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Helicobacter pylori infection selectively increases the risk for carotid atherosclerosis in young males

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HIGHLIGHTS

- *H. pylori* infection might be a novel risk factor for carotid atherosclerosis for young males.
- The findings might provide an explanation for the observation that males develop atherosclerosis earlier than females.
- The data could justify screening and treatment for *H. pylori* infection in young males with premature atherosclerosis.

ARTICLE INFO

Keywords:
Helicobacter pylori
Carotid atherosclerosis
Gender difference
Cardiovascular risk factor

ABSTRACT

Background and aims: Atherosclerosis is an important contributing factor to cardiovascular mortality. The role of *Helicobacter pylori* (*H. pylori*) infection in atherosclerosis is inconsistent and sometimes controversial. The present study aimed to determine if *H. pylori* infection is associated with carotid atherosclerosis.

Methods: 17,613 males and females with both carotid ultrasonic examination and ^{13}C-urea breath test for *H. pylori* infection were screened by a major Chinese university hospital from March 2012 to March 2017 for the study. Baseline demographics, cardiac risk factors, and laboratory studies were obtained. After exclusion for pre-specified conditions, 12,836 individuals were included in the analysis, including 8157 men (63.5%) and 4679 women (36.5%). Analysis was also made for 5-year follow-up data of 1216 subjects (869 males and 347 females) with and without *H. pylori* infection for development and progression of carotid atherosclerosis.

Results: After adjusting for age, sex, body mass index, lipid profile, hypertension, renal function, diabetes mellitus, and smoking, *H. pylori* infection was found as an independent risk factor for carotid atherosclerosis in males under 50 years, but not in older males or females (odds ratio 1.229, 95% CI 1.054–1.434, $p = 0.009$). Follow-up data analysis showed that the incidence of carotid atherosclerosis from no atherosclerosis to detectable lesions was significantly higher in young males with persistent *H. pylori* infection than those without *H. pylori* infection ($p = 0.028$) after 3 years.

Conclusions: These data suggest that *H. pylori* infection might be an important risk factor for carotid atherosclerosis in young Chinese males under 50.

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1. Introduction

Atherosclerosis is among the principal contributors to cardiovascular diseases (CVDs), especially coronary artery diseases (CAD) and stroke [1]. The incidence of stroke in China has increased dramatically in the last thirty years [2], and is a leading cause of death [3]. Although traditional CVD risk factors in the Chinese population are common [4–6], other novel risk factor for the development of atherosclerosis in the carotid artery are being explored as additional reasons for the increased rate of stroke.

Gut microorganisms have been shown to significantly contribute to the development of atherosclerosis and related CVD [7]. *Helicobacter pylori* (*H. pylori*) colonizes the human gastric epithelium in a significant portion of the general population worldwide, from 30% to 50% in developed countries up to 80% in developing countries [8]. Increasing data indicated that *H. pylori* infection is associated with extra gastrointestinal diseases including CVDs [9,10]. However, the relationship between *H. pylori* infection and atherosclerosis in both coronary artery and carotid artery has been inconsistent and sometimes controversial, with the findings ranging from a strong positive association to a mild association, to no association [11–13]. The association of *H. pylori* infection and carotid atherosclerosis in Chinese patients has not been defined in an adequate sample size. The present study aimed to determine if *H. pylori* infection could be associated with increased risk for carotid atherosclerosis.

2. Patients and methods

2.1. Study population

Patients who underwent a carotid ultrasonic examination and a ^{13}C-urea breath test [^{13}C-UBT]) at the Third Xiangya Hospital of Central South University in Changsha, Hunan, China, during their annual health evaluation were screened from March 2012 to March 2017 for the study. Based on the study methods, the population was divided into two groups: a cross-sectional study for the single measurement group, and a retrospective cohort study for patients with follow up measurements up to 5 years (Fig. 1A). Patients were excluded from the study if any of the following conditions was present: 1) history of *H. pylori* eradication, 2) use of any antibiotics, proton pump inhibitors, or H_2-receptor blockers 3 months before the tests, 3) age < 20 or > 70 years, 4) connective tissue diseases or immunological diseases,5) mental disorders, 6) asthma or COPD, 7) hematological disorders, 8) thyroid diseases, 9) malignancies, 10) recent (within 3 months) or chronic infection (over 3 months) except *H. pylori* infection, 11) congestive heart failure, and 12) abnormal liver function. Patients with CAD were not excluded from the study since carotid atherosclerosis and CAD share similar risk factors, and it was felt that exclusion of the subjects with CAD could remove the subgroup population who might be at increased risk for carotid atherosclerosis with *H. pylori* infection, leading to potential selection bias. Of note, the patients with CAD accounted only for about 3% of all participating subjects for the present study, and there was no stroke patient in the database. The study was conducted according to the principles of the Declaration of Helsinki, and approved by the Clinical Research Ethics Committee of the Third Xiangya Hospital of Central South University, Changsha, Hunan, China. Written informed consent was obtained from all patients prior to their participation.

2.2. Carotid ultrasonography and atherosclerosis detection

Carotid intima-media thickness (CIMT) was defined as the distance between the aortic intima and the media-adventitia interface. The presence of increased CIMT and carotid atherosclerosis was determined with a Siemens Acuson™ Sequoia 512 Doppler ultrasound (Siemens, German) at 1 cm proximal to the common carotid artery bifurcation of the left and right common carotid arteries. The average CIMT of three separate measurements was used for analysis for each subject. Carotid atherosclerotic plaque was defined as CIMT > 1.4 mm, or the presence of focal wall thickening at least 50% greater than that of the surrounding vessel wall as described [14].

2.3. Detection of H. pylori infection

On the same day as the carotid ultrasound examination, a two-stage ^{13}C-UBT test was performed for each subject to determine the presence of *H. pylori* infection after fasting for at least 6 h. The status of *H. pylori* infection was determined by analyzing the exhaled breath samples using ^{13}C infrared spectrometry for each patient. A receiver-operating characteristic curve analysis was performed to define the cut-off delta-over-baseline (DOB) values. DOB ≥ 4 [15] was considered as a positive reaction, and DOB < 4 as a negative reaction.

2.4. Other clinical data collection

Other clinical data including anthropometry and laboratory tests were collected for the study as described [16]. The height and weight were taken without shoes and with light clothing. Body-mass-index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Waist circumference was taken at the minimum circumference between the iliac crest and the rib cage using a non-stretchable standard tape. Seated blood pressures were obtained by skilled medical personnel after subjects rested for 15 min using an electronic sphygmomanometer, and the average of three readings was recorded for analysis. The individual was considered to be hypertensive when the systolic blood pressure was over 130 mmHg or diastolic blood pressure over 80 mmHg or on anti-hypertensive drugs.

An overnight fasting blood sample was obtained from an antecubital vein for each subject for measurements of serum lipids, glucose, creatinine, blood urea nitrogen, and uric acid with a Hitachi 7170S auto-analyzer (Hitachi, Tokyo, Japan). The subject was considered to have hyperlipidemia when the individual's triglyceride (TG) was ≥ 2.26 mmol/L, or total cholesterol (TC) ≥ 6.22 mmol/L, or HDL-C < 1.04 mmol/L. The patient was classified as diabetic when the fasting plasma glucose concentration was over 6.11 mmol/L or on anti-diabetic drugs like insulin.

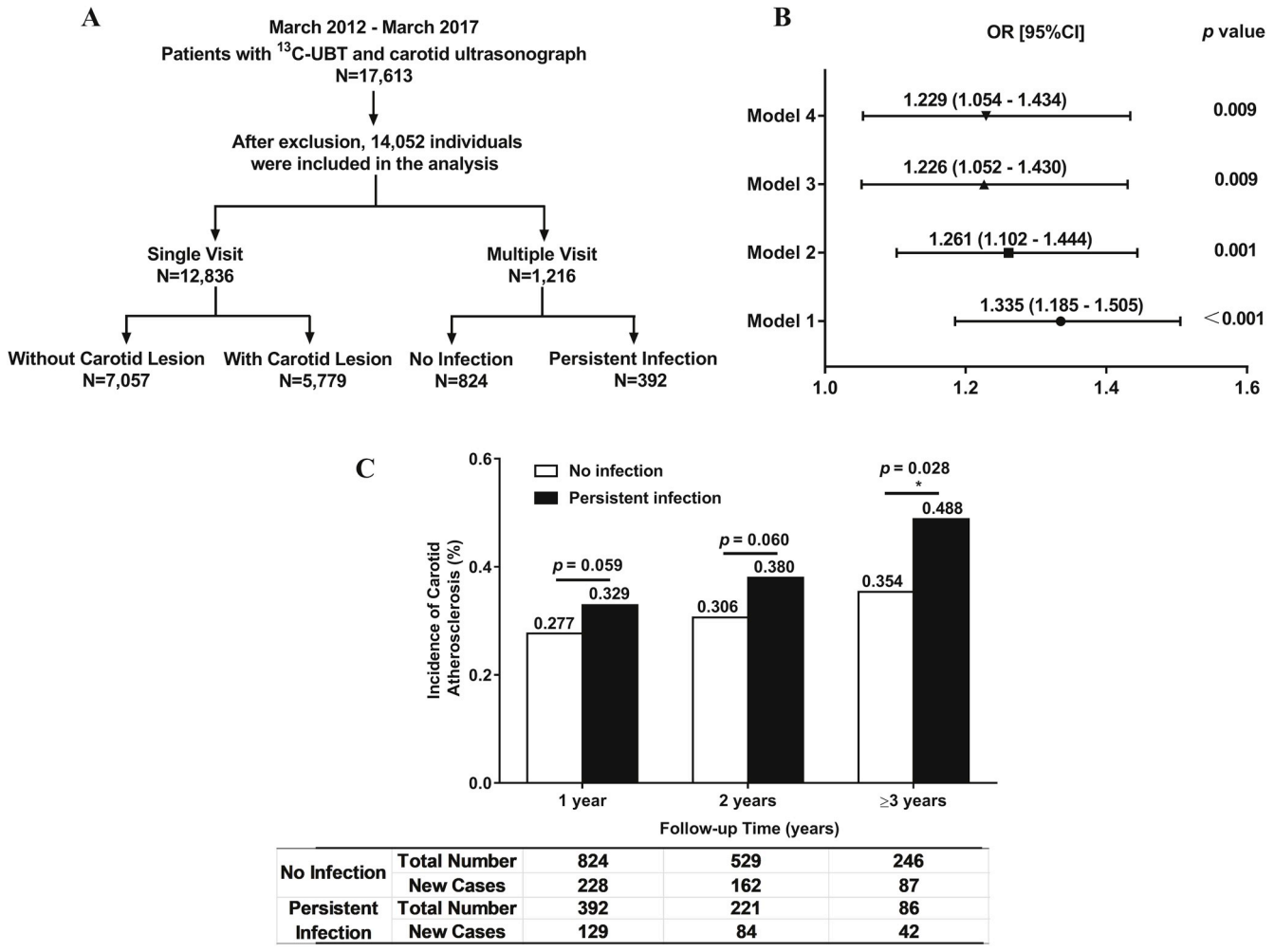
2.5. Statistical analysis

Categorical variables were expressed as percentage (%), and analyzed using chi-square (x2) test. Quantitative variables were expressed as mean ± standard deviation (SD) (X ± SD), and analyzed using one-way ANOVA. Adjusted odds ratios (ORs) were estimated with logistic regression analysis models. A cross-sectional study was performed for the single measurement group to determine the association between *H. pylori* infection and carotid atherosclerosis. A retrospective cohort study was performed for the incidence of carotid atherosclerosis for the patients with follow up measurements. Based on the distribution of patients with carotid atherosclerosis in different age groups, the cut-off age of 50 years old was used to identify the specific population with increased risk for carotid atherosclerosis associated with *H. pylori* infection. All statistical analyses were performed using the SPSS software (Windows Version 25.0, Chicago, IL, USA). The difference was considered statistically significant when a p value was < 0.05.

3. Results

3.1. Factors associated with carotid atherosclerosis

A total of 17,613 patients were screened with both carotid ultrasonography and a ^{13}C-urea breath test. The study population included 12,836 individuals of whom 8157 men (65.5%) and 4679 women



No Infection	Total Number	824	529	246
	New Cases	228	162	87
Persistent Infection	Total Number	392	221	86
	New Cases	129	84	42

Fig. 1. Study design and relationship between *H. pylori* infection and carotid atherosclerosis.
(A) The subjects were screened and divided into different groups based on the methods of analysis for the study. (B) After adjusting for age, sex, BMI, lipid profile, HTN, DM, smoking, and alcohol use, *H. pylori* infection was found to be an independent risk factor for carotid atherosclerosis for male patients ≤50 years. Model 1: not adjusted; Model 2: adjusted for age, sex, smoking, alcohol use, and BMI; Model 3: adjusted for all the factors in Model 2 plus blood pressure, HDL, LDL, and total cholesterol; Model 4: adjusted for all the factors in Model 3 plus diabetes mellitus. BMI: body mass index; DM: diabetes mellitus; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HTN: hypertension. (C) Analysis on the follow-up patients showed that patients with persistent *H. pylori* infection had significantly increased risk for carotid atherosclerosis after 3 years of follow up only in males under 50 years, not in females ($p = 0.028$).

(36.5%) (Table 1). Based on the presence of carotid atherosclerosis on carotid artery color ultrasonography, the patients were divided into two groups: 5779 patients with carotid atherosclerosis, and 7057 individuals without carotid atherosclerosis.

Patients with atherosclerosis had significantly higher rate of *H. pylori* infection, and had higher BMI, higher incidence of HTN, DM, smoking, alcohol use, higher levels of total cholesterol and low-density lipoprotein cholesterol (LDL), and lower level of high-density lipoprotein cholesterol (HDL) than those without carotid atherosclerosis ($p < 0.05$) (Table 1). Male patients had a significantly higher prevalence of carotid atherosclerosis than females (46.7% *vs.* 42.1%, $p < 0.001$).

3.2. *H. pylori* infection and carotid atherosclerosis: differences in age and gender

H. pylori-positive male patients had a significantly higher incidence of carotid atherosclerosis (48.54% *vs.* 45.67%, $p = 0.006$) and thicker CIMT (0.713 ± 0.098 *vs.* 0.700 ± 0.100, $p = 0.001$) compared with *H. pylori*-negative male subjects. However, no difference in the incidence of carotid atherosclerosis or CIMT was observed in females with and without *H. pylori* infection (Table 2). Further analysis showed that there was an age difference in male patients in the association between *H. pylori* infection and atherosclerosis. Fig. 1B showed that *H. pylori* infection significantly increased the risk for carotid atherosclerosis (OR = 1.335, 95% CI = 1.185–1.505, $p < 0.001$) and CIMT (0.689 ± 0.084 *vs.* 0.672 ± 0.087, $p < 0.001$) (Table 2) for males younger than 50 years, but not in males over 50 years.

Binary logistic regression analysis was performed to determine the impact of various factors on the likelihood for carotid atherosclerosis for male patients under 50 years old. Model 4 included all predictors that were statistically significant with single factor analysis (Fig. 1B). The p value of Omnibus test for the model coefficients was < 0.001, indicating that the model was able to identify the factors for male patients under 50 years of age with carotid atherosclerosis. As shown in Table 3, *H. pylori* infection, alcohol use, age, systolic blood pressure, HTN, CAD, and LDL-cholesterol were independent factors for increased risk of carotid atherosclerosis for males under 50 years. *H. pylori* infection was associated with a significant increase in CIMT for the patients without carotid atherosclerosis (0.664 ± 0.084 *vs.* 0.637 ± 0.088, $p = 0.002$). However, there was no difference in CIMT between subjects with and without *H. pylori* infection in patients with carotid atherosclerosis (0.732 ± 0.091 *vs.* 0.732 ± 0.094, $p = 0.989$) (Supplementary Table I), suggesting that the existing atherosclerotic

Table 1
Baseline characteristics for the participants with and without carotid atherosclerosis.

	Without carotid atherosclerosis (N = 7057)	With carotid atherosclerosis (N = 5779)	*p* value
H. pylori infection, n (%)	2348 (33.3%)	2079 (36.0%)	0.001
Age (years)	41.7 ± 7.7	54.0 ± 9.5	0.000
Male, n (%)	4347 (61.6%)	3810 (65.9%)	0.000
BMI (kg/m^2)	24.4 ± 3.5	25.1 ± 3.2	0.000
Waist-hip ratio	0.891 ± 0.073	0.915 ± 0.062	0.000
SBP (mmHg)	121.4 ± 15.5	133.1 ± 18.6	0.000
DBP (mmHg)	78.3 ± 12.0	83.1 ± 12.1	0.000
Hypertension, n (%)	1482 (21.0%)	2699 (46.7%)	0.000
Diabetes mellitus, n (%)	1369 (19.4%)	2092 (36.2%)	0.000
Hyperlipidaemia, n (%)	1750 (24.8%)	2231 (38.6%)	0.000
Smoking, n (%)	2865 (40.6%)	2456 (42.5%)	0.031
Alcohol, n (%)	3057 (43.3%)	3230 (55.9%)	0.000
Coronary heart disease, n (%)	176 (2.5%)	220 (3.8%)	0.000
Family history of CHD, n (%)	816 (11.6%)	701 (12.1%)	0.067
ALT (U/L)	30.0 ± 23.0	28.8 ± 20.0	0.051
AST (U/L)	24.0 ± 11.0	24.5 ± 10.4	1.000
Serum total bilirubin (umol/L)	15.4 ± 5.6	15.6 ± 5.5	0.697
Serum total protein (g/L)	72.8 ± 4.4	72.4 ± 4.4	0.370
Serum albumin (g/L)	46.7 ± 2.8	45.7 ± 2.9	0.476
A/G	1.8 ± 0.3	1.8 ± 0.3	0.969
Seroglobulin (g/L)	26.1 ± 3.6	26.7 ± 3.9	0.890
Blood urea nitrogen (mmol/L)	4.6 ± 1.2	5.1 ± 1.4	1.000
Creatinine (umol/L)	68.8 ± 15.5	72.0 ± 29.5	0.500
Uric acid (mg/dL)	317.7 ± 96.0	331.6 ± 92.2	0.346
Total cholesterol (mmol/L)	5.01 ± 0.97	5.31 ± 1.05	0.000
Triglycerides (mmol/L)	2.00 ± 2.07	2.12 ± 1.95	0.014
HDL-cholesterol (mmol/L)	1.46 ± 0.38	1.42 ± 0.37	0.001
LDL-cholesterol (mmol/L)	2.66 ± 0.83	2.95 ± 0.89	0.000
Fibrinogen (g/L)	2.7 ± 0.6	2.9 ± 0.7	0.200

Data were expressed as mean ± standard deviation or n (%), where appropriate. A/G: serum albumin/seroglobulin; ALT: alanine aminotransferase; AST: aspartate transaminase; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: Low-density lipoprotein; SBP: systolic blood pressure.

burden might overshadow the effect of *H. pylori* infection on CIMT.

3.3. Persistent H. pylori infection increased the incidence of carotid atherosclerosis in males

A total of 1216 patients had follow-up carotid ultrasonography for up to 5 years. All study patients received an annual carotid ultrasound and ^{13}C-UBT test. Patient with a continuous positive breath test every year was considered persistent *H. pylori* positive while patients who never had a positive breath test during the annual breath test were considered persistent negative for *H. pylori* infection. The incidence of carotid atherosclerosis was significantly higher in subjects with persistent *H. pylori* infection than those without infection after three years (Fig. 1C). A total of 332 individuals without carotid atherosclerosis at the initial ultrasound study were followed for 3–5 years and had follow-up carotid ultrasonography (Supplementary Table II). Of these, 246 patients were persistently negative for *H. pylori* infection, and 86 patients were persistently positive for *H. pylori* infection. A total of 129 patients developed carotid atherosclerosis during follow up from 2012 to 2017. Among them, 94 cases (72.87%) were males, and 35 cases (27.13%) were females. Males with persistent *H. pylori* infection had a significantly higher incidence of carotid atherosclerosis than those never infected after 3 years (50.91% *vs*. 35.29%, $p = 0.040$), especially in males under 50 years (48.00% *vs*. 30.72%, $p = 0.028$) (Table 4), but not in older males or female patients.

4. Discussion

The present study demonstrated that (1) *H. pylori* infection is common in China, with an infection rate of 36.1% for males and 31.6% for females; (2) after adjusting for age, gender, BMI, and other risk factors for atherosclerosis, *H. pylori* infection is an independent risk factor for carotid atherosclerosis, especially in Chinese males under 50 years of age, but not in older males nor in females; (3) progression of atherosclerosis can be detected in young Chinese males who have persistent *H. pylori* infection, when followed over at least 3 years.

The relationship between *H. pylori* infection and atherosclerosis has been inconsistent and sometime controversial. The prevalence of serologically confirmed *H. pylori* infection was significantly higher in patients with angiographically documented CAD, supporting a positive association between *H. pylori* infection and CAD [17–19]. However, a meta-analysis with inclusion of 18 epidemiological studies and over 10,000 patients showed no positive relationship between *H. pylori* infection and CAD [20]. In contrast, data supporting a positive

Table 2
Incidence of carotid atherosclerosis and carotid intima-media thickness in subjects with and without *H. pylori* infection.

	Incidence of carotid atherosclerosis		*p* value	Carotid intima-media thickness (mm)		*p* value
	Without *H. pylori* infection	With *H. pylori* infection		Without *H. pylori* infection	With *H. pylori* infection	
Male	2381 (45.67%)	1429 (48.54%)	0.006	0.700 ± 0.100	0.713 ± 0.098	0.001
≤50	945 (27.09%)	659 (33.17%)	0.004	0.672 ± 0.087	0.689 ± 0.084	< 0.001
> 50	1436 (83.25%)	770 (80.46%)	0.514	0.756 ± 0.106	0.763 ± 0.120	0.607
Female	1301 (42.13%)	668 (41.99%)	0.700	0.665 ± 0.106	0.662 ± 0.093	0.052

Data were expressed as mean ± standard deviation or n (%), where appropriate.

Table 3
Risk factors for carotid atherosclerosis in male patients under 50 years.

Binary logistic regression analysis was performed to assess the impact of a number of factors on the likelihood for carotid atherosclerosis.

Risk factor	Odds ratio (95%CI)	*p* value
H. pylori infection, n (%)	1.229 (1.054–1.434)	0.009*
Age (years)	1.144 (1.126–1.163)	< 0.001*
Alcohol, n (%)	1.445 (1.204–1.734)	< 0.001*
BMI (kg/m^2)	0.997 (0.97–1.025)	0.849
SBP (mmHg)	1.014 (1.007–1.021)	< 0.001*
Blood glucose, (mmol/L)	1.057 (0.965–1.157)	0.235
Total cholesterol, (mmol/L)	1.033 (0.813–1.313)	0.790
LDL-cholesterol, (mmol/L)	1.243 (1.106–1.397)	< 0.001*
HDL-cholesterol, (mmol/L)	0.825 (0.318–2.141)	0.692
HDL/TC	0.132 (0.001–1.721)	0.412
Hypertension, n (%)	1.476 (1.198–1.820)	< 0.001*
Diabetes mellitus, n (%)	1.225 (0.925–1.621)	0.157
Hyperlipidaemia, n (%)	1.040 (0.822–1.314)	0.745
Coronary heart disease, n (%)	2.995 (1.418–6.324)	0.004*
Serum total bilirubin, (umol/L)	0.924 (0.852–1.002)	0.057
Serum albumin, (g/L)	1.080 (0.946–1.23)	0.243
Uric acid, (mg/dL)	1.001 (1.000–1.002)	0.092
A/G	0.390 (0.12–1.262)	0.116
Blood urea nitrogen, (mmol/L)	1.057 (0.991–1.127)	0.094

A/G: serum albumin/seroglobulin; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; TC: total cholesterol.

Table 4
Incidence of carotid atherosclerosis in men and women after follow up for over 3 years.

	No infection			Persistent infection			*p* value
	Total number	**New cases**	Incidence	Total number	New cases	Incidence	
Male	187	66	35.29%	55	28	50.91%	0.040*
≤50	166	51	30.72%	50	24	48.00%	0.028*
> 50	21	15	71.43%	5	4	80.00%	1.000
Female	59	21	35.59%	31	14	45.16%	0.495

*$p < 0.05$.

relationship between *H. pylori* infection and carotid atherosclerosis with increased CIMT were consistent in most of the studies [21–25]. The reason(s) for the significant difference in consistency on the relationship between *H. pylori* infection and CAD *vs*. carotid atherosclerosis is unclear. It could be very likely due to the different imaging modalities used for detection of CAD (coronary angiogram) and carotid atherosclerosis (carotid ultrasound). Carotid ultrasound could easily detect early atherosclerotic lesions, while coronary angiogram could not. In a recent study, investigators used cardiac multidetector computed tomography to identify subclinical coronary atherosclerotic lesions in healthy subjects without clinical CVD, and found that patients with current *H. pylori* infection were 3-fold more likely to have subclinical and yet significant coronary atherosclerosis than patients without *H. pylori* infection [26]. One of the major features of atherosclerosis is thickening of the intima-media in the arteries that could not be detected with angiogram. Carotid artery is considered an early site of atherosclerosis and superficial. Thus, carotid ultrasound examination is an ideal and sensitive non-invasive image modality to diagnose and monitor the progression of atherosclerosis [27], although it has not been widely used clinically for atherosclerosis screening at this point.

It is very concerning that cardiovascular mortality has been increasing since 2010, especially in males, for unknown reasons [28]. It is also reported that patients with ST elevation myocardial infarction over the past 20 years are getting younger [29]. The reasons for this reverse trend in cardiovascular mortality and mobility have yet to be defined. In the present study, we found that *H. pylori* infection selectively increased the risk for carotid atherosclerosis in young male patients (≤50 years), not in older males or female patients. A recent study [30] that analyzed a large database with a study population of 208,196 showed that mortality rate was significantly lower in patients with early eradication of *H. pylori* infection. The cumulative CAD rate was significantly decreased in younger patients (< 65 years old) with *H. pylori* eradication therapy within 1 year compared to those patients without eradication at all. Interestingly, the treatment of *H. pylori* eradication did not have a benefit in older patients (> 65 years old). These data strongly suggested that *H. pylori* infection could be a significant risk factor for atherosclerosis and CAD in young patients, and could provide a potential explanation for young patients who develop CAD without a clear etiology. It is unclear why *H. pylori* infection dose not increase the risk for atherosclerosis in patients older than 50 years. It is possible that other significant risk factors like diabetes mellitus, hypertension, and hyperlipidemia play a dominant role in the development of atherosclerosis in this age group of patients. Further studies are needed to investigate the mechanism(s) on the selective effect of *H. pylori* infection on atherosclerosis in the young population.

There are substantial gender differences in many CVDs including (but not limited to) myocardial infarctions, heart failure, hypertension, and cardiac hypertrophy [31]. It is well known that premenopausal women are relatively protected from CVDs when compared to men. Typically, women are almost 10 years older than men when they have their first myocardial infarction [32]. It was believed that the decreased cardiovascular morbidity and mortality in young females was due to possible cardio-protective effects of estrogen [33]. However, several large clinical studies, including the HERS trials and the Women's Health Initiative study [34,35], showed that hormone replacement therapies (HRT) had no cardiovascular benefit in post-menopausal women. In contrast, there might have been an increased risk of CAD during the first year of HRT, and there was an increased risk of nonfatal ventricular arrhythmias among women on HRT [34]. Thus, the mechanism(s) for decreased CVD risk in premenopausal women is still unclear. Data from the present study showed that the prevalence of *H. pylori* infection was the same in males and females, and yet, *H. pylori* infection only increased the risk for carotid atherosclerosis in male patients ≤50 years, but not in older males or female patients. It is possible that the significant gender and age difference in the development of atherosclerosis associated with *H. pylori* infection may be one of the reasons for the decreased risk of CAD in young females. Further studies are needed to confirm these findings with both patients and experimental models.

It is not surprising that *H. pylori* infection increases the risk for atherosclerosis. It has been reported that *H. pylori* infection promotes the release of IL-1, IL-6, TNF-α, and other cytokines, and activates local and systemic inflammatory response, thus accelerating the development of atherosclerosis [36–38]. *H. pylori* infection could also lead to malabsorption of vitamin B12, which could increase serum level of homocysteine, and promote the development of atherosclerosis [39]. In addition, *H. pylori* could promote the oxidation of low-density lipoproteins (LDL) and increase atherosclerotic plaque formation with decreased plaque stability [40,41]. In the present study, we observed that the blood lipid profiles were different between *H. pylori*-infected patients and those without *H. pylori* infection. The levels of LDL-cholesterol in patients with *H. pylori* infection were significantly higher than those without *H. pylori* infection, while the level of high-density lipoprotein cholesterol (HDL-C) was significantly decreased in patients with *H. pylori* infection than those without *H. pylori* infection (Supplementary Table III). Patients with *H. pylori* seropositivity were shown to have increased brachial-ankle pulse wave velocity (a marker of atherosclerosis), and impaired glucose metabolism [42]. It is believed that *H. pylori* could interact with gastric epithelial cells to upregulate the expression of adhesion molecules, and secrete cytokines, which could activate leukocytes, damage the vascular endothelium, aggravate local and systematic inflammatory responses, and thus promote the development and progression of atherosclerosis.

There were a few limitations in the present studies, including (1) the retrospective nature of the study and the fact that it involved only one center with one ethnic population, (2) there was no detailed information on medications for the subjects in the database, and (3) there might be potential intra- and inter-observer variation in the assessment of CIMT. The database did not provide adequate information for the evaluation of potential intra- and inter-observer variation in the assessment of CIMT. However, the possibility for potential intra- and inter-observer variation could be the same for each subject in the study.

4.1. Conclusions

The data from the present study suggested that *H. pylori* infection was an independent risk factor for carotid atherosclerosis only in male patients under 50 years, not in older males or female patients.

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Author contributions

Zhenguo Liu and Canxia Xu generated the idea and designed the study. Linfang Zhang, Zhiheng Chen, Xiujuan Xia, Jingshu Chi collected the data. Linfang Zhang, Zhenguo Liu, Hong Hao, Greg C. Flaker, and Greg F. Petroski analyzed the data. Linfang Zhang, Da Liu, Delin Tian, and Hui Wang prepared the initial draft of the manuscript. Huan Li, Xiaoming Liu, Rong Li, Yixi Li helped with the preparation of the figures and tables. Greg C. Flaker and Zhenguo Liu critically reviewed and revised the manuscript. All authors reviewed the final version of the manuscript.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.10.005.

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