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Dietary magnesium, calcium:magnesium ratio and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma: a population-based case–control study

Qi Dai[1], Marie M. Cantwell[2], Liam J. Murray[2], Wei Zheng[1], Lesley A. Anderson[2] and Helen G. Coleman[2]* on behalf of the FINBAR study group

[1]*Vanderbilt Epidemiology Center, Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN 37203, USA*
[2]*Cancer Epidemiology & Health Services Research Group, Centre of Excellence for Public Health Northern Ireland, Centre for Public Health, Queens University Belfast, Belfast, BT12 6BJ, Northern Ireland*

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Abstract

Evidence suggests a role of Mg and the ratio of Ca:Mg intakes in the prevention of colonic carcinogenesis. The association between these nutrients and oesophageal adenocarcinoma – a tumour with increasing incidence in developed countries and poor survival rates – has yet to be explored. The aim of this investigation was to explore the association between Mg intake and related nutrients and risk of oesophageal adenocarcinoma and its precursor conditions, Barrett's oesophagus and reflux oesophagitis. This analysis included cases of oesophageal adenocarcinoma (*n* 218), Barrett's oesophagus (*n* 212), reflux oesophagitis (*n* 208) and population-based controls (*n* 252) recruited between 2002 and 2005 throughout the island of Ireland. All the subjects completed a 101-item FFQ. Unconditional logistic regression analysis was applied to determine odds of disease according to dietary intakes of Mg, Ca and Ca:Mg ratio. After adjustment for potential confounders, individuals consuming the highest amounts of Mg from foods had significant reductions in the odds of reflux oesophagitis (OR 0·31; 95 % CI 0·11, 0·87) and Barrett's oesophagus (OR 0·29; 95 % CI 0·12, 0·71) compared with individuals consuming the lowest amounts of Mg. The protective effect of Mg was more apparent in the context of a low Ca:Mg intake ratio. No significant associations were observed for Mg intake and oesophageal adenocarcinoma risk (OR 0·77; 95 % CI 0·30, 1·99 comparing the highest and the lowest tertiles of consumption). In conclusion, dietary Mg intakes were inversely associated with reflux oesophagitis and Barrett's oesophagus risk in this Irish population.

Key words: Diets: Magnesium: Calcium: Vitamin D: Reflux oesophagitis: Barrett's oesophagus: Oesophageal adenocarcinoma

Mg, the most abundant intracellular divalent cation in the body, plays an essential role in over 300 biological activities[1–6]. The major food sources of Mg are whole-grain foods, nuts, legumes, green leafy vegetables and deep-ocean fish[7]. Epidemiological studies have found low Mg intake to be related to an elevated risk of colorectal neoplasia in some[8–11] but not all studies[12–14]. One potential explanation for the inconsistency is that the interaction between Mg and Ca was not considered. Several studies have suggested that Ca and Mg may directly or indirectly compete for intestinal absorption[15,16]. Over 80 % of plasma Mg is ultrafiltrated and reabsorbed in the kidneys. A high Ca intake consistently leads to significantly increased excretion of Mg via urine[17–21]. Thus, it is possible that long-term consumption of a high Ca:Mg ratio diet may lead to Mg deficiency, even in the context of adequate Mg intake[22].

We have reported that only when individuals consume diets with low Ca:Mg ratios (i.e. below median ratios between 2·6 and 2·8) intakes of Ca and Mg may be related to a reduced risk of colorectal adenoma[8], and Ca supplementation led to a reduced risk of adenoma recurrence in one randomised clinical trial[23]. Further, Ca:Mg intake ratios modified the associations of dietary intakes of Mg and Ca and risks of mortality due to cancer and CVD in two large-scale population-based cohort studies conducted in Chinese populations with very low (median ratio of 1·7) Ca:Mg ratios[24]. Very recently, we reported potential interactions between dietary Mg with dietary vitamin D and serum 25-hydroxyvitamin D[25].

Previous findings from our Irish population-based case–control study found no association between Ca intake and risk of oesophageal adenocarcinoma, Barrett's oesophagus or reflux oesophagitis, whereas high vitamin D intakes were unexpectedly associated with an increased risk of oesophageal adenocarcinoma[26]. Given the emerging evidence of Mg as a chemopreventive dietary agent for colorectal neoplasia described above, and its intrinsic relationship with Ca[8,15–24] and vitamin D[25], we hypothesised that the previously observed associations for Ca and vitamin D intake may differ according to Mg intake. Furthermore, to our knowledge, no

* **Corresponding author:** Dr H. G. Coleman, fax +44 2890 235900, email h.coleman@qub.ac.uk

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study to date has investigated Mg intake in relation to risk of these oesophageal disorders. Identifying potential risk factors for oesophageal adenocarcinoma is of strong public health relevance, given its rising incidence in Western populations and associated poor survival rates[27,28]. Differences in the prevalence of oesophageal cancer and gastro-oesophageal reflux disease between Eastern and Western populations lend further support to dietary risk factors potentially contributing to their aetiology[29,30]. Gastro-oesophageal reflux is a major risk factor for oesophageal adenocarcinoma and medications commonly used to treat reflux symptoms, such as proton pump inhibitors[31], may lead to Mg deficiency[32,33]. Therefore, it may be even more pertinent to intervene to achieve optimal Mg intakes in this patient group.

The primary aim of this investigation was to evaluate the association between Mg intake and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma. Secondary aims of this study were to evaluate the associations between intakes of the inter-related nutrients of Mg, Ca and vitamin D according to Ca:Mg intake ratios and the risk of oesophageal lesions.

Methods

Study design

Study participants were drawn from the Factors INfluencing the Barrett's Adenocarcinoma Relationship study, an all-Ireland population-based case–control study established to investigate the aetiology of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma[34–36]. In brief, incident cases of oesophageal adenocarcinoma (*n* 227), long-segment Barrett's oesophagus (*n* 224) and population controls (*n* 260) were recruited from Northern Ireland and the Republic of Ireland between March 2002 and July 2004. Reflux oesophagitis cases (*n* 230) were recruited from Northern Ireland only between 2004 and 2005. Barrett's oesophagus, reflux oesophagitis and control subjects were frequency-matched within 5-year age and sex strata to oesophageal adenocarcinoma cases, upto a maximum age of 85 years. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Research Ethics Committee of the Queen's University Belfast, Northern Ireland, Clinical Research Ethics Committee of Cork Teaching Hospitals and Research Ethics Committee Board of St. James's Hospital, Dublin. All the subjects provided written informed consent to participate in the study.

Study participants

Incident cases of histologically confirmed oesophageal adenocarcinoma were identified from electronic pathology records in Northern Ireland and hospital clinical records in the Republic of Ireland. Non-dysplastic long-segment (≥3 cm) Barrett's oesophagus cases were recruited if specialised intestinal metaplasia had been histologically confirmed. Reflux oesophagitis cases had erosions of the oesophageal mucosa diagnosed at endoscopy, classified as grades 2–4 or grades B, C or D using the Savary-Miller/Hetzel-Dent or Los Angeles methods[37], respectively. Population-based controls were adults with no previous history of Barrett's oesophagus, oesophageal or other gastrointestinal cancer. Randomly selected controls were recruited via the General Practice Master Index in Northern Ireland and from four General Practices in the Republic of Ireland, representing both urban and rural areas within the Dublin and Cork regions. Response rates ranged from 42 % for controls to 69, 82 and 74 % for reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma cases, respectively.

Data collection

Trained interviewers collected data from study participants using an electronic questionnaire, which captured information on demographics, lifestyle, medication and co-morbidities. Dietary intake was assessed using a 101-item FFQ, adapted from a version of the European Prospective Investigation into Cancer and Nutrition FFQ[38], by incorporating additional foods reported as commonly eaten in the North/South Ireland Food Consumption Survey[39]. Mean daily dietary intakes were calculated from the FFQ using Q-Builder (Tinuviel Software). Participants were asked to recall their dietary habits over the 12-month period 5 years before interview; BMI 5 years before the interview was calculated using self-reported weight (kg) divided by current height (m^2), as measured by the interviewer. *Helicobacter pylori* infection status was assessed from serum samples using a Western blot assay, as previously described[40].

Statistical analysis

Participants were excluded from the analysis if they failed to complete the FFQ (*n* 22) or did not complete the FFQ section on dairy product intake (*n* 29), given our interest in studying the relationship between Mg and Ca intakes. This left 252 controls, 208 reflux oesophagitis, 212 Barrett's oesophagus and 218 oesophageal adenocarcinoma cases for consideration in the current analysis.

Characteristics and mean nutrient intakes were compared between groups using independent *t* tests for continuous variables and χ^2 tests for categorical variables. Unconditional logistic regression analysis was applied to generate OR and corresponding 95 % CI for oesophageal lesions according to tertiles of intake. Reflux oesophagitis analyses were restricted to controls from Northern Ireland only, as these patients were recruited from Northern Ireland only. Tertiles of energy-adjusted nutrient intakes were defined by distribution in the appropriate controls. In order to test for trend, each person within a particular tertile was assigned the median intake value for that tertile before inclusion in the regression model.

The nutrient density method was utilised to adjust for energy intake, which calculates intakes per 4184 kJ/d (1000 kcal/d) in addition to including log kJ/d (kcal/d) in the regression models[41]. Other confounders included in the models were age (years), sex, smoking status (current/previous/never), education (years), BMI 5 years before the interview (kg/m^2), occupation (manual/non-manual), alcohol intake (g/d), regular non-steroidal anti-inflammatory drug use (weekly use for at

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least 6 months duration), *H. pylori* infection (seronegative/seropositive) and location (Northern Ireland/Republic of Ireland). We also tested for energy-adjusted intakes of carbohydrate, fat, Ca and vitamin D, as well as for antioxidant score (a summary of combined intake of vitamin C, vitamin E, total carotenoids and Se, as previously described[42,43]). Confounders were selected due to being previously known risk factors for oesophageal lesions within this study population[26,34–36,40,42,44,45]. In separate models, we further tested for regular gastro-oesophageal reflux symptoms (ever/never) and hiatus hernia (ever/never), as it is debatable whether reflux symptoms or hiatus hernia may confound or be on the causal pathway between disease risk and the dietary variables of interest. We also sought to adjust for dietary fibre intake; however, it was too highly correlated with Mg intake (r 0·58) to be included in the statistical models. In an attempt to explore this further, we used the residuals method (regressing energy-adjusted Mg and fibre intakes) to test for fibre as a potential confounder[41]. Further testing for diabetes history, in line with a peer-review suggestion, was also conducted.

Stratified analyses were carried out according to categories of vitamin D intake and Ca:Mg intake ratios. The likelihood-ratio test was applied to evaluate potential interactions in stratified analyses. All the statistical analyses were carried out using Intercooled Stata version 12.0 (StataCorp LP).

Results

Descriptive characteristics for reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma cases as well as controls are shown in Table 1. Oesophageal adenocarcinoma cases were more likely to be smokers, consume more alcohol, have a higher BMI, have worked in manual occupations and completed fewer years of education compared with controls (as did Barrett's oesophagus cases). All three case groups were more likely to have experienced gastro-oesophageal reflux symptoms compared with controls.

Daily nutrient intakes of cases and controls are outlined in Table 2. Total energy and energy-adjusted fat intakes were greater across all case groups compared with controls. Energy-adjusted carbohydrate, fibre, antioxidant, Fe and Mg intakes were lower among all case groups compared with controls. Energy-adjusted Ca intake was lower in reflux oesophagitis cases only compared with controls, although Barrett's oesophagus and oesophageal adenocarcinoma cases were more likely than controls to have a high Ca:Mg intake ratios (Table 2). There were no significant differences in energy-adjusted vitamin D intakes from foods between case groups and controls.

The association between Mg intake and disease risk is shown in Table 3. After adjustment for potential confounders, individuals having the highest Mg intakes from foods had significant reductions in odds of reflux oesophagitis (OR 0·31; 95 % CI 0·11, 0·87) and Barrett's oesophagus (OR 0·29; 95 % CI 0·12, 0·71) compared with individuals having the lowest Mg intakes. Similarly strong inverse associations were detected for oesophageal adenocarcinoma in baseline models, but these became attenuated after adjustment for further confounders (tertile 3 (T3) *v.* T1; OR 0·77; 95 % CI 0·30, 1·99). Sensitivity analysis was conducted including further adjustment for gastro-oesophageal reflux symptoms, history of hiatus hernia, history of diabetes and daily fibre, vitamin D and Ca intakes, but these did not markedly alter the magnitude of associations observed (data not shown).

Table 4 displays results from the stratified analysis of Ca and Mg intakes according to Ca:Mg intake ratios, in relation to reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma risk. The previously observed protective effect of high Mg intake was more evident in the context of a low Ca:Mg ratio intake for reflux oesophagitis (OR 0·12; 95 % CI 0·02, 0·73) and Barrett's oesophagus (OR 0·24; 95 % CI 0·06, 0·96), although tests for interaction failed to achieve statistical significance ($P=0·13$ and $P=0·26$, respectively). Individuals having high Ca intakes also had reduced odds of reflux oesophagitis and Barrett's oesophagus in the context of a low dietary Ca:Mg ratio. Ca:Mg ratio did not alter the null associations between either Ca or Mg and oesophageal adenocarcinoma risk (Table 4).

We also investigated the association between disease risk and intakes of Ca, Mg and Ca:Mg intake ratios according to strata of vitamin D intakes, although no significant interactions with vitamin D intakes were detected (online Supplementary Table S1). Furthermore, the association between vitamin D intake and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma did not differ by strata of Ca:Mg intake ratios (online Supplementary Table S2).

Discussion

In this all-Ireland population-based study, high Mg intake was associated with a reduced risk of reflux oesophagitis and Barrett's oesophagus but not oesophageal adenocarcinoma. The protective effect of Mg was particularly pronounced in the context of a low Ca:Mg ratio intake. This differential effect also applied to Ca intakes, whereby high Ca intakes were associated with reduced odds of reflux oesophagitis and Barrett's oesophagus in the context of a low Ca:Mg intake ratio.

It is unclear why high Mg intake might particularly influence the earlier stages of cancer development, but not oesophageal adenocarcinoma. Growing evidence indicates that people with insulin resistance, the metabolic syndrome and type 2 diabetes are at high risk of Barrett's oesophagus[46–50]. Moreover, inflammation and reactive oxygen species play an important in the aetiology of Barrett's oesophagus[51,52]. A number of epidemiological studies have linked low dietary intake of Mg to elevated risks of systemic inflammation[53,54], insulin resistance[55–59], the metabolic syndrome[60–62] and type 2 diabetes[58,63–67]. In addition, Mg deficiency increased oxidative stress[68], whereas Mg supplementation reduced oxidative stress in animal models[6]. Thus, it is biologically plausible that high intakes of Mg protect against Barrett's oesophagus development.

Furthermore, one striking observation from animal studies is that Ca-adequate and Mg-deficient diets (i.e. diets with higher Ca:Mg ratios) led to increase in inflammatory responses and heart lipid peroxidation levels. Conversely, Ca-deficient and Mg-deficient diets (i.e. diets with lower Ca:Mg ratios) caused a significant reduction in heart lipid peroxidation and a normalisation of inflammatory responses[54,69]. Thus, these findings

Table 1. Characteristics of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma cases and controls (Numbers and percentages for categorical variables; mean values and standard deviations for continuous data)

	Northern Ireland controls (*n* 115)		Reflux oesophagitis (*n* 208)			All controls (*n* 252)		Barrett's oesophagus (*n* 212)			Oesophageal adenocarcinoma (*n* 218)		
Characteristics	*n*	%	*n*	%	*P**	*n*	%	*n*	%	*P*†	*n*	%	*P*†
Age (years)					<0·001					0·67			0·15
Mean	67·8		62·2			62·8		62·3			64·4		
SD	10·3		11·5			12·8		12·1			11·2		
Males	80	69·6	178	85·6	0·001	213	84·5	175	82·6	0·57	183	83·9	0·86
Location													0·40
Northern Ireland	115	100	208	100	–	115	45·6	146	68·9	<0·001	108	49·5	
Republic of Ireland	0	0	0	0		137	54·4	66	31·1		110	50·5	
Smoking status													<0·001
Never	51	45·1	97	47·8	0·60	100	40·8	85	40·3	0·40	44	20·7	
Previous	40	35·4	61	30·0		101	41·2	78	37·0		94	44·1	
Current	22	19·5	45	22·2		44	18·0	48	22·7		75	35·2	
Occupation type													0·02
Manual	52	46·8	100	49·0	0·71	121	49·4	122	58·4	0·06	127	59·9	
Non-manual	59	53·2	104	51·0		124	50·6	87	41·6		85	40·1	
Regular GOR symptoms‡	28	24·4	84	40·4	0·04	49	19·5	153	72·2	<0·001	106	48·6	<0·001
History of hiatus hernia	7	6·1	51	24·5	<0·001	16	6·4	101	47·6	<0·001	39	17·9	<0·001
History of diabetes§	9	7·8	21	10·2	0·49	16	6·4	16	7·7	0·56	19	8·8	0·32
Regular NSAID use‖	15	13·1	33	15·9	0·52	31	12·4	28	13·2	0·80	22	10·1	0·44
Helicobacter pylori positive	74	65·5	89	43·2	0·001	143	58·6	102	50·3	0·08	100	49·5	0·06
Education (years)					0·12					<0·01			<0·001
Mean	11·1		10·7			12·0		11·2			10·6		
SD	2·6		2·1			3·2		2·9			2·5		
BMI 5 years ago (kg/m^2)					0·24					0·75			<0·001
Mean	27·2		27·8			27·1		26·9			28·5		
SD	4·1		4·5			3·9		4·0			4·7		
Alcohol intake (g/d)					0·48					0·08			<0·01
Mean	19·9		22·1			26·3		21·8			19·4		
SD	22·2		21·7			23·1		23·7			21·8		

GOR, gastro-oesophageal reflux; NSAID, non-steroidal anti-inflammatory drug.
* Cases compared with Northern Ireland controls only, calculated using the *t* test (continuous variables) or χ^2 test (categorical variables).
† Cases compared with all controls, calculated using the *t* test (continuous variables) or χ^2 test (categorical variables).
‡ Heartburn/acid reflux symptoms experienced at least once weekly or >50 times/year >5 years before the interview date.
§ Includes both type 1 and type 2 diabetes – the majority of diabetes cases were type 2 diabetics, *n* 4 were type 1 diabetics.
‖ Ever used, defined as use at least once weekly for ≥6 months' duration.

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Table 2. Nutrient intakes of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma cases and controls (Mean values and standard deviations for continuous data; numbers and percentages for categorical variables)

	Northern Ireland controls (*n* 115)		Reflux oesophagitis (*n* 208)			All controls (*n* 252)		Barrett's oesophagus (*n* 212)			Oesophageal adenocarcinoma (*n* 218)		
Daily intakes	Mean	SD	Mean	SD	*P**	Mean	SD	Mean	SD	*P*†	Mean	SD	*P*†
Energy (kJ)	10870	3791	11 288	3159		11 380	3184	11 380	3184		11 414	3339	
Energy (kcal)	2598	906	2698	755	0·29	2720	761	2720	761	0·06	2728	798	0·04
Total fat (g/4184 kJ (1000 kcal))‡	40·1	5·5	41·4	5·3	0·03	36·5	7·2	39·3	6·5	<0·001	41·2	6·0	<0·001
Total carbohydrate (g/4184 kJ (1000 kcal))‡	119·7	15·3	114·3	14·8	0·002	123·5	18·4	120·6	17·3	0·09	115·9	15·4	<0·001
Fibre (g/4184 kJ (1000 kcal))‡	7·1	2·5	5·7	2·1	<0·001	6·7	2·7	5·7	2·2	<0·001	5·9	2·3	<0·001
Antioxidant index score (per 4184 kJ (1000 kcal))‡,§	11·1	5·3	9·3	4·0	<0·001	9·7	5·2	8·8	4·1	0·03	8·4	4·3	0·004
Vitamin D (μg/4184 kJ (1000 kcal))‡	1·2	0·6	1·1	0·5	0·11	1·1	0·6	1·1	0·5	0·71	1·2	0·5	0·13
Fe (mg/4184 kJ (1000 kcal))‡	5·4	0·8	5·0	0·7	<0·001	5·4	1·0	5·0	0·9	<0·001	5·2	1·0	<0·01
Ca (mg/4184 kJ (1000 kcal))‡	453·5	95·9	418·7	97·5	0·002	443·7	98·6	434·9	109·1	0·36	437·4	106·3	0·51
Mg (mg/4184 kJ (1000 kcal))‡	144·8	24·0	132·6	24·3	<0·001	147·5	27·5	133·0	24·5	<0·001	133·7	25·4	<0·001
Ca:Mg ratio‖					0·61					0·02			0·04
<Median													
n	57		97			126		82			88		
%	49·6		46·6			50·0		38·7			40·4		
≥Median													
n	58		111			126		130			130		
%	50·4		53·4			50·0		61·3			59·6		

* Cases compared with Northern Ireland controls only, calculated using the *t* test (continuous variables) or χ^2 test (categorical variables).
† Cases compared with all controls, calculated using the *t* test (continuous variables) or χ^2 test (categorical variables).
‡ Energy-adjusted where indicated per 4184 kJ (1000 kcal).
§ Antioxidant index score reflects a summary of combined intake of vitamin C, vitamin E, total carotenoids and Se.
‖ Ca:Mg intake ratio categories defined by the median value in Northern Ireland controls (3·15) for reflux oesophagitis analysis and all controls (3·05) for Barrett's oesophagus and oesophageal adenocarcinoma analysis.

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Table 3. Magnesium intake from foods and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma (Numbers; odds ratios and 95 % confidence intervals)

	Controls	Cases	Model 1*		Model 2†		Model 3‡	
	n	*n*	OR	95 % CI	OR	95 % CI	OR	95 % CI
Reflux oesophagitis§	115	208						
Mg (mg/4184 kJ per d (1000 kcal per d))								
<130·6	38	109	1·00		1·00		1·00	
130·6–<155·6	39	59	0·49	0·27, 0·89	0·44	0·19, 1·00	0·44	0·18, 1·09
≥155·6	38	40	0·33	0·17, 0·64	0·28	0·11, 0·68	0·31	0·11, 0·87
P_{trend}				0·001		0·006		0·03
Barrett's oesophagus	252	212						
Mg (mg/4184 kJ per d (1000 kcal per d))								
<134·0	84	109	1·00		1·00		1·00	
134·0 <157·7	84	70	0·66	0·42, 1·03	0·68	0·36, 1·26	0·72	0·37, 1·40
≥157·7	84	33	0·32	0·19, 0·54	0·25	0·12, 0·52	0·29	0·12, 0·71
P_{trend}				<0·001		<0·001		0·008
Oesophageal adenocarcinoma	252	218						
Mg (mg/4184 kJ per d (1000 kcal per d))								
<134·0	84	121	1·00		1·00		1·00	
134·0 <157·7	84	56	0·50	0·32, 0·78	0·69	0·39, 1·34	0·77	0·37, 1·61
≥157·7	84	41	0·37	0·22, 0·61	0·43	0·20, 0·92	0·77	0·30, 1·99
P_{trend}				<0·001		0·03		0·58

* Model 1: adjusted for age (years), sex, energy intake (by nutrient density method + log kJ/d (kcal/d)).
† Model 2: adjusted for model 1 + smoking status (current/previous/never), BMI 5 years ago, education (years), occupation (manual/non-manual), alcohol (g/d), regular non-steroidal anti-inflammatory drug use (ever/never), *Helicobacter pylori* infection (seropositive/seronegative) and location (Northern Ireland/Republic of Ireland).
‡ Model 3: adjusted for model 2 + antioxidant index score, energy-adjusted daily intakes of fat (g/4184 kJ per d (1000 kcal per d)) and carbohydrate (g/4184 kJ per d (1000 kcal per d)).
§ Analysis limited to Northern Ireland controls only.

indicate that in addition to intake of Mg, the Ca:Mg intake ratios contribute to the Mg status and, in turn, oxidative stress and inflammation status related to the development of Barrett's oesophagus. One relevant observation is that, although Barrett's oesophagus incidence is increasing, the prevalence rate is much lower in Asian populations[70] who have much lower Ca:Mg ratios compared with their Western counterparts[24].

Interestingly, we also found that high Ca intake was related to reduced risks of reflux oesophagitis and Barrett's oesophagus when the Ca:Mg intake ratios were below median levels. These findings are consistent with our earlier results on other gastrointestinal pre-malignant diseases, colorectal adenoma[8] and adenoma recurrence[23]. On the basis of our previous studies conducted in US populations with high Ca:Mg ratios[8,23] and in Chinese population with a very low Ca:Mg intake ratios[24], it is likely that Ca:Mg ratios between 1·70 and 2·63 may be required for high intake of Mg or Ca to be protective against colorectal cancer and CVD[24]. Further studies are warranted to examine whether this is also true for reflux oesophagitis and Barrett's oesophagus.

Adjustment for gastro-oesophageal reflux symptoms did not influence the results shown; therefore, it is unlikely that dietary Mg and Ca are mimicking properties of Ca/Mg-containing antacids in order to reduce the odds of reflux oesophagitis and Barrett's oesophagus. However, little is known about the role of micronutrients in gastro-oesophageal reflux aetiology, and thus this potential mechanism cannot be ruled out.

We have not found a significant association between intake of Mg and risk for oesophageal adenocarcinoma or a significant interaction between intakes of vitamin D and Mg. Future larger studies are needed. Regarding the interaction with vitamin D, serum concentrations of 25-hydroxyvitamin D should also be used in future studies, as it is a more accurate biomarker of body vitamin D status than dietary intake of vitamin D.

This study has several strengths. It is a large population-based study that enabled the role of these dietary factors to be investigated throughout the oesophageal carcinogenesis pathway. Statistical analyses took into consideration a large number of potential confounders. To our knowledge, it is the first study to assess dietary Mg and Ca:Mg ratio in relation to oesophageal lesion risk.

Similar to all case–control studies, there is potential for recall bias due to the use of FFQ to enquire about habitual diet 5 years before interview. Such retrospective questioning of dietary habits is necessary to help overcome the impact of symptoms associated with prevalent disease and resulting changes to eating habits. However, it is unlikely that cases would have differentially reported food sources rich in Mg due to their diagnoses. The response rate for controls was lower than that observed for cases; however, the daily Mg intake from food in our population-based controls was similar to that estimated in national dietary surveys in Ireland, suggesting that our controls are representative of the general population[71]. A further limitation of our study is that we considered only nutrient intake from foods and did not account for supplement usage. However, supplements were estimated to contribute to <5 % of total mineral intake (with the exception of Fe in females) in adults in the population at this time[71]. This may lead to non-differential misclassification of Ca and Mg intakes, which usually biases associations towards the null. Future studies should take supplement usage into account and investigate their contribution to overall mineral intakes in association with risk for these diseases. Owing to the asymptomatic nature of

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Table 4. Calcium and magnesium intake from foods and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma, stratified by Ca:Mg intake ratios
(Odds ratios and 95 % confidence intervals)

	Ca:Mg ratio < median*			Ca:Mg ratio ≥ median*			
		Adjusted†			Adjusted†		
	Controls/cases	OR	95 % CI	Controls/cases	OR	95 % CI	$P_{interaction}$
Reflux oesophagitis‡							
Ca (mg/4184 kJ per d (1000 kcal per d))							
<399·7	30/71	1·00		8/22	1·00		
399·7–<482·9	21/26	0·42	0·14, 1·24	18/42	1·39	0·32, 6·00	
≥482·9	6/0	Not calculable		32/47	0·93	0·21, 4·08	
P_{trend}			0·01			0·83	0·03
Mg (mg/4184 kJ per d (1000 kcal per d))							
<130·6	9/37	1·00		29/72	1·00		
130·6–<155·6	23/37	0·19	0·04, 0·96	16/22	0·43	0·10, 1·88	
≥155·6	25/23	0·12	0·02, 0·73	13/17	0·92	0·17, 4·94	
P_{trend}			0·04			0·88	0·13
Barrett's oesophagus							
Ca (mg/4184 kJ per d (1000 kcal per d))							
<395·5	69/61	1·00		15/19	1·00		
395·5–<474·0	39/20	0·78	0·32, 1·92	45/43	0·70	0·22, 2·18	
≥474·0	18/1	0·14	0·01, 1·27	66/68	0·74	0·23, 2·36	
P_{trend}			0·09			0·74	0·10
Mg (mg/4184 kJ per d (1000 kcal per d))							
<134·0	21/36	1·00		63/73	1·00		
134·0 <157·7	46/29	0·43	0·14, 1·35	38/41	0·88	0·34, 2·31	
≥157·7	59/17	0·24	0·06, 0·96	25/16	0·31	0·08, 1·23	
P_{trend}			0·05			0·13	0·26
Oesophageal adenocarcinoma							
Ca (mg/4184 kJ per d (1000 kcal per d))							
<395·5	69/64	1·00		15/22	1·00		
395·5–<474·0	39/12	0·60	0·21, 1·75	45/44	0·52	0·14, 1·95	
≥474·0	18/12	1·70	0·51, 5·68	66/64	0·56	0·14, 2·29	
P_{trend}			0·61			0·56	0·83
Mg (mg/4184 kJ per d (1000 kcal per d))							
<134·0	21/34	1·00		63/87	1·00		
134·0 <157·7	46/30	0·65	0·18, 2·34	38/26	0·50	0·16, 1·59	
≥157·7	59/24	0·86	0·20, 3·67	25/17	0·40	0·08, 1·88	
P_{trend}			0·97			0·20	0·97

* Ca:Mg intake ratio categories defined by the median value in Northern Ireland controls (3·15) for reflux oesophagitis analysis and all controls (3·05) for Barrett's oesophagus and oesophageal adenocarcinoma analysis.
† Adjusted for age (years), sex, energy intake (by nutrient density method + log kJ/d (kcal/d)), smoking status (current/previous/never), BMI 5 years ago, education (years), occupation (manual/non-manual), alcohol (g/d), regular non-steroidal anti-inflammatory drug use (ever/never), *Helicobacter pylori* infection (seropositive/seronegative), location (Northern Ireland/Republic of Ireland), antioxidant index score and energy-adjusted daily intakes of fat (g) and carbohydrate (g).
‡ Analysis limited to Northern Ireland controls only.

Barrett's oesophagus, and potentially oesophagitis, it is also possible that some of our control population may have had these conditions. Arguably, a superior control population would be individuals who have undergone endoscopy with negative findings; however, such a study design may impact on the generalisability of such controls.

Our findings indicate that high intake of Mg may protect against reflux oesophagitis and Barrett's oesophagus. The protective effect of Mg may be particularly pronounced in the context of a low Ca:Mg ratio intake. This is also true for Ca. Future studies including cohort studies and clinical trials are necessary to confirm our findings. Our findings, if confirmed, will have important public health significance.

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The authors have no conflicts of interest to declare.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S0007114515004444

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