Minireview

Prevalence of Chronic Atrophic Gastritis in Different Parts of the World

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Abstract

Chronic atrophic gastritis (CAG) is a well-established precursor of intestinal gastric cancer, but epidemiologic data about its occurrence are sparse. We provide an overview on studies that examined the prevalence of CAG in different parts of the world. Articles containing data about the prevalence of chronic atrophic gastritis in unselected population samples and published until November 2005 were identified by searching the MEDLINE database. Furthermore, the references in the identified publications were screened for additional suitable studies. Studies comprising at least 50 subjects were included. Forty-one studies providing data on the prevalence of CAG in unselected population samples could be identified. CAG was determined by gastroscopy in 15 studies and by pepsinogen serum levels in 26 studies.

Although results are difficult to compare due to the various definitions of CAG used, a strong increase with age, the lack of major gender differences, and strong variations between populations and population groups (in particular, relatively high rates in certain Asian populations) could be observed quite consistently. We conclude that CAG is relatively common among older adults in different parts of the world, but large variations exist. Large-scale international comparative studies with standardized methodology to determine CAG are needed to provide a coherent picture of the epidemiology of CAG in various populations. Noninvasive measurements of CAG by pepsinogen levels may be particularly suited for that purpose. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1083–94)

Introduction

Chronic atrophic gastritis (CAG) plays a crucial role in the development of intestinal gastric cancer, the most common type of gastric cancer, which continues to be one of the leading cancer causes of death in the world. Mortality rates of gastric cancer are particularly high in Asia, South America, and parts of Europe (1). It is well established that gastric carcinogenesis is a continuous process leading from nonatrophic gastritis to glandular atrophy (loss of specialized glands), to metaplasia and dysplasia, and finally to adenocarcinoma (2, 3). This process usually takes decades and seems to be initiated by infection with the gastric bacterium *Helicobacter pylori* in many if not most cases (4-7). The long-term development may thus potentially provide opportunities for early detection of precancerous lesions and intervention. However, because the majority of individuals carrying CAG do not suffer from any symptoms, CAG and early-stage gastric cancer remain unrecognized in most cases.

Presence of CAG may be determined either by gastroscopy with subsequent histologic analysis of obtained biopsies (8) or by investigating the pepsinogen (PG I and PG II) concentrations in serum (9, 10); both PG I and the PG I/PG II ratio are decreased in CAG. A number of epidemiologic studies have meanwhile assessed the prevalence of CAG in different populations, but the selection of study samples and the definitions of CAG have been quite diverse. In this article,

we provide a comprehensive review of published data on the prevalence of chronic atrophic gastritis, with particular attention to differences and similarities in the methods used. We thereby aim to delineate the current state of knowledge regarding the epidemiology of CAG and the need for further investigation.

Materials and Methods

Studies investigating the prevalence of chronic atrophic gastritis were identified by searching for articles in the MEDLINE database, using various combinations of the terms "chronic atrophic gastritis," "CAG," "prevalence," "atrophic gastritis," "atrophic," "gastritis," "(gastric) atrophy," "pepsinogen(s)," "precancerous lesion(s)," "stomach", and "(mass) screening." The references in the thus acquired articles were also screened for suitable studies (cross-referencing). The analysis was restricted to studies published in English until November 30, 2005.

To ensure reasonable levels of precision of prevalence estimates, we excluded studies with <50 participants. We also excluded studies where patients were preselected according to gastrointestinal symptoms (e.g., gastroscopy-based studies where gastroscopy was employed due to symptoms rather than as a primary screening tool). These criteria were employed to avoid biased estimates of prevalences.

Information retrieved from the publications are place and time of the study, constitution of the study population, number of participants, male/female ratio, age (range and mean), type of measurement of CAG, and criteria for diagnosis. Whenever possible, the prevalence of CAG was extracted in terms of an overall value and stratified by gender, by age, and by location of the lesion (latter for gastroscopy screenings only). In some of the publications, the actual numbers were not stated but could be derived from published graphs.

According to type of measurement of CAG, the studies were grouped into gastroscopy-based screenings with subsequent histologic examination on one hand and in studies that determined serum pepsinogen levels on the other hand. Prevalences extracted from the gastroscopy-based studies include both CAG with and without more advanced lesions.

Results

The literature search identified 89 studies providing data about CAG prevalences. Of these, 48 studies were excluded from this review for the following reasons: preselection of study population due to symptoms (44 studies) and size of the study population (four studies). References of excluded studies are given in Appendix 1.

As the numbers indicate, the selection of the study participants turns out to be the most critical criterion. It was paid close attention to exclude all studies showing any evidence of a preselection of participants related to gastritis. Nevertheless, not all included studies do include perfectly representative population samples. Study samples also accepted were blood donors, elderly people, hospital workers, industry workers, smokers, and people taking part in an annual health examination or a CVD screening and self-defense forces. These primarily non–population-based study populations were tolerated because even a selection via population registers cannot assure perfect random samples when taking response rates into account.

Among the 41 studies that met the inclusion criteria, there are 15 gastroscopy-based studies (11-28) and 26 studies measuring pepsinogen concentrations (29-60). In all but two of the latter, pepsinogen levels were measured by RIA; in the studies by Sipponen et al. (54) and Green et al. (59), measurements were done by enzyme immunoassay. Not all of the studies had the primary intention to determine the CAG prevalence. Some of the studies collected the data primarily for other purposes, such as to study the role of CAG and other risk factors in the development of gastric cancer (15, 18, 19, 32, 33, 35, 37, 43, 55, 56), or to assess the association of CAG with *H. pylori* infection (25, 44). An overview on the studies is given in Table 1 (gastroscopy-based studies) and Table 2 (studies based on serum pepsinogen levels), respectively.

Due to use of different methods of measurements and varying definitions and cut points, a direct comparison of prevalences among the studies is difficult. Despite this difficulty, a number of patterns become apparent when looking at the data.

Gastroscopy-based studies have been conducted in all continents except for Africa, with a main focus on high-risk areas of gastric cancer. In detail, they were done in Asia [Japan (25) and China (22, 26)], in Europe [Finland (11, 14), Estonia (12, 16), the Netherlands (13), Norway (20), Sweden (27), Italy (15, 18), and Hungary (15)], in Columbia (19), in Iran (28), and in Australia (24), with the first study being published in 1968 by Siurala et al. (11) from Finland. The number of participants varied widely among the different studies. By inclusion criteria, the smallest study population enclosed 50 participants. Most of the gastroscopy-based studies comprised between 100 and 250 participants, but there were also three studies examining >1,000 persons, the maximum number being 3,400. One study was restricted to males, all others comprised both males and females. The age of participants varied considerably among the studies because some population registry-based studies investigated people with an age range from 16 to 69 years, but narrower age ranges were included in several other studies.

Prevalence rates vary widely between the populations screened by gastroscopy and even within population groups.

Although most studies show prevalences below 50%, some studies conducted in Japan and China reveal much higher prevalences (22, 25, 26). An increase of CAG prevalence with age was consistently found in most studies looking at age-specific prevalences. However, two studies (22, 26) from a Chinese population with one of the world's highest rates of stomach cancer showed prevalences of CAG or even more advanced lesions close to 100% even among the youngest of the included age groups. Most studies do not reveal any differences between males and females. Except for one study (16), CAG was always more frequent in the antrum than in the fundus/corpus.

Measurement of pepsinogen serum levels was carried out by 11 studies in Japan (33, 35, 44, 49, 51-53, 55-58), two studies among Japanese living abroad (48, 50), several others in Europe [United Kingdom (31, 40), Italy (32), Finland (43, 46, 54) and the Netherlands (47)], two in the United States (29, 45), and one in New Zealand (59). International comparative studies included population samples from 13 (37), 4 (60), and 2 (42) nations, respectively. The period of pepsinogen-based studies started about 20 years later than the gastroscopy based studies, with the first pepsinogen-based prevalence study being published by Krasinski et al. (29) in 1986. Studies measuring serum pepsinogen levels, which are both less invasive and less costly than gastroscopy-based screening, mostly included much larger study populations. The smallest sample comprised 105 persons, and eight studies, six studies, and two studies included between 500 and 1,000, between 1,000 and 10,000, or even >10,000 persons, respectively. Most of the studies included both genders, eight studies were restricted to males. The age of participants that were included varied considerably among the different studies. Some studies investigated people with broad age ranges, such as from 20 to 86 years, but much narrower age ranges were included in other studies, such as age groups 25 to 34 and 55 to 64 years, which were included in the largest international comparative study (37).

Prevalences determined in the pepsinogen-based studies may be influenced by factors that modify pepsinogen levels, and prevalences are comparable only as far as identical cut points are used. The very low prevalences found in the EUROGAST study (37), an international comparative study, including 17 populations from 13 countries, primarily reflect the very restrictive cut point used in this study (PGI < 25 ng/mL), which delineates quite severe forms of CAG. Apart from Algeria, prevalences of severe CAG were below 5% in age groups 25 to 34 in all countries included in this study, but ranged up to 11% in age group 55 to 64. Prevalences were higher in Algeria (10.4% and 16.0% in age groups 25 to 34 and 55 to 64, respectively) and Japan than in European and U.S. populations, and there was major variation even within different populations from Japan. Much higher prevalences delineating less severe forms of CAG were found in studies with less restrictive pepsinogen cut points of CAG. An increase of prevalence with age was observed by most of the studies. Most studies did not detect relevant differences in gender, even after stratification by age. Interestingly, the multicenter EUROGAST study (37) detected a higher (or equal) prevalence for women in all 17 populations except for Italy and one population in Japan, but these mostly small differences have to be interpreted with caution given the relatively low number of subjects within the populations. This study is also the only pepsinogen-based study that analyzed age-specific differences by sex, and it found a significantly increased prevalence for women versus men ($P = 0.002$) in the age group of 25 to 34 but not in the age group of 55 to 64 years (all nations combined).

Time trends in prevalence of CAG can only be judged from studies applying the same methodology in comparable

Table 1. Gastroscopy-based studies

Author(s), year (ref.*)	Study population				Prevalence of CAG in %				Performance of gastrostroscopy and histology§
	Country (time of survey)	Setting	No. participants (gender), response rate	Age (mean)	Overall (severe)	By sex (severe)	By age†,‡ (severe)	By location (severe)	
Siurala et al., 1968 (11, 16)	Finland (1966)	Population registry based	142 (M, 45.1%; F, 54.9%), 74%	16-65 (42)		M, 20.3; F, 34.6	Age: body 16-20: 6 21-30: 10 31-40: 21 41-50: 20 51-60: 51 61-65: 60	Body: 28 (2.8)	• Suction tube method (blind) • Mostly three biopsies per subj. • crit.: Siurala et al. (11)
Villako et al., 1976 (12, 16)	Estonia	Population registry based	155 (M, 38.0%; F, 62.0%), 62%	16-69 (46)			Age: fundus/ antrum 16-19: 0/29 20-29: 0/8 30-39: 11/11 40-49: 21/33 50-59: 27/42 60-69: 31/35	Fundus: 20 (6), antrum: 29 (1)	• Mostly four biopsies per subj. (fundus and antrum, each posterior and anterior wall) • crit.: Siurala et al. (11)
Kreuning et al., 1978 (13)	Netherlands	Hospital workers + ''healthy'' volunteers	50 (M, 54%; F, 46%)	20-58 (33)	34 (4)	M, 22; F, 43	20-29: 10 30-39: 31 40-49: 80 50-59: 50	Fundus: 30, antrum: 34	• Biopsies from seven standard sites‖ • crit.: Whitehead (73)
Ihamaki et al. 1979 (14)	Finland	Population registry based (controls for GC relatives)	358 (M, 50.2; F, 49.8), 87%	15 to ≥66 (46.0)	Body/antrum: M, 13/26; F, 18/29		Age: body/ antrum 15-30: 6/10 31-50: 7/24 51-65: 27/44 ≥65: 42/49	Body: 16, antrum: 28	• Biopsies: at least three from antrum plus at least six from body • crit.: Siurala et al. (11)
Cheli et al., 1980 (15)	Italy	''Randomly chosen'' (hospital based)	100		22		20-29: 6.7 30-39: 17.6 40-49: 22.2 50-59: 33.3 60-69: 18.8 70-79: 40.0		• Biopsies: one from fundus plus one from antrum • crit.: Valencia-Parparcen et al. (74)
	Hungary		100		37		20-29: 14.3 30-39: 22.2 40-49: 33.3 50-59: 29.4 60-69: 44.4 70-79: 80.0		
Villako et al., 1982 (16, 17)	Estonia (1979)	Population registry based	227 (M, 45.4%; F, 54.6%), 85%	15-69 (39.9)	Body/antrum: M, 41/38¶; F, 33/31¶		Age: fundus/ antrum 15-19: 21/16 20-29: 20/29 30-39: 24/25 40-49: 35/35 50-59: 64/54 60-69: 67/45	Body: 37 (6), antrum: 34 (1)	• Biopsies: at least three from antrum plus at least six from body • crit.: Siurala et al. (11)
Cheli et al., 1986 (18)	Italy	Controls for duodenal ulcer patients (hospital based)	60 (M, 68%; F, 32%)	20-69 (42)			Age: fundus/ antrum <40: 7.2/3.6 >40: 25.0/25.0	Fundus: 16.6, antrum: 15.0	• Biopsies: three from body and two from antrum‖ • crit.: Cheli et al. (77)

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Table 1. Gastroscopy-based studies (Cont'd)

Author(s), year (ref.*)	Study population				Prevalence of CAG in %				Performance of gastrostroscopy and histology[§]
	Country (time of survey)	Setting	No. participants (gender), response rate	Age (mean)	Overall (severe)	By sex (severe)	By age[†,‡] (severe)	By location (severe)	
Correa et al., 1990 (19)	Columbia (1973-1983)	Household based	1,670 (M, 49.9%; F, 50.1%)	15 to ≥55	45	M, 48; F, 41	15-24: 23 25-34: 37 35-44: 49 45-54: 64 ≥55: 59		• Multiple biopsies (at least four sites plus at gastroscopic suspect regions)[‖] • crit: Correa (75) and Correa et al. (76)
Johnsen et al., 1991 (20, 21)	Norway (1987)	Population registry based (controls for dyspeptic persons)	273 (M/F, ~50%/ 50%), 65%	20-69	50.5				• Biopsies from corpus and antrum, including both greater and lesser curvature • crit.: Whitehead (72) and Owen (78)
You et al., 1993 (22, 23)	China (1989-1990)	Population registry based	3,400 (M, 52.7%; F, 47.3%), 93%	35-64	98.1		Age: male/female 35-39: 97.3/97.3 40-44: 98.4/98.2 45-49: 98.4/99.5 50-54: 97.7/100.0 55-59: 98.4/99 60-64: 100/99.2	Cardia: 48-58**, body: 29-66**, angulus: 82-83**, antrum: 76-90**	• Multiple biopsies (at least seven sites plus at gastroscopic suspect regions)[‖] • crit.: You et al. (22)
Katelaris et al., 1993 (24)	Australia	Healthy volunteers (recruited via advertising)	50 (only men)	18-30 (mean 23) and ≥50 (mean 73)	22		18-30: 0 ≥50: 39	Fundus: 16, body: 16, antrum: 22	• Biopsies: four from antrum, three from corpus, four from fundus • crit: Sydney system (69)
Asaka et al., 1996 (25)	Japan	Health screening	85	30 to ≥60	52.9		Age: Hp[+]/Hp[−] [††] 30-39: 49/0 40-49: 60/12 50-59: 69/15 ≥60: 87/30		• Biopsies: paired biopsy specimen from antrum and corpus • crit: Sydney system (69, 71)
You et al., 1998 (26)	China (1994)	Population registry based	214[‡‡] (M, 50%; F, 50%)	35-64	82.2	M, 80.4; F, 84.1	35-39: 81.6 40-44: 80.9 45-49: 76.9 50-54: 86.6 55-59: 78.6 60-64: 87.0	Body: 13.2, angulus: 59.1, antrum: 70-79[§§]	• Biopsies: 4[‖] • crit: You et al. (22)
Borch et al., 2000 (27)	Sweden	Population registry based	501 (M, 55%; F, 45%), 25%	35-85	28 (8.2)		35-44: 8 45-54: 19 55-64: 21 65-74: 36 ≥75: 56		• Biopsies: three from body (major, anterior, posterior) and three from antrum (within 3 cm of pylorus) • crit.: Sydney system (69, 70)

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Table 1. Gastroscopy-based studies (Cont'd)

Author(s), year (ref.*)	Study population				Prevalence of CAG in %				Performance of gastrostroscopy and histology[§]
	Country (time of survey)	Setting	No. participants (gender), response rate	Age (mean)	Overall (severe)	By sex (severe)	By age[†,‡] (severe)	By location (severe)	
Malekzadeh et al., 2004 (28)	Iran (2000-2001)	Population registry based	1,001 (M, 48.9%; F, 51.1%), 91.5%	40-92 (53)				Cardia: 21.9, corpus: 46.9, antrum: 45.2	• Multiple biopsies (at least four sites plus at gastroscopic suspect regions)[‖] • crit.: Malekzadeh et al. (28)

Abbreviations: crit., criteria for diagnosis of CAG; F, female; GC, gastric cancer; M, male; subj., subject.

*When multiple references are listed: the first publication contains data on prevalence rates; the others contain information on additional extracted study details.

†Age-stratified data were derived from graphs in Kreuning et al. (13), Ihamaki et al. (14), and Asaka et al. (25).

‡Age-stratified data are subdivided in severe and nonsevere forms (data not shown in the table because numbers are too small) in Siurala et al. (11), Villako et al. (12), Ihamaki et al. (14), and Villako et al. (16).

§The numbers of biopsies refer to the aspired quantity; sometimes, not all of them could be obtained in a subject.

‖Exact sites for biopsies: Kreuning et al. (13): (*1*) prepyloric; (*2*) minor curvature just above the angulus; (*3*) major curvature opposite to *2*; (*4*) high up the minor curvature, just below the cardia; (*5*) antrum; (*6*) middle of corpus, posterior wall; (*7*) fundus. Cheli et al. (18): (*1*) middle portion of the lesser curvature, just proximal to the incisure; (2) high on the lesser curvature, 3 cm below the cardia; (3) middle portion of the greater curvature; (4) antral anterior wall, within 2 cm of the pylorus; (5) antral posterior wall within 2 cm of the pylorus. Correa et al. (19): (*1*) midportion of antral lesser curvature; (2) midportion of antral greater curvature; (3) transition zone; (*4*) midanterior wall of body; (5+) additional biopsies; (6+) gastroscopic suspect lesions. You et al. (22): (*1*) midway between cardia and angulus on the lesser curvature; (2) middle of the greater curvature of the corpus; (3) center of the angulus along the middle portion of the lesser curvature; (4) 1 cm from the pylorus along the lesser curvature; (5) posterior wall of the antum; (6) anterior wall of the antrum; (7) greater curvature of the antrum; (*8+*) if severe lesions were visually at gastroscopy. You et al. (26): (*1*) greater curvature of the body, (2) angulus, (3) lesser curvature of the antrum, (4) greater curvature of the antrum. Malekzadeh et al. (28): (*1*) antrum between the incisura angularis and pyloric canal; (2) antrum, on the opposite of *1* over the greater curvature; (3) cardia, 0.5 to 1.0 cm below the gastrooesophageal junction on the anterior wall; (4) same as 3 but on posterior wall; (*5-6*) in some subjects: corpus greater and lesser curvature; (*7+*) at all visible lesions.

¶Difference not significant.

**Variations in location-stratified values depend on sex and exact biopsy site.

††The age-stratified data are subdivided between *H. pylori*–infected subjects (Hp+) and those who are not infected (Hp−).

‡‡Only participants from Cangshan are included because results from Linqu are already analyzed in You et al. (22).

§§Variations in location-stratified values depend on the exact biopsy site.

samples of participants from the same country/region at various points of time. Such pepsinogen-based studies were reported by Kobayashi et al. (55) conducted in Japan in 1989/1990 and 1996, respectively, and revealed a decrease in age-specific CAG prevalences over time.

H. pylori infection in the study population was determined in four gastroscopy-based studies (24, 25, 27, 28) and in 17 pepsinogen-based studies (34, 35, 37, 40, 42-44, 47-53, 56, 58, 60). However, only the minority of them reported the prevalence of CAG by *H. pylori* infection.

Discussion

Although CAG is an important step in the development of intestinal gastric cancer, data on prevalence are rare and even lacking entirely for most countries of the world. Due to selection of study samples, to varying definitions of CAG used and to differing cutoff values available, results are difficult to compare even among the few studies reported to date. Nevertheless, it becomes clear that CAG is relatively common among the elderly population. In addition, strong variations between populations and population groups, with much higher rates in some Chinese and Japanese populations than in other parts of the world, as well as an increase with age and the absence of differences between males and females were detectable throughout.

The absence of differences by sex is surprising because men have an increased rate of gastric cancer compared with women (1, 19). Interestingly, reported prevalences even tended to be higher in women in the international EUROGAST study (37). However, this difference in gender seemed to be

partly due to body weight and disappeared after adjusting for it (37). Furthermore, in a study by Sipponen et al., the risk of developing gastric cancer was shown to be much smaller for women with CAG than for men with CAG (61). The increase in CAG with age may reflect progression of gastritis with age. However, it may also reflect a birth cohort effect, as pointed out by Sipponen (62): *H. pylori* gastritis is a birth cohort-related phenomenon, with different cohorts showing different prevalences. Higher CAG prevalences in cohorts born in the beginning of the century in those born later may thus be caused by a decline in infection with *H. pylori* in younger birth cohorts. The much higher rates of CAG reported from Asian populations may also be related to the very high prevalence of *H. pylori* infection found in these countries (63, 64). Likewise, the decrease in age-specific CAG prevalence over time suggested by a study from Japan (55) may be related to decreasing *H. pylori* prevalences in younger birth cohorts.

A most crucial aspect in studying the epidemiology of CAG is the type of ascertainment of the diagnosis. In the history of screening for atrophic gastritis, several other methods and markers have also been tested, such as measurement of serum gastrin (65, 66), acid secretion (9), the Azure-A test (67), uropepsin determination (67), and investigation of mucins (2, 3) or multiple serum nutrient levels (68). However, only microscopic histologic assessment and serum pepsinogen measurement (occasionally in combination with *H. pylori* serology) are widely used today.

Considering gastroscopy with subsequent histologic investigation of biopsies, the grading scheme used for defining gastritis has to be taken into account. The Sydney system (69-71) and the Whitehead classification (72, 73) are used most

Table 2. Pepsinogen-based studies

Authors, year (ref.*)	Study population				Prevalence of pepsinogen defined CAG in %			Criteria for diagnosis
	Country (time of survey)	Setting	No. participants (gender), response rate	Age (mean†)	Overall (severe)	By sex (severe)	By age‡ (severe)	
Krasinski et al., 1986 (29, 30)	USA (1981-1984)	Elderly people (recruited via advertising)	359 (M, 34.8%; F, 65.2%)	60-99 (76 ± 9)	31.5 (8.1)		60-69: 24.0 (4.8) 70-79: 31.7 (7.3) 80-99: 37.1 (11.1)	all: PGI/PGII <2.9 sev: (PGI/ PGII <2.9 and PGI <20 ng/ml)
Burr et al., 1987 (31)	UK	Two towns with different GC-death rate (GP lists)	513 (only men), 75%	65-74 (69)	(7.7)§ (14.5)§			sev: PGI <20 ng/ml
Palli et al., 1991 (32)	Italy (1985-1989)	Population registry based (four regions)	930 (M, 58 %; F, 42 %), 61%	35-74 (58.9)	12.1 (5.8)	M, 13.3 (6.5); F, 10.5 (4.9)	35-49: 5.6 (1.3) 50-64: 9.9 (4.5) 65-74: 18.6 (10.0)	all: (PGI >20 ng/ml and PGI/PGII ≤2.9) or PGI ≤20 ng/ml sev: PGI ≤20 ng/ml
Fukao et al., 1993 (33, 34)	Japan (1991-1992)	Blood donors (four regions)	1,815 (M, 51.2%; F, 48.8%)		13-38‖	M, 13.9-38.8 5; F, 12.3-37.8 5	Age: male/ female 16-19: 3-13/5-15‖ 20-29: 5-20/0-20‖ 30-39: 10-40/3 -33‖ 40-49: 17-42/12-45‖ 50-59: 22-66/15-62‖ 60-64: 26-62/28-69‖	all: PGI <70 ng/ml and PGI/PGII <3.0
Tsugane et al., 1993 (35, 36)	Japan (1989-1991)	Population registry based (five regions)	624 (only men), 60-80%	40-49	9.4-26.6			all: PGI <70 ng/ml and PGI/PGII <3.0
Webb et al., 1994 (37–39)	13 nations¶ (17 populations) (1989-1991)	Population registry offices; GP lists; driver's license rosters; health screenings	3,195 (M/F, ~50%/50%)	25-34 and 55-64	(4.8)	M, (4.1)¶; F, (5.5)¶	25-34: (2.1)¶ 55-64: (7.5)¶	sev: PGI <25 ng/ml
		Europe	2,410		(3.3)	M, (2.4)¶; F, (4.2)¶	25-34: (1.3)¶ 55-64: (5.3)¶	
		Japan	386		(6.1)	M, (7.5)¶; F, (4.8)¶	25-34: (1.5)¶ 55-64: (10.8)¶	
		US	198		(1.5)	M, (1.1)¶; F, (2.0)¶	25-34: (0)¶ 55-64: (3.1)¶	
		Algeria	200		(14.2)	M, (10.7)¶; F, (20.0)¶	25-34: (10.4)¶ 55-64: (16.0)¶	
Knight et al., 1995 (40, 41)	UK	Industry workers (recruited from four factories)	420 (only men)	18-63 (40)	(3.1)			moderate and severe: PGI/PGII <2.5
Schlemper et al., 1995 (42)	the Netherlands (1991)	Medical examination at workplace	498 (M, 85%; F, 15%), 95%	22-71 (48)	3.6 (1.6)			all: PGI/PGII <1.3 sev: PGI <17 ng/ml
	Japan (1988)		225 (M, 84%; F, 16%), 99%		32.4 (4.4)			
Aromaa et al., 1996 (43)	Finland (1968-1972)	Health screening (controls for cancer cases)	146 (M, 63.7%; F, 36.3%), 82.5%	≥15 (61)	19.9			all: PGI <49 ng/ml
Watanabe et al., 1997 (44)	Japan (1987)	Annual health examination	1,290 (M, 34.3%; F, 65.7%)	≥35	40.4	M, 41; F, 40	Age: male/ female 35-39: 20/14 40-49: 32/29 50-59: 44/39 60-69: 38/42 70-79: 45/52 ≥80: 41/43	all: PGI ≤70 ng/ml and PGI/PGII ≤3.0

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Table 2. Pepsinogen-based studies (Cont'd)

Authors, year (ref.*)	Study population				Prevalence of pepsinogen defined CAG in %			Criteria for diagnosis
	Country (time of survey)	Setting	No. participants (gender), response rate	Age (mean[†])	Overall (severe)	By sex (severe)	By age[‡] (severe)	
Hurwitz et al., 1997 (45)	USA (1991-1993)	"Volunteers" (older adults; recruited via advertising)	243 (M, 29%; F, 71%)	65-96 (79)	9 (5)			all: PGI/PGII <2.9 sev: PGI <20 ng/ml
Varis et al., 1998 (46)	Finland (1985-1988)	Smokers (population registry based)	29,133 (only men)	50-69 (57)	(6.0)			sev: PGI <25 ng/ml
van Asselt et al., 1998 (47)	the Netherlands (1993)	Older adults ("randomly chosen")	105 (M, 44%; F, 56%)	74-80 (76)	32.4 (12.7)			all: PGI/PGII <1.6 sev: PGI/PGII <1.6 and PGI <17 ng/ml
Tsugane et al., 1999 (48)	Japanese in Brazil (1989)	Population registry based	168 (M, 48%; F, 52%), 64%	40-59	39.3 (25.0)	M, 33.3 (22.2); F, 44.8 (27.6)	40-49: 31.9 (26.6) 50-59: 48.7 (23.0)	all: PGI <70 ng/ml and PGI/PGII <3.0 sev: PGI <30 ng/ml
	Japanese in Peru (1995)		110 (M, 38%; F, 62%), 80%		18.2 (9.1)	M, 16.7 (16.7); F, 19.1 (4.4)	40-49: 11.4 (9.1) 50-59: 22.7 (9.1)	
Kuwahara et al., 2000 (49)	Japan (1993-1994)	Self-defense forces (pre-retirement examination)	566 (only men)	50-55	35.7 (17.1)			all: PGI <70 ng/ml and PGI/PGII <3.0 sev: PGI <70 ng/ml and PGI/P GII <2.0
Namekata et al., 2000 (50)	Japanese in USA (1994)	CVD-screening	776 (M, 53.5 %; F, 46.5 %)	20-86		M, 14.5; F, 11.9	Age: male/ female <50: 3/2 50-64: 15/16 65-74: 28/20 75-82: 35/37	all: PGI <70 ng/ml and PGI/PGII <3.0
Shibata et al., 2000 (51)	Japan (1997)	Health screening	636 (M, 39%; F, 61%), 71%	30-64	34.1	M, 33.5; F, 34.5	age: male/ female 30-34: 8/11 35-39: 12/23 40-44: 22/25 45-49: 31/27 50-54: 39/32 55-59: 33/39 60-64: 51/49	all: PGI <70 ng/ml and PGI/PGII <3.0
Ito et al., 2000 (52)	Japan (1997)	Health checkup	210 (M, 38%; F, 62%)	40 to ≥70	44	M, 46.3; F, 44.6	Age: male/ female 40-49: 36.8/44.2 50-59: 43.5/55.6 60-69: 50.0/31.4 ≥70: 41.7/42.9	all: PGI ≤70 ng/ml and PGI/PGII ≤3.0
Shibata et al., 2002 (53)	Japan (1993)	Health screening	954 (M, 33%; F, 67%), 47%	30-79	26.6	M, 30.1; F, 24.9	Age: male/ female 30-39: 0/7 40-49: 13/19 50-59: 26/21 60-69: 37/28 70-79: 38/45	all: PGI <70 ng/ml and PGI/PGII <3.0
Sipponen et al., 2003 (54)	Finland (1994-1996)	Population registry based	12,252 (only men)	51-65	(5.2)			sev: PGI <25 ng/ml
Kobayashi et al., 2004 (55)	Japan (1989)	Health checkup	4,486	20-59			Age: male/ female 20-29: 9/11 30-39: 20/23 40-49: 30/51 50-59: 45/38	all: PGI ≤70 ng/ml and PGI/PGII ≤3.0
	Japan (1996)		4,506				Age: male/female 20-29: 3/3	

(Continued on the following page)

Table 2. Pepsinogen-based studies (Cont'd)

Authors, year (ref.*)	Study population				Prevalence of pepsinogen defined CAG in %			Criteria for diagnosis
	Country (time of survey)	Setting	No. participants (gender), response rate	Age (mean†)	Overall (severe)	By sex (severe)	By age‡ (severe)	
							30-39: 5/5 40-49: 12/14 50-59: 25/27	
Ohata et al., 2004 (56)	Japan (1994-1995)	Annual health checkup	4,655 (only men)	40-59 (50)	28.9			all: PGI <70 ng/ml and PGI/PGII <3.0
Sato et al., 2004 (57)	Japan (1997)	Annual health checkup	438 (only men)	39-60 (48)	19.6			all: PGI ≤70 ng/ml and PGI/PGII ≤3.0
Kikuchi et al., 2005 (58)	Japan (1988-1990)	Controls for cancer cases (health checkup based)	633 (M, 55%; F, 45%)	40 to ≥70	60 (29)	M, 61 (31); F, 58 (27)	Age: male/female 40-49: 41 (12)/38 (10) 50-59: 61 (27)/57 (27) 60-69: 61 (30)/60 (28) ≥70: 64 (39)/67 (39)	all: (PGI <70 ng/ml and PGI/PGII <3.0) or (PGI <50 ng/ml and PGI/PGII <2.0) sev: PGI < 50 ng/ml and PGI/PGII < 2.0
Green et al., 2005 (59)	New Zealand (1997)	Population registry based	466 (M, 49%; F, 51%), 53%	≥65	6.7 (3.1)			all: PGI/PGII ≤2.9 sev: PGI/PGII ≤2.9 and PGI <20 ng/ml
Aoki et al., 2005 (60)	Japan (1991)	Health checkup	859 (M, 37%; F, 63%)	20-87 (60)			Age: male/female ≤29: 8/18 30-39: 21/41 40-49: 41/43 50-59: 50/47 60-69: 61/55 ≥70: 58/59	all: PGI ≤70 ng/ml and PGI/PGII ≤3.0
	China (1996-1997)	Health survey	1,741 (M, 37%; F, 63%)	17-85 (43)			Age: male/female ≤29: 5/9 30-39: 11/10 40-49: 11/7 50-59: 17/11 60-69: 19/18 ≥70: 29/19	
	Tanzania (2001)	All inhabitants of four villages	573 (M, 43%; F, 57%), 100%	7-90 (24)			Age: male/female ≤29: 29/32 30-39: 21/35 40-49: 24/37 50-59: 11/56 60-69: 39/47 ≥70: 27/41	
	Dominican Republic (2001-2002)	All inhabitants of randomly selected communities	1,215 (M, 37%; F, 63%), 100%	14-92 (33)			Age: male/female ≤29: 13/13 30-39: 14/23 40-49: 33/31 50-59: 24/29 60-69: 25/26 ≥70: 37/21	

Abbreviations: all, mild, moderate, and severe forms of CAG; CVD, cardiovascular disease; F, female; GC, gastric cancer; GP, general practitioner; Hp-gastritis, *H. pylori*–induced gastritis; M, male; sev, severe form of CAG.

*When multiple references are listed: the first publication contains data on prevalence rates, the others contain information on additional extracted study details.

†Median (instead of mean) in Knight et al. (40), Varis et al. (46), van Asselt et al. (47) and Aoki et al. (60).

‡Age-stratified data were derived from graphs in Fukao et al. (33), Kobayashi et al. (55) and Aoki et al. (60).

§The two different prevalence rates refer to the two examined towns with different stomach cancer death-rates.

‖Variations refer to different regions (the overall values are age adjusted for the different regions).

¶Prevalences in the different populations are alphabetically listed in detail in the following [with the following structure: country (city): young males/young females/old males/old females]: Algeria (Algiers): 4.4/20.4/12.5/19.6; Belgium (Ghent): 0/1.9/0/3.9; Denmark (Copenhagen): 0/2.7/2.9/2.9; Germany (Augsburg): 0/5.6/8.5; Germany (Deggendorf): 0/1.7/4.4/4.4; Germany (Mosbach): 0/0/2.5/4.6; Greece (Crete): 0/0/8.3/9.8; Iceland (S Region): 2.1/3.9/3.9/5.8; Italy (Florence): 2.2/0/5.6/3.7; Japan (Miyagi): 0/0/17.8/4.8; Japan (Yokote): 2.0/4.0/10.2/10.2; Poland (Adamowka): 0/4.6/5.3/12.5; Portugal (Gaia): 0/3.3/5.4/9.7; Slovenia (Ljubljana): 0/6.1/6.3/10.0; United Kingdom (Oxford): 0/0/2.4/8.3; United Kingdom (Stoke): 2.1/3.9/4.1/5.9; United States (Minneapolis-St. Paul): 0/0/2.1/4.0.

frequently, but a number of authors included in this review also applied other criteria (11, 22, 28, 74-78). Knowledge about the method of extraction of biopsies (blind or under view) and number and location of biopsy sites is of great importance because these aspects have a major influence on results as shown by Kimura et al. (79) and Satoh et al. (80). Unfortunately, the few reported studies showed quite substantial variation in biopsy sites. Optimal biopsy quality and proper orientation are further prerequisites for reliable grading (81), and even the two sides of a biopsy may lead to different results (intrabiopsy variability; ref. 82).

Although biopsy via gastroscopy is often considered to be the gold standard for diagnosing CAG, definition and usage of the terms ''atrophic gastritis'' and ''gastric atrophy'' (83-85) are often inconsistent and intraobserver and interobserver variation concerning presence and severity of atrophy is rather large (86). This is true both for pathologists using individual criteria (87) and for those relying on general

criteria of the (original and updated) Sydney system (81, 88-90), partly caused by their training in different cultures (Asia and Western countries) with different working hypotheses (85). A new classification and scoring system published in 2002 by Rugge et al. (85, 91) and a morphometric assessment of antral atrophy (92) yet have to be validated. Apart from these difficulties, the procedure of biopsy sampling via gastroscopy is rather unpleasant. Although the feasibility of population-based gastroscopy screenings has been proven in areas of high risk for *H. pylori*, CAG, and gastric cancer, such as Iran (28), China (22), and Columbia (19), the realization of such large-scale screenings seems unlikely in Western countries with a low risk for CAG and gastric cancer.

In contrast, screenings based on pepsinogen measurements, which are both less expensive and less invasive, have been conducted successfully in several European countries (31, 32, 40, 43, 46, 47, 54). In Japan, about five million people are screened annually for gastric cancer by X-rays (93). In this high-risk country, measurement of serum pepsinogen concentrations may provide an opportunity to include larger proportions of the population in stomach cancer examination programs (94).

The use of a number of different definitions and cutoff values limits comparability of studies relying on pepsinogen concentrations. Early studies establishing cutoff values were conducted by Samloff et al. (9) in 1982 and Miki et al. in 1987 (95) and 1989 (96). In most studies included in this review, CAG was defined by a combination of the PG I concentration and the ratio of PG I to PG II. However, some studies relied solely on the PG I concentration (measuring exclusively corpus atrophy), and some others relied solely on the PG I/PG II ratio. Furthermore, the cutoff values widely differed among the studies: 70 ng/mL (indicating mild, moderate, and severe CAG) was most frequently used as PG I threshold, but there are also studies using 17, 20, or 25 ng/mL (indicating exclusively severe CAG) and one study each with 30, 49, and 50 ng/mL, a pattern that inevitably leads to differences in prevalence estimates. In contrast, the threshold for the PG I/PG II ratio was 3.0 (or 2.9) mostly, but a threshold of 1.3, 1.6, 2.0, and 2.5 was also used in single studies (40, 42, 47, 49, 58).

Specificity and sensitivity of the CAG diagnosis via serum pepsinogen concentrations have been investigated in numerous studies. Samloff et al. (9) predicted the correct mucosal status in 70% of biopsies according to his established cutoff values. Dinis-Ribeiro et al. (10) published a meta-analysis on the validity of pepsinogen tests in 2004 and found that a combination of both PG I and PG I/PG II ratio was required to achieve homogenous high levels of sensitivity and specificity. It is important to bear in mind that all validations refer to comparison with gastroscopy and histologic assessment, which itself cannot claim to be free of inaccuracy. A possible drawback of pepsinogen levels is their possible dependence of additional factors that are difficult to identify. Several studies have shown that smoking elevates both the PG I level and the PG I/PG II ratio (97), and this effect seems to depend on the status of *H. pylori* infection (98). The influence of alcohol is not yet clear (97). Interestingly, pepsinogen concentrations measured in some parts of Asia partly seem to be higher in general than those in Western countries: in Linqu (China) where CAG is virtually universal, median PG I levels exceeded 90 ng/mL (probably not due to assay procedures; ref. 23), whereas they are usually below 70 ng/mL in European countries (99). Furthermore, the only pepsinogen-based study from China included in this review would suggest much lower CAG prevalences than the multiple gastroscopy-based studies from this country. Different patterns of location and spread of CAG have been forwarded as possible explanations and may compromise the

use of pepsinogen levels for international comparative studies.

In this review, only studies published as full articles were included. Most likely, additional results have been presented at conferences and published as meeting proceedings, but the lack of detail and accessibility of pertinent publications would not have allowed comparably detailed presentation of methods and results of those studies in this review.

In conclusion, despite the limited number and comparability of studies, this review indicates that CAG is relatively common among older adults in different parts of the world, but large variations exist. Particularly high prevalences even among younger adults are found in some high-risk regions of gastric cancer in Asia. Large-scale international comparative studies with standardized methodology to determine CAG are needed to provide a more coherent and complete picture of the epidemiology of CAG. Noninvasive measurements of CAG by combined measurement of PG I and the PG I/PG II ratio and potentially additional serum markers may be particularly suited for population-based studies but may require careful consideration of potentially different patterns of CAG in different parts of the world.

Appendix 1

Studies excluded from this review because of:

(A) Preselection of the study population

1. Risk factors for atrophic chronic gastritis in a European population: results of the Eurohepygast study. Gut 2002;50:779-85.
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(B) Size of the study population

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