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The International Digestive Experts Articles Journal is a peer-reviewed journal on prevention, diagnosis and management of gastrointestinal disorders. The journal is primarily intended for the update of gastroenterologists, hepatologists, and all medical doctors focusing their practice on digestive pathologies.

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Tables can be included in the main manuscript file, before Bibliography.

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Editorial

Updates on Literature

In this third number of *The IDEA Journal 2022*, four new studies from the gastroenterology literature are discussed.

In one editorial contribution, Antonelli and Hassan comment an interesting work addressing the *protopathic bias* in pharmacological studies. This bias refers to a systematic error that affects observational studies and that occurs when a drug is prescribed for an early manifestation of a disease that has not yet been diagnostically detected through clinical examination, but that then appears to be the cause of the disease when it is eventually diagnosed. The study showed that after applying a lag-time to define Proton Pump Inhibitors exposure periods, this drug was no longer associated with adverse outcomes − all-cause mortality, cancer mortality (both total and cancer-specific), cardiovascular mortality, respiratory and digestive diseases − in patients undergoing this treatment.

In another editorial contribution, Bredenoord discusses a recent study that evaluated the so-called *Crohn's disease exclusion diet* in adult patients with active Crohn's disease. The results showed that this diet, which excludes products with known pro-inflammatory effects on the intestinal mucosa, proved to be an effective therapy in inducing clinical remission also via reduced levels of calprotectin. These findings are encouraging, especially considering that adults with this disease, as compared with children, find more difficult to adhere to the enteral nutrition. Further and better controlled trials are nevertheless warranted.

To stay on the subject, the third editorial contribution is a comment on a recent study investigating the relation between *food neophobia*, bitter taste genotype, and gut-brain hormones. Food neophobia is rather common in children and those with food neophobia were found, in the study in object, to be more often hypersensitive to the bitter taste than those in the control group. However, no link between the development of food neophobia and the bitter taste genotype was found. At the same time, food neophobia did correlate positively with the level of the neuropeptide Y, while the body mass index correlated negatively with the neuropeptide Y and positively with leptin. These results heighten attention toward programmes aiming at improving children nutrition by focusing on the determinants of eating habits development, like behavioural strategies and exposure in the environment.

In the fourth editorial contribution, Bredenoord discusses another article, this time investigating the effectiveness of *gastric per-oral endoscopic myotomy* in severe gastroparesis. Treatment success, measured 6 months after treatment and defined as a reduction of at least half in symptoms as compared to before treatment, was achieved in a significantly larger number of patients undergoing the experimental procedure as compared to those undergoing a sham treatment, and this effect was even larger in patients with diabetic gastroparesis. The overall impression is that this invasive and irreversible treatment will likely become a viable option if medical and dietary treatments have failed.

The Editorial Board

Proton Pump Inhibitors: friends or foe?

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Comment to: Lo, C. H., Ni, P., Yan, Y., Ma, W., Joshi, A. D., Nguyen, L. H., Mehta, R. S., Lochhead, P., Song, M., Curhan, G. C., Cao, Y., & Chan, A. T. (2022). Association of Proton Pump Inhibitor Use With All-Cause and Cause-Specific Mortality. Gastroenterology. https://doi.org/10.1053/j.gastro.2022.06.067

Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs worldwide (1). Since their inception, more then 30 years ago, they have revolutionised treatment of once life-threatening conditions such as gastrointestinal acute bleeding, pre-cancerous esophageal conditions and many more. However, many concerns about overuse of PPIs have been growing in the last years (2). In a report summarizing prescription drug use in Canada, pantoprazole was the fifth most common drug prescribed, with more than 11 million prescriptions dispensed in 2012 and similar numbers have been shown in the US and in Europe (3). Most common indications such as gastroesophageal reflux disease (GERD) require short-term treatment (i.e. up to 4-8 weeks), however, the chronic use of these drugs is common, with studies showing a lack of documented ongoing indication for between 40% and 65% of hospitalized patients in the United States and Australia, and between 40% and 55% of primary care patients in the United States and the United Kingdom (4). PPIs are often viewed as safe and well tolerated medications, and while the incidence of side effects might be small, older people might be at higher risk of these conditions. Described side effects of PPIs include diarrhea, impaired B12 absorption, hypomagnesemia, Clostridium difficile infection, osteoporosis and impaired calcium/vitamin D absorption, and pneumonia. When PPIs are inappropriately prescribed or used for too long, they can contribute to polypharmacy with its consequent risks on elderly patients' health. In addition, the economic implication of public spending of PPIs must be considered. Only in Canada, a yearly expenditure of 250 million US dollars was calculated (3). In recent years, conflicting evidence has linked PPIs use to a general increase in all-cause mortality as well as mortality from specific health conditions, although some studies were specific to certain health conditions (5). It is still unclear if PPIs use represents a health threat in the unselected general population. In this study recently published in Gastroenterology, authors have tried to shed

Protopathic bias occurs when a medication is prescribed for an early manifestation of a disease and later appears to cause the disease when it is eventually diagnosed. The use of **proton pump inhibitors** (PPIs) has been associated with a possible increased risk of death. However, upon implementing lag times of up to 6 years, the association was attenuated and no longer significant. Thus, this study does not support positive associations between PPIs use and mortality risks, highlighting the importance of accounting for protopathic bias.

some light on this dilemma. The most interesting addition to previous studies was the inclusion of the calculation of protopathic bias, namely a kind of bias, common in pharmacoepidemiologic studies, occurring when a specific medication prescribed for early symptoms of a certain disease seems to subsequently cause the disease itself upon later diagnosis (see in-depth Box 1). PPIs are commonly prescribed for a number of upper gastrointestinal symptoms in patients with various comorbidities that are likely to ultimately cause death. The authors of this paper employed the use of lag times in the calculation of PPIs exposure, excluding the theoretical increased use of PPIs caused by comorbid conditions in the final stages of disease (Figure 1). In addition, they extracted data from two large prospectively collected databases containing detailed information on medication use, lifestyle habits and comorbidities with a long term follow up, guaranteeing high quality and informative observations.

The final cohort included more than 70,000 patients for more than 300,000 person years of follow-up. PPIs users were more likely to harbour serious medical conditions. When compared to non-users of PPIs, PPIs users were found to be at significantly increased risk of all-cause mortality as well as to cause specific mortality like cancer death, cardiovascular death, and many others. However, when applying lag times to PPIs use, the association with all-cause mortality, cancer mortality (both total and cancer-specific), cardiovascular mortality, respiratory and digestive diseases became non-significant. The only statistically significant association was found with renal diseases, that appeared to be increased by more than 2-fold. Interestingly, this was the only association that appeared to increase in time rather than the opposite. Although the cohort was apparently lacking reliable data on kidney diseases, this is not the first evidence linking PPIs use to renal conditions and warrants further research in this specific topic of interest.

This study adds to existing evidence from a high quality randomised controlled trial (6) and various observational trials in affirming that PPIs use is not associated with an increase in mortality from

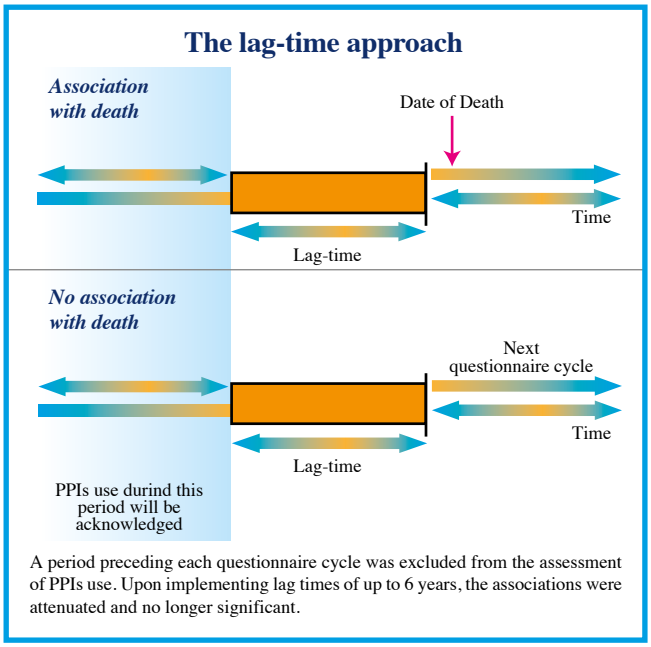

Figure 1

any cause, except renal diseases. Interestingly, the strongest associations with mortality were found in patients using PPIs for less than 2 years, with hazard ratios constantly reducing at the increase in the time length of PPIs use. This was especially observed in cancer- and cardiovascular-related mortality, both conditions in which PPIs are used both to reduce symptom burden and to prevent gastroduodenal ulcers due to chronic nonsteroidal anti-inflammatory drugs (NSAIDs) use. Another strength of this study was to adopt H2Ra-users as an active comparator, finding similar associations with PPIs users, and similar "nulling" effect of lag time applications, further reducing the class-specific concerns on PPIs.

In conclusion, with the exception of renal conditions, the use of PPIs was not found to be associated with adverse outcomes in a large prospectively collected cohort of unselected patients, reducing the concerns on this drug class. However, PPIs remain one of the most inappropriately prescribed drugs in the world, demanding specific attention especially in elderly, frail, and comorbid patients. As concluded also by the authors, it remains important to evaluate PPIs indication, terminate therapy when recommended, and deprescribe them when inappropriate.

The protopathic bias is a systematic error that affects observational studies and that occurs when the outcome is associated with an exposure that results, in fact, from early signs and symptoms of the outcome under study. In pharmacoepidemiological studies, this bias can occur when a drug is prescribed for an early manifestation of a disease that has not yet been diagnostically detected through clinical examination (i.e., a disease with a latent onset as compared with its early signs), but that then appears to be the cause of the disease when it is eventually diagnosed. To control for this bias, some researchers have introduced in their study design the approach of lag-time to define drug exposure periods. To adopt this approach, it is necessary to exclude from the exposure assessment a specific time period before the date of the diagnosis, so that any increase in drug use during the excluded period, which could be due to early symptoms of the disease in the subclinical phase, will not be considered in the quantification of the exposure, and thus, protopathic bias would be avoided (7).

Box 1. The protopathic bias

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Treatment of adults with Crohn's disease with a diet instead of medication

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Comment to: Effectiveness of Crohn's Disease Exclusion Diet for Induction of Remission in Crohn's Disease Adult Patients. Szczubełek M, Pomorska K, Korólczyk-Kowalczyk M, Lewandowski K, Kaniewska M, Rydzewska G. Nutrients. 2021 Nov 17;13(11):4112.

In the presence of Crohn's disease, the adherence to dietary treatment is more challenging for adults than it is for children. The Crohn's disease exclusion diet was developed in order to avoid products with known pro-inflammatory effect on the intestinal mucosa. The results of this pilot study suggest that this is an effective therapy for inducing remission in the adult patients.

The pathophysiology of Crohn's disease is not fully understood, and it is likely that environmental, genetic and immune factors all play a role (see in-depth Box 1) (1). The importance of diet and the role of the microbiome has received much attention in lately. Dietary factors can modulate the microbiome and play a role in mucosal permeability changes. The microbiome itself plays a role in the regulation of mucosal immunity and integrity and it can be affected by changes in dietary components as well as medication such as antibiotics and systemic host factors.

In children, exclusive enteral nutrition is the first line treatment for new-onset mild to moderate Crohn's disease. This formula is based on a protein combination that covers 100% of daily caloric intake, usually delivered through a feeding tube. The efficacy is impressive; up to 80% of children with mild to moderate Crohn's disease will get into remission, which is similar to the efficacy of corticosteroids while much less side effects are seen (2).

There is less enthusiasm for the use of exclusive enteral nutrition for the treatment of Crohn's disease in adults. It is less studied in this population and some studies have shown disappointing results due to poor adherence to the diet, poor motivation, lack of support, costs, and an unpalatable formula. However, there are also reports describing that the results of exclusive enteral nutrition were similar to corticosteroids in adults that were compliant and completed the diet. It seems that the adherence to dietary treatment is more challenging for adults than it is for children: apparently, many adults are not able to use exclusive enteral nutrition for several weeks. It probably helps to include regular food products in the diet, to make it more diverse. However, it has been shown that partial enteral nutrition, combing enteral nutrition with free diet, is ineffective in inducing remission in Crohn's disease with an efficacy of only 15%, while this was 42% in exclusive enteral nutrition. It is likely that the consumption of dietary factors with a negative effect on the intestines, not the enteral nutrition itself, is responsible for whether mucosal healing occurs or not. With this in mind, the Crohn's disease exclusion diet (CDED) was developed (3). The CDED was developed in order to avoid products with known pro-inflammatory effect on the intestinal

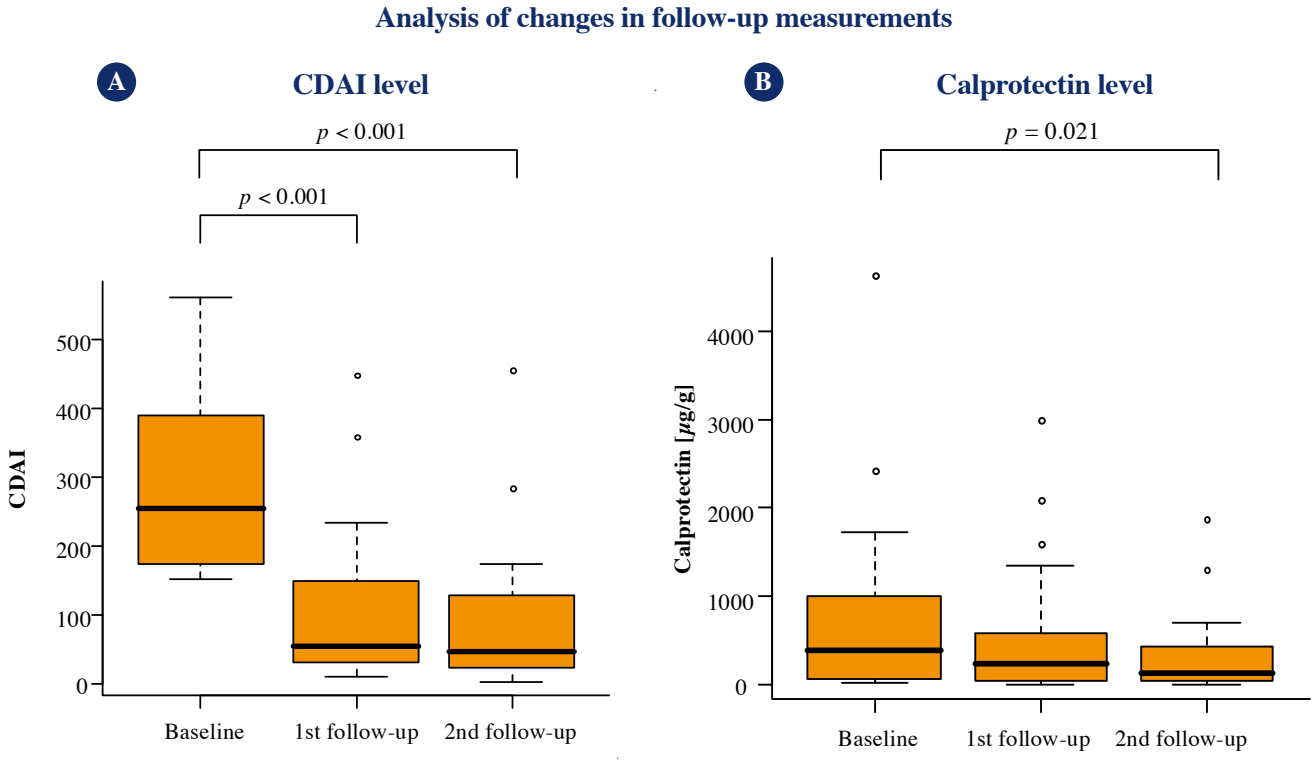

Figure 1

mucosa. A prospective cohort of 47 children followed the CDED diet for 12 weeks, which resulted in a response in 78.7% of the participants, and 70.6% of the patients went into remission.

These positive results prompted Szczubelek and colleagues to evaluate the effectiveness of CDED for inducing remission in adult patients with active Crohn's disease.

The authors describe the results of a group of 32 adult patients with active Crohn's disease who were treated for 12 weeks according to the principles of the CDED. The patients were seen at baseline, at week 6, and at week 12 of the study.

The results were encouraging, with clinical remission obtained (defined as Crohn's Disease Activity Index CDAI > 450) in 76.7% of patients after 6 weeks and in 82.1% after 12 weeks of dietary therapy. Calprotectin levels were significantly lower in the second follow-up compared with baseline. A clinical response, defined as a reduction in the CDAI level of more than 100, was noted in 83.3% of the patients after 6 weeks and in 85.7% after 12 weeks of treatment. The severity type of Crohn's disease was almost reduced during the trial; at baseline 46.9% had moderate disease, compared to 10.0% with moderate disease after 6 weeks of dietary treatment and 3.6% after 12 weeks.

The results of this study thus suggest that the CDED is an effective therapy for inducing remission in the adult patients with Crohn's disease as well. However, there are several methodological shortcomings that will need to be considered. The open-label, uncontrolled design of the study is less suitable for a disease characterized by spontaneous remissions and flares like Crohn's disease. This is particularly important given the fact that the most objective endpoint in Crohn's disease, mucosal healing as assessed with endoscopy, was not measured. This makes highly likely that a considerable sham-effect was present.

Before recommendation of this dietary approach to patients with Crohn's disease in clinical practice, a randomized controlled trial is warranted.

Crohn's disease is a relapsing inflammatory disease, mainly affecting the gastrointestinal tract. Patients frequently present with abdominal pain, fever, and clinical signs of bowel obstruction or diarrhoea with passage of blood or mucus, or both (1).

Baumgart and Sandborn (2012) recommend to adhere to the following **key points** when caring for a patient with Crohn's disease:

- Do a careful work-up considering important differential diagnoses
- Establish the complete disease phenotype including extraintestinal symptoms
- Screen for predictors and biomarkers of a complicated disease course
- Individualise therapeutic guideline recommendations to your patient
- Consider involving an inflammatory bowel disease expert for optimum treatment choice
- Educate and counsel your patient about disease and therapy associated risks and complications
- Enrol your patient in surveillance programmes and follow-up the patient closely

Box 1.

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The relation between food neophobia, bitter taste genotype, and gut-brain hormones

Written by the Editorial Secretariat

Comment to: Wiernicka, A., Piwczynska, K., Mika-Stepkowska, P., Kazimierska, D., Socha, P., & Rybak, A. (2022). Impact of the Gut-Brain Hormonal Axis and Enteric Peptides in the Development of Food Neophobia in Children with Genetically Determined Hypersensitivity to the Bitter Taste. Gastrointestinal Disorders, 4(4), 237–248. https://doi.org/10.3390/gidisord4040023

Food neophobia is characterized by the reluctance to consume or the unwillingness to try unknown foods (i.e. avoidance of new foods), and it is often observed in children (1). While this behaviour can have evolutionary drives, nowadays it brings negative consequences like unbalanced diet and lack of nutrients and energy. Many factors are deemed to influence the development of food neophobia in children, among which can be mentioned the parents' control and pressure on children's eating habits, the food sensory aspects, and the innate preference for sweet and savoury flavours (1) (see the in-depth Box 1). On the other hand, the bitter taste perception is genetically determined but is also developed with time and with repeated exposures to the individual foods. Specifically, it differs due to the haplotypes generated by three polymorphisms in the region of the gene encoding TAS2R83 receptor (2), which is a member of the bitter taste receptors family and is associated with the sensitivity to taste phenyltiocarbamide (PTC) and 6-propylthiouracil (6-PROP). Thus, subjects can be divided into tasters (with strong perception of bitter taste) and non-tasters (with weak or no reaction to PTC or 6-PROP). Moreover, two most common haplotypes of the gene are the recessive AVI and the dominant PAV. Interestingly, people with the particular combination of haplotypes AVI/PAV are more likely to change sensitivity to 6-PROP bitterness over time (i.e. gradual decrease in bitterness sensitivity) (3). Increased sensitivity to 6-PROP has been associated with the lower acceptance of green vegetables in children and adults (4), and taste sensitivity to 6-PROP has been related to higher body mass index (BMI) in children (5). Since subjects with different taste sensitivities may present different responses to the same nutrient, they may also present different metabolic hormone secretions. Thus, the neurohormones linked to the gut-brain axis might be involved in the process.

Food neophobia is rather common in children. The present study investigated the role of genetic predisposition as well as the role of gut-brain hormones on its development.

The study in object aimed at determining the role of the gut-brain hormonal axis and the effects of the enteric peptides, as well as the role of the genetically determined sensitivity to the bitter taste on the development of food neophobia in children and its potential association with nutritional status. Over the span of 2 years, n = 114 healthy children were enrolled in the study, including 50 subjects aged 6–8 months (prospective group), 43 subjects aged 18–36 months with diagnosed food neophobia

(food neophobia group), and 21 children aged 18–36 months (control group) (see supplemental Figure 1). Children were assigned to the food neophobia group or to the control group based on the 8-item Child Food Neophobia Scale (CFNS) score, which measures the degree of food neophobia or avoidance of new food as estimated by parents ($p < 0.001$). Gastrointestinal and metabolic diseases were the exclusion criteria for both control and neophobia groups. The study had two parts: the first part was performed on the food neophobia group and on the age-matched control group; the second part involved the prospective assessment of the infants in the prospective group at 6–8 months of age with a follow-up investigation at 18–36 months of age. All participants were assessed via the CFNS, underwent an oral 6-PROP test, a buccal swab for bitter-taste genotyping, anthropometric measurements, were tested for serum levels of leptin, adiponectin, insulin-like growth factor-1 (IGF-1), ghrelin and neuropeptide Y (NPY), and had a complete blood count (CBC). Measurements were taken from a blood sample after 4 h fasting.

Overall, the most frequent diplotypes among all subjects (from both parts of the study) were heterozygous AVI (40.2%) and homozygous PAV (36.6%). **Comparing the food neophobia group and the control group, subjects in the first group resulted to be more often hypersensitive to the**

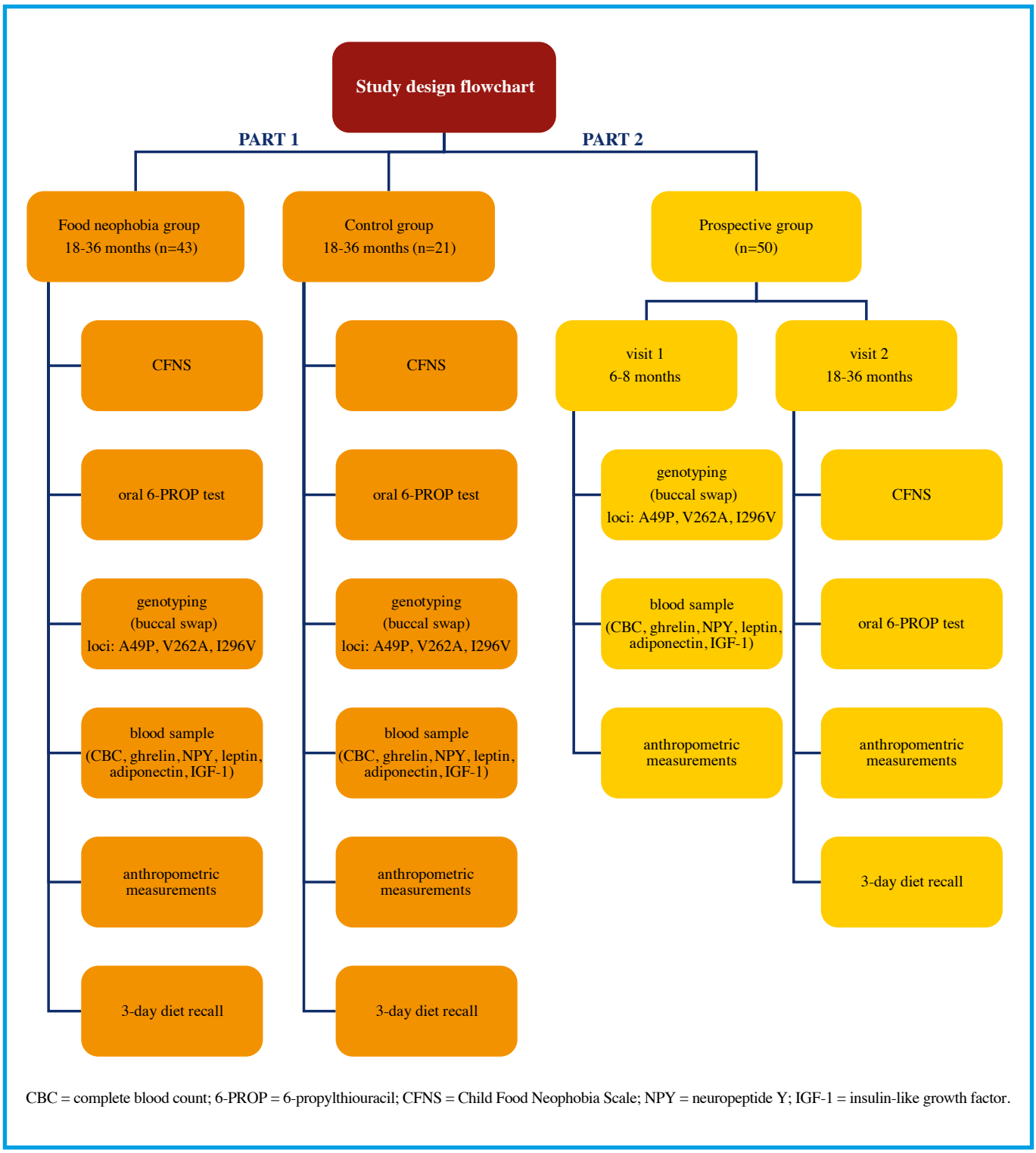
PART 1 OF THE STUDY			
		CFNS	BMI
Adiponectin	r Pearson's	0.12	0.10
	Relevance	0.364	0.430
NPY	r Pearson's	0.28	-0.28
	Relevance	0.030	0.030
IGF-1	r Pearson's	0.02	0.17
	Relevance	0.870	0.190
Ghrelin	r Pearson's	0.21	0.02
	Relevance	0.097	0.875
Leptin	rho Spearman	-0.03	0.28
	Relevance	0.809	0.027

PART 2 OF THE STUDY				
		CFNS	BMI	
			Visit 1 Age of 6-8 Months	Visit 2 Age of 18-36 Months
Adiponectin	r Pearson's	-0.06	-0.08	0.33
	Relevance	0.760	0.600	0.073
NPY	r Pearson's	-0.16	-0.11	0.00
	Relevance	0.387	0.443	0.994
IGF-1	r Pearson's	-015	-0.04	-0.07
	Relevance	0.420	0.787	0.683
Ghrelin	r Pearson's	0.00	0.02	0.06
	Relevance	0.991	0.902	0.737
Leptin	r Pearson's	-0.09	0.19	0.23
	Relevance	0.622	0.188	0.204

CFNS = Child Food Neophobia Scale, BMI = body mass index, NPY = Neuropeptide Y, IGF-1 = Insulin-like growth factor.

Table 1. Correlation between the serum level of the gut-brain hormones and enteric peptides with CFNS score and BMI (percentile) in participants from the first part of the study and in participants from the second part of the study.

bitter taste (i.e. 6-PROP tasters) than subjects in the latter group ($p < 0.001$). However, no significant difference emerged between the two groups in terms of overall genotype ($p = 0.919$). Concerning enteral hormones, in all participants from the first part of the study, **food neophobia correlated positively with the level of NPY, while the BMI correlated negatively with NPY and positively with leptin** (Table 1). The two groups' diplotypes did not differ in terms of gut-brain hormones and enteric peptides serum levels. In the respondents of the prospective groups, in the second part of the study, correlations



CBC = complete blood count; 6-PROP = 6-propylthiouracil; CFNS = Child Food Neophobia Scale; NPY = neuropeptide Y; IGF-1 = insulin-like growth factor.

Supplementary Figure 1

between the severity of neophobia (based on CFNS scores), BMI, level of gut-brain hormones, and enteric peptides were not significant (Table 1). Considering subjects altogether, no gender or anthropometric differences in the prevalence of food neophobia in children aged 18–36 months emerged. Moreover, no correlation between genetic measures and the CFNS score or BMI at the age of 18–36 months was found. Finally, no correlation between 6-PROP perception and genotype emerged, and no significant difference was found between the groups PAV+ and PAV- in bitter taste perception to a 6-PROP.

Overall, this study showed that **while hypersensitivity to bitter taste plays a role in the development of food neophobia, there is no link between 6-PRO perception and genotype**. Although this study has the limitation of a small sample size, the results are reasonable considering that there are many other, direct and indirect (e.g. the mother's diet during lactation) factors that can influence children development of food neophobia. The impact of good nutrition early in life can indeed reach far into the future. Thus, programmes aiming at improving children nutrition should focus on the determinants of eating habits development like behavioural strategies and exposure in the environment. Due to their selective diet, children with neophobia may be at risk of malnutrition and, in light of their elevated serum NPY levels (which has functions that are closely related to appetite regulation and obesity formation), as documented by this study, these children should be checked regularly in order to monitor their nutritional status at an older age. Moreover, the authors of the study in object suggest that the food choices of children with food neophobia may be directed toward a higher carbohydrate intake, which may increase the risk of being overweight or obese in the future, thus heightening attention.

A 2020 systematic review revealed that the prevalence of food neophobia in children ranged from 12.8 to 100% (i.e. moderate to high) (1). This aversion, from an evolutionary perspective, can minimize risks of eating foods that can be harmful to health but it can also cause food monotony, resulting in nutritional deficiencies. The authors pointed out that food should not be seen as a basic need only, but also as a source of pleasure, socialization, and cultural transmission (1). These aspects influence indeed the formation of eating habits and its consequences on health, which mostly originate in childhood, and the family plays a crucial role. In the papers included in this systematic review, food neophobia was assessed via several scales and samples were retrieved from school environment, home environment, and pediatric outpatient clinics. The following were the main factors associated with this condition: parental influence on eating habits, children's innate preference for sweet and savory flavours, influence of food sensory aspect, parents' behaviour during mealtime (i.e. pressure for the child to eat; lack of encouragement and/or affection), diets with low availability of/variety and low nutritional quality, childhood anxiety, little time to prepare the meals, mothers' food neophobia, lack of exposure to new foods, preference for foods rich in fat and/or sugar, parents' difficulty in interpreting signs of hunger and satiety, child's lack of autonomy in eating, negative reactions to new stimuli, family residing in rural areas, mothers' low education level (1). The authors recommended to offer a varied diet, also including foods that are not part of the family eating habits, to give children autonomy in their feeding habits, to emotionally support them, in addition to motivating them to participate in the preparation of meals, making the moment pleasant and affectionate (1).

Box 1.

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Gastric Per-Oral Endoscopic Myotomy (G-POEM) of endoscopic pylorotomy for gastroparesis

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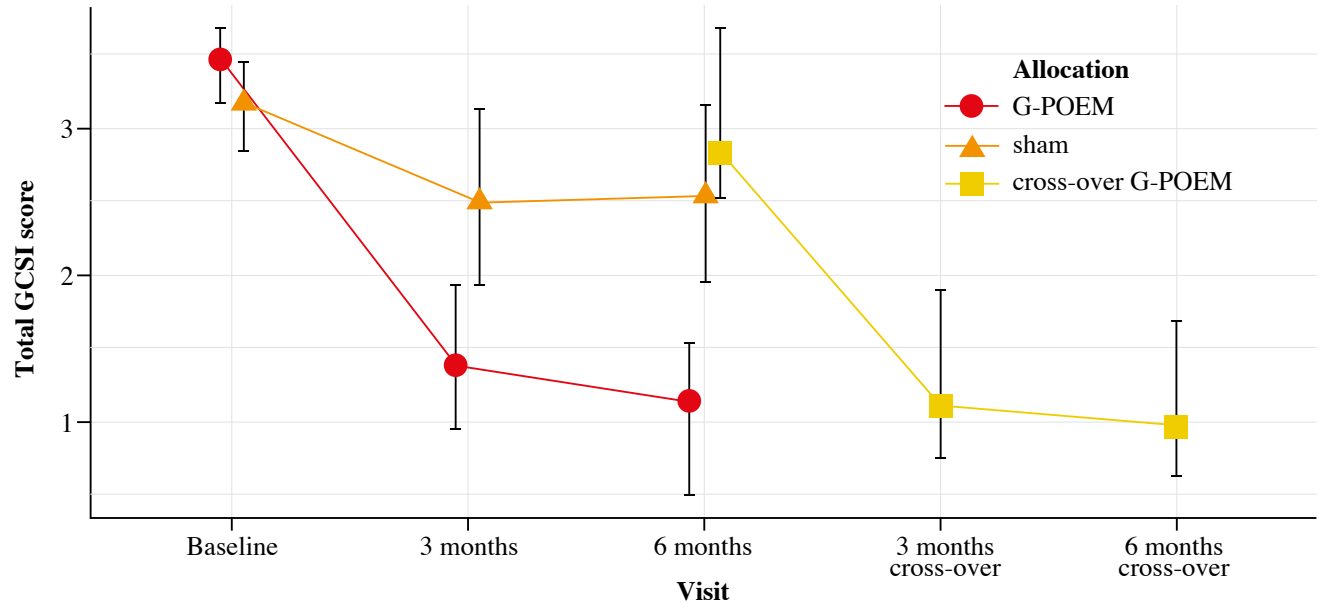
The function of the stomach is storage of ingested foods, with slowly dosed passage to the small bowel through the pylorus, so that nutrients are gradually offered to the duodenum and not overcome the capacity of the small bowel to absorb these. Gastric acid has an antimicrobial role and play a first step in digestion of nutrients. Ingested foods and fluids are stored in the gastric fundus and the antrum grinds solid foods until only small particles remain, which can move through the pylorus after relaxation. The driving force behind emptying of liquids is the pressure difference between stomach and duodenum. The relaxation of the pylorus is thus one of the factors that play a role in normal gastric function allowing passage of nutrients.

In gastroparesis, the normal emptying process of the stomach is disturbed to such a degree that it causes symptoms such as early satiation, vomiting after eating, nausea, weight loss and abdominal pain. In the American clinical practice and scientific literature, the presence of these symptoms is sufficient to make a diagnosis of gastroparesis, in the absence of another explanation for these symptoms such as a gastric cancer. In Europe, there needs to be objective evidence of delayed gastric emptying to such a degree it can cause these symptoms. The underlying thinking is that this differentiates gastroparesis from functional dyspepsia. Gastric emptying can be measured via scintigraphically marked test meals, with breath testing using carbon isotopes and with less known techniques such as 3D ultrasound.

In **gastroparesis**, the normal emptying process of the stomach is disturbed to such a degree that it causes symptoms such as early satiation, vomiting after eating, nausea, weight loss and abdominal pain. In this study patients with severe gastroparesis were randomized to undergo either **gastric per-oral endoscopic myotomy** or sham procedure to prove the treatment effectiveness.

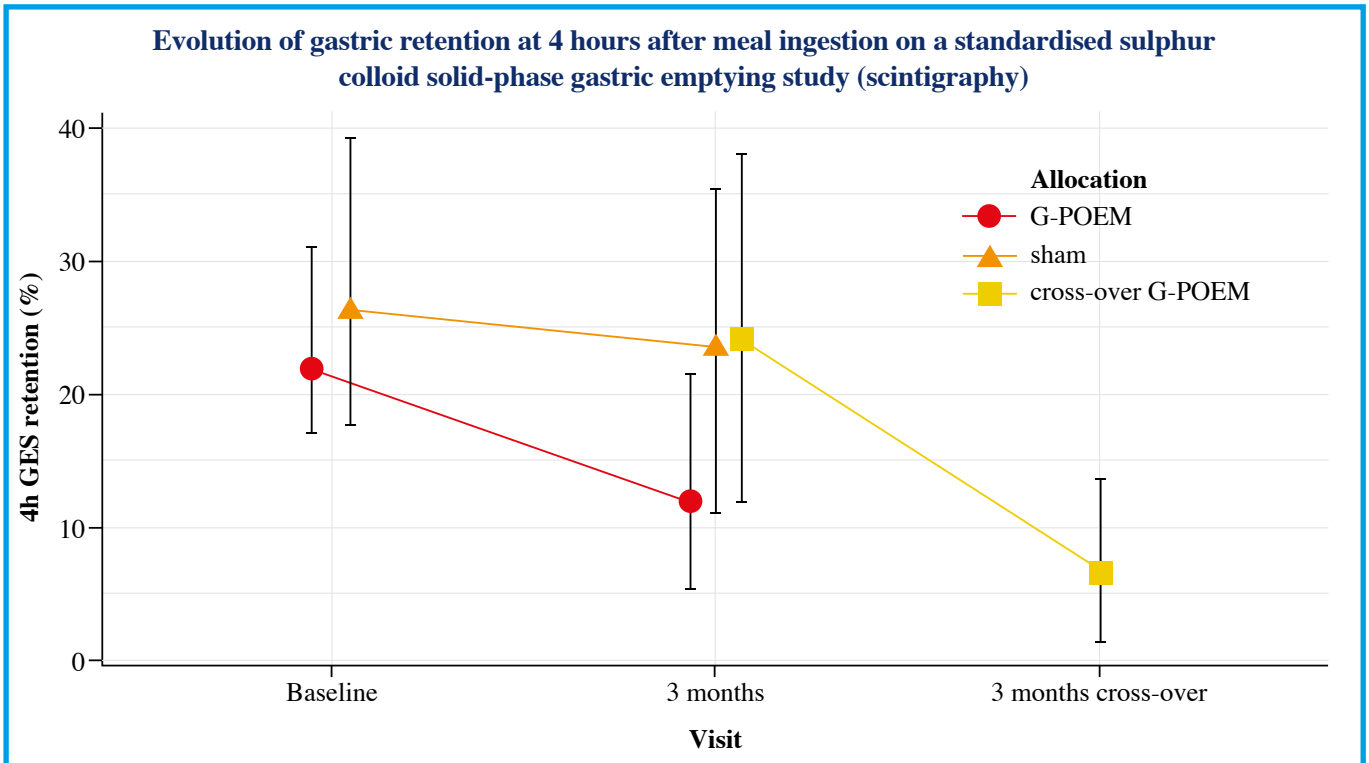
The treatment of gastroparesis is aimed at increasing gastric emptying rate and improving nutritional state. Gastric emptying can be stimulated using promotility agents such as domperidon, metoclopramide, prucalopride and erythromycin. When these agents fail to have an effect, few options remain. Botox injections in the pyloric sphincter have been explored, with the idea of relaxing a spastic sphincter, but the results were disappointing (1).

With the successes of high efficacy and low complication rates of per-oral endoscopic myotomy (POEM) of the lower esophageal sphincter in achalasia, the idea grows that perhaps a similar technique targeting the pyloric sphincter could be used for gastropareses treatment (2). So-called gastric-POEM (G-POEM) of endoscopic pylorotomy was described in case series as successful and equally safe as esophageal-POEM (3). However, high quality evidence in the form of a randomized controlled trial including a proper control



Point estimates of medians with 95% CIs calculated on the intention to treat (ITT) population are shown for patients after the endoscopic pyloromyotomy (G-POEM) procedure (red circles, N=21), sham procedure (orange triangles, N=20, imputed 1 value (5%) for 3 months and 1 value (5%) for 6 months), and cross-over G-POEM procedure (yellow squares, N=12). For the cross-over G-POEM group, the value at 6 months reflects only the data for the patients in this group (who subsequently underwent the cross-over G-POEM procedure). The GCSI score may range from 0 (no symptoms) to 5 (maximally severe symptoms).

Figure 1



Point estimates of medians with 95% CIs are shown for patients after the G-POEM procedure (red circles, N=21, imputed 2 values (10%) for 3 months), sham procedure (orange triangles, N=20, imputed 1 value (5%) for 3 months), and cross-over GPOEM procedure (yellow squares, N=12). For the cross-over G-POEM group, the value at 3 months reflects only the data for the patients in this group (who subsequently underwent the cross-over G-POEM procedure). GES, gastric emptying study; G-POEM, endoscopic pyloromyotomy.

Supplementary Figure 1

arm, objective measurements, and long term follow up was lacking. This is why the recently study published by Martinek and colleague is so important.

In this study patients with gastroparesis documented on gastric emptying studies were randomized to undergo either G-POEM or sham procedure. Treatment success 6 months after treatment, defined as a 50% or larger reduction in symptoms, was seen in 71% of the patients treated with G-POEM and in 22% in the patients undergoing the sham treatment (Figure 1). Median gastric retention at 4 hours after intake of a test meal decreased from 22% to 12% after G-POEM and did not change after sham: 26% versus 24% (see supplemental Figure 1). Twelve patients crossed over 6 months after sham treatment to G-POEM with 9 of them (75%) achieving treatment success. Due to clear differences between groups at interim analysis, the Data and Safety Monitoring Board stopped recruitment after the first 41 patients of the originally planned sample of 86 patients. Although the change in gastric emptying rate is not as impressive as the symptomatic improvement, the conclusion is that in severe gastroparesis, G-POEM is superior to a sham procedure. Subgroup analysis showed that the effect was most pronounced for those patients with diabetic gastroparesis.

For idiopathic and post-surgical gastroparesis larger studies seem to be required to see if the effects of G-POEM are persuading as well for these patients.

The consequences of this study are that G-POEM will likely be a new option for the treatment of patients with severe gastroparesis. The position of this invasive and irreversible treatment will likely be if medical and dietary treatments have failed.

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