Association of *Helicobacter pylori* Positivity With Risk of Disease and Mortality

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**INTRODUCTION:** *Helicobacter pylori* colonizes the human stomach. Infection causes chronic gastritis and increases the risk of gastroduodenal ulcer and gastric cancer. Its chronic colonization in the stomach triggers aberrant epithelial and inflammatory signals that are also associated with systemic alterations.

**METHODS:** Using a PheWAS analysis in more than 8,000 participants in the community-based UK Biobank, we explored the association of *H. pylori* positivity with gastric and extragastric disease and mortality in a European country.

**RESULTS:** Along with well-established gastric diseases, we dominantly found overrepresented cardiovascular, respiratory, and metabolic disorders. Using multivariate analysis, the overall mortality of *H. pylori*–positive participants was not altered, while the respiratory and Coronavirus 2019–associated mortality increased. Lipidomic analysis for *H. pylori*–positive participants revealed a dyslipidemic profile with reduced high-density lipoprotein cholesterol and omega-3 fatty acids, which may represent a causative link between infection, systemic inflammation, and disease.

**DISCUSSION:** Our study of *H. pylori* positivity demonstrates that it plays an organ- and disease entity–specific role in the development of human disease and highlights the importance of further research into the systemic effects of *H. pylori* infection.

**KEYWORDS:** *H. pylori*; mortality; morbidity; dyslipidemia; gastric cancer

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/CTG/A973

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**INTRODUCTION**

*Helicobacter pylori* is a human pathogen that chronically colonizes the stomach of approximately the half of the world’s population. Infection with *Helicobacter* sp. usually occurs during childhood and persists for decades. Infection is linked to various gastric disorders. While infection causes gastritis, it remains asymptomatic in most individuals. However, approximately 5% of individuals with *H. pylori* develop gastric or duodenal ulcers, and approximately 1% develop gastric cancer, with infection being the most relevant risk factor for both (1–3).

While the long-known epidemiologic association of *H. pylori* with gastric diseases is well established, novel findings on induction of chronic inflammation and changes in gastric (stem) cell physiology due to infection raise the question whether infection may also be associated with systemic alterations and development of extragastric diseases. Indeed, several disorders have been linked to *H. pylori* infection, and eradication is suggested in individuals with several extragastric disorders such as unexplained iron deficiency anemia (IDA) and immune thrombocytopenia. However, results are heterogenous, and response to eradication is higher in countries with high *H. pylori* prevalence in the background population. In patients with IDA, main benefits for eradication are achieved in children in contrast to adults, while for immune thrombocytopenia, the evidence is less compelling for children and benefits are achieved in adults (2,4,5). An association with cardiovascular diseases has also been previously suggested, although the strength of this association is controversial and a definite mechanistic explanation is missing (6,7).

Using the well-characterized, community-based UK Biobank (UKB) that comprises a large dataset of directly measured anti–*H. pylori* antibodies in serum samples consisting of more than...
9,000 participants, we analyzed overall and disease-specific morbidity in a country with rather medium prevalence of \textit{H. pylori} up to 40\% (8). To this end, we explored the association between \textit{H. pylori} positivity at baseline and 457 PheCodes, available in the dataset over the threshold of 5 observations per PheCode. This approach demonstrates that \textit{H. pylori} positivity predisposes to specific organ dysfunctions including well-established gastric diseases, anemia, and various cardiovascular and respiratory disorders. Because cardiometabolic diseases were among the strongest associations with \textit{H. pylori} positivity, we analyzed 143 metabolites measured at the same time as the \textit{H. pylori} test was performed and analyzed their association with \textit{H. pylori} positivity, mortality, and morbidity. \textit{H. pylori} positivity was associated with lower levels of sphingomyelins, total esterified cholesterol, docosahexaenoic acid, large and very large high-density lipoprotein (HDL), and smaller average HDL diameter.

\textbf{METHODS}

\textbf{Study cohort}

The UKB is a community-based cohort study conducted in the United Kingdom at 22 participating centers. The baseline examinations were conducted from 2006 to 2010 and recruited 502,505 volunteers aged 37–73 years. All participants gave informed consent for data linkage to medical reports. At the baseline assessment (2006–2010), the participants provided demographic and physical measures. Ongoing inpatient hospital records beginning in 1996 were used to identify diagnoses according to \textit{International Classification of Diseases} 9th and 10th edition (ICD-10 and ICD-9) codes. All reported ICD codes were assigned to the respective date of their first diagnosis.

The UKB receives death notifications (age at death and primary ICD diagnosis that led to death) through linkage to national death registries. End of follow-up was defined as death or end of hospital inpatient data collection in January 2023. Causes of death included all malignancies (C00–C97), cardiovascular diseases (100–199), respiratory diseases (100–199), nonmalignant digestive diseases (K00–K93), and COVID-19 (U0). This research has been conducted using the UKB Resource under Application Number 71300.

\textbf{Case definition}

In a subset of UKB participants, seropositivity status of 20 pathogens was measured in a pilot study using multiplex serology (9,10). \textit{H. pylori} positivity is defined as 2 or more positive antibodies against the following antigens (with the following cutoff values): antigen VacA $>100$, antigen outer membrane protein $>170$, antigen GroEL $>80$, antigen Catalase $>180$, and antigen UreA $>130$ (UKB datafile 23074). The descriptive statistics of this cohort are summarized in Supplementary Table 1 (see Supplementary Digital Content, http://links.lww.com/CTG/A973).

\textbf{Propensity score matching}

Propensity score matching was applied using the \textit{Psmpy} (0.3.13, (11)) python package (python $\geq$3.7). After logistic regression–based propensity score with k-nearest neighbor (k-NN) allocation, 2 iterations were performed, resulting in a 2:1 balance of controls over cases and a reduced standardized mean effect size by variable shown in Figure 1 and summarized in Table 1. The propensity score was estimated using age, sex, body mass index (BMI), ethnic background, and socioeconomic status (Townsend deprivation index) at baseline as predictive covariates in the regression. In total, 8,898 cases were enrolled in further regressions (See Supplementary Figure 1, Supplementary Digital Content, http://links.lww.com/CTG/A973).

\textbf{PheWAS analysis}

We performed a phenome-wide association study (PheWAS). The coding for clinical diagnoses in our dataset followed the ICD-10 and ICD-9 coding systems. The ICD is a list of codes for diseases, symptoms, findings, and injuries. Most of the world’s health expenditures are allocated with ICD (12). For each study subject, ICD codes from the electronic health record diagnoses throughout the study period were collated and duplicates removed. We converted the ICD codes of the 8,898 enrolled participants into 457 associated PheCodes using the pyPheWAS package (13). PheCodes are manually compiled groups of ICD codes used to characterize and scale clinically relevant conditions with wide ranges of diagnoses or symptoms and were created to enable PheWAS (14). PheCodes are maintained by the Center for Precision Medicine at Vanderbilt University Medical Center and are available at https://www.phewascatalog.org/phecodes. A series of case-control tests was performed by fitting multiple logistic regression models, 1 for every PheCode of interest. The influence of the analyzed PheCode was then determined through evaluating the beta and testing for statistical significance. To further reduce the influence of age, sex, BMI, self-reported ethnic background, and socioeconomic status after propensity score matching, they were used as “constant” covariates in every regression (13). We analyzed PheCodes from the following 7 disease groups: digestive, respiratory, neoplasms, infections, circulatory, hematopoietic, endocrine/metabolic.

In total, 457 PheCodes were analyzed (See Supplementary Table 2, Supplementary Digital Content, http://links.lww.com/CTG/A973).

\textbf{Metabolomics}

To further dissect the metabolic effects of \textit{H. pylori} positivity, we analyzed 143 metabolites that were measured through nuclear magnetic resonance spectroscopy in a subset of 1,436 \textit{H. pylori}–negative participants and 677 \textit{H. pylori}–positive participants (See Supplementary Table 3, Supplementary Digital Content, http://links.lww.com/CTG/A973). Details on measurements through nuclear magnetic resonance can be accessed here: https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/nmrn_companion_doc.pdf.

\textbf{Statistical analysis}

All continuous variables were analyzed by unpaired, 2-tailed $t$ tests or the Mann-Whitney $U$ test and by an appropriate multivariable model. The results are presented as mean $\pm$ SD (normal distribution) or median [IQR] (non-normal distribution). All categorical variables were displayed as relative (%) frequencies, and the corresponding contingency tables were analyzed using the $\chi^2$ test. Odds ratios/hazard ratios (ORs/HRs) were presented with their corresponding 95\% confidence intervals (CIs) given in brackets. HRs were calculated using Cox proportional hazard regression models. Multivariable logistic regression was performed to test for independent associations. The PheWAS analysis was performed using the “pyPheWAS” python package (15). Differences were statistically significant when $P < 0.05$. For PheWAS analyses, an false discovery rate-adjusted
The significance level of $P \leq 0.0038$ was calculated using the implemented false discovery rate correction for multiple testing. Data were analyzed using Python 3.11.2, R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and Prism version 8 (GraphPad, LaJolla, CA).

**RESULTS**

The UKB dataset consists of 9.967 individuals with valid information on the presence of *H. pylori* antibodies in the serum at baseline, with 2.966 being *H. pylori* positive (Table 2). Before matching, we found that *H. pylori* positivity was associated with higher age, male sex, and obesity (See Supplementary Table 1, Supplementary Digital Content, http://links.lww.com/CTG/A973). After propensity score 2:1 matching, age was well balanced, and for all cohort variables, a reduction in mean effect size could be achieved (See Supplementary Figure 1, Supplementary Digital Content, http://links.lww.com/CTG/A973).

**Table 1. Mortality analyses after a mean follow-up of 13.6 years, corrected for age, sex, BMI, and socioeconomic status**

<table>
<thead>
<tr>
<th>Mortality (ICD-10 code)</th>
<th><em>H. pylori</em> positive (n = 2,966)</th>
<th>Controls (n = 5,932)</th>
<th>$P$</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (ICD-10 code)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms (C)</td>
<td>263</td>
<td>432</td>
<td>0.39</td>
<td>1.07</td>
<td>0.91</td>
</tr>
<tr>
<td>Neurological diseases (G)</td>
<td>136</td>
<td>240</td>
<td>0.84</td>
<td>1.02</td>
<td>0.81</td>
</tr>
<tr>
<td>Cardiovascular diseases (I)</td>
<td>14</td>
<td>20</td>
<td>0.37</td>
<td>1.36</td>
<td>0.68</td>
</tr>
<tr>
<td>Respiratory diseases (J)</td>
<td>52</td>
<td>91</td>
<td>0.83</td>
<td>0.96</td>
<td>0.62</td>
</tr>
<tr>
<td>Digestive diseases (K)</td>
<td>17</td>
<td>15</td>
<td>0.25</td>
<td>2.16</td>
<td>1.48</td>
</tr>
<tr>
<td>Coronavirus disease 2019 (U0)</td>
<td>5</td>
<td>0.27</td>
<td>0.08</td>
<td>3.53</td>
<td>2.49</td>
</tr>
</tbody>
</table>

Mortality categories with at least 5 deaths per group are displayed with ICD groups. For categories that are significantly different between *H. pylori*-positive individuals and controls, the most common subgroups are displayed. BMI, body mass index; ICD, International Classification of Diseases.

* $P < 0.05$. 

Figure 1. Manhattan plot of sex, age, body mass index, ethnic background, and socioeconomic status (Townsend deprivation index) adjusted $-\log_{10}(P$ values) for all selected PheCodes comparing their occurrence in *Helicobacter pylori*-positive individuals with controls. Highlighted are associations with $P$ values $<0.05$ (corrected for multiple testing by false discovery rate to the threshold [dotted line] 0.0038). Upward/downward pointing triangular markers refer to PheCodes, that are overrepresented or underrepresented, respectively, in *H. pylori*-positive individuals compared with controls. CHF, congestive heart failure; NOS, not otherwise specified.
We compared routine serum parameters between *H. pylori*–positive individuals and controls. *H. pylori*–positive individuals had higher mean levels of total protein (73.1 vs 72.4 g/L), lower levels of cholesterol (5.6 vs 5.8 mmol/L), and lower levels of insulin-like growth factor 1 (21.0 vs 21.6 nmol/L) compared with controls. *H. pylori*–positive individuals also had higher levels of sex hormone binding globulin (51.9 vs 51.7 nmol/L) and alkaline phosphatase (85.7 vs 83.7 U/L) compared with controls (Table 2).

To obtain insight into conditions associated with *H. pylori* positivity, we performed a multi/mass monovariate PheWAS analysis. Of 457 selected PheCodes, 25 were significantly overrepresented and 2 were underrepresented in *H. pylori*–positive subjects (Figures 1 and 2, Supplementary Table 2 [see Supplementary Digital Content, http://links.lww.com/CTG/A973]). We found a significant overrepresentation of several gastric disorders that are known to be driven by *H. pylori* infection such as “bacterial gastritis,” “other specified gastritis,” and “gastric cancer.” Moreover, there was a strong positive association with IDA, which confirmed previous data (16,17). In addition, various other diseases showed a significant correlation. Of the 25 most overrepresented disorders, 11 belonged to circulatory diseases, including congestive heart failure, cardiomegaly, angina pectoris, essential hypertension, hypotension, myocardial infarction, IDA, and 7 respiratory disorders such as postinflammatory pulmonary fibrosis and chronic obstructive pulmonary disease (COPD) (Figure 2, Supplementary Table 2 [see Supplementary Digital Content, http://links.lww.com/CTG/A973]). The underrepresented PheCodes included “benign neoplasm of other parts of digestive system” and “ulcer of esophagus” (Figure 2).

Next, we analyzed whether increased morbidity in *H. pylori*–positive individuals is also linked to increased mortality (Table 1). During the mean follow-up of 13.6 years, 263 of the *H. pylori*–positive participants (8.8%) and 432 (7.2%, Table 1) of *H. pylori*–negative individuals died. The univariate analysis revealed a significant increase in the overall mortality of the *H. pylori*–positive participants (univariate *P* value 0.012; See Supplementary Figure 2, Table 2. Comparison of baseline characteristics and serum parameters in *Helicobacter pylori*–positive individuals vs controls

<table>
<thead>
<tr>
<th></th>
<th>H. pylori positive (n = 2,966)</th>
<th>Controls (n = 5,932)</th>
<th>Multivariable P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>27.4 ± 4.8</td>
<td>27.8 ± 4.9</td>
<td>2.3E-08*</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>57.0 ± 7.9</td>
<td>57.3 ± 8.2</td>
<td></td>
</tr>
<tr>
<td><strong>Sex (n, %women)</strong></td>
<td>1,483 (50%)</td>
<td>2,966 (50%)</td>
<td></td>
</tr>
<tr>
<td>Townsend deprivation index</td>
<td>−1.7 ± 2.9</td>
<td>−0.7 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (n, % White)</td>
<td>2,652 (90.4%)</td>
<td>5,717 (96.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total protein (g/L)</strong></td>
<td>73.1 ± 4.4</td>
<td>72.4 ± 4.1</td>
<td>0.008*</td>
</tr>
<tr>
<td><strong>Cholesterol (mmol/L)</strong></td>
<td>5.6 ± 1.2</td>
<td>5.8 ± 1.2</td>
<td>0.009*</td>
</tr>
<tr>
<td><strong>IGF-1 (nmol/L)</strong></td>
<td>21.0 ± 6.0</td>
<td>21.6 ± 5.9</td>
<td>0.004*</td>
</tr>
<tr>
<td><strong>SHBG (nmol/L)</strong></td>
<td>51.9 ± 27.2</td>
<td>51.7 ± 27.4</td>
<td>0.008*</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase (U/L)</strong></td>
<td>85.7 ± 28.4</td>
<td>83.7 ± 24.9</td>
<td>0.023*</td>
</tr>
<tr>
<td><strong>Vitamin D (nmol/L)</strong></td>
<td>45.5 ± 21.1</td>
<td>46.2 ± 20.2</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Albumin (g/L)</strong></td>
<td>45.1 ± 2.6</td>
<td>45.3 ± 2.5</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Glucose (mmol/L)</strong></td>
<td>5.1 ± 1.1</td>
<td>5.1 ± 1.1</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Total bilirubin (umol/L)</strong></td>
<td>9.0 ± 4.3</td>
<td>9.1 ± 4.7</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>C-reactive protein (mg/L)</strong></td>
<td>2.7 ± 3.9</td>
<td>2.6 ± 4.6</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>HbA1c (mmol/mol)</strong></td>
<td>36.6 ± 6.7</td>
<td>35.9 ± 6.3</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Creatinine (umol/L)</strong></td>
<td>73.2 ± 17.3</td>
<td>72.8 ± 21.5</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Urate (umol/L)</strong></td>
<td>26.6 ± 11.1</td>
<td>26.1 ± 9.5</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Gamma-glutamyltransferase (U/L)</strong></td>
<td>314.3 ± 82.1</td>
<td>310.0 ± 80.0</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Direct bilirubin (umol/L)</strong></td>
<td>38.9 ± 48.1</td>
<td>37.6 ± 43.5</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Urea (mmol/L)</strong></td>
<td>5.5 ± 1.4</td>
<td>5.5 ± 1.5</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Quantitative measures are expressed as mean with SD or relative frequency (%) and their corresponding multivariate P values, sex, age, BMI, ethnic background, and socioeconomic status (Townsend deprivation index) adjusted. Relative measures are expressed as n with percentage of modus.

BMI, body mass index; IGF-1, insulin-like growth factor 1; SHBG, sex hormone binding globulin.

*P* < 0.05.
Supplementary Digital Content, http://links.lww.com/CTG/A973), which did not stay significant after adjustment for age, sex, BMI, ethnicity, and socioeconomic status (multivariate \( P \) value 0.4, Table 1). However, \( H. pylori \) positivity was associated with a significant increase in respiratory-associated mortality (HR 2.16; 95% CI [1.48–2.84], Table 1) and increased death due to COVID-19 (HR 3.53; 95%CI [2.49–4.58]).

Last, we dissected the effect of \( H. pylori \) positivity on 143 serum metabolites (Figure 3). \( H. pylori \) positivity was associated with lower levels of sphingomyelins, total esteriﬁed cholesterol, docosahexaenoic acid, large and very large HDL, and smaller average HDL diameter (Figure 3).

DISCUSSION
We aimed to analyze the UKB database to delineate the relevance of \( H. pylori \) positivity for human health. Our data demonstrate that \( H. pylori \) positivity plays an organ- and disease entity–speciﬁc role in the development of cardiovascular, digestive, and metabolic diseases. Given the large number of recruited individuals, the long follow-up period (>10,000 person-years) and a precise collection of disease phenotypes, we were able to gain unprecedented insights and discovered 27 PheCodes that are signiﬁcantly associated with \( H. pylori \) positivity.

Our data conﬁrm previous well-established links between \( H. pylori \) and gastric disorders, which are based on bacterial lifelong persistence in the human gastric mucosa of approximately 50% of the world’s population (18–21). Using a potent ﬂagellar system and chemotactic receptors, \( H. pylori \) can penetrate the mucus and colonize gastric epithelial cells in the pit and deep in gastric glands (20,22,23). Recent studies have revealed the interplay between bacterium and host epithelium, demonstrating key mechanisms in activation of stem cells leading to hyperplasia and a robust and sustained innate and adaptive immune response that fails to clear \( H. pylori \), rather supporting a chronic inﬂammatory condition, laying ground for cancer initiation and progression (20,24–29). In addition to being linked to gastritis and gastroduodenal ulcers, our data conﬁrm an association between \( H. pylori \) positivity and IDA. Experimental data from mice studies revealed that CagA \( H. pylori \) acquire iron from host cells through transfer of transferrin receptors from the basolateral membrane to the apical surface where the bacteria locate (30). This and gastric hypochlorhydria in chronic gastritis, which interferes with iron reduction and absorption, may aﬀect the systemic iron level leading to anemia (31). Notably, iron deﬁciency has been associated with accelerated premalignant and malignant gastric lesions in mice and humans (32). The link between infection and noncardia gastric cancer has been demonstrated in various studies, and \( H. pylori \) is considered a WHO type I carcinogen (1). It should be noted that most datasets that link \( H. pylori \) infection and gastric cancer risk are from Asian countries, an area with high prevalence of \( H. pylori \) infection (33). While large cohort studies from the United States have also demonstrated this association (34,35), there is still a debate on whether this applies to European countries because the reduction for \( H. pylori \) is larger than the reduction in gastric cancer from 1993 to 2007 (36). Still most patients with noncardia gastric cancer were tested \( H. pylori \) positive in a European case–control study and 2 studies in the Swedish population reported a high association of

![Figure 2. The 27 most overrepresented/underrepresented PheCodes in individuals with \( Helicobacter pylori \), adjusted for age, sex, BMI, ethnic background, and socioeconomic status. ORs are given as log (OR) and 95% confidence intervals. Only PheCodes that remained significant after adjustment for multiple testing are displayed and have thereby a \( P \) value of \( \leq 0.0038 \). BMI, body mass index; CI, confidence interval; NOS, not otherwise specified; OR, odds ratio.](http://links.lww.com/CTG/A973)
Our study found a positive association of *H. pylori* infection with several cardiovascular disorders such as heart failure, angina pectoris, or cerebrovascular disease, consistent with recent meta-analyses: *H. pylori* infection in >20,000 patients was associated with an increased risk of myocardial infarction, OR: 2.10 (CI: 1.75–2.53) (6); second, an increased risk of acute coronary syndrome, OR: 2.03 (CI: 1.66–2.47) (41), and third, an increased risk by 51% of adverse cardiovascular events, including foremost myocardial infarction and cerebrovascular disease (42). A recent
meta-analysis of observational studies in >270,000 individuals further linked *Helicobacter pylori* infection to an increased risk of stroke (43). The latest meta-analysis of cohort studies on *Helicobacter pylori* infection and the risk of cardiovascular disease including 230,288 patients found only a mild increase of cardiovascular risk (relative risk 1.10, 95% CI 1.03, 1.18), much smaller than previous meta-analyses and our data and no significant association with the risk of stroke (7). The cardiovascular risk, even if limited, has significant impact on public health and might become evident because *Helicobacter pylori*, especially CagA-positive strains, may contribute synergistically with a high-fat diet to the development of atherosclerosis and cardiovascular disease through chronic inflammatory and immunological processes (44–46). In addition, a correlation of *Helicobacter pylori* infection with changes in lipids might contribute to a higher cardiovascular risk (47). In accordance with previous publications (44,48,49), we found a prominent decrease in HDL cholesterol, contributing to dyslipidemia as an important factor for atherosclerosis. Of importance, eradication was successful in restoring HDL levels (50), indicating that eradication could have an inhibitory effect on the onset of cardiovascular disease, although this is yet unknown. We also found a negative association with docosahexaenoic acid, an omega-3 fatty acid that has been found to protect cardiovascular health (51). Bacterial properties enable *Helicobacter pylori* also to directly extract cholesterol from epithelial cells, which may also affect the systemic lipid levels (29,52). This and the atherogenic modification in lipid metabolism may be associated with proinflammatory signaling (53). The proinflammatory signaling may explain the positive correlation with type 2 diabetes mellitus found in the *Helicobacter pylori*-positive cohort and elsewhere (54), which in turn drives further unfavorable effects on cardiovascular disease. While our data provide additional evidence for an increased cardiometabolic risk in individuals infected with *Helicobacter pylori*, less biased studies as randomized controlled trials are needed for definite conclusion on this association. Further prospective studies should also address whether eradication prevents the development of atherosclerosis and its complications to clarify the role of this bacterium in cardiovascular pathology.

The potential involvement of *Helicobacter pylori* infection in respiratory diseases is still under debate. We found a positive association for 7 respiratory disorders such as postinflammatory pulmonary fibrosis, and COPD. A recent review summarized predominantly case-control studies with controversial findings on respiratory diseases concluding that so far in face of missing prospective studies, no clear evidence supports a casual relation between infection and respiratory diseases (55). Still, inflammatory and endothelial changes associated with lung injury have been described in mice (56). Besides proving data on a larger sample size, we, in this study, report data on a significant increase in respiratory-associated mortality in individuals with positive *Helicobacter pylori* serology, which is in line with a previous report in individuals with COPD (57). The association with lung cancer is under debate (58) and was not specifically obvious in our study. Noteworthy, we found a positive association of *Helicobacter pylori* positivity with deaths of individuals with COVID-19 (SARS-CoV-2) infection, although limited by small death rate. Previous data suggested that *Helicobacter pylori*-infected people may be more susceptible to COVID-19, which may be explained by the increased expression of SARS-CoV-2 entry receptors such as angiotensin-converting enzyme 2 in the affected gastric mucosa or elevated gastric pH that no longer inactivates SARS-CoV-2 (59,60). In addition, as found in this study, the *Helicobacter pylori*-associated inflammatory response and cardiocirculatory and respiratory morbidity may promote a risk status for COVID-19. The understanding of gastrointestinal and respiratory disease course in the complex interplay of both highly prevalent human infectious diseases is of emerging interest.

While the PhEwAS analysis is well suited to identify an extensive repertoire of *Helicobacter pylori* positivity–associated conditions, our analysis has some limitations. First, a causal link between diseases and mechanisms cannot be explained. Second, the UKB is not an entirely representative population sample because 94% of subjects are White British and from higher-income classes. Moreover, outcomes based on ICD codes may experience some degree of misclassification or underdiagnosis. We were not able to distinguish active or past *Helicobacter pylori* infection and to analyze the influence of eradication treatment on gastric and extragastric disease because patients were enrolled based on anti-*Helicobacter pylori* antibodies, and data on *Helicobacter pylori* eradication in the past or during follow-up were not available. In summary, our large study of *Helicobacter pylori* positivity demonstrates that it plays an organ- and disease entity-specific role in the development of human disease. However, an association study cannot distinguish between causes and consequences. Although this study design is based on a correlational relationship, our findings might help to provide a framework for patient recommendations.

**CONFLICTS OF INTEREST**

**Guarantor of the article:** Carolin V. Schneider, MD.

**Specific author contributions:** C.V.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. P.K. and C.V.S. analyzed the data. J.W., M.S., and C.V.S. conceptualized and drafted the manuscript. C.V.S. and M.S. supervised the work. All authors agreed to submit the manuscript, read, edited, and approved the final draft.

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**Potential competing interests:** None to report.

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**Study Highlights**

<table>
<thead>
<tr>
<th>WHAT IS KNOWN</th>
<th>WHAT IS NEW HERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>✅ <em>Helicobacter pylori</em> colonizes the human stomach and increases the risk of gastroduodenal ulcer and gastric cancer.</td>
<td>✅ <em>H. pylori</em> positivity is associated with specific cardiovascular, respiratory, and metabolic disorders.</td>
</tr>
<tr>
<td></td>
<td>✅ Multivariate analysis shows no change in overall mortality in <em>H. pylori</em>-positive participants.</td>
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<tr>
<td></td>
<td>✅ Lipidomic analysis reveals dyslipidemic profile in <em>H. pylori</em>-positive participants, which may link <em>H. pylori</em> to systemic inflammation and disease.</td>
</tr>
</tbody>
</table>
REFERENCES


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