Microb Health Dis 2023; 5: e908

REVIEW: *HELICOBACTER PYLORI* AND EXTRAGASTRIC DISEASES

L.E. Del Vecchio[1,2,3], S. Bibbò[1,2,3], S. Porcari[1,2,3], G. Cammarota[1,2,3], G. Ianiro[1,2,3]

[1]Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome, Italy
[2]Department of Medical and Surgical Sciences, UOC Gastroenterologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[3]Department of Medical and Surgical Sciences, UOC CEMAD Centro Malattie dell'Apparato Digerente, Medicina Interna e Gastroenterologia, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy

Corresponding Author: Livio Enrico Del Vecchio, MD; e-mail: livioenricodelvecchio@gmail.com

Abstract – Peptic ulcer disease and several gastrointestinal diseases have been directly related to *Helicobacter pylori (H. pylori)* infection. The extraintestinal symptoms of *H. pylori*, as more data suggests, may be linked to disease states in various organ systems. Numerous illnesses from the hematologic, cardiac, metabolic, neurologic, and dermatologic systems are connected to *H. pylori* infection. This article's goal is to give a succinct overview of the latest information supporting or disputing the connections between *H. pylori* and its alleged extraintestinal symptoms.

In the past year, some intriguing new information has emerged on the involvement of *Helicobacter pylori* infection in the emergence of extra-gastric illnesses. Major cardiovascular events, hypertension, atherosclerosis and diabetes have all been linked to *H. pylori*. On the other hand, it was demonstrated that there is a correlation between *H. pylori* and other extra-gastric digestive diseases, such as inflammatory bowel disease, irritable bowel syndrome, coeliac disease, or Barrett's esophagus. Patients with chronic urticaria were shown to have higher *H. pylori* prevalence, indicating that the inflammation brought on by the infection may be the cause of this condition. Different correlations have been found with neurological disorders and with other systemic disorders (thyroid disease, osteoporosis, thrombocytopenia, anemia, asthma, systemic sclerosis, pre-eclampsia and erectile dysfunction).

Keywords: *Helicobacter pylori*, Atherosclerosis, Coronary feart disease, Esophageal disorders, cancer, Non-alcoholic-fatty liver disease, Diabetes, Parkinson's disease, Alzheimer's disease.

INTRODUCTION

Helicobacter pylori infection (HPI) may be associated with various extradigestive manifestations and disorders, biological evidence of the bacterium's pathogenic potential outside the gastrointestinal tract.

In this review article, we provide an overview of the most recent evidence (published in 2022-2023) of extragastric manifestations of HPI in the last year, including cardiometabolic disorders, gastrointestinal (but extragastric) disorders, cancer, neurological disorders, and others.

METABOLIC DISEASES

Obesity

A BMI of 30 kg/m^2 or higher is commonly used to define obesity, a medical condition characterized by excessive body fat. In Europe, where 60% of the population is either overweight or obese, obesity is still a major public health problem, according to the latest 2022 report from WHO[1,2].

The association between obesity and HPI remains controversial. In a meta-analysis[2] based on 15 studies, the estimated Odds Ratio was 1.42 (95% CI; 1.12-1.81, p=0.003), suggesting a possible role of HP in the development of overweight[2].

Evidence suggests that eradicating HP may affect metabolic parameters, including HDL cholesterol levels. One study[3] conducted on 2,267 patients found that the eradication of HP was associated with increased HDL cholesterol levels during a 5-year follow-up period. However, the study may have some limitations, and at one year of follow-up, the male population even recorded an increase in BMI, although not statistically significant (p=0.089)[3].

For patients with a BMI higher than 40 kg/m^2, or a BMI of 35 with obesity-related health conditions (sleep apnea, diabetes, or high blood pressure), a sleeve gastrectomy is frequently performed as a treatment option for obesity. The surgery is generally considered safe and effective for weight loss, with studies showing that patients can lose an average of 50-60% of their excess body weight. In this context, *H. pylori* could influence the post-operative complications[4-6]. Intriguingly, HP infection does not seem to impact post-operative complications, but LSG could reduce the presence of HP. Specifically, a study by Akbulut et al[6] showed that only 62 of 99 patients with preoperative HP were still present on biopsies after LSG ($p < 0.01$).

However, post-operative nausea and vomiting (PONV) was not linked to post-operative HP, according to a study on 656 patients undergoing LSG[7].

Diabetes

Diabetes mellitus is a growing problem worldwide. Currently, the prevalence is estimated at 6,059 cases per 100,000, resulting in over 1,000,000 deaths per year[8].

Contradictory evidence has been published about the association with HP infection. A Chinese cross-sectional study [9] showed that HP had a higher prevalence in participants with type 2 diabetes mellitus compared to healthy controls (26.67 *vs.* 18.11%, p = 0.045), and HP increased the risk of DM (OR 1.77, 95% CI; 1.04-3.00)[9].

Additionally, in people with type 1 diabetes (T1DM), the presence of HP was linked to a higher level of advanced glycation end products (AGEs), a sign of chronic complications building up in the skin[10].

Atherosclerosis

Atherosclerosis is a chronic disease of the arteries characterized by the buildup of plaques, which are fatty deposits of cholesterol, calcium, and other substances. While some research suggests a possible link between HPI and atherosclerosis, the evidence is not yet conclusive[11].

In the Iranian population, a meta-analysis[12] of 12 studies found a positive correlation between HPI and the risk of atherosclerosis (OR 1.44; 95% CI; 1.07-1.95).

Similarly, a European multicentre retrospective study[13] showed HP as an independent positive factor associated with carotid plaques (OR 2.15, 95% CI 1.14-4.09) after adjusting for potential confounders, such as BMI, age, cigarette smoking, sex, dyslipidemia, and diabetes.

The development of atherosclerosis, a condition marked by the accumulation of fatty plaques in the arteries, is significantly influenced by lipids. In 174 dyspeptic HP seropositive patients[13], dyslipidemia was 68.39%. After adjusting for confounders, the authors found an Odd Ratio of 0.555 (95% CI 0.318-0.967, p=0.038), suggesting a role of HP in determining dyslipidemia, i.e., the presence of increased low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, and high triglycerides[13].

Hypertension

Hypertension has been strongly associated with chronic inflammation caused by autoimmune processes or infections.

HP shows the most remarkable association among the hypothesized infections as risk factors. A meta-analysis[14] involving 11,317 patients with hypertension demonstrated that HP was linked to a 13.4% increased risk (95% CI:11-16.3%, $p = 0.002$)[14].

In addition, further analysis[15] conducted on 55 studies found a significant increase in systolic blood pressure (SBP) compared to diastolic blood pressure (DBP). Specifically, HP impacted more on the SBP (WMD: 186, 95% CI: 1.21-2.50) than on the DBP (WMD: 1.12, 95% CI: 0.81-1.43)[15].

Coronary Heart Disease

Cardiovascular diseases (CVD) represent one of the major problems for healthcare systems. A growing number of studies support the link between HP and CVD[16].

According to a meta-analysis by Tong et al[17], the presence of anti-HP antibodies was associated with a higher presence of Coronary Heart Disease (CHD) (OR, 1.58; 95% CI: 1.34-1.87) and, similarly, positive HP stool antigen almost quadrupled the risk of CHD (OR: 3.50, 95% CI: 1.60-7.66)[17].

Gonciarz et al[18] suggested a hypothesis to explain this association. By testing serum from HP seropositive patients with CHD, they discovered the presence of particular antibodies against bacterial components. These antibodies also target an amino acid sequence of tumor necrosis factor receptor (TNFR), suggesting molecular mimicry mechanisms able to activate inflammatory cascade[18].

In addition, another study[19] found higher HP seropositivity in people with premature coronary artery disease (pCAD) compared to controls (87.7 *vs.* 63.1%, $p = 7 \times 10\text{-}23$). This significant association (OR = 2.729, $p = 1.0 \times 10\text{-}6$) could be fundamental to developing pCAD in highly susceptible patients with rs13420827G allele[19].

Cardiovascular (CV) risk and HPI were also assessed in a cohort of 3,284 asymptomatic patients[20]. Calculating SCORE2 to assess 10-year CV risk, the researchers discovered a critical association with HP (aOR 1.03 95% CI 1.01-1.05; $p = .02$), but no evidence of dissimilar all-cause and CV mortality (HR 1.20 95% CI 0.77-1.87; $p = .43$ and HR 0.60 95% CI 0.14-2.63; $p = .50$ respectively)[20].

However, the eradication of HP was seen to impact the presence of CHD. Specifically, the eradication helped to prevent CHD in males ≤65 years (HR 0.133, 95% CI: 0.039-0.455, $p = .001$) and in females aged >65 years (HR 0.260, 95% CI: 0.110-0.615, $p = .002$)[20].

Atrial Fibrillation

Atrial fibrillation (AF) is a form of abnormal heartbeat or arrhythmia that affects the upper chambers of the heart. Some studies[21] have investigated the potential link between *H. pylori* infection and AF, suggesting that HPI eradication may improve symptoms and reduce the risk of AF[21].

A recent Israeli study[22] on 180 patients found a statistically significant association between HP and AF ($p<0.001$). Furthermore, the association between HP and AF resulted in higher levels of C-reactive protein (CRP), compared to patients with HP but without AF ($p<0.001$)[22].

EXTRA-GASTRIC DIGESTIVE AND LIVER DISORDERS

Esophageal Disorders

In the last year, several studies evaluated the relationship between HPI and oesophageal disorders. We summarized them in Table 1.

While some research suggests a possible negative link between HPI and reflux esophagitis, gastroesophageal reflux disease, and Barrett's esophagus, conversely, an unclear relationship has been highlighted between HP and esophageal squamous cell carcinoma.

TABLE 1. RECENT STUDIES ON THE ASSOCIATION BETWEEN ESOPHAGEAL DISORDERS AND *HELICOBACTER PYLORI*.

Disease	Study design	Number of patients	Principal findings	Doi
Motility				
GERD	Cross-sectional study	1916 (874 with GERD, 442 with HPI)	No association between GERD and active HPI ($p = 0.214$).	10.1186/s12879-022-07278-6[23]
GERD	Retrospective study	1226 (752 with GERD in 24h pH monitoring)	No association between GERD or LES laxity, and active HPI.	10.14744/SEMB.2022.55476[24]
GERD	Prospective study	68 with GERD and HP	After the eradication: -lower DCI (610.40 vs. 444.90) -higher IEM (36.00 vs. 60.00) - higher number of reflux episodes during 24-hour esophageal monitoring ($p < 0.05$) -higher GerdQ ($p < 0.05$)	10.3389/fcimb.2023.1082620[25]
Inflammatory lesions				
RE	Retrospective study	3741 (359 with RE)	Inverse relation between RE and active HPI with gastric inflammation (OR 0.754, 95% CI, 0.600-0.949; p =0.016], No association between RE and HP seropositive ($p = 0.281$).	10.3760/cma.j.cn11 2138-20220214-00107[26]
EoE	Prospective study	190 (38 with EoE)	Inverse association between EoE and HPI (OR 0.21, 95% CI, 0.08-0.69; $p = 0.001$)	10.1016/j.gastrohep.2023.03.002[27]
Cancer and precancerous lesions				
BE	Case-control study	594 (169 with BE)	In men positive association between BE and HP seronegative (OR 2.28, 95 % CI, 1.27-4.12)	10.1158/1055-9965.EPI-22-0234[28]
BE	Meta-analysis	1354369 from 24 studies	Inverse relation between BE and active HPI (OR 0.53, 95% CI, 0.45-0.64; $p < 0.001$) and active CagA neg strains (OR 0.25, 95% CI, 0.15-0.44; $p < 0.000$).	10.1177/20406223221117971[29]
EPL for ESCC	Case-control study	400 (200 with EPL)	Inverse relation between EPL and HP seropositive (OR 0.32, 95% CI, 0.11-0.95)	10.4251/wjgo.v14.i9.1689[30]
ESCC	Case-control study	213 (105 with ESCC)	Positive association between ESCC and HPI in esophageal biopsies (OR 2.76, 95% CI, 3.11-10.48; $p < 0.001$)	10.31557/APJCP.2023.24.3.1073[31]

GERD: Gastroesophageal reflux disease; HPI: *Helicobacter pylori* infection; LES: lower esophageal sphincter; DCI: distal contractile integral; IEM: inefficient esophageal motility; GerdQ: Gastroesophageal Reflux Disease Questionnaire; OR: Odd Ratio; CI: confidence interval; RE: reflux esophagitis; EoE: eosinophilic esophagitis; BE: Barrett's esophagus; CagA: Cytotoxin-associated Gene A; EPL: esophageal precancerous lesions; ESCC: esophageal squamous cell carcinoma.

Celiac Disease

Celiac disease is a gluten-related autoimmune disorder that affects the small intestine. A bacterial infection does not cause it, but studies have suggested a possible link between coeliac disease and HP[32].

A meta-analysis by Yue et al [33] showed a statistically inverse association between HPI and celiac disease (OR = 0.57, 95% CI [0.44, 0.75]), but no clear causality has emerged yet[33].

Whipple's Disease

Whipple's disease represents a rare bacterial infection that primarily affects the small intestine, but also other organs, such as the brain, heart, and eyes, may be involved. It is caused by a bacterium called *Tropheryma whipplei*[34].

HP could be a differential diagnosis in these cases, and frequently it has a higher prevalence among patients with Whipple's disease, as demonstrated by Scalvini et al[35] in a retrospective study of 34 patients.

Inflammatory Bowel Disease

The complete pathogenesis of inflammatory bowel disease (IBD) is still unknown, but it is thought to result from a complex interplay of genetic, environmental, and immune system factors[36].

Although a prospective observation Egyptian study[37] failed to associate IBD flares and symptoms with HPI, a subsequent study[38] found a relation between colonic HP and ulcerative colitis (UC). Specifically, the presence of HP in colonic biopsies was linked to higher serum levels of pro-inflammatory cytokine IL-17, lower levels of anti-inflammatory cytokine IL-10, and higher clinical activity of this disease[37,38].

Conversely, patients with T2DM who received HP eradication because of peptic ulcer disease showed an increased prevalence of IBD (5.60% *vs.* 3.25%; $p<0.0001$), resulting in a controversial relation between IBD and this bacterium[39].

Irritable Bowel Syndrome

Dysbiosis, food intolerance, low-grade inflammation, and abnormal brain-gut interaction have also been implicated in the pathogenesis of IBS. These infections are usually caused by certain bacteria, viruses, or parasites that can affect the gut, such as HP[40].

A meta-analysis[41] with 13,173 participants discovered that HPI was associated with IBS (adjusted OR 1.29, 95% CI, 1.03,1.62; $p = 0.03$), and this relation even grew up for IBS with diarrhea-predominant subtype (OR: 1.54; 95% CI, 1.22,1.95; $p = 0.0003$). Moreover, the authors also found a positive relation with CagA positive HP without reaching statistical significance (4.3, 95% CI, 0.51-36.17; $p = 0.18$), suggesting a role of these strains in developing IBS[41].

A recent study [42] confirmed that the OR between HPI and IBS was 2.53 (95% IC, 1.02-6.29), with no significant difference in BMI, occupation, gender or age[42].

Non-Alcoholic Fatty Liver Disease

The relationship between HP infection and non-alcoholic fatty liver disease (NAFLD) remains controversial[43,44]. Bidirectional Mendelian randomization (MR) study[44] used genome-wide association (GWAS) data to define the mutual relation between HPI and NAFLD[44,43]. After analyzing lipid profiles, they found no significant relation (p=0.759, 0.308, 0.543), excluding HPI as a risk factor for NAFLD[44].

Inversely, a meta-analysis involving 10,7306 patients recorded a significative association both for non-Asian (OR = 1.42, 95% CI, 1.04-1.94; p=0.03) and Asian participants (OR = 1.30, 95% CI, 1.13-1.49; $p < 0.01$)[43].

NAFLD is a disorder in which fat builds up in the liver, causing inflammation and tissue damage over time. Elastography is a sort of ultrasound imaging that aids in the detection and degree of liver fibrosis[45].

Filho et al[46] found that HP patients showed more severe steatosis (p=0.015), suggesting HP as an independent factor for NAFLD and steatosis (OR 4.36, 95% CI,1.09-14.78; p=0.037)[46].

Similarly, severe (OR = 1.71, 95% CI, 1.30-2.24; $p < 0.001$) and moderate (OR = 1.67, 95% CI, 1.17-2.39; $p = 0.005$) liver steatosis were more frequently linked to HPI[47].

Furthermore, [48]AFLD could evolve in non-alcoholic steatohepatitis (NASH), characterized by liver injury, higher Fibrosis-4 (FIB-4), and increased levels of aspartate aminotransferase (AST). In this context, HP could be a significant risk factor for NASH and for early liver injury (OR FIB-4, 1.145, $p = 0.032$; OR AST, 1.33, $p = 0.034$), suggesting that HP infection should be considered in case of early liver injury to prevent the damage progression[49].

Cirrhosis

The last stage of liver damage is cirrhosis, and in the last year, some studies have tried to associate the presence of HPI with the common complication of cirrhosis[50].

For instance, a study by Alarfaj et al[51] showed that portal hypertensive gastropathy (PHG) was worse in patients with concomitant HP infection ($p < 0.001$), and vice-versa, HP had a higher prevalence among patients with more severe PHG. The authors also found a significant decrease in PHG severity after eradication therapy[51], but these results were not confirmed by further studies conducted on the Pakistani population[52].

Interestingly, Indian research[53] showed that HP could be protective against variceal rebleeding. Specifically, considering 190 participants, the presence of active HPI was associated with a lower risk of rebleeding (adjusted risk AR 0.682), and this risk could be correlated to higher levels of gastric acid output[53].

CANCERS

Pancreatic Cancer

Pancreatic cancer (PC) is a deadly malignant tumor that is the fourth most prominent cause of cancer death in the United States and Europe. PC kills about 50,000 individuals in North America alone each year[54].

Although precedent studies seemed to confirm a correlation between HPI and PC, a growing number of studies are finding controversial results. Specifically, a retrospective case-control study[55] did not record any significative association between HPI and patients with PC compared to healthy controls (76.5% *vs.* 78.6%, p=0.76)[55]. Likewise, a meta-analysis[56] of 20 studies failed to associate HPI and PC (OR 1.20, 95% CI = 0.95-1.51, $p = 0.13$), with no significative difference in association with CagA + strains or VacA + strains[56].

Similarly, CagA + HP seropositive patients did not show a cumulative risk of PC (OR 0.83, 95% CI 0.65-1.06), according to data from 5 prospective U.S. cohorts[57].

Colorectal Cancer

Colorectal cancer (CRC) is a complex neoplasia influenced by various genetic, lifestyle, and environmental factors[58]. Recently, the role of the gut microbiota in CRC has gained considerable attention. One of the most well-studied associations between the gut microbiota and CRC involves the bacterium *Fusobacterium nucleatum*, implicated in promoting tumorigenesis through various mechanisms, such as inducing inflammation, promoting tumor cell growth and invasion, and inhibiting the immune response[58].

Similarly, recent research[59-61] has investigated HP's role in CRC and colorectal adenoma. Zhuang et al[59] found that HPI was more prevalent in patients with colorectal adenoma than HP-negative controls (48.59% *vs.* 37.66, p <0.001). Moreover, the analysis of HP enrichment

in colorectal adenomas demonstrated a significative correlation with the lesion dimensions, malignancy, and pathological type (OR 3.536, 2.833, 3.652; $p < 0.001$)[59].

Further study[60] confirmed the association between HPI and colorectal neoplasia (aOR 1.20 1.08-1.32; $p < 0.001$) but without clear association with histological malignancy (aOR 1.26; 0.96-1.64; $p = 0.10$)[60].

In a recent large multicenter U.S. cohort[61], alongside the traditional risk factors, such as smoking or obesity, the researchers found a significative association between a history of HPI and CRC (OR 1.89, 95%CI 1.69-2.10)[61].

Moreover, in East Asian patients[62], HPI seemed to be significantly associated with CRC (OR 1.48, 95% CI: 1.10-1.99), suggesting further study on the role of HP eradication in the prevention programs[62].

Melanoma and Lung Cancer

The relationship between HP infection and lung cancer remains uncertain. Yoon et al[63] found no significant overall association (OR: 1.29; 95% CI: 0.85-1.95), but in the case of VAC+ strains and catalase +, with Odd Ratio 1.64 (95% CI: 1.02-2.62) and 1.75, (95% CI: 1.11-2.77) respectively[63].

In subgroups analysis, among smokers with ≥ 30 pack-years, they recorded different overall Odd Ratio (OR: 1.85; 95% CI: 1.02-3.35), CagA+ (OR: 2.77; 95% CI: 1.35-5.70) and VacA+ (OR: 2.53; 95% CI: 1.25-5.13)[63].

Immunotherapy has shown promising results in treating lung cancer, particularly in patients with advanced or metastatic disease[64].

Similarly, another aggressive immunogenic tumor that seems to benefit massively from the use of checkpoint inhibitors is melanoma[65].

Several studies investigated the aspects linked to better or worse clinical responses to immune checkpoint inhibitors (ICIs). In particular, a study[66] conducted on patients with advanced melanoma treated with ICIs assessed the influence of HP on the outcomes. HP-positive patients showed reduced objective response rate and overall survival ($p = .02$), potentially independent from gut microbiome composition[66].

NEUROLOGICAL DISORDERS

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia, which worsens with time, affecting memory, thinking, and behaviour[67].

According to the last report by Global Burden of Diseases (GBD), an estimated 152 million people worldwide will live with dementia in 2050[68].

Overall, Alzheimer's disease pathogenesis is complicated and multifaceted, comprising a combination of genetic, environmental, and behavioural variables that form beta-amyloid plaques and tau protein aggregates. In this context, recent research[69,70] found that urease, produced by HP, increased the levels of IL-1β, TNF-α, reactive oxygen species (ROS) and phosphorylated tau proteins in cultured neuroblastoma cells[69].

However, in a prospective cohort of 268 patients with dementia, a history of HP was associated with a more significative decrease in Mini-Mental State Examination (MMSE) at two years of follow-up (HR: 2.701; 95% CI: 1.392 to 5.242), suggesting a faster longitudinal cognitive decline[70].

Sleep-Related Movement Disorders

Similarly to AD, Parkinson's disease was frequently associated with HP infection. Recent research investigated the role of HP in the development of sleep-related movement disorders (SRMD)[71].

Enrolling 9,393 patients, Sung et al[72] discovered a strong association between SRMD and HP, with an increased the risk of SRMD (HR 2.18, 95% CI; 1.26-3.82, $p < 0.01$). In subgroups analysis, even more risk was present at 5th year after the initial diagnosis of HPI (HR 3.33, 95% CI; 1.97-5.89, $p < 0.001$) and in patients aged ≥65 years (HR 3.01, 95% CI; 1.90-5.30, $p < 0.001$)[72].

Stroke

Thrombotic stroke is the most common ischemic stroke, caused by the formation of a blood clot within an artery supplying the brain. While HP is not typically associated with thrombotic events, chronic inflammation due to HP could lead to atherosclerosis[73,74].

Although the evidence for a causal relation between *H. pylori* infection and thrombotic events is still limited, some studies have found an increased risk of stroke among people with *H. pylori* infection.

In particular, a meta-analysis by Keikha et al[74] found a significant association between HP infection and ischemic stroke (OR: 1.704; 1.57-1.84 with 95% CIs; $p = 0.01$), probably caused also by the cross-reaction with β2-glycoprotein-I, a protein involved in preventing blood clots[74].

Moreover, while CagA+ strains seem to have an increased association with the risk of CVD compared to Cag- strains (RR 1.58, 95% CI 1.03, 2.41), no clear link was found with the occurrence of stroke (RR 1.08, 95% CI 0.94, 1.23)[75].

MISCELLANEOUS

Thyroid

Various factors, including inflammation and autoimmune disorders, can cause hypothyroidism in children. Thyroiditis can damage the thyroid cells, leading to decreased thyroid hormone production[76].

Inflammation caused by HPI may be implicated in the pathogenesis of autoimmune thyroid disease (ATD). A cross-sectional study of 142 children[77] failed to establish a causative role of HP in the development of ATD. However, a relation between lower T3 serum levels and HPI was found ($p = 0.001$), indicating a possible temporary thyroid impairment by HPI in children with hypothyroidism[78].

In addition, women aged >40 y.o. with HPI had over 2.5 times higher risk of clinical hyperthyroidism (HR 2.85, 95% CI 1.45, 5.61, $p = 0.048$)[77].

This evidence could be explained by the inflammatory stimulus of HP, resulting in an independent factor in thyroid dysfunction in children and adults.

Osteoporosis

Chronic low-grade inflammation, often associated with ageing, can lead to increased bone resorption and decreased bone formation, ultimately resulting in bone loss and osteoporosis[79].

Hence, the hypothesis is that HP could be a risk factor for osteoporosis, but this association remains controversial. Although two retrospective studies conducted on 1,388 and 2,555 patients[80,81] failed to demonstrate this link between HP active infection and bone mineral density, a recent meta-analysis involving 22 studies found different results. Specifically, the odds ratio (OR) between CagA-positive HP infection and the risk of osteoporosis was 1.42 (95% CI, 1.09; 1.85)[80-82].

Thrombocytopenia

Some evidence suggests a possible association between HPI and thrombocytopenia, a medical condition characterized by low platelet count in the blood. Although the exact mechanism by which *H. pylori* infection causes thrombocytopenia is poorly understood, studies have shown that eradicating *H. pylori* infection can improve thrombocytopenia in some patients[83].

A multicenter phase 3 study[84] was conducted to establish the role of HP eradication for patients with moderate immune thrombocytopenia (ITP). After eradication, a significative difference was observed between controls and cases ($p = 0.017$), suggesting a possible future role of HP eradication in this disease[84].

Anemia

HPI has also been associated with an increased risk of anemia, particularly iron-deficiency anemia[85]. A study of 902 children[86] found a higher incidence of iron-deficiency anaemia in the HP group compared to the control group (9.112 *vs.* 4.478; $p < 0.05$), and different factors, such as living in the city, higher family income or higher education background of parents were linked to HP infection[86].

Beyond iron-deficiency anemia, in the paediatric population, HP was also associated with sickle cell anemia (SCA), a condition predisposed to a higher infection rate[87]. A cross-sectional study on 340 SCA children reported an HP infection rate of 49% (CI 95%: 44.1-54.7)[87].

Conversely, in 842 adults with dyspepsia in Cameron[88], the researchers found a prevalence of HP infection of 80.88%. Notably, HP patients were 1.56 times (CI 95% 1.0206-2.3953) at higher risk of having anemia[88].

Returning to the pediatric population, in Eastern Europe[89], iron-deficiency anemia was found only in 14.5% of 542 patients with HP infection, demonstrating a reduced prevalence compared with African countries[89].

Asthma

There is an undetermined association between HP and childhood asthma. A meta-analysis of 18 studies[90] demonstrated an inverse relation (OR 0.68; 95% CI, 0.54-0.87; $p = 0.002$), both for Cag+ strains (OR 0.58; 95% CI, 0.35-0.96; $p = 0.034$) and for CagA – strains (OR 0.52; 95% CI, 0.12-2.28; $p = 0.387$)[90].

Similarly, a Chinese cross-sectional study[91] found that children with asthma HP infections had lower prevalence, compared to healthy children (3.77 *vs.* 7.23% respectively), with OR 1.995 (95% IC; 1.003-3.968; $p < .05$)[91].

HPI may influence the immune system and lead to changes in the balance between two types of immune responses called Th1 and Th2 responses. Th2 responses are associated with allergic and asthmatic responses and tend to be reduced in people with *H. pylori* infection[92]. Hence, the possible protective role of HP in the development of asthma[92].

Systemic Sclerosis

Systemic sclerosis (SSc), commonly known as scleroderma, is a connective-tissue autoimmune disease that affects various organs in the body. Its pathogenesis is complex and involves multiple mechanisms, including immune dysregulation, vascular dysfunction, and fibrosis. Previous studies[93] investigated the possible association between SSc and *H. pylori*.

A recent cross-sectional study on 42 patients with HPI[94] described the effects of HP eradication in variable disease activity. Specifically, after HP eradication, the authors found a significant improvement in terms of disease severity and activity ($p < 0.001$ and $p < 0.01$, respectively), and a significant reduction of C reactive protein (CRP), erythrocyte sedimentation rate (ESR) and a modified Rodnan skin score ($p = 0.001$, < 0.001 and < 0.001, respectively)[94].

Periodontal Disease

Some evidence suggests a relation between periodontal disease and *Helicobacter pylori (H. pylori)* infection. No clear evidence demonstrates that HP could use the oral cavity as a reservoir to infect and re-infect the gastric mucosa, and its presence ranged from 5.4 to 83.3%[95-97].

In children with carious lesions, classified with ICDAS II and DMFT scores, HP was present in 70% of them (95% CI, 46%-88%), with an increased presence in patients with higher severity, playing a role in impairing healthy oral ecosystem and perpetuating the damage[96].

Inversely, no clear association was found between oral cancer and oncogenic HP proteins, such as CagA and VacA, according to a cross-sectional study of 90 participants[97].

Pre-eclampsia

Untreated HPI during pregnancy may increase the risk of complications such as preterm delivery, low birth weight, and gestational diabetes[98].

It is estimated that, in poor-income countries, almost 32.5% of women with nausea and vomiting could be infected with HP[99].

In Ethiopia, a study including 186 controls and 93 cases[100] found a significant link between pre-eclampsia *H. pylori* infection (OR: 2.45; 95% CI: 2.41-4.10), although the study showed several selection biases, such as older age and higher BMI in cases[100].

The link between *H. pylori* and pre-eclampsia requires additional investigation. Chronic inflammation has been implicated in developing pre-eclampsia, and HPI could contribute to this process. HPI causes chronic gastric inflammation, which may spread to other body parts, including the placenta[101].

Erectile Dysfunction

Erectile dysfunction (ED) is the failure to achieve or maintain a satisfactory erection for sexual activity. Many reasons might contribute, including psychological disorders, physical conditions (such as heart disease, diabetes, or high blood pressure), drugs, and lifestyle choices[102].

Intriguingly, in a study by Yagmur et al[103], 30 patients with arteriogenic erectile dysfunction (ED) showed significantly higher levels of Hp-specific antibodies compared to controls (39.7 ± 23.2 *vs.* 21.0 ± 19.8 arbU/ml, $p = .001$), and C-reactive protein (CRP) (0.3 ± 0.2 *vs.* 0.1 ± 0.1 mg/dl, $p = .01$)[103].

A subsequent study[104] found that patients with ED, compared to healthy men, had higher levels of HP-IgG titer and lower levels of B12 (195 *vs.* 338, $p < .001$) and folic acid (4.66 *vs.* 10.31, $p < .001$), suggesting that HP could reduce the absorption of folic acid and B12, which might lead to ED[104].

CONCLUSIONS

The extra-gastric manifestations of HPI and the influence of HPI-related pathogenic pathways, driving extra-gastric diseases, have been deeply evaluated in recent years.

A considerable number of studies released throughout the last year have strengthened this evidence, showing different associations between HPI and extraintestinal diseases.

While some diseases, such as cardiometabolic disorders, liver disorders, asthma, periodontal disease, neurological disorders, thrombocytopenia, systemic sclerosis, and endocrinological and sexual disorders, seem to be positively related to the presence of HP, other diseases, such as celiac disease, esophageal and neoplastic disorders, record a controversial relationship.

In the future, further studies may better elucidate the causal relationships between the presence of HP and various systemic disorders and the molecular mechanisms involved.

Authors' Contributions

Writing-original draft preparation: L.E. Del Vecchio, S. Bibbò, S. Porcari; Supervision and Conceptualization: G. Ianiro and G. Cammarota. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Acknowledgments

The authors thank the Italian Ministry of Health and Fondazione Roma (Italy) for their continuous support of our scientific research.

Conflict of Interest

The authors declare no conflict of interest.

ORCID ID

Livio Enrico Del Vecchio: https://orcid.org/0000-0003-1777-7740
Stefano Bibbò: https://orcid.org/0000-0002-8043-4807
Serena Porcari: https://orcid.org/0000-0003-0085-3954
Gianluca Ianiro: https://orcid.org/0000-0002-8318-0515
Giovanni Cammarota: https://orcid.org/0000-0002-3626-6148

REFERENCES

1 Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 2022; 133: 155217.
2 Kamarehei F, Mohammadi Y. The Effect of Helicobacter pylori Infection on Overweight: A Systematic Review and Meta-Analysis. Iran J Public Health 2022; 51: 2417-2424.
3 Kim S Bin, Kim N, Park J, Hwang I-C, Lim SH, Song DH, Choi Y, Yoon H, Shin CM, Park YS, Lee DH, Ahn S. Preventive effect of Helicobacter pylori eradication on the coronary heart diseases depending on age and sex with a median follow-up of 51 months. Helicobacter 2023; e12969.
4 Heydari MA, Hadavi H, Kouhestani M, Iranpour M. The evaluation of the relationship between Helicobacter pylori infection and frequency of postoperative complications of laparoscopic sleeve gastrectomy in Shahid Bahonar Hospital in Kerman between 2018 and 2020; a cross-sectional study. Ann Med Surg 2022; 76: 103548.
5 Abu Abeid A, Abeid SA, Nizri E, Kuriansky J, Lahat G, Dayan D. The Association of Helicobacter pylori, Eradication, and Early Complications of Laparoscopic Sleeve Gastrectomy. Obes Surg 2022; 32: 1617-1623.
6 Akbulut S, Seyit H, Peker KD, Karabulut M, Alıs H. Is Helicobacter pylori eradication required after laparoscopic sleeve gastrectomy? Wideochir Inne Tech Maloinwazyjne 2022; 17: 705-709.
7 Song Y, Zhu J, Dong Z, Wang C, Xiao J, Yang W. Incidence and risk factors of postoperative nausea and vomiting following laparoscopic sleeve gastrectomy and its relationship with Helicobacter pylori: A propensity score matching analysis. Front Endocrinol 2023; 14: 1102017.
8 Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health 2020; 10: 107-111.
9 Zhou J, Wang X, Liu K, Chen K. Association between Helicobacter pylori infection and the risk of type 2 diabetes mellitus based on a middle-aged and elderly Chinese population. Endocr J 2022; 69: 839-846.
10 Zawada AE, Naskręt D, Piłaciński S, Adamska A, Grzymisławski M, Eder P, Grzelka-Woźniak A, Zozulińska-Ziółkiewicz D, Dobrowolska A. Helicobacter pylori infection is associated with increased accumulation of advanced glycation end products in the skin in patients with type 1 diabetes: A preliminary study. Adv Clin Exp Med 2023; 32: 1009-1016.
11 Xu Z, Li J, Wang H, Xu G. Helicobacter pylori infection and atherosclerosis: is there a causal relationship? Eur J Clin Microbiol Infect Dis 2017; 36: 2293-2301.
12 Keikha M, Karbalaei M. A Comprehensive Survey of the Relationship between Helicobacter pylori Infection and Atherosclerosis in the Iranian Population: A Systematic Review and Meta-analysis. Arch Iran Med 2022; 25: 257-266.
13 Dore MP, Saba PS, Tomassini G, Niolu C, Monaco M, Pes GM. Increased Risk to Develop Hypertension and Carotid Plaques in Patients with Long-Lasting Helicobacter pylori Gastritis. J Clin Med 2022; 11: 2282.
14 Fang Y, Xie H, Fan C. Association of hypertension with helicobacter pylori: A systematic review and metaanalysis. PLoS one 2022; 17.
15 Yue L, Zhang R, Chen S, Duan G. Relationship between Helicobacter pylori and Incident Hypertension as well as Blood Pressure: A Systematic Review and Meta-Analysis. Dig Dis 2023; 41: 124-137.
16 Kucukazman M, Yeniova O, Dal K, Yavuz B. Helicobacter pylori and cardiovascular disease. Eur Rev Med Pharmacol Sci 2015; 19: 3731-3741.
17 Tong L, Wang BB, Li FH, Lv SP, Pan FF, Dong XJ. An Updated Meta-Analysis of the Relationship Between Helicobacter pylori Infection and the Risk of Coronary Heart Disease. Front Cardiovasc Med 2022; 9: 794445.

18 Gonciarz W, Tomaszewska A, Krupa A, Rechciński T, Chałubiński M, Broncel M, Chmiela M. Antibodies towards TVLLPVIFF Amino Acid Sequence of TNF Receptor Induced by Helicobacter pylori in Patients with Coronary Heart Disease. J Clin Med 2022; 11: 2545.
19 Vargas-Alarcón G, Avilés-Jiménez F, Mejía-Sánchez F, Pérez-Hernández N, Cardoso-Saldaña G, Posadas-Sánchez R. Helicobacter pylori infection and DNMT3a polymorphism are associated with the presence of premature coronary artery disease and subclinical atherosclerosis. Data from the GEA Mexican Study. Microb Pathog 2022; 170: 105719.
20 Wernly S, Semmler G, Völkerer A, Flamm M, Aigner E, Niederseer D, Wernly B, Datz C. Helicobacter pylori and cardiovascular risk: Only a dead Helicobacter is a good Helicobacter? Helicobacter 2022; 27: e12928.
21 Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015; 12: 230-243.
22 Farah R, Hanna T, Levin G. Is there a link between atrial fibrillation and Helicobacter pylori infections? Minerva Gastroenterol (Torino) 2023. doi: 10.23736/S2724-5985.23.03323-5. Epub ahead of print.
23 Niknam R, Lankarani KB, Moghadami M, Taghavi SA, Zahiri L, Fallahi MJ. The association between helicobacter pylori infection and erosive gastroesophageal reflux disease; a cross-sectional study. BMC Infect Dis 2022; 22: 267.
24 Bacaksiz F, Ozturk O, Tenlik I, Ebik B, Ari D, Gokbulut V, Akdogan O, Ozin YO, Kilic ZMY, Kayacetin E. Relationship Among Helicobacter Pylori, Lower Esophagus Sphincter Pressure, and Gastroesophageal Reflux: A Single-Center Experience. Sisli Etfal Hastan Tip Bul 2022; 56: 408-413.
25 Zhao T, Liu F, Li Y. Effects of Helicobacter pylori eradication on esophageal motility, esophageal acid exposure, and gastroesophageal reflux disease symptoms. Front Cell Infect Microbiol 2023; 13: 1082620.
26 Du YL, Hu N, Wang K, Cui RL, Zhang HJ, Ke Y, Pan KF, Duan LP. [The correlation between reflux esophagitis and Helicobacter pylori infection based on natural population]. Zhonghua Nei Ke Za Zhi 2022; 61: 1330-1335.
27 Cessa-Zanatta JC, García-Compeán D, Maldonado-Garza HJ, Borjas-Almaguer OD, Jiménez-Rodríguez AR, Del Cueto-Aguilera ÁN, González-González JA. Helicobacter pylori infection is associated with decreased odds for eosinophilic esophagitis in Mexican patients. Gastroenterol Hepatol 2023: S0210-5705(23)00065-1. English, Spanish. doi: 10.1016/j.gastrohep.2023.03.002. Epub ahead of print.
28 Wang SE, Dashti SG, Hodge AM, Dixon-Suen SC, Castaño-Rodríguez N, Thomas RJS, Giles GG, Milne RL, Boussioutas A, Kendall BJ, English DR. Mechanisms for the Sex-Specific Effect of H. Pylori on Risk of Gastroesophageal Reflux Disease and Barrett's Esophagus. Cancer Epidemiol Biomarkers Prev 2022; 31: 1630-1637.
29 Ma S, Guo X, Wang C, Yin Y, Xu G, Chen H, Qi X. Association of Barrett's esophagus with Helicobacter pylori infection: a meta-analysis. Ther Adv Chronic Dis 2022; 13: 20406223221117971.
30 Pan D, Sun GJ, Su M, Wang X, Yan QY, Song G, Wang YY, Xu DF, Wang NN, Wang SK. Inverse relations between Helicobacter pylori infection and risk of esophageal precancerous lesions in drinkers and peanut consumption. World J Gastrointest Oncol 2022; 14: 1689-1698.
31 Poosari A, Nutravong T, Namwat W, Sa-Ngiamwibool P, Ungareewittaya P, Boonyanugomol W. Relationship between Helicobacter Pylori Infection and the Risk of Esophageal Cancer in Thailand. Asian Pac J Cancer Prev 2023; 24: 1073-1080.
32 Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. Eur J Nutr 2020; 59: 3369-3390.
33 Yue M, Chen Q, Zhou X, Li L, Lu C. Is Helicobacter pylori Infection Associated with Celiac Disease? A Meta-analysis. Turk J Gastroenterol 2022; 33: 205-212.
34 El-Abassi R, Soliman MY, Williams F, England JD. Whipple's disease. J Neurol Sci 2017; 377: 197-206.
35 Scalvini D, Cambieri P, Schiepatti A, Maimaris S, Lusetti F, Vattiato C, Marone P, Villani L, Biagi F. Patients with Whipple's disease have a high prevalence of Helicobacter pylori infection. Eur J Intern Med 2023; 111: 77-81.
36 Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. World J Gastroenterol 2014; 20: 91-99.
37 Abd El-Wahab EW, Youssef EI, Hassouna E. Helicobacter pylori infection in patients with inflammatory bowel diseases: a single-centre, prospective, observational study in Egypt. BMJ Open 2022; 12: e057214.
38 Ranjbar J, Geramizadeh B, Bagheri Lankarani K, Jowkar Z, Mirzai M, Moazamian E. Is the Presence of Helicobacter Pylori in the Colonic Mucosa, Provocative of Activity in Ulcerative Colitis? Clin Pathol 2022; 15: 2632010X221096660.
39 Sheu NW, Huang SH, Wu DC, Kao JY, Lin KD. Effects of Helicobacter pylori treatment on the incidences of autoimmune diseases and inflammatory bowel disease in patients with diabetes mellitus. PLoS One 2022; 17: e0265323.
40 Sebastián Domingo JJ. Irritable bowel syndrome. Med Clin (Barc) 2022; 158: 76-81. English, Spanish.
41 Wang Z, Liu Y, Peng Y, Peng L. Helicobacterpylori Infection-A Risk Factor for Irritable Bowel Syndrome? An Updated Systematic Review and Meta-Analysis. Medicina (Kaunas) 2022; 58: 1035.
42 Hamad AJ, Alnaji EK, Almohana SJ, Kareem YS, Albdairi AJ. ASSOCIATION BETWEEN H. PYLORI INFECTION AND IRRITABLE BOWEL SYNDROME. Wiad Lek 2023; 76: 406-414.
43 Ma Z, Chu X, Yan X, Wang W. Association between Helicobacter pylori infection and non-alcoholic fatty liver disease for Asian and non-Asian population: A systematic review and meta-analysis. Front Public Health 2022; 10: 1062942.
44 Liu Y, Xu H, Zhao Z, Dong Y, Wang X, Niu J. No evidence for a causal link between Helicobacter pylori infection and nonalcoholic fatty liver disease: A bidirectional Mendelian randomization study. Front Microbiol 2022; 13: 1018322.
45 Tapper EB, Loomba R. Noninvasive imaging biomarker assessment of liver fibrosis by elastography in NAFLD. Nat Rev Gastroenterol Hepatol 2018; 15: 274-282.
46 Fialho A, Fialho A, Ribeiro B, Malespin M, De Melo S, Schey R, Ghali P. Association Between Helicobacter pylori and Steatosis Severity on Transient Elastography. Cureus 2023; 15: e34042.
47 Wei L, Ding HG. Relationship between Helicobacter pylori infection and nonalcoholic fatty liver disease: What should we expect from a meta-analysis? Medicine (Baltimore) 2021; 100: e26706.
48 Chen Y, You N, Shen C, Wu J, Zhang J. Helicobacter pylori infection increases the risk of nonalcoholic fatty liver disease in diabetic population. Front Nutr 2023; 10: 1076579.
49 Chang W, Cai L, Chen T, Ni W, Xie Z, Yang C, Liao J. Current Helicobacter pylori Infection Is Associated with Early Liver Injury: A Cross-Sectional Study in the General Population. Am J Trop Med Hyg 2023; 108: 684-692.

50 Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014; 383: 1749-1761.
51 Alarfaj SJ, Abdallah Mostafa S, Abdelsalam RA, Negm WA, El-Masry TA, Hussein IA, El Nakib AM. Helicobacter pylori Infection in Cirrhotic Patients With Portal Hypertensive Gastropathy: A New Enigma? Front Med (Lausanne) 2022; 9: 902255.
52 Noor, Mansoor H, Ud Din R, Asif Farooq M, Asghar A, Siddique M. The Association of Helicobacter pylori With Portal Hypertensive Gastropathy in Patients With and Without Cirrhosis. Cureus 2022; 14: e31183.
53 Varuna S, Sureshkumar S, Gurushankari B, Archana E, Mohsina S, Kate V, Balasubramanian V, Mahalakshmy T. Is There an Association between Variceal Bleed and Helicobacter pylori Infection in Cirrhotic Patients with Portal Hypertension?: A prospective cohort study. Sultan Qaboos Univ Med J 2022; 22: 539-545.
54 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7-33.
55 Laya GB, Anandhi A, Gurushankari B, Mandal J, Kate V. Association Between Helicobacter pylori and Periampullary and Pancreatic Cancer: a Case-Control Study. J Gastrointest Cancer 2022; 53: 902-907.
56 Zhou BG, Mei YZ, Wang JS, Xia JL, Jiang X, Ju SY, Ding YB. Is Helicobacter pylori infection associated with pancreatic cancer? A systematic review and meta-analysis of observational studies. Ther Adv Chronic Dis 2023; 14: 20406223231155119.
57 Lee AA, Wang QL, Kim J, Babic A, Zhang X, Perez K, Ng K, Nowak J, Rifai N, Sesso HD, Buring JE, Anderson GL, Wactawski-Wende J, Wallace R, Manson JE, Giovannucci EL, Stampfer MJ, Kraft P, Fuchs CS, Yuan C, Wolpin BM. Helicobacter pylori Seropositivity, ABO Blood Type, and Pancreatic Cancer Risk From 5 Prospective Cohorts. Clin Transl Gastroenterol 2023; 14: e00573.
58 Sun CH, Li BB, Wang B, Zhao J, Zhang XY, Li TT, Li WB, Tang D, Qiu MJ, Wang XC, Zhu CM, Qian ZR. The role of Fusobacterium nucleatum in colorectal cancer: from carcinogenesis to clinical management. Chronic Dis Transl Med 2019; 5: 178-187.
59 Zhuang Z, Yu B, Xie M, Zhang Y, Lv B. Association of Helicobacter pylori enrichment in colorectal adenoma tissue on clinical and pathological features of adenoma. Clin Res Hepatol Gastroenterol 2022; 46: 101961.
60 Wernly S, Semmler G, Flamm M, Rezar R, Aigner E, Datz C, Wernly B. The Association between Helicobacter pylori and Colorectal Neoplasia. Med Princ Pract 2023; 32: 77-85.
61 Boustany A, Onwuzo S, Almomani A, Asaad I. Epidemiology and risk of colorectal cancer in patients with a history of Helicobacter pylori infection: a population-based study. Ann Gastroenterol 2023; 36: 203-207.
62 Ma L, Guo W, Zeng Z, Yang F, Tang S, Ling Y. Colorectal cancer risk in East Asian patients with Helicobacter pylori infection: A systematic review and meta-analysis. Medicine (Baltimore) 2023; 102: e33177.
63 Yoon HS, Shu XO, Cai H, Zheng W, Wu J, Wen W, Courtney R, Shidal C, Waterboer T, Blot WJ, Cai Q. Associations of lung cancer risk with biomarkers of Helicobacter pylori infection. Carcinogenesis 2022; 43: 538-546.
64 Lv B, Wang Y, Ma D, Cheng W, Liu J, Yong T, Chen H, Wang C. Immunotherapy: Reshape the Tumor Immune Microenvironment. Front Immunol 2022; 13: 844142.
65 Tagliaferri L, Lancellotta V, Fionda B, Mangoni M, Casà C, Di Stefani A, Pagliara MM, D'Aviero A, Schinzari G, Chiesa S, Mazzarella C, Manfrida S, Colloca GF, Marazzi F, Morganti AG, Blasi MA, Peris K, Tortora G, Valentini V. Immunotherapy and radiotherapy in melanoma: a multidisciplinary comprehensive review. Hum Vaccin Immunother 2022; 18: 1903827.
66 Tonneau M, Nolin-Lapalme A, Kazandjian S, Auclin E, Panasci J, Benlaifaoui M, Ponce M, Al-Saleh A, Belkaid W, Naimi S, Mihalcioiu C, Watson I, Bouin M, Miller W, Hudson M, Wong MK, Pezo RC, Turcotte S, Bélanger K, Jamal R, Oster P, Velin D, Richard C, Messaoudene M, Elkrief A, Routy B. Helicobacter pylori serology is associated with worse overall survival in patients with melanoma treated with immune checkpoint inhibitors. Oncoimmunology 2022; 11: 2096535.
67 Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. Alzheimers Dement 2016; 12: 719-732.
68 GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health 2022; 7: e105-e125.
69 Uberti AF, Callai-Silva N, Grahl MVC, Piovesan AR, Nachtigall EG, Furini CRG, Carlini CR. Helicobacter pylori Urease: Potential Contributions to Alzheimer's Disease. Int J Mol Sci 2022; 23: 3091.
70 Wang J, Yu NW, Wang DZ, Guo L, Yang S, Zheng B, Guo FQ, Wang JH. Helicobacter pylori Infection Is Associated with Long-Term Cognitive Decline in Older Adults: A Two-Year Follow-Up Study. J Alzheimers Dis 2023; 91: 1351-1358.
71 Merlino G, Gigli GL. Sleep-related movement disorders. Neurol Sci 2012; 33: 491-513.
72 Sung YF, Yin JH, Lee KH, Tsai CL, Lin YK, Chen SY, Chung CH, Chien WC, Lee JT, Chou CH. Increased risk of sleep-related movement disorder in patients with Helicobacter pylori infection: A nationwide population-based study. Front Neurol 2022; 13: 953821.
73 Chow YL, Teh LK, Chyi LH, Lim LF, Yee CC, Wei LK. Lipid Metabolism Genes in Stroke Pathogenesis: The Atherosclerosis. Curr Pharm Des 2020; 26: 4261-4271.
74 Keikha M, Karbalaei M. A Comprehensive Survey of the Relationship between Helicobacter pylori Infection and Atherosclerosis in the Iranian Population: A Systematic Review and Meta-analysis. Arch Iran Med 2022; 25: 257-266.
75 Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. Helicobacter pylori and extragastric diseases: A review. World J Gastroenterol 2018; 24: 3204-3221.
76 Sweeney LB, Stewart C, Gaitonde DY. Thyroiditis: an integrated approach. Am Fam Physician 2014; 90: 389-396.
77 Zhang J, Hai X, Wang S, Zhu F, Gu Y, Meng G, Zhang Q, Liu L, Wu H, Zhang S, Zhang T, Wang X, Sun S, Zhou M, Jia Q, Song K, Niu K. Helicobacter pylori infection increase the risk of subclinical hyperthyroidism in middle-aged and elderly women independent of dietary factors: Results from the Tianjin chronic low-grade systemic inflammation and health cohort study in China. Front Nutr 2023; 10: 1002359.
78 Silva IN, Marçal LV, Queiroz DMM. Helicobacter pylori Infection Is Associated With Thyroid Dysfunction in Children With Congenital Hypothyroidism. Front Pediatr 2022; 10: 875232.

79 Lacativa PGS, Farias MLF de. Osteoporosis and inflammation. Arquivos Brasileiros de Endocrinologia e Metabologia 2010; 54: 123-132.
80 Ye YF, Chen YH, Hong D, Jiesisibieke ZL, Tung TH, Zhang MX. Association of Helicobacter pylori infection with osteoporosis risk in a physical examination population. Arch Osteoporos 2022; 17: 35.
81 Huang J, Liu Z, Ma J, Liu J, Lv M, Wang F, Tang X. The Association between Helicobacter pylori Seropositivity and Bone Mineral Density in Adults. Mediators Inflamm 2022; 2022: 2364666.
82 Xiong C, Zhao R, Xu J, Liang H, Zhang J, Huang Y, Luo X. Is Helicobacter pylori infection associated with osteoporosis? a systematic review and meta-analysis. J Bone Miner Metab 2023; 41: 74-87.
83 Marini I, Bakchoul T. Pathophysiology of Autoimmune Thrombocytopenia: Current Insight with a Focus on Thrombopoiesis. Hamostaseologie 2019; 39: 227-237.
84 Han B, Kim HJ, Yhim HY, Oh D, Bae SH, Shin HJ, Lee WS, Kwon J, Lee JO, Kim HJ, Bang SM. Sequential eradication of Helicobacter pylori as a treatment for immune thrombocytopenia in patients with moderate thrombocytopenia: a multicenter prospective randomized phase 3 study. Ann Hematol 2022; 101: 1435-1445.
85 Yuan W, Li Yumin, Yang Kehu, Ma Bin, Guan Quanlin, Wang D, Yang L. Iron deficiency anemia in Helicobacter pylori infection: meta-analysis of randomized controlled trials. Scand J Gastroenterol 2010; 45: 665-6676.
86 Zhang Y, Bi J, Wang M, Deng H, Yang W. Correlation between helicobacter pylori infection and iron deficiency in children. Pak J Med Sci 2022; 38: 1188-1192.
87 Mubiru IS, Kasirye PG, Hume H, Ndeezi G. Prevalence and factors associated with Helicobacter Pylori infection among children with sickle cell anemia attending Mulago hospital, in Uganda. Afr Health Sci 2022; 22: 135-145.
88 Eyoum Bille BB, Kouitcheu Mabeku LB. Relationship between active Helicobacter pylori infection and anemia, iron deficiency, iron deficiency anemia: A cross-sectional study in a sub-Saharan setting. JGH Open 2022; 6: 554-568.
89 Lupu A, Miron IC, Cianga AL, Cernomaz AT, Lupu VV, Munteanu D, Ghica DC, Fotea S. The Relationship between Anemia and Helicobacter Pylori Infection in Children. Children (Basel) 2022; 9: 1324.
90 Chen Y, Zhan X, Wang D. Association between Helicobacter pylori and risk of childhood asthma: a meta-analysis of 18 observational studies. The Journal of Asthma 2022; 59: 890–900. doi:10.1080/02770903.2021.1892752
91 Chen Y, Zhan X, Wang D. Association between Helicobacter pylori and risk of childhood asthma: a meta-analysis of 18 observational studies. The Journal of Asthma 2022; 59: 890–900. doi:10.1080/02770903.2021.1892752
92 Zhang X, Sun K, Tang C, Cen L, Li S, Zhu W, Liu P, Chen Y, Yu C, Li L. LECT2 modulates dendritic cell function after Helicobacter pylori infection via the CD209a receptor. J Gastroenterol Hepatol 2023; 38: 625-633.
93 Zullo A, Bruzzese V, Pellegrino G, Scolieri P, Stefanantoni K, Angelelli C, Riccieri V. Helicobacter pylori and Upper Endoscopy in Systemic Sclerosis: A Cross-sectional Study in the Real World. J Clin Rheumatol 2021; 27: 40-41.
94 Radić M, Kaliterna DM, Bonacin D, Vergles JM, Radić J, Fabijanić D, Kovačić V. Beneficial effects of Helicobacter pylori eradication in systemic sclerosis patients. Wien Klin Wochenschr 2023; 135: 414-419.
95 López-Valverde N, Macedo de Sousa B, López-Valverde A, Suárez A, Rodríguez C, Aragoneses JM. Possible Association of Periodontal Diseases With Helicobacter pylori Gastric Infection: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 2022; 9: 822194.
96 Sruthi MA, Mani G, Ramakrishnan M, Selvaraj J. Dental caries as a source of Helicobacter pylori infection in children: An RT-PCR study. Int J Paediatr Dent 2023; 33: 82-88.
97 Sekar R, Murali P, Junaid M. Quantification of Helicobacter pylori and its oncoproteins in the oral cavity: A cross-sectional study. Oral Dis 2023; 29: 1868-1874.
98 Tang Y, Yang Y, Lv Z. Adverse pregnancy outcomes and Helicobacter pylori infection: A meta-analysis. Int J Clin Pract 2021; 75: e14588.
99 Zanzal Ra'ad Al-Dorri A, Ibraheem Salih N, Saleh Khuder H. Serological Detection of Helicobacter pylori Infection in Pregnant Women Related to ABO Blood Group. Arch Razi Inst 2022; 77: 591-597.
100 Tsegaye N, Diriba R, Araya S. Magnitude of H. pylori and Its Association with Preeclampsia Among Pregnant Women in Ethiopia: A Case Control Study. Int J Womens Health 2022; 14: 635-642.
101 Herrock O, Deer E, LaMarca B. Setting a stage: Inflammation during preeclampsia and postpartum. Front Physiol 2023; 14: 1130116.
102 Irwin GM. Erectile Dysfunction. Prim Care 2019; 46: 249-255.
103 Yağmur I, Demir M, Çiftçi H, Yildiz Zeyrek F, Yeni E, Verit A. Relationship between erectile dysfunction and Helicobacter pylori: A prospective controlled pilot study. Andrologia 2022; 54: e14444.
104 Xu J, Xu Z, Pan H, Zhou Z. Association between erectile dysfunction and Helicobacter pylori, folic acid, vitamin B12, and homocysteine: a cross-sectional study. Sex Med 2023; 11: qfac018.