Contribution of *Helicobacter pylori* Infection and Obesity on Heartburn in a Japanese Population

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**Summary** Heartburn is the main symptom of gastro-oesophageal reflux disease (GORD) which is a common disorder and is detrimental to health-related quality of life. The aim of the present study is to investigate the role of both *Helicobacter pylori* (*H. pylori*) infection and obesity to heartburn in a Japanese population. This was a cross-sectional study of 7386 (3789 male, mean age 52.5 yr), performed in 2002. Age, sex, smoking, drinking status, and presence/absence of heartburn were recorded. Body mass index (BMI) was calculated and anti-*H. pylori* antibodies were measured. For subjects aged 30–39 years and aged 50–59 years, heartburn reported by 7.8% and 9.1%, respectively, and antibodies to *H. pylori* were detected in 20.2% and 63.3%, respectively. Among younger individuals (≤39 years) with *H. pylori* infection, the adjusted odds ratio (OR) for having heartburn was 2.41, compared with those without infection. Overall, 21.3% were obese (BMI ≥25). Among middle-aged individuals (40–59 years) who were obese, the adjusted OR for having heartburn was 1.41, compared who were not obese. In conclusion, *H. pylori* infection and obesity are independently associated with increased risk of heartburn in the younger-aged and the middle-aged Japanese population, respectively.

**Key Words:** heartburn, *H. pylori* infection, obesity, cross-sectional study

**Introduction**

Heartburn is the main symptom in patients with gastro-oesophageal reflux disease (GORD) and adversely affects health-related quality of life [1, 2]. GORD is a common disorder in both Western [3] and Japanese [4, 5] populations. It is a multifactorial disorder, characterized by reflux of acidic gastric contents into the oesophagus with resultant tissue damage and clinical symptoms. The chief risk factors for GORD are hiatus hernia, a high dietary fat intake, smoking and alcohol consumption[6], retardation of gastric emptying, and obesity[7]. *Helicobacter pylori* (*H. pylori*) infection is well documented as a causative factor for gastric cancer, and eradication of *H. pylori* is recommended[8, 9]. Interestingly, attention has been recently focused on GORD induced by *H. pylori* eradication [10, 11].

In East Asian countries, *H. pylori* infection is a protective factor against GORD development. *H. pylori*-induced gastritis is frequently so severe that it suppresses acid secretion to a level that renders gastric juice relatively harmless to oesophageal mucosa. In these patients, acid secretion recovers substantially after *H. pylori* eradication and this can
lead to the development of GORD symptoms including mild oesophagitis \([11, 12]\).

By contrast, in Western countries, \textit{H. pylori} infection is not associated with GORD development. \textit{H. pylori} eradication eliminates gastric mucosal inflammation and then induces regression of corpus glandular atrophy. Consequently, acid secretion can fully recover without exacerbation of reflux disease \([13, 14]\).

Previous population-based cross-sectional studies have shown a positive relationship between obesity and GORD symptoms in Western countries \([3, 15]\). In contrast, two other large-scale population-based studies in Sweden \([16]\) and Denmark \([17]\) found no relation between obesity and the presence of GORD symptoms.

Based on the results of these studies, the contribution of both \textit{H. pylori} infection and obesity to GORD symptoms appears controversial. Moreover, there are few large studies designed to assess the role of \textit{H. pylori} infection and obesity in the development of heartburn as the main symptom of GORD in a Japanese population. The aim of the present study was to examine the role of \textit{H. pylori} infection and obesity in heartburn development in a Japanese population.

**Materials and Methods**

**Study design**

This was a cross-sectional study to investigate whether obesity and having \textit{H. pylori} infection, as determined by \textit{H. pylori} antibody status, is associated with heartburn in a Japanese population.

**Study population**

A total of 8680 individuals (4448 men and 4232 women), who underwent a medical checkup at Okazaki City Medical Association Public Health Center from January to December 2002, were enrolled in this study. Okazaki city is located as a major urban city in the Central District along the Pacific coast of Japan. The population of the city stands at around 350,000, largely comprising educated people who are concerned with their health. All subjects in this study were gave a written informed consent for study participation.

**Questionnaire**

Subjects were self-reportedly questioned on their age, gender, smoking status, alcohol intake, the use of anti-acid secretory drugs (including proton pump inhibitors and histamine 2 receptor antagonists), their present health and past history of gastroduodenal ulcers, other digestive diseases and upper gastrointestinal surgery. Height and weight were also measured. Smoking status was classified as presently smoked/had smoked at least one cigarette a day within 2 years before the study, or had never smoked. Alcohol intake was classified as none, occasional (alcohol less than once per month) or regular (alcohol more than once a week). For each subject, the body mass index (kg/m$^2$) was calculated and subjects were classified as thin (BMI $\leq$ 18.5 kg/m$^2$), normal (BMI 18.6–24.9 kg/m$^2$), and obese (BMI $\geq$ 25 kg/m$^2$) using a criterion of the Japan Society for the Study of Obesity \([18]\). Subjects were also questioned on the presence/absence of eight gastrointestinal tract symptoms: laryngeal discomfort, dysphagia, heartburn, epigastric pain, abdominal discomfort, abdominal pain, constipation and diarrhea. Of these eight symptoms only heartburn is reported in the present study. Heartburn was defined underlying the appearance of heartburn symptom at least 2 days a week. Exclusion criteria included the presence of ulcers and cancers of the gastrointestinal tract and other digestive diseases, regular use of anti-acid secretory drugs and a past history of upper gastrointestinal surgery.

**Assessment for prevalence of Helicobacter pylori infection**

A chemiluminescence enzyme immunoassay (CLEIA) was used to measure serum anti-\textit{H. pylori} IgG antibody directed against the sonicate of \textit{H. pylori}. This assay was performed by EIKEN CHEMICAL CO., LTD (Tokyo, Japan). Subjects with a titer of above 10 (CLEIA value) was considered to have \textit{H. pylori} infection. The presence of anti-\textit{H. pylori} antibodies has been previously shown to be associated with the presence of \textit{H. pylori} in biopsy samples in 96% of cases (data published by EIKEN CHEMICAL CO., LTD).

**Statistics**

Subjects were classified into three age groups: the younger-aged group ($\leq$ 39 years), the middle-aged group (40–59 years), and the older-aged group ($\geq$ 60 years). The relationship between \textit{H. pylori} infection, BMI and heartburn was analyzed by age group using logistic regression analysis, and the odds ratio (OR) with 95% confidence intervals (95% CI) were calculated. Analyses were performed with StatView statistical software. Statistical significant was considered as $p<0.05$.

**Results**

Of the 8680 subjects enrolled, 1294 were excluded due to the presence of gastroduodenal ulcer (592 individuals), the self-reporting of gastrectomy (100 individuals) and other digestive diseases (413 individuals) and the use of anti-acid secretory drugs (189 individuals) since these factors mask or are associated with heartburn \([19, 20]\). Overall 7386 individuals were considered in the analysis. The mean age was 52.5 years old, with a range of 18–91 years. Table 1 shows that the characteristics of subjects in the present study. Nearly one third (30.9%) of subjects were 50–59 years, while 1.2% were $\leq$ 29 years and 5.9 % were $\geq$ 70 years. The majority of subjects (72.7%) were in normal BMI groups (BMI 18.6–
24.9 kg/m²), while 21.3% were obese (BMI ≥ 25 kg/m²). Subjects who had occasionally or regularly smoked and drank made up 71.2% and 74.0% of the study population, respectively.

The prevalence of heartburn increases with age

Overall, the proportion of subjects reporting heartburn was 8.4%. Subjects in the age cohorts ≥ 50 years had the highest prevalence of heartburn (>9%) (Table 2).

The prevalence of H. pylori infection increases with age

The overall prevalence of H. pylori infection was 57.7%, and the prevalence increased with age from 20.2% for subjects ≤ 29 years to 71.4% for subjects ≥ 70 years (Table 3).

The prevalence of heartburn is linked to H. pylori status

For subjects ≤ 29, 16.6% of H. pylori-positive individuals reported having heartburn compared with 4.2% of H. pylori-negative individuals (Figure 1). With increasing age, the proportion of H. pylori-positive individuals reporting heartburn generally decreased, while the proportion of H. pylori-negative individuals reporting heartburn increased (Figure 1). In the younger-aged group (≤ 39 years), the adjusted OR of having heartburn was 2.41 (95% CI 1.52-3.82, P<0.001) for those with H. pylori infection compared...
with *H. pylori* negative individuals. There was no significant association between the presence/absence of *H. pylori* infection and heartburn in the middle-aged, the older-aged group and overall. (Table 4).

Heartburn is linked to obesity

BMI by age group is shown in Table 5. Among the middle-aged group (40–59 years) and overall in those who were obese (BMI ≥25), the adjusted ORs for having heartburn were 1.41 (95% CI 1.09–1.82, \( P < 0.05 \)) and 1.39 (95% CI 1.15–1.68, \( P < 0.05 \)), respectively compared with those who were not obese (Table 6). No significant association between obesity and having heartburn was found in the younger-aged and the older-aged subjects.

**Discussion**

The present study showed that *H. pylori* infection and obesity are independently associated with the heartburn in a Japanese population.

The prevalence of heartburn was 8.4% in this study similar to the prevalence of GORD previously reported for Japanese populations [5, 6]. It is possible that we underestimated the prevalence of heartburn in the present study, however, due to the exclusion criteria for this study. Unfortunately, composition of population in this study was different from that of the target population because we analyzed the data from subjects who underwent medical checkup.

In Japan and East Asia, it has been suggested that *H. pylori* infection is protective against GORD in older individuals [11, 12, 21]. The prevalence of *H. pylori* infection in Japan and East-Asia is particularly high and it is likely that the infection has been present for many years in the infected elderly. Thus, *H. pylori*-induced gastric atrophy may have become severe enough that acid secretion is inhibited to the extent that it does little damage to the oesophageal mucosa. A recent prospective cohort study in a German population also demonstrated a negative association between *H. pylori* infection and GORD symptoms with an odds ratio of 0.61 (95% CI 0.44–0.85, \( P < 0.01 \)) compared with a small and statistical non-significant difference in the prevalence of heartburn, as compared with no infection (OR; 1.05, 95% CI 0.97–1.14) and that *H. pylori* eradication treatment had no significant effect on the prevalence of heartburn two years after treatment (OR; 0.99, 95% CI 0.88–1.12) [23].

In the present study, there was no significant association

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Body mass index</th>
<th>% with symptom</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All age (n = 4105)</td>
<td>≤18.5</td>
<td>444 (0.6)</td>
<td>1</td>
<td>reference</td>
</tr>
<tr>
<td></td>
<td>18.6–24.9</td>
<td>5371 (72.7)</td>
<td>10.8</td>
<td>1.07  0.90–1.27</td>
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<td></td>
<td>≥25</td>
<td>1571 (21.3)</td>
<td>5.7</td>
<td>0.73  0.29–1.79</td>
</tr>
<tr>
<td>From 40 to 59 years old (n = 4105)</td>
<td>≤18.5</td>
<td>21 (23.6)</td>
<td>5.5</td>
<td>0.97  0.50–1.77</td>
</tr>
<tr>
<td></td>
<td>18.6–24.9</td>
<td>57 (64.0)</td>
<td>11.4</td>
<td>1.39  0.90–1.97</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
<td>11 (12.4)</td>
<td>1.41</td>
<td>1.05  0.61–1.72</td>
</tr>
<tr>
<td>Greater than 59 years old (n = 2223)</td>
<td>≤18.5</td>
<td>26 (6.0)</td>
<td>8.79</td>
<td>0.74  0.55–1.01</td>
</tr>
<tr>
<td></td>
<td>18.6–24.9</td>
<td>318 (73.4)</td>
<td>89 (20.6)</td>
<td>1.26  0.90–1.77</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
<td>433</td>
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</table>

Number of subjects is shown with percentage values in parentheses.

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<tr>
<th>Age Group</th>
<th>BMI</th>
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<th>Adjusted odds ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>All age (n = 7386)</td>
<td>≤18.5</td>
<td>444 (0.6)</td>
<td>1</td>
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<td>1571 (21.3)</td>
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<td>0.73  0.29–1.79</td>
</tr>
<tr>
<td>Less than 40 years old (n = 1058)</td>
<td>≤18.5</td>
<td>21 (23.6)</td>
<td>5.5</td>
<td>0.97  0.50–1.77</td>
</tr>
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between *H. pylori* infection and heartburn in the middle-aged and older-aged subjects. These results suggest that *H. pylori* infection is not associated with development of heartburn in these individuals. In those ≤39 years, a positive relationship between *H. pylori* infection and heartburn suggests that atrophic gastritis is mild and gastric acid secretion has not been reduced so dramatically, perhaps due to the shorter time span of infection. Labenz *et al.* proposed that *H. pylori*-induced gastritis in the antrum increases gastrin secretion and gastric acid secretion, so *H. pylori* infection could exacerbate heartburn. However, the damage to the oesophageal mucosa could be reduced by lower gastric acid secretion during *H. pylori*-induced pangastritis or severe corpus-predominant gastritis [24]. The results of our study are in support of this hypothesis. Moreover, *H. pylori* eradication may also lead to relief of heartburn in a younger Japanese population. Endoscopic and pathological prospective studies of reflux oesophagitis and gastric atrophy are needed to address this more specifically.

With respect to heartburn and obesity, the adjusted ORs for having heartburn when obese versus not obese were 1.41 (95%CI 1.09–1.82, P<0.05) and 1.39 (95%CI 1.15–1.68, P<0.05) in the middle-aged group and overall, respectively. These results demonstrated a positive relationship between obesity and having heartburn. This is of concern, since the prevalence of obesity has recently increased in Japan as a result of the rapid changes to a Westernized lifestyle [25]. The mechanism by which obesity increases the risk of GORD is unclear. However, it has been suggested that obesity results in an increase in risk of hiatus hernia [26], increased intra-abdominal pressure [27] and an increased frequency of transient lower oesophageal sphincter relaxation [28].

Other epidemiological studies have not shown obesity to correlate with the presence of GORD [16, 29], and different findings between studies may reflect population differences, for example in a Swedish case-control study of oesophageal cancer, the population was largely male and older [16]. Moreover, previous studies of BMI and erosive oesophagitis were performed among patients referred for endoscopy [26, 29]. In the present study, subjects were not selected based on their disease status. On the other hand, the recent meta-analysis showed obesity to be responsible for the development of GOR symptoms [30]. Our result was also in support of these prior findings.

In the present study, there is no significant association between *H. pylori* infection and obesity (OR; 0.993, 95%CI 0.978–1.009). Interestingly, Suzuki *et al.* reported that *H. pylori* infection reduced secretion level of ghrelin, an appetite-stimulating gastric peptide, in the stomach of Mongolian gerbils [31], so the eradication of *H. pylori* might induce obesity through the increasing the fundic source of ghrelin, and finally lead to onset of GORD.

In conclusion, the presence of *H. pylori* infection and obesity are independently associated with the presence of heartburn, the main symptom of GORD. *H. pylori* eradication may also lead to relief of heartburn in the younger Japanese population.

References


