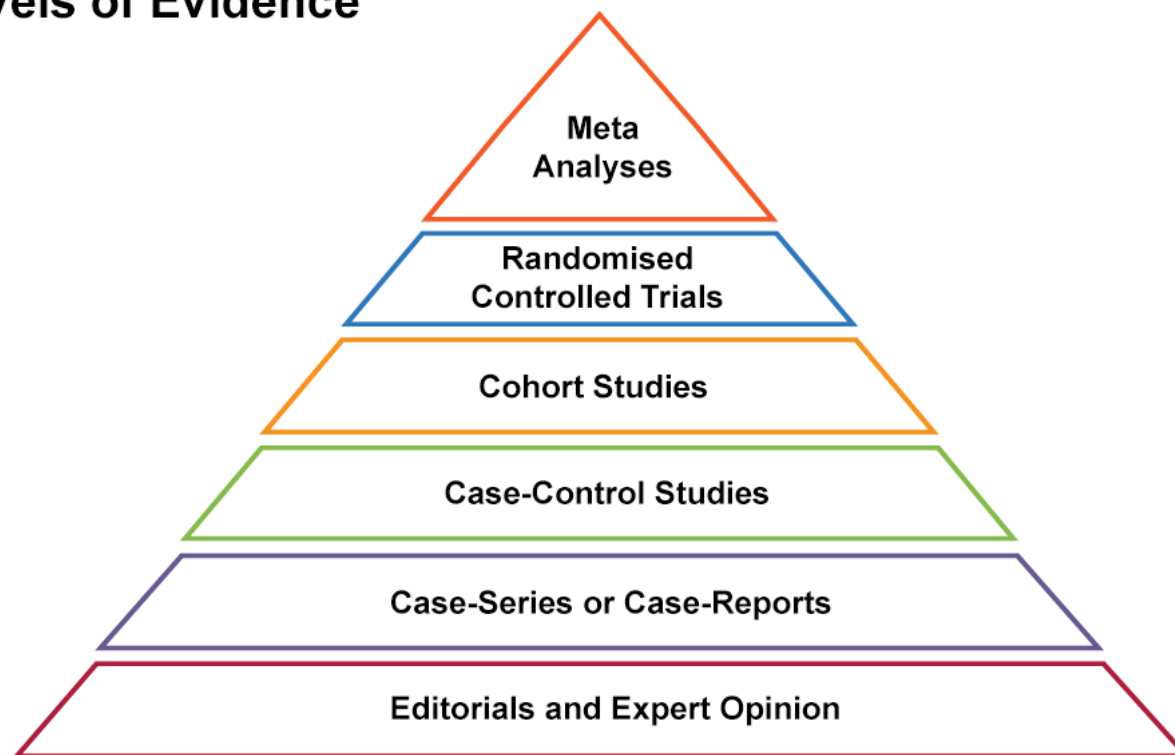
AHVAZ JUNDISHAPUR UNIVERSITY OF MEDICAL SCIENCES

TWO CARDINAL RULES OF EBM

- **Not all evidence is created equal.**
 - A hierarchy of evidence guides clinical decision-making.
- **Evidence alone is never enough.**
 - Competent physicians balance risks and benefits of management strategies in the context of patient values and preferences.

EVIDENCE BASED MEDICINE PYRAMID

Levels of Evidence



NOTICE

- Please note that most of the studies that are described below are observational studies.

FOOD ALLERGY SIGNS AND SYMPTOMS

FOOD ALLERGY SIGNS AND SYMPTOMS



ECZEMA



ABDOMINAL PAIN



SWELLING FACE



SWELLING TONGUE



SWELLING LIPS



NAUSEA OR VOMITING



TINGLING IN THE MOUTH



DIZZINESS



TROUBLE BREATHING



DIARRHEA

NOWAK-WEGRZYN, A., SZAJEWSKA, H. & LACK, G. FOOD ALLERGY AND THE GUT. NAT REV GASTROENTEROL HEPATOL 14, 241–257 (2017).

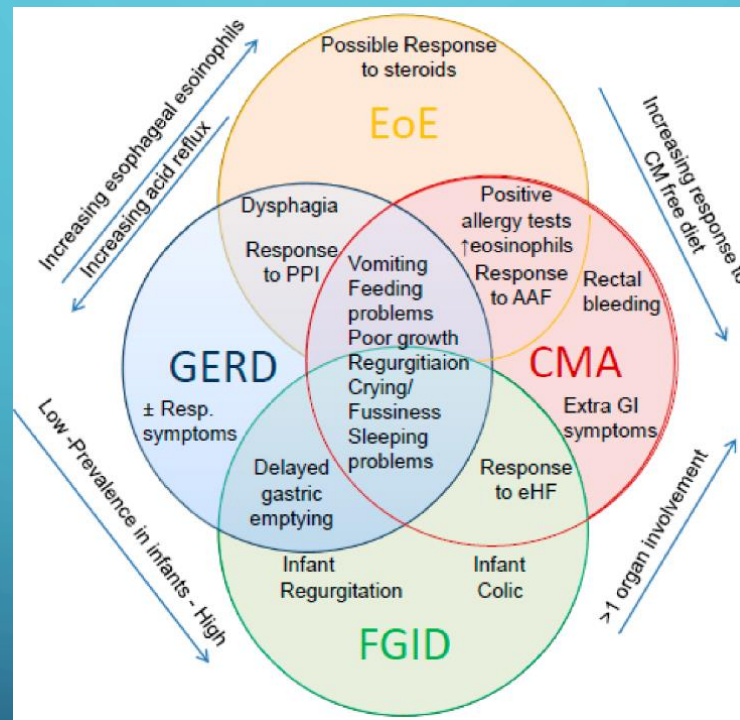
[HTTPS://DOI.ORG/10.1038/NRGASTRO.2016.187](https://doi.org/10.1038/NRGASTRO.2016.187)

- Gastrointestinal manifestations of food allergy include
 - Emesis,
 - Nausea,
 - Diarrhoea,
 - Abdominal pain,
 - Dysphagia, (GERD?)
 - Food impaction,
 - Protein-losing enteropathy
 - Failure to thrive.

RELATIONSHIP BETWEEN GERD AND FOOD ALLERGIES

- There is a recognized relationship between GERD (Gastroesophageal Reflux Disease) and food allergies, particularly in infants and children.
- Food proteins, especially cow's milk protein, can contribute to food allergy-associated GERD.
- However, distinguishing between GERD caused by food allergy and non-food allergy-related GERD can be difficult. The diagnosis often involves an elimination diet followed by reintroduction of the suspected allergen. Breastfeeding is recommended in such cases, and careful dietary management is essential to avoid nutritional deficiencies.

THE CHALLENGING CLINICAL OVERLAP AMONG FUNCTIONAL GASTROINTESTINAL DISORDER (FGID), GERD, CMA AND EOSINOPHILIC ESOPHAGITIS (EOE) IN INFANTS (MODIFIED FROM NIELSEN 2006)



GERD shares several overlapping symptoms with CMA, particularly gastrointestinal symptoms such as regurgitation, vomiting, and irritability. Both conditions can also present with failure to thrive in severe cases, complicating the diagnostic process.

CMA AND GERD: A PATHOGENIC TWIST

- GER and other persistent gastrointestinal symptoms in allergic patients are predominantly associated with cellular immune mechanisms and delayed reactions. In non-IgE mediated CMA, activated mast-cells, eosinophils and Th2 lymphocytes, release histamine, tryptase, IL-4, IL-5, IL-13, eotaxin and other chemokines that lead to increased permeability, epithelial dysfunction, inflammatory infiltration in the mucosal, submucosal and, in some cases, muscle layers and nociception [25,27,28,36].
- A migration of activated mast cells in proximity of enteric nervous system has been demonstrated in allergic children exposed to CM proteins and may determine gastrointestinal dysmotility and related symptoms [37].
- GER and regurgitation are commonly related to overfeeding, short length of the (intra-abdominal) esophagus, obtuse His angle, horizontal position of the infant. Inappropriate relaxations of the lower esophageal sphincter (LES), ineffective clearance and the impaired resistance of the esophageal mucosa contribute to GERD [34].
- Crying and pain in infants and children are determined by interplaying factors such as esophageal and gastrointestinal distension, dysmotility, visceral hyperalgesia, genetics, early life events, inflammatory and microbiota components, increased permeability, stress, parental and individual coping and perception [4,38,39].
- GER and CMA can coexist in the same patient and it has been reported that CMA can induce GER and also be a predisposing factor for gastrointestinal functional disorders [22,27]. Conversely, treatment with acid inhibitors for GERD increase the risk of allergy later in life [40,41].

CMA AND GERD: A PATHOGENIC TWIST

- Crying and pain in infants and children are determined by interplaying factors such as esophageal and gastrointestinal distension, dysmotility, visceral hyperalgesia, genetics, early life events, inflammatory and microbiota components, increased permeability, stress, parental and individual coping and perception [[4](#),[38](#),[39](#)].
- GER and CMA can coexist in the same patient and it has been reported that CMA can induce GER and also be a predisposing factor for gastrointestinal functional disorders [[22](#),[27](#)]. Conversely, treatment with acid inhibitors for GERD increase the risk of allergy later in life [[40](#),[41](#)].

DISTINGUISH BETWEEN GERD AND GERD ASSOCIATED CMPA

- Diagnostic tools such as pH monitoring for GERD or elimination diets for CMPA can help distinguish between the two conditions and guide appropriate management strategies

REFLUX SYMPTOMS AND FOOD ALLERGIES/SENSITIVITIES

- The link between CMA and GORD symptoms in infants is widely recognized in the literature, with 40% of infants referred for specialist management of GORD receiving a diagnosis of CMA³¹⁻³³ with IgE and/or non-IgE involvement.^{23, 34}
Reflux symptoms and food allergies/sensitivities
- Fiocchi A, Brozek J, Schünemann H, et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *Pediatr Allergy Immunol.* 2010; 21(Suppl. 21): 1-125.
- Ho MH-K, Wong WH-S, Chang C. Clinical spectrum of food allergies: a comprehensive review. *Clin Rev Allergy Immunol T.* 2014; 46(3): 225-240.

SEMIENIUK J, KACZMARSKI M. 24-HOUR ESOPHAGEAL PH-MONITORING IN CHILDREN SUSPECTED OF GASTROESOPHAGEAL REFLUX DISEASE: ANALYSIS OF INTRAESOPHAGEAL PH MONITORING VALUES RECORDED IN DISTAL AND PROXIMAL CHANNEL AT DIAGNOSIS. WORLD J GASTROENTEROL. 2007; 13(38): 5108-5115.

- Semeniuk and colleagues orchestrated a series of studies evaluating the relationship between CMA/food allergy and GORD in a group of 138 children diagnosed with acidic reflux.
- The authors observed that GORD secondary to food allergy does not respond to traditional reflux treatment in the same way as primary GORD and reflux symptoms are more diverse in those children with food allergy

CORRELATION BETWEEN GERD AND ALLERGY

A similar correlation between GORD and allergy was evident in a cross-sectional analysis of 1828 Taiwanese adolescents where GORD was significantly higher in asthmatics ($p < 0.0001$) and those with allergic conditions ($p < 0.0001$), particularly in relation to dairy produce.⁴¹

Chen J-H, Wang H-Y, Lin HH, et al. Prevalence and determinants of gastroesophageal reflux symptoms in adolescents. J Gastroenterol Hepatol. 2014; 29(2): 269-275.

FOOD ALLERGIES AND GERD

- Food allergies can cause or worsen GERD (Gastroesophageal Reflux Disease) symptoms.
- Certain food allergies, particularly to dairy or gluten, can trigger or exacerbate reflux symptoms by causing inflammation or allergic reactions in the esophagus. Allergies can increase mucus production and lead to postnasal drip, which irritates the esophagus and worsens acid reflux. Additionally, eosinophilic esophagitis (EoE), an allergic inflammation of the esophagus triggered by food allergies, can mimic or worsen GERD symptoms.
- In summary, food allergies do play a significant role in causing or worsening GERD symptoms, and recognizing this relationship is key for effective management.

There is an association between gastro-oesophageal reflux and cow's milk protein intolerance. doi: 10.1007/s11845-021-02757-2. Epub 2021 Sep 30.

- **Methods**

- A literature review was conducted via PubMed, Sciencedirect and Google scholar using search terms “gastro-oesophageal reflux” + “cow’s milk protein intolerance”. The inclusion criteria were studies from 1985 to present, studies involving infants and studies involving both GOR and CMPI. Exclusion criteria were studies not including infants, or studies involving GOR or CMPI independently.

- **Results**

- This review revealed varying degrees of co-existence of GOR and CMPI. Iacono et al., Farahmand et al., Kamer et al., and Semeniuk and Kaczmarek, displayed co-occurrence of GOR and CMPI in 41.8%, 33.3%, 46.5%, and 44.9% of infants respectively. In two separate studies by Cavataio et al., concomitance was apparent in 41.6% and 30% of infants. Others suggested a less significant link at 16–20%. Nielsen et al. found 18/42 children to have severe GORD, 10 of whom had CMPI in addition.

- **Conclusion**

- This review highlights an association between GOR and CMPI. CMPI should be considered, particularly in cases of reflux resistant to pharmacological therapy, as a co-existing or causative entity accounting for symptoms.

Table 1 The various gastrointestinal effects of cow's milk in humans

Items	Details
Cow's milk protein allergy	Pediatric onset: (1) IgE-mediated; (2) Non-IgE-mediated; and (3) Mixed type Adult onset: (1) Mostly IgE-mediated; and (2) Pregnancy-induced CMPA Pediatric onset with adulthood persistence
Lactose intolerance	Developmental Congenital (inherited) Primary (aging-induced) Secondary
Cow's milk-related functional gastrointestinal disorders	Functional dyspepsia Persistent regurgitation and gastroesophageal reflux Infant colic Functional constipation Irritable bowel syndrome
Cow's milk and inflammatory bowel diseases	Crohn's disease
Cow's milk-related gastrointestinal cancer	Anti-colorectal cancer
Milk-born gastrointestinal infections	<i>Mycobacterium avium</i> , <i>Mycobacterium bovis</i> , <i>Salmonella species</i> , brucellosis, streptococcal infections, "summer diarrhea", <i>Yersinia enterocolitica</i> , diphtheria, <i>Escherichia coli</i> (<i>E. coli</i>), <i>Campylobacter jejuni</i> , <i>Citrobacter species</i> , Shiga toxin-producing <i>E. coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Proteus mirabilis</i> , and <i>Klebsiella species</i>

CHARACTERIZATION OF UPPER GASTROINTESTINAL MOTILITY IN INFANTS WITH PERSISTENT DISTRESS AND NON-IGE-MEDIATED COW'S MILK PROTEIN ALLERGY

TAHER OMARI, JACINTA M. TOBIN, LISA MCCALL, KARINA SAVAGE, LARA FERRIS, PAUL HAMMOND, STAMATIKI KRITAS, PATRICK QUINN, RAMMY ABU-ASSI, DAVID MOORE, GEOFFREY DAVIDSON, MICHAEL GOLD, RALF G. HEINE

FIRST PUBLISHED: 01 APRIL 2020

• **Background: <https://doi.org/10.1097/MPG.0000000000002600>**

- Infants aged 2 to 26 weeks with persistent crying, GERD symptoms and possible CMPA were included. Symptoms were recorded by 48-hour cry-fuss chart and validated reflux questionnaire (infant GERD questionnaire [IGERDQ]). Infants underwent a blinded milk elimination-challenge sequence to diagnose CMPA. GERD parameters and mucosal integrity were assessed by 24-hour pH-impedance monitoring before and after cow's milk protein (CMP) elimination. ¹³C-octanoate breath testing for gastric emptying dynamics, dual-sugar intestinal permeability, fecal calprotectin, and serum vitamin D were also measured.
- Results:
- Fifty infants (mean age 13 ± 7 weeks; 27 boys) were enrolled. On the basis of CMP elimination-challenge outcomes, 14 (28%) were categorized as non-IgE-mediated CMPA, and 17 (34%) were not allergic to milk; 12 infants with equivocal findings, and 7 with incomplete data were excluded. There were no baseline differences in GERD parameters between infants with and without CMPA. In the CMPA group, CMP elimination resulted in a significant reduction in reflux symptoms, esophageal acid exposure (reflux index), acid clearance time, and an increase in esophageal mucosal impedance.
- Conclusions:
- In infants with persistent crying, upper gastrointestinal motility parameters did not reliably differentiate between non-IgE-mediated CMPA and functional GERD. In the group with non-IgE-mediated CMPA, elimination of CMP significantly improved GERD symptoms, esophageal peristaltic function, and mucosal integrity.

FOOD ALLERGY IN CHILDREN WITH REFRACTORY GASTROESOPHAGEAL REFLUX DISEASE

AYFER YUKSELEN, COSKUN CELTIK

FIRST PUBLISHED: 08 AUGUST 2015

[HTTPS://DOI.ORG/10.1111/PED.12779](https://doi.org/10.1111/ped.12779)

- **Abstract**
- **Methods**
- A total of 151 children resistant to pharmacologic GERD treatment underwent skin prick test, specific immunoglobulin E, eosinophil count, atopy patch test (APT), and oral food challenge, and were then divided into three groups according to the results of oral milk challenge and allergy work-up: group A1, positive oral milk challenge and positive IgE-mediated allergy test; group A2, positive milk challenge and negative IgE-mediated allergy test; and group B, negative oral milk challenge and negative allergy tests.
- **Results**
- There were 35, 30 and 86 patients in group A1, group A2 and group B, respectively. A total of 28 of 35 patients in group A1 had cow's milk allergy and the other seven patients had egg allergy. APT positivity was more common in group A2. Endoscopic esophagitis was observed in six group A1 patients and in four group A2 patients. Bloody stools, atopic dermatitis and recurrent wheezing episodes were significantly more common in group A1 than in group A2 and group B ($P < 0.001$, for both).
- **Conclusion**
- Cow's milk allergy was observed frequently in children resistant to pharmacologic GERD treatment. Combined skin prick and specific IgE tests, APT and oral food challenge is essential for avoidance of unnecessary elimination diet.

DEVELOPMENT OF FOOD ALLERGIES IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE TREATED WITH GASTRIC ACID SUPPRESSIVE MEDICATIONS

ANITA TRIKHA, JACQUES G. BAILLARGEON, YONG-FANG KUO, ALAI TAN, KAREN PIERSON, GULSHAN SHARMA, GREGG WILKINSON, RANA S. BONDS

FIRST PUBLISHED: 02 AUGUST 2013

[HTTPS://DOI.ORG/10.1111/PAI.12103](https://doi.org/10.1111/pai.12103)

- **Abstract**
- **Background**
- The prevalence of food allergy has steadily increased, especially in children. Reflux disease, a very common problem in children, is often treated with gastric acid suppressive (GAS) medications which may alter the processing of food allergens, thereby affecting oral mucosal tolerance.
- **Objective**
- The purpose of this study was to determine if use of GAS medications is associated with the occurrence of food allergies in children.
- **Methods**
- Using a large national commercial insurance database, we identified 4724 children aged 0–18 yrs who were diagnosed with Gastroesophageal Reflux Disease (GERD) and treated with GAS medications between January 1, 2008 and September 30, 2009. We then matched 4724 children with GERD not treated with GAS medications and 4724 children without GERD and not treated with GAS medications, at a 1:1 ratio, on age, gender and number of atopic risk factors. Patients were followed for 12 months.
- **Results**
- In comparison to the referent (children without GERD who received no GAS medications), children with GERD who were treated with GAS were more likely to be diagnosed with a food allergy (Hazard ratio (HR): 3.67, 95% CI 2.15–6.27), as were children with GERD diagnosis but who were not treated with GAS medications (HR: 2.15, 95% CI: 1.21–3.81). A direct comparison of the two GERD cohorts showed that children with GERD who were treated with GAS had a greater risk of food allergy than those with GERD who were untreated (HR, 1.68, 95%CI, 1.15–2.46).
- **Conclusion**
- Treatment with GAS medications is associated with the occurrence of food allergy, an effect not apparently related to a diagnosis of GERD alone.

NIELSEN ET AL.

- Nielsen *et al.* identified a GERD–cow milk hypersensitivity association in 10 of 17 patients with severe GERD using strict criteria for both GERD and food hypersensitivity.

Nielsen RG, Bindslev-Jensen C, Kruse-Andersen S, Husby S. Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: Disease association and evaluation of a new challenge procedure. *J. Pediatr. Gastroenterol. Nutr.* 2004; **39**: 383–91.

- Iacono *et al.* reported that food allergy was diagnosed in 41.8% of children with pathological gastroesophageal reflux.
- Iacono G, Carroccio A, Cavataio F *et al.* Gastroesophageal reflux and cow's milk allergy in infants: A prospective study. *J. Allergy Clin. Immunol.* 1996; **97**: 822–7.

- Janiszewska and Czerwionka-Szaflarska studied a large group of children aged 1–16 years with diagnosed acidic gastroesophageal reflux based on 24 h esophageal pH-metry, and in 48% of cases found IgE-dependent food allergy
- Janiszewska T, Czerwionka-Szaflarska M. IgE-dependent allergy: An intensifying factor of gastroesophageal reflux in children and adolescents. *Med. Wieku Rozwoj.* 2003; **7**: 211–22.

REFLUX SYMPTOMS AND FOOD ALLERGIES/SENSITIVITIES

- The link between CMA and GORD symptoms in infants is widely recognized in the literature, with 40% of infants referred for specialist management of GORD receiving a diagnosis of CMA³¹⁻³³ with IgE and/or non-IgE involvement.^{23, 34}
Reflux symptoms and food allergies/sensitivities
- Fiocchi A, Brozek J, Schünemann H, et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *Pediatr Allergy Immunol.* 2010; 21(Suppl. 21): 1-125.
- Ho MH-K, Wong WH-S, Chang C. Clinical spectrum of food allergies: a comprehensive review. *Clin Rev Allergy Immunol T.* 2014; 46(3): 225-240.

SEMENIUK J, KACZMARSKI M. 24-HOUR ESOPHAGEAL PH-MONITORING IN CHILDREN SUSPECTED OF GASTROESOPHAGEAL REFLUX DISEASE: ANALYSIS OF INTRAESOPHAGEAL PH MONITORING VALUES RECORDED IN DISTAL AND PROXIMAL CHANNEL AT DIAGNOSIS. **WORLD J GASTROENTEROL. 2007; 13(38): 5108-5115.**

- Semeniuk and colleagues orchestrated a series of studies evaluating the relationship between CMA/food allergy and GORD in a group of 138 children diagnosed with acidic reflux. The authors observed that GORD secondary to food allergy does not respond to traditional reflux treatment in the same way as primary GORD and reflux symptoms are more diverse in those children with food allergy

GASTROESOPHAGEAL REFLUX AND COW MILK ALLERGY: IS THERE A LINK

- Gastroesophageal reflux (GER) and cow milk allergy (CMA) occur frequently in infants younger than 1 year. In recent years, the relation between these 2 entities has been investigated and some important conclusions have been reached: in up to half of the cases of GER in infants younger than 1 year, there may be an association with CMA. In a high proportion of cases, GER is not only CMA associated but also CMA induced. The frequency of this association should induce pediatricians to screen for possible concomitant CMA in all infants who have GER and are younger than 1 year. With the exception of some patients with mild typical CMA manifestations (diarrhea, dermatitis, or rhinitis), the symptoms of GER associated with CMA are the same as those observed in primary GER. Immunologic tests and esophageal pH monitoring (with a typical pH pattern characterized by a progressive, slow decrease in esophageal pH between feedings) may be helpful if an association between GER and CMA is suspected, although the clinical response to an elimination diet and challenge is the only clue to the diagnosis. This article reviews the main features of GER and CMA, focusing on the aspects in common and the discrepancies between both conditions.

PREVALENCE AND DETERMINANTS OF GASTROESOPHAGEAL REFLUX SYMPTOMS IN ADOLESCENTS

- Multivariate logistic regression analyses showed that the cumulative prevalences of GERD symptoms were significantly correlated with bi-ethnicities, cigarette smoking, and symptoms of asthma and food allergy.
- An increased prevalence of GERD symptoms in subjects who had food-related allergic symptoms was observed in the present study.
- Chen, H., Wang, Y., Lin, H. H., Wang, C., & Wang, Y. (2014). Prevalence and determinants of gastroesophageal reflux symptoms in adolescents. *Journal of Gastroenterology and Hepatology*, 29(2), 269-275. <https://doi.org/10.1111/jgh.12330>

CONCLUSION

- As mentioned above, there is correlation between GERD and food allergy, but systematic review and meta analysis study should be carried out for better elucidation.

