Helicobacter Pylori Infection is Associated With Neurodegeneration in Cognitively Normal Males

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Abstract

Background

An association between *Helicobacter pylori* (*H. pylori*) infection and dementia was reported in previous studies, however, the evidence is inconsistent. In the present study, the association between *H. pylori* infection and brain cortical thickness as a biomarker of neurodegeneration was investigated.

Methods

A cross-sectional study of 1,446 healthy adults who underwent a medical health check-up, including an esophagogastroduodenoscopy and 3.0 T magnetic resonance imaging was performed. *H. pylori* infection status was assessed based on histology. Multiple linear regression analysis was conducted to evaluate the relationship between *H. pylori* infection and brain cortical thickness.

Results

Males with *H. pylori* infection exhibited cortical thinning in the bilateral lateral temporal, lateral frontal, and right occipital areas compared with non-infected males after controlling for age, educational level, alcohol intake, smoking status, and intracranial volume. The association remained significant after further adjusting for inflammatory marker (C-reactive protein) and metabolic factors (obesity, dyslipidemia, fasting glucose, and blood pressure). However, an association between *H. pylori* infection and brain cortical thickness was not observed in females.

Conclusions

The findings indicate *H. pylori* infection is associated with neurodegenerative changes in cognitive normal males, independent of chronic inflammation or metabolic syndrome.

Background

The association between *Helicobacter pylori* (*H. pylori*) infection and neurodegenerative diseases is an important issue for *H. pylori*-related extragastric manifestations [1–3]. In several studies, a possible link between *H. pylori* infection and cognitive impairment was reported [1, 2, 4–8]. Alzheimer's disease patients were shown to have more frequent histologically proven *H. pylori* infections and had higher anti-*H. pylori* IgG concentrations than controls [4]. There are several possible pathomechanisms that link *H. pylori* infection and neurodegeneration. First, the systemic inflammation provoked by *H. pylori* can contribute to neurodegeneration [9–11]. Second, *H. pylori*-related metabolic dysfunction can increase the risk of cardiovascular disease which in turn increases the risk of Alzheimer's disease [12, 13]. Third, *H. pylori* can directly damage the central nervous system (CNS) by producing toxic materials [14] or by

mechanically invading the CNS through gastrointestinal tract-associated retrograde axonal transport pathway or *H. pylori*-infected monocyte circulation [15]. Finally, *H. pylori* induces dysbiosis of microbiota in the gastrointestinal tract that alters the gut-brain-axis toward neurodegenerative cascade [3, 16]. Because human biology is complex and one pathway cannot be completely separated from the other, the aforementioned mechanisms may co-exist and interplay with one another.

Cortical thickness is a widely used neurodegeneration marker that may predict an individual's cognitive decline [17, 18]. We learned from previous studies that various dementia risk factors are associated with cortical thinning even in cognitively normal state [19–22]. Although in many studies *H. pylori* infection was suggested to be associated with dementia [3–5, 15], the direct association of *H. pylori* infection with neurodegeneration has not yet been reported. Because *H. pylori* infection leading to dementia is a chronic process, it is likely that patients go through subclinical changes, such as cortical thinning, before infected patients reach dementia stage.

We hypothesized that *H. pylori*-infected individuals have more cortical thinning than non-infected individuals, even in a cognitively normal state. In a previous epidemiologic study, sex was shown to greatly influence the effects of *H. pylori* on dementia [23]. In addition, socioeconomic status, chronic inflammation, and metabolic syndrome are associated with both *H. pylori* infection and neurodegeneration. Therefore, the association between *H. pylori* infection and cortical thickness in each sex was evaluated in the present study after carefully controlling for confounding factors such as socioeconomic status (educational level, alcohol intake, smoking status), chronic inflammation (C-reactive protein, CRP), and metabolic syndrome.

Methods

Study population

We conducted a cross-sectional study of healthy adultswho participated in a health-screening program for disease prevention from September 2008 to December 2014 at the Health Promotion Center of the Samsung Medical Center, Seoul, South Korea. Data were collected from 1,808subjects who underwent Mini-Mental State Examination (MMSE), brain magnetic resonance imaging (MRI) including 3-dimentional (3D) volume images and esophagogastroduodenoscopy. The following subjects were excluded:11subjects under 45 years of age; 82 subjects with significant cognitive impairment which was definedaccording toMMSE scores below the 16^{th} percentile of age- and education-matched normal population; 102 subjects whose education data were missing; 17 subjects with large brain lesions such as hemorrhage, ischemia, and mass;76subjects with missing data for CRP and 25 subjects with increased CRP (>1.0 mg/dL) which indicates superimposed active inflammation; 49 subjects with missing data for alcohol intake or smoking status. Thefinal sample size in this study was 1,446 subjects.

Data collection

The comprehensive health-screening program included demographic characteristics, anthropometric measurements, detailed physical examination, serum biochemical measurements, and a self-administered health questionnaire regardingyears of formal education, smoking status, alcohol consumption, medication use, and personal medical history such asdiabetes, hypertension, dyslipidemia, and cardiovascular disease. Smoking status was categorized into 3 groups including never, former, and current smoker. Alcohol consumption status was categorized into never drinker and drinker.Blood samples were collected from theantecubital vein after at least 10 hours of fasting.Detailed information regarding this screening program was previously provided[24].

Metabolic syndrome-related factorswere reviewed according tothe 2006 International Diabetes Federation (IDF) criteria for metabolic syndrome[25].We granted 1 point for each five factors of IDF criteria (1) body mass index (BMI)> 30kg/m^2; (2) fasting plasma glucose >100mg/dL or on diabetes medication (3)blood pressure > 130/85 or on anti-hypertensive medication; (4)triglycerides>150mg/dL or on lipid lowering agent; (5)high-density lipoprotein (HDL) cholesterol< 40mg/dL for males, <50mg/dL for females or on treatment for dyslipidemia. Subjects were scored on a 0 to 5 scale for metabolic syndrome.

Assessment of *H.pylori* infection

The diagnosis of *H. pylori* infection was based on histological assessment. Board-certified gastroenterologists performed agastroendoscopyfor subjects who fasted overnight. Biopsy samples were taken from any region of the stomach and sent to the pathology department where the tissues were stained with hematoxylin and eosin and examined by qualified pathologists[26].

Measurement of brain cortical thickness

All subjects underwent a 3D volumetric brain MRI scan. An Achieva 3.0-Tesla MRI scanner (Philips, Best, the Netherlands) was used to obtain3DT1 turbo field echo MRI data.The following imaging parameters were included: sagittal slice thickness, 1.0-mm-thick sagittal slices with 50% overlap; no gap; repetition time of 9.9 milliseconds; echo time of 4.6 milliseconds; flip angle of 8°; and matrix size of 240 x 240 pixels reconstructed to 480 x 480 over a 240mm field of view.

The standard Montreal Neurological Institute image processing software (CIVET) was used to automatically processing ofT1-weighted MRIs to measure the cortical thickness. Native MRIs were first registered into a standardized stereotaxic space using an affine transformation[27]. Nonuniformity artifacts were corrected using the N3 algorithm, and the registered and corrected volumes were classified as white matter, gray matter, *cerebrospinal fluid*, and background using an artificial neural net classifier[28, 29]. The surfaces of inner and outer cortices were automatically extracted by deforming a spherical mesh onto the gray/white boundary in each hemisphere using the Constrained Laplacian-Based Automated Segmentation with Proximities algorithm[30, 31]. Cortical thickness was calculated as the Euclidean distance between the linked vertices of the inner and outer surfaces. To control for brain size, intracranial volume (ICV)was computed using classified tissue information and a skull mask, which was acquired from the T1-weighted image. Classified gray matter, white matter, cerebrospinal fluid, and

background within the mask were transformed back into individual native space. To compare the thicknesses of corresponding regions among the subjects, the thicknesses were spatially registered on an unbiased iterative group template by matching the sulcal folding pattern using a surface-based registration that performs sphere-to sphere warping. We used SUMA[32]to parcellate lobar regions - frontal, temporal, parietal, and occipital lobes. Averaged values for the thickness of the whole vertex in each hemisphere were used for global analysis.

Statistical Analysis

To compare the difference in demographics of *H. pylori*-infected and-non-infected subjects, we used Student's*t*-test for continuous variables and chi-square test for categorical variables(Table 1).To evaluate the relationship between *H.pylori* infection and the braincortical thickness, we performed multiple linear regression analysis for each sex. Model 1 wasadjusted for age, ICV, years of education, alcohol intake, and smoking status (Table 2).Model 2 was further adjusted for CRP to Model 1. Model 3 was further adjusted for metabolic syndrome score to Model 1. Finally, Model 4 was adjusted for CRP and metabolic syndrome score to Model 1. For the analysis, *H.pylori* negative subjects were set as the reference group. Statistically significant cutoff value was defined as P-value<0.05. SPSS 25.0 (IBM, Armonk, NY, USA) was used for statistical analyses.

For evaluating the topography of cortical thickness differences associated with *H.pylori* infection, the MATLAB-based toolboxwas used[33].To blur each cortical thickness map, full-width half-maximum diffusion smoothing of 20 mm was used, resulting in increased signal-to-noise ratio and statistical power[34]. Linear mixed models were used, vertex by vertex, to analyze the localized differences and the statistical map of cortical thickness on the surface model.Each gender was analyzed after controlling for possible confounders as described in Models 1, 2, 3, and 4. The thresholds for statistical map results were determined using a false discovery rate (FDR) with a Q-value of 0.05 after pooling the P-values from regression analyses.

Results

The baseline characteristics of study subjects are summarized in Table 1. A total of 1,446 cognitively normal adults (882 males and 624 females) were included, with a mean (standard deviation, SD) age of 63.6 (6.9) years. The educational level was higher for both males (P = 0.022) and females (P = 0.024) in the *H. pylori*-positive group. Other characteristics including age, ICV, MMSE, alcohol intake, smoking status, diabetes mellitus, hypertension, dyslipidemia, BMI, and CRP were not significantly different according to *H. pylori* infection status.

In multiple linear regression models adjusted for age, educational level, ICV, smoking status, and alcohol intake (Model 1), males with *H. pylori* infection exhibited overall brain cortical thinning (P = 0.022), especially in the parietal (P = 0.008) and occipital lobes (P = 0.050) compared with non-infected males (Table 2). When further adjusting for CRP and/or metabolic syndrome score (Models 2, 3, and 4), *H. pylori* infection remained significantly associated with cortical thickness in the parietal and occipital lobes.

However, females with *H. pylori* infection did not exhibit any cortical thinning compared with non-infected females (Table 2).

Statistical map revealed that *H. pylori* infected males had cortical thinning in focal areas of bilateral lateral temporal, lateral frontal, and right occipital lobes. More specifically, cortical thinning in the bilateral primary motor cortex, anterior portion of left middle temporal gyrus, anterior portion of right superior and middle temporal gyri, and right cuneus areas were associated with *H. pylori* infection (Fig. 2A). These cortical thinning areas associated with *H. pylori* infection remained significant after further adjusting for CRP (Fig. 2B), metabolic syndrome score (Fig. 2C), or CRP and metabolic syndrome score (Fig. 2D).

Discussion

In the present study, we evaluated the association between *H. pylori* infection and cortical thinning in a large cohort of cognitively normal adults. *H. pylori* infection was associated with cortical thinning in cognitively normal males in focal areas of bilateral lateral temporal, lateral frontal, and right occipital lobes. This association was independent of systemic inflammation or metabolic syndrome. The results indicate that gut microbiota pathophysiology might contribute to neurodegeneration in cognitively normal older males.

The results of the present study are in agreement with previous research indicating the association between *H. pylori* and dementia or neurodegenerative disorders [3–5, 7, 15, 35]. *H. pylori* infection is associated with higher risk of Alzheimer's disease, vascular dementia, Parkinson's disease, and neuromyelitis optica [14, 36–42]. However, the contribution of *H. pylori* to the development of neurodegeneration showing specific topography of cortical thinning, was not previously reported. Data from the present study showed that lateral temporal, lateral frontal, and right occipital areas were vulnerable to neurodegeneration in subjects with *H. pylori* infection. To the best of our knowledge, this is the first study in which the actual relationship between *H. pylori* infection and cortical thickness was demonstrated using visualized 3D topographical map.

Complex pathomechanisms may be involved in the relationship between *H. pylori* and cortical thinning. Increased metabolic syndrome [43–46] and vascular disorders [2] due to *H. pylori* infection were previously suggested [47, 48]. Others suggested the chronic inflammation induced by persistent *H. pylori* infection could produce CRP and proinflammatory cytokines [49] that could directly damage neurons or activate neuroinflammatory cascades leading to Alzheimer's disease [9]. Increased CRP level, a marker indicative of chronic inflammation, is reportedly associated with cardiovascular disease even within the normal range [50, 51]. To account for the above-mentioned hypotheses, metabolic syndrome factors and CRP level were further adjusted in the analyses. The data showed that even after adjusting for metabolic syndrome factors and/or CRP, the relationship between *H. pylori* and cortical thinning remained significant. Therefore, other factors than chronic inflammation or metabolic syndrome hypothetically link *H. pylori* infection and cortical thinning.

The associations between microbiota and dementia have been supported in numerous studies [52–58]. *H. pylori* is suggested as the main microbiota associated with cognitive impairment [3]. Evidence shows that *H. pylori* induce dysbiosis that increases harmful microbiota composition [59]. *H. pylori* infection also modifies gut-brain-axis by direct invasion into the CNS *via* several pathways, which could lead to CNS degeneration. Pathways of CNS invasion include oral-nasal olfactory pathway, *H. pylori* infected monocyte pathway, and retrograde up-climbing of gastrointestinal tract pathway [15]. The microbiota composition is known to be different according to sex [60–62]. Experimental mice models showed that hormonal changes in the host can alter gut microbiota composition [63]. Microbiota differences can be associated with the immune and cardiometabolic functions of the host, which are different according to sex [63, 64], which might explain the results in the present study showing the effects of *H. pylori* infection on cortical thinning were observed only in males.

Limitations

The present study had several limitations. First, because this was a cross-sectional study, the causal relationship between *H .pylori* and cortical thinning could not be elucidated. However, that cortical thinning may cause *H. pylori* infection is biologically unlikely, thus, we suggest that *H. pylori* infection may have caused cortical thinning. Further longitudinal studies are needed to verify whether *H. pylori*-infected individuals are more likely to develop dementia. Second, the study was based on a single medical center in South Korea which limits ethnic and socioeconomic variability. Further multi-center and worldwide studies are needed. Third, CRP was used as a chronic inflammation marker. Further studies using other markers such as interleukin (IL)-1β, IL-4, IL-10, IL-17, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ that reflect modulated immune reactions, might be necessary to determine whether our results can be replicated.

Conclusion

The results of the present study showed that *H. pylori*-infected males had cortical thinning in a cognitively normal state. Although the exact pathogenesis of *H. pylori* on CNS degeneration was not provided, this study is noteworthy in that our results suggest one of various pathogenesis of dementia, which is a multifactorial complex disease.

Abbreviations

H.pylori, Helicobacter pylori; AD, Alzheimer's disease;CNS, Central nervous system; MRI, magnetic resonance image;MMSE, Mini-Mental State Examination; BMI, body mass index; CRP, C-reactive protein; IgG, immunoglobulin G; HDL, high-density lipoprotein; ICV, intracranial volume; SD, standard deviation;IL, interleukin; TNF, tumor necrosis factor; IFN-γ,interferon-γ

Declarations

Ethical approval and consent to participate

This study was approved by the Institutional Review Board ofthe Samsung Medical Center. The requirement for informed consent was waived because onlyde-identified data routinely collected during healthscreening visits were used.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Tabels

Table 1.Baseline characteristics of study subjects based on*Helicobacter pylori*(*H. pylori*) status

	Males (n = 822)			Females (n = 624)		
	H.Pylori(-) (n = 559)	*H.Pylori* (+) (n = 263)	P-value	*H.Pylori* (-) (n = 381)	*H.Pylori* (+) (n = 243)	P-value
Age, years	64.8 ± 6.5	65.1 ± 6.8	0.199	62.3 ± 6.6	61.3 ± 7.4	0.133
Education, years	14.1 ± 3.6	14.6 ± 3.3	0.022	11.8 ± 4.3	12.1 ± 3.8	0.024
Alcohol intake (%)	435 (77.8)	209 (79.5)	0.592	92 (24.1)	61 (25.1)	0.787
Smoking status			0.561			0.847
Never smoker (%)	136 (24.3)	73 (27.8)		364 (95.5)	230 (94.7)	
Ex-smoker (%)	346 (61.9)	154 (58.6)		10 (2.6)	7 (2.9)	
Current smoker (%)	77 (13.8)	36 (13.7)		7 (1.8)	6 (2.5)	
ICV (mL) x 10^5	14.3 ± 1.0	14.3 ±1.0	0.411	12.8 ± 0.9	12.8 ± 0.9	0.590
CRP (mg/dL)	0.10 ± 0.13	0.10 ± 0.12	0.801	0.09 ± 0.11	0.09 ± 0.11	0.958
Factors of metabolic syndrome						
Diabetes mellitus (%)	116 (20.8)	61 (23.2)	0.427	34 (8.9)	30 (12.3)	0.169
Fasting glucose(mg/dL)	101.7 ± 20.5	102.7 ± 20.2	0.522	94.8 ± 12.8	96.6 ± 19.3	0.195
Hypertension (%)	265 (47.4)	141 (53.6)	0.097	146 (38.3)	89 (36.6)	0.670
Systolic blood pressure(mmHg)	121.1 ± 16.4	122.8 ± 16.6	0.171	122.4 ± 17.4	122.8 ± 19.0	0.803
Diastolic blood pressure(mmHg)	75.1 ± 9.8	75.2 ± 9.9	0.821	71.3 ± 10.3	71.9 ± 10.3	0.432
Dyslipidemia (%)	184 (32.9)	94 (35.7)	0.424	131 (34.4)	69 (28.4)	0.118
Triglyceride(mg/dL)	118.9 ± 59.3	118.2 ± 66.4	0.878	110.0 ± 56.0	118.1 ± 73.3	0.145
High density lipoprotein(mg/dL)	52.8 ± 13.5	54.1 ± 13.7	0.195	60.6 ± 15.0	59.0 ± 15.3	0.188
Body mass	24.3 ± 2.7	24.6 ± 2.4	0.661	23.6 ±	23.4 ± 2.8	0.549

index(kg/m^2)				2.9		
MMSE	28.3 ± 1.5	28.3 ± 1.6	0.296	28.1 ± 1.8	28.1 ± 1.6	0.192

Values are expressed as means ± standard deviation ornumber (percentages).

ICV, intracranial volume; MMSE, Mini-Mental State Examination; CRP, C-reactive protein.

Table 2. Mean cortical thickness based on *Helicobacter pylori (H. pylori)* infection in cognitively normal adults

	H. pylori (-)	*H. pylori* (+)	P-value			
			Model 1	Model 2	Model 3	Model 4
Males, n	559	263				
Total	3.055 ± 0.103	3.037 ± 0.115	0.022	0.022	0.021	0.021
Frontal lobe	3.099 ± 0.111	3.084 ± 0.123	0.065	0.065	0.063	0.063
Temporal lobe	3.213 ± 0.152	3.205 ± 0.156	0.487	0.489	0.483	0.485
Parietal lobe	2.915 ± 0.142	2.888 ± 0.137	0.008	0.008	0.008	0.008
Occipital lobe	2.704 ± 0.119	2.686 ± 0.125	0.050	0.049	0.049	0.048
Females, n	381	243				
Total	3.051 ± 0.105	3.061 ± 0.109	0.411	0.412	0.411	0.411
Frontal lobe	3.099 ± 0.109	3.109 ± 0.118	0.540	0.54	0.53	0.53
Temporal lobe	3.214 ± 0.147	3.223 ± 0.157	0.634	0.634	0.601	0.601
Parietal lobe	2.919 ± 0.139	2.931 ± 0.135	0.457	0.458	0.479	0.479
Occipital lobe	2.680 ± 0.126	2.700 ± 0.121	0.132	0.133	0.135	0.136

Model1: Adjusted for ICV, age, years of education, alcohol intake, and smokingstatus

Model2: Adjusted for ICV, age, years of education, alcohol intake, and smokingstatus, and CRP

Model3: Adjusted for ICV, age, years of education, alcohol intake, and smokingstatus, and metabolic syndrome score

Model4: Adjusted for ICV, age, years of education, alcohol intake, and smokingstatus, CRP, and metabolic syndrome score

ICV, intracranial volume; CRP, C-reactive protein

Figures

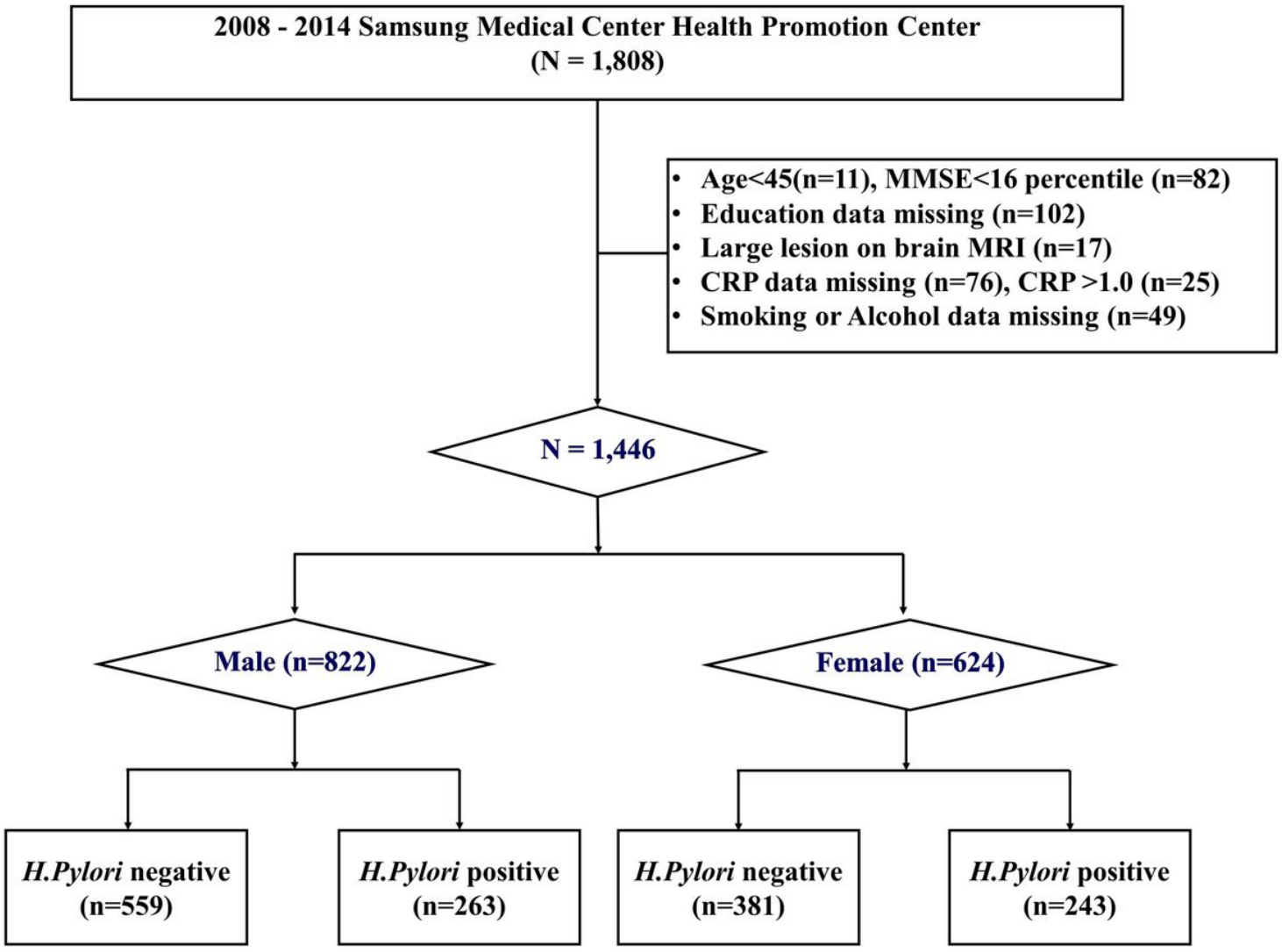

Figure 1

Flow chart of study subjects MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; CRP, C-reactive protein

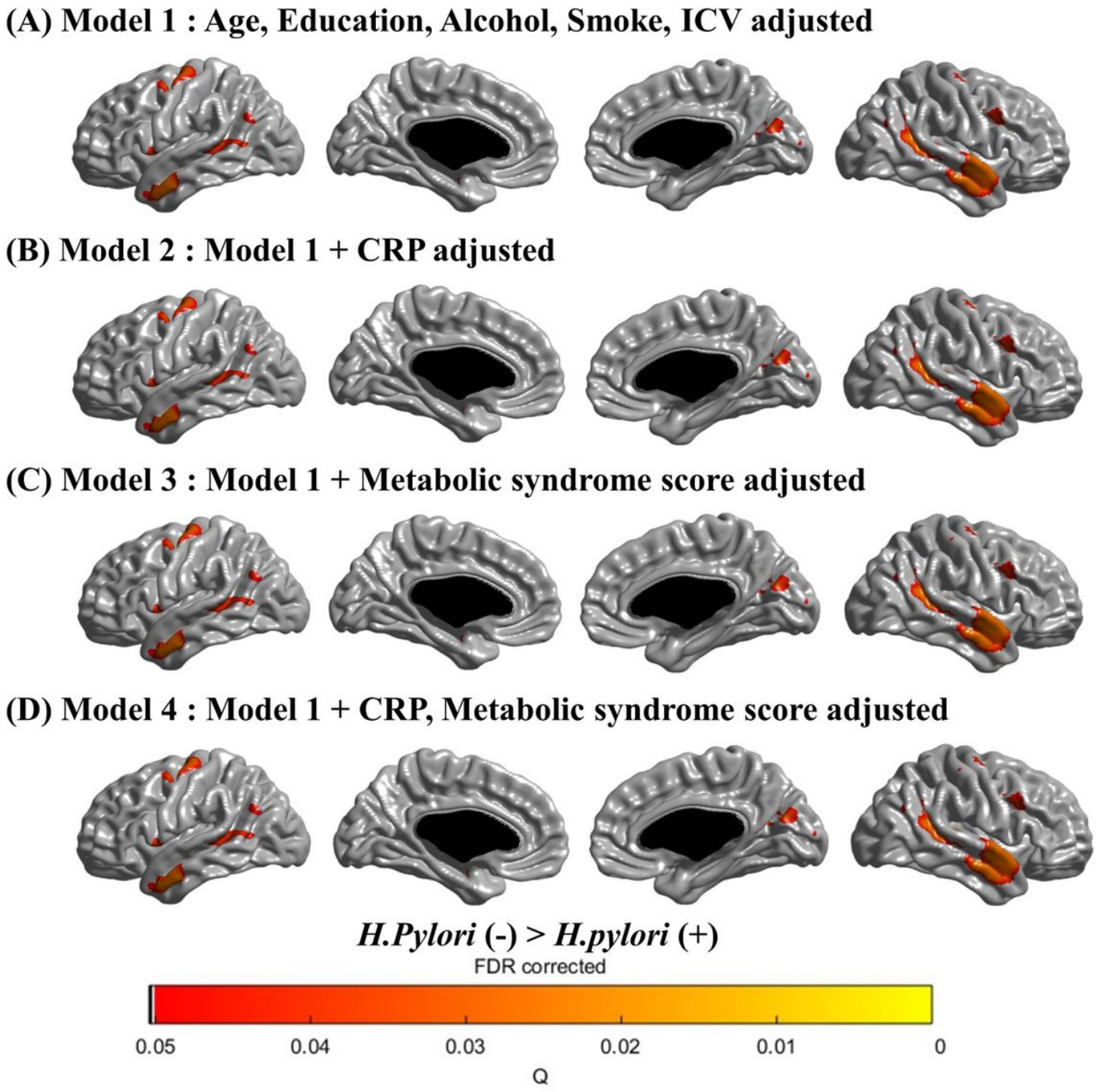

Figure 2

Three-dimensional (3D) reconstruction for correlation between Helicobacter pylori(H. pylori) infection and cortical thickness in males (A) Model 1: Adjusted for age, years of education, alcohol intake, smoking status, and intracranial volume(ICV),(B) Model 2: Further adjusted for C-reactive protein(CRP)in addition to Model 1, (C) Model 3: Further adjusted for metabolic syndrome scorein addition to Model 1, (D) Model 4: Further adjusted for CRP and metabolic syndromescorein addition to Model 1.False discovery rate (FDR) corrected (Q value <0.05)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx