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Dietary composition of adult eosinophilic esophagitis patients is related to disease severity

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Abstract

Background: In addition to the elimination diet, dietary composition may influence disease severity in patients with eosinophilic esophagitis (EoE) through modulation of the immune response.

Aim: To explore the immunomodulatory role of nutrition before and during elimination diet in adult EoE patients.

Methods: Nutritional intake was assessed in 39 Dutch adult EoE patients participating in the Supplemental Elemental Trial (Dutch trial registry NL6014, NTR6778) using 3-day food diaries. In this randomized controlled trial, diagnosed patients received either a four-food elimination diet alone (FFED) or FFED with addition of an amino acid-based formula for 6 weeks. Multiple linear regression analyses were performed to assess associations between the intake of nutrients and food groups per 1000 kCal and peak eosinophil count/high power field (PEC), both at baseline and after 6 weeks.

Results: At baseline, we found a statistically significant negative (thus favorable) relationship between the intake of protein, total fat, phosphorus, zinc, vitamin B12, folate, and milk products and PEC ($p < .05$), while calcium ($p = .058$) and full-fat cheese/curd ($p = .056$) were borderline (favorably) significant. In contrast, total carbohydrates, prepacked fruit juice, and white bread were significantly positively (unfavorable) related to PEC ($p < .05$), while ultra-processed meals ($p = .059$) were borderline (unfavorably) significant. After dietary intervention, coffee/tea were significantly negatively (favorably) related to PEC, hummus/legumes were significantly positively (unfavorably) related with PEC, while peanuts were borderline significantly positively related ($p = .058$).

Clinical Trial Registration: The trial was prospectively registered in the Dutch trial registry NL6014 (NTR6778).

Conclusion: Dietary composition may be related to inflammation in adult EoE patients. High-quality and anti-inflammatory diets may be a promising adjuvant therapy in the dietary management of EoE.

KEYWORDS
anti-inflammatory diet, disease severity, eosinophilic esophagitis, foods, immunomodulation, inflammation, nutrients

1 | INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease characterized by inflammation of the esophagus, food impaction, and dysphagia.[1,2] During the last two decades, the incidence and prevalence of EoE in adults have increased significantly, especially in the Western countries.[3–5] Currently, worldwide, an estimate of 50–100 cases/100,000 citizens are diagnosed with this allergic disease.[4] To date, there is no explanation for the rapid increase of prevalence of EoE over the past two decades.

Diagnosis of EoE is confirmed if an esophageal biopsy contains at least 15 eosinophils per "High Power Field" (HPF),[6–9] indicating esophageal inflammation. Although the disease pathology of EoE is complex, food allergens seem to have a causative role. The avoidance diet is one of the major therapeutic options in EoE.[1,2] Typically, two-food elimination diets (dairy and gluten/wheat), four-food elimination diets (FFED) (cow's milk, gluten/wheat, eggs, and soy or legumes), or six-food elimination diets (cow's milk, gluten/wheat, eggs, soy, peanuts/nuts, and fish/shellfish) are applied.[6,7,9–12] Alternatively, amino acid-based diets, that is, liquid formulas based on amino acids, are most effective in achieving disease remission. However, poor taste and lack of solid food intake make adherence to elemental diets challenging.[8,9,12,13]

As EoE is a chronic disease, symptoms and inflammation recur if management is discontinued. It has been shown that the exclusion of food allergens from the diet induces histological and clinical remission in patients, while the introduction of food allergens after remission leads to rapid disease relapse.[11] Thus, EoE patients who achieve histologic remission are subject to long-term maintenance dietary elimination therapy. Consequently, the impact on quality of life is significant due to the required efforts to adhere to dietary constraints, limited food choice and the psycho-sociological consequences. Hence, long-term adherence to maintenance diet therapy is difficult and lower than expected.[14] Therefore, adjuvant management options to support and alleviate dietary maintenance therapy are urgently needed.

Ample evidence has accumulated in recent years for the immunomodulatory effects of foods and nutrients.[15,16] The European Food Safety Authority has recognized the immunomodulatory effects of the following nutrients: proteins, iron, selenium, copper, zinc, and vitamins (A, B6, B12, C, D, folate).[17] Moreover, long-chain polyunsaturated fatty acids (LCPUFAs) are known for their immune-modulatory properties. These fatty acids serve as specific precursors of immune regulatory eicosanoids.[18] Additionally, dietary components, for instance, vitamin A, iron, dietary fibers, and zinc, have shown to have a local effect on both the mucosal integrity, as well as on the mucosal cells of the gastrointestinal tract.[19–27] Furthermore, nutritional intake of plant-based and animal-based proteins, fruits and vegetables, dietary fibers, fat, LCPUFAs, and polyphenols influence the gut microbiota composition,[28–32] which may indirectly influence the inflammatory response. Finally, due to epigenetic effects, nutrients may alter gene expression together with disease susceptibility.[33]

We hypothesized that through immunomodulatory effects, the nutritional composition of the diet (other than elimination) may play an important role in the pathology of EoE. If that is true, a healthful high-quality diet with anti-inflammatory properties could be applied as adjuvant therapy to support management and disease control during the maintenance phase of EoE.

Studies investigating EoE patients' habitual dietary intake and its link to disease severity are scarce. To the best of our knowledge, only one previous study by our group examined the relationship between the habitual diet and esophagus inflammation in a small adult EoE study population, showing promising results.[34] Results indicated a statistically significant negative (and thus favorable) relationship between the intake of dietary fiber, soy, rice/pasta and iron, and eosinophil count, whereas the intake of phosphorus was significantly positively (and thus unfavorably) associated to eosinophil count. In addition, we showed that the composition of the habitual diet of adult EoE patients had several proinflammatory and thus unfavorable immunomodulatory properties, just as the general Dutch population, however, EoE patients had lower overall diet quality scores than the general population.[35]

Based on these results, we performed this exploratory study aimed to evaluate associations between the nutritional intake and disease severity in another adult patient population to gain more insights into the possible aggregating and protecting effects of nutrients and food groups involved in the pathophysiology of EoE.

2 | METHODS

2.1 | Study design and study population

Nutritional intake was assessed in 39 out of 40 Dutch adult EoE patients participating in the single-center, open-label, randomized controlled Supplemental Elemental Trial (Dutch trial registry NL6014, NTR6778) between December 2017 and March 2020. Adult patients were eligible for enrollment if EoE was diagnosed according to the consensus guidelines, defined as having symptoms of esophageal dysfunction (Straumann Dysphagia Instrument score of ≥1) and ≥15 eosinophils per microscopic HPF on baseline biopsy.[1] Exclusion criteria included severe comorbidities, the use of systemic corticosteroids, leukotriene inhibitors, monoclonal antibodies, or anticoagulants in the month preceding the study, and the inability to stop the use of topical corticosteroids. Further details of inclusion and exclusion criteria can be found elsewhere.[36] After confirming patients' eligibility and obtaining written informed consent for study participation, the patients were randomized to receive either a standard FFED, excluding cow's milk, eggs, soy, and gluten, or FFED with the addition of an amino acid-based formula (Neocate Junior) (FFED + AAF) providing 30% of the calory needs for 6 weeks.[36] At baseline and after 6 weeks of dietary intervention, histological disease activity (peak eosinophil count/HPF (PEC)) was measured by histological examination and dietary intake was assessed. The study was approved by the Amsterdam University Medical Center Institutional Review Board.

2.2 | Outcome parameters

2.2.1 | Histological disease activity

An esophagogastroduodenoscopy (EGD) was performed at baseline and after 6 weeks of dietary intervention to assess PEC.[36] All endoscopic images were scored according to the Endoscopic Reference Score by a single-blinded gastroenterologist with expertise in EoE.[36,37]

2.2.2 | Nutritional intake assessment

At baseline and after 6 weeks of dietary intervention, patients' habitual diet and nutritional intake during FFED or FFED + AAF were assessed using a 3-day food diary. In addition, in order not to miss any information on infrequently consumed nutrients and foods, patients' intake of docosahexaenoic acid, eicosapentaenoic acid, and fish was assessed by means of a Food Frequency Questionnaire.[38] Patients were asked to record amounts of foods used in grams or household portion sizes, as well as to record types and brand names of foods consumed in detail. Portion sizes were coded using Compl-eat software (Wageningen University, Human Nutrition WUR).[39] Patients also recorded the type and use of dietary supplements (yes/no/infrequently). The food diaries were reviewed by an allergy specialist dietitian with experience in EoE using a checklist for completeness. Patients were contacted in case of unclear or missing data. This was done promptly to minimize the length of the recall period and reduce the risk of recall bias. The average nutrient intake of the 3-day diaries (without supplements) was calculated using the Dutch NEVO-online Food Composition Database[40] and Compl-eat software[39] for energy (kCal) and 41 nutrients. All foods consumed were allocated to one of the 23 main food groups, 83 subgroups at level 1 or 19 subgroups at level 2 adapted from Compl-eat (Supporting Information S2: Table 1).

2.2.3 | Dietary advice

All patients received dietary advice from the dietitian regarding the FFED or FFED + AAF. The dietitian recommended that the diet met the Dutch dietary guidelines as set by the Dutch National Health Council[41] with adequate replacement of cow's milk by AAF or plant-based milk replacers supplemented with calcium, vitamin B2, and D. Information on individualized sample menus, brands, label reading, and recipes was provided to the patients. During the 6-week intervention period, patients were monitored twice by the dietitian to evaluate diet compliance, adverse effects, and body weight maintenance.

2.2.4 | Statistical analyses

All nutritional intake data were calculated per 1000 kCal per day, to correct for differences between patients in energy intake. The Wilcoxon test was used to compare the intake of nutrients and food groups at baseline and

the intake after the 6-week intervention period. Subsequently, data were checked for model assumptions of normality, linearity, and homoscedasticity of residuals. In case of nonlinearity, a log-transformation was used. Multivariate linear regression analyses were performed to investigate the relationships between the intake of nutrients and food groups per 1000 kCal and PEC, both at baseline and after 6 weeks. Gender and age were included as covariates into the multiple regression models. In addition, for the analyses at 6 weeks, baseline PEC and use of AAF (yes/no) were included as covariates. $p < .05$ were considered statistically significant. IBM SPSS Statistics version 20.0 (SPSS) was used for all statistical analyses.

3 | RESULTS

3.1 | Inclusion and patient characteristics

At baseline, initially, 52 patients were enrolled and underwent EGD (Day 0), after which 11 patients were excluded due to spontaneous disease remission. Of the 41 patients who eventually were enrolled and participated in the study, one patient was excluded due to noncompliance to the diet during the 6-week diet intervention period. Overall, of the 40 patients who completed the 6-week diet intervention, 39 patients were eligible for dietary baseline analysis, while 35 patients were eligible after the 6-week intervention period (Figure 1). The patient characteristics are depicted in Table 1. The median age was 34.2 years and 60% of the patients were males. Median body mass index (BMI) was 24.1 kg/m^2 and 2.5%, 37.5%, and 5.0% of patients, were respectively, underweight (BMI < 18.5 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2), that is, comparable to the general Dutch population.[42]

There were no statistically significant differences between the FFED and FFED + AAF groups at baseline, except for the intake of calcium, folate, candy/sweets, and low-fat margarine.[36] Overall, adherence to the dietary intervention was high and did not differ between the groups.[36]

3.2 | PEC and nutritional intake analysis

The relationships between the intake of nutrients and food groups and PEC are presented in Table 2. Results for

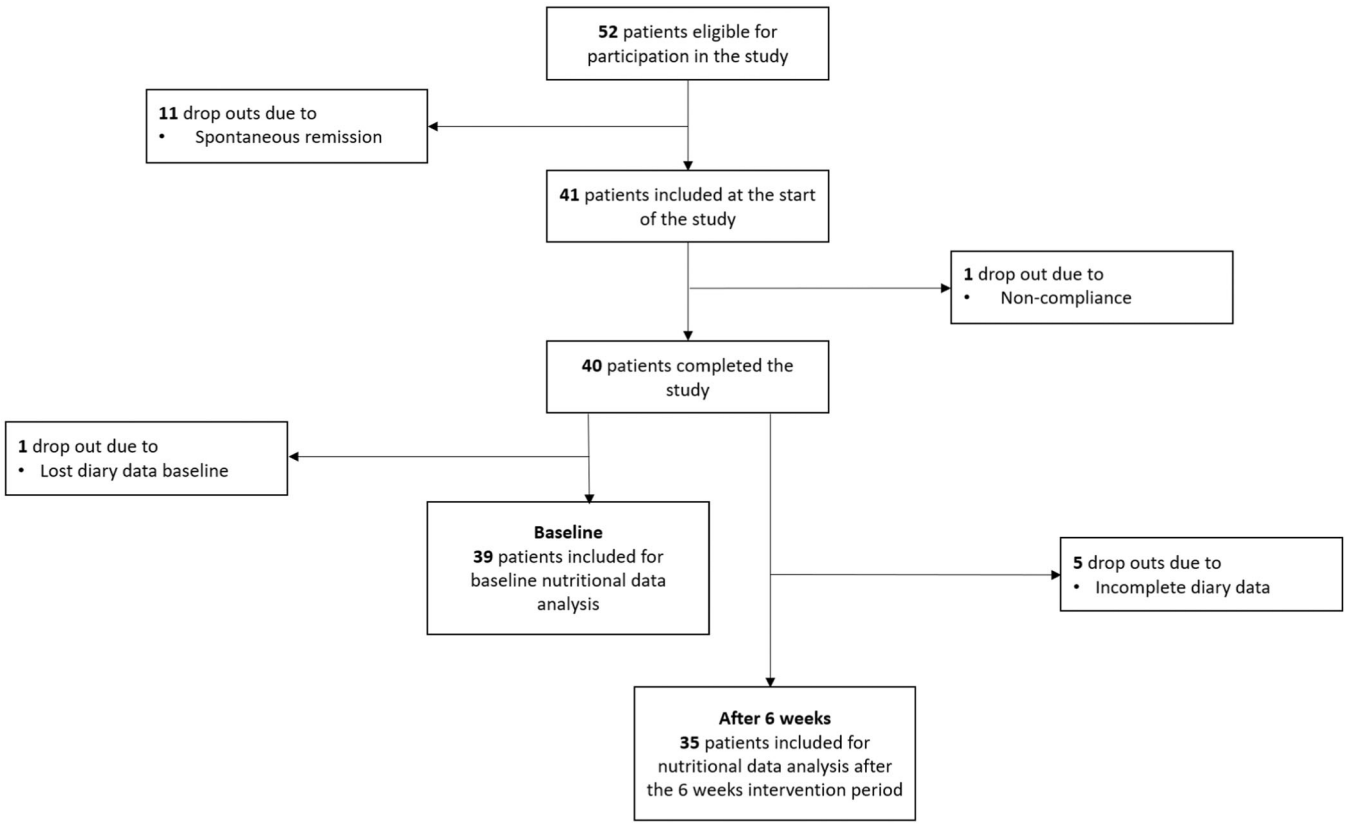

FIGURE 1 Flow chart of the patients included for data analysis.

TABLE 1 Baseline characteristics of all patients who completed the trial ($n = 40$) in both groups.

	FFED ($n = 20$)	FFED + AAF (n = 20)	*p* Value
Male gender, *n* (%)	12 (60)	12 (60)	ns
Age, *years*, median (IQR)	32.0 (27.5–43)	36.5 (29.25–42)	ns
Race, *Caucasian, n* (%)	19 (95)	19 (95)	ns
History of allergic disease, *n* (%)	17 (85)	17 (85)	ns
Allergic rhinitis	14 (70)	13 (65)	ns
Asthma	6 (30)	6 (30)	ns
Atopic dermatitis	5 (25)	7 (35)	ns
Food allergy	6 (30)	5 (25)	ns
Angioedema	1 (5)	2(10)	ns
Oral allergy syndrome	7 (35)	7 (35)	ns
PPIs at baseline, *n* (%)	7 (35)	9 (45)	ns
Prior use of topical steroids, *n* (%)	10 (50)	8 (40)	ns
Esophageal stricture dilation, *n* (%)	1 (5)	2 (10)	ns
Previous endoscopic intervention with food bolus extraction, *n* (%)	7 (35)	10 (50)	ns
Diagnostic delay,[a] median (IQR)	4.5 (1–7.5)	3 (1–9.75)	ns
BMI (kg/m^2), median (IQR)	24.1 (22.4–28.4)	24.0 (22.3–26.7)	ns
Nutrient intake			
Calcium (mg)	9.640	15.640	**.043***
Folate (mg)	9.730	15.570	**.049***
Food group intake			
Candy/sweets (g)	15.140	10.270	**.047***
Low-fat margarine (g)	15.540	9.770	**.045***

Note: Bold values demonstrate significant values of $p < .05$.

Abbreviations: BMI, body mass index; EoE, eosinophilic esophagitis; FFED, four-food elimination diet; FFED + AAF, four-food elimination diet with addition of amino acid-based formula; IQR, interquartile range; PPIs, proton pump inhibitors.

[a]Time interval between first reported EoE symptoms and year of diagnosis.

*$p < .05$.

$p < .1$ are shown. All presented data are corrected for energy intake.

3.2.1 | Relationship between nutrient intake and PEC at baseline

The intake of total protein ($\beta = -.416$; $p = .006$), total fat ($\beta = -.357$; $p = .026$), phosphorus ($\beta = -.377$; $p = .013$), zinc ($\beta = -.395$; $p = .009$), vitamin B12 ($\beta = -.319$; $p = .039$), and folate ($\beta = -.360$; $p = .018$) showed a negative (and thus favorable) statistically significant relationship with PEC. In contrast, the intake of total carbohydrates ($\beta = .389$; $p = .013$) showed a positive (and thus unfavorable) statistically significant relationship with PEC.

3.2.2 | Relationship between intake of foods and food groups and PEC at baseline

The intake of milk products ($\beta = -.341$; $p = .031$) showed a negative (and thus favorable) statistically significant relationship with PEC, whereas the intake of prepacked fruit juice/vegetable juice ($\beta = .431$; $p = .005$) as well as the intake of white bread ($\beta = .326$; $p = .035$) showed a positive (and thus unfavorable) statistically significant relationship with PEC.

TABLE 2 Multiple multivariate regression analyses of the relationships between nutrients and food groups (per 1000 kCal), and PEC, corrected for age, gender, amino acid-based formula use (yes/no) (only after 6 weeks), and baseline PEC (only after 6 weeks).

	Standardized beta (SE)	*p* Value	Adjusted explained variance	Nature of relationship
Relationship between nutrients per 1000 kCal intake and PEC *at baseline* ($n = 39$)				
Total carbohydrates (g)	0.389 (0.160)	**.013**	0.214	Unfavorable
Total protein (g)	−0.416 (0.160)	**.006**	0.245	Favorable
Total fat (g)	−0.357 (0.160)	**.026**	0.185	Favorable
Saturated fatty acids (g)	−0.305 (0.160)	.067	0.146	Favorable
Polyunsaturated fatty acids (g)	−0.274 (0.160)	.087	0.136	Favorable
Calcium (mg)	−0.327 (0.160)	.058	0.152	Favorable
Phosphorus (mg)	−0.377 (0.160)	**.013**	0.213	Favorable
Zinc (mg)	−0.395 (0.160)	**.009**	0.228	Favorable
Vitamin B12 (mg)	−0.319 (0.160)	**.039**	0.168	Favorable
Folate (mg)	−0.360 (0.160)	**.018**	0.199	Favorable
Relationship between nutrients per 1000 kCal intake and PEC *at 6 weeks* ($n = 35$)				
Vitamin C (mg)	−0.282 (0.169)	.066	0.321	Favorable
Relationship between foods/food groups per 1000 kCal intake and PEC *at baseline* ($n = 39$)				
Processed fruit juice/vegetable juice (g) ($n = 14$)	0.431 (0.160)	**.005**	0.254	Unfavorable
Beer (g) ($n = 14$)	0.273 (0.160)	.093	0.133	Unfavorable
White bread (g) ($n = 21$)	0.326 (0.160)	**.035**	0.173	Unfavorable
Ultra-processed meals (ready-to-eat) (g) ($n = 11$)	0.302 (0.160)	.059	0.151	Unfavorable
Full-fat cheese, and semiskimmed and full-fat curd (g) ($n = 22$)	−0.331 (0.160)	.056	0.154	Favorable
Milk products (g) ($n = 10$)	−0.341 (0.160)	**.031**	0.178	Favorable
Relationship between foods/food groups and PEC *at 6 weeks* ($n = 35$)				
Food groups per 1000 kCal intake				
Coconut yogurt (g) ($n = 10$)	0.296 (0.169)	.087	0.310	Unfavorable
Hummus/legumes (g) ($n = 20$)	0.432 (0.169)	**.003**	0.441	Unfavorable
Peanuts (g) ($n = 10$)	0.293 (0.169)	.058	0.326	Unfavorable
Coffee/tea (g) ($n = 32$)	−0.316 (0.169)	**.048**	0.333	Favorable

Note: Bold values demonstrate significant values of $p < .05$, all values are presented for $p < .1$.

Abbreviation: PEC, peak eosinophil count/high power field.

3.2.3 | Relationship between nutrient intake and PEC after 6 weeks of dietary intervention

None of the nutrients showed a statistically significant relationship with PEC after the 6-weeks intervention period.

3.2.4 | Relationship between intake of foods and food groups and PEC after 6 weeks of dietary intervention

The intake of coffee/tea ($\beta = -.316$; $p = .048$) showed a negative (and thus favorable) statistically significant relationship with PEC. The intake of hummus/legumes ($\beta = .432$; $p = .003$) revealed a positive (and thus unfavorable) statistically significant relationship with PEC.

4 | DISCUSSION

In this prospective study, we evaluated associations between the nutritional intake of patients with EoE and disease severity to gain more insights into the possible aggregating and protecting effects of nutrients and food groups involved in EoE. Our findings suggest that

nutritional components may either favorably or unfavorably impact the inflammation of the esophagus and thus the pathophysiology of EoE. This is an important finding as increased inflammation leads to damage of the epithelial surface, which lies at the origin of various manifestations of allergic diseases.[43]

Food sources rich in nutrients for which we found a favorable relationship with PEC are found in both animal and plant foods. Protein, fat, phosphorus, zinc, and vitamin B12 are found in meat, fish, dairy, and cheese (i.e., animal foods), while also several plant foods are rich in protein (e.g., nuts, legumes, soy), phosphorus (e.g., potatoes), and zinc (e.g., whole grains, nuts). The nutrients for which we found a *trend* for a favorable relationship with PEC, that is, saturated fat, LCPUFAs, calcium, and vitamin C are mostly found in meat, processed foods and full-fat dairy and cheese (saturated fat, calcium), fatty fish, nuts and seeds, oil and margarines (LCPUFAs), and fruits and vegetables (vitamin C).

The favorable effect of total fat and saturated fat seems unexpected. However, the relevance of nutrients should be interpreted in light of foods consumed, thus by the source of the nutrients. The significant favorable effect of total protein, (saturated) fat, phosphorus, vitamin B12, zinc, and calcium could be partly explained by the intake of milk products, full-fat cheese and semi-skimmed or full-fat curd, as these foods were related to lower inflammation. There is increasing evidence that moderate amounts of saturated fats from dairy products, in contrast to fat from meat and trans fatty acids, have anti-inflammatory effects. We hypothesize that, due to its anti-inflammatory effects, the intake of dairy, specifically full-fat cheese in contrast to low-fat cheese, could have a protective effect on esophageal inflammation as long as cow's milk allergy in EoE has not yet fully developed. In addition, LCPUFAs, including omega-3 fatty acids (in fatty fish, walnuts, canola oil), contributed to the total fat intake and these fatty acids are known for their anti-inflammatory effects.[44] Furthermore, in contrast to skimmed dairy, full-fat dairy is a source of vitamins A and D, and both are known for their immunomodulatory effects. Vitamin A is further acknowledged for its role in protective immune response mechanisms, since vitamin A is a key nutrient for mucosal integrity.[23,45] Moreover, fermented products, such as cheese, are increasingly recognized for their potential probiotic and postbiotic effects.[8] Finally, cheese is a food product with a relatively high pH which could have a favorable effect in the esophagus.[46,47]

The favorable effect of zinc on the disease severity of EoE can also be explained by its immunomodulatory effects. Zinc is suggested to exhibit a local effect on both the mucosal integrity, as well as on the mucosal cells of the gastrointestinal tract.[19–25] Meat, dairy, and whole grains are rich sources of zinc.

The favorable effect of the intake of folate, and a trend for a favorable effect of vitamin C indicate that the intake of fruits and vegetables has beneficial effects, as fruits and vegetables are the major sources of folate and vitamin C.

These observations show similarities to the results of our previous study on habitual diet as related to the severity of EoE.[34] In that study, we also found protective effects of dairy products, in particular fermented dairy, on the mucosal permeability of adult EoE patients.[34] However, the favorable impact of protein, phosphorus, and vitamin B12 on inflammation in EoE in this study is in contrast to the unfavorable relationship of these nutrients with inflammation in EoE in our previous study by De Kroon et al.[34] This could be explained by the fact that cheese intake in the study of De Kroon et al. was much lower (37 g/day), as compared to this study population, in which the intake of cheese products at baseline was twice as high (76 g/day).

The favorable relationship we found for coffee/tea might be explained by the high levels of polyphenols and flavonoids in coffee and (green) tea, associated with antioxidant, antiproliferative, and anti-inflammation properties.[48,49]

The observed unfavorable effect of the intake of total carbohydrates and white bread on the disease severity of EoE, can be explained by an unfavorable effect of mono- and disaccharides and refined grains. White bread consists of refined grains and is low in fiber. Fiber is known for its beneficial effects on the microbiome. These findings are in line with results of our previous study on habitual diet as related to the severity of EoE[34] where we found a favorable relationship between dietary fiber intake and inflammation.

Another unfavorable effect was observed for processed food products, that is, processed fruit/vegetable juice and ultra-processed meals, such as frozen pizza and ready-to-eat meals. Ultra-processed foods have been consistently linked to other Western inflammatory diseases.[50] Their adverse effects might be caused by their proinflammatory properties such as high levels of saturated or trans fatty acids, lack of dietary fiber, and low nutrient density,[48] as well as by chemically modified ingredients, food additives, and ingredients produced under high pressure and extensive heat management methods. The presence of additives such as emulsifiers may negatively impact on the mucosal integrity,[51] while highly heated foods may have high levels of advanced glycation end products which are suggested to have proinflammatory properties.[51–54] In addition, the

unfavorable effect might be explained by the acidic effects of these food products. We hypothesize that the level of acidity of food products might influence the integrity of the esophagus mucosa, in which acidic foods might irritate the esophagus mucosa. Hence, products like soda and fruit juices have irritable effects due to their acidity, while, in contrast, basic foods with a higher pH such as cheese,[55] could have a favorable effect. Finally, we hypothesize that the lack of microbial content of ultra-processed foods is harmful, because these foods do not contribute to the total microbial exposure in the gut.

A remarkable finding was the unfavorable relationships of hummus (containing chickpeas and sometimes sesame), peanuts and dairy replacers based on coconut with PEC. Possibly, legumes, sesame, and peanut could be underestimated allergens for patients with EoE in the Netherlands. Coconut is high in (proinflammatory) saturated fatty acids,[40] and showed a trend for an unfavorable effect on the disease severity of EoE.

Our findings do not implicate that the higher the intake of protein and fat the better, but they suggest that both animal foods, specifically (full-fat and fermented) dairy, and plant foods in the right amounts may contribute beneficially to decreased inflammation. From many other studies, it is known that a healthy diet consists of the right proportions of plant and animal protein, (poly-unsaturated) fat, and also carbohydrates rich in dietary fiber, predominantly provided by whole grains.[53,56]

Overall, our results are in line with established anti- and proinflammatory effects of foods in other chronic inflammatory diseases as defined in the Dietary Inflammatory Index Development Study following an extensive literature review.[48,57]

Strengths of the study were the accurate and standardized approach of obtaining patients' diet history and the reliable assessment of PEC using biopsies. In addition, this study further builds on our previous study[34] on the relationship between patients' habitual diet and esophagus permeability and inflammation. These two studies are currently the only two studies looking at the effects of the habitual diet on EoE, making our study unique by highlighting immunomodulatory effects of the diet, other than elimination, and the link to the disease severity of EoE as a novel approach in the management and prevention of EoE.

This study has a few limitations. First, the relatively small sample size limits the reliability of the findings of our study. Second, the observational nature of our study design limits the ability to assign causality and may have led to residual confounding from unmeasured factors. Also, no correction for multiple testing was made as this study aimed to generate hypotheses. Third, the assessment of patients' nutritional status could be improved. We assessed BMI but did not determine vitamin and mineral status in patients. Malnutrition in chronic disease, such as allergic disease and Irritable Bowel Disease, promotes inflammation and vice versa,[58,59] in which iron is playing a key role.[60] Malnutrition in EoE patients, specifically vitamin D deficiency, has been reported, although data are limited.[61,62] Also, the division of the food groups could be improved. For example, ready-to-eat and prepared meals were categorized as either Pancake and pizza or ready meals, and were not further divided into main ingredient or processing and preparation method. Also, the intake of herbs, spices, salt, and iodine (fortified in salt) was not reliably measured as we had not asked patients to weigh herbs, spices, and salt. Therefore, we could not reliably assess the intake of iodine as a significant amount of iodine intake in the Netherlands is supplied by the use of fortified salt. The intake of supplements was not assessed due to irregular intake. Fourth, in this study, no division was made for animal versus plant nutrients and food groups, while they have very distinctive effects, for instance, at the gut microbiome level.[28,63,64] Furthermore, it is essential to note that some nutrients and food groups could have a synergistic, cumulative, or interactive effect on the disease severity of EoE.[57] Therefore, in future studies, also food patterns should be studied. Finally, due to the known anti-inflammatory effects of the AAF, we were not able to distinguish the nutritional effect from the intervention effect.

In conclusion, dietary compounds may play an important role in the pathology of EoE, in which dietary compounds have immunomodulatory effects, such as pro- or anti-inflammatory influences. In addition to the elimination diet, a high-quality and anti-inflammatory composition of the diet of EoE patients is a promising adjuvant therapy for disease control during management and during the maintenance phase in EoE following disease remission to prevent relapse in EoE. In contrast, a proinflammatory diet could aggravate symptoms and decrease or even mask the management effects of elimination dietary therapy. Intervention trials with larger samples sizes that accurately quantify food intake and food patterns are needed for definite conclusions. Overall, better understanding of the possible aggravating or protecting effects of nutritional compounds is necessary for improved dietary advice and disease control in EoE.

AUTHOR CONTRIBUTIONS

Simone R. B. M. Eussen: Conceptualization (supporting); methodology (supporting); software (lead); formal

analysis (lead); writing—original draft (lead). **Sanne Wielders**: Software (supporting); formal analysis (supporting); writing—original draft (supporting); writing—review and editing (equal). **Willemijn E. de Rooij**: Writing—review and editing (equal). **Marleen T. J. Van Ampting**: Writing—review and editing (equal). **Betty C. A. M. Van Esch**: Conceptualization (supporting); writing—review and editing (equal). **Jeanne H. M. de Vries**: Writing—review and editing (equal). **Albert J. Bredenoord**: Conceptualization (supporting); writing—review and editing (equal). **Berber Vlieg-Boerstra**: Conceptualization (lead); methodology (lead); writing—original draft (supporting); writing—review and editing (equal).

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CONFLICTS OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study protocol was approved by the Medical Ethics Committee of Amsterdam University Medical Center, Amsterdam, the Netherlands. All participants provided written informed consent before taking part and were given a unique study ID to ensure anonymity.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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