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/m² 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 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.

Evidence suggests that eradicating HP may affect metabolic parameters, including HDL cholesterol levels. One study 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 (\( p=0.089 \)).

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, \textit{H. pylori} could influence the post-operative complications. 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 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.

**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.

Contradictory evidence has been published about the association with HP infection. A Chinese cross-sectional study 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).

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.

**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 HP and atherosclerosis, the evidence is not yet conclusive.

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

Similarly, a European multicentre retrospective study 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, 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.

**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 involving 11,317 patients with hypertension demonstrated that HP was linked to a 13.4% increased risk (95% CI: 11-16.3%, \( p = 0.002 \)).

In addition, further analysis 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).

**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.

According to a meta-analysis by Tong et al, 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). Gonciarz et al 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.

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

Cardiovascular (CV) risk and HPI were also assessed in a cohort of 3,284 asymptomatic patients. Calculating SCORE2 to assess 10-year CV risk, the researchers discovered a critical association with HP (aOR 1.03 95% CI 0.77-1.87; \( p = .43 \)) and HP (aOR 0.60 95% CI 0.14-2.63; \( p = .50 \)).

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, \( p = .002 \)).

**Atrial Fibrillation**

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

A recent Israeli study 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 (\( p<0.001 \)).

**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>
<thead>
<tr>
<th>Disease</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Principal findings</th>
<th>Doi</th>
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<tbody>
<tr>
<td><strong>Motility</strong></td>
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<tr>
<td>GERD</td>
<td>Cross-sectional</td>
<td>1916 (874 with GERD, 442 with HPI)</td>
<td>No association between GERD and active HPI (p = 0.214).</td>
<td>10.1186/s12879-022-07278-6</td>
</tr>
<tr>
<td></td>
<td>Retrospective study</td>
<td>1226 (752 with GERD in 24h pH monitoring)</td>
<td>No association between GERD or LES laxity, and active HPI.</td>
<td>10.14744/SEMB.2022.55476</td>
</tr>
<tr>
<td></td>
<td>Prospective study</td>
<td>68 with GERD and HP</td>
<td>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 &lt; 0.05) -higher GerdQ (p &lt; 0.05)</td>
<td>10.3389/fcimb.2023.108260</td>
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<tr>
<td><strong>Inflammatory lesions</strong></td>
<td></td>
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<tr>
<td>RE</td>
<td>Retrospective study</td>
<td>3741 (359 with RE)</td>
<td>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).</td>
<td>10.3760/cma.j.cn11 2138-20220214-00107</td>
</tr>
<tr>
<td>EoE</td>
<td>Prospective study</td>
<td>190 (38 with EoE)</td>
<td>Inverse association between EoE and HPI (OR 0.21, 95% CI, 0.08-0.69; p = 0.001)</td>
<td>10.1016/j.gastrohep.2023.03.002</td>
</tr>
<tr>
<td><strong>Cancer and precancerous lesions</strong></td>
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<tr>
<td>BE</td>
<td>Case-control study</td>
<td>594 (169 with BE)</td>
<td>In men positive association between BE and HP seronegative (OR 2.28, 95% CI, 1.27-4.12)</td>
<td>10.1158/1055-9965.EPI-22-0234</td>
</tr>
<tr>
<td>BE</td>
<td>Meta-analysis</td>
<td>1354369 from 24 studies</td>
<td>Inverse relation between BE and active HPI (OR 0.53, 95% CI, 0.45-0.64; p &lt; 0.001) and active CagA neg strains (OR 0.25, 95% CI, 0.15-0.44; p &lt; 0.000).</td>
<td>10.1177/204062232117971</td>
</tr>
<tr>
<td>EPL for ESCC</td>
<td>Case-control study</td>
<td>400 (200 with EPL)</td>
<td>Inverse relation between EPL and HP seropositive (OR 0.32, 95% CI, 0.11-0.95)</td>
<td>10.4251/wjgo.v14.i9.1689</td>
</tr>
<tr>
<td>ESCC</td>
<td>Case-control study</td>
<td>213 (105 with ESCC)</td>
<td>Positive association between ESCC and HP in esophageal biopsies (OR 2.76, 95% CI, 3.11-10.48; p &lt; 0.001)</td>
<td>10.31557/APJCP.2023.24.3.1073</td>
</tr>
</tbody>
</table>

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 HP32.

A meta-analysis by Yue et al33 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 yet33.

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 whipplei34.

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 al35 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 factors36.

Although a prospective observation Egyptian study37 failed to associate IBD flares and symptoms with HPI, a subsequent study38 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 disease37,38.

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 bacterium39.

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 HP40.

A meta-analysis41 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 IBS41.

A recent study42 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 age42.

Non-Alcoholic Fatty Liver Disease

The relationship between HP infection and non-alcoholic fatty liver disease (NAFLD) remains controversial43,44. Bidirectional Mendelian randomization (MR) study44 used genome-wide association (GWAS) data to define the mutual relation between HPI and NAFLD44,43. After analyzing lipid profiles, they found no significant relation (p=0.759, 0.508, 0.543), excluding HP as a risk factor for NAFLD44.

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.

Filho et al. 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; $p=0.037$).

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.

Furthermore, 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.

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.

For instance, a study by Alarfaj et al. 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, but these results were not confirmed by further studies conducted on the Pakistani population.

Interestingly, Indian research 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.

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.

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 did not record any significative association between HPI and patients with PC compared to healthy controls (76.5% vs. 78.6%, $p=0.76$). Likewise, a meta-analysis 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.

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.

Colorectal Cancer

Colorectal cancer (CRC) is a complex neoplasia influenced by various genetic, lifestyle, and environmental factors. 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.

Similarly, recent research has investigated HP’s role in CRC and colorectal adenoma. Zhuang et al. 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 significant correlation with the lesion dimensions, malignancy, and pathological type (OR 3.536, 2.833, 3.652; p < 0.001)\(^9\).

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)\(^9\).

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. discovered a strong association between SRMD and HP, with an increased 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).

**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.

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. 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.

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).

**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.

Inflammation caused by HPI may be implicated in the pathogenesis of autoimmune thyroid disease (ATD). A cross-sectional study of 142 children 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.

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).

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.

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 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).

**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.
A multicenter phase 3 study\textsuperscript{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\textsuperscript{84}.

Anemia

HPI has also been associated with an increased risk of anemia, particularly iron-deficiency anemia\textsuperscript{85}. A study of 902 children\textsuperscript{86} found a higher incidence of iron-deficiency anemia 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\textsuperscript{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\textsuperscript{87}. A cross-sectional study on 340 SCA children reported an HP infection rate of 49\% (CI 95\%: 44.1-54.7)\textsuperscript{87}.

Conversely, in 842 adults with dyspepsia in Cameron\textsuperscript{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\textsuperscript{88}.

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

Asthma

There is an undetermined association between HP and childhood asthma. A meta-analysis of 18 studies\textsuperscript{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; $p = 0.387$)\textsuperscript{90}.

Similarly, a Chinese cross-sectional study\textsuperscript{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; $p < .05$)\textsuperscript{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 \textit{H. pylori} infection\textsuperscript{92}. Hence, the possible protective role of HP in the development of asthma\textsuperscript{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\textsuperscript{93} investigated the possible association between SSc and \textit{H. pylori}.

A recent cross-sectional study on 42 patients with HPI\textsuperscript{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)\textsuperscript{94}.

Periodontal Disease

Some evidence suggests a relation between periodontal disease and \textit{Helicobacter pylori} (\textit{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\%\textsuperscript{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. 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.

Pre-eclampsia

Untreated HPI during pregnancy may increase the risk of complications such as preterm delivery, low birth weight, and gestational diabetes. It is estimated that, in poor-income countries, almost 32.5% of women with nausea and vomiting could be infected with HP.

In Ethiopia, a study including 186 controls and 93 cases 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.

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.

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.

Intriguingly, in a study by Yagmur et al., 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).

A subsequent study 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 folate (4.66 vs. 10.31, p < .001), suggesting that HP could reduce the absorption of folate and B12, which might lead to ED.

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

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Conflict of Interest
The authors declare no conflict of interest.

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