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Association of Helicobacter Pylori Positivity with Risk of Disease and Mortality

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Abstract

Background: *Helicobacter pylori* colonizes the human stomach. Infection causes chronic gastritis and increases the risk for 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 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 extra gastric 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 COVID-19 associated mortality increased. Lipidomic analysis for *H. pylori* positive participants revealed a dyslipidemic profile with reduced HDL cholesterol and omega-3 fatty acids, which may represent a causative link between infection, systemic inflammation, and disease.

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

Study highlights

What is known

- H. pylori colonizes the human stomach and increases risk of gastroduodenal ulcer and gastric cancer.

What is new here

- H. pylori positivity is associated with specific cardiovascular, respiratory, and metabolic disorders.
- Multivariate analysis shows no change in overall mortality in H. pylori positive participants.
- Lipidomic analysis reveals dyslipidemic profile in H. pylori positive participants, which may link H. pylori to systemic inflammation and disease.

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Introduction

Helicobacter pylori (H. pylori) is a human pathogen that chronically colonizes the stomach of about the half of the world´s population. Infection with helicobacter usually occurs during childhood and persist for decades. Infection is linked to various gastric disorders. While infection causes a gastritis, it remains asymptomatic in most individuals. However, about 5% of individuals with *H. pylori* develop gastric or duodenal ulcers and about 1% develop gastric cancer, with infection being the most relevant risk factor for both (Amieva & El-Omar, 2008; Chey et al., 2017; Liabeuf et al., 2022).

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 extra gastric diseases. Indeed, several disorders have been linked to *H. pylori* infection and eradication is suggested in individuals with several extra gastric disorders such as unexplained iron deficiency anemia (IDA) and immune thrombocytopenia (ITP). However, results are heterogenous and response to eradication is higher in countries with high *H. pylori* prevalence in the background population. In IDA patients main benefits for eradication are achieved in children in contrast to adults, while for ITP the evidence is less compelling for children and benefits are achieved in adults (Chey et al., 2017; Hudak et al., 2017; Malfertheiner et al., 2022). An association with cardiovascular diseases has also been suggested previously, although the strength of this association is controversial and a definite mechanistic explanation is missing (Liu et al., 2015; Sun et al., 2023)

Using the well characterized, community-based 'UK Biobank' (UKB) that comprises a large dataset of directly measured anti-Helicobacter pylori antibodies in serum samples consisting of more than 9.000 participants, we analyzed overall as well as disease-specific morbidity in a country with rather medium prevalence of *H. pylori* up to 40% ("National Institute for Health and Care Excellence: Guidelines," 2014). To this end, we explored the association between *H. pylori* positivity at baseline and 457 PheCodes, available in the dataset over the threshold of 5 observation per PheCode. This approach demonstrates that *H. pylori* positivity predisposes to specific organ dysfunctions including well-established gastric diseases, anemia as well as various cardiovascular and respiratory disorders. As cardiometabolic diseases were among the strongest associations with *H. pylori* positivity, we analyzed 143 metabolites measured at the same time as the *H. pylori* test was performed and analyzed their association with *H. pylori* positivity, mortality, and morbidity. *H. pylori* positivity was associated with lower levels of sphingomyelins, total esterified cholesterol, docosahexaenoic acid, large and very large HDL as well as smaller average HDL diameter.

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Methods

Study cohort

The 'UK Biobank' (UKB) is a community-based cohort study conducted in the United Kingdom at 22 participating centers. The baseline examinations were carried out from 2006 to 2010 and recruited 502.505 volunteers aged 37 to 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 ICD-10 and 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 (I00–I99), respiratory diseases (J00–J99), non-malignant digestive diseases (K00–K93) as well as COVID-19 (U0). This research has been conducted using the UKB Resource under Application Number 71300.

Case definition

In a subset of UKB participants sero-positivity status of 20 pathogens were measured in a pilot study using Multiplex Serology

(Waterboer et al., 2005; Waterboer et al., 2006). *H. pylori* positivity is defined as two or more positive antibodies against the following antigens (with the following cut-off values): antigen VacA > 100, antigen OMP > 170, antigen GroEL > 80, antigen Catalase > 180, antigen UreA > 130 (UKB datafield 23074). The descriptive statistics of this cohort can be found in Suppl. Table 1.

Propensity Score Matching

Propensity-score matching was applied using the *PsmPy* (0.3.13, (Kline & Luo, 2022)) python package (python ≥3.7). After logistic-regression based propensity score with k-nearest neighbors (k-NN) allocation, two 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 Table 2. The propensity score was estimated using age, sex, BMI, ethnic background, and socioeconomic status (Townsend deprivation index) at baseline as predictive covariates in the regression. In total 8898 cases were enrolled in further regressions (Suppl. Figure 1).

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PheWAS analysis

We performed a phenome-wide association study (PheWAS). The coding for clinical diagnoses in our data set followed the WHO's International Classification of Diseases (ICD) 10th and 9th generation (ICD-10 and ICD-9) coding systems. The ICD is a list of codes for diseases, symptoms, findings, and injuries. The majority of the world´s health expenditures are allocated with ICD (Beck & Margolin, 2007). For each study subject, ICD-codes from the electronic health records (EHR) diagnoses throughout the study period were collated and duplicates removed. We converted the ICD-codes of the 8898 enrolled participants into 457 associated PheCodes using the pyPheWAS package (Kerley et al., 2022). 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 (Bastarache, 2021). 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, one for every PheCode of interest. The influence of the analyzed PheCode was than 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 (Kerley et al., 2022). We analyzed PheCodes from the following 7 disease groups:

- digestive
- respiratory
- neoplasms
- infections
- circulatory
- hematopoietic
- endocrine/metabolic

In total 457 PheCodes were analyzed (Suppl. Table 2).

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Metabolomics

To further dissect the metabolic effects of *H. pylori* positivity, we analyzed 143 metabolites that were measured via nuclear magnetic resonance (NMR) spectroscopy, in a subset of 1.436 *H. pylori* negative participants and 677 *H. pylori* positive participants (Suppl. Table 3). Details on measurements via NMR can be accessed here: https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/nmrm_companion_doc.pdf.

Statistical analysis

All continuous variables were analyzed by unpaired, two-tailed t-tests or Mann-Whitney U test, and by an appropriate multivariable model. The results are presented as mean ± standard deviation (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-square test. Odds/hazard ratios (ORs/HRs) were presented with their corresponding 95% confidence intervals (CI) 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 (Carroll et al., 2014). Differences were statistically significant when $p < 0.05$. For PheWAS analyses a fdr-adjusted significance level of $p \leq 0.0038$ was calculated using the implemented FDR correction for multiple testing. The 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, USA).

Results

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

We compared routine serum parameters between *H. pylori* 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 IGF-1 (21.0 vs 21.6 nmol/L) compared to

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controls. Helicobacter-positive individuals also had higher levels of SHBG (51.9 vs 51.7 nmol/L), and alkaline phosphatase (85.7 vs 83.7 U/L) compared to controls (Table 1).

To obtain insight into conditions associated with *H. pylori* positivity, we carried out a multi/mass-monovariate PheWAS analysis. Out of 457 selected PheCodes, 25 were significantly over- and 2 were underrepresented in *H. pylori* positive subjects (Figure 1-2, Suppl. Table 2). 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”, as well as “gastric cancer“. Moreover, there was a strong positive association with iron deficiency anemia, which confirmed previous data (Muhsen & Cohen, 2008; Qu et al., 2010). In addition, various other diseases showed a significant correlation. Out of the 25 most overrepresented disorders 11 belonged to circulatory diseases, including congestive heart failure, cardiomegaly, angina pectoris, essential hypertension, hypotension, myocardial infraction and 7 respiratory disorders such as post-inflammatory pulmonary fibrosis and chronic obstructive pulmonary disease (COPD) (Figure 2, Suppl. Table 2). The underrepresented PheCodes included “benign neoplasm of other parts of digestive system” and “Ulcer of esophagus” (Figure 2).

Next, we analyzed if increased morbidity in *H. pylori* positive individuals is also linked to increased mortality (Table 2). During the mean follow-up of 13.6 years 263 of the *H. pylori* positive participants (8.8%) and 432 (7.2%, Table 2) 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; Suppl. Figure 2), which did not stay significant after adjustment for age, sex, BMI, ethnicity, and socioeconomic status (multivariate p-value 0.4, Table 2). However, *H. pylori* positivity was associated with a significant increase in respiratory associated mortality (HR 2.16; 95%CI (1.48-2.84), Table 2) as well as increased death of COVID-19 (HR 3.53; 95%CI (2.49-4.58).

Lastly, 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 as well as smaller average HDL diameter (Figure 3).

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	H. pylori positive (n = 2966)		controls (n = 5932)		
	Mean	**SD**	**Mean**	**SD**	**multivariable p**
BMI (kg/m^2)	27,4	4,8	27,8	4,9	
AGE (years)	57,0	7,9	57,3	8,2	
SEX (n, %women)	1483	50	2966	50	
Townsend deprivation index	-1,7	2,9	-0,7	3,4	
Ethnicity (n, % white)	2652	89,4	5717	96,4	
Serum Metabolites					
Total protein (g/L)	73,1	4,4	72,4	4,1	**2,3E-08**
Cholesterol (mmol/L)	5,6	1,2	5,8	1,2	**0,0009**
IGF-1 (nmol/L)	21,0	6,0	21,6	5,9	**0,004**
SHBG (nmol/L)	51,9	27,2	51,7	27,4	**0,008**
Alkaline phosphatase (U/L)	85,7	28,4	83,7	24,9	**0,023**
Vitamin D (nmol/L)	45,5	21,1	46,2	20,2	0,09
Albumin (g/L)	45,1	2,6	45,3	2,5	0,13
Alanine aminotransferase (U/L)	23,6	12,9	23,6	13,6	0,16
Glucose (mmol/L)	5,1	1,1	5,1	1,1	0,21
Total bilirubin (umol/L)	9,0	4,3	9,1	4,7	0,24
C-reactive protein (mg/L)	2,7	3,9	2,6	4,6	0,31
HbA1c (mmol/mol)	36,6	6,7	35,9	6,3	0,31
Creatinine (umol/L)	73,2	17,3	72,8	21,5	0,38
Aspartate aminotransferase(U/L)	26,6	11,1	26,1	9,5	0,45
Urate (umol/L)	314,3	82,1	310,0	80,0	0,51
Gamma-glutamyltransferase (U/L)	38,9	48,1	37,6	43,5	0,63
Direct bilirubin (umol/L)	1,9	0,8	1,8	0,8	0,80
Urea (mmol/L)	5,5	1,4	5,5	1,5	0,93

Table 1: Comparison of baseline characteristics and serum parameters in H. pylori positive individuals vs. controls. Quantitative measures are expressed as mean with standard deviation 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. Abbreviations: BMI, body mass index.

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	H. pylori positive (n = 2966)		controls (n = 5932)					
	n	**%**	**n**	**%**	**p**	**OR**	**CI**	
Mortality (ICD10 code)	263	8,87	432	7,28	0,39	1,07	0,91	1,23
Neoplasms (C)	136	4,59	240	4,05	0,84	1,02	0,81	1,24
Neurological diseases (G)	14	0,47	20	0,34	0,37	1,36	0,68	2,05
Cardiovascular diseases (I)	52	1,75	91	1,53	0,83	0,96	0,62	1,30
Respiratory diseases (J)	17	0,57	15	0,25	**0,026**	**2,16**	**1,48**	**2,84**
Digestive diseases (K)	8	0,27	20	0,34	0,25	0,60	0,29	1,48
COVID-19 (U0)	12	0,4	5	0,08	**0,018**	**3,53**	**2,49**	**4,58**

Table 2: Mortality analyses after a mean follow up of 13.6 years, corrected for age, sex, BMI and socioeconomic status. 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.

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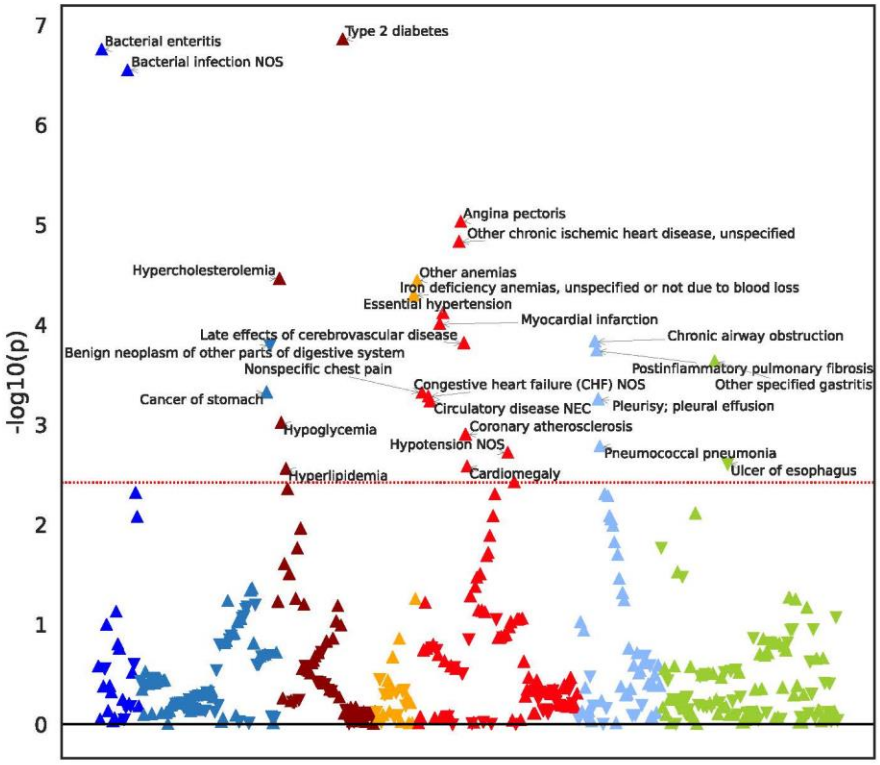
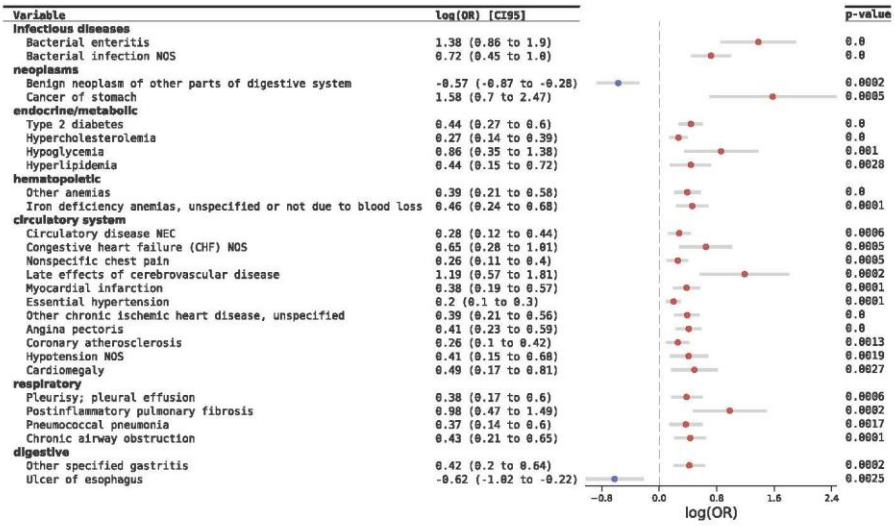
Figure 1: Manhattan plot of sex, age, BMI, ethnic background, and socioeconomic status (Townsend deprivation index) adjusted −log10 (*P*-values) for all selected PheCodes comparing their occurrence in *H. pylori* positive individuals vs. controls.



Highlighted are associations with p-values < 0.05 (corrected for multiple testing by fdr to the threshold *(dotted line)* 0.0038). Upwards/downwards pointing triangular markers refer to PheCodes, that are over- or underrepresented, respectively in *H. pylori* positive individuals compared to controls.

Figure 2: The 27 most over-/under-represented PheCodes in individuals with *Helicobacter pylori*, adjusted for age, sex, BMI, ethnic background, and socioeconomic status.



Odds ratios (ORs) are given as log (OR) and 95% confidence intervals (Cis). Only PheCodes that remained significant after adjustment for multiple testing are displayed and have thereby a (p-value of ≤0.0038).

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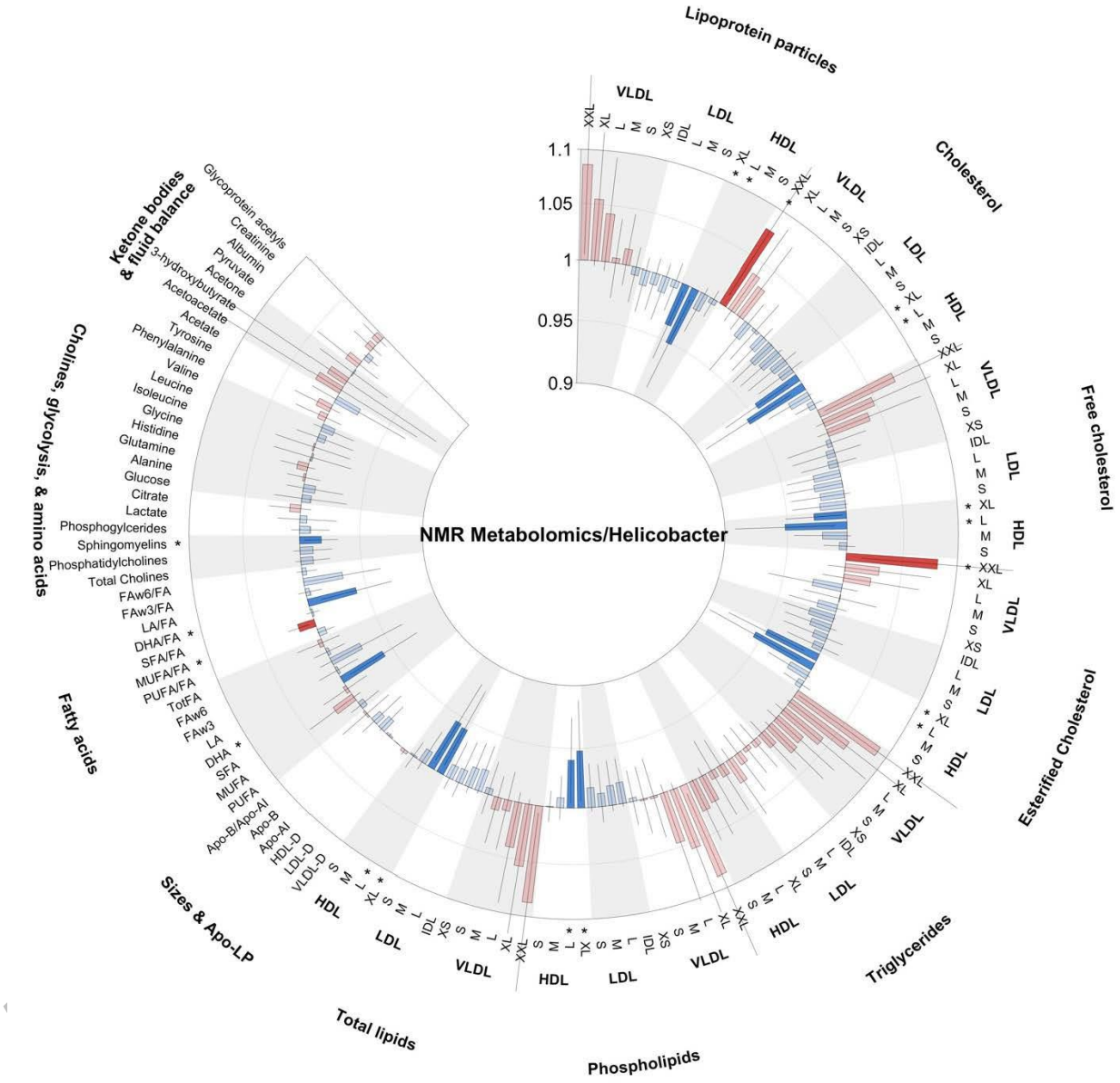
Figure 3: Circle plot for lipidomic analysis for *Helicobacter pylori* positive UKB participants compared to controls.



Lipidomic parameters were measured via nuclear magnetic resonance spectroscopy (NMR). Hazard ratios (with 95% confidence intervals) are presented per 1-SD higher metabolic biomarker on the natural log scale, stratified by age, sex, BMI, and Townsend deprivation index. * p<0.05. DHA, docosahexaenoic acid; FA, fatty acids; FAw3, omega-3 fatty acids; FAw6, omega-6 fatty acids; HDL-D, high-density lipoprotein particle diameter; LA, linoleic acid; LDL, low-density lipoproteins; LDL-D, low-density lipoprotein particle diameter; LP, lipoprotein; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; VLDL-D, very low-density lipoprotein particle diameter; (original code by Diego J Aguilar-Ramirez).

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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 development of cardiovascular, digestive, and metabolic disease. 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 is based on bacterial lifelong persistence in the human gastric mucosa of approximately 50% of the world´s population (Bauer & Meyer, 2011; Katelaris et al., 2023; Salama et al., 2013; Sigal et al., 2015). 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 (Howitt et al., 2011; Johnson & Ottemann, 2018; Sigal et al., 2015). 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 (Morey et al., 2018; Pfannkuch et al., 2019; Sigal et al., 2017; Sigal et al., 2019; Sigal et al., 2015; Wizenty et al., 2022; Zimmermann et al., 2017). In addition to being linked to gastritis and gastroduodenal ulcers, our data confirm an association between *H. pylori* positivity and iron deficiency anemia. Experimental data from mice studies revealed that CagA+ *H. pylori* acquire iron from host cells via transfer of transferrin receptors from the basolateral membrane to the apical surface where the bacteria locate (Tan et al., 2011). This and gastric hypochlorhydria in chronic gastritis which interferes with iron reduction and absorption may affect the systemic iron level leading to anemia (Betesh et al., 2015). Notably, iron deficiency has been associated with accelerated premalignant and malignant gastric lesions in mice and humans (Noto et al., 2013). The link between infection and non-cardia gastric cancer has been demonstrated in various studies and *H. pylori* is considered a WHO type I carcinogen (Amieva & El-Omar, 2008). 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 (Fock & Ang, 2010). While large cohort studies from the United States have also demonstrated this association (Parsonnet et al., 1991; Talley et al., 1991), there is still a debate on whether this applies to European countries as the reduction for *H. pylori*

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is larger than the reduction in gastric cancer from 1993 to 2007 (Roberts et al., 2016). Still most patients with non-cardia gastric cancer were tested *H. pylori* positive in a European case-control study and two studies in the Swedish population reported a high association of *H. pylori* seropositivity with non-cardia gastric cancer (González et al., 2012; Persson et al., 2011; Simán et al., 2007). Our data now clearly demonstrate an association between *H. pylori* positivity and gastric cancer in the UK, together supporting the critical role of *H. pylori* for this disorder also in Europe. Heterogeneity of the strength of the association with gastric cancer may be explained by the not yet routinely analyzed genetic risk status of infected individuals (Usui et al., 2023). Whether *H. pylori* infection is associated with other extra-gastric cancers remains controversial. We found no clear association with extra-gastric cancers.

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] (Liu et al., 2015). Second an increased risk for acute coronary syndrome, OR: 2.03 [CI: 1.66–2.47] (Fang et al., 2019) and third an increased risk by 51% of adverse cardiovascular events, including foremost myocardial infarction and cerebrovascular disease (Wang et al., 2020). A recent meta-analysis of observational studies in > 270.000 individuals further linked *H. pylori* infection to an increased risk for stroke (Doheim et al., 2021). The latest meta-analysis of cohort studies on *H. pylori* infection and the risk of cardiovascular disease including 230.288 patients found only a mild increase of cardiovascular risk (RR 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 (Sun et al., 2023). The cardiovascular risk, even if limited, has significant impact on public health and might become evident as *H. pylori,* especially CagA-positive strains may contribute synergistically with a high-fat diet to the development of atherosclerosis and cardiovascular disease via chronic inflammatory and immunological processes (Krupa et al., 2021; Martínez Torres & Martínez Gaensly, 2002; Sharma & Aggarwal, 2015). In addition, a correlation of *H. pylori* infection with changes in lipids, might contribute to a higher cardiovascular risk (Rader & Hovingh, 2014). In accordance with previous publications (Adachi et al., 2018; Kim et al., 2016; Martínez Torres & Martínez Gaensly, 2002), we found a prominent decrease in HDL cholesterol, contributing to dyslipidemia as important factor for atherosclerosis. Importantly, eradication was successful in restoring HDL levels (Scharnagl et al., 2004), indicating that eradication could have an inhibitory effect on onset of cardiovascular disease, although this is yet unknown. We also found a

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negative association with docosahexaenoic acid, an omega-3 fatty acid that has been found to protect cardiovascular health (Khan et al., 2021). Bacterial properties enable *H. pylori* also to directly extract cholesterol from epithelial cells, which may also affect the systemic lipid levels (Morey et al., 2018; Wunder et al., 2006). This and the atherogenic modification in lipid metabolism may be associated with pro-inflammatory signaling (Chen et al., 2019). The pro-inflammatory signaling may explain the positive correlation with Type 2 diabetes mellitus found in the *H. pylori* positive cohort here and elsewhere (Mansori et al., 2020), 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 *H. 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 *H. pylori* infection in respiratory diseases is still under debate. We found a positive association for 7 respiratory disorders such as post-inflammatory 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 (Durazzo et al., 2021). Still inflammatory and endothelial changes associated with lung injury have been described in mice (Arismendi Sosa et al., 2018). Besides proving data on a larger sample size, we here report data on a significant increase in respiratory associated mortality in individuals with positive *H. pylori* serology, which is in line with a previous report in COPD individuals (Sze et al., 2015). The association with lung cancer is under debate (Yoon et al., 2022) and was not specifically obvious in our study. Noteworthy, we found a positive association of *H. pylori* positivity with deaths of individuals with COVID-19 (SARS-CoV-2) infection, although limited by small death rate. Previous data suggested that *H. 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 ACE in the affected gastric mucosa or elevated gastric pH that no longer inactivates SARS-CoV-2 (Gonzalez et al., 2022; Heuberger et al., 2021). In addition, as found here, the *H. pylori* associated inflammatory response as well as 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.

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While the PheWAS analysis is well suited to identify an extensive repertoire of *H. 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, as 94% of subjects are White British and from higher-income classes. Moreover, outcomes based on ICD codes may suffer from some degree of misclassification or underdiagnosis. We were not able to distinguish active or past *H. pylori* infection and to analyze the influence of eradication treatment on gastric and extra-gastric disease, as patients were enrolled based on anti-*H. pylori* antibodies and data on *H. pylori* eradication in the past or during follow-up were not available. In summary, our large study of *H. 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 upon a correlational relationship, our findings might help to provide a framework for patient recommendations.

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