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Body mass index, chronic atrophic gastritis and heartburn: a population-based study among 8936 older adults from Germany

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1 **Original Article**

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4 **Title:**

5 Body mass index, chronic atrophic gastritis and heartburn: a
6 population-based study among 8936 older adults from Germany

7
8 **Short title:**

9 Body mass index, chronic atrophic gastritis and heartburn

10
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31 **Keywords:**

32 Chronic atrophic gastritis; body mass index; heartburn

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5 **1 ABSTRACT**
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8 **2 Background:** Obesity and overweight have been positively related to
9 gastroesophageal reflux disease (GERD). It has been suggested, that this relation is
10 due to an increased gastric acid reflux which is caused by an enhanced
11 intra-abdominal pressure.
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17 **6 Aim:** We aimed to assess potential interaction of the association between body mass
18 index (BMI) and GERD by chronic atrophic gastritis (CAG) which goes along with
19 reduced acid production.
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24 **9 Methods:** In the baseline examination of ESTHER, a study conducted in 9953 older
25 adults in Saarland, information on frequency of heartburn, potential risk factors and
26 medical history were obtained by self-administered standardized questionnaire.
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47 **13 Results:** In total, 2,565 (28.7%) of the included subjects experienced heartburn within
48 the past 4 weeks. A pronounced dose-response relation was observed between BMI
49 and heartburn occurrence ($p < 0.001$) among people without CAG, but not among
50 people with CAG (p -value for interaction=0.018). Obese/overweight people with
51 CAG had a much lower risk of heartburn compared to obese/overweight people
52 without CAG (OR=0.31, 95% CI=0.24-0.40).
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62 **19 Conclusions:** Our results are consistent with the hypothesis that BMI is positively
63 related to GERD symptoms by its impact on acid reflux.
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4 1 INTRODUCTION
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7 Gastroesophageal reflux disease (GERD) is defined as chronic symptoms and/or
8 mucosal damage produced by the abnormal reflux in the esophagus, with heartburn
9 and acid regurgitation being the most common symptoms. GERD has become a
10 worldwide frequent health problem in the past decades and been related to the
11 development of esophagus cancer.^{1,2} There is substantial evidence to suggest a causal
12 link between the increasing of body mass index (BMI) and GERD symptoms.³⁻⁵ Apart
13 from the parallel trends in frequency of obesity and GERD, the proposed underlying
14 mechanisms are also physiologically plausible.⁶ Overweight and obesity have been
15 suggested to be associated with increased intra-abdominal pressure and subsequent
16 relaxation of the lower esophagus sphincter, thus leading to increased esophagus acid
17 exposure and higher risk of GERD.⁷⁻⁹
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30 Chronic atrophic gastritis (CAG) is an established precursor of gastric cancer, which
31 is most frequently caused by infection with *Helicobacter pylori*.^{10,11} CAG is a process
32 of chronic inflammation of the stomach mucosa, leading to loss of gastric glandular
33 cells and their eventual replacement by intestinal and fibrous tissues.¹²⁻¹⁴ GERD has
34 been suggested to be inversely associated with CAG due to impaired gastric acid
35 secretion.¹⁵⁻¹⁷ Therefore, assessing the effect of CAG on the association between BMI
36 and GERD may help to confirm the postulated underlying mechanisms. However, to
37 our knowledge, this study question has not been addressed so far.
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21 The objective of this study was to assess potential effect modification of the relation
22 between BMI and the frequency of heartburn by CAG in a large population-based
23 study among older adults from Germany.

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4 1 MATERIALS AND METHODS
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7 2 Study population
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10 3 Our analyses are based on baseline data of ESTHER, a large population-based cohort
11 4 study conducted among older adults in Germany to investigate new avenues of
12 5 prevention and early detection of chronic diseases in the elderly. Details of the study
13 6 design have been described elsewhere.¹⁸ Briefly, 9953 participants (45% males), aged
14 7 50-74 years (mean age: 62 years) were recruited between July 2000 and December
15 8 2002 by their general practitioners during a general health check-up in Saarland, a
16 9 state in the south-west of Germany. The distribution of major sociodemographic
17 10 factors and risk factors was very similar as in representative samples from the general
18 11 population.¹⁹ The study was approved by the ethics committees of the medical faculty
19 12 of the University of Heidelberg and of the medical board of the state of Saarland.
20 13 Written informed consent was obtained from each participant.
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33 14 Data collection
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36 15 *Questionnaires*
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40 16 **A detailed questionnaire was completed by every participant, asking for information**
41 17 **on socio-demographic characteristics, medical history, health status, family history**
42 18 **and lifestyle factors in a standardized manner.** Alcohol and coffee drinking was
43 19 quantified by the self-reported average consumption within the past 12 months.
44 20 Self-reported smoking status was classified into three groups (current smoker, former
45 21 smoker and never smoker). The frequency of heartburn was reported as never, seldom,
46 22 sometimes, frequently and always within the past 4 weeks. It was dichotomously
47 23 classified as presence (sometimes, frequently or always) and absence (never or
48 24 seldom) in our main analyses. In additional sensitivity analysis, subjects reporting to
49 25 have heartburn seldom were included in the former rather than the latter group.
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26 *Serological examinations*

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4 1 Serum samples were obtained from all participants and stored at -80°C . Serum
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6 2 concentrations of pepsinogen (PG) I and II were measured by ELISA (Biohit, Helsinki,
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8 3 Finland). Presence of CAG was determined by the following serological definition
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10 4 which has been used in previous epidemiological studies: PG I < 70 ng/mL and PG
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12 5 I/PG II < 3 .²⁰ All analyses were carried out in a blinded fashion in the same
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14 6 laboratory.

17 7 Statistical analysis

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20 8 The study population was characterized with respect to sex, age, education, smoking,
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22 9 alcohol drinking, coffee drinking, history of diabetes, presence of CAG and BMI.
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24 10 Differences in frequency of heartburn according to these variables were assessed by
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26 11 Pearson's chi-square test. In addition, Mantel-Haenszel chi-square test was used to
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28 12 assess dose-response trends.

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31 13 The association of BMI with heartburn prevalence was estimated with odds ratios
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33 14 (OR) and 95% confidence intervals (CI) using unconditional multiple logistic
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35 15 regression. BMI was categorized into 4 subgroups: <18.5 (underweight); 18.5 to 25.0
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37 16 (normal); 25.0 to 30.0 (overweight); and ≥ 30.0 (obese). Estimates of association were
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39 17 adjusted for age and sex, and, in addition, for other covariates that were previously
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41 18 reported to be associated with gastrointestinal reflux including education, smoking,
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43 19 alcohol drinking, coffee drinking and history of diabetes.²¹⁻²³ Evidence for interaction
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45 20 of BMI with sex and CAG were assessed using the likelihood ratio test (LRT) by
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47 21 comparing logistic regression models with and without an interaction term. Tests for
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49 22 trend by BMI were performed by treating BMI categories as continuous variable in
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51 23 the logistic regression analysis.

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55 24 All statistical analyses were carried out using SAS statistical software, release 9.1.
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4 1 RESULTS
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7 2 Of the 9953 participants in the ESTHER baseline examination, 8 were excluded from
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9 3 the analyses because of a history of gastroesophageal cancer, 502 because PG
10 4 concentrations were not available and 507 because information on heartburn was
11 5 missing, leading to a final study population of 8936. Overall, 4105 men and 4831
12 6 women were included with a mean age of 62 years. Table 1 shows the main
13 7 characteristics of the study population with respect to the presence of heartburn. The
14 8 overall prevalence of heartburn was 28.7%, no substantial difference was observed
15 9 between men (28.3%) and women (29.1%). A positive trend of prevalence of
16 10 heartburn with increasing age was observed ($p < 0.001$). Among participants with
17 11 serologically defined CAG, much lower prevalence (13.2%) was found as compared
18 12 to those without CAG (29.6%) ($p < 0.001$). History of diabetes was not found to be
19 13 related with heartburn. Furthermore, frequency of heartburn also varied with
20 14 education, smoking, alcohol consumption and coffee drinking (data not shown).
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34 15 As shown in Table 2, a clear dose-response relationship between BMI and frequency
35 16 of heartburn persisted in logistic regression analysis ($p < 0.001$) after adjustment for
36 17 age and sex, and in addition, for other multiple covariates including education,
37 18 smoking, alcohol drinking, coffee drinking and history of diabetes. Such a
38 19 dose-response relationship was observed both for men and women. The associations
39 20 were more pronounced for women than for men (p value of LRT for interaction
40 21 < 0.001).
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50 22 As shown in Figure 1 and Table 3, the dose-response relationship between BMI and
51 23 frequency of heartburn was pronounced among participants without CAG and
52 24 essentially absent among those with CAG (p value of LRT for interaction = 0.018).
53 25 **When the analyses were restricted to obese/overweight subjects (BMI ≥ 25.0), people**
54 26 **with CAG showed a significantly lower risk of heartburn compared to those without**
55 27 **CAG with a fully adjusted OR of 0.31 (95%CI: 0.24-0.40).** Alternative classification
56 28 of heartburn prevalence in additional sensitivity analyses as outlined in the methods
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1 section did not materially alter the results (data not shown).

For Peer Review

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4 1 DISCUSSION
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7 2 To our knowledge, this is the first epidemiological study addressing potential
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9 3 modification of the association between BMI and occurrence of heartburn by CAG.
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11 4 Our results are consistent with the hypothesis that BMI is positively related to GERD
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13 5 symptoms by its impact on acid reflux which is reduced in the presence of CAG.
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16 6 The prevalence of GERD has steadily increased to 10-20% in Western countries in the
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18 7 past decades.¹ This increase closely paralleled an increase in obesity.²⁴ Epidemiologic
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20 8 studies have consistently found positive associations between BMI and symptoms of
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22 9 GERD.^{3, 4} In this study population among 8936 older adults from Germany, we also
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24 10 observed the prevalence of heartburn to gradually increase from 16.7% for
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26 11 underweight subjects to 34.5% for obese subjects. There are two major physiological
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28 12 mechanisms that have been suggested to account for this association. First, the
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30 13 relation between BMI and GERD symptoms might be mediated by hormonal factors.
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32 14 Studies from Northern Europe suggested that circulating estrogen may play an
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34 15 important role in the presence of GERD symptoms, because obese women had an
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36 16 increased risk compared to obese men, and because the highest risk was found for
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38 17 postmenopausal women receiving estrogen therapy.^{25, 26} Effect modification by sex
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40 18 showed a stronger association of BMI with heartburn among women than among men
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42 19 in our study and would be consistent with this hypothesis. Second, weight gain may
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44 20 lead to an increase of intra-gastric pressure due to the extrinsic gastric compression
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46 21 caused by surrounding adipose tissue, and subsequent relaxation of the lower
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48 22 esophagus sphincter may increase esophagus acid exposure and risk of related
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50 23 symptoms.^{7, 8, 27} This mechanism is physiologically plausible and the dose-response
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52 24 relation consistently observed among both men and women in our study suggest that it
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54 25 may play a major role for the presence of GERD symptoms independent of potential
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56 26 estrogen mediated effects.
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59 27 Our findings on the modifying effect of CAG are of particular interest with respect to
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28 the second hypothesis. In our study population, lower prevalence of heartburn was

1 observed for subjects with CAG, which is consistent with the hypothesis that GERD is
2 inversely associated with the presence of CAG due to the impaired gastric acid
3 secretion.^{16, 17} This mechanism may also partly contribute to the increase of
4 prevalence of GERD symptoms in recent decades, because over the same period the
5 incidence of CAG has substantially decreased.^{28, 29} More intriguingly, the positive
6 relation between BMI and heartburn was not observed among subjects with CAG, **and**
7 **a significantly lower risk of heartburn was found among obese/overweight people**
8 **with CAG as compared to obese/overweight people without CAG.** CAG related
9 impaired gastric acid secretion which attenuates the risk of esophagus acid exposure
10 caused by weight gain associated intra-gastric pressures might be a plausible
11 explanation. It is worthy, however, to note that among participants with CAG, as
12 shown in Figure 1, there was a slight increase for the prevalence of heartburn in the
13 obese group (BMI \geq 30.0) as compared to the normal and overweight groups. This
14 observation suggests that CAG might not completely neutralize the effect of obesity.

15 In the interpretation of our data, some limitations have to be considered. First, data of
16 heartburn symptoms, socio-demographic and lifestyle factors were based on a
17 self-administered standardized questionnaire. Potential bias caused by inaccurate
18 response can therefore not be excluded. Second, we can not completely exclude that
19 the effect of BMI on the presence of heartburn may be confounded by dietary intake
20 or physical activity, even though the effect of BMI has been suggested to be
21 independent of these factors.^{3, 30, 31} No definitive data exist regarding the role of diet
22 and, in particular, of specific foods or drinks, in influencing GERD clinical
23 manifestations.^{32, 33} The negative relations of heartburn with the consumption of
24 alcohol and coffee observed in our study might be explained by the possibility that
25 people who are prone to heartburn avoid coffee and alcohol since they know it might
26 stimulate the stomach and trigger symptoms. In addition, using of proton pump
27 inhibitors (PPIs), which has been related to both CAG and GERD,³⁴ might be a
28 potential confounder. However, it was rare in our study population (3.7%) and
29 exclusion of people with PPI intake in sensitivity analyses did not affect the results

1 (data not shown). Third, the definition of CAG based on serum pepsinogen
2 concentrations cannot be claimed to be perfect. However, high levels of agreement
3 with classification by gastroscopy with subsequent histological examination of
4 biopsies have been observed.³⁵ Also, studies with CAG definitions based on
5 gastroscopy with either biopsy or the PG I/PG II ratio (alone or in combination with
6 PG I) yielded similarly strong associations of *H. pylori* with CAG.³⁶ Furthermore, a
7 commonly used definition for severe CAG (PG I < 20 ng/mL)¹⁸ was used in the
8 sensitivity analysis in this study, which did not materially alter the results (data not
9 shown).

10 In conclusion, our results are consistent with the hypothesis that overweight and
11 obesity are positively related to GERD symptoms. Furthermore, this association was
12 found to be modified by the presence of CAG which supports the hypothesis that acid
13 reflux might be the underlying key mechanism.

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For Peer Review

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5 **REFERENCE**
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- 8 1. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of
9 gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;**54**(5):710-7.
10
11 2. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA, Jr. Body-mass
12 index and symptoms of gastroesophageal reflux in women. *N Engl J Med*
13 2006;**354**(22):2340-8.
14
15 3. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for
16 gastroesophageal reflux disease and its complications. *Ann Intern Med*
17 2005;**143**(3):199-211.
18
19 4. Corley DA, Kubo A. Body mass index and gastroesophageal reflux disease: a
20 systematic review and meta-analysis. *Am J Gastroenterol* 2006;**101**(11):2619-28.
21
22 5. Friedenberg FK, Xanthopoulos M, Foster GD, Richter JE. The association
23 between gastroesophageal reflux disease and obesity. *Am J Gastroenterol*
24 2008;**103**(8):2111-22.
25
26 6. El-Serag H. The association between obesity and GERD: a review of the
27 epidemiological evidence. *Dig Dis Sci* 2008;**53**(9):2307-12.
28
29 7. O'Brien TF, Jr. Lower esophageal sphincter pressure (LESP) and esophageal
30 function in obese humans. *J Clin Gastroenterol* 1980;**2**(2):145-8.
31
32 8. Orlando RC. Overview of the mechanisms of gastroesophageal reflux. *Am J Med*
33 2001;**111 Suppl 8A**:174S-177S.
34
35 9. Barak N, Ehrenpreis ED, Harrison JR, Sitrin MD. Gastro-oesophageal reflux
36 disease in obesity: pathophysiological and therapeutic considerations. *Obes Rev*
37 2002;**3**(1):9-15.
38
39 10. Weck MN, Brenner H. Prevalence of chronic atrophic gastritis in different parts
40 of the world. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(6):1083-94.
41
42 11. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric
43 cancer epidemiology. *Lancet* 1975;**2**(7924):58-60.
44
45 12. El-Zimaity H. Gastritis and gastric atrophy. *Curr Opin Gastroenterol*
46
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49
50
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56
57
58
59
60

- 1
2
3
4 1 2008;**24**(6):682-6.
5
6 2 13. Rugge M, M DEB, Pennelli G, et al. Gastritis OLGA-staging & gastric cancer
7
8 3 risk: a twelve year clinico-pathological follow-up study. *Aliment Pharmacol Ther*. In
9
10 4 press.
11
12 5 14. Vannella L, Lahner E, Osborn J, et al. Risk factors for progression to gastric
13
14 6 neoplastic lesions in patients with atrophic gastritis. *Aliment Pharmacol Ther*. In
15
16 7 press.
17
18 8 15. Fujiwara Y, Higuchi K, Shiba M, et al. Association between gastroesophageal flap
19
20 9 valve, reflux esophagitis, Barrett's epithelium, and atrophic gastritis assessed by
21
22 10 endoscopy in Japanese patients. *J Gastroenterol* 2003;**38**(6):533-9.
23
24 11 16. Koike T, Ohara S, Sekine H, et al. *Helicobacter pylori* infection inhibits reflux
25
26 12 esophagitis by inducing atrophic gastritis. *Am J Gastroenterol* 1999;**94**(12):3468-72.
27
28 13 17. Yamaji Y, Mitsushima T, Ikuma H, et al. Inverse background of *Helicobacter*
29
30 14 *pylori* antibody and pepsinogen in reflux oesophagitis compared with gastric cancer:
31
32 15 analysis of 5732 Japanese subjects. *Gut* 2001;**49**(3):335-40.
33
34 16 18. Brenner H, Rothenbacher D, Weck MN. Epidemiologic findings on serologically
35
36 17 defined chronic atrophic gastritis strongly depend on the choice of the cutoff-value.
37
38 18 *Int J Cancer* 2007;**121**(12):2782-6.
39
40 19 19. Low M, Stegmaier C, Ziegler H, Rothenbacher D, Brenner H. [Epidemiological
41
42 20 investigations of the chances of preventing, recognizing early and optimally treating
43
44 21 chronic diseases in an elderly population (ESTHER study)]. *Dtsch Med Wochenschr*
45
46 22 2004;**129**(49):2643-7.
47
48 23 20. Weck MN, Stegmaier C, Rothenbacher D, Brenner H. Epidemiology of chronic
49
50 24 atrophic gastritis: population-based study among 9444 older adults from Germany.
51
52 25 *Aliment Pharmacol Ther* 2007;**26**(6):879-87.
53
54 26 21. Dore MP, Maragkoudakis E, Fraley K, et al. Diet, lifestyle and gender in
55
56 27 gastro-esophageal reflux disease. *Dig Dis Sci* 2008;**53**(8):2027-32.
57
58 28 22. Watanabe Y, Fujiwara Y, Shiba M, et al. Cigarette smoking and alcohol
59
60 29 consumption associated with gastro-oesophageal reflux disease in Japanese men.
30 *Scand J Gastroenterol* 2003;**38**(8):807-11.

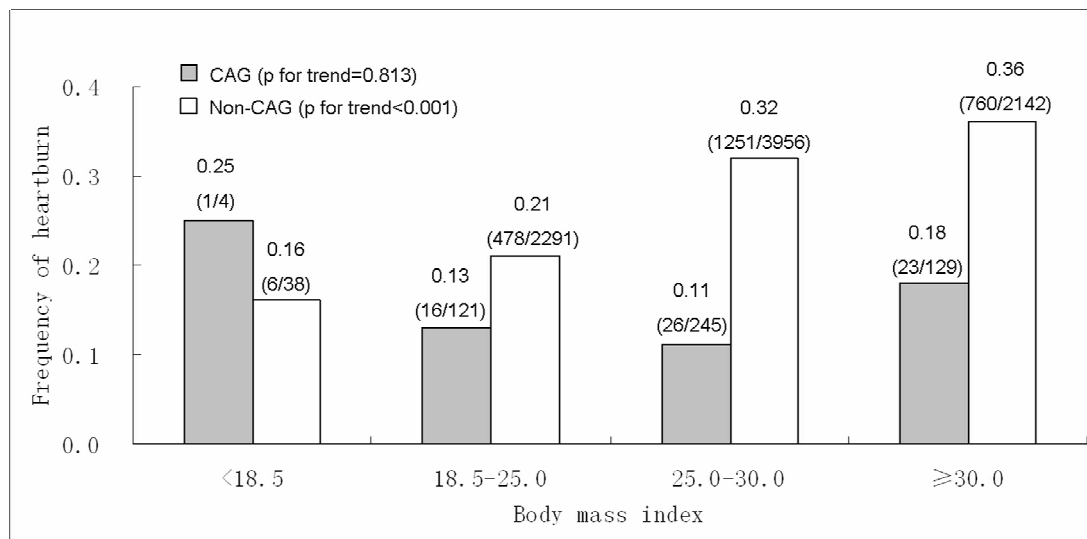
- 1
2
3
4 1 23. Nocon M, Labenz J, Willich SN. Lifestyle factors and symptoms of
5
6 2 gastro-oesophageal reflux -- a population-based study. *Aliment Pharmacol Ther*
7
8 3 2006;**23**(1):169-74.
9
10 4 24. Moayyedi P. The epidemiology of obesity and gastrointestinal and other diseases:
11
12 5 an overview. *Dig Dis Sci* 2008;**53**(9):2293-9.
13
14 6 25. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk
15
16 7 factors for gastroesophageal reflux symptoms. *Jama* 2003;**290**(1):66-72.
17
18 8 26. Nilsson M, Lundegardh G, Carling L, Ye W, Lagergren J. Body mass and reflux
19
20 9 oesophagitis: an oestrogen-dependent association? *Scand J Gastroenterol*
21
22 10 2002;**37**(6):626-30.
23
24 11 27. Sise A, Friedenberg FK. A comprehensive review of gastroesophageal reflux
25
26 12 disease and obesity. *Obes Rev* 2008;**9**(3):194-203.
27
28 13 28. Sipponen P, Helske T, Jarvinen P, Hyvarinen H, Seppala K, Siurala M. Fall in the
29
30 14 prevalence of chronic gastritis over 15 years: analysis of outpatient series in Finland
31
32 15 from 1977, 1985, and 1992. *Gut* 1994;**35**(9):1167-71.
33
34 16 29. de Vries AC, Meijer GA, Looman CW, et al. Epidemiological trends of
35
36 17 pre-malignant gastric lesions: a long-term nationwide study in the Netherlands. *Gut*
37
38 18 2007;**56**(12):1665-70.
39
40 19 30. Murray L, Johnston B, Lane A, et al. Relationship between body mass and
41
42 20 gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. *Int J*
43
44 21 *Epidemiol* 2003;**32**(4):645-50.
45
46 22 31. Nandurkar S, Locke GR, 3rd, Fett S, Zinsmeister AR, Cameron AJ, Talley NJ.
47
48 23 Relationship between body mass index, diet, exercise and gastro-oesophageal reflux
49
50 24 symptoms in a community. *Aliment Pharmacol Ther* 2004;**20**(5):497-505.
51
52 25 32. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients
53
54 26 with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med*
55
56 27 2006;**166**(9):965-71.
57
58 28 33. Festi D, Scaioli E, Baldi F, et al. Body weight, lifestyle, dietary habits and
59
60 29 gastroesophageal reflux disease. *World J Gastroenterol* 2009;**15**(14):1690-701.
30 34. Lodato F, Azzaroli F, Turco L, et al. Adverse effects of proton pump inhibitors.

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3
4 1 *Best Pract Res Clin Gastroenterol*;24(2):193-201.
5
6 2 35. Storskrubb T, Aro P, Ronkainen J, et al. Serum biomarkers provide an accurate
7
8 3 method for diagnosis of atrophic gastritis in a general population: The Kalixanda
9
10 4 study. *Scand J Gastroenterol* 2008;43(12):1448-55.
11
12 5 36. Weck MN, Brenner H. Association of *Helicobacter pylori* infection with chronic
13
14 6 atrophic gastritis: Meta-analyses according to type of disease definition. *Int J Cancer*
15
16 7 2008;123(4):874-81.
17
18 8
19 9

For Peer Review

1 **FIGURE LEGEND**

2 Figure 1. Body mass index and prevalence of heartburn by chronic atrophic gastritis



1 **Table 1. Characteristics of the study population and presence of heartburn**

2

	Heartburn*		p for difference
	n/N [#]	%	
Total	2565/8936	28.7	
Sex			
Male	1160/4105	28.3	
Female	1405/4831	29.1	0.401
Age			
50-54 years	386/1570	24.6	
55-59 years	434/1526	28.4	
60-64 years	721/2437	29.6	
65-69 years	614/2036	30.2	
70-74 years	410/1367	30.0	0.002
History of diabetes			
Presence	252/943	26.8	
Absence	2141/7554	28.3	0.321
Chronic atrophic gastritis			
Presence	66/499	13.2	
Absence	2499/8437	29.6	<0.001

3 *Sometimes, often or always within the past four weeks.

4 [#]Sum may not always add up to total because of missing data.

1 **Table 2. Association between BMI and presence of heartburn**

2

BMI	Heartburn*		Adjusted OR (95% CI) [#]	Adjusted OR (95% CI) [§]
	n/N	%		
Total				
<18.5	7/42	16.7	0.77 (0.34-1.74)	0.54 (0.19-1.55)
≥18.5-<25.0	494/2412	20.5	Ref.	Ref.
≥25.0-<30.0	1277/4201	30.4	1.70 (1.51-1.92)	1.71 (1.50-1.95)
≥30.0	783/2271	34.5	2.05 (1.80-2.34)	1.99 (1.71-2.30)
p for trend			<0.001	<0.001
Males				
<18.5	0/14	0	NA	NA
≥18.5-<25.0	197/886	22.2	Ref.	Ref.
≥25.0-<30.0	637/2181	29.4	1.43 (1.19-1.72)	1.48 (1.21-1.81)
≥30.0	325/1020	31.9	1.63 (1.32-2.00)	1.64 (1.31-2.07)
p for trend			<0.001	<0.001
Females				
<18.5	7/28	25.0	1.29 (0.54-3.07)	0.92 (0.30-2.80)
≥18.5-<25.0	297/1526	19.5	Ref.	Ref.
≥25.0-<30.0	640/2020	31.7	1.87 (1.60-2.19)	1.83 (1.53-2.18)
≥30.0	458/1251	36.6	2.35 (1.98-2.79)	2.21 (1.81-2.69)
p for trend			<0.001	<0.001

3 Abbreviation: BMI, body mass index; CI, confidence interval; NA, not available; OR, odds ratio.

4 *Sometimes, often or always within the past four weeks.

5 [#]Partly adjusted for age and sex.6 [§]Fully adjusted for age, sex, education, smoking, alcohol drinking, coffee drinking and history of diabetes.

1 **Table 3. Interaction between BMI and CAG regarding presence of heartburn**

2

CAG	BMI	Heartburn*		Adjusted OR (95% CI) [#]	Adjusted OR (95% CI) [§]
		n/N	%		
Absence	<25.0	484/2329	20.8	Ref.	Ref.
	≥25.0	2011/6098	33.0	1.88 (1.68-2.11)	1.86 (1.64-2.11)
Presence	<25.0	17/125	13.6	Ref.	Ref.
	≥25.0	49/374	13.1	0.99 (0.54-1.80)	1.11 (0.54-2.32)
p for likelihood ratio test				0.003	0.018

3 Abbreviation: BMI, body mass index; CAG, chronic atrophic gastritis; CI, confidence interval; OR, odds ratio.

4 *Sometimes, often or always within the past four weeks.

5 [#]Partly adjusted for age and sex.

6 [§]Fully adjusted for age, sex, education, smoking, alcohol drinking, coffee drinking and history of diabetes.

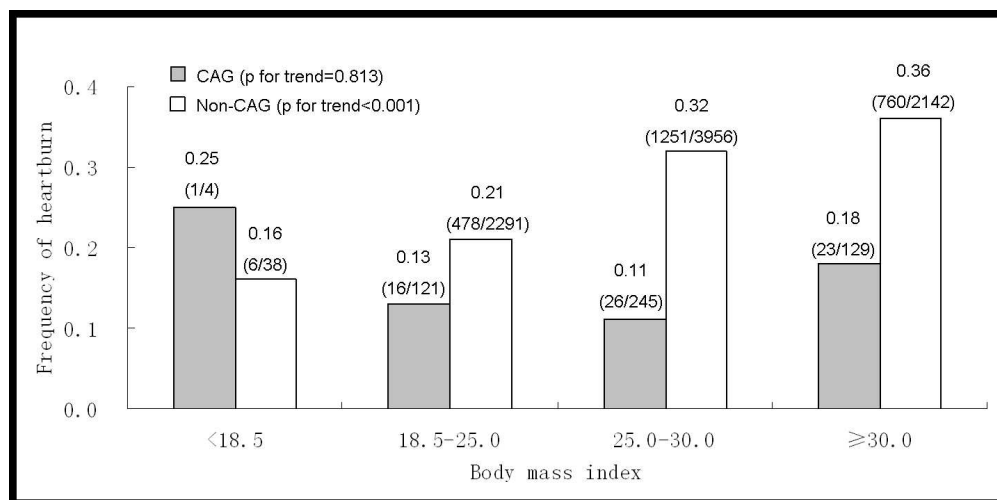


Figure 1. Body mass index and prevalence of heartburn by chronic atrophic gastritis
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