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Short Report

Helicobacter pylori and the risk of dementia: A population-based study

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Abstract

Introduction: *Helicobacter pylori* infection might increase risk of dementia, but available evidence is inconsistent, and longitudinal studies are sparse. We investigated the association between *H. pylori* serology and dementia risk in a population-based cohort.

Methods: Between 1997 and 2002, we measured *H. pylori* serum IgG titers in 4215 nondemented participants of the Rotterdam Study with a mean age of 69 years. We determined the association between *H. pylori* at baseline and dementia incidence until 2015, per natural log (U/mL) increase in titer, and for seropositive/seronegative, using Cox models adjusting for cohort, sex, age, education, and cardiovascular risk factors.

Results: During a median follow-up of 13.3 years, 529 participants developed dementia, of which 463 had Alzheimer's disease. *H. pylori* was not associated with risk of dementia (hazard ratio [95% confidence interval] for antibody titer: 1.04 [0.90–1.21]; for seropositivity 1.03 [0.86–1.22]), or Alzheimer's disease.

Discussion: In this community-dwelling population, *H. pylori* was not associated with dementia risk.

Keywords: Alzheimer's disease; *Helicobacter pylori*; Dementia; Infection; Longitudinal

1. Introduction

Helicobacter pylori is a gram-negative bacillus that colonizes the stomach and is estimated to infect half of the world's population [1]. The bacterium is generally acquired during childhood by oral ingestion. In adults, the infection is usually chronic and will not heal without specific therapy. The clinical course, however, is highly variable. While in some individuals infections remain asymptomatic, others may develop serious gastric complications, such as ulcers or gastric carcinoma [2].

In addition, recent evidence suggests that *H. pylori* infection might be associated with extra-gastric diseases, including dementia [3–5]. This may be due to detrimental consequences of *H. pylori* associated anemia, inflammation, and hyperhomocysteinemia on vascular and neuronal health [6,7]. A recent systematic review and meta-analysis [8] showed a 71% increased risk of dementia with *H. pylori* infection, but heterogeneity across studies was high. This may relate to differences in (geographical) setting and study design, with current evidence mainly arising from cross-sectional studies. We aimed to investigate the association of *H. pylori* with dementia in a prospective population-based cohort study.

2. Methods

2.1. Design and study population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study among middle-aged and elderly individuals in the Netherlands [9]. A detailed description is provided in the online

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Supplementary Material. Established in 1990, participants were invited every 4–5 years to undergo follow-up examinations at the research center. Between 1997 and 2002, a total of 7444 participants from two subcohorts visited the research center, of which 4215 dementia-free subjects provided blood samples for measurement of *H. pylori* titer (Supplementary Fig. S1).

The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, and written informed consent was obtained.

2.2. Assessment of anti-H. pylori antibodies

Blood was drawn at baseline. To obtain serum and plasma, tubes were centrifuged according to a protocol standardizing time and conditions from the drawing of blood to centrifugation. All samples were snap-frozen at −196°C using liquid nitrogen and stored at −80°C. Anti-*H. pylori* serum IgG antibody titers were measured in 2011 using commercial enzyme immunoassays (Pyloriset EIA-G III ELISA; Orion) as described earlier [10]. We used anti-*H. pylori* serum IgG antibody titers primarily as a continuous variable. In addition, seropositivity was defined as an anti-*H. pylori* IgG titer equal to or greater than 20 U/mL, according to the manufacturer's recommendation.

2.3. Ascertainment of incident dementia

Participants were screened for dementia at baseline and subsequent center visits with the Mini–Mental State Examination and the Geriatric Mental Schedule organic level. Those with a Mini–Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study center with medical records from general practitioners and the regional institute for outpatient mental health care. A consensus panel headed by a consultant neurologist established the final diagnosis according to standard criteria for dementia (DSM-III-R) and Alzheimer's disease (AD) (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association). Follow-up until January 1, 2015, was virtually complete (99.1% of potential person-years in the original cohort and for 97.0% of potential person-years in the extended cohort). Within this period, participants were censored at date of dementia diagnosis, death, loss to follow-up, or administrative censoring date, whichever came first.

2.4. Covariables

Potential confounding factors for dementia were chosen on the basis of previous literature [8,11]. In all models, we adjusted for cohort, sex, and age at baseline. In multivariate adjusted models, we additionally adjusted for education, smoking, systolic and diastolic blood pressure, anti-hypertensive drug use, body mass index, cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein E (APOE) ε carrier status, stroke, diabetes mellitus, ethnicity, and serum lipid–reducing agents at baseline. APOEε carrier status was corrected since a study has shown that *H. pylori* and ApoE 4 polymorphism may be associated with dysphagic symptoms in older adults [12]. Assessment methods of the covariates are described in the Supplementary Materials. Blood samples for determination of levels of hemoglobin, homocysteine, C-reactive protein (CRP), interleukin-6 (IL6), α1-antitrypsin (α1-AT), lipoprotein-associated phospholipase A2 activity, and fibrinogen were obtained at the research center.

2.5. Statistical analysis

Because of a skewed distribution of anti-*H. pylori* serum IgG antibody titers, we performed a natural log transformation. Differences in baseline characteristics between the *H. pylori*-positive and *H. pylori*-negative groups were assessed using Student's *t*-test and chi-squared test. We determined the association between *H. pylori* (continuously as well as dichotomized for seroprevalence) and risk of dementia, using Cox regression models, adjusting for age, sex, study cohort, education, and cardiovascular risk factors. The proportional hazards assumption was met.

We repeated analysis only for Alzheimer's disease and used higher cutoffs for seroprevalence (in steps of 5 U/mL from the manufacturer's recommended cutoff) to explore differential effects among individuals with more profound antibody response. We assessed interaction by age, sex, or medication use by stratification and testing for multiplicative interaction. In addition, we tested for multiplicative interaction between *H. pylori* titer and CRP to assess if there is a difference in dementia risk between more severely infected and less severely infected groups. Finally, we computed Pearson correlation coefficients for the association of *H. pylori* titer with levels of hemoglobin, homocysteine, and CRP, with homocysteine and CRP both natural log transformed. In addition to CRP, which was available for all participants, we also determined the correlation between *H. pylori* and four other inflammatory biomarkers that have previously been related to dementia risk [13] and were available in a subsample of approximately 500 participants with *H. pylori* measurement.

All analyses were performed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY).

3. Results

Baseline characteristics of the study population are presented in Table 1. During a mean follow-up of 10.6 (±4.5) years and median follow-up of 13.3 years (interquartile