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Impact of socioeconomic status and sibling number on the prevalence of *Helicobacter pylori* infection: a cross-sectional study in a Japanese population

Moaz Elshair[1,2,3,4], Tomotaka Ugai[1], Isao Oze[1], Yumiko Kasugai[1,3], Yuriko N. Koyanagi[5], Kazuo Hara[2], Hidemi Ito[5,6] and Keitaro Matsuo[1,3]

[1]*Division of Cancer Epidemiology and Prevention, Department of Preventive Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan*
[2]*Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan*
[3]*Division of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[4]*Department of Hepatology, Gastroenterology and Infectious Diseases, Faculty of Medicine, Al-Azhar University, Cairo, Egypt*
[5]*Division of Cancer Information and Control, Department of Preventive Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan*
[6]*Division of Descriptive Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

ABSTRACT

Helicobacter pylori infection is a significant risk factor for gastric cancer. The infection is acquired mainly in early childhood and is influenced by environmental factors, including socioeconomic status and sibling number. However, the impact of socioeconomic status and sibling number on *Helicobacter pylori* infection has not been well studied in Japan. We conducted a cross-sectional study to evaluate the impact of socioeconomic status, represented by education level, and sibling number on the prevalence of *Helicobacter pylori* infection among 3,423 non-cancer subjects who visited Aichi Cancer Center between 2005 and 2013. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using a logistic regression model adjusted for potential confounding variables. Of the 3,423 subjects, 1,459 (42.6%) were *Helicobacter pylori*-positive. The prevalence of *Helicobacter pylori* infection linearly decreased with increasing socioeconomic status [ORs (95% CIs) of moderate and high socioeconomic status relative to low socioeconomic status of 0.67 (0.53–0.84) and 0.43 (0.34–0.54), respectively; P trend=9.7×10^{-17}]. In contrast, the prevalence of *Helicobacter pylori* infection linearly increased with increasing sibling number [ORs (95% CIs) of SN 3–4 and ≥5 relative to sibling number ≤2 of 1.74 (1.47–2.06) and 2.54 (2.12–3.04), respectively; P trend=1.2×10^{-24}]. This study showed that socioeconomic status and sibling number were significantly associated with the prevalence of *Helicobacter pylori* infection.

Keywords: *Helicobacter pylori*, socioeconomic status, sibling number

Abbreviations:
H. pylori: *Helicobacter pylori*
SES: socioeconomic status
SN: sibling number
HERPACC: Hospital-based Epidemiologic Research Program at Aichi Cancer Center

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Corresponding Author: Keitaro Matsuo, MD, PhD, MSc
Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
Tel: +81-52-762-6111, Fax: +81-52-763-5233, E-mail: kmatsuo@aichi-cc.jp

BMI: body mass index

INTRODUCTION

Helicobacter pylori (H. pylori) is a Gram-negative bacteria that infects human gastric mucosa,[1] and was first isolated by Marshall and Warren in 1983.[2] Several studies have indicated that *H. pylori* infection is associated not only with gastrointestinal diseases, such as peptic ulcer disease, atrophic gastritis and distal gastric cancer,[3] but also with extra-gastrointestinal diseases, including ischemic heart disease and iron deficiency anemia.[4]

H. pylori infects almost 50% of people worldwide.[5] However, there is a substantial difference in the prevalence of *H. pylori* infection between developing and developed countries.[6] In developing countries, prevalence is very high, reaching 70% among children, whereas in developed countries it is generally less than 40% in the general population, and is significantly lower in children and adolescents than in the general population.[7] In Japan, the prevalence of *H. pylori* infection was historically very high, but has been decreasing by birth cohort from 80–90% in the older population born before 1950 to less than 2% in children born after 2000.[8] This wide difference in *H. pylori* prevalence between developing and developed countries and across birth cohorts may be attributable to geography, ethnicity, living conditions and socioeconomic factors.[5]

Lower socioeconomic status (SES) is thought to be associated with higher prevalence of *H. pylori* infection because low SES is associated with poor hygiene and unfavorable sanitary conditions, which are considered important risk factors for *H. pylori* infection.[9] On the other hand, high sibling number (SN) may negatively affect general health, and can be positively correlated with higher prevalence of *H. pylori* infection.[10] *H. pylori* transmission between siblings might be facilitated by close interpersonal contact (sharing cups, sharing a bed and close playing).[11] Previous studies showed that the prevalence of *H. pylori* infection is associated with SES[12] and SN.[10] However, the impact of SES and SN on the prevalence of *H. pylori* infection in the Japanese population, who historically have high prevalence, is largely unknown.

Here, we conducted a cross-sectional study to investigate the impact of SES and SN on the prevalence of *H. pylori* infection after adjustment for confounding factors.

MATERIALS AND METHODS

Study design, participants and data

We selected subjects who were enrolled in the Hospital-based Epidemiological Research Program III at Aichi Cancer Center (HERPACC III), which ran from November 2005 to March 2013. Briefly, first-visit outpatients at Aichi Cancer Center Hospital (Nagoya, Japan) were asked to fill out a self-administered questionnaire describing their level of education and SN, in addition to basic characteristics of age, sex, birth year, height, current weight, weight at age 20, smoking status and alcohol drinking status. They were also asked to provide blood samples for *H. pylori* testing. Approximately 66.4% of all visiting outpatients enrolled in HERPACC III during this period.[13]

Subject selection for this study from among HERPACC III participants is shown in Fig. 1. A total of 11,559 subjects filled out a self-administered questionnaire and provided blood samples between November 2005 and March 2013. Among non-cancer subjects, we randomly selected

3,423 subjects for this study (male, 1,869; female, 1,554). These were categorized as *H. pylori*-positive, n = 1,459 (42.6%) and *H. pylori*-negative, n = 1,964 (57.4%).

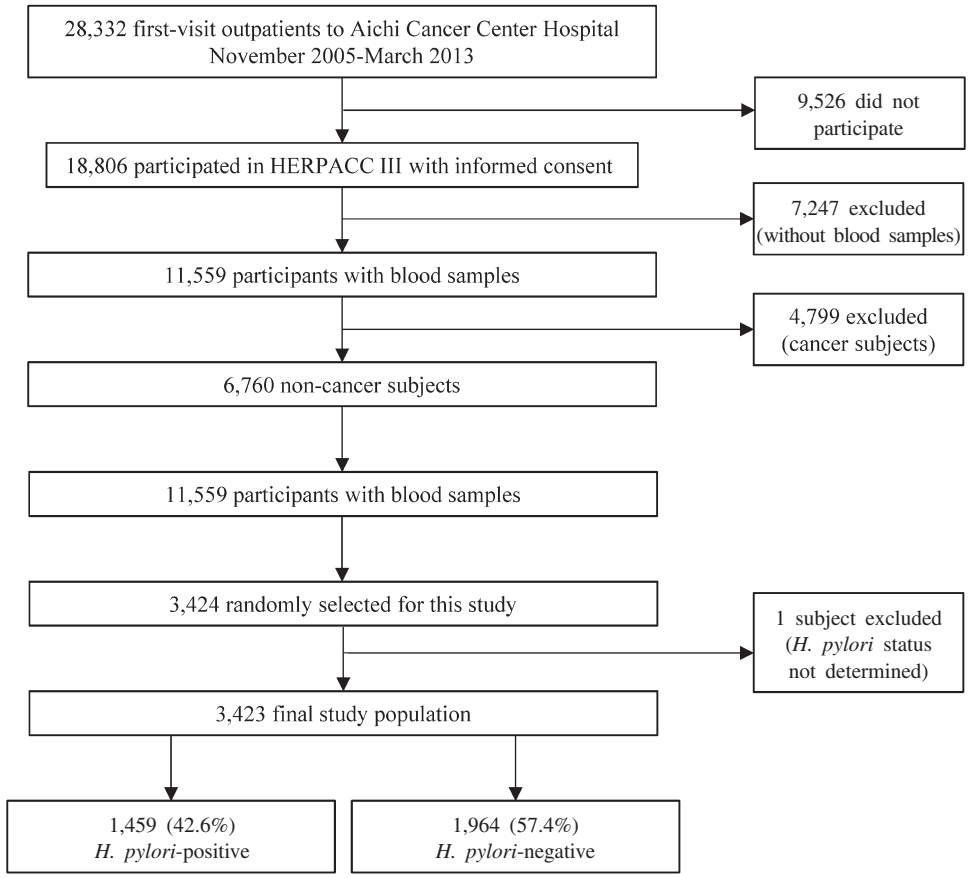

Fig. 1 Flowchart of subject selection
Flow shows the process of subject selection for the study, Impact of Socioeconomic Status and Sibling Number on the Prevalence of *H. pylori* Infection. The study was conducted based on the Hospital-based Epidemiology Research Program III at Aichi Cancer Center (HERPACC III) (Nagoya, Japan).

Evaluation of H. pylori infection and pepsinogen levels

Serum IgG levels for *H. pylori* were measured using a commercially available direct enzyme-linked immunosorbent assay (ELISA) kit ('E Plate "Eiken" *H. pylori* Antibody'; Eiken Kagaku, Tokyo, Japan). *H. pylori* infection was defined as an anti-*H. pylori* IgG > 10 U/ml in serum. The sensitivity and specificity of this cut-off value are 90.7% and 91.5%, respectively, when validated against the 13C urea breath test.[13] Serum pepsinogen (PG) levels were measured by chemiluminescence enzyme immunoassay, and atrophic gastritis was defined by PG I ≤ 70 ng/ml and PG I/PGII ≤ 3.[14]

Subjects who had atrophic gastritis (defined as PG I ≤ 70 ng/ml and PG I/PG II ≤ 3) but were anti-*H. pylori* IgG-negative on testing were considered to be *H. pylori*-positive in this study, with reference to the natural history of *H. pylori* infection (negative seroconversion of *H.*

pylori antibodies).[15]

Subjects with anti-*H. pylori* IgG less than 10 U/ml might had been infected with *H. pylori* in the past,[16] and the low titer is due to either a defective immune response to *H. pylori* antigen or eradication therapy. Therefore, we re-examined the association between SES/SN and *H. pylori* infection with consideration to all those with anti-*H. pylori* IgG ≥ 3 U/ml as *H. pylori*-positive subjects.

SES and SN measurement

We obtained information on SES and SN from self-administered questionnaires. Education level, a principle SES measure, was classified into five groups, namely low (primary/junior-high school), moderate (senior-high school), high (college/university/graduate school), others, and unknown. We classified total number of siblings into four groups, namely ≤2, 3–4, ≥5 and unknown.

Lifestyle measurement

We obtained lifestyle information using self-administered questionnaires. Alcohol consumption was estimated from the amount consumed in grams per day (g/day) and classified as follows: non-drinker; light drinker, defined as alcohol consumption less than 23 g/day; moderate drinker, defined as alcohol consumption (23.0–45.9) g/day; and heavy drinker, defined as alcohol consumption ≥46 g/day.[17] Body mass index (BMI) was calculated using the following equation: BMI = self-reported body weight (kg)/height (m^2), and categorized as follows: underweight, defined as BMI less than 18.5 kg/m^2; normal, defined as BMI 18.5–23 kg/m^2; overweight, defined as BMI 23–27.5 kg/m^2; and obese, defined as BMI >27.5 kg/m^2.[18] Cumulative exposure to smoking was estimated using pack-years (PYs), calculated by multiplying the number of cigarettes packs smoked per day by the number of years of smoking, and categorized as follows: 0, <20, <40, <60, and ≥60.[19]

Statistical Analyses

We compared basic characteristics between *H. pylori*-positive and -negative groups using the chi-squared test. We used logistic regression models to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for *H. pylori* infection associated with SES and SN.

We estimated ORs using the following four models: Model 1 (crude analyses); Model 2, a multivariable model which adjusted for age category (<40, 40–49, 50–59,60-70, >70) and sex; Model 3, which adjusted for birth year (<1950, 1950–1960, >1960), current BMI (<18.5, 18.5–23, 23–27.5, ≥27.5), BMI at age 20, age category and sex; and Model 4, which further adjusted for drinking category (never, light, moderate and heavy) and smoking category (PYs 0, <20, <40, <60 and ≥60). Furthermore, we estimated *P* values for trend by assigning ordinal variables in SES and SN categories as continuous variables in each model.

We explored stratified analysis to examine differential associations by respective lifestyle factors. We then examined possible interactions by including the interaction term between SES category (low, moderate and high)/SN category (≤2, 3–4 and ≥5) and categories of different confounding variables (age, sex, birth year, BMI at age 20, current BMI, smoking and drinking). Finally, we examined the statistical interaction between SES and SN by including an interaction term between SES categories (low, moderate and high) and SN categories (≤2, 3–4 and ≥5). *P* values for interaction were calculated using the likelihood ratio test. Statistical analyses were conducted using STATA statistical software version 14.0 (Stata Corp., College Station, Texas, USA), and *P* values <0.05 were considered statistically significant.

RESULTS

Participants

Baseline characteristics of the study population are shown in Table 1. Of the 3,423 participants, 1,459 (42.6%) were *H. pylori*-positive and 1,964 (57.4%) were *H. pylori*-negative. *H. pylori* prevalence was higher among elderly participants than younger participants. Similarly, it was higher among the population born before 1950 than among populations born after 1950. *H. pylori* prevalence was higher in males than in females and in those with a high BMI either at age 20 or currently than in those with a low BMI. There was no clear difference in the proportion of heavy smokers or drinkers between the *H. pylori*-positive and -negative groups.

Table 1 Characteristics of the study population

Variable	***H. pylori* status[a], N (%)**		
	Positive	Negative	Total
	1,459	1,964	3,423
Age category			
<40	68 (4.7)	252 (12.8)	320
40–49	138 (9.5)	419 (21.4)	557
50–59	302 (20.7)	471 (23.9)	773
60–70	581 (39.8)	536 (27.3)	1,117
>70	370 (25.3)	286 (14.6)	656
Birth year category			
<1950	974 (66.8)	817 (41.6)	1,791
1950–1960	296 (20.3)	500 (25.5)	796
>1960	189 (12.9)	647 (32.9)	836
Sex			
Male	880 (60.3)	989 (50.3)	1,869
Female	579 (39.7)	975 (49.7)	1,554
Current BMI[b]			
Underweight	118 (8.1)	174 (8.9)	292
Normal	727 (49.8)	1,010 (51.4)	1,737
Overweight	523 (35.9)	650 (33.1)	1,173
Obese	82 (5.6)	121 (6.2)	203
Unknown	9 (0.6)	9 (0.4)	18
BMI at age 20			
Underweight	177 (12.1)	306 (15.6)	483
Normal	1,007 (69.0)	1,319 (67.2)	2,326
Overweight	197 (13.6)	260 (13.2)	457
Obese	24 (1.6)	24 (1.2)	48
Unknown	54 (3.7)	55 (2.8)	109
PYs[c]			
None	699 (47.9)	991 (50.5)	1,690
<20	212 (14.5)	361 (18.4)	573
<40	242 (16.5)	292 (14.9)	534

<60	165 (11.3)	166 (8.4)	331
≥60	110 (7.5)	112 (5.7)	222
Unknown	31 (2.1)	42 (2.1)	73
Alcohol drinking category[d]			
Never	611 (41.9)	802 (40.8)	1,413
Light	486 (33.3)	740 (37.7)	1,226
Moderate	171 (11.7)	201 (10.2)	372
Heavy	176 (12.1)	207 (10.6)	383
Unknown	15 (1.0)	14 (0.7)	29

BMI: body mass index
PYs: pack-years
[a] *H. pylori* status was evaluated by measuring anti-*H. pylori* IgG antibody in the studied population, negative: IgG <10.0 units/mL, positive: IgG ≥10.0 units/ml.
[b] BMI was calculated using the following equation: BMI = self-reported body weight (kg)/height (m^2), and categorized as follows: underweight, defined as BMI less than 18.5 kg/m^2; normal, defined as BMI 18.5–23 kg/m^2; overweight, defined as BMI 23–27.5 kg/m^2; and obese, defined as BMI >27.5kg/m^2.
[c] PYs, pack-years represents cumulative exposure to smoking, calculated by multiplying the number of cigarettes packs smoked per day by the number of years of smoking and categorized as 0, <20, <40, <60, ≥60.
[d] Alcohol drinking category: light: <23 g/day, moderate: ≥23–<46 g/day, and heavy: ≥4 and heavy: ≥46 g/day.

Association between SES and H. pylori infection

Table 2 shows the crude and adjusted ORs for *H. pylori* infection associated with SES. Overall, there was a statistically significant dose-dependent negative association between SES and *H. pylori* infection in the crude analysis (Low: reference, Moderate: OR = 0.67, 0.53–0.84, High: OR = 0.43, 0.34–0.54; *P* for trend < 0.001). To control for potential confounders, we adjusted for age, sex, birth year, current BMI, BMI at age 20, drinking and smoking in Models 2, 3 and 4. The association between SES and *H. pylori* infection remained statistically significant in all models (Low: reference, Moderate: OR = 0.86, 0.68–1.08, High: OR = 0.67, 0.52–0.84; *P* for trend < 0.001, Model 4).

Table 2 Association between socioeconomic status (SES) and *H. pylori* infection

Socioeconomic status (SES)	HP-positive/-negative (n)		Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Low	232/179		Reference	Reference	Reference	Reference
Moderate	603/692	OR	0.67	0.85	0.86	0.86
		95%CI	(0.53–0.84)	(0.68–1.07)	(0.68–1.09)	(0.68–1.08)
		P	< 0.001	0.191	0.217	0.211

High	607/1,077	OR	0.43	0.66	0.67	0.67
		95%CI	(0.34–0.54)	(0.52–0.83)	(0.53–0.85)	(0.52–0.84)
		P	< 0.001	0.001	0.001	0.001
		P for trend	< 0.001	< 0.001	< 0.001	< 0.001
Others	6/5	OR	0.92	0.76	0.76	0.74
		95%CI	(0.27–3.08)	(0.22–2.55)	(0.22–2.55)	(0.22–2.49)
		P	0.9	0.66	0.659	0.632
Unknown	11/11	OR	0.77	0.92	0.87	
		95%CI	(0.32–1.81)	(0.38–2.21)	(0.36–2.10)	(0.35–2.09)
		P	0.554	0.855	0.759	0.744

SES: socioeconomic status
Low: primary and junior high school
Moderate: senior high school
High: graduate school, university, college or higher
HP: *H. pylori* status
OR: odds ratio
CI: confidence interval

[a] Model 1: Crude odds ratios.

[b] Model 2: Odds ratios adjusted for age category (<40, 40–49, 50–59, 60–70, >70) and sex.

[c] Model 3: Odds ratios adjusted for birth year category (<1950, 1950–1960, >1960), current BMI (<18.5, 18.5–23, 23–27.5, ≥27.5), BMI at age 20 (<18.5, 18.5–23, 23–27.5, ≥27.5), age category and sex.

[d] Model 4: Odds ratios adjusted for drinking category (never, light, moderate, heavy), smoking category by PYs (0, <20, <40, <60, ≥60, unknown), birth year category, current BMI, BMI at age 20, age category and sex.

In the stratified analyses by potential confounding factors, we observed similar findings within each stratum, and no statistically significant interaction. Although there was no statistically significant interaction between SES and birth cohort, the protective effect of high SES appeared to be stronger among subjects born after 1960 (Low: reference, Moderate: OR = 0.41, 0.16–1.03, High: OR = 0.27, 0.11–0.68; *P* for trend= 0.002) compared to those born before 1950 (Low: reference, Moderate: OR = 0.96, 0.73–1.24, High: OR = 0.77, 0.59–1.01; *P* for trend= 0.045).

Association between SN and the prevalence of H. pylori infection

Table 3 illustrates the crude and adjusted ORs for the association between SN and *H. pylori* infection. We observed a statistically significant dose-dependent positive association between SN and *H. pylori* infection in the crude analysis (≤2: reference, 3–4: OR = 1.74, 1.47–2.06, ≥5: OR = 2.54, 2.12–3.04; *P* for trend= *P* < 0.001). After adjustment for potential confounders (age, sex, birth year, current BMI, BMI at age 20, drinking categories and smoking categories), the association was attenuated, but was still statistically significant in Models 2, 3 and 4 (≤2: reference, 3–4: OR =1.31, 1.10–1.57, ≥5: OR = 1.29, 1.04–1.59; *P* for trend= 0.022, Model 4). In the stratified analyses by individual covariates, we did not observe any statistically significant interaction between SN and any covariate.

Table 3 Association between sibling number and *H. pylori* infection

Number of siblings	HP-positive/-negative (n)		Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
0–2	342/755		Reference	Reference	Reference	Reference
3–4	582/737	OR	1.74	1.34	1.31	1.31
		95%CI	(1.47–2.06)	(1.12–1.60)	(1.09–1.56)	(1.10–1.57)
		P	< 0.001	0.001	0.001	0.001
5–	524/455	OR	2.54	1.38	1.29	1.29
		95%CI	(2.12–3.04)	(1.12–1.70)	(1.04–1.59)	(1.04–1.59)
		P	< 0.001	0.002	0.019	0.019
		P for trend	< 0.001	0.004	0.022	0.022
Unknown	11/17	-	-	-	-	-

HP: *H. pylori* status
OR: odds ratio
CI: confidence interval
[a] Model 1: Crude odds ratios.
[b] Model 2: Odds ratios adjusted for age category (<40, 40–49, 50–59, 60–70, >70) and sex.
[c] Model 3: Odds ratios adjusted for birth year category (<1950, 1950–1960, >1960), Current BMI (<18.5, 18.5–23,23–27.5, ≥27.5), BMI at age 20 (<18.5, 18.5–23, 23–27.5, ≥27.5), age category and sex.
[d] Model 4: Odds ratios adjusted for drinking category (never, light, moderate, heavy), smoking category by PY (0, <20, <40, <60, ≥60, unknown), birth year category, current BMI, BMI at age 20, age category and sex.

Interaction between SES and SN on the prevalence of H. pylori infection

Table 4 presents the stratified analyses by SN for the association between SES and *H. pylori* infection. The association remained consistent within each SN category.

In the interaction analyses between SES categories (low, moderate and high) and SN categories (≤2, 3–4 and ≥5) for developing *H. pylori* infection, we did not observe a significant interaction (*P* interaction = 0.991), suggesting that both variables are independently associated with *H. pylori* infection.

Table 4 Stratified analyses of the association between socioeconomic status (SES) and *H. pylori* infection by sibling number

		SES[a]							
		Low		Moderate			High		P for trend
Sibling number			OR	95%CI	P	OR	95%CI	P	
0–2	HP-positive/-negative (n)	26/19		116/208			198/524		
		Reference	0.56	(0.28–1.13)	0.108	0.41	(0.21–0.82)	0.013	0.004
≥3	HP-positive/-negative (n)	202/158		486/476			403/547		
		Reference	0.91	(0.71–1.17)	0.494	0.73	(0.57–0.95)	0.022	0.009

HP: *H. pylori* status
OR: odds ratio
CI: confidence interval
OR: Odds ratios adjusted for drinking category (never, light, moderate, heavy), smoking category by PYs (0, <20, <40, <60, ≥60, unknown), birth year category, current BMI, BMI at age 20, age category and sex.
[a] SES: Socioeconomic status, Low: primary and junior high school, Moderate: senior high school, High: graduate school, university, college or higher.

Association between SES/SN and H. pylori infection, including subjects with anti-H. pylori IgG ≥ 3 U/ml as H. pylori-positive

SES was found to be more negatively and dose-dependently correlated with *H. pylori* infection when all subjects with anti-*H. pylori* IgG ≥ 3 U/ml were considered *H. pylori*-positive (Low: reference, Moderate: OR = 0.58, 0.46–0.74, High: OR = 0.37, 0.29–0.47; *P* for trend< 0.001, crude analyses). On adjustment for potential confounders, the association weakened substantially but remained statistically significant (Low: reference, Moderate: OR = 0.80, 0.62–1.02, High: OR = 0.63, 0.49–0.082; *P* for trend< 0.001, Model 4). In contrast, we observed a statistically significant and linear positive correlation between SN and *H. pylori* infection (≤2: reference, 3–4: OR = 1.68, 1.43–1.97, ≥5: OR = 2.69, 2.25–3.22; *P* for trend< 0.001, crude analyses). After adjustment for the same potential confounders, the association was attenuated, but also remained statistically significant (0–2: reference, 3–4: OR =1.21, 1.01–1.44, >5: OR = 1.18, 0.95–1.46; *P* for trend= 0.127, Model 4).

DISCUSSION

In this cross-sectional study, we observed a negative association between high SES and the prevalence of *H. pylori* infection after controlling for confounding variables, including birth year, BMI, smoking, and drinking. In addition, we found a positive association between higher SN

and the prevalence of *H. pylori* infection. SES and SN were independently associated with *H. pylori* infection, and no obvious interaction between these two factors was observed. This is the first study to show a statistically significant association of SES and SN with the prevalence of *H. pylori* infection in Japan.

The estimated prevalence of *H. pylori* infection in the overall studied population was 42.6%, which is consistent with other studies from Japan[20] as well as other Eastern Asian countries[21] which defined *H. pylori* positivity according to serum antibody titer. The relatively low prevalence in the present study compared to other studies from Japan[22] could be attributed to the nature of the study population or the diagnostic testing. In the present study we defined *H. pylori* positivity as an anti-*H. pylori* IgG > 10 U/ml in serum, with sensitivity and specificity of 90.7% and 91.5%, respectively, as validated against the urea breath test. In addition, our study subjects were all first-visit outpatients at our hospital, which is located in an area with a relatively high SES in Nagoya. It is reported that *H. pylori* prevalence differs geographically in Japan, and Aichi prefecture is among those prefectures with a relatively low prevalence.[20]

We adjusted our analyses with respect to common lifestyle factors in addition to the basic characteristics of the study population. We found that *H. pylori* prevalence increased with age and male sex. These findings are consistent with other reports.[23,24] Such tendencies could be explained by the decrease in *H. pylori* prevalence among younger generations due to the steady improvement in SES. The higher prevalence of *H. pylori* infection among males might be related to their higher exposure to potential environmental sources of infection than females. The seroprevalence of *H. pylori* was positively correlated with BMI, especially that at age 20, as was also seen in other epidemiological studies.[25] Such a trend could be explained by the impaired intestinal immune response and defective function of macrophage and natural killer (NK) cells in obese patients, which might facilitate *H. pylori* survival.[26] We adjusted for tobacco smoking and alcohol drinking as confounding factors because SES is well recognized to highly correlate with smoking/drinking behavior. The possible mechanisms behind smoking/drinking and *H. pylori* are as follows: heavy smoking is associated with decreased gastric mucosal blood flow, favoring the colonization of *H. pylori*[27]; and heavy alcohol consumption might disrupt the gastric mucosal barrier and increase the mucosa's permeability, resulting in inflammation which augments the adherence of *H. pylori*.[28]

Our study is consistent with several previous studies which reported that the prevalence of *H. pylori* was high among individuals with low SES,[6,29,30] albeit that the SES surrogates among these studies differed. Among several SES measures, educational level is thought to be strongly correlated with personal hygiene measures and child care.[31] Accordingly, a higher educational level is associated with a greater knowledge of sanitation and mitigation of unsanitary conditions, which consequently act to reduce the risk of *H. pylori* infection.[32]

Our results showed that SN has a significant positive correlation with the prevalence of *H. pylori* infection. This finding is in agreement with the results of several previous studies demonstrating that high SN was a risk factor for *H. pylori* infection. Whitaker et al reported that the risk of *H. pylori* infection is higher among adults who shared a bedroom during childhood than among those who did not, suggesting possible transmission between siblings.[33] Another study demonstrated that domestic overcrowding during childhood was independently associated with *H. pylori* infection.[34] In contrast to our study, Nishise et al reported no significant association between *H. pylori* seropositivity and SN among participants in a general health checkup program in Yamagata prefecture in Japan.[30] This inconsistency might be due to a difference in housing between Nagoya city and Yamagata prefecture: given the population densities of these two cities, overcrowding due to SN might be more evident in Nagoya than Yamagata. Moreover, the relatively smaller sample size of that study (n=695) might had been insufficient to elicit the exact

correlation between SN and *H. pylori* infection. Parental transmission of *H. pylori* has also been described as an important pathway of intrafamilial transmission from parents to their children.[35] In Japan, Osaki et al assessed the genomic profiles of *H. pylori* isolated from *H. pylori*-positive family members and showed that intrafamilial transmission (particularly from mother to child) occurred in all studied families.[36] Parents can transmit the infection through tasting or chewing food for a child. Hulten et al reported that intrafamilial transmission of *H. pylori* was due to contaminated water sources.[37] Although intrafamilial transmission is usually attributed to common environmental sources, parents might act as mediators of horizontal transmission among siblings. Considering these lines of evidence, high SN might facilitate the spread of *H. pylori* infection either by close contact between siblings or by intrafamilial transmission mediated by parents.

The exact route of transmission of *H. pylori* infection is not clearly understood. One possible route of transmission is interpersonal transmission.[35] The observed association between SN and the increased risk of *H. pylori* infection in this study supports the possibility of an oral-oral transmission pathway.[38] The oral-oral transmission likely favors the hypothesis that overcrowding and close interpersonal contact are important risk factors for *H. pylori* infection. Another plausible route for *H. pylori* transmission is fecal-oral transmission[30,35] which has been suggested for its link with socioeconomic.[39,40] Accumulating evidence from epidemiological studies supports transmission by the fecal-oral route. Previous reports showed that *H. pylori* DNA was detected in drinking well water in Japan[41] and in municipal water in Peru,[37] supporting the assumption that *H. pylori* could be transmitted via drinking water after contamination with feces. Our results are consistent with both possible pathways.

This study has a number of strengths. First, it is a relatively large-scale study, which allowed us to control for major confounders and provide detailed data on SES and SN. Potential confounding by birth year, age, sex, BMI, smoking and drinking was carefully considered, and our findings showed that SES and SN are independently associated with *H. pylori* infection. Second, the *H. pylori* infection status of the study subjects was examined by serology testing, which is a reasonable indicator for past infection. In the natural history of *H. pylori* infection, some *H. pylori* antibody-positive subjects develop chronic atrophic gastritis with negative seroconversion of *H. pylori* antibody.[15] Our study design took negative seroconversion into consideration appropriately. Third, we re-evaluated the association between SES/SN and *H. pylori* infection defining *H. pylori*-positivity as an anti-*H. pylori* IgG ≥ 3 U/ml in serum to include those who might had been infected before. The association was consistent which confirm and validate our primary results.

Several limitations also warrant mention. First, the study might have been affected by recall bias. Nevertheless, the HERPACC system is less prone to this bias than typical hospital-based studies as lifestyle information was collected before diagnosis. In addition, we previously reported that questionnaire-based lifestyle factors in this population were similar to those of the general population in Nagoya in terms of the exposures of interest in HERPACC-1.[42] Our findings therefore appear applicable to the general population. Second, the study was conducted under a cross-sectional design in which exposure and outcome measurements were performed at the same time. Accordingly, the causal sequence may be still undetermined and it would be difficult to infer causality. Nevertheless, the observed association of SES and SN with *H. pylori* may be still valid because *H. pylori* infection is predominantly acquired in early childhood, which is affected first by living conditions. Third, SES was evaluated based on subjects' educational level only. Taken the fact *H. pylori* infection happens in early life,[7] direct indicators of SES in early life should be desirable measurement. However, the fact that current educational level is reflecting how the living condition was in the past[43] partly justify our use of current educational level as a surrogate of SES in early life. Future studies may consider other indicators of SES in early

life, such as parents' educational levels, income and occupation. Fourth, we did not examine the impact of birth order in our analysis. Further studies to investigate the variable would be informative. Finally, our study findings were limited to a Japanese population and the results are not necessarily applicable to other populations.

CONCLUSION

This study showed that the prevalence of *H. pylori* infection is high among individuals with low SES and among those with a high SN. Our findings indicate that close person-to-person transmission and unfavorable sanitary conditions are the main mechanisms of *H. pylori* infection spread. Our results warrant further investigation to clarify the natural history of *H. pylori* transmission over lifetime.

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CONFLICT OF INTEREST DISCLOSURE

The authors have nothing to disclose.

ETHICS STATEMENT

This research project was approved by the ethics committee at Aichi Cancer Center (IRB-approval ID: 2020-2-25). All participants provided written informed consent as approved by the ethics committee of Aichi Cancer Center.

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