



Gender-specific Effect of Micronutrient on Non-erosive Reflux Disease and Erosive Esophagitis

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Background/Aims

The effect of dietary micronutrients on non-erosive reflux disease (NERD) and reflux esophagitis is unclear. We aim to evaluate the gender-specific effect of micronutrient on erosive esophagitis and NERD.

Methods

A total of 11 690 participants underwent endoscopy and completed 3-day recordings for dietary intake and questionnaires for reflux symptoms from 2004 to 2008. To evaluate the effect of dietary micronutrients on NERD or erosive esophagitis, adjusted regression analysis with odds ratio (OR) and 95% confidence interval (CI) was used. In addition, we performed gender-specific analysis.

Results

Prevalence of NERD and erosive esophagitis was 6.8% and 11.2% in men and 9.1% and 2.4% in women. In adjusted analysis, high intake of vitamin A (OR, 0.78; 95% CI, 0.64-0.96), retinol (OR, 0.73; 95% CI, 0.59-0.90), vitamin B2 (OR, 0.68; 95% CI, 0.54-0.87), vitamin B6 (OR, 0.75; 95% CI, 0.58-0.96), folic acid (OR, 0.77; 95% CI, 0.62-0.96), calcium (OR, 0.66; 95% CI, 0.53-0.82), and iron (OR, 0.68; 95% CI, 0.53-0.87) had an inverse association with NERD. However, erosive esophagitis has no relationship with micronutrients except vitamin C (OR, 0.78; 95% CI, 0.62-0.98). High dietary intake of calcium reduced the risk of NERD in men and high dietary intake of many micronutrients reduced NERD in women.

Conclusions

While many dietary micronutrients reduced NERD, they had no effect on erosive esophagitis. The effect of micronutrient on NERD was more prominent in women than men.

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Key Words

Esophagitis; Gender identity; Micronutrients; Non-erosive reflux disease

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Introduction

Gastroesophageal reflux disease (GERD) is common in the world¹⁻³ and is a multifactorial disease. Although some foods may induce GERD, study results for reflux inducing foods have conflicts.⁴⁻⁸ In a previous large study, many food groups were strongly associated with non-erosive reflux disease (NERD) but not with erosive esophagitis.⁹ However, a rare study presented the association between dietary micronutrient and GERD.⁴ Although some dietary micronutrients looks to be associated with Barrett's esophagus,^{10,11} dietary micronutrients had no effect on GERD.^{4,12}

Even if NERD shares pathogenesis and risk factors with erosive esophagitis, NERD and erosive esophagitis have many different phenotypes.¹³ Responsiveness of proton pump inhibitors (PPI) is higher in erosive esophagitis than NERD.¹³ Thus, we estimated the effect of micronutrients on NERD and erosive esophagitis in a large health screening population. Recent studies suggested gender difference in many diseases. In our previous study, the effect of dietary food group on erosive esophagitis and NERD had gender differences.⁹ Therefore we further analyzed the gender-specific effect of dietary micronutrient on NERD and erosive esophagitis.

Materials and Methods

Study Population

This was a cross-sectional study from health check-up population at the National Cancer Center, Korea.⁹ Participants underwent comprehensive health screening from September 2004 to December 2008. Participants undergoing previous gastric surgery, subjects who did not undergo endoscopy or *Helicobacter pylori* tests, current users of PPI, or incomplete responders of questionnaire were excluded (Figure). The National Cancer Center Institutional Review Board approved this study (No. NCCNCS-10359). Written informed consent were obtained from subjects before endoscopy.

Questionnaire Assessment

Demographic data (age, gender, chronic diseases, medication history, alcohol consumption, and smoking status), gastrointestinal symptoms, and dietary intake were collected before endoscopy. The questionnaires included typical GERD symptoms (heartburn and acid regurgitation) and atypical symptoms (globus sensation, hoarseness, epigastric soreness, and chronic cough).¹⁴ Smoking and alcohol drinking status were classified as current (daily or occasionally) or noncurrent. Current means daily or occasional users within the recent 1 year. Noncurrent means never users or past users.

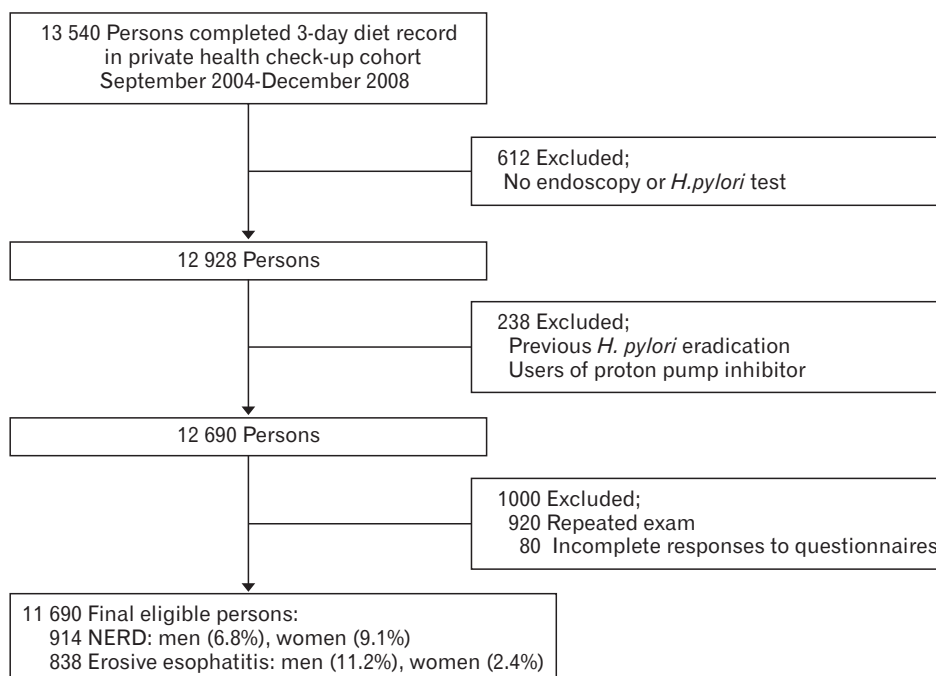


Figure. Study flow of health check-up cohort. *H. pylori*, *Helicobacter pylori*.

Weight and height were measured (InBody Co, Ltd, Seoul, Korea), and body mass index (BMI) was calculated as weight/height² (kg/m²).

Dietary Assessment

We used a 3-day diet record to assess dietary intake of nutrients.⁹ We described the assessment process in a previous study.⁹ In summary, participants recorded both type and amount of all foods consumed during three days, including 2 days among the weekday and one weekend day before health check-up. On the examination day, dietitians interviewed the participants for the accuracy of the food record, and they discussed the recorded contents with participants using real-size food models (Korea Mirage Replica Inc., Incheon, Korea), measuring spoons, measuring cups, and eye measurements of foods that were assisted by photographs (Korean Nutritionist Association, 1999).⁹ Data based on the results of the dietary intake records were analyzed using the CAN-Pro 3.0 Nutrient Database (The Korean Nutrition Society, Seoul, South Korea) and converted into each nutrient.

Endoscopy

Erosive esophagitis was defined as endoscopic esophagitis and NERD was defined as weekly typical GERD symptoms without endoscopic esophagitis. Subjects who had fasted overnight underwent under conscious sedation using a flexible endoscope (Q260; Olympus Optical Co, Ltd, Tokyo, Japan).¹⁴ Specialized gastroenterologists performed the endoscopy. The severity of reflux esophagitis was measured according to the Los Angeles classification system.¹⁵ Hiatal hernia was recorded if the gastroesophageal junction extended at least 2 cm above the diaphragmatic hiatal impression during quiet respiration. During endoscopic examination, *H. pylori* infection was evaluated using the rapid urease test (Pronto Dry; Medical Instruments Corporation, Solothurn, Switzerland).¹⁶

Statistical Methods

Chi-square tests or *t* tests were used to compare the differences between the 2 groups (normal vs NERD and normal vs erosive esophagitis) for demographic characteristics. Demographic characteristics included age, gender, BMI, smoking status, and drinking status. We used *t* test to measure differences of each nutrient between the 2 groups.

For regression analysis of dietary nutrients, they were categorized to quartiles. Nutrients were categorized to 3 groups to analyse the gender-specific effect on GERD because of sample size and GERD prevalence. Contributing factors for erosive esophagitis

and NERD were evaluated by regression analysis using odds ratios (OR) and 95% confidence intervals (CI). Age, gender, total energy intake, BMI, presence of *H. pylori*, presence of hiatal hernia, smoking, and alcohol consumption were adjusted. Dietary micronutrients showing differences between control and GERD in univariate analysis were additionally adjusted. For gender-specific analysis, we classified micronutrients into three groups (tertile). We further analysed the gender-specific effect of micronutrient on NERD and erosive esophagitis.

We used STATA software (version 12; College Station, Texas, USA). All statistical tests were two-sided, and *P*-values less than 0.05 were considered statistically significant.

Results

Characteristics of Participants and Intake of Micronutrients

A total of 11 690 participants were finally included (Figure).¹³ The prevalence of NERD and erosive esophagitis was 6.8% and 11.2% in men and 9.1% and 2.4% in women (Table 1). BMI, presence of *H. pylori*, presence of hiatal hernia, current smoker, and current drinker were markedly higher in men than in women (Table 1). Table 2 provides intake of total energy and micronutrients in control, NERD, and erosive esophagitis. Total energy intake had no statistical difference between control and NERD but several micronutrient intakes had a difference between control and NERD in *t* test (Table 2). However, dietary intakes of total energy and many micronutrient markedly differed between control and erosive esophagitis in *t* test (Table 2).

Table 1. Characteristics of Participants by Gender

Contributing factors	Men (n = 6276)	Women (n = 5414)
NERD (n [%])	424 (6.8)	490 (9.1)
Erosive esophagitis (n [%])	706 (11.2)	132 (2.4)
Age (mean [SD], yr)	50.4 (9.7)	49.0 (9.5)
Body mass index (mean [SD])	24.2 (2.8)	22.8 (2.9)
Current smoker (n [%])	2653 (42.3)	280 (5.2)
Current drinker (n [%])	5097 (82.1)	2349 (44.9)
Presence of <i>H. pylori</i> (n [%])	3215 (51.2)	2535 (47.0)
Presence of hiatal hernia (n [%])	174 (2.8)	35 (0.6)

NERD, non-erosive reflux disease; *H. pylori*, *Helicobacter pylori*.

Table 2. Comparison of Dietary Micronutrient Intake for Erosive Esophagitis and Non-erosive Reflux Disease

Contents of micronutrients	Control (n = 9938)	NERD (n = 914)	P-value ^a	Erosive esophagitis (n = 838)	P-value ^b
Total energy (kcal/day)	1799 (498)	1819 (519)	0.271	1989 (528)	< 0.001
Micronutrients (without supplement)					
Calcium (mg/day)	534 (230)	513 (252)	0.011	557 (243)	0.004
Iron (mg/day)	13.8 (6.6)	13.3 (5.4)	0.020	15.1 (10.2)	< 0.001
Phosphate (mg/day)	1053 (331)	1037 (350)	0.162	1130 (332)	< 0.001
Sodium (mg/day)	4141 (1640)	4218 (1811)	0.209	4520 (1875)	< 0.001
Potassium (mg/day)	2910 (1037)	2867 (1037)	0.241	3065 (1085)	< 0.001
Vitamin A (µg/day)	709 (489)	688 (501)	0.218	731 (414)	0.212
Retinol (µg/day)	112 (169)	122 (322)	0.119	112 (105)	0.943
Carotene (µg/day)	3419 (2600)	3257 (2166)	0.069	3551 (2270)	0.149
Vitamin B1 (mg/day)	1.29 (3.05)	1.30 (2.22)	0.951	1.40 (1.65)	0.361
Vitamin B2 (mg/day)	1.12 (0.59)	1.08 (0.45)	0.091	1.20 (0.59)	0.001
Vitamin B6 (mg/day)	2.08 (1.61)	2.00 (0.72)	0.138	2.20 (0.87)	0.032
Vitamin C (mg/day)	118.9 (79)	117 (78)	0.512	112 (69)	0.011
Vitamin E (mg/day)	12.7 (5.8)	12.6 (7.3)	0.713	13.2 (5.9)	0.012
Niacin (mg/day)	17.8 (7.1)	17.9 (7.4)	0.832	20.2 (8.1)	< 0.001
Folic acid (µg/day)	249 (140)	240 (108)	0.071	255 (128)	0.232
Zinc (mg/day)	9.9 (6.9)	10.2 (9.1)	0.323	10.6 (4.6)	0.007

^aP-values comparing control and non-erosive reflux disease (NERD).

^bP-values comparing control and erosive esophagitis.

Values are expressed as the mean (SD).

P-values were derived from t test.

Effects of Micronutrients on Non-erosive Reflux Disease and Erosive Esophagitis

In an adjusted analysis for the quartile of micronutrients, higher intake of calcium (*P* for trend < 0.001), iron (*P* for trend < 0.001), phosphate (*P* for trend < 0.001), vitamin A (*P* for trend = 0.007), retinol, vitamin B2 (*P* for trend < 0.001), vitamin B6 (*P* for trend = 0.007), and folic acid (*P* for trend = 0.020) reduced NERD (Table 3). Even though almost all micronutrients affected erosive esophagitis in unadjusted analysis, only the fourth quartile of vitamin C decreased erosive esophagitis compared to the lowest quartile in adjusted analysis (OR, 0.78; 95% CI, 0.62-0.98; Supplementary Table 1). The second quartile of sodium decreased erosive esophagitis compared to the lowest quartile (OR, 0.74; 95% CI, 0.59-0.94). Erosive esophagitis was associated with male sex, higher BMI, negative *H. pylori*, current smoker, current drinker, and high total energy intake (data not shown). NERD was associated with female sex, younger age, current smoker, and high total energy intake (data not shown).

Effects of Micronutrients on Non-erosive Reflux Disease by Gender (Adjusted Analysis)

In men, high calcium intake (OR, 0.72; 95% CI, 0.55-0.95) and moderate intake of phosphate (OR, 0.74; 95% CI, 0.57-0.97) and potassium (OR, 0.75; 95% CI, 0.58-0.97) reduced NERD (Table 4). In women, high dietary intake of calcium (OR, 0.77; 95% CI, 0.61-0.98) and potassium (OR, 0.75; 95% CI, 0.57-1.00), and moderate to high intake of iron and phosphate reduced NERD (Table 4). High dietary intake of vitamin A (OR, 0.76; 95% CI, 0.59-0.97), retinol (OR, 0.75; 95% CI, 0.59-0.96), vitamin B2 (OR, 0.74; 95% CI, 0.56-0.97), and vitamin B6 (OR, 0.73; 95% CI, 0.55-0.97) also reduced NERD (Table 4).

Effects of Micronutrients on Erosive Esophagitis by Gender (Adjusted Analysis)

In men, any dietary intake of micronutrients had no association with erosive esophagitis and high dietary intake of retinol increased erosive esophagitis in women (Supplementary Table 2).

Table 3. Effects of Micronutrients on Non-erosive Reflux Disease

Daily intake	Unadjusted		Adjusted ^a		
	OR (95% CI)	P-value	OR (95% CI)	P-value	P for trend
Calcium (mg/day)					
1st quartile (< 376)	1		1		
2nd quartile (376-< 510)	0.75 (0.63-0.91)	0.003	0.74 (0.61-0.89)	0.002	
3rd quartile (510-< 644)	0.69 (0.57-0.83)	< 0.001	0.67 (0.55-0.83)	< 0.001	
4th quartile (≥ 644)	0.72 (0.59-0.87)	0.001	0.66 (0.53-0.82)	< 0.001	< 0.001
Iron (mg/day)					
1st quartile (< 10.2)	1		1		
2nd quartile (10.2-< 13.2)	0.92 (0.77-1.10)	0.381	0.86 (0.70-1.05)	0.141	
3rd quartile (13.2-< 16.1)	0.76 (0.63-0.92)	0.005	0.68 (0.54-0.86)	0.001	
4th quartile (≥ 16.1)	0.78 (0.65-0.95)	0.011	0.68 (0.53-0.87)	0.002	< 0.001
Phosphate (mg/day)					
1st quartile (< 828)	1		1		
2nd quartile (828-< 1033)	0.92 (0.76-1.10)	0.349	0.83 (0.68-1.01)	0.069	
3rd quartile (1033-< 1238)	0.89 (0.74-1.08)	0.223	0.77 (0.62-0.96)	0.022	
4th quartile (≥ 1238)	0.84 (0.69-1.02)	0.078	0.63 (0.47-0.84)	0.001	< 0.001
Vitamin A (µg/day)					
1st quartile (< 434)	1		1		
2nd quartile (434-< 643)	0.83 (0.69-1.00)	0.049	0.81 (0.67-0.98)	0.033	
3rd quartile (643-< 852)	0.87 (0.72-1.05)	0.151	0.84 (0.69-1.02)	0.079	
4th quartile (≥ 852)	0.82 (0.68-0.99)	0.043	0.78 (0.64-0.96)	0.022	0.007
Retinol (µg/day)					
1st quartile (< 44.9)	1		1		
2nd quartile (44.9-< 87.7)	0.82 (0.68-0.99)	0.043	0.79 (0.65-0.96)	0.021	
3rd quartile (87.7-< 130.4)	0.93 (0.77-1.12)	0.462	0.87 (0.72-1.06)	0.163	
4th quartile (≥ 130.4)	0.85 (0.70-1.02)	0.089	0.73 (0.59-0.90)	0.003	0.021
Vitamin B2 (mg/day)					
1st quartile (< 0.82)	1		1		
2nd quartile (0.82-< 1.07)	0.93 (0.77-1.12)	0.471	0.86 (0.71-1.05)	0.149	
3rd quartile (1.07-< 1.33)	0.80 (0.66-0.98)	0.023	0.70 (0.57-0.86)	0.001	
4th quartile (≥ 1.33)	0.86 (0.71-1.03)	0.109	0.68 (0.54-0.87)	0.002	< 0.001
Vitamin B6 (mg/day)					
1st quartile (< 1.56)	1		1		
2nd quartile (1.56-< 1.99)	0.92 (0.76-1.11)	0.391	0.87 (0.72-1.06)	0.178	
3rd quartile (1.99-< 2.43)	0.84 (0.69-1.02)	0.069	0.77 (0.62-0.96)	0.022	
4th quartile (≥ 2.43)	0.87 (0.72-1.05)	0.148	0.75 (0.58-0.96)	0.023	0.007
Folic acid (µg/day)					
1st quartile (< 174)	1		1		
2nd quartile (174-< 232)	0.89 (0.75-1.08)	0.271	0.89 (0.73-1.08)	0.243	
3rd quartile (232-< 290)	0.79 (0.66-0.96)	0.021	0.78 (0.63-0.96)	0.021	
4th quartile (≥ 290)	0.83 (0.69-1.01)	0.059	0.77 (0.62-0.96)	0.022	0.02

^aAdjusted for age, gender, body mass index, total energy intake, presence of hiatal hernia, presence of *Helicobacter pylori*, and smoking. Age and body mass index were continuous variables. Total energy intake was quartile.

Discussion

This study showed gender-specific effects of the dietary intake

of micronutrients on NERD and erosive esophagitis. While higher dietary intake of calcium, iron, phosphate, vitamin A, retinol, vitamin B2, vitamin B6, and folic acid reduced the risk of NERD, only vitamin C reduced the risk of erosive esophagitis. In gender-specific

Table 4. Effects of Micronutrients on Non-erosive Reflux Disease by Gender

Daily intake		Men		Women	
		Adjusted OR ^a (95% CI)	P-value ^a	Adjusted OR ^a (95% CI)	P-value ^a
Calcium (mg/day)	1st group	1		1	
	2nd group	0.90 (0.71-1.15)	0.411	0.86 (0.68-1.08)	0.191
	3rd group	0.72 (0.55-0.95)	0.018	0.77 (0.61-0.98)	0.032
Iron (mg/day)	1st group	1		1	
	2nd group	0.97 (0.75-1.25)	0.792	0.74 (0.58-0.94)	0.011
	3rd group	0.75 (0.56-1.01)	0.059	0.79 (0.62-1.01)	0.059
Phosphate (mg/day)	1st group	1		1	
	2nd group	0.74 (0.57-0.97)	0.032	0.74 (0.57-0.94)	0.021
	3rd group	0.73 (0.53-1.02)	0.061	0.69 (0.50-0.94)	0.019
Sodium (mg/day)	1st group	1		1	
	2nd group	0.90 (0.70-1.16)	0.432	0.87 (0.68-1.11)	0.261
	3rd group	0.86 (0.65-1.13)	0.281	1.16 (0.90-1.50)	0.251
Potassium (mg/day)	1st group	1		1	
	2nd group	0.75 (0.58-0.97)	0.030	0.97 (0.77-1.23)	0.803
	3rd group	0.76 (0.57-1.02)	0.069	0.75 (0.57-1.00)	0.051
Vitamin A (µg/day)	1st group	1		1	
	2nd group	0.86 (0.67-1.11)	0.242	0.86 (0.68-1.08)	0.201
	3rd group	0.87 (0.67-1.12)	0.271	0.76 (0.59-0.97)	0.029
Retinol (µg/day)	1st group	1		1	
	2nd group	0.96 (0.75-1.24)	0.772	0.85 (0.67-1.06)	0.151
	3rd group	0.94 (0.73-1.22)	0.651	0.75 (0.59-0.96)	0.020
Vitamin B2 (mg/day)	1st group	1		1	
	2nd group	0.88 (0.68-1.14)	0.353	0.80 (0.63-1.02)	0.071
	3rd group	0.79 (0.58-1.07)	0.131	0.74 (0.56-0.97)	0.027
Vitamin B6 (mg/day)	1st group	1		1	
	2nd group	0.86 (0.67-1.12)	0.272	0.78 (0.61-0.99)	0.043
	3rd group	0.83 (0.61-1.12)	0.221	0.73 (0.55-0.97)	0.028
Vitamin C (mg/day)	1st group	1		1	
	2nd group	0.79 (0.61-1.02)	0.071	0.86 (0.68-1.09)	0.212
	3rd group	0.96 (0.74-1.23)	0.743	0.94 (0.74-1.20)	0.631
Folic acid (µg/day)	1st group	1		1	
	2nd group	0.84 (0.65-1.09)	0.191	1.08 (0.85-1.37)	0.523
	3rd group	0.89 (0.68-1.17)	0.401	0.86 (0.66-1.12)	0.261

^aAdjusted for age, body mass index, total energy, presence of hiatal hernia, presence of *Helicobacter pylori*, and smoking. Body mass index were continuous variables.

analysis, high dietary intake of calcium reduced NERD in men and high dietary intake of many micronutrients reduced NERD in women. High dietary intake of retinol increased erosive esophagitis in women but any micronutrients had no effect on erosive esophagitis in men.

Interestingly, NERD strongly correlated with many dietary micronutrients. High intake of calcium, iron, phosphate, vitamin A, retinol, vitamin B2, vitamin B6, and folic acid decreased NERD. High dietary intake of vitamin C decreased erosive esophagitis. In a previous small study (total study population is 371), micronutri-

ents had no effect on GERD.⁴ Plausible mechanisms of the inverse relationship of NERD with calcium, iron, and phosphate intake are unknown. We suggest that micronutrients affect gastric acidity and lower esophageal sphincter (LES) tone for the following reasons. Both calcium and iron can bind chloride, thus decreasing intragastric acidity. Calcium bicarbonate has been used as an antacid. The myogenic component of LES is calcium dependent,¹⁷ and extrinsic neurogenic control of LES contraction is primarily vagal and cholinergic.¹⁸ In vitro experiments showed that acetylcholine-induced contraction decreases with decreasing extracellular calcium ions and

can be blocked by incubation in a calcium ion-free solution.¹⁹ The study suggested that contraction in response to acetylcholine is mediated by an influx of extracellular ionized calcium.¹⁹ Actually, calcium channel blockers have been shown to decrease LES pressure. Therefore, insufficient calcium intake may induce LES relaxation in vivo.

In this study, antioxidants (vitamin A, retinol, vitamin B2, vitamin B 6, and folic acid) were associated with 22-32% reduction in the risk of NERD and vitamin C had an association with 22% reduction in the risk of erosive esophagitis. In a previous study, intake of dietary antioxidants (vitamin C and beta-carotene), fruits, and vegetables was inversely associated with the risk of Barrett's esophagus, but supplement intake had no association with Barrett's esophagus.¹¹ In a Chinese cross-sectional study, vitamin C was inversely related with reflux esophagitis.²⁰ Some dietary micronutrients was associated with Barrett's esophagus,^{10,11} but dietary micronutrients had no effect on GERD.^{4,12} The sample size of previous studies were relatively small and so they may not conclude significant results. Erosive esophagitis had no association with micronutrient except vitamin C, whereas it was strongly associated with body mass index, negative *H. pylori*, and total energy intake in this study and also previous our studies.^{9,14,21}

This is the first study about the gender-specific effect of micronutrients on NERD and erosive esophagitis. Gender-specific analysis showed that the effect of micronutrients on NERD was more prominent in women than men. In men, high calcium intake and moderate intake of phosphate and potassium reduced NERD. In women, high intake of calcium and potassium, and moderate to high intake of iron and phosphate reduced NERD. High intake of vitamin A, retinol, vitamin B2, and vitamin B6 also reduced NERD. The effect of micronutrient on NERD in women was similar with that in the overall population. Less prominent association and borderline association between micronutrient and NERD in men may be related to low prevalence of NERD in men (6.8%) comparing to women (9.1%). Dietary intake of micronutrients had no association with erosive esophagitis in men and high dietary intake of retinol increased erosive esophagitis in women.

The cause of gender discrepancy of dietary micronutrient effect on NERD is unclear. Gender difference may exist in sensitivity of inflammation or the pathogenesis of distal esophageal inflammation. First, female hormone, estrogen has anti-inflammatory activities in animal studies.^{22,23} Esophageal damage increased in male rats and ovariectomised rats comparing to female rats and the aggravated esophageal damage was attenuated by 17 β -estradiol in a recent animal study.²² Inflammatory cytokines have an association with reflux

esophagitis^{24,25} and their expression has gender difference.²⁴ The gender difference in sex hormones and inflammatory cytokines may affect the inflammation of distal esophagus by micronutrients. Second, gender difference in esophageal nociception may be a plausible mechanism. Up-regulation of transient receptor potential cation channel subfamily V member 1 (TRPV1) in esophageal mucosa of NERD and reflux esophagitis patients comparing to healthy control was observed.^{26,27} TRPV1 looks as one of the important mechanisms of GERD symptoms.^{28,29} Up-regulation of TRPV1 in distal esophageal mucosa may be the potential mechanism of the visceral hypersensitivity in NERD. Gender difference in TRPV1 expression by external factors such as acid or micronutrients might contribute to different effect of micronutrient on NERD by gender. It is needed to elucidate the mechanism of gender discrepancy of the effect of dietary micronutrients on GERD in the future.

Regardless of the insufficient evidence of the effect of dietary habits and dietary modification on GERD, dietary modification have been recommended as first-line therapies.³⁰ Evidence-based Japanese guideline for GERD recommend that lifestyle modifications with PPI therapy is effective for GERD.³¹ Our results that sufficient of micronutrients have an inverse association with NERD provide the evidence of the dietary modification to prevent or manage NERD.

This study has some strengths. First, we used 3-day records, the gold standard of diet assessment to evaluate dietary intake. While Food frequency questionnaire is a semi-quantitative assessment method, 3-day records quantify the diet items and nutrient components. Therefore, it provides the most accurate evaluation of food intake compared with other diet assessment methods. Second, we separately analyzed NERD and erosive esophagitis, which are different phenotypes of GERD.¹³ The third, the large size allowed us to evaluate many confounding factors, including demographic factors and clinical factors, and permitted us to perform more detailed analyses. Fourth, we evaluated GERD using endoscopy, current infection of *H. pylori*, and body mass index by direct measurement. Endoscopy allowed an accurate evaluation of erosive esophagitis according to the Los Angeles classification system. We could adjust for *H. pylori*, which has strongly inverse association with erosive esophagitis in Asia.¹⁴ Lastly, we assessed the gender-specific contribution of dietary micronutrients on NERD and erosive esophagitis.

Nevertheless, this study has some limitations. First, health screening may change the diet habit thereby result in a selection bias. Second, physical activity, which is associated with obesity, was not adjusted in this study. However, a previous study suggested

that physical activity had no association with erosive esophagitis.⁵ Psychologic distress, which may be affected on NERD, was not adjusted. Food consumption pattern such as speed or frequency of food consumption also was not adjusted. Third, we did not validate this result in other groups. Therefore, further studies in other institutes or countries need to acquire generalizability. Finally, the cross-sectional study is insufficient to provide the definitive causality.

In conclusion, sufficient intake of micronutrients and antioxidants reduced NERD but the effect of dietary micronutrient on erosive esophagitis was minimal. Erosive esophagitis had an association with high total energy intake. Gender-specific analysis showed more prominent effect of micronutrient on NERD in women than men. Gender-specific different approaches may need to manage and prevent NERD and erosive esophagitis. Mechanism of different effect of dietary micronutrients on NERD and erosive esophagitis and longitudinal studies for this topic need to be researched in the near future.

Supplementary Materials

Note: To access the supplementary tables mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at <http://www.jnmjournal.org/>, and at <https://doi.org/10.5056/jnm18114>.

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Author contributions: Su Youn Nam had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and contributed to the study concept and design; Su Youn Nam, Kum Hei Ryu, and Bum Joon Park performed endoscopic procedures; Yeong-Ah Cho converted the diet records of each nutrient to electrical data; and all authors have read and approved the final version of the manuscript.

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