Association of *Helicobacter pylori* infection with metabolic syndrome in aged Chinese females

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Abstract. The association between *Helicobacter pylori (H. pylori)* infection and metabolic syndrome (MetS) determined in different cohorts from different countries is currently inconclusive. In the majority of previous studies, *H. pylori* infection was diagnosed based on the presence of *H. pylori* IgG antibody in the serum. However, to the best of our knowledge, only few studies have investigated the association between *H. pylori* infection and MetS using the urea breath test (UBT) as a diagnostic tool. The present study was performed with the aim of providing a detailed analysis of the association between *H. pylori* infection, as diagnosed by the UBT method, and MetS in a large community from Zhejiang province in eastern China. The results indicated that *H. pylori* infection increases the risk of MetS in the aged female population.

Introduction

Metabolic syndrome (MetS) comprises a group of metabolic abnormalities, including central obesity, impaired glucose tolerance, insulin resistance (IR), lipid metabolism disorders and hypertension, which markedly increase the risk of diabetes mellitus and cardio-cerebrovascular disease (1-3). Approximately one-quarter of the population worldwide have been reported to suffer from MetS (2). Chronic inflammation was previously suggested to be implicated in MetS (4).

Helicobacter pylori (*H. pylori*) infection is one of the most common infections globally, affecting >50% of the world's population, particularly in developing countries. Its prevalence varies across different cohorts with differences in age and developmental status (5,6). *H. pylori* infection may cause chronic gastritis, peptic ulcers and gastric cancer (7-9). More recently, *H. pylori* gastritis was considered as an infectious disease (10). *H. pylori* infection has been indicated to increase systemic inflammation by producing inflammatory factors, including C-reactive protein (CRP), tumor necrosis factor-α, interferon-γ and interleukin-1, -6 and -8, and these factors were confirmed to be involved in the pathogenesis of IR (11,12). In addition to gastrointestinal infections, *H. pylori* has also been reported to be associated with various extra-intestinal diseases, including MetS (13-20).

At present, the association between *H. pylori* infection and MetS determined in different cohorts of different countries remains inconclusive (17,20-32). In the majority of those studies, *H. pylori* infection was diagnosed based on the presence of *H. pylori* IgG antibody in the serum (29-31); however, serum IgG may persist after *H. pylori* is eradicated and may therefore not reflect the current infection status (33). The ^{13}C-urea breath test (UBT) is a non-invasive method for detecting current *H. pylori* infection. The sensitivity and specificity of the UBT are ~0.96 [95% confidence interval (CI): 0.95-0.97] and 0.93 (95% CI: 0.91-0.94), respectively (34). While it may be assumed that only current infection is able to cause systemic inflammatory reactions, few studies have investigated the association between *H. pylori* infection and MetS using UBT as the diagnostic method, to the best of our knowledge.

Therefore, given the diversity of the incidence of *H. pylori* infection across different countries and the controversial results of the studies investigating the association between *H. pylori* infection and MetS, particularly in East Asia, it is crucial to further investigate this association in a large population. The aim of the present study was to provide a detailed analysis of the association between *H. pylori* infection, as diagnosed by UBT, and MetS in a large community from Zhejiang province in eastern China.

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Abbreviations: H. pylori, *Helicobacter pylori*, MetS, metabolic syndrome; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; UA, uric acid; HCY, homocysteic acid; CYSC, serum cystatin C; HS-CRP, high-sensitivity C-reactive protein; HbA1c, glycosylated Hb; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; 95% CI, 95% confidence interval; OR, odds ratio

Key words: Helicobacter pylori, metabolic syndrome, insulin resistance, 13C-urea breath test, Chinese aged women

Materials and methods

Study participants. Participants who voluntarily underwent a general health screening between January 2014 and December 2015 were recruited at the International Health Care Center of the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China). Participants with any of the following characteristics were excluded from the study: i) History of gastric surgery; ii) history of anti-*H. pylori* therapy; iii) use of antibiotics, proton pump inhibitors, H2 blockers or bismuth within the previous 4 weeks; iv) severe mental or neurological disorders; v) history of cancer(s). All subjects underwent a detailed physical examination, including UBT detection of *H. pylori* infection.

Diagnosis of H. pylori infection. After fasting for at least 2 h, all of the participants underwent a ^{13}C-UBT (Richen-Force, Beijing, China) for the detection of *H. pylori* infection. After collecting the baseline breath sample, the participants ingested a ^{13}C-urea reagent dissolved in water. The second breath sample was collected and analyzed after 30 min. A delta over baseline value ≥4.0 indicated a positive result for *H. pylori* infection.

Definitions of the study variables. For each participant, age, sex, weight, height, body mass index (BMI) and waist circumference were recorded. Blood pressure was measured after at least 10 min of rest. Waist circumference was measured with a measuring tape while standing, midway between the lowest rib and the iliac crest. The BMI was calculated as follows: Weight (kg)/[height (m)]^2.

Information on the history of smoking and alcohol consumption, as well as the medical history, including hypertension, hyperlipidemia and/or diabetes, was also collected using a questionnaire. The questionnaire also included the history of the present illness, previous diagnoses of *H. pylori* infection, history of anti-*H. pylori* therapy and confirmation of eradication after treatment. If the questionnaire was incomplete, the patient was contacted to ensure for integrity of the data.

Laboratory examinations were performed after a 10-h fast, including white blood cell (WBC) count, hemoglobin (Hb), platelet count, high-sensitivity (HS)-CRP, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total bilirubin, alanine aminotransferase (ALT), γ-glutamyl transpeptidase, aspartate aminotransferase (AST), fasting plasma glucose, glycosylated Hb (HbA1c), 2-h postprandial plasma glucose, fasting insulin, blood urea nitrogen, creatinine (Cr), uric acid (UA), homocysteic acid (HCY) and serum cystatin C (CYSC).

The identification of individuals with MetS was based on the definition of the International Diabetes Federation (35) as follows: i) Central obesity (waist circumference, ≥90 and ≥80 cm in Chinese males and females, respectively); ii) a combination of any of the following four indicators: TG level increased to >150 mg/dl (1.7 mmol/l), or treated accordingly; HDL-C level decreased to <40 mg/dl (0.9 mmol/l) in males and <50 mg/dl (1.1 mmol/l) in females, or the patient receiving corresponding treatment; systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg, or treated accordingly, or previous diagnosis of hypertension; and fasting plasma glucose level increased to ≥100 mg/dl (5.6 mmol/l), or previous diagnosis of type 2 diabetes mellitus, or the patient receiving corresponding treatment.

IR is generally considered to be the most important pathophysiological basis for MetS. The homeostasis model assessment (HOMA) score may be used to estimate IR, which is defined as follows: [Fasting plasma insulin (mU/l) x fasting plasma glucose (mmol/l)]/22.5. A high HOMA-IR score denotes low insulin sensitivity and IR (36). Based on a previous study (17), three cut-off values of the HOMA-IR index (2, 2.5 and 3) were adopted to evaluate IR.

Statistical analysis. The statistical analysis was performed using IBM-SPSS 24.0.0.0 software (IBM Corp.) and Python. Wilcoxon's rank-sum test was used to evaluate differences between groups for quantitative data, and the Chi-squared test was used for qualitative data. All P-values were based on a two-sided test of statistical significance. P<0.05 was considered to indicate a statistically significant difference. The optimal cut-off point of age was calculated using the maximization of Youden's index (sensitivity+specificity-1) in the receiver operating curve analysis. The association between *H. pylori* status and MetS characteristics was evaluated by a multivariate logistic regression (LR) analysis model following adjustment for age, sex, alcohol consumption, smoking, WBC count, HS-CRP, ALT, AST, HbA1C, HCY, CYSC, Cr and UA levels. The patients were further stratified into subgroups based on age and sex.

Results

Clinical and demographic characteristics. In the present study, 5,884 participants were included after screening of a total of 10,602 subjects (Fig. 1). The study subjects had a mean age of 46.81±10.13 years and 2,053 (34.9%) were female. A total of 1,265 (21.5%) had MetS, with a different percentage among males and females (24.8 vs. 15.3%, respectively; P<0.001). In addition, the prevalence of MetS was identified to increase with age, particularly in females.

The overall prevalence of *H. pylori* infection in this cohort was 46%, and it was higher in male compared with female patients (47.1 vs. 43.9%, respectively; P=0.023), however, it did not exhibit any differences across different age groups.

A statistically significant difference in the presence of *H. pylori* was observed between subjects with and those without MetS (50.4 vs. 44.8%, respectively; P<0.001; Table I).

Overall, age and sex subgroup analyses for the risk of MetS associated with H. Pylori infection. A multivariate LR model was constructed for predicting MetS by considering the *H. pylori* infection status and other potential covariates, including sex, age and HOMA-IR. It was observed that *H. pylori* infection was a significant risk factor contributing to the prediction of MetS with a broad-line risk of 1.2 (95% CI: 1.02-1.36, P=0.028; Table II). Subsequently, a receiver operating characteristic curve analysis on age was performed to segment participants, which indicated the age of 50 years as an optimal threshold (i.e., maximizing Youden's index; Table III). It was also used to differentiate the MetS distribution between subjects with or without *H. pylori* infection. Furthermore, A multivariate LR model analyses revealed that

Table I. Demographic characteristics of subjects with or without MetS.

Features	MetS		P-value
	Yes	No	
Sex (female%)	315 (24.9)	1738 (32.6)	<0.001
Age (years)	50.9±9.9	46.3±10.3	<0.001
Height (cm)	167.8±8.0	165.7±7.8	<0.001
Weight (kg)	75.8±10.5	63.8±10.2	<0.001
BMI (kg^2/m^2)	26.8±2.6	23.2±2.7	<0.001
Waist (cm)	94.1±6.7	82.2±8.3	<0.001
WBC ($x10^9/l$)	6.51±1.6	6.1±1.6	<0.001
Hb (g/l)	150.5±14.5	144.7±16.1	<0.001
PLT($x10^9/l$)	214.0±55.7	212.5±53.6	0.390
T-BiL (μmol/l)	13.7±5.3	13.7±5.7	0.790
ALT (U/l)	34.5±26.99	23.5±23.1	<0.001
GGTP (U/l)	56.8±54.4	34.0±38.99	<0.001
AST (U/l)	27.0±12.7	22.9±13.2	<0.001
Hs-CRP (mg/l)	2.1±3.1	1.2±2.4	<0.001
BUN (mmol/l)	5.3±1.2	4.98±1.2	<0.001
Cr (mmol/l)	65.2±14.0	63.1±13.97	<0.001
UA (μmol/l)	387.2±90.9	336.3±86.8	<0.001
HCY (μmol/l)	11.2±5.3	10.5±5.2	<0.001
CYS (mg/l)	0.95±0.2	0.9±0.2	<0.001
TC (mmol/l)	5.2±1.1	4.9±0.9	<0.001
TG (mmol/l)	2.7±2.3	1.4±1.3	<0.001
LDL (mmol/l)	2.9±0.8	2.8±0.7	<0.001
HDL (mmol/l)	1.07±0.3	1.2±0.3	<0.001
FBG (mg/dl)	5.9±1.7	5.0±0.8	<0.001
HbA1c (%)	7.4±1.1	6.8±0.7	<0.001
PBG (mg/dl)	9.0±4.1	6.5±2.5	<0.001
FINS (pmol/l)	100.8±51.9	63.6±35.9	<0.001
DBP (mmHg)	83.4±10.6	74.3±11.3	<0.001
SBP (mmHg)	136.7±16.6	121.6±16.9	<0.001
H. pylori infection (%)	637 (50.4)	2068 (44.8)	<0.001
HOMA-IR	3.8±2.3	2.1±1.5	<0.001
>2 (%)	1057 (87)	1958 (42.8)	<0.001
>2.5 (%)	888 (71.5)	1180 (25.8)	<0.001
>3 (%)	711 (57.2)	689 (15.3)	<0.001
Carotid atherosclerosis (%)	441 (37.1)	949 (22.8)	<0.001
Diabetes (%)	201 (15.9)	174 (3.8)	<0.001
Fatty liver (%)	1037 (82)	1520 (32.9)	<0.001
Drinking (%)	700 (55.3)	2055 (44.5)	<0.001
Smoking (%)	528 (42.1)	1429 (30.9)	<0.001
Hypertension (%)	416 (32.9)	499 (10.8)	<0.001
Hyperlipidemia (%)	70 (5.5)	53 (1.1)	<0.001

H. pylori, Helicobacter pylori; MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; PLT, platelets; T-BiL, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; HCY, homocysteic acid; CYSC, serum cystatin C; ALT, alanine aminotransferase; GGTP, γ-glutamyltranspeptidase; AST, aspartate aminotransferase; HS-CRP, high-sensitivity C-reactive protein; FPG, fasting blood glucose; PBG, 2-hour postprandial blood glucose; FINS, fasting insulin; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; TG, triglyceride.

Table II. LR analysis of MetS risk associated with *H. pylori* and other factors.

Variables	OR [95% CI]	P-value
H. pylori infection	1.21 [1.02-1.36]	0.028
HOMA-IR	2.13 [1.98-2.20]	<0.001
Age (years)	1.11 [1.04-1.16]	<0.001
Gender	1.54 [1.27-1.75]	<0.001

H. pylori, Helicobacter pylori; HOMA-IR, homeostasis model assessment of insulin resistance; 95% CI, 95% confidence interval; OR, odds ratio.

Table III. Sensitivity, specificity and Youden's index at different age cut-off points.

Age	Sensitivity	1-Specificity	Youden's index
15	1	1	0.000
20	0.999	0.998	0.001
30	0.986	0.928	0.058
40	0.846	0.699	0.147
50	0.48	0.313	0.167
60	0.158	0.081	0.077
70	0.024	0.011	0.013
80	0.005	0.003	0.002

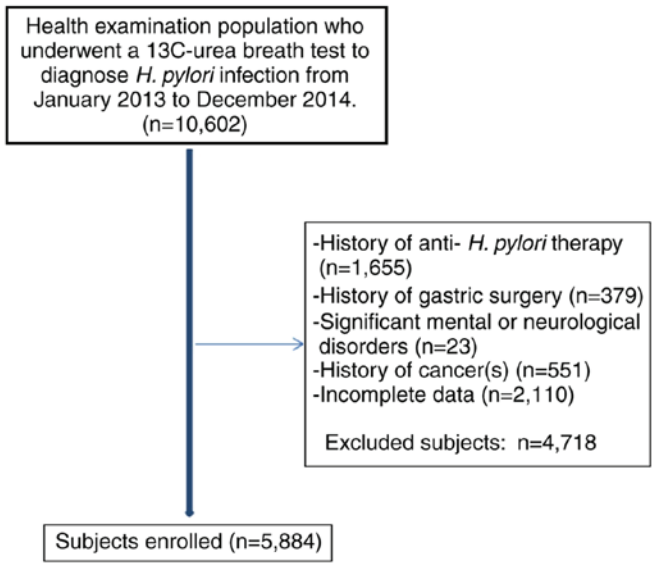

Figure 1. Flow chart depicting the enrolment of subjects in the present study.

H. pylori infection was a significant risk factor for MetS in male participants aged <50 years and in female participants aged ≥50 years (Table IV).

Multivariate LR analysis of H. pylori infection and other factors with MetS. A multivariate LR analysis was performed to determine the risk of MetS associated with the *H. pylori* infection status and other metabolic-associated parameters,

Table IV. LR analysis of the risk of MetS associated with *H. pylori* infection in different groups.

H. pylori groups	OR [95% CI]	P-value
Males		
<50 years	1.28 [1.04-1.56]	0.017
≥50 years	1.21 [0.97-1.50]	0.088
Females		
<50 years	0.87 [0.58-1.30]	0.495
≥50 years	1.53 [1.10-2.10]	0.010

H. pylori, Helicobacter pylori; 95% CI, 95% confidence interval; OR, odds ratio.

Table V. Predictors of MetS by LR based on *H. pylori infection* and other factors.

Variables	OR [95% CI]	P-value
Age (years)	0.95 [0.68-0.98]	<0.001
Sex	4.40 [4.27-6.97]	<0.001
HS-CRP (mg/l)	1.94 [1.80-2.80]	<0.001
ALT (U/l)	0.92 [0.85-0.99]	<0.001
AST (U/l)	1.92 [1.19-3.15]	<0.001
HbA1c (%)	1.51 [1.32-2.92]	<0.001
Cr (mmol/l)	1.01 [1.39-1.80]	0.001
UA (μmol/l)	1.99 [1.59-3.49]	<0.001
H. pylori infection	1.12 [1.02-1.59]	0.017

H. pylori, Helicobacter pylori; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS-CRP, high-sensitivity C-reactive protein; HbA1c, glycosylated hemoglobin; Cr, creatinine; UA, uric acid; 95% CI, 95% confidence interval; OR, odds ratio.

which were not direct variables in defining MetS, including WBC count, HS-CRP, ALT, AST, HbA1c, HCY, CYSC, Cr and UA. It was observed that *H. pylori* infection, age, sex, HS-CRP, HbA1c, UA and Cr were also positively associated with MetS (Table V). When stratifying participants into different gender groups and different age groups, similar patterns among contributors for predicting MetS were revealed. It was noted that, when the subjects were stratified by sex and further by age, *H. pylori* infection was significantly associated with MetS in female patients aged ≥50 years [odds ratio (OR)=1.29, 95% CI: 1.09-1.91; Table VI].

Discussion

The present study investigated the prevalence of *H. pylori* infection in subjects with MetS, and further explored the association of *H. pylori* infection and other factors with MetS. A significant difference was identified in the presence of *H. pylori* infection between subjects with and those without MetS (50.4 vs. 44.8%, respectively; P<0.001). In a multivariate LR analysis, *H. pylori* infection was determined to be significantly associated with MetS in female patients aged ≥50 years.

Table VI. Predictors of MetS by LR from subjects of sex groups with different ages.

	Males				Females			
	<50 years		≥50 years		<50 years		≥50 years	
Variables	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value
HS-CRP (mg/l)	1.94 [1.9-1.99]	0.010	1.54 [1.49-1.59]	0.013	0.91 [0.81-1.03]	0.150	0.97 [0.92-1.03]	0.340
ALT (U/l)	1.89 [1.84-1.93]	<0.001	0.96 [0.91-1.02]	0.180	1.80 [1.71-1.91]	0.003	1.01 [0.92-1.11]	0.890
AST (U/l)	2.07 [1.51-2.84]	<0.001	1.62 [1.15-2.27]	<0.001	5.53 [2.91-10.51]	<0.001	1.15 [0.75-1.77]	0.520
HbA1c (%)	1.53 [1.44-1.64]	<0.001	1.33 [1.26-1.62]	<0.001	1.22 [1.12-1.39]	<0.001	1.27 [1.19-1.4]	<0.001
Cr (mmol/l)	1.02 [1.01-1.04]	0.001	1.00 [0.99-1.01]	0.800	1.06 [1.02-1.11]	0.007	1.01 [0.98-1.03]	0.700
UA (μmol/l)	1.10 [1.05-1.2]	<0.001	1.09 [1.01-1.12]	<0.001	1.02 [1.01-1.99]	<0.001	1.05 [1.03-1.20]	0.003
H. pylori infection	0.82 [0.63-1.06]	0.130	0.79 [0.59-1.06]	0.120	1.39 [0.80-2.41]	0.250	1.29 [1.09-1.91]	0.002

H. pylori, Helicobacter pylori; MetS, metabolic syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS-CRP, high-sensitivity C-reactive protein; HbA1c, glycosylated hemoglobin; Cr, creatinine; UA, uric acid; 95% CI, 95% confidence interval; OR, odds ratio.

Several studies have identified *H. pylori* infection as a risk factor for MetS (17,20-25). Chen *et al* (17), reported that the prevalence of MetS was higher among *H. pylori*-positive individuals of either gender in a Chinese adult cohort. Upala *et al* (21) demonstrated that *H. pylori* infection was positively associated with IR using a meta-analysis. Yang and Xuan (25) indicated that elderly patients (aged 73.19±11.03 years) with *H. pylori* infection had a higher BMI and fasting glucose levels and a higher incidence of MetS. Furthermore, certain studies suggested that *H. pylori* infection has a causative association with MetS through pathophysiological analysis (26-28). By contrast, other studies failed to prove this association (29-32). For instance, Naja *et al* (31) reported no suggested association of *H. pylori* infection with IR or MetS in Lebanese adults. Similarly, Tamura *et al* (32), identified no association between *H. pylor*i infection and diabetes in a Japanese population.

In addition to national and regional factors, these inconsistent results may be due to the different screening methods for *H. pylori* infection among different studies. *H. pylori* infection is diagnosed on the basis of clinical and laboratory findings, as well as microbiological and histopathological examinations following endoscopy. Shin *et al* (37), observed that MetS was more closely associated with histological positivity for *H. pylori* (adjusted OR=1.26; 95% CI: 1.08-1.48) rather than serological positivity (adjusted OR=1.12, 95% CI: 0.95-1.32). This conclusion was attributed to the fact that serological positivity for *H. pylori* does not necessarily indicate current infection. Only few studies have been performed to assess the effects of *H. pylori* infection on MetS in Chinese populations, and most of those are based on the detection of IgG antibody in the serum. Although Chen *et al* (17) used ^{13}C-UBT to demonstrate that *H. pylori* infection is positively associated with MetS, the systemic association among MetS, *H. pylori* infection and other variables has remained to be elucidated.

In the present study, a different prevalence of *H. pylori* infection was observed between male and female subjects (47.1 vs. 43.9%, respectively; P=0.023), whereas Chen *et al* (17) reported a similar prevalence in either gender (20%) in an adult population from Taiwan. In addition, there was no difference in the prevalence of *H. pylori* infection among different age groups; however, they reported an increase in prevalence with advancing age in males and females (17). Those results indicate a different prevalence (also between the two sexes) of MetS and *H. pylori* infection across the Chinese population, suggesting that different measures have to be taken accordingly. In addition, the present study also observed a difference in the prevalence of MetS between sexes (24.8 vs. 15.3% in male and female subjects, respectively), consistently with the results of a more recent study (38).

This association was further investigated by stratifying the subjects into males and females, and into different age groups. An increased significance was observed in aged females, which was consistent with a previous study reporting that *H. pylori* infection was a predictor of MetS in elderly patients (aged 73.19±11.03 years) (25). Although in the present study, *H. pylori* infection was significantly associated with MetS, it was observed that *H. pylori* infection per se was only a weak predictor of MetS (accuracy, 65%) regardless of sex and age (all these models achieved an accuracy of ~65%). Furthermore, *H. pylori* infection was not the major contributor in the LR model compared with other metabolism-associated parameters, but it may be an important contributor to MetS when combined with other factors. Due to the higher incidence of hyperlipidemia, hyperglycemia or hypertension among individuals aged >50 years, *H. pylori* infection has a greater impact in this population. In addition, it has been demonstrated that post-menopausal females have significantly reduced estrogen levels, reduced resistance to inflammatory reactions and increased levels of inflammatory factors (39,40), which may explain for the more pronounced inflammatory response of aged females to *H. pylori* infection compared with males.

The health check-up population at our center mainly comprised residents from Zhejiang province, so the economic level is expected not to differ significantly. In fact, the questionnaire included queries associated with socioeconomic conditions and eating habits. However, a previous statistical analysis indicated that their impact was not significant, so they were not included in the present study.

Of note, the present study had certain limitations. First, the subjects were recruited from a single center. Second, the present study was an observational study, and conclusions may only be drawn regarding the association between *H. pylori* infection and other factors with MetS.

In conclusion, *H. pylori* infection increases the risk of MetS in aged females. However, these observations are inconsistent across different cohorts, which warrants further investigation by prospective or biochemical studies. If confirmed, eradication of *H. pylori* infection may be of therapeutic value for MetS.

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Availability of data and materials

All the datasets generated and analyzed in the present study are included in this published article.

Authors' contributions

YY and JC contributed to the literature search and the writing of the manuscript; JW and LW contributed to data collection and analysis; ZS designed the study.

Ethics approval and consent to participate

All of the participants provided written informed consent prior to the examination. The present study was reviewed and approved by the Ethics Committee of the 2nd Affiliated

Hospital, School of Medicine, Zhejiang University (Hangzhou, China; no. 2013-218).

Patient consent for publication

Not applicable.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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