Association between Helicobacter pylori infection and incident risk of dementia: The AMI cohort

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Running title: *H. pylori* and incident dementia: the AMI cohort.

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KEY POINTS

- In a population-based cohort of older farmers in Southwest France, seropositivity to *H. pylori* infection was independently associated with all-cause incident dementia during a 7-year follow-up.
- After adjustment for numerous dementia risk factors, the observed association was stronger for Alzheimer's disease.
- Despite a decreasing prevalence of *H. pylori* infection in high-income countries (29% in our study versus 65% reported in a previous epidemiological study conducted in the same area 15 years ago), a significant association with incident dementia is still observed.

WHY DOES THIS MATTER?

Infectious diseases are increasingly being considered as potential contributors to the risk of all-cause dementia. Despite a decreasing prevalence, *H. pylori* infection remains one of the major causes of chronic gastritis worldwide. In this sense, the results reported in this study provide evidence of one relevant potentially modifiable risk factor for dementia that may also be of particular interest in low and middle-income countries where *H. pylori* infection remains frequent, and where the number of older adults is steadily growing, and the largest dementia increases are occurring.

ABSTRACT

Background: Chronic infectious diseases are increasingly being considered as potential contributors to dementia risk. Among those infections, *Helicobacter pylori*, the main cause of chronic gastritis worldwide, has been suggested. As the prevalence of *H. pylori* infection has decreased, the main objective of this work was to reconsider the association between *H. pylori* infection and the risk of incident dementia, including Alzheimer's disease.

Methods: Prospective cohort of 689 older (≥65 years) agricultural workers from Southwest France. Descriptive and comparative analyses were performed according to *H. pylori* status determined by serology at baseline. The risk of incident dementia according to *H. pylori* status over a 7-year follow-up was explored by survival analyses: Kaplan Meier curve and Cox proportional hazards models.

Results: Two-hundred (29.0%) participants were *H. pylori* positive at baseline. Compared to *H. pylori* negative participants, they showed worse cognitive performances at baseline. Eighty-five incident dementia cases were diagnosed during the follow-up period. After adjustment for age, sex, education, apolipoprotein ε4, and several cardiovascular risk factors, *H. pylori* remained associated with an increased risk of dementia (HR 1.70, 95% CI, 1.05-2.74). The risk was stronger for Alzheimer's disease (HR 2.85, 95% CI, 1.58-5.12).

Conclusions: Despite an observed decrease in *H. pylori* infection prevalence, this study provides evidence for the association between *H. pylori* infection and dementia. These results should encourage further research on the mechanisms underlying the contribution of infectious diseases to pathological brain aging, especially the influence of gut inflammation on the brain.

Abstract word count: 242 words

Key words: *H. pylori*, dementia, Alzheimer's disease

INTRODUCTION

Alzheimer's disease (AD) accounts for nearly 80% of dementia cases, and is one of the leading causes of disability worldwide.[1,2] Besides well-known risk factors (i.e., socioeconomic conditions, genetics, lifestyle, etc.), several pathophysiological hypotheses have been explored to explain the disease, including the amyloid cascade and the accumulation of abnormal forms of various proteins leading to neurodegeneration.[1,3] However, the view considering the disease as a multifactorial phenomenon to which different mechanisms contribute over time is commonly accepted.[2]

Among those factors, a growing body of evidence focuses on infectious diseases. Either through common or microorganism-specific mechanisms, some infections could trigger or worsen neurodegeneration.[4] In the long list of infectious diseases which have been suggested, infection by *Helicobacter pylori*, a Gram-negative bacillus and the main cause of chronic gastritis worldwide, is a relevant candidate.[4] As an infection often contracted during childhood, and mostly asymptomatic, *H. pylori* usually remains undiagnosed along with a low-grade lifelong chronic inflammatory state, which could participate in extra-digestive manifestations of disease including neurodegeneration.[5,6]

Even though *H. pylori* prevalence has tended to decrease these last decades, cross-sectional studies hint toward a high prevalence of this infection in older adults with cognitive disorders.[7-9] Likewise, longitudinal studies report different rates of negative cognitive outcomes in *H. pylori* positive individuals or those treated for the infection.[10-12] Therefore, a few population-based studies have re-evaluated these associations, in particular the risk of incident dementia but with inconsistent results.[13-15]

Given the contrasting results published to date, as well as the prevalence of *H. pylori* infection in high-income countries which may have decreased these last decades, further epidemiological research is needed.[9]

Therefore, this work investigated the association between *H. pylori* infection and the incidence of dementia within a prospective cohort of older adults in Southwest France[16] involving a 7-year follow-up.

METHODS

Population and study design

The participants were recruited from the AMI (Aging Multidisciplinary Investigation) cohort, an ongoing epidemiological prospective study on aging initiated in 2007 (complete methodology previously published).[16] At baseline, 1002 retired farmers aged ≥65 years and living in Southwest France were randomly recruited from the Farmers Health Insurance System. Written informed consent was obtained from all participants. The ethics committee of the University Hospital of Bordeaux approved this research according to the principles of the Helsinki Declaration.

The present study included the 689 participants who agreed to provide blood samples and with available *H. pylori* serology at baseline.

Data Collection and Laboratory Samples

Psychologists conducted standardized at-home evaluations every two to three years (4 waves, from 2007 – 2015), collecting sociodemographic, environmental, neuropsychological, functional, and medical information at each wave. Blood samples were collected at baseline,

frozen, and stored for ancillary studies. Serological detection of *H. pylori* infection was performed using a two-step approach. 1) Enzyme-linked immunosorbent assay (BIOHIT *H. pylori* IgG ELISA kit, Biohit Health Care, Ellesmere Port, UK) testing for IgG anti-*H. pylori* antibodies; identifying an active infection. 2) If negative, a western blot (HELICO BLOT, Genelabs Diagnostics, Singapore) was performed to detect persistent anti-*H. pylori* antibodies; accounting-for a past infection. However, serological results from ELISA tests may not reliably distinguish between active and past infections. Participants were considered as "*H. pylori* positive" if one of the two tests was positive.

Outcome

Comprehensive neuropsychological assessment included global cognitive abilities [Mini Mental State Examination[17] (MMSE)], episodic memory [Free and Cued Selective Reminder Test (FCSRT), Grober & Buschke[18]], abstract thinking (WAIS similarities subtest[19]), and verbal fluency (Isaacs' set test[20]). Afterwards, neuropsychologists selected those participants with suspected dementia and proposed a visit by a neurologist or a geriatrician for a clinical examination to confirm the diagnosis and the etiology.

Dementia diagnosis relied on a 3-step procedure: 1) Neuropsychological evaluation with a criteria checklist for dementia using the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III R); 2) A neurologist or geriatrician reevaluated individuals who met dementia criteria to confirm or exclude the diagnosis, and 3) An independent committee of experts reviewed and validated all the diagnoses and their etiology according to current standards.[16] AD etiology was assigned according to the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[21]

Covariates

Sociodemographic variables included age, sex, and educational level (lower defined by less than 7 years of schooling). Lifestyle-related factors included current or former consumption of tobacco and alcohol, weight and height allowing body mass index calculation (BMI=weight (kg)/height $(m)^2$). Health-associated variables included chronic diseases (*e.g.*, hypercholesterolemia, hypertension, and diabetes), cardiovascular diseases (arterial disease, chronic heart failure, stroke and coronary disease; assessed from the second wave of data collection and onwards), and apolipoprotein ε4 (ApoE-ε4) status (at least one allele). Depressive symptomatology was assessed using the Center for Epidemiologic Studies Depression (CES-D) scale.[22,23] Functional status was assessed by instrumental activities of daily living[24] (IADL), basic activities of daily living[25] (ADL), and the Rosow-Breslau scale.[26] A hierarchical dependency indicator combining the three previous scales was categorized in increasing levels, as previously published [full independence, mild dependency (mobility limitation only), moderate dependency (mobility and IADL limitation), and severe dependency (mobility, IADL, and ADL limitation)].[27]

Statistical analysis

A description and comparative analyses of the participants by *H. pylori* infection status were performed. For quantitative variables, Student's t and Wilcoxon tests were used and for qualitative variables, the $\chi 2$ and Fisher tests.

Multivariate logistic regression analyses were performed to identify the variables associated with *H. pylori* infection. The initial model included all factors associated with *H. pylori* in the univariate analysis at a 20% threshold. Afterwards, a stepwise regression analysis allowed the identification of factors independently associated with the infection at a 5% threshold.

The risk of incident dementia (all type and AD specifically) was explored over a 7-year period according to *H. pylori* infection status by survival analyses (dementia-free) with two complementary approaches:

1) A Kaplan Meier curve to estimate the survival function (participants without dementia) in the population, according to the infection status.
2) Delayed-entry Cox proportional hazards model to estimate the risk of incident dementia. Prevalent dementia cases at baseline, participants with no follow-up, with an undetermined cognitive diagnosis or / and with missing data for the explanatory variables were excluded. The models were adjusted for the main dementia risk factors (sex, educational level, ApoE-ε4, cardiovascular diseases, hypercholesterolemia, hypertension, diabetes, obesity, alcohol and tobacco consumption), and factors found to be associated with the infection in the logistic regression analyses.

Statistical analyses were performed with R Studio (Version 4.0.3).

RESULTS

Participants' characteristics at baseline and comparison according to H. pylori status

The mean age of the 689 participants was 75.8 years (SD 6.4), and 262 (38.0%) were women (**Table 1**). Two-hundred participants had a positive *H. pylori* serology (29.0%). *H. pylori* positive participants were more likely to have a low educational level [128 (64.3%) vs 224 (45.8%), p <0.001], age ≥80 years [64 (32%) vs 119 (24.3%), p = 0.038], and lower limb arterial disease [15 (7.5%) vs 18 (3.7%), p = 0.033].

196 *H. pylori* positive participants had a lower MMSE score [24.3 (SD 4.2) vs. 25.5 (SD 3.9),
197 $p<0.01$] and showed worse performances in the other two tests considered (Similarities and
198 Isaacs set tests). **Supplementary Table 1**. Dementia at inclusion was not different according
199 to infection status.

200 For the multivariate logistic regression analyses, after excluding the 60 participants with
201 missing data, a sample of 629 participants was available. **Supplementary Table 2** presents the
202 initial and final models after stepwise regressions.

203 In the final model (5% threshold), MMSE score <24 at baseline (OR=1.76; 95% CI, 1.15-2.71;
204 p=0.009), lower educational level (OR=1.71; 95% CI, 1.15-2.52; p=0.007), and age ≥80 years
205 (OR=1.49; 95% CI, 1.0-2.21; p=0.043) were independently associated with *H. pylori* infection.

206 *Risk of incident dementia according to H. pylori status*

207 Of the 689 participants, 74 prevalent dementia cases were excluded, as well as 45 participants
208 with no follow-up data, and 1 with an undetermined cognitive diagnosis. Thus, the Kaplan-
209 Meier curve included 569 participants. Concerning the Cox model, 45 additional participants
210 were excluded due to missing data for the adjustment variables, resulting in 524 participants.

211 The Kaplan-Meier curves show the probability of dementia-free survival over time from
212 baseline according to *H. pylori* status. Within the 569 participants, 90 incident dementia cases
213 were identified during the 7-year follow-up. The dementia risk was significantly lower in
214 *H. pylori* negative participants (Log-Rank test, p=0.031). **Figure 1**.

215 Of the 524 participants included in the Cox model, 144 (27.5%) were *H. pylori* positive. Over
216 the 7-year follow-up, 85 incident dementia cases were identified, of whom 55 were *H. pylori*
217 negative, and 30 were positive. In the complete multivariate model, after adjustment for
218 potential confounders, *H. pylori* infection was independently associated with an increased risk
219 of dementia (HR 1.70; 95% CI, 1.05-2.74; p=0.03). **Table 2**. In the model focusing on AD

220 cases, of the 524 participants considered, 54 developed AD of whom 30 cases were *H. pylori*
221 negative, and 24 were positive. After adjustment for potential confounders, *H. pylori* remained
222 independently associated with an increased risk for AD (HR 2.85; 95% CI, 1.58-5.12; $p<0.001$).
223 **Table 2**.

224

225 **DISCUSSION**

226 Based on data from a prospective population-based cohort of retired farmers, this study reports
227 a prevalence of *H. pylori* of 29%, which is much lower than the 65% reported in another French
228 cohort (PAQUID), a study conducted in the same area of France nearly 20 years earlier.[14]
229 Therefore, *H. pylori* prevalence is substantially decreasing in high-income countries, probably
230 due to an improvement in hygiene standards, as already reported in the literature.[9]

231 Regarding cognition, *H. pylori* status was associated with lower baseline performances as
232 reported by previous cross-sectional studies.[7,8] Beyond baseline cognitive scores, this study
233 prospectively examined the risk of incident dementia according to *H. pylori* status. During the
234 7-year follow-up, *H. pylori*-positive participants had an increased risk of dementia,
235 independently of various dementia risk factors [HR=1.70], the risk of AD being still stronger
236 [HR=2.85]. Few longitudinal studies have addressed this issue.[10,11] For instance, retrospective
237 analyses from US-based surveys reported an association between *H. pylori* seropositivity with
238 incident all-cause dementia.[13,28] The PAQUID study reported similar results (HR 1.46; 95% CI,
239 1.01-2.11)[14] while a population-based cohort from the Netherlands with a 13-year follow-up
240 did not find an association between *H. pylori* seropositivity and dementia risk (HR 1.03; 95%
241 CI, 0.86-1.22).[15] However, potential implications of evaluating this association without longer-
242 lasting antibodies (i.e., case underestimation) have been discussed elsewhere.[29]

Concerning the potential mechanisms linking *H. pylori* to an increased risk of dementia, diverse pathways have been proposed. *H. pylori* infection is indeed a source of gastric inflammation, but also of chronic low-grade systemic inflammation which, in turn, may activate neuro-inflammatory pathways that end-up participating in neurodegeneration.[5,6] Likewise, a vascular hypothesis suggests that the vitamin B12 deficiency induced by the disease may lead to hyper-homocysteinemia, a known risk factor for cardiovascular disease and AD.[30] Furthermore, recent studies discuss the role of the "*gut-brain*" axis, and a bidirectional communication between the enteric and central nervous systems, which can be altered by *H. pylori*.[31]

Finally, the increased incidence of dementia observed in older adults with *H. pylori* infection may not be explained by a single phenomenon. The infection itself could reflect a series of conditions (childhood, hygiene, nutritional, economic, etc.) that also influence dementia risk. Improvement of those conditions over time may explain the lower seroprevalence observed in this cohort compared to another French study.[14] Nonetheless, despite this decreasing prevalence, the previously reported association with dementia and AD is maintained.[14] Further studies are needed to determine whether *H. pylori* infection is related to dementia by inducing lifelong gastritis or because it is a marker of poor socioeconomic conditions during childhood.

The methodological strengths of this study should be highlighted, such as the robust clinical diagnosis of dementia, the 7-year follow-up, the availability of relevant variables used for statistical adjustment, as well as the detection of longer-lasting antibodies against *H. pylori*. Likewise, the findings may also be of particular interest to low-and middle-income countries where *H. pylori* infection remains high and where the biggest increases in the population of older adults and dementia are occurring. Our study also has limitations. The study sample is relatively small, selection bias cannot be entirely excluded (participants who refused blood sampling), nor unmeasured residual confounding, as in other observational epidemiological studies. Concerning the serological diagnosis, ELISA results may not reliably distinguish active

and former infections. Finally, the sample is not representative of the general population, as it consists of agricultural workers. Inherent factors of living in a rural environment could have an influence on both *H. pylori* infection and dementia.

In conclusion, while the prevalence of *H. pylori* infection is decreasing, this study found that the infection was still associated with an increased risk of dementia, particularly AD. Therefore, this study adds to the growing evidence of the contribution that infectious diseases may have on the development of neurodegenerative diseases.

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Conflict of Interest

The authors have no financial/personal conflict of interest to disclose.

Authors' contribution

VH, CR, HA, and KP designed, and drafted the manuscript, interpreted the data, and directly accessed and verified the underlying data reported in the manuscript. HVC, FM and CH contributed to the critical analysis, and data interpretation. NR performed statistical analyses.

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

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Data Sharing

The dataset presented in this article is not readily available as it is property of the University of Bordeaux. Requests to access the dataset should be directed to: Karine Pérès, Ph.D. karine.peres@u-bordeaux.fr

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390 **Table 1. Characteristics of the population at baseline, and comparisons according to their**
391 ***Helicobacter pylori* serology**

Characteristics	Total (N=689)	*H. pylori* positive (N=200)	*H. pylori* negative (N=489)	*P*-value
Age, mean (SD)	75.8 (6.4)	76.2 (6.8)	75.6 (6.3)	0.270
Age ≥ 80, n (%)	183 (26.6)	64 (32.0)	119 (24.3)	0.038
Women, n (%)	262 (38.0)	76 (38.0)	186 (38.0)	0.992
Low educational level, n (%)	352 (51.2)	128 (64.3)	224 (45.8)	<.001
Obesity (BMI ≥30), n (%)	182 (27.0)	48 (24.9)	134 (27.9)	0.429
Hypertension, n (%)	477 (69.2)	131 (65.5)	346 (70.8)	0.174
Diabetes, n (%)	108 (15.7)	34 (17.0)	74 (15.1)	0.540
Arterial disease (lower limbs), n (%)	33 (4.8)	15 (7.5)	18 (3.7)	0.033
Heart failure, n (%)	85 (12.3)	23 (11.5)	62 (12.7)	0.669
Stroke, n (%)	18 (2.6)	8 (4.0)	10 (2.0)	0.144
Coronary disease, n (%)	77 (11.2)	24 (12.0)	53 (10.8)	0.660
Apolipoprotein ε4 (at least one allele), n (%)	112 (17.5)	32 (17.4)	80 (17.5)	0.972
Hypercholesterolemia, n (%)	351 (50.9)	94 (47.0)	257 (52.6)	0.185
Tobacco, n (%)				0.897
Stopped for > 6 months	209 (30.9)	63 (32.1)	146 (30.4)	
Active or stopped for < 6 months	24 (3.6)	7 (3.6)	17 (3.5)	
Hierarchic dependence indicator, n (%)				0.111
Full independence	239 (36.1)	61 (31.8)	178 (37.8)	
Slight dependence	279 (42.1)	78 (40.6)	201 (42.7)	
Moderate dependence	105 (15.8)	40 (20.8)	65 (13.8)	
Severe dependence	40 (6.0)	13 (6.8)	27 (5.7)	
Depressive symptoms – CESD, n (%)	81 (12.7)	28 (15.5)	53 (11.6)	0.182

392 SD: Standard Deviation, BMI: Body Mass Index

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397 **Table 2. Longitudinal association between *Helicobacter pylori* and incident dementia: delayed-**
398 **entry Cox model**

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Characteristics	All types of dementia N=85 incident cases			Alzheimer's disease N=54 incident cases		
	Hazard Ratio	95% CI	*P*-value	Hazard Ratio	95% CI	*P*-value
***H. pylori* seropositivity**	1.70	1.05-2.74	0.030	2.85	1.58-5.12	<.001
Women	0.86	0.48-1.55	0.617	0.48	0.23-0.98	0.044
Low educational level	1.26	0.78-2.03	0.340	0.85	0.46-1.55	0.586
Apolipoprotein ε4	1.61	0.95-2.74	0.077	1.54	0.79-2.99	0.202
Coronary disease	0.76	0.36-1.61	0.469	0.73	0.30-1.78	0.485
Arterial disease (lower limbs)	0.44	0.15-1.34	0.149	0.68	0.21-2.18	0.518
Heart failure	0.62	0.30-1.26	0.186	0.59	0.25-1.42	0.238
Stroke	1.96	0.55-6.90	0.297	0.48	0.06-4.11	0.506
Hypercholesterolemia	1.03	0.63-1.67	0.910	1.79	0.96-3.33	0.067
Hypertension	0.98	0.60-1.60	0.940	0.96	0.51-1.81	0.910
Diabetes	1.54	0.87-2.73	0.136	1.38	0.67-2.85	0.385
Obesity	0.78	0.44-1.35	0.372	0.89	0.44-1.80	0.749
Alcohol	0.77	0.46-1.28	0.307	0.54	0.29-1.03	0.061
Tobacco			0.046			0.056
Former smoker	1.51	0.86-2.66	0.153	0.94	0.46-1.90	0.854
Current smoker	3.24	1.21-8.69	0.020	3.78	1.21-11.82	0.022

402 CI: Confidence interval

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405 **Figure 1. Kaplan Meier curve estimating dementia-free survival in the population**
406 **according to the infection status.**

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