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The Coeliac Stomach: Gastritis in Patients with Coeliac Disease

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Abstract

Background—Lymphocytic gastritis (LG) is an uncommon entity with varying symptoms and endoscopic appearances. This condition, as well as two forms of *H. pylori*-negative gastritis (chronic active gastritis [CAG] and chronic inactive gastritis [CIG]), appears to be more common in patients with coeliac disease (CD) based on single-center studies.

Aim—To compare the prevalence of LG, CAG, and CIG among those with normal duodenal histology (or non-specific duodenitis) and those with CD, as defined by villous atrophy (Marsh 3).

Methods—We analyzed all concurrent gastric and duodenal biopsy specimens submitted to a national pathology laboratory during a six-year period. We performed multiple logistic regression to identify independent predictors of each gastritis subtype.

Results—Among patients who underwent concurrent gastric and duodenal biopsy (n=287,503), the mean age was 52 and the majority (67%) was female. Compared to patients with normal duodenal histology, LG was more common inpartial villous atrophy (OR 37.66; 95% CI 30.16–47.03), and subtotal/total villous atrophy (OR 78.57; 95% CI 65.37–94.44). CD was also more common in CAG (OR for partial villous atrophy 1.93; 95%CI 1.49–2.51, OR for subtotal/total

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Disclosures:
All authors declare that they have no conflicts of interest and nothing to declare.

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Acquisition of data: BL, RMG
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villous atrophy 2.42; 95%CI 1.90–3.09) and was similarly associated with CIG (OR for partial villous atrophy 2.04; 95%CI 1.76–2.35, OR for subtotal/total villous atrophy 2.96; 95% CI 2.60–3.38).

Conclusion—LG is strongly associated with CD, with increasing prevalence correlating with more advanced villous atrophy. CAG and CIG are also significantly associated with CD. Future researchshould measure the natural history of these conditions after treatment with a gluten-free diet.

INTRODUCTION

Coeliac disease (CD) is a systemic immune-based disorder triggered by dietary gluten, the protein component of wheat, rye and barley.[1] The prevalence of CD has increased in recent decades [2] and the cause for this rise has not been determined. The loss of immune tolerance to gluten can occur at any age, and hypothesized triggers for this event include infections [3] and host factors relating to prenatal exposures[4] perinatal events[5] and the intestinal microbiome.[6] Alteration of the gastric environment has also been proposed as a contributor to the pathophysiology of CD; use of proton pump inhibitors and lack of colonization with *Helicobacter pylori* have been association with an increased risk of CD.[78]

Lymphocytic gastritis (LG) is an uncommon histopathologic finding with diverse clinical manifestations and poorly characterized natural history. [9] While it can be idiopathic or drug-induced, LG also appears to be associated with CD, appearing in up to 30% of such patients.[10] The clinical significance of LG, in patients with or without CD, is unknown, and there is no recognized treatment strategy for this histologic finding apart from institution of the gluten-free diet in patients with CD. Investigations of LG in patients with CD have been limited to single-center studies involving fewer than 300 patients with CD. Moreover, data regarding other forms of gastritis in patients with CD are lacking. In our recent study that found a lower prevalence of *H. pylori* colonization in patients with CD, we noted a surprisingly high prevalence of *H. pylori*-negative gastritis in this population, both chronic active gastritis (CAG) and chronic inactive gastritis (CIG).[7] This led us to hypothesize that these gastric abnormalities correlate with the severity of villous atrophy in patients with CD.

We therefore aimed to characterize the relationship between CD and three forms of gastritis: LG, *H. pylori*-negative CAG, and *H. pylori*-negative CIG using data from a national pathology database.

METHODS

We performed a cross-sectional analysis of histopathology specimens submitted to Miraca Life Sciences (Irving, TX), a United States pathology laboratory that receives specimens from 43 states, the District of Columbia, and Puerto Rico. Specimens are interpreted at threesites by a group of 35 gastrointestinal pathologists who use standardized reporting language and diagnostic criteria when formulating reports, as previously described.[7] We included procedures in which a concurrent gastric and duodenal biopsy specimenwas submitted to during a six-year period (January 2, 2008 through January 2, 2014), excluding patients with a previous diagnosis of upper gastrointestinal surgery or cancer.

Coeliac Disease

Patients were considered to have CD if their duodenal biopsy demonstrated villous atrophy (corresponding to a Marsh score of 3),[11] with accompanying duodenal intraepithelial lymphocytosis(Figure 1). Patients were further subdivided into partial villous atrophy (Marsh 3A) and subtotal or total villous atrophy (Marsh 3B/C). Although duodenal intraepithelial lymphocytosis with normal villous architecture may represent a mild histologic form of CD (Marsh 1), due to its relative lack of specificity we have not included patients with this finding in our definition of CD, in accordance with our previous analyses.[7,12,13] Patients without these findings were classified as having a normal duodenal biopsy; those with duodenitis (active mucosal inflammation with or without erosions or foveolar cell metaplasia) were classified as normal for the purposes of this analysis.

Lymphocytic Gastritis

LG was defined as the presence of at least 25 lymphocytes per 100 epithelial cells on the surface and foveolar epithelium, with chronic inflammation also noted in the lamina propria (Figure 2).

Chronic H. pylori-negative Gastritis

Chronic active gastritis was defined as the presence of polymorphonuclear cells in the lamina propria in the absence of *H. pylori* organisms.[14] Chronic inactive gastritis was defined as the presence of dense populations of lymphocytes and plasma cells within the lamina propria, in the absence of activity or *H. pylori* organisms.[15] Gastric specimens were considered to be *H. pylori*-negative if *H. pylori* was not detected on a specific polyclonal immunochemical stain (Cell Marque Corporation, Rocklin, California)that is routinely performed on all gastric specimens.

Statistical Analysis

We calculated the prevalence of LG, CAG, and CIG according to the following *a priori* categories: age (0–19, 20–39, 40–59, and >60 years), gender, and duodenal histology. The latter category was divided into the following categories: normal, duodenal intraepithelial lymphocytosis (DIL) with normal villi, partial villous atrophy, and subtotal/total villous atrophy. For the analysis of LG (but not CAG or CIG) we also calculated the prevalence stratified by *H. pylori* colonization. We used the chi square test to compare the prevalence of these gastritis subtypes in each of these categories, and we subsequently performed multivariate logistic regression using models that included all of the above variables to report odds ratios (OR) and corresponding 95% confidence intervals (CI) for the independent association between each variable and the presence of LG, CAG, or CIG.

All p values reported are two-sided. This study was deemed “non-human subjects research” by the Institutional Review Board of Columbia University Medical Center since all data was de-identified prior to being provided to the investigators.

RESULTS

Of 292,336 individuals who underwent concurrent gastric and duodenal biopsy during the specified time period. 4,833 were excluded due to a history of upper gastrointestinal surgery or cancer, leaving 287,503 for this analysis. Demographic and histologic characteristics are listed in Table 1. The median age was 53 years, and the majority were older than 40. Some 67% were female. Overall 64% of gastric biopsies were normal. LG was present in 818 (0.3%) individuals, chronic active *H. pylori*-negative gastritis (CAG) was present in 4,619 (2%) and chronic inactive *H. pylori*-negative gastritis (CIG) was present in 16,155 (6%), including 15,882 (5.5%) who had no evidence of *H. pylori* on immunostain. CD was present in 3,948 individuals (1.4%), including 2062 (0.7%) with partial villous atrophy and 1,886 (0.7%) with subtotal/total villous atrophy. Among the 3,948 patients with CD only 619 (16%) had normal gastric histology.

Increasing age was associated with an increased risk of LG (Table 2), while gender and *H. pylori* status were not. The prevalence of LG was 7.3% in patients with CD and the degree of villous atrophy directly correlated with the probability of concurrent LG; those with partial villous atrophy had an LG prevalence of 5.0%, while those with subtotal/total villous atrophy had an LG prevalence of 9.7%. On multivariate analysis, age remained a significant predictor of LG (OR for age ≥60 years compared to 20–39 years 1.83; 95%CI 1.51–2.21). Among individuals older than 60 years who had CD (n=1,246), 128 (10.3%) had LG. CD was strongly associated with LG on multivariate analysis (OR for partial villous atrophy 37.66; 95% CI 30.16–47.03, OR for subtotal/total villous atrophy 78.57; 95% CI 65.37–94.44).

H. pylori-negative CAG was most common in children, prevalent in 2% of individuals younger than 20 years (Table 3). In contrast, *H. pylori*-negative CIG was most common in older individuals, affecting 6.1% of subjects older than 60, compared to 5.1% of children (Table 4). These differences in CAG and CIG prevalence according to age remained significant on multivariate analysis. CD was more likely in those with CAG (OR for partial villous atrophy 1.93; 95%CI 1.49–2.51, OR for subtotal/total villous atrophy 2.42; 95%CI 1.90–3.09) and was similarly associated with CIG (OR for partial villous atrophy 2.04; 95%CI 1.76–2.35, OR for subtotal/total villous atrophy 2.96; 95% CI 2.60–3.38).

Duodenal intraepithelial lymphocytosis with normal villous architecture was positively associated with LG (OR 6.15; 95% CI 5.06–7.47), CAG (OR 1.65; 95%CI 1.50–1.82), and CIG (OR 1.42; 95%CI 1.34–1.51). In each category of gastritis, the association with intraepithelial lymphocytosis was weaker than the association with CD.

DISCUSSION

In this analysis of a nationwide pathology database of patients undergoing concurrent gastric and duodenal biopsies, we found that the prevalence of LG was significantly greater in those with CD (7.3%) than those without CD (0.15%), with an increasing prevalence correlating with the degree of villous atrophy. While gender and *H. pylori* status were not associated with LG, increasing age was, with the consequence that patients with CD older than 60 years

had a prevalence of 10.3%. *H. pylori*-negative CAG and CIG were also more common in patients with CD than those with normal duodenal biopsies, and a similar relationship between degree of villous atrophy and prevalence of gastritis was present. Villous atrophy was an independent risk factor for LG, CAG, and CIG on multivariate analysis.

The association between CD and LG is well established. The common feature of intraepithelial lymphocytosis in these two entities was invoked in an early series of patients with LG[16] and subsequent studies confirmed this association, [9,10,17] with one series noting that increased gastric intraepithelial lymphocyte counts decreased on follow-up biopsy in 5 patients.[18] In a study of 39 patients with CD and LG, Bhatti and colleagues found that these patients had more severe villous atrophy, higher transglutaminase antibody levels, and lower serum albumin than those patients with CD who did not have LG. [19]

More recently LG has been reported as a drug-induced entity; in a case series of 22 patients with severe sprue-like enteropathy attributed to the angiotensin receptor blocker olmesartan, LG was reported in 5 patients.[20] Our current study, which includes the largest number of CD patients with LG to date, found a gradient of LG prevalence according to the degree of villous atrophy, suggesting that LG reflects the host immune response to dietary gluten.

We found that there was no association between gastric *H. pylori* colonization and LG. This is consistent with a recent single-center investigation by Nielsen, et al that found that among 56 cases of LG, 54 had a predominant intraepithelial lymphocytosis and lacked *H. pylori*, while the 2 *H. pylori*-positive cases had a prominent neutrophilic infiltrate in the epithelium and lamina propria.[21] Given that our previous study found a negative association between *H. pylori* and CD,[7] and that the present analysis found a positive association between LG and CD, it is not surprising that on multivariate analysis (Table 2), *H. pylori* was negatively associated with LG, though this finding did not meet statistical significance (OR 0.87; 95%CI 0.67–1.12).

To our knowledge, this is the first investigation testing for an association between *H. pylori*-negative CAG or CIG with CD. This study has a number of strengths, including its large sample size and uniform definitions and reporting terminology. The multicenter setting allowed us to generate prevalence data more reflective of the true prevalence of LG and non-*H. pylori* CAG and CIG as compared to single-center studies. Our study was limited by the lack of serological details of patients with villous atrophy, leaving open the possibility of misclassification, since not all patients with villous atrophy have CD (though this is the most common cause of villous atrophy, even among patients with negative CD serologies).[22] We also lacked details regarding the clinical presentation of patients with these three types of gastritis. As such, the clinical implications of these gastric histologic abnormalities, and how they may affect of the natural history of CD, are not known. As this was a cross-sectional study, we do not know if gastritis preceded CD, occurred synchronously, or appeared subsequent to the development of villous atrophy. It therefore cannot be determined whether LG, CAG, or CIG triggers CD in certain individuals, is a consequence of gluten exposure, or reflects an autoimmune diathesis that is independent of CD activity.

Gastric biopsies are often taken when a patient undergoes duodenal biopsy. This is advocated partially to explore for the presence of *H pylori* gastritis that may be a cause of DIL.[23] The very frequent finding of abnormal gastric histology in patients with CD is corroborated in our data, with only 16% having normal gastric histology in this group. This finding may be noted by the clinician, but there is typically no further action initiated after the report is noted. This is because we have no information about the clinical significance of non-*Helicobacter*gastritis. Our results support the strong association between CD and gastric pathology, with increasing rates of gastric pathology corresponding to the severity of villous atrophy. These findings open avenues of research regarding the role of the stomach in the pathogenesis of CD. Specifically, questions arise about the influence of gastric pathology on digestion, drug metabolism or the microbiome as well on the long-term effect on general health of an individual. In recent years there has been consideration that long term blocking of gastric acid production by PPIs may have a deleterious effect on health.[824] Longitudinal studies of patients with gastric pathology in those with CD are warranted, especially in children.

We acknowledge that in this observational study we restricted our analysis to those individuals who underwent concurrent gastric and duodenal biopsy. Among all patients undergoing duodenal biopsy during the time period of this analysis (January 2, 2008 through January 2, 2014), 65% of those with CD had a gastric biopsy, compared to 82% of those without CD. As such, the prevalence estimates of LG may differ from that of a protocolized study in which every patient undergoing duodenal biopsy undergoes a concurrent gastric biopsy. Nevertheless, our risk estimates would only be biased if those patients with CD and LG were more likely to undergo gastric biopsy compared to non-CD patients with LG. Given that gastric biopsy is determined by a multitude of factors apart from CD (particularly the endoscopic appearance of the stomach) it is unlikely that these large difference in gastritis prevalence is driven by these different rates of gastric biopsy.

In conclusion, we found a strong association between CD and LG, and a weaker (but significant) association between CD and two other forms of *H. pylori*-negative gastritis, CAG and CIG. For all three of these gastritis subtypes, these outcomes were more common among patients with more severe villous atrophy. Future studies should determine the clinical implications and natural history of gastritis among patients with CD.

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Abbreviations used in this article

CD	coeliac disease
OR	Odds Ratio
CI	Confidence interval

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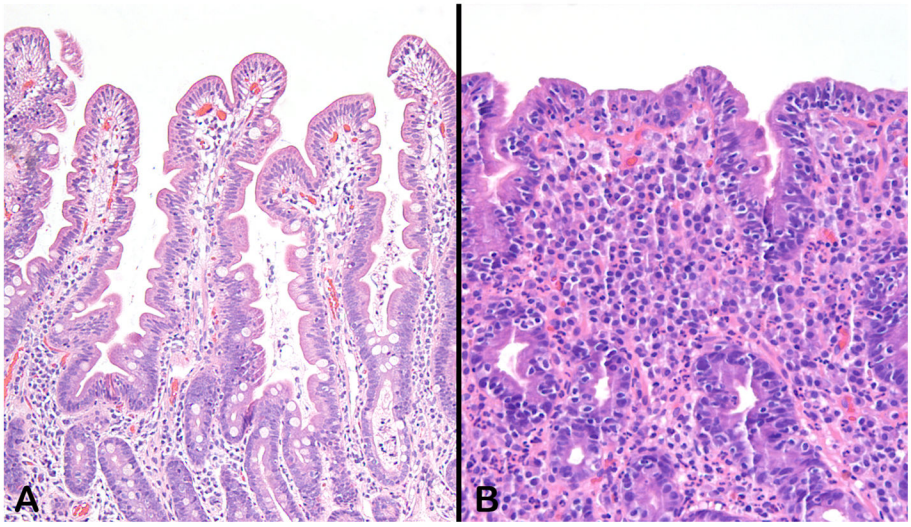

Figure 1.

Sections from normal duodenal mucosa (A) and from a mucosal biopsy with coeliac disease (B). In contrast to the long villi with only minimal numbers of intraepithelial lymphocytes, panel B shows an epithelium studded with lymphocytes and a lamina propria obliterated by a mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, eosinophils, and rare neutrophils. The normal mucin content of the normal goblet cells, evident in panel A, is completely depleted in the mucosa depicted in panel B. Both sections were stained with hematoxylin and eosin and photographed at an original magnification of 10X.

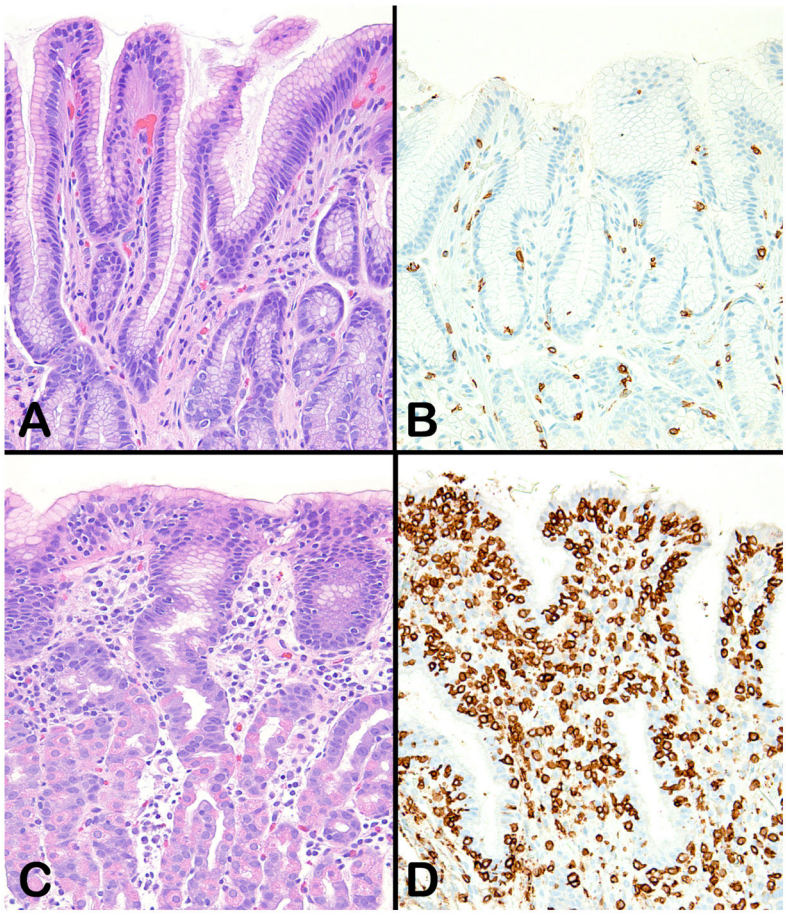

Figure 2.

Normal gastric mucosa stained with hematoxylin and eosin (A) and an anti-CD3 immunohistochemical stain (B). The normal gastric epithelium contains no intraepithelial lymphocytes; the rare CD3-positive cells seen in panel B are in the lamina propria. Panel C shows transitional gastric mucosa from a patient with lymphocytic gastritis. Although intraepithelial lymphocytes can be seen, particularly in the surface epithelium, their large numbers are best appreciated in sections stained with an anti-CD3 immunohistochemical stain (D). Original magnification 200X for all panels.

Table 1

Characteristics of patients who underwent concurrent gastric and duodenal biopsy during a six year period (n=287,503):

Characteristic	Number (%)
Age, years	
Mean/median (SD)	51.7/53 (18)
0–19	12,415 (4)
20–39	60,360 (21)
40–59	110,210 (38)
≥60	104,518 (36)
Gender*	
Male	96,722 (34)
Female	190,678 (67)
Gastrichistology	
Normal	183,325 (64)
Active *H. pylori* gastritis	27,366 (10)
Chronic active gastritis, *H. pylori* negative	4,619 (2)
Chronic inactive gastritis	16,155 (6)
Lymphocytic gastritis	818 (0.3)
Reactive gastropathy	46,790 (16)
Intestinal metaplasia	20,223 (7)
Atrophic gastritis	1,647 (0.6)
Duodenal histology	
Normal/duodenitis	264,739 (92)
Duodenal intraepithelial lymphocytosis	18,816 (7)
Partial villous atrophy	2,062 (0.7)
Subtotal/total villous atrophy	1,886 (0.7)

* Gender data missing for 103 patients (0.04%)

Table 2

Univariate and multivariate analysis of predictors of lymphocytic gastritis.

	Univariate Analysis		Multivariate Analysis	
Characteristic	**Prevalence of Lymphocytic Gastritis**	**P value**	**OR (95% CI)**	**P value**
Age, years		<0.0001		
0–19	26 (0.2)		0.75 (0.50–1.45)	0.1860
20–39	160 (0.3)		1.0 (ref)	ref
40–59	246 (0.2)		0.94 (0.77–1.53)	0.5632
≥60	386 (0.4)		1.83 (1.51–2.21)	<0.0001
Gender		0.3463		
Male	288 (0.3)		1.0 (ref)	ref
Female	530 (0.3)		0.88 (0.76–1.02)	0.0925
H. pylori status		0.1249		
H. pylori	65 (0.2)		0.87 (0.67–1.12)	0.2765
No *H. pylori*	753 (0.3)		1.0 (ref)	ref
Duodenal histology		<0.0001		
Normal/duodenitis	385 (0.15)		1.0 (ref)	ref
Duodenal intraepithelial lymphocytosis	146 (0.8)		6.15 (5.06–7.47)	<0.0001
Partial villous atrophy	104 (5.0)		37.66 (30.16–47.03)	<0.0001
Subtotal/total villous atrophy	183 (9.7)		78.57 (65.37–94.44)	<0.0001

Table 3

Univariate and multivariate analysis of predictors of chronic active (*H. pylori*-negative) gastritis.

	Univariate Analysis		Multivariate Analysis	
Characteristic	**Prevalence of Chronic Active Gastritis**	**P value**	**OR (95% CI)**	**P value**
Age, years		<0.0001		
0–19	249 (2.0)		1.21 (1.05–1.39)	0.0091
20–39	1,017 (1.7)		1.0 (ref)	ref
40–59	1,612 (1.5)		0.88 (0.82–0.96)	0.0022
≥60	1,741 (1.7)		1.03 (0.95–1.11)	0.4620
Gender		0.8880		
Male	1,550 (1.6)		1.0 (ref)	ref
Female	3,069 (1.6)		0.99 (0.93–1.06)	0.8405
Duodenal histology		<0.0001		
Normal/duodenitis	4,027 (1.5)		1.0 (ref)	ref
Duodenal intraepithelial lymphocytosis	464 (2.5)		1.65 (1.50–1.82)	<0.0001
Partial villous atrophy	60 (2.9)		1.93 (1.49–2.51)	<0.0001
Subtotal/total villous atrophy	68 (2.6)		2.42 (1.90–3.09)	<0.0001

Table 4

Univariate and multivariate analysis of predictors of chronic inactive (*H. pylori*-negative) gastritis.

	Univariate Analysis		Multivariate Analysis	
Characteristic	**Prevalence of Chronic Inactive Gastritis**	**P value**	**OR (95% CI)**	**P value**
Age, years		<0.0001		
0–19	634 (5.1)		0.91 (0.84–1.0)	0.05
20–39	3,384 (5.6)		1.0 (ref)	ref
40–59	5,447 (4.9)		0.89 (0.85–0.93)	<0.0001
≥60	6,417 (6.1)		1.14 (1.09–1.19)	<0.0001
Gender		0.0040		
Male	5,176(5.4)		1.0 (ref)	
Female	10,699(5.6)		1.05 (1.01–1.08)	0.0106
Duodenal histology		<0.0001		
Normal/duodenitis	14,046(5.3)		1.0 (ref)	ref
Duodenal intraepithelial lymphocytosis	1,361 (7.2)		1.42 (1.34–1.51)	<0.0001
Partial villous atrophy	210 (10.2)		2.04 (1.76–2.35)	<0.0001
Subtotal/total villous atrophy	265 (14.1)		2.96 (2.60–3.38)	<0.0001