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► To cite this version:

Virgilio Hernandez-Ruiz, Claire Roubaud-Baudron, Hugo von Campe, Noelia Retuerto, Francis Megraud, et al.. Association between *Helicobacter pylori* infection and incident risk of dementia: The AMI cohort. *Journal of the American Geriatrics Society*, 2024, 10.1111/jgs.18748 . hal-04472757

HAL Id: hal-04472757

<https://hal.science/hal-04472757v1>

Submitted on 27 Nov 2024

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1 **Association between *Helicobacter pylori* infection and incident risk of dementia: the AMI**
2 **cohort.**

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

4

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21

22 **Word Count: 2119 Tables and Figures: 3**

23

24

25 **Funding Sources:**

26 The AMI project was funded by AGRICA (CAMARCA, CRCCA, CCPMA PREVOYANCE,
27 CPCEA, AGRI PREVOYANCE), the Mutualité Sociale Agricole (MSA) de Gironde, and the
28 Caisse Centrale de la MSA. The funding sources had no role in the design, analysis, and data
29 interpretation, writing, or reporting of the manuscript.

30

31 **KEY POINTS**

- 32 • In a population-based cohort of older farmers in Southwest France, seropositivity to *H.*
33 *pylori* infection was independently associated with all-cause incident dementia during a
34 7-year follow-up.
- 35 • After adjustment for numerous dementia risk factors, the observed association was
36 stronger for Alzheimer’s disease.
- 37 • Despite a decreasing prevalence of *H. pylori* infection in high-income countries (29%
38 in our study versus 65% reported in a previous epidemiological study conducted in the
39 same area 15 years ago), a significant association with incident dementia is still
40 observed.

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47 **WHY DOES THIS MATTER?**

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

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60 **ABSTRACT**

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

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

71 **Results:** Two-hundred (29.0%) participants were *H. pylori* positive at baseline. Compared to
72 *H. pylori* negative participants, they showed worse cognitive performances at baseline. Eighty-
73 five incident dementia cases were diagnosed during the follow-up period. After adjustment for
74 age, sex, education, apolipoprotein $\epsilon 4$, and several cardiovascular risk factors, *H. pylori*
75 remained associated with an increased risk of dementia (HR 1.70, 95% CI, 1.05-2.74). The risk
76 was stronger for Alzheimer's disease (HR 2.85, 95% CI, 1.58-5.12).

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

81 **Abstract word count:** 242 words

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

83 INTRODUCTION

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

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

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

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

108 Therefore, this work investigated the association between *H. pylori* infection and the incidence
109 of dementia within a prospective cohort of older adults in Southwest France¹⁶ involving a 7-
110 year follow-up.

111

112 **METHODS**

113

114 **Population and study design**

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

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

124 **Data Collection and Laboratory Samples**

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

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

136 **Outcome**

137 Comprehensive neuropsychological assessment included global cognitive abilities [Mini
138 Mental State Examination¹⁷ (MMSE)], episodic memory [Free and Cued Selective Reminder
139 Test (FCSRT), Grober & Buschke¹⁸], abstract thinking (WAIS similarities subtest¹⁹), and
140 verbal fluency (Isaacs' set test²⁰). Afterwards, neuropsychologists selected those participants
141 with suspected dementia and proposed a visit by a neurologist or a geriatrician for a clinical
142 examination to confirm the diagnosis and the etiology.

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

151 **Covariates**

152 Sociodemographic variables included age, sex, and educational level (lower defined by less
153 than 7 years of schooling). Lifestyle-related factors included current or former consumption of
154 tobacco and alcohol, weight and height allowing body mass index calculation ($BMI = \text{weight}$
155 $(\text{kg}) / \text{height}^2 (\text{m}^2)$). Health-associated variables included chronic diseases (*e.g.*,
156 hypercholesterolemia, hypertension, and diabetes), cardiovascular diseases (arterial disease,
157 chronic heart failure, stroke and coronary disease; assessed from the second wave of data
158 collection and onwards), and apolipoprotein $\epsilon 4$ (ApoE- $\epsilon 4$) status (at least one allele).
159 Depressive symptomatology was assessed using the Center for Epidemiologic Studies
160 Depression (CES-D) scale.^{22,23} Functional status was assessed by instrumental activities of
161 daily living²⁴ (IADL), basic activities of daily living²⁵ (ADL), and the Rosow-Breslau scale.²⁶
162 A hierarchical dependency indicator combining the three previous scales was categorized in
163 increasing levels, as previously published [full independence, mild dependency (mobility
164 limitation only), moderate dependency (mobility and IADL limitation), and severe dependency
165 (mobility, IADL, and ADL limitation)].²⁷

166 **Statistical analysis**

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

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

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

177 1) A Kaplan Meier curve to estimate the survival function (participants without dementia)
178 in the population, according to the infection status.

179 2) Delayed-entry Cox proportional hazards model to estimate the risk of incident
180 dementia. Prevalent dementia cases at baseline, participants with no follow-up, with an
181 undetermined cognitive diagnosis or / and with missing data for the explanatory
182 variables were excluded. The models were adjusted for the main dementia risk factors
183 (sex, educational level, ApoE-ε4, cardiovascular diseases, hypercholesterolemia,
184 hypertension, diabetes, obesity, alcohol and tobacco consumption), and factors found to
185 be associated with the infection in the logistic regression analyses.

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

187

188 **RESULTS**

189

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

191 The mean age of the 689 participants was 75.8 years (SD 6.4), and 262 (38.0%) were women
192 (**Table 1**). Two-hundred participants had a positive *H. pylori* serology (29.0%). *H. pylori*
193 positive participants were more likely to have a low educational level [128 (64.3%) vs 224
194 (45.8%), $p < 0.001$], age ≥ 80 years [64 (32%) vs 119 (24.3%), $p = 0.038$], and lower limb arterial
195 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

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

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

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

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

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

275

276 **ACKNOWLEDGMENTS**

277 **Conflict of Interest**

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

279 **Authors' contribution**

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

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

285 **Funding / Sponsor's Role**

286 The AMI project was funded by AGRICA (CAMARCA, CRCCA, CCPMA PREVOYANCE,
287 CPCEA, AGRI PREVOYANCE), the Mutualité Sociale Agricole (MSA) de Gironde, and the
288 Caisse Centrale de la MSA. The funding source had no role in the design, analysis, and data
289 interpretation, writing, or reporting of the manuscript.

290 VHR was supported by the National Council of Humanities, Science and Technology
291 (CONAHCYT) in Mexico.

292 **Data Sharing**

293 The dataset presented in this article is not readily available as it is property of the University of
294 Bordeaux. Requests to access the dataset should be directed to: Karine Pérès, Ph.D.
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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)	<i>H. pylori</i> positive (N=200)	<i>H. pylori</i> negative (N=489)	<i>P</i>-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
<i>H. pylori</i> 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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