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Helicobacter pylori in the Philippines: Social and Ecological Determinants of Seropositivity and Lack of Association With Systemic Inflammation

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ABSTRACT

Helicobacter pylori (*H. pylori*) is a bacterium that infects the stomach and is associated with various gastrointestinal outcomes and increased cardiovascular disease risk. We examined the role of sex in and the social and ecological factors associated with *H. pylori* seropositivity ($n = 124$) and the relationship between seropositivity and systemic inflammation ($n = 116$) among adults in Metro Cebu, Philippines. Data were drawn from the Cebu Longitudinal Health and Nutrition Survey when participants were 21 years old. Anti-*H. pylori* antibody concentrations and C-reactive protein (CRP) concentrations were analyzed in dried blood spots and plasma, respectively. The seroprevalence of *H. pylori* in this sample was 32.3%. In logistic regression analyses adjusting for sex, higher socioeconomic status (i.e., asset index) was associated with decreased likelihood of *H. pylori* seropositivity (OR = 0.723, $p = 0.015$). Higher assets (OR = 0.688, $p = 0.002$) and higher hygiene (OR = 0.754, $p = 0.026$) were associated with decreased odds of *H. pylori* seropositivity. Any level of excrement near the household, relative to no excrement (low excrement OR = 3.45, $p = 0.036$; high excrement OR = 3.96, $p = 0.021$), was associated with increased odds of seropositivity. Sex was not associated with seropositivity. Seropositivity was not associated with CRP concentrations ($p = 0.52$). Our results support the role of both socioeconomic and hygienic determinants of *H. pylori* infection risk. These findings provide new insight into factors associated with *H. pylori* seropositivity in a population with no previously identified infection risk factors.

1 | Introduction

Helicobacter pylori (*H. pylori*) is a bacterium that infects the gastrointestinal tract (Mahachai et al. 2018). While often asymptomatic or mild, severe infection increases the risk of developing gastrointestinal diseases such as peptic ulcer disease and gastric cancer (Nomura et al. 1994; Uemura et al. 2001). Additionally, *H. pylori* infection has been associated with elevated cardiovascular disease risk, though evidence of this association remains controversial (He et al. 2022; Koenig et al. 1999; Torres and Gaensly 2002). While the global prevalence of *H. pylori* infection has decreased from an estimated 58.2%–43.1% between 1980 and 2022, inequalities in infection risk persist within and across populations (Li et al. 2023). According to a survey conducted during the 2015 Bangkok consensus on the management of *H. pylori* within countries under the Association of Southeast Asian Nations, the prevalence of *H. pylori* infection in the Philippines was 34% (Vilaichone et al. 2018).

H. pylori infections are often acquired in childhood, although infection can occur at any point throughout the lifespan (Mahachai et al. 2018). The transmission routes of *H. pylori* have not been fully established; however, interpersonal fecal–oral transmission is one likely pathway (Bui et al. 2016). Other possibilities for transmission are the oral–oral route and gastro–oral route (Burucoa and Axon 2017). Since routes of transmission remain uncertain, exploring the risk factors associated with infection can direct resources to reduce the incidence of *H. pylori* infection. Previous studies have found household crowding, poor hygiene, being married, contaminated water sources, and lower socioeconomic status to be associated with *H. pylori* infection (Brenner et al. 1999; Chen et al. 2014; Cheng et al. 2009; Emerenini et al. 2021; Khoder et al. 2019; Melius et al. 2013; Nurgalieva et al. 2002). However, there is limited evidence on the social and ecological determinants of *H. pylori* infection in the Philippines (Quebral et al. 2022).

Furthermore, studies have suggested a male sex bias for infection due to gendered differences in exposure to *H. pylori* and sex-based differences in protective immunity (de Martel and Parsonnet 2006; Tallman et al. 2024). For example, exposure to *H. pylori* may differ due to gendered differences in exposure to various social and ecological factors, such as through occupation, travel, and diet (Tallman et al. 2024). Gendered differences in education, the labor market, and land inheritance in the Philippines exist and may contribute to differences in exposures to social and ecological determinants of *H. pylori* infection (Estudillo et al. 2001; Yamauchi and Tiongco 2013). Therefore, examining the role of sex in exposure to social and ecological determinants of *H. pylori* infection is necessary to explore the apparent sex bias in *H. pylori* infection documented in other studies (de Martel and Parsonnet 2006; Tallman et al. 2024).

Finally, while *H. pylori* infection primarily manifests as gastric infection, it has also been associated with extra-gastric diseases, such as elevated cardiovascular disease risk (Shi et al. 2022; Torres and Gaensly 2002). Specifically, the increased production of pro-inflammatory cytokines in response to *H. pylori* infection could cause increased systemic inflammation and subsequently an increased risk for cardiovascular disease (Ishida et al. 2008; Nakagawa et al. 2013). C-reactive protein (CRP) is a commonly measured marker of systemic inflammation that is an established predictor of cardiovascular disease (de Ferranti and Rifai 2002; Ridker et al. 2002). Current evidence suggests that CRP is likely an indicator of inflammation resulting from an increased production of pro-inflammatory cytokines rather than a causal factor in cardiovascular disease (Sethwala et al. 2021). Nevertheless, higher concentrations of CRP indicate systemic inflammation and an elevated risk of atherosclerosis and other cardiovascular diseases (Pearson et al. 2003). Thus, the relationship between cardiovascular disease risk and *H. pylori* infection may be elucidated by examining the association between CRP and *H. pylori* seropositivity (Ishida et al. 2008).

Cardiovascular disease has been increasing in the Philippines and was the leading cause of death in 2022 (Corpuz 2024). Diet, exercise, and smoking have been identified as additional risk factors associated with the increased prevalence of cardiovascular disease (Brindley et al. 2023). Examining the relationship between systemic inflammation, measured through CRP, and *H. pylori* seropositivity may identify whether *H. pylori* infection is also an independent risk factor contributing to the overall burden of cardiovascular disease in the Philippines.

Focusing on adults living in Metropolitan Cebu, Philippines, this study aims to (1) examine the social and ecological determinants of *H. pylori* seropositivity, (2) examine the role of sex as a determinant of *H. pylori* seropositivity, and (3) examine the relationship between *H. pylori* seropositivity and systemic inflammation, proxied by CRP concentrations. For the first hypothesis, we expect social variables such as socioeconomic status and urbanicity and ecological variables such as household crowding, water source, and hygiene to be associated with seropositivity. For the second hypothesis, we hypothesize a male sex bias for *H. pylori* seropositivity. For the third hypothesis, we expect increased systemic inflammation, as measured by CRP, to be associated with *H. pylori* seropositivity.

2 | Materials and Methods

2.1 | Study Participants

This is a cross-sectional study drawing on data from the 2005 follow-up of the Cebu Longitudinal Health and Nutrition Survey (CLHNS). The CLHNS is a study of health-related outcomes among a one-year birth cohort born between 1983 and 1984 in Metro Cebu, Philippines (Adair et al. 2011). Methods describing the recruitment of the birth cohort are described by Adair et al. (2011) elsewhere. Follow-up surveys and other data collection have occurred over the years, collecting information on individual, household, and community-level characteristics. A total of 1678 plasma and dried blood spot (DBS) samples were collected during the 2005 follow-up survey from the adults who were born at baseline (McDade et al. 2009). Written informed consent was obtained from all participants with the approval of the Institutional Review Boards of the University of North Carolina at Chapel Hill and Northwestern University.

We selected 160 participants from the 1678 samples available using stratified random sampling, intentionally encompassing participants from barangays across various levels of urbanicity, socioeconomic status, and sex and excluding those who were pregnant at the time of sample collection (McDade et al. 2009). Of the 160 individuals selected, 128 had DBS with sufficient sample that could be analyzed for *H. pylori* antibody concentrations.

2.2 | Measurement of *H. pylori* Antibodies

The measurement of anti-*H. pylori* antibody concentrations can be used to establish serostatus, though it cannot distinguish between past and active *H. pylori* infections (Rothenbacher et al. 1998; Sabbagh et al. 2019). Past infections refer to *H. pylori* infections that have been previously cleared, likely eradicated through antibiotic treatment (Sabbagh et al. 2019). Seropositivity for *H. pylori* was determined through the analysis of DBS samples using a modified protocol of the Abnova *H. pylori* IgG ELISA kit (#KA0220) (Miller et al. 2022). High and low controls were analyzed on each ELISA plate, with inter-assay coefficients of variation of 5.6% and 12.6%, respectively. We established a DBS seropositivity cutoff of 13.2 EU/mL equivalent to the kit serum cutoff (20.0 EU/mL), along with a 95% confidence interval of <12.2 EU/mL as negative and >15.3 EU/mL as positive (Miller et al. 2022). The DBS equivalent and 95% confidence interval cutoff values were derived from the regression of 37 matched DBS and plasma samples (Miller et al. 2022). In analysis, we used the 95% confidence interval of the DBS equivalent plasma cutoff to reduce the misclassification of serostatus. The exclusion of equivocal samples is consistent with prior studies that exclude equivocal samples when examining seropositivity in *H. pylori* and other analytes (Bui et al. 2016; Vijh et al. 2021). Of the 128 samples analyzed, four samples were equivocal for seropositivity and removed from this analysis. The remaining 124 samples were operationalized as a binary variable of having a past or active *H. pylori* infection (seropositive) or never having an *H. pylori* infection (seronegative) in their lifetime.

2.3 | Measurement of C-Reactive Protein

Systemic inflammation was determined through analysis of CRP concentrations. Blood was collected in EDTA-coated evacuated tubes in the morning after an overnight fast, and plasma samples were analyzed using a high-sensitivity immunoturbidimetric method (Synchron LX20, lower detection limit: 0.1 mg/L; Beckman Coulter, Fullerton, CA). Additional details of the laboratory analysis are described by McDade et al. (2009). An upper limit of 10 mg/L was set to exclude samples that indicated unrelated active infections (Pearson et al. 2003). Eight of 124 samples had CRP concentrations above 10 mg/L and were removed from CRP analysis, resulting in a final sample of 116 for the systemic inflammation analysis. Consistent with prior studies examining the relationship between systemic inflammation and *H. pylori* seropositivity, a cutoff of >1.0 mg/L was used to indicate elevated levels of CRP indicative of chronic, systemic inflammation (Ishida et al. 2008; Pearson et al. 2003).

2.4 | Independent Variables

Consistent with previous studies, ownership of common items (electricity, ownership of house, housing material, air conditioning, television, tape recorder/stereo set, refrigerator, electric fan, jeepney, and car) was reported by participants and summed for an asset score on a 0- to 10-point scale, with higher asset scores reflecting greater access to socioeconomic resources (McDade et al. 2018; Varghese et al. 2021). An asset score, rather than income, was used as the indicator of socioeconomic status due to its greater stability in measuring relative access to socioeconomic resources over time (Filmer and Scott 2011; Howe et al. 2012; Vyas and Kumaranayake 2006). Sex was operationalized as biological sex at birth. Marriage was operationalized as whether or not individuals had ever had a history of marriage. Urbanicity was assessed using a seven-component urbanicity scale reflecting population size, density, communications, transportation, educational facilities, health services, and markets (Dahly and Adair 2007). Urbanicity was split into tertiles for analysis to capture varying urban, peri-urban, and rural environmental health dynamics (Nasim et al. 2022).

Categorical ecological variables were recategorized to increase the number of observations in categories with few samples. Table S1 contains details about how categorical ecological variables from the CLHNS datasets were created and operationalized. Household crowding was reported as the number of people usually living in the house divided by the number of rooms and log-transformed for analysis due to a right-skewed distribution. Measures of water, sanitation, and hygiene included the amount of excrement near the household, garbage disposal containment and method, toilet privacy and type, and the usual source of drinking water. The amount of excrement near the household was operationalized with a reference level of “none.” The usual source of drinking water was categorized as improved and unimproved water sources according to the World Health Organization (WHO) standards (WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation and UNICEF 2005). Using methods described elsewhere (Carba et al. 2009), a hygiene index was also calculated as a composite score of the type of toilet facility used, the amount of excrement around the house, the method of garbage disposal, and the cleanliness of the area where food is kept, reported as a scale from 0 to 9. In multivariable analysis, this hygiene index was retained as the measure of hygiene and sanitation.

2.5 | Data Analysis

Data were analyzed using R version 4.3.3. Prior to analyzing our hypotheses, we examined differences in the social and ecological variables across sex and urbanicity to understand how social and ecological exposures varied by sex and urbanicity.

For our first and second hypotheses, logistic regression was used to examine the role of sex and of social and ecological determinants in *H. pylori* seropositivity. Unadjusted models between *H. pylori* seropositivity and sex, social variables, and ecological variables were used to identify variables of interest in multivariable regression. Four separate multivariable models were created: (1) a social and ecological model using assets and composite hygiene index, (2) a social model using assets, (3) an ecological model using the composite hygiene index, and (4) an ecological model using components of the disaggregated hygiene index. Separate social and ecological models were explored due to moderate correlation between assets and hygiene index ($r = 0.469$). Sex was included in all social and ecological models because literature suggests a male sex bias in *H. pylori* infection while our unadjusted regression results showed a female sex bias (Table 2) (de Martel and Parsonnet 2006; Ferro et al. 2019; Ibrahim et al. 2017). All other social and ecological variables of interest were excluded from the models due to a lack of independence from assets, hygiene, or sex.

For our third hypothesis, multivariable logistic regression was used to examine the relationship between *H. pylori* seropositivity and systemic inflammation. Since body mass index (BMI) is associated with increased cardiovascular and metabolic health risks such as hypertension, coronary artery disease, and insulin resistance, BMI weight categories were adjusted for in the analysis of systemic inflammation (Poirier et al. 2006; Weir and Jan 2023). Within this sample, individuals were categorized as underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5–22.9 kg/m^2), overweight (BMI 23.0–27.4 kg/m^2) or obese (BMI > 27.5 kg/m^2) based on WHO classification for Asian populations (WHO expert consultation 2004). Additionally, we adjusted for sex to account for sex-based differences in cardiovascular disease risk due to the influence of genetics and sex hormones (Regitz-Zagrosek and Gebhard 2023).

2.6 | Sensitivity Analysis

Finally, a sensitivity analysis of the operationalization of serostatus was performed. To examine if removing the four individuals equivocal for seropositivity from the analysis impacted the results and interpretation of this analysis, cutoff values for seropositivity ≥ 12.2 and > 15.3 EU/mL were examined. These values correspond to the upper and lower bounds of the 95% confidence interval for seropositivity derived from the regression between DBS and plasma samples (Miller et al. 2022). Using the ≥ 12.2 EU/mL cutoff value, the four individuals originally equivocal for seropositivity were categorized as seropositive. Using the > 15.3 EU/mL cutoff value, the four individuals originally equivocal for seropositivity were categorized as seronegative.

3 | Results

The sample was split almost evenly between male (46.8%) and female (53.2%) participants, the average age of individuals was 21.0 years old (range 20–22), and few had a history of marriage (15.3%). Women were more likely to have a history of marriage, higher household crowding, and lower hygiene indices compared to men (Table 1). Assets, household crowding, hygiene index, and usual source of drinking water varied significantly across urbanicities (Table S2).

3.1 | Objectives 1 and 2: Social and Ecological Determinants and Role of Sex in *H. pylori* Seropositivity

Unadjusted logistic regression between seropositivity and each social and ecological variable showed that assets, history of marriage, sex, urbanicity, excrement near house, and hygiene index were associated with *H. pylori* seropositivity (Table 2).

Four multivariable models were created using social and ecological variables of interest identified in unadjusted logistic regressions (Table 3). The first model included both assets and hygiene index to assess the impact of both social and ecological variables together. The second model included only assets to assess the impact of social variables. The third model included only hygiene index to assess the impact of ecological variables. The

TABLE 1 | Sex differences in social and ecological characteristics of sample ($N = 124$).

Characteristic	Male, $N = 58$[a]	Female, $N = 66$[a]	p
Social variables			
Assets	5.62 (1.89)	5.17 (1.81)	0.20[b]
History of marriage			
Never married	54 (93.1%)	51 (77.3%)	**0.015**[c]
Married	4 (6.90%)	15 (22.7%)	
Urbanicity scale			
High (51–70)	20 (34.5%)	21 (31.8%)	0.70[c]
Medium (39–50)	17 (29.3%)	24 (36.4%)	
Low (0–38)	21 (36.2%)	21 (31.8%)	
Ecological variables			
Log crowding	0.686 (0.592)	0.907 (0.543)	**0.024**[b]
Excrement near house level			
None	25 (43.1%)	12 (18.2%)	**0.007**[c]
Low	20 (34.5%)	27 (40.9%)	
High	13 (22.4%)	27 (40.9%)	
Garbage disposal containment			
Contained	58 (100%)	64 (97.0%)	0.50[d]
Uncontained	0 (0.000%)	2 (3.03%)	
Garbage disposal method			
Collected	35 (60.3%)	32 (48.5%)	0.21[d]
Burned	23 (39.7%)	32 (48.5%)	
Composted	0 (0.000%)	2 (3.03%)	
Hygiene index	6.84 (1.66)	5.94 (1.54)	**< 0.001**[b]
Toilet privacy			
Yes	41 (70.7%)	44 (66.7%)	0.63[c]
No	17 (29.3%)	22 (33.3%)	
Toilet type			
Flush/water-sealed	53 (91.4%)	55 (83.3%)	0.18[c]
Field or latrine/pit	5 (8.62%)	11 (16.7%)	
Usual source of drinking water			
Improved	42 (72.4%)	46 (69.7%)	0.74[c]
Unimproved	16 (27.6%)	20 (30.3%)	

Note: Bold indicates $p < 0.05$.
[a]Mean (SD); n (%).
[b]Wilcoxon rank sum test.
[c]Pearson's chi-squared test.
[d]Fisher's exact test.

TABLE 2 | Unadjusted logistic regression models predicting *H. pylori* seropositivity in relation to sex and social and ecological variables ($N = 124$).

Characteristic	OR	95% CI	p
Social variables			
Assets	0.678	0.528, 0.851	**0.001**
History of marriage			
Never married	—	—	
Married	2.78	1.02, 7.66	**0.044**
Urbanicity scale			
High (51–70)	—	—	
Medium (39–50)	3.56	1.37, 9.99	**0.012**
Low (0–38)	1.85	0.682, 5.27	0.23
Ecological variables			
Log crowding	1.67	0.863, 3.34	0.13
Excrement near house level			
None	—	—	
Low	3.97	1.39, 13.3	**0.015**
High	4.73	1.61, 16.1	**0.007**
Garbage disposal containment			
Contained	—	—	
Uncontained	2.13	0.083, 54.8	0.60
Garbage disposal method			
Collected	—	—	
Burned	0.915	0.422, 1.97	0.82
Composted	2.05	0.078, 53.4	0.62
Hygiene index	0.720	0.559, 0.912	**0.008**
Toilet privacy			
Yes	—	—	
No	1.77	0.794, 3.92	0.16
Toilet type			
Flush/ water-sealed	—	—	
Field or latrine/ pit	1.77	0.587, 5.15	0.30
Usual source of drinking water			
Improved	—	—	
Unimproved	0.613	0.246, 1.43	0.27
Sex			
Sex			
Male	—	—	
Female	2.40	1.11, 5.40	**0.030**

Note: Bold indicates $p < 0.05$.
Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 3 | Adjusted social and ecological logistic regression models for odds of *H. pylori* seropositivity ($N = 124$).

Characteristic	OR	95% CI	p
Social and ecological model			
Assets	0.723	0.551, 0.932	**0.015**
Hygiene index	0.875	0.659, 1.16	0.35
Sex			
Male	—	—	
Female	2.00	0.865, 4.76	0.11
Social model			
Assets	0.688	0.534, 0.866	**0.002**
Sex			
Male	—	—	
Female	2.20	0.978, 5.12	0.060
Ecological model (composite hygiene index)			
Hygiene index	0.754	0.583, 0.963	**0.026**
Sex			
Male	—	—	
Female	1.93	0.855, 4.47	0.12
Ecological model (disaggregated hygiene index)			
Excrement near house level			
None	—	—	
Low	3.45	1.14, 12.1	**0.036**
High	3.96	1.30, 13.9	**0.021**
Garbage disposal method			
Contained	—	—	
Uncontained	2.03	0.062, 65.6	0.66
Toilet type			
Flush/ water-sealed	—	—	
Field or latrine/ pit	1.34	0.415, 4.16	0.61
Sex			
Male	—	—	
Female	1.79	0.784, 4.19	0.17

Note: Bold indicates $p < 0.05$.
Abbreviations: CI, confidence interval; OR, odds ratio.

fourth model used available components of the hygiene index (type of toilet facility used, the amount of excrement around the house, and the method of garbage disposal) to assess the impact of individual hygiene and sanitation factors. All models adjusted for sex to examine if sex itself was a determinant of *H. pylori* seropositivity. Due to the lack of independence of other social and ecological variables of interest from assets, hygiene index, and sex, all other variables were excluded from multivariable analysis. There was low multicollinearity in all four models, with scaled generalized variable inflation factors for all variables in each model equal to or below 1.229.

When assessing assets and hygiene index together, assets (OR = 0.723, $p = 0.015$) remained significantly associated with *H. pylori* seropositivity, while hygiene index (OR = 0.875, $p = 0.35$) was no longer associated (Table 3). In separate social and ecological multivariable models for *H. pylori* seropositivity, assets (OR = 0.688, $p = 0.002$) and hygiene (OR = 0.754, $p = 0.026$) remained associated with seropositivity (Table 3). The model examining the disaggregated components of the hygiene index showed that any level of excrement near the house compared to no excrement near the house (low excrement OR = 3.45, $p = 0.036$; high excrement OR = 3.96, $p = 0.021$) remained significantly associated with *H. pylori* seropositivity, while no other components of the hygiene index were associated. Sex was not associated with *H. pylori* seropositivity in any models (Table 3).

3.2 | Objective 3: Systemic Inflammation and *H. pylori* Seropositivity

In multivariable analysis for CRP concentration, seropositivity was not associated with increased systemic inflammation (Table 4). As expected, having a high BMI category was associated with increased systemic inflammation ($\beta = 3.52$, $p = 0.032$) (Table 4). Sex was not significantly associated with increased systemic inflammation (Table 4).

3.3 | Sensitivity Analysis

By including the four equivocal individuals who were excluded from the main analysis as either seropositive or seronegative for *H. pylori*, one result in each of the following analyses differed: the distribution of social and ecological variables across urbanicity, unadjusted regression of *H. pylori* seropositivity and social and ecological determinants, and regression of systemic inflammation and *H. pylori* (Tables S3–S5). However, the differences do not detract from the primary objectives of this analysis or affect the interpretation of results.

TABLE 4 | Adjusted logistic regression model for odds of high systemic inflammation ($N = 116$).

Characteristic	OR	95% CI	*p*
Seropositivity			
Negative	—	—	
Positive	1.39	0.495, 3.77	0.52
BMI category			
Normal weight	—	—	
Underweight	2.36	0.776, 7.08	0.12
Overweight or obese	3.52	1.09, 11.2	**0.032**
Sex			
Male	—	—	
Female	1.15	0.439, 3.04	0.78

Note: Bold indicates $p < 0.05$.
Abbreviations: CI, confidence interval; OR, odds ratio.

4 | Discussion

In this study, we examined the role of sex and of social and ecological determinants of *H. pylori* seropositivity in Metro Cebu, Philippines. We also analyzed the relationship between systemic inflammation indicated by CRP concentration and *H. pylori* seropositivity.

Similar to the previously reported Philippine national prevalence of *H. pylori* infection (34%), 32.3% of the samples in this study were seropositive (Vilaichone et al. 2018). Our findings showed that socioeconomic status and hygiene were critical determinants of *H. pylori* seropositivity. This aligns with previous studies on the risk factors and transmission of *H. pylori* globally showing that lower socioeconomic status and poor hygiene practices predict seropositivity for *H. pylori* (Chen et al. 2014; Nurgalieva et al. 2002).

Socioeconomic status as a predictor of *H. pylori* seropositivity is likely mediated by household ecological characteristics. Specifically, socioeconomic status often reflects access to sanitation services, which more directly impact disease transmission (Akpakli et al. 2018; Rhodes and McKenzie 2018). In this population, higher socioeconomic status may reflect the ability to invest in household water, sanitation, and hygiene infrastructure that reduces the transmission of *H. pylori*. Additionally, the association between hygiene index and seropositivity lends support to the hypothesis that *H. pylori* is transmitted via the fecal–oral route (Bui et al. 2016). Epidemiological studies and studies identifying the presence of *H. pylori* in various water sources suggest that fecal contamination of drinking water is a likely source of infection (Aziz et al. 2015). However, exposure to fecal matter is unlikely to be mediated through exposure to contaminated drinking water in this context because analysis did not show a significant association between the usual source of drinking water and *H. pylori* seropositivity. Rather, our analyses of the disaggregated hygiene index suggest that the level of excrement near households may directly expose individuals to *H. pylori* and increase the risk of seropositivity in this context. Indirect fecal–oral transmission through other pathways such as food is also possible.

Previous studies have reported a male sex bias in *H. pylori* infection attributed to both biological characteristics of immune response and social and ecological differences in exposure (de Martel and Parsonnet 2006; Ferro et al. 2019; Ibrahim et al. 2017; Tallman et al. 2024). However, our unadjusted regression analysis showed a female sex bias. Because sex was not a predictor of seropositivity in adjusted analysis, biological explanations for a female sex bias are unlikely. Instead, differences in exposure to social and ecological determinants of seropositivity may account for a female sex bias. For example, although there is no difference in access to private toilets and toilet types between men and women, the difference in the level of excrement around households suggests that men and women may have differential access to sanitation and waste management infrastructure for the disposal of sewage (Table 1). This may be due to a lack of a centralized sewage system, such as in Cebu City; however, there is limited data on the specific pathway by which excrement accumulates around houses (Ostojic et al. 2013). Thus, while in other contexts men tend to have greater levels of seropositivity, the opposite, though not statistically significant, relationship between sex and seropositivity occurred among respondents in this study (de Martel and Parsonnet 2006; Ferro et al. 2019; Ibrahim et al. 2017).

H. pylori seropositivity was not a driver of systemic inflammation in this population. Although prior evidence for the relationship between *H. pylori* seropositivity and cardiovascular disease is conflicting, our results suggested that *H. pylori* seropositivity and associated systemic inflammation may not be a significant driver of increased cardiovascular disease risk in this population (Kim et al. 2018). It is possible that in this population, there is no relationship between *H. pylori* seropositivity and extra-gastric diseases, such as cardiovascular disease. This may be due to differences in the virulence of different strains of *H. pylori*. For example, while studies have shown that CagA-positive strains of *H. pylori* play an important role in the development of extra-gastric diseases such as atherosclerosis, there is limited research about the specific sub-types of CagA-positive strains (East-Asian and Western) and their effects on the development of extra-gastric diseases (Niccoli et al. 2010; Yamaoka 2010; Zhang et al. 2008). Cortes et al. (2010) reported that although all Philippine *H. pylori* strains identified were CagA-positive, 73.7% of these strains contained the less virulent, Western type of CagA-positive strains. Conflicting findings on the relationship between infection and increased cardiovascular disease risk may reflect differences in systemic inflammation caused by less virulent strains of CagA-positive *H. pylori* (He et al. 2022; Koenig et al. 1999; Torres and Gaensly 2002). More research on the differences between East-Asian and Western CagA-positive *H. pylori* strains and their impact on cardiovascular disease risk is needed to clarify this relationship.

There are several key limitations to this analysis. First, the role of sex and the social and ecological determinants of seropositivity are specific to Cebu as of 2005 when the samples and data were collected. Certain determinants, particularly sex as a social determinant, may no longer be as strongly associated with seropositivity due to gradual improvements in gender equality (Asian Development Bank 2013). Additionally, while the use of *H. pylori* antibody concentration from DBSs as a measure of *H. pylori* seropositivity is a field-friendly method, we were unable to distinguish between past and active infections. This limitation does not impact the analysis of *H. pylori* seropositivity in relation to social and ecological determinants of infection; however, it limits our ability to examine the relationship between cardiovascular disease risk and *H. pylori* infection. There is some evidence that *H. pylori* eradication decreases CRP concentration (Watanabe and Kotani 2021). Thus, it is possible that the relationship between systemic inflammation and *H. pylori* infection only persists during active, chronic infections. The measurement of *H. pylori* seropositivity rather than a method that allows for the distinction between past and active *H. pylori* infections does not allow for this analysis. Furthermore, we only examined one measure of inflammation, and it is possible that CRP does not capture the relationship between *H. pylori* infection and increased cardiovascular disease risk. Finally, although our results corroborate previous studies on the determinants of *H. pylori* seropositivity, the small sample size limits the generalizability of this study and may overlook more nuanced relationships between seropositivity and its determinants (Brenner et al. 1999; Chen et al. 2014; Cheng et al. 2009; Emerenini et al. 2021; Khoder et al. 2019; Melius et al. 2013; Nurgalieva et al. 2002).

5 | Conclusion

Given the persistent prevalence of *H. pylori* and the associated health consequences, it is important to identify the social and ecological determinants of seropositivity to inform prevention strategies (Nomura et al. 1994; Uemura et al. 2001).

Increased socioeconomic status (i.e., assets) and hygiene were associated with decreased odds of *H. pylori* seropositivity, while increased levels of excrement near households were associated with increased odds of seropositivity in this study. These findings support the hypothesis that *H. pylori* is transmitted by the fecal–oral route. In this context, however, transmission through direct contact with fecal matter is more likely than transmission through contaminated drinking water. We also found a superficial female sex bias that may be attributed to gender differences in access to sanitation, hygiene, and waste management infrastructure. This sex bias is contrary to most prior studies, which have shown either no sex bias or a male sex bias, but indicates that specific actions to address gender disparities in access to sanitation, hygiene, and waste management could reduce the incidence of *H. pylori* in women.

We did not identify an association between CRP levels and seropositivity, suggesting that the strains of *H. pylori* most prevalent in the Philippines may not increase cardiovascular disease risk through increased systemic inflammation. Further research should identify the impact of specific CagA-positive *H. pylori* strains on extra-gastric diseases to better understand the impact of *H. pylori* infection on health overall.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Survey data are available through the Cebu Longitudinal Health and Nutrition Survey Dataverse, and biomarker data are available to qualified investigators upon request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.