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Featured Article

Helicobacter pylori seropositivity and its association with incident all-cause and Alzheimer's disease dementia in large national surveys

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Abstract

Introduction: Infectious agents were recently implicated in Alzheimer's disease (AD) and etiology of other dementias, notably *Helicobacter pylori*.
Methods: We tested associations of *H. pylori* seropositivity with incident all-cause and AD dementia and with AD-related mortality among US adults in a retrospective cohort study. Data from the National Health and Nutrition Surveys III, phase 1 (1988–1991) and 1999–2000 linked with Medicare and National Death Index registries, were used (baseline age ≥45 y, follow-up to 2013, N_{pooled} = 5927).
Results: A positive association between *H. pylori* seropositivity and AD mortality was found in men (hazard $ratio_{adj,\ pooled}$ = 4.33, 95% confidence interval: 1.51–12.41, P = .006), which was replicated for incident AD and all-cause dementia, with hazard $ratio_{adj,\ pooled}$ = 1.45 (95% confidence interval: 1.03–2.04, P = .035) and hazard $ratio_{adj,\ III}$ = 1.44 (95% confidence interval: 1.05–1.98, P = .022), respectively. These associations were also positive among higher socioeconomic status groups.
Discussion: In sum, *H. pylori* seropositivity's direct association with AD mortality, all-cause dementia, and AD dementia was restricted to men and to higher socioeconomic status groups.
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Keywords: Helicobacter pylori; Dementia; Alzheimer's disease; Mortality; Aging

1. Background

The prevalence of all-cause dementia among older adults aged ≥60 y is estimated at 4.7% [1], with 4.6–7.7 million new annual cases worldwide (3.5–10.5 per 1000 in various world regions) [1–3]. Around 60%–80% of dementia is caused by Alzheimer's disease (AD) [1], a progressive neurodegenerative disorder with multifactorial etiology. AD manifests itself with a progressive episodic memory deterioration followed by impairment in other cognitive domains [4]. Biologically speaking, AD is thought to be caused by age-dependent and progressive amyloid β deposition in the brain—"the amyloid cascade hypothesis" [5]. Neurofibrillary tangles arising from hyperphosphorylated tau constitute the second pathological hallmark of AD [6]. AD is the leading cause of disability in old age [7] and healthcare burden in developed countries [8]. It is also the sixth leading cause of death in the United States [9]. Currently, around 5.4 million Americans have AD, a number expected to reach 13.8 million by 2050 [9]. In 2016, long-term and hospice care for all-cause dementia cost the United States around $236 billion [9]. Awaiting an effective treatment, research has uncovered important genetic risk factors for late-onset AD (e.g., apolipoprotein E [ApoE] *ε4*). Recent reviews indicated that education, smoking, physical inactivity, depression, midlife obesity, hypertension, and type 2 diabetes collectively account for ∼54% of AD risk [10], but much variation remains unexplained. Therefore, identifying

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[1]This author had complete access to the data and has primary responsibility for the accuracy of the statistical analyses.

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novel midlife risk factors is essential for planning cost-effective interventions. Infectious agents have recently been implicated in AD etiology [8], most notably *Helicobacter pylori* [11–22].

H. pylori is a heterogeneous bacterial species causing numerous upper digestive diseases (e.g., peptic ulcer) [23], with similar degenerative features with AD. In fact, peptic ulcer's etiology is multifactorial with contributions from infection, stress, chemical irritants, and genetic susceptibility [24]. Found in gastric mucosa of ≥50% of humans worldwide, *H. pylori* can infect children, becoming chronic during adulthood if untreated. Its seroprevalence increases with age and poorer socioeconomic conditions and was observed to be higher among minority groups [19,25,26]. Recently, a link between *H. pylori* and extra-digestive disorders was found. Some of those disorders, which include atherosclerosis [27], hypertension, and stroke [28], were also related to increased risk of AD through impairment of the blood-brain barrier [29–31]. Specifically, with respect to atherosclerosis, a causal relationship was suggested given the simultaneous drop in duodenal ulcer and coronary heart disease occurrence in the United States over the past 40 y, coupled with *H. pylori* DNA detection in atherosclerotic plaques. Underlying mediators may include inflammation, dyslipidemia, hyperglycemia, arterial stiffness, and hypertension. Other research, however, suggested that both *H. pylori* infection and atherosclerosis have common causes, such as smoking, low socioeconomic status (SES), and high salt intake [32].

Importantly, several hypothesized mechanisms have been identified recently for the potential causal association between *H. pylori* and AD: (1) Folate and vitamin B-12 malabsorption triggering increased serum homocysteine concentrations and neurotoxicity [33]; (2) apoptosis by T cell-mediated immune response, overexpression of nitric oxide, or molecular mimicry of host structures [33]; (3) increased cytokines, platelet activation, acute phase proteins, and eicosanoids [33] and; (4) *H. pylori* infection potentially crossing the blood-brain barrier and contributing to amyloid deposition [34]. Though slowly mounting, evidence from epidemiological studies remains limited [11–19], and most studies are case-control or cross-sectional investigations. Furthermore, given race- and sex-specific differences in *H. pylori* seroprevalence [19,26], there is a need to test longitudinal associations between *H. pylori* status and cognitive outcomes across those sociodemographic factors. Finally, there are effective ways to eradicate *H. pylori*, and research is under way to develop vaccines, which strengthen the rationale to study this modifiable factor [35].

Consequently, our present study examined associations of *H. pylori* seropositivity with incident all-cause and AD dementia, and with AD-related mortality, among US middle-aged and older adults (45 + y at baseline), (objective A). We further explored whether those associations were specific to certain sociodemographic groups, including sex, race/ethnicity, age, income, and education (objective B).

2. Methods

2.1. Database: National Health and Nutrition Surveys-Centers for Medicare and Medicaid Services

The National Health and Nutrition Examination Surveys (NHANES) provide nationally representative cross-sectional data on U.S. civilian populations health and nutritional status. Initiated in the 1970s by the National Center for Health Statistics at the Centers for Disease Control and Prevention, NHANES was noncontinuous waves before 1999, becoming a continuous survey afterward. Following a stratified, multistage probability cluster sampling design, the surveys included in-home basic health and demographic interviews followed by in-depth health examinations in a mobile examination center (MEC) completed by physicians, medical/health technicians, and dietary and health interviewers [36].

NHANES followed established guidelines of the Declaration of Helsinki, and the National Center for Health Statistics Institutional Review Board approved all procedures involving human subjects. Informed written and verbal consent were obtained from all participants, with verbal consent witnessed and formally recorded [36]. Moreover, our study was approved by the institutional review board of the National Institute on Aging, Intramural Research Program.

Centers for Medicare and Medicaid Services (CMS)-Medicare data were linked to NHANES III and 1999–2013 wave participants (Supplementary Appendix I). Finalized CMS-Medicare claim files are available ∼9 months into the following calendar year. The annual files are available throughout the follow-up period for part A (inpatient, outpatient, Skilled Nursing Facility, hospice, or Home Health Agency) and for part B (Carrier, Durable Medical Equipment). All restricted CMS data analyses were conducted at the Research Data Center in the National Center for Health Statistics, in Rockville, MD.

2.2. Study sample

Among 16,970 participants (aged 1–90 y) interviewed in phase 1 NHANES III (1988–1991, 3 yrs) with complete sociodemographics (e.g., age, sex), 5115 were aged 45 y or older, of whom *H. pylori* exposure is available for n = 3798 (MEC examination). Similarly, 1999–2000 NHANES (2 yrs) consisted of 9965 participants aged 0–85 y at examination, of whom we selected those who are aged ≥45 y (N = 2770), with N = 2305 having complete data on *H. pylori*. Participants without matched CMS-Medicare data were assumed without follow-up event until December 31st, 2011, or censored on death. Finally, we excluded participants with Health Maintenance Organization–related CMS data to reduce bias from irregular follow-up. Therefore, the total unweighted selected sample consisted of N = 5927 adult participants, in which 84 AD-related deaths occurred up to December 31st, 2011, whereas incident all-cause dementia and AD dementia were 1350 and 682, respectively (Fig. 1).

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