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# *Helicobacter pylori* infection: association with chronic atrophic gastritis, peptic ulcer disease and major cardiovascular events

Promotionsfach: Epidemilogie

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Chronic atrophic gastritis (CAG) is a well-established precursor of intestinal gastric cancer. As it is typically asymptomatic, epidemiological data on the incidence and risk factors for CAG development are sparse. *Helicobacter pylori* has been identified as a major risk factor for the development of CAG. However, most of the reported results on this association are based on cross-sectional studies. Infection with *H. pylori* has also been suggested to be a key risk factor for the development of peptic ulcer disease (PUD). However, the role of this infection as either a bystander of PUD or as a causal risk factor is subject to ongoing debate. It has been further suggested that infection with *H. pylori* and CAG might play a role in the development of cardiovascular diseases (CVDs). However, there are conflicting results in the literature on these associations.

The aims of this project were to assess the association of *H. pylori* infection in older adults with CAG by systematically reviewing published data on CAG incidence and associated risk factors from cohort studies and by estimating the incidence of CAG and its association with *H. pylori* infection in a large population-based cohort study (by means of analysing data from the ESTHER study), to assess the association of *H. pylori* infection and other putative risk factors with PUD in both cross-sectional and longitudinal analyses (by means of analysing data from the ESTHER study). And finally to assess the association of *H. pylori* infection and CAG with incident myocardial infarction, incident stroke, CVD mortality and all-cause mortality in the ESTHER study.

Articles with information on incidence of CAG published in English until 26th of July 2009 were identified through a systematic MEDLINE and EMBASE search. Data extracted include study characteristics and key findings regarding the incidence of CAG. A meta-analysis was performed on the association between *H. pylori* infection and CAG incidence. Serological measurements of pepsinogen I and II and *H. pylori* antibodies were performed at baseline and 5-year follow-up in the ESTHER study participants (age 50-74 years at baseline). Detailed medical data, including lifetime history of major diseases and data on lifetime history of potential risk factors were collected at baseline. At 2- and 5-year follow-up, information on vital status and incidence of major diseases (by means of questionnaire with subsequent validation by medical records) was obtained.

Overall, data on CAG incidence were available from 14 studies, in 7 studies incidence could be estimated according to *H. pylori* infection. Incidence estimates ranged from 0 to 11% per year and were consistently below 1% in patients not infected with *H. pylori*. Rate ratios for the association between *H. pylori* infection and CAG incidence ranged from 2.4 to 7.6 with a summary estimate of 5.0 [95% confidence interval (CI): 3.1-8.3].

In the ESTHER study, there were 58 (1.1%) incident CAG cases. CAG incidence increased with age. Seropositivity for *H. pylori* was strongly associated with CAG incidence, with adjusted odds ratios (OR) of 5.0 (95% CI: 1.6-15.8) and 11.3 (95% CI: 4.2-30.0) for participants with cagA negative and cagA positive *H. pylori* infection at both baseline and follow-up compared to those without *H. pylori* infection, respectively.

Lifetime history of PUD was reported by 1,233 participants at baseline (13.0%), and there were 49 incident cases during the 5-year follow-up among participants with no previous history of the disease. Smoking, family history of PUD and infection with *H. pylori* strains positive for cagA were strongly related to PUD in both cross-sectional and longitudinal analyses. The association of cagA positive *H. pylori* infection was particularly strong in the longitudinal analysis [hazard ratio (HR) 2.5, 95% CI 1.3-4.8].

During follow-up 497 study participants died, from these 162 from a CVD. Lifetime history of myocardial infarction and stroke was reported by 530 and 329 participants at baseline, respectively. There were 169 incident myocardial infarction and 241 incident stroke cases during follow-up among participants with no previous history of the disease. Myocardial

infarction, stroke, and all-cause mortality were neither associated with CAG nor with *H. pylori* infection. CVD mortality was inversely associated with cagA positive type of *H. pylori* infection (HR: 0.56, 95% CI 0.35-0.89), while none of the other risk factors were significantly associated with this outcome.

In summary, the review infers that CAG incidence is very low in the absence of *H. pylori* infection. This project further concludes that incidence of CAG is rather low in the German population. Older age and infection with *H. pylori* are key risk factors for the development of CAG in this population. In addition, these results give further support for a causal role of *H. pylori* infection in PUD development and do not support the hypothesis that CAG or infection with *H. pylori* play a role in the development of myocardial infarction and stroke.