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Association between histological severity of *Helicobacter pylori* infection and cardiovascular risk scores in the Korean population

Jaehoon Chung [a,1], Kyueng-Whan Min [b,1], Byoung Kwan Son [c], Dong-Hoon Kim [d,*], Hack-Lyoung Kim [e,**]

[a] Division of Cardiology, Department of Internal Medicine, National Medical Center, Seoul, Republic of Korea
[b] Department of Pathology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri-si, Gyeonggi-do, Republic of Korea
[c] Department of Internal Medicine, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu-si, Gyeonggi-do, Republic of Korea
[d] Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[e] Division of Cardiology, Department of Internal Medicine, Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background and aims: Although there have been several reports on the association between *Helicobacter pylori* (HP) infection and cardiovascular disease (CVD), most studies have been done through noninvasive testing such as serologic test or urea breath test. This study investigated the relationship between histological features of HP gastritis and cardiovascular risk scores.

Methods: A total of 21,251 subjects (mean age, 43.8 ± 9.6 years; males, 72.1%) who underwent routine health checkup and gastric biopsy were retrospectively analyzed. The severity of gastritis was assessed using the updated Sydney system (USS). With four different risk predicting algorithms, we calculated Framingham coronary heart disease (CHD) risk score, ATP III revised Framingham CHD risk score, generalized Framingham risk against total CVD, and ACC/AHA 10-year risk of a first hard atherosclerotic-CVD event in each subject.

Results: About half of the study subjects (51.2%, n = 10,890) were confirmed to have HP infection. Subjects with HP infection were younger (42.9 ± 9.0 *vs.* 44.7 ± 10.2 years, $p < 0.001$) than those without. After adjustment for age, most of the estimated 10-year cardiovascular risk increased as the grade of USS elements increased. As the sum of the USS scores increased, all the 4 estimated 10-year cardiovascular risk scores increased proportionally ($p < 0.05$ for each).

Conclusions: The histological features of gastritis assessed using USS were associated with various cardiovascular risk scores. This study provides strong evidence on an association between chronic inflammation and increased cardiovascular risk.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and is a significant social and economic burden worldwide [1,2]. Therefore, it is very important to find high-risk subjects and provide them with intensive treatment. To stratify and predict CVD risk, various risk prediction models have been developed. In 1998, Framingham risk score was first developed to estimate 10-year risk of developing coronary heart disease (CHD) [3]. In 2002, the National Cholesterol Education Program Expert Panel published the Adult Treatment Panel III (ATP III) and developed a scoring system to predict 10-year risk of hard CHD including myocardial infarction and coronary death [4]. In 2008, the Framingham Heart Study Group suggested a new algorithm to predict 10-year general atherosclerotic CVD (ASCVD) including not only CHD, but also cerebrovascular disease, peripheral vascular disease, and heart failure [5]. More recently, in 2013, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the assessment of cardiovascular risk introduced a new equation estimating 10-year risk of hard

* Corresponding author. Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29, Saemunan-ro, Jongno-gu, Seoul 03181, Republic of Korea.
** Corresponding author. Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, Boramae Medical Center, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea.
E-mail addresses: idavid.kim@samsung.com (D.-H. Kim), khl2876@gmail.com (H.-L. Kim).
[1] These authors contributed equally to this work.

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ASCVD including nonfatal myocardial infarction, CHD death, and fatal or nonfatal stroke [6]. Although there are some criticisms on the inaccuracy of risk-predicting models, these risk prediction models are widely used to estimate future CVD risks and to prescribe statins [7].

Besides traditional risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, and family history, some studies have recently suggested that immune response or inflammation is associated with the development of CVD [8,9]. *Helicobacter pylori* (HP), a gram-negative bacterium, induces recruitment of inflammatory cells to gastric mucosa and triggers the secretion of proinflammatory cytokines, resulting in mild and chronic systemic inflammation [10]. There have been several studies showing the association between HP and CHD [11–14]. However, all these studies are based on serological findings. The updated Sydney system (USS) is a widely used method of grading the severity of gastritis that provides topographical, morphological, and etiological information. The USS includes HP, neutrophils, mononuclear cells, atrophy, and intestinal metaplasia as evaluation factors [15]. Until now, there have been few studies showing the association between HP related histological findings and CVD risk. Investigations based on histological findings of biopsy samples provide strong evidence for an association between chronic inflammation induced by HP and CV risk.

Therefore, in this study, we investigated the relationship between HP-related histological gradings based on the USS and the commonly used cardiovascular risk models mentioned above.

2. Materials and methods

2.1. Study population

Between August 2006 and September 2009, 21,600 subjects who visited the Kangbuk Samsung Medical Center (Seoul, Republic of Korea) for health checkup and underwent gastroscopy and histological examination of gastric mucosa were retrospectively reviewed. Patients with the following conditions were excluded: (1) age under 18 years, (2) history of HP eradication or gastric surgery, and (3) unavailable clinical and laboratory data. Finally, a total of 21,251 subjects were analyzed in this study. Our study protocol was approved by the Institutional Review Board (IRB) of Kangbuk Samsung Medical Center (Seoul, Republic of Korea) (IRB number 2016-04-44). Written informed consent was waived by IRB due to the retrospective study design and routine nature of information collected.

2.2. Clinical and laboratory data

Body mass index (BMI) was calculated as body weight divided by the square of height in meters (kg/m^2). Systolic and diastolic blood pressure was measured in the right upper arm using an oscillometric device by a trained nurse. Hypertension was defined as previous diagnosis of hypertension, the use of antihypertensive medications or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Diabetes mellitus was defined as previous diagnosis of diabetes mellitus, the use of oral hypoglycemic agents or insulin, or serum fasting glucose levels ≥126 mg/dL. Subjects were classified as smokers if they smoked regularly for the past 12 months. History of coronary artery disease and stroke was obtained with a standardized questionnaire. The following laboratory data was obtained by sampling venous blood in the morning after overnight fasting: white blood cell count, hemoglobin, fasting blood glucose, creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride. Estimated glomerular filtration rate (GFR) was calculated with a Modification of Diet in Renal Disease (MDRD) equation based on age, sex, race, and serum creatinine.

2.3. Microscopic examination for gastric mucosa

Gastric mucosal tissues sized over 2 mm obtained from gastroscopy biopsy were assessed using the USS [16]. The specimens were fixed in 10% formalin, embedded in paraffin on the oriented edge, and cut into 4-μm-thick sections. All sections were stained with hematoxylin-eosin and Giemsa stain for histopathological evaluation. The histological evaluation of gastric mucosa through a light microscope was blindly conducted. According to the USS, density of HP, mononuclear cells, neutrophils, degree of atrophy, and intestinal metaplasia were assessed. Each of the histological parameters was graded as 0 (absence), 1 (mild), 2 (moderate), or 3 (severe) according to the USS. The grades were evaluated based on the highest level when 2 or more tissues were acquired.

2.4. Cardiovascular risk estimation

Of various scoring systems, Framingham CHD risk score (FRS 1998), ATP III revised Framingham CHD risk score (ATP III FRS 2002), generalized Framingham risk against total CVD (generalized FRS 2008), and ACC/AHA 10-year risk of a first hard ASCVD event (ACC/AHA ASCVD 2013) were used to assess estimated cardiovascular risk for the next 10 years [3–6]. According to each system, age, sex, blood pressure, level of serum cholesterol, status of hypertension, diabetes mellitus, and cigarette smoking were used for risk estimation. More detailed features of each prediction model, including covariates and outcomes, are shown in Supplementary Table 1.

2.5. Statistical analysis

The results are expressed as the mean ± standard deviation (SD) for continuous variables and as percentage for categorical variables. Study subjects were stratified into 2 groups according to the presence of HP. Continuous variables were compared using Student's *t*-test and categorical variables were compared using Pearson's chi-square test to assess differences between the 2 groups. There was a significant difference in age between subjects with and without HP, and age is a key factor for cardiovascular risk estimation. Therefore, analysis of covariance (ANCOVA) was used to compare age-adjusted mean value of risk scores among 4 groups stratified based on USS findings. All analyses were 2-tailed, and clinical significance was defined as $p < 0.05$. Statistical analyses were performed with the statistical package SPSS version 23.0 (IBM Co., Armonk, NY, USA).

3. Results

In the total study population, the mean age was 43.8 ± 9.6 years, and 15,322 (72.1%) were men. About a half of the study subjects (51.2%, n = 10,890) had HP. The clinical characteristics of the study subjects according to the presence of HP are shown in Table 1. Subjects with HP were younger (42.9 ± 9.0 *vs.* 44.7 ± 10.2 years, $p < 0.001$) and more male-predominant (74.7% *vs.* 69.3%, $p < 0.001$) than those without. Both systolic and diastolic blood pressures were similar between the 2 groups. For cardiovascular risk factors, hypertension (20.7% *vs.* 22.4%), and previous history of coronary artery disease (11.5% *vs.* 12.8%) and stroke (0.3% *vs.* 0.6%) were less frequently observed in subjects with HP than those without ($p < 0.05$ for each). However, there were more smokers in subjects with HP than in those without (62.0% *vs.* 56.8%, $p < 0.001$). For laboratory test results, subjects with HP showed higher levels of white blood cell count, hemoglobin, estimated GFR, total cholesterol, LDL cholesterol, TG, and lower level of HDL cholesterol than those without ($p < 0.05$ for each).

Table 2 and Fig. 1 demonstrate age-adjusted 10-year cardiovascular risks according to histological findings based on the USS. The ATP III FRS 2002 and the generalized FRS 2008 were significantly different according to the grade of HP density ($p < 0.05$ for each). The association between FRS 1998 and HP density showed statistically marginal significance ($p = 0.054$). However, ACC/AHA ASCVD 2013 were not associated with HP density ($p = 0.410$). All the 4 estimated 10-year

Table 1
Characteristics of study subjects.

Characteristics	With HP (n = 10,890)	Without HP (n = 10,361)	p value
Age, years	42.9 ± 9.0	44.7 ± 10.2	<0.001
Male, n (%)	8140 (74.7)	7182 (69.3)	<0.001
Body mass index, kg/m^2	24.2 ± 3.0	24.1 ± 3.0	0.001
Systolic blood pressure, mmHg	116.0 ± 12.9	116.0 ± 13.3	0.805
Diastolic blood pressure, mmHg	75.3 ± 9.0	75.2 ± 9.0	0.350
Cardiovascular risk factors, n (%)			
Hypertension	2258 (20.7)	2326 (22.4)	0.002
Diabetes mellitus	507 (4.7)	521 (5.0)	0.205
Cigarette smoking	6752 (62.0)	5883 (56.8)	<0.001
Coronary artery disease	1255 (11.5)	1331 (12.8)	0.003
Stroke	31 (0.3)	61 (0.6)	0.001
Major laboratory findings			
White blood cell count, per μL	6406 ± 1,609	6202 ± 1,662	<0.001
Hemoglobin, g/dL	15.0 ± 1.5	14.8 ± 1.5	<0.001
Fasting blood glucose, mg/dL	98.0 ± 18.6	97.9 ± 17.9	0.700
Estimated GFR, mL/min/1.73 m^2	79.6 ± 10.5	79.2 ± 10.8	0.005
Total cholesterol, mg/dL	198.1 ± 33.9	197.2 ± 34.1	0.042
LDL cholesterol, mg/dL	116.4 ± 30.2	115.5 ± 30.5	0.033
HDL cholesterol, mg/dL	52.5 ± 12.0	53.3 ± 12.5	<0.001
Triglyceride, mg/dL	140.5 ± 91.9	135.8 ± 86.6	<0.001

HP, *Helicobacter pylori*; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

cardiovascular risk scores increased as the grade of neutrophil and mononuclear cell infiltration, glandular atrophy, and intestinal metaplasia increased ($p < 0.05$ for each), except statistically marginal significance for the association between ACC/AHA ASCVD 2013 and mononuclear cell infiltration ($p = 0.05$). Similar results are shown not only for each component of the USS, but also for the sum of the USS scores. All the 4 estimated 10-year cardiovascular risk scores were significantly different according to the sum of the USS scores and tended to increase as the sum of the USS scores increased (Fig. 2).

The statistical significances of the associations between risk scores and the grade of histology in different study groups are showed in Table 3. Overall, the correlations between cardiovascular risk scores and the grades of gastritis histology were stronger in subjects with male sex, younger age less than 40 years, non-obesity (body mass index < 25 kg/m^2), and without cardiovascular risk factors.

4. Discussion

The main finding of this study is that degree of histological findings of HP gastritis assessed using the USS was associated with 4 different estimated cardiovascular risks in Korean subjects who underwent gastroscopy during routine health checkup. To the best of our knowledge, this is the first study demonstrating the relationships between histological findings of gastritis and various cardiovascular risk scoring systems. Our study result provides additional evidence for the relationships between local inflammation, immunological process, and the risk of CVD.

Atherosclerosis is a complex disease that affects various areas from head to toe. Understanding the pathophysiology of atherosclerosis is important for treating and preventing atherosclerosis and its consequences. Associations between inflammation and the development of CVD has been shown in many studies. There is increasing evidence to indicate that inflammatory markers, such as C-reactive protein (CRP), are associated with CVD [8,9,17,18]. In a study with 543 apparently

Table 2
Age adjusted 10-year cardiovascular risks according to Updated Sydney System.

	Grade of HP density				
Estimated 10-year cardiovascular risk	0 (n = 10,361)	1 (n = 4,438)	2 (n = 4,532)	3 (n = 1,920)	p value
Framingham CHD risk (1998), %	5.65 (5.58–5.73)	5.76 (5.64–5.87)	5.80 (5.69–5.92)	5.86 (5.68–6.03)	0.054
ATP III revised Framingham CHD risk (2002), %	5.64 (5.54–5.75)	6.10 (5.93–6.26)	5.90 (5.74–6.06)	6.11 (5.86–6.36)	<0.001
Generalized Framingham risk against total CVD (2008), %	8.20 (8.09–8.32)	8.48 (8.30–8.65)	8.46 (8.29–8.63)	8.65 (8.38–8.91)	0.002
ACC/AHA 10-year risk of a first hard ASCVD event, %	4.24 (4.16–4.32)	4.31 (4.19–4.43)	4.28 (4.16–4.40)	4.39 (4.21–4.57)	0.410
	Grade of neutrophil infiltration				
	0 (n = 5,556)	1 (n = 4,929)	2 (n = 8,388)	3 (n = 2,378)	p value
Framingham CHD risk (1998), %	5.64 (5.53–5.74)	5.68 (5.57–5.78)	5.73 (5.65–5.82)	6.02 (5.86–6.17)	0.001
ATP III revised Framingham CHD risk (2002), %	5.58 (5.43–5.72)	5.75 (5.60–5.91)	5.92 (5.80–6.04)	6.32 (6.09–6.54)	<0.001
Generalized Framingham risk against total CVD (2008), %	8.18 (8.03–8.34)	8.22 (8.06–8.39)	8.39 (8.26–8.52)	8.92 (8.68–9.15)	<0.001
ACC/AHA 10-year risk of a first hard ASCVD event, %	4.18 (4.07–4.28)	4.25 (4.13–4.36)	4.29 (4.21–4.38)	4.52 (4.36–4.68)	0.006
	Grade of mononuclear cell infiltration				
	0 (n = 336)	1 (n = 7,282)	2 (n = 12,286)	3 (n = 1,347)	p value
Framingham CHD risk (1998), % (95% CI)	5.33 (4.91–5.74)	5.60 (5.51–5.69)	5.81 (5.75–5.88)	5.67 (5.47–5.88)	0.001
ATP III revised Framingham CHD risk (2002), % (95% CI)	5.48 (4.88–6.08)	5.58 (5.45–5.71)	5.99 (5.90–6.09)	5.86 (5.56–6.16)	<0.001
Generalized Framingham risk against total CVD (2008), % (95% CI)	7.94 (7.31–8.57)	8.10 (7.97–8.24)	8.51 (8.40–8.61)	8.45 (8.13–8.76)	<0.001
ACC/AHA 10-year risk of a first hard ASCVD event, % (95% CI)	4.04 (3.61–4.47)	4.19 (4.10–4.28)	4.34 (4.27–4.41)	4.22 (4.01–4.44)	0.050
	Grade of glandular atrophy				
	0 (n = 19,157)	1 (n = 1,374)	2 (n = 657)	3 (n = 63)	p value
Framingham CHD risk (1998), % (95% CI)	5.70 (5.65–5.76)	5.95 (5.74–6.15)	5.78 (5.48–6.07)	7.44 (6.48–8.39)	0.001
ATP III revised Framingham CHD risk (2002), % (95% CI)	5.78 (5.70–5.86)	6.28 (5.99–6.58)	6.28 (5.86–6.71)	7.50 (6.11–8.88)	<0.001
Generalized Framingham risk against total CVD (2008), % (95% CI)	8.31 (8.23–8.39)	8.75 (8.44–9.07)	8.64 (8.18–9.09)	10.69 (9.23–12.14)	<0.001
ACC/AHA 10-year risk of a first hard ASCVD event, % (95% CI)	4.27 (4.21–4.32)	4.38 (4.17–4.59)	4.23 (3.92–4.53)	5.60 (4.61–6.59)	0.047
	Grade of intestinal metaplasia				
	0 (n = 14,669)	1 (n = 3,757)	2 (n = 2,243)	3 (n = 582)	p value
Framingham CHD risk (1998), % (95% CI)	5.63 (5.57–5.70)	5.84 (5.72–5.97)	6.01 (5.85–6.17)	6.21 (5.89–6.52)	<0.001
ATP III revised Framingham CHD risk (2002), % (95% CI)	5.61 (5.51–6.70)	6.13 (5.95–6.31)	6.51 (6.27–6.74)	7.20 (6.75–7.66)	<0.001
Generalized Framingham risk against total CVD (2008), % (95% CI)	8.16 (8.07–8.26)	8.58 (8.39–8.76)	8.95 (8.71–9.20)	9.47 (8.99–9.95)	<0.001
ACC/AHA 10-year risk of a first hard ASCVD event, % (95% CI)	4.18 (4.12–4.25)	4.39 (4.26–4.52)	4.56 (4.39–4.73)	4.91 (4.58–5.24)	<0.001

CI, confidence interval; HP, *Helicobacter pylori*; CHD, coronary heart disease; ATP, adult treatment panel; CVD, cardiovascular disease; ACC/AHA, American college of cardiology/American heart association; ASCVD, atherosclerotic cardiovascular disease. p value for difference was obtained from ANCOVA analysis adjusted for age.

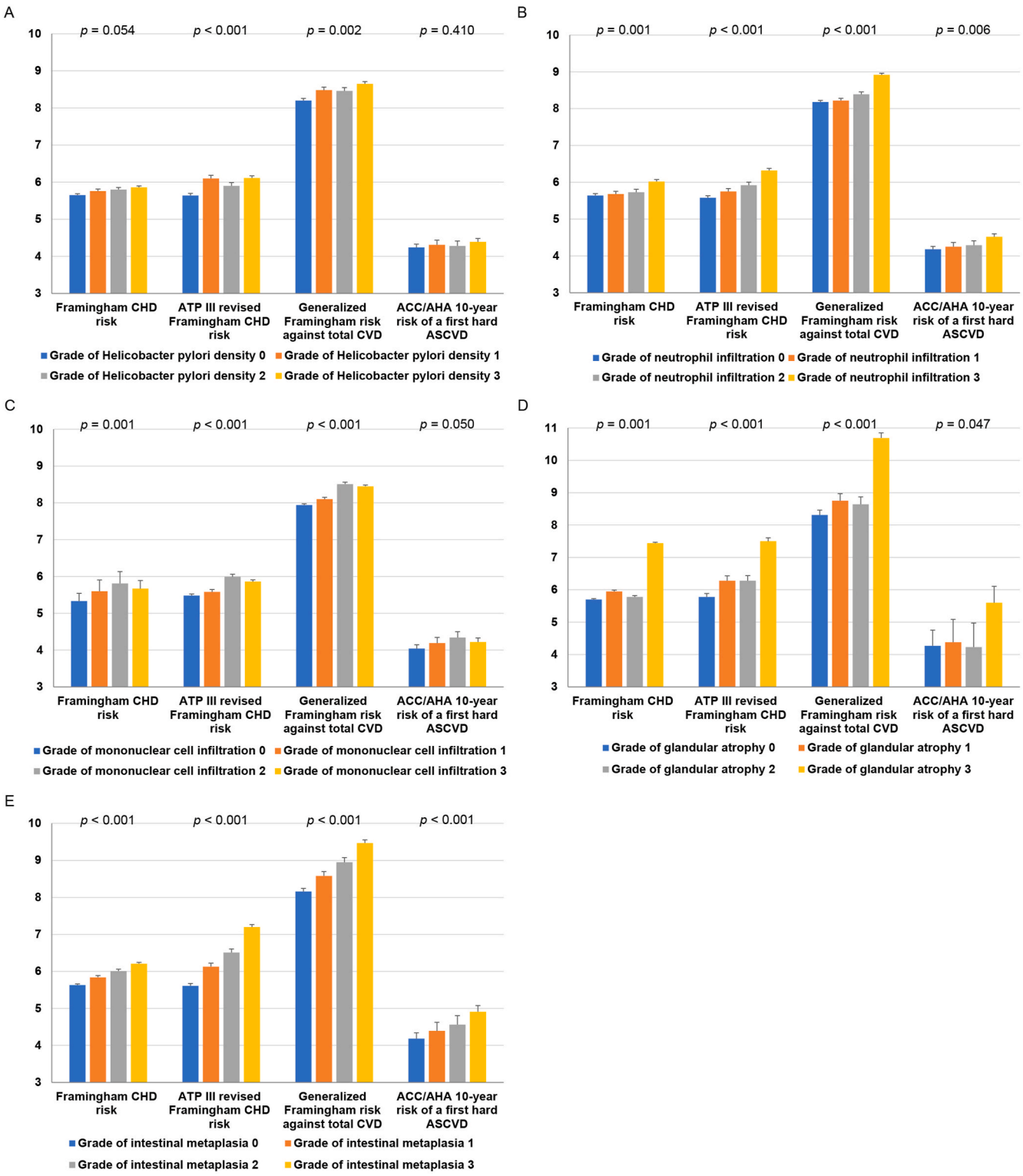

Fig. 1. Age adjusted estimated cardiovascular risk for next 10 years based on the updated Sydney system.
(A) According to density of *Helicobacter pylori*, (B) according to grade of neutrophil infiltration, (C) according to grade of mononuclear cell infiltration, (D) according to grade of glandular atrophy, (E) according to grade of intestinal metaplasia.

healthy men, the baseline high CRP level was associated with future myocardial infarction or stroke. In that study, the relative risk of myocardial infarction was 2.9 and that of stroke was 1.9 in the highest quartile CRP with the lowest quartile used as reference [17]. Besides CRP, in a case control study with over 28,000 apparently healthy post-menopausal women, serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule type 1 were associated with cardiovascular events [9]. In a recent Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with monoclonal antibody, canakinumab, significantly reduced high-sensitive CRP (hs-CRP) and recurrent cardiovascular events, independent of the LDL cholesterol

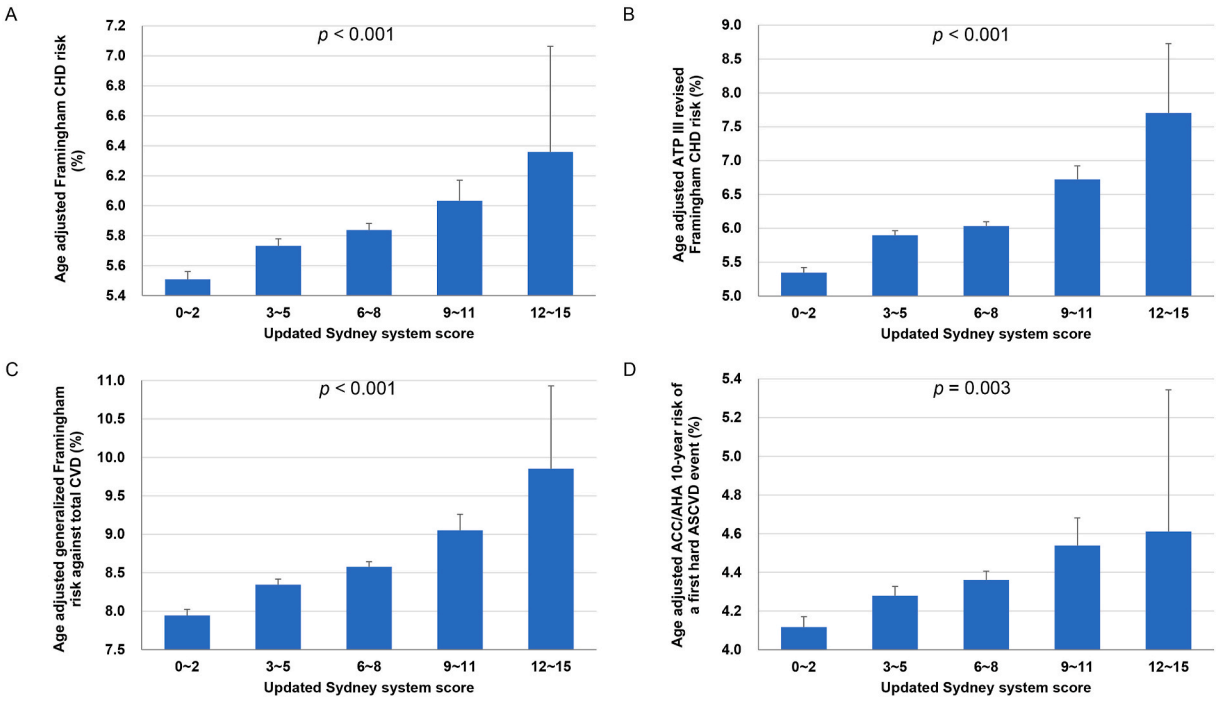

Fig. 2. Age adjusted estimated cardiovascular risk for the next 10 years based on the sum of the updated Sydney system.
(A) Framingham CHD risk, (B) ATP III revised Framingham CHD risk, (C) generalized Framingham risk against total CVD, (D) ACC/AHA 10-year risk of a first hard ASCVD event.

level [18]. In addition, in a secondary analysis from CANTOS, patients who achieved on-treatment hs-CRP less than 2 mg/L had greater reductions in cardiovascular mortality and all-cause mortality compared with those with hs-CRP greater than or equal to 2 mg/L within the first 3 months of receiving canakinumab [19].

HP infection is one of the most common infections, and globally more than half of the world's population is infected with HP [20]. The seroprevalence of HP infection in Korea was 41.5% and about 95% of HP infections are of the East Asian cytotoxin-associated gene A (*CagA*) strain [21,22]. HP infection is an important etiological factor for gastritis, gastric ulcer, and cancer [23]. It has been suggested that HP infection is associated with extra-gastrointestinal diseases involving hematological, skin, neurological, and circulatory systems including the heart [24–26]. Several previous studies suggested that chronic HP infection may be associated with atherosclerosis. The association between seropositivity of HP and CHD has been reported in population-based case-control studies [12,27]. Izadi et al. detected HP using polymerase chain reaction in coronary plaques of patients who underwent coronary artery bypass graft surgery [28]. Bacterial cytotoxins can induce production of several proinflammatory cytokines, facilitate vascular endothelial cell activation, which can increase expression of procoagulant substances, and down-regulate the fibrinolytic system [29–32]. In HP infection, *CagA*, which is involved in enhancing virulence and cytotoxin production, may play a role in the pathogenesis of CHD [11,13]. Besides the immunological process, abnormal cholesterol metabolism caused by HP may be also involved in the development of CVD. Several studies have shown that chronic HP infection was associated with unfavorable lipid profiles such as increased total cholesterol, LDL cholesterol, and TG as well as decreased HDL cholesterol [33,34].

4.1. Subgroup analysis

Our results showed that the association between the grade of HP gastritis histology and cardiovascular risk scores was more pronounced in young and non-obese men without cardiovascular risk factors than in other subjects. In older subjects with more cardiovascular risk factors, it is speculated that in addition to HP infection, there are other factors that have a greater influence on the cardiovascular risk score. Further research is needed to determine why HP gastritis was more significantly correlated with cardiovascular risk scores in young and low-risk subjects.

4.2. Clinical implications

Since CVD has high prevalence and poor prognosis, it is very important to prevent the occurrence of CVD based on the pathophysiology well supported by scientific evidence.

In addition to traditional risk factors, chronic inflammation has recently been known to trigger CVD [35]. In this study, the association between HP gastritis and cardiovascular risk scores was identified using histological results from a large number of gastric biopsies. Our findings provided strong evidence for an association between chronic inflammatory reaction and increased cardiovascular risk. More active cardiovascular screening and aggressive preventive management are recommended in subjects with more advanced stage of HP gastritis in gastric mucosal biopsy. These strategies should be more emphasized for young men without cardiovascular risk factors. This is because in our study the grade of HP gastritis predicted cardiovascular risk better in these subjects. However, whether HP eradication will reduce the risk of CVD needs to be studied further.

4.3. Limitations

There are several limitations to this study. First, this study was designed cross-sectionally, and there were no data on clinical follow-up. Therefore, the causal relationship between HP infection and development of CVD could not be confirmed. Secondly, only subjects who underwent gastroscopy during routine health checkup were included in this study, so there could be a selection bias. Thirdly, there are no data on medications that subjects were taking. Since the risk can be significantly lowered with cardiovascular medications such as statin, a gap

Table 3
Statistical significance of the associations between risk scores and the grade of histology in different groups.

Subgroup	Risk score	Presence of HP	Grade (0–3)				
			HP density	Neutrophil infiltration	Mononuclear cell infiltration	Glandular atrophy	Intestinal metaplasia
Male	FRS 1998	0.885	0.952	0.256	0.097	0.015b	0.959
	ATP III FRS 2002	0.087[a]	0.104	0.043[b]	0.013[b]	0.601	0.203
	Generalized FRS 2008	0.049[b]	0.697	0.016[b]	0.037[b]	0.071b	0.890
	ACC/AHA ASCVD 2013	0.134	0.867	0.116	0.384	0.003c	0.154
Female	FRS 1998	0.134	0.382	0.559	0.775	0.386	0.006[c]
	ATP III FRS 2002	0.971	0.311	0.148	0.118	0.240	0.075[b]
	Generalized FRS 2008	0.336	0.893	0.156	0.448	0.328	0.008[c]
	ACC/AHA ASCVD 2013	0.004[c]	0.238	0.869	0.708	0.236	0.708
<40 years	FRS 1998	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	0.001[c]	0.388
	ATP III FRS 2002	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	0.007[c]	0.092[a]
	Generalized FRS 2008	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	0.010[c]	0.147
	ACC/AHA ASCVD 2013	<0.001[d]	<0.001[d]	<0.001[d]	<0.001[d]	0.047[b]	0.016[b]
≥40 years	FRS 1998	0.134	0.515	0.035[b]	0.034[b]	0.009[c]	<0.001[d]
	ATP III FRS 2002	0.018[b]	0.048[b]	0.022[b]	0.015[b]	0.010[c]	<0.001[d]
	Generalized FRS 2008	0.021[b]	0.079[a]	0.001[c]	0.007[c]	0.006[c]	<0.001[d]
	ACC/AHA ASCVD 2013	0.066[a]	0.216	0.006[c]	0.071[b]	0.090[a]	<0.001[d]
BMI < 25 kg/m^2	FRS 1998	0.009[c]	0.057[a]	<0.001[d]	0.006[c]	0.001[c]	<0.001[d]
	ATP III FRS 2002	0.002[c]	<0.001[d]	<0.001[d]	0.001[c]	<0.001[d]	<0.001[d]
	Generalized FRS 2008	<0.001[d]	0.007[c]	<0.001[d]	0.001[c]	<0.001[d]	<0.001[d]
	ACC/AHA ASCVD 2013	0.196	0.300	0.002[c]	0.143	0.048[b]	<0.001[d]
BMI ≥ 25 kg/m^2	FRS 1998	0.894	0.969	0.142	0.295	0.259	0.036
	ATP III FRS 2002	0.364	0.201	0.093[a]	0.124	0.550	<0.001[d]
	Generalized FRS 2008	0.071[a]	0.756	0.099[a]	0.225	0.450	<0.001[d]
	ACC/AHA ASCVD 2013	0.818	0.972	0.679	0.399	0.387	0.016[b]
Without risk factors	FRS 1998	<0.001[d]	0.019[b]	0.002[c]	0.002[c]	<0.001[d]	<0.001[d]
	ATP III FRS 2002	<0.001[d]	<0.001[d]	<0.001[d]	0.001[c]	<0.001[d]	<0.001[d]
	Generalized FRS 2008	<0.001[d]	0.001[c]	<0.001[d]	0.001[c]	<0.001[d]	<0.001[d]
	ACC/AHA ASCVD 2013	<0.001[d]	0.013[b]	<0.001[d]	0.020[b]	0.001[c]	<0.001[d]
With risk factors	FRS 1998	0.437	0.772	0.100	0.117	0.096a	<0.001d
	ATP III FRS 2002	0.069[a]	0.364	0.008[c]	0.023[b]	0.105	<0.001[d]
	Generalized FRS 2008	0.104	0.384	0.015[b]	0.016[b]	0.021[b]	<0.001[d]
	ACC/AHA ASCVD 2013	0.944	0.898	0.499	0.459	0.573	<0.001[d]

HP, *Helicobacter pylori*; FRS, Framingham risk score; ATP, adult treatment panel; ACC/AHA, American college of cardiology/American heart association; ASCVD, atherosclerotic cardiovascular disease. [a] $0.05 \leq p < 0.1$, [b] $0.01 \leq p < 0.05$, [c] $0.001 \leq p < 0.01$, [d] $p < 0.001$.

between the calculated risk and the actual event may occur. Finally, this study was conducted on healthy Koreans, and there could be discrepancy in applying the predictive risk system developed mainly for Caucasians and African Americans.

4.4. Conclusions

In this large-scale cohort study among healthy Koreans, histological features of gastritis assessed using the USS was associated with various cardiovascular risk scores. This study provides strong evidence for an association between chronic inflammation and increased cardiovascular risk. Longitudinal studies with various ethnic groups are needed to confirm our findings.

CRediT authorship contribution statement

Jaehoon Chung: Conceptualization, Formal analysis, Visualization, Writing – original draft. **Kyueng-Whan Min:** Investigation, Resources, Data curation, Visualization, Writing – review & editing. **Byoung Kwan Son:** Writing – review & editing. **Dong-Hoon Kim:** Writing – review & editing, Data curation, Supervision. **Hack-Lyoung Kim:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.08.019.

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