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REVIEW ARTICLE

WILEY Helicobacter

The epidemiology of *Helicobacter pylori* infection in Europe and the impact of lifestyle on its natural evolution toward stomach cancer after infection: A systematic review

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Abstract

Background: *Helicobacter pylori* is a recognized cause of stomach cancer, but only a fraction of infected subjects develop cancer. This systematic review 1, summarizes the prevalence of infection with this bacterium in Europe; and 2, reviews the possible impact of particular lifestyles in progression from infection to stomach cancer.

Materials and Methods: A systematic literature search was conducted in two databases by two independent investigators. Studies describing prevalence of infection among European healthy adult populations and worldwide studies analyzing the impact of lifestyle factors in association with *H. pylori* on stomach cancer risk were included.

Results: Variable *H. pylori* infection prevalence was observed depending on region and study period. The lowest infection prevalences were found in Northern Europe, while the highest were in Eastern and Southern Europe, up to 84% in Portugal and Poland. Studies on smoking, salt, and meat consumption demonstrated increased risks of developing stomach cancer among *H. pylori*-infected individuals, while studies relating the intake of fruit, vegetables, and vitamins demonstrated decreased risks, but the levels of significance differed importantly between studies. No significant interaction could be found for alcohol consumption or physical activity.

Conclusions: Recent data showed remaining high *H. pylori* infection rates in several European regions. This systematic review suggests that a number of correctable lifestyle factors could impact the disease progression toward *H. pylori*-associated stomach cancer. However, additional research is required to determine the potential role of targeted interventions in reducing stomach cancer development after *H. pylori* infection.

KEYWORDS
epidemiology, *Helicobacter pylori*, lifestyle, prevention, stomach cancer

Venneman and Huybrechts contributed equally to the manuscript (shared first authorship).

1 | INTRODUCTION

In 2008, two million of the 12.7 million new cancer cases were attributable to infections, specifically caused by hepatitis B viruses, hepatitis C viruses, human papillomaviruses, and *Helicobacter pylori* (*H. pylori*).[1] The International Agency for Research on Cancer (IARC) estimated that 6.2% of all cancers were attributable to *H. pylori*.[2] The bacterium is a recognized cause of stomach cancer, which is the third leading cause of cancer death worldwide.[3] In 2012, an estimated 81 500 new cases of stomach cancer and 58 500 associated deaths occurred in Europe.[4] The survival rate for stomach cancer is estimated to be around 27% in Western Europe and only 15.5% in Eastern Europe.[5] Despite the described annual percentage decline in stomach cancer incidence (−2.5% per year), the absolute burden remains important because it is balanced by demographic growth.[6]

The routes of transmission *of H. pylori* still remain unclear, but interhuman transmission seems to be the main route.[7-9] *Helicobacter pylori* colonization in the stomach can lead to atrophic gastritis and intestinal metaplasia as important precursor lesions toward the development of stomach cancer. The carcinogenic effect of *H. pylori* is dependent on the specific strain, the immune response of the host and environmental factors.[10]

Guidelines addressing stomach cancer prevention strategies in Europe emphasize the need to identify the subpopulations most at risk for developing stomach cancer to implement the most appropriate targeted strategies.[11,12] Therefore, collecting information on *H. pylori* infection prevalence is useful to identify the high-risk regions.[13] The overall prevalence of *H. pylori* infection in adults in Europe is estimated to be 20%-40%.[14] It is known that infection rates are linked to socioeconomic factors such as hygienic standards, which have improved in Europe since the 1950s.[15] Screening and eradication programs are mainly implemented in a few Asian countries, while in Europe the control efforts are limited because of the rather low and declining rates of the disease and unclear efficacy and cost-effectiveness of available interventions. Focusing on modifiable lifestyle factors could have an impact on reducing the risk of *H. pylori*-associated stomach cancer.[16] Studies usually investigate the independent impact of lifestyle factors on stomach cancer risk, but less is known about the impact of lifestyle in association with this bacterium. This systematic review offers an overview of current knowledge on the impact of lifestyle factors toward gastric atrophy and stomach cancer among subjects infected with *H. pylori*. This knowledge could be used in the development and testing of alternative prevention strategies to reduce the burden of stomach cancer in Europe.

2 | METHODS

2.1 | Search strategy

An exploratory search for relevant existing systematic reviews on the topic was carried out to avoid overlap and to guarantee the added value of our review. The search strategy, used in the search engines PubMed and Web of Science, was discussed and agreed upon within the review panel to find all relevant literature. The appropriate keywords were found by exploring the MesH library and by exploring interesting studies including their references. The search strategy was continuously improved by repetitive small screenings to find all relevant articles. In the end, the following keywords were used with the Boolean technique: helicobacter infections, *H. pylori*, campylobacter pylori, stomach neoplasms, gastritis, tobacco use, diet, lifestyle, risk factors, transmission, prevalence, incidence, epidemiology, seroepidemiologic studies, socioeconomic factors, and Europe. A more detailed overview of the search is shown in the flowchart (see Table 1).

2.2 | Selection of the studies

A systematic literature search was conducted in PubMed and Web of Science until October 2015. There was no time restriction. The only preselected limit used in PubMed was "humans." Articles on the epidemiology of *H. pylori* infection in healthy adults in European countries defined according to the European Union (EU); and worldwide articles on the possible impact of lifestyle factors among *H. pylori*-infected subjects toward the associated stomach cancer were eligible for this review. Adulthood was defined as the age of fifteen years and older. Studies were excluded according to predefined criteria which are extensively described in Table 2. The Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to achieve a properly substantiated review.[17] Search results were imported into reference software (Endnote, version X7.5) for a first screening based on title by one investigator. In case of doubt, references were retained for further assessment based on abstract. The screening based on abstract was conducted independently by two investigators. This resulted in a 59.7% agreement after the first review. Differences between both investigators in the selection by abstract were discussed in the review panel until consensus was reached. Subsequently, the main investigator further screened the selection based on full text. An update on new articles, based on the same search strategy, was investigated only by the main investigator from June 2015 up to March 2016 in both search engines. Due to reasonable efforts including contacting the authors through e-mail and research platforms such as ResearchGate, the full texts of half the nonretrieved articles could still be retrieved for further screening. Relevant articles were also searched through the reference lists of relevant studies. Furthermore, the methodological quality of studies was assessed by one reviewer based on the tool of Fowkes and Fulton[18] The main reasons for exclusion were a nonrepresentative sample and an inappropriate control group. In the end, fifty-two publications were included.

Studies on the impact of lifestyle factors among *H. pylori*-infected groups used interaction terms in their models. Using interaction terms, one can test the hypothesis that the main effect depends on the interaction between the other variables, in our particular study, if the risk for progressing from *H. pylori* infection to stomach cancer depends on interaction with lifestyle factors.

TABLE 1 Flowchart of the methodology (last update 05/03/2016)

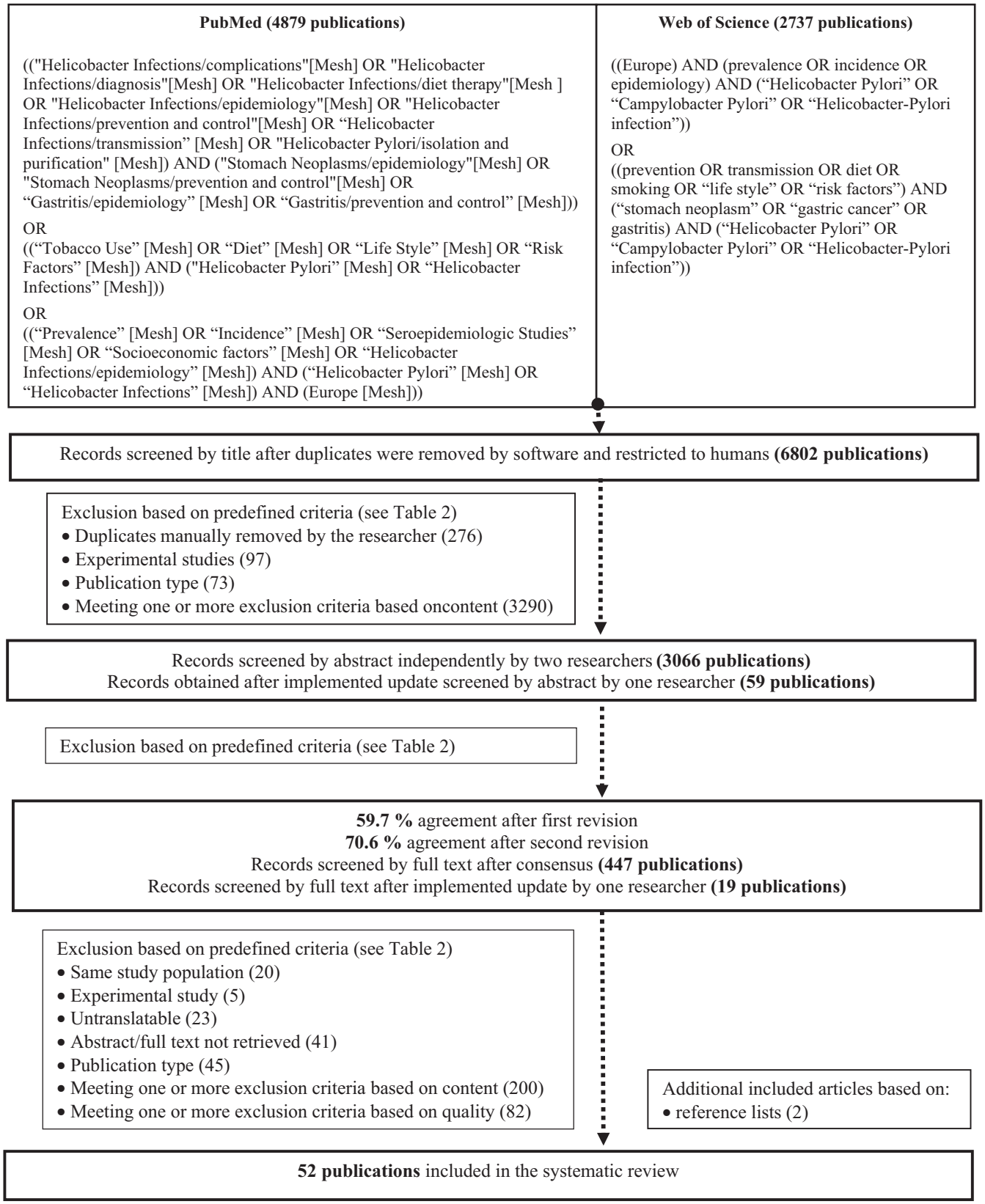

TABLE 2 Inclusion and exclusion criteria

Inclusion criteria
1. Data relating to *Helicobacter pylori* infection in physically and mentally healthy adult populations (ie, 15 y or more) in Europe defined by the European Union or articles worldwide focusing on the impact of lifestyle factors in the natural progression toward *H. pylori*-related stomach cancer among infected individuals. Considered lifestyle factors: smoking, diet, alcohol consumption, and physical activity
Exclusion criteria
General exclusion
1. Animal or in vitro experimental studies
2. Full text not retrieved despite all reasonable efforts
3. Unable to translate (ie, Spanish, Portuguese, Italian, Rumanian, Czech, Croatian, Polish, Finnish, Danish, Hungarian, Japanese, Korean, Chinese, and Russian)
4. Duplicates or epidemiological publications from the same study population
5. Publication types: reviews, editorials, comments, case reports, meta-analyses, guidelines
Exclusion by content
Concerning epidemiological references
1. Data relating to epidemiological data other than population-based prevalence rates of *H. pylori* (eg, the prevalence of gastric cancer) or relating to children (ie, under 15 y old)
2. Studies relating to the epidemiology of *H. pylori* in a sick or symptomatic subpopulation (eg, ischemic heart diseases, cirrhosis, kidney failures, diabetes, dyspepsia, gastrointestinal diseases,...) and in the population of healthcare workers including medical students because of the potential overestimation in a general population
3. Studies only focusing on the prevalence of specific *H. pylori* strains among an infected population (eg, prevalence of vacA genes in *H. pylori* isolated from adults in Poland)
Concerning lifestyle references
1. Studies relating to (lifestyle) factors before *H. pylori* infection and/or relating to person-to-person transmission including familial transmission or transmission in medical setting (eg, by endoscopy)
2. Data relating to other lifestyle factors than considered or articles relating to the considered lifestyle factors but not associated with *H. pylori* infection in the associated evolution from infection—gastritis-metaplasia-dysplasia—to gastric cancer (ie, not toward peptic ulcer, not toward nonulcer dyspepsia)
3. Studies focusing on the eradication therapy of *H. pylori* by pharmaceutical medications (eg, antibiotics, vaccinations); or studies relating the lifestyle topic but during or after eradication therapy because of the focus on the natural evolution (eg, the effect of smoking on failure for eradication therapy)
4. Studies explaining the mechanisms behind the impact of considered lifestyle factors in the *H. pylori*-associated process to stomach cancer (eg, regulatory B-cell function is suppressed by smoking and obesity in infected subjects)
5. Studies only relating to histological features (eg, the effect of smoking on gastric histology in infected subjects)
Exclusion by quality
1. Data not representative for an entire adult population (eg, only men, only the elderly, only shepherds)
2. Insufficient quality based on a tool by Fowkes et al (eg, inappropriate control group)

3 | RESULTS

3.1 | Epidemiology of *Helicobacter pylori* infection in Europe

3.1.1 | Prevalence

Data concerning the prevalence of *H. pylori* infection in European adults are shown in Table 3 for the following countries: Belgium, Croatia, Czech Republic, Denmark (including Greenland), Estonia, Finland, Germany, Greece, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden, and the United Kingdom.[19-45]

The majority of these studies did not show a significant difference in the prevalence of *H. pylori* infection between men and women. If there was a gender difference, the infection rate was higher in men. Nearly, all these European epidemiological studies found mostly statistically significant, higher prevalence rates of *H. pylori* infection in the older age groups. However, two studies showed conflicting results. A Spanish study showed less infected individuals in the oldest age groups (>75 years), but these groups consisted of fewer participants.[41] In a Swedish study, the prevalence of *H. pylori* infection among blood donors was lower after the age of 50.[26]

Geographical variability

The prevalence of *H. pylori* infection varies considerably according to region. In a randomized cross-sectional study with participants from the *European Community Respiratory Health Survey* (ECRHS), prevalence of *H. pylori* was higher in Estonia (69.2%) in comparison with its prevalence in Sweden (11.2%) using the same method of data collection in the same time period. The studied groups had approximately the same mean age, but the participant group in Estonia consisted of more women (60% vs 48%) and more smokers (40.1% vs 15.3%).[19]

As shown in Table 3, studies from Northern Europe with the exception of Ireland showed relatively low prevalences of *H. pylori* infection. The most remarkable observation in Central Europe was the major difference in the observed infection rates between two studies both conducted in the Netherlands in the first decade of the 21st century (72% in the study of De Vries et al vs 31.7% in the study of

TABLE 3 The prevalence of *Helicobacter pylori* infection in Europe

Country	Ref. (publication year)	Period of data collection	Study population	Age range (years)	Number	Prevalence (%)	Bias/remarks
Northern Europe							
Denmark	Wildner-Christensen et al (2003)[20]	⊦	Random selection from the population of Odense and surrounding towns (rural and urban)	40-64	5749	18[b]	Randomized study population Infection confirmed by ^{13}C-urea breath test
	Webb et al (1999)[21]	⊦	Random selection from population-based registries	25-64	140	23[a]	Randomized study population
	Milman et al (1998)[22]	1982-1984	Random selection from the civil registration system	30-60	2794	26	Randomized study population Exclusion of Danes of foreign origin 95% was healthy based on self-reports
Greenland (Denmark)	Koch et al (2005)[23]	1996-1998	Selection based on a population-based survey to measure the seroprevalence of several infectious agents	15-87	392	58	Unclear whether the study population was randomized
Norway	**Asfeldt et al (2008)[24]**	**2004**	All adult inhabitants of Sørreisa were invited	20-69	398	**24**[c]	No randomized study population Prevalence among those without dyspepsia Exclusion of reported peptic ulcer
	Breckan et al (2009)[25]	**2004-2005**	Representative sample in Bodø drawn by Statistics Norway was invited and all residents of Sørreisa were invited	18-85	1414	**33**[c]	No randomized study population Calculations made for sample size
Sweden	Sorberg et al (2003)[26]	1995-1999	Voluntary blood donors across Sweden and a random sample based on a population register of Stockholm	17-80+	3502 1030	18 25	Randomized study population but not the voluntary blood donor group across the country
	Thjodleifsson et al (2007)[19]	1990-1994	Random selection from the population of Uppsala (database ECRHS)	20-44	359	11	Randomized study population
Finland	Kosunen et al (1997)[27]	1994	Random selection from the National Population Register by computer	15-74	504	31	Randomized study population
Ireland	Buckley et al (1998)[28]	⊦	Voluntary blood donors	18-60	1000	43	No randomized study population Exclusion of volunteers who previously had received *H. pylori* eradication therapy or who had a history of gastric surgery
	Murray et al (1997)[29]	1986-1987	Random selection from three population surveys using the same protocol	20-64	3874	57	Randomized study population

(Continues)

TABLE 3 (Continued)

Country	Ref. (publication year)	Period of data collection	Study population	Age range (years)	Number	Prevalence (%)	Bias/remarks
United Kingdom	Lane et al (2002)[30]	1996-1999	Selection from registries of seven primary care centers in Bristol and surrounding areas (England)	20-59	10 537	16[b]	Unclear whether the study population was randomized Exclusion if allergy to the study medication or severe renal impairment
	Woodward et al (2000)[31]	1995	Random selection from lists of randomly sampled general practitioners (Scotland)	25-64	1631	66	Randomized study population Self-assessed expected number of infected individuals in North Glasgow
	Webb et al (1999)[21]	⊦	Random selection from the lists of general practitioners	25-64	294	28[a]	Randomized study population
Central Europe							
Belgium	Webb et al (1999)[21]	⊦	Random selection from population-based registries	25-64	188	36[a]	Randomized study population
Germany	Seher et al (2000)[32]	1997-1999	Representative sample selection from population registries in 120 communities	18-79	6748	40	Unclear whether the study population was randomized Exclusion if insufficient knowledge of the German language
	Webb et al (1999)[21]	⊦	Random selection from population-based registries	25-64	522	49[a]	Randomized study population
The Netherlands	**van Blankenstein et al (2013)[33]**	**2001-2010**	Voluntary blood donors from two regional blood banks	18-70	1551	**32**	Randomized study population after donation Non-European immigrants not included
	De Vries et al (2008)[34]	**2004-2005**	Selection from the civil registration system in Rotterdam	18-65	288	**72**	Randomized study population but only mentioned in abstract Remarkable low participation rate (16%)
Czech Republic	**Bures et al (2012)[35]**	**2011**	Random selection from fifteen centers of general practitioners	15-98	1406	**29**[b]	Randomized study population
Southern Europe							
Greece	Webb et al (1999)[21]	⊦	Random selection from health-screening programs	25-64	209	64[a]	Randomized study population
	Pateraki et al (1990)[36]	⊦	Recruits from all provinces and blood donors from blood banks in Athens	20-50	610	69	Unclear whether the study population was randomized

(Continues)

TABLE 3 (Continued)

Country	Ref. (publication year)	Period of data collection	Study population	Age range (years)	Number	Prevalence (%)	Bias/remarks
Portugal	**Bastos et al (2013)**[37]	**1999-2003**	Random selection from the population of Porto	18-92	2067	**84**	Randomized study population
	Webb et al (1999)[21]	ŀ	Random selection from population-based registries	25-64	119	63[a]	Randomized study population
Eastern Europe							
Poland	**Laszewicz et al (2014)**[43]	**2002-2003**	Random selection drawn from ten regions representing the country	19-89	3307	**84**	Randomized study population
	Webb et al (1999)[21]	ŀ	Random selection from population-based registries	25-64	158	80[a]	Randomized study population
Latvia	**Leja et al (2012)**[44]	**2008-2009**	Random selection from the national population registry	24-74	3564	**79**	Randomized study population
Estonia	Thjodleifsson et al (2007)[19]	1990-1994	Random selection from the population of Tartu (database ECRHS)	20-44	240	69	Randomized study population
Slovenia	Webb et al (1999)[21]	ŀ	Random selection from population-based registries	25-64	182	56[a]	Randomized study population
Croatia	Babus et al (1998)[45]	ŀ	The first people of corresponding age and sex signing up at two local hematology laboratories	25-64	456	51	No randomized study population Exclusion of digestive disorders and the blood sample had to be provided for a certain reason

Ref., reference; ŀ, information not reported; HIV, human immunodeficiency virus; HBV, hepatitis B virus.
Only the most recent prevalence data within the studies are shown. Data collected in the 21st century are highlighted in bold font type.
[a]Average of the age groups and the Eurogast centers.
Used as detection method: [b] ^{13}C-urea breath test; [c]Stool sample; remaining studies used blood sample.

TABLE 4 Overview of the studies on the impact of smoking on the development of stomach cancer after *Helicobacter pylori* infection

Study reference	Type of cancer	OR	95% CI	Adjusted for
Simán et al[51]	Stomach	2.3	1.1-4.7	Occupation as an indicator of socioeconomic status
Machida-Montani et al[48]	Noncardia	3.0	1.4-6.6	Family history of gastric cancer, one specific diet, total vegetable intake, total fruit intake, and salt intake
Epplein et al[49]	Noncardia	3.2	1.7-6.2	Sex, age, and ethnicity
Wang et al[50]	Noncardia	2.7	1.3-4.9	Family history of gastric cancer, education, and alcohol consumption

OR, odds ratio; CI, confidence interval.
Studies from European regions are highlighted in bold font type.
All risks compared to infected nonsmoking individuals.

van Blankenstein et al).[33,34] In Eastern Europe and Southern Europe, the highest *H. pylori* infection rates were found, especially in Portugal, Poland, and Latvia. Almost all studies from these two European regions are showing prevalences higher than 50% in the population.

Variability over time

The prevalence of *H. pylori* infection changes throughout the years. In the Czech Republic, the infection rate was statistically significantly lower in 2011 (prevalence of 23.5%) compared to 10 years before (prevalence of 41.7% in 2001). These two studies used the same detection method, applied in the same region.[35] A similar trend could be found in Finland where the prevalence of *H. pylori* infection decreased by about 28% over a 21-year period in all age groups in both genders.[27] Among nondyspeptic women in a representative community in Norway, the prevalence of *H. pylori* also decreased significantly within a time period of 17 years (19.9% decrease), but among nondyspeptic men, the decrease of 6% was not statistically significant.[27]

3.2 | Impact of lifestyle factors on progression toward stomach cancer after *Helicobacter pylori* infection

An overview of the design and methods applied in the studies on the impact of smoking and diet on the development of stomach cancer after *H. pylori* infection is included in Appendices S1 and S2.

3.2.1 | Smoking

Atrophic gastritis

Studies could not find any significant interaction of smoking with *H. pylori* for developing gastric atrophy. An Asian matched case-control study showed that the *H. pylori*-infected ever-smokers (including current smokers) had a slightly decreased risk of gastric atrophy (OR 0.8; 95% CI 0.6-1.1), but they had an increased risk for developing the severe form of gastric atrophy (OR 1.3; 95% CI 0.8-2.0). Nevertheless, both outcomes adjusted for age and sex were not significant.[46] Similarly, a cross-sectional study within a European population infected with the bacterium could not demonstrate any significant association between smoking and this precursor stage.[47]

Stomach cancer

As shown in Table 4, multiple studies demonstrated a significantly increased risk among smokers for developing *H. pylori*-associated stomach cancer. A Japanese matched case-control study found an increased risk for noncardia stomach cancer in the *H. pylori*-positive smokers group. After adjustments, this group had 3 times the risk of developing noncardia cancer compared to infected individuals without smoking history, but the interaction term was not significant (*P*-value .52).[48] Another matched case-control study conducted in Hawaii also showed that *H. pylori*-seropositive smokers, but only those who smoked more than 38 packs per year, had approximately 3 times the risk of developing stomach cancer compared to nonsmoking seropositives. There was a significant interaction term (*P*-value .0004).[49] A third case-control study conducted in China also confirmed this association among *H. pylori*-infected individuals. A significantly increased risk of noncardia stomach cancer was shown among smokers while not among never-smokers. When a smoker was infected with the CagA-positive strain, the higher risk increased dramatically (OR 19.5; 95% CI 10.3-42.2). This study demonstrated a significant interaction between smoking and positivity for CagA, suggesting a synergistic association (*P*-value .021).[50] The same conclusion was reached in a Swedish case-control study whereby smokers also had a significantly increased risk of stomach cancer compared to the nonsmoking infected group. However, there was no significant interaction term and the number of cases was limited.[51]

3.2.2 | Alcohol consumption

Atrophic gastritis

An association between alcohol use and *H. pylori*-related atrophic chronic gastritis could not be demonstrated in one cross-sectional study within a European infected population. There was no association with alcohol drinking after an unadjusted analysis.[47]

Stomach cancer

Alcohol consumption at least once a week was not associated with an increased risk of *H. pylori*-associated stomach cancer in a

case-control study conducted in Hawaii. Compared with abstaining alcohol among *H. pylori*-infected individuals, the risk was slightly increased but not significant (OR 1.3; 95% CI 0.8-2.1).[49] Similarly, in a Korean cohort study no significant association could be demonstrated between drinking alcohol and the development of stomach cancer among infected residents. Neither the number of years of alcohol drinking, nor the drinking frequency, nor the average dose were associated with stomach cancer compared to infected alcohol abstainers after adjustments for age, sex, body mass index, educational level, and smoking status.[52]

3.2.3 | Dietary factors

Atrophic gastritis

A high rice intake significantly increased risk of atrophic gastritis in female seropositive participants in a cross-sectional study after adjustment for age (OR 1.6; 95% CI 1.1-2.3; *P*-value .02). Other dietary factors such as salted fish, sodium, vitamin C, carotene, and several types of vegetables or fruits were not associated with atrophic gastritis; nor was a protective effect observed in this Japanese study population infected with *H. pylori*.[53] These last-mentioned dietary factors plus the consumption of meat and potatoes were also not associated with atrophic gastritis among a European dyspeptic population in a cross-sectional study. Only the consumption of coffee was significantly associated with atrophic gastritis after a multivariate analysis (OR 2.35; 95% CI 1.07-5.16; *P*-value for interaction .033).[47] In a randomized controlled study with fifty *H. pylori*-positive volunteers with gastritis, the intervention group was instructed to consume sulforaphane-rich broccoli sprouts daily. The gastritis was reduced afterward only in the intervention group and not in the control group consuming no sulforaphane-containing sprouts.[54]

Stomach cancer

In a Portuguese case-control study, one dietary pattern showed an increased risk for developing stomach cancer in association with *H. pylori* after adjusting for age, gender, education, and total energy intake (OR 1.8; 95% CI 1.3-2.41). This pattern consisted of a less frequent consumption of dairy products, fish, fruits, salads, vegetables, and meat. However, the trend for interaction was not significant (*P*-value .166).[55]

Salt In a Japanese prospective study, salt intake higher than 10 g/d significantly increased the risk of developing stomach cancer among *H. pylori*-infected individuals (age- and sex-adjusted HR 2.4; 95% CI 1.3-4.6; *P*-value <.01). Among the infected individuals with atrophic gastritis, the risk was slightly higher (HR 2.9; 95% CI 1.1-7.2; *P*-value <.05).[56] The higher the salt intake, the higher the risk was for developing noncardia cancer in another Japanese case-control study in the infected group. The outcome was adjusted for a family history of stomach cancer, for membership of the Japan Agricultural Cooperatives, and for total vegetable or fruit intake. The highest risk was observed among the *H. pylori* positives with high salt intakes compared to *H. pylori* negatives with low intakes (OR 14.2; 95% CI 3.9-52.3). However, the trend for interaction was not significant (*P*-value .56).[48]

An European case-control study demonstrated a significant interaction between salt consumption and the risk of stomach cancer among infected individuals after adjustments. However, this significant interaction could only be found using food frequency questionnaires (*P*-value .045). When other methods such as a visual analogical scale were used to verify a total dietary salt intake, the risk was increased, but the interaction terms were not significant (*P*-values >.05). Furthermore, there was no significant risk difference related to sodium intake when the infected group was stratified by virulence of the bacterium (whether or not being infected with the CagA-strain).[57]

Foods and components with antioxidant potential As shown in Table 5, three European studies investigated the association between the total intake of fruits or vegetables and stomach cancer in interaction with *H. pylori* infection. The nested case-control study with participants from the *European Prospective Investigation into Cancer and nutrition* (EPIC) could not demonstrate any significant association. EPIC was a large European prospective study investigating the relationships between diet, lifestyle, genetic and environmental factors, and the incidence of cancer. This important study consisted of 521 457 subjects, aged 35-70 years.[58] A Portuguese case-control study demonstrated that the infected individuals within the group of median intakes of fruit and vegetables had a significantly reduced risk of stomach cancer. Nevertheless, the interaction term was not significant (*P*-value .25).[59] A similar conclusion was found in a case-control study in Sweden. They investigated the total antioxidant potential of fruit and vegetables through calculations based on food databases. *Helicobacter pylori*-infected individuals with median intakes of total calculated antioxidant potential had a lower risk of stomach cancer, and there was a significant interaction trend (*P*-value <.05).[60]

In Hawaii, a case-control study showed a significantly decreased risk of *H. pylori*-related stomach cancer when consuming higher quantities of vegetables. The trend for interaction was significant (*P*-value .02).[49] Among *H. pylori*-infected Japanese subjects in another case-control study, the adjusted risk of noncardia cancer was lower within the subgroups with high intakes of fruits and vegetables. However, the confidence intervals were wide and the interaction terms were not significant (*P*-value .60 and .32 for total vegetable intake and fruit intake, respectively).[48] In another Asiatic case-control study, a significantly increased risk was observed among the infected individuals consuming low quantities. Significant interactions could be found between vegetables, fruit, and *H. pylori* infection (*P*-values <.05).[61]

As shown in Table 6, a case-control study by Ekstrom et al[62] showed that higher dietary intakes of vitamin C and β-carotene significantly decreased the risk of noncardia cancer among European *H. pylori*-seropositive individuals. The same trend was observed in a Hawaiian case-control study whereby higher intakes

TABLE 5 Overview of the studies on the impact of total fruit and vegetable intake on the development of stomach cancer after *Helicobacter pylori* infection

Study reference	Diet factor	Cancer	Intake	HR/OR	95% CI	Adjusted for
Gonzalez et al[58]	Vegetables	Stomach	High	1.11	0.71-1.74	Sex, age, center, date of blood extraction, height, weight, education level, tobacco smoking, cigarette smoking, work and leisure physical activity, alcohol intake, energy intake, red meat intake, processed meat intake
		Cardia		1.42	0.58-3.45	
		Noncardia		1.25	0.71-2.20	
	Fruit	Stomach	High	0.98	0.81-1.20	
		Cardia		0.76	0.48-1.22	
		Noncardia		1.10	0.87-1.39	
Lunet et al[59]	Fruit and vegetables	Stomach	High	0.54	0.26-1.10	Age, sex, education, number of siblings, vitamin and mineral supplement use, total caloric intake, vitamin C, vitamin E, and carotenoids intake
			Median	0.42	0.24-0.74	
Serafini et al[60]	Total antioxidant potential of fruit and vegetables	Stomach	High	0.56	0.30-1.06	Age, sex, body mass index, salt intake, total caloric intake, and number of meals per day
			Median	0.41	0.22-0.78	
Epplein et al[49]	Vegetables	Noncardia	High	0.4	0.2-0.8	Age, sex, ethnicity, cigarette smoking, education, NSAID use, family history of cancer, and total calories
Machida-Montani et al[48]	Vegetables	Noncardia	High	7.6[HR]	2.3-25.2[a]	JA membership, family history of gastric cancer, total vegetable or fruit intake, salt intake and total energy intake
			Low	8.5[HR]	2.4-29.9[a]	
	Fruit		High	5.8[HR]	2.0-16.9[a]	
			Low	10.6[HR]	3.3-33.9[a]	
Wang et al[61]	Vegetables	Noncardia	High	0.8	0.5-3.5[a]	Education, smoking, alcohol consumption, family history, total fruit intake or total vegetable intake, pickled food, and soya products
			Low	2.9	1.5-9.7[a]	
	Fruit		High	0.9	0.3-3.1[a]	
			Low	2.0	1.2-6.7[a]	

OR, odds ratio; HR, hazard ratio; CI, confidence interval; JA, Japan Agriculture cooperatives; NSAID, nonsteroidal anti-inflammatory drugs.
Studies from European regions are highlighted in bold font type.
[a]Compared to *H. pylori*-negative individuals (reference).

TABLE 6 Overview of the studies on the impact of vitamin intake on the development of stomach cancer after *Helicobacter pylori* infection

Vitamin	Study reference	Type of cancer	Intake	HR/OR	95% CI	Adjusted for
Vitamin C	**Ekstrom et al**[62]	Cardia	High	0.8	0.3-2.0	Socioeconomic status and total caloric intake
		Noncardia	High	0.5	0.3-0.9	
	Lunet et al[59]	Stomach	High	0.80	0.40-1.59	Education, number of siblings, vitamin and mineral supplement use, total caloric intake, vitamin C, vitamin E, and carotenoids intake
	Epplein et al[49]	Noncardia	High	0.5	0.2-0.9	Ethnicity, cigarette smoking, education, NSAID use, family history of cancer, and total calories
	Kim et al[64]	Stomach	High	0.72	0.32-1.65[a]	History of gastritis or gastric ulcer and educational level
			Low	4.68	1.97-11.1[a]	
	Kim et al[63]	Stomach	High	0.10	0.02-0.63	Socioeconomic status, family history, refrigerator use, supplement use, and specific foods[b]
β-carotene	**Ekstrom et al**[62]	Cardia	High	0.6	0.2-1.5	Socioeconomic status and total caloric intake
		Noncardia	High	0.5	0.3-0.8	
	Epplein et al[49]	Noncardia	High	0.3	0.2-0.7	Ethnicity, cigarette smoking, education, NSAID use, family history of cancer, and total calories
	Kim et al[63]	Stomach	High	0.54	0.12-2.52	Socioeconomic status, family history, refrigerator use, supplement use, and specific foods[b]
Vitamin A	**Lunet et al**[59]	Stomach	High	1.48	0.82-2.69	Education, number of siblings, vitamin and mineral supplement use, total caloric intake, vitamin C, vitamin E, and carotenoids intake
	Epplein et al[49]	Noncardia	High	0.3	0.2-0.6	Ethnicity, cigarette smoking, education, NSAID use, family history of cancer, and total calories
	Miyazaki et al[66]	Stomach	High	2.00[HR]	1.08-3.70	Body mass index, diabetes, serum total cholesterol, smoking habit, alcohol intake, regular exercise, and other dietary factors
	Kim et al[63]	Stomach	High	0.32	0.07-1.52	Socioeconomic status, family history, refrigerator use, supplement use, and specific foods[b]
Vitamin E	**Lunet et al**[59]	Stomach	High	1.15	0.64-2.07	Education, number of siblings, vitamin and mineral supplement use, total caloric intake, vitamin C, vitamin E, and carotenoids intake
	Ekstrom et al[62]	Cardia	High	0.3	0.1-1.0	Socioeconomic status and total caloric intake
		Noncardia	High	0.7	0.4-1.1	
	Epplein et al[49]	Noncardia	High	0.4	0.2-0.9	Ethnicity, cigarette smoking, education, NSAID use, family history of cancer, and total calories
	Kim et al[63]	Stomach	High	0.16	0.03-0.83	Socioeconomic status, family history, refrigerator use, supplement use, and specific foods[b]

HR, hazard ratio; OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs.
Studies from European regions are highlighted in bold font type. All studies adjusted for age and sex.
[a]Compared to *H. pylori*-negative persons (reference); remaining studies compared to infected individuals with low intakes of the specific component.
[b]Specific foods included charcoal grilled beef, spinach, garlic, mushroom, and kimchi types.

of β-carotene, vitamin C, and vitamin E significantly decreased the risk for noncardia stomach cancer among those infected with the bacterium. In contrast to the previous study, the trend for interaction was significant (*P*-value .03).[49] A European case-control study of the association with vitamin C, vitamin E, and vitamin A equivalents could not demonstrate any difference in the risk for developing *H. pylori*-related stomach cancer.[59] A Korean case-control study showed significant interactions for vitamin C and vitamin E (*P*-values, respectively, .015 and .028). High intakes of these vitamins showed a significant protective effect toward the associated stomach cancer among *H. pylori*-infected individuals. No association was found for other vitamins, nor for folate (OR 0.6; 95% CI 0.1-2.78).[63] Another case-control study was stratified based on vitamin C intake. High intakes slightly decreased the risk among the infected ones suggesting a protective inhibition of *H. pylori* activity.[64] In association with the more virulent type of the bacterium, namely the CagA-positive strain, a matched case-control study showed no significant interaction with vitamin C toward stomach cancer (*P*-value .874).[65] Among all those infected in the cohort study by Miyazaki et al, the subjects with a high dietary vitamin A intake were more at risk for developing stomach cancer compared to those with low intakes of this vitamin. However, there was no significant interaction between vitamin A intake and *H. pylori* for stomach cancer diagnosis (*P*-value .27).[66] The interaction term was also not significant in the study by Epplein et al[49] (*P*-value .56), but they observed among the infected an inverse association at higher intakes of vitamin A.

One case-control study explored the association between flavonoids and *H. pylori* infection. Among *H. pylori*-infected individuals, the risk of getting stomach cancer was reduced within the group with the highest intakes of total flavonoids. However, after additional adjustments, the trends were not significant for most flavonoids, except among women (*P*-values <.05).[67]

Meat The association between meat intake and risk of stomach cancer in interaction with *H. pylori* infection was investigated in a nested case-control study within the EPIC cohort study. They demonstrated a significant association for total meat intake and processed meat, especially toward the development of gastric noncardia adenocarcinoma. A daily intake increase of 100 g total meat increased the risk for developing noncardia stomach cancer among the infected subjects (adjusted OR 5.3; 95% CI 2.1-13.4). No association could be found for red meat or poultry, in contrast to processed meat. A daily intake increase of 50 g processed meat resulted in a risk twice as high for developing stomach cancer (adjusted OR 2.0; 95% CI 1.1-3.8). More specifically, it led to an increased risk of noncardia gastric adenocarcinoma (adjusted OR 2.7; 95% CI 1.2-5.9).[68] Another case-control study in Hawaii found a similar association with processed meat among the *H. pylori* infected. A daily intake of 8.7-25.4 g (or more) of processed meats increased the risk of stomach cancer compared to those consuming less than 8.7 g (OR 2.7; 95% CI 1.4-5.2).[49] High intakes of meat in infected Japanese subjects compared to noninfected subjects with low intakes of meat were also associated with an increased risk in this case-control study (OR 3.0; 95% CI 1.1-8.8).[61] Of note, the interaction terms were not significant in all the above-mentioned studies investigating the effect of meat consumption on the development of *H. pylori*-related stomach cancer (*P*-values >.05).

3.2.4 | Physical activity

One European cohort study (the EPIC study) investigated the association between physical activity and *H. pylori*-associated stomach cancer. Different types and intensities of physical activity during working hours as well as during leisure time were studied, but no association between any kind of physical activity and *H. pylori*-related stomach cancer could be found.[69]

4 | DISCUSSION

This systematic review demonstrates that the *H. pylori* infection rate is still high in several regions in Europe. Recent large-scale European studies showed the lowest prevalence of *H. pylori* infection among adults in the Czech Republic, where still almost a third of the individuals was infected. Other large studies from this century showed much higher infection rates, up to 84% in Portugal and Poland. The fraction of infected individuals varies considerably according to region and time. In Europe, the infection rates were generally lower in Northern Europe and the highest infection rates could be found in Eastern and Southern Europe which are also the regions with the highest stomach cancer incidence rates in the European Union. However, due to the discrepancy between these high *H. pylori* prevalence and the stomach cancer incidence rates, factors other than *H. pylori* infection are also important.[5]

It is important to identify high-risk subpopulations that could benefit most from interventions.[70] This systematic review showed that residents in particular European regions are more likely to be infected than other Europeans. This could be explained by the different risk factors for infection by region. Repeatedly documented risk factors include older age, limited hygiene, lower socioeconomic status, smoking, and overcrowding.[31] In industrialized regions, the prevalence of *H. pylori* infection is low early in childhood and slowly rises with increasing age.[10] These rising infection rates with increasing age were confirmed in our systematic review for European industrialized countries, a finding most likely explained by an aging cohort effect, in which older individuals were infected with *H. pylori* in childhood when the infection was more prevalent.[71] Throughout time, the prevalence of *H. pylori* infection can change as found in the Czech Republic, Finland, and Norway, which makes it more difficult to compare the different studies conducted in different time periods. The difference in infection rates between two studies from the Netherlands was remarkable, which could be possibly explained by the inclusion of Non-European immigrants in the study of De Vries et al,

while this population group was not included in the study of van Blankenstein et al[33,34] Migrants originating from high prevalence areas might already be infected with this persistent bacterium in childhood.[72] Information about the infection rate itself is not enough. The specific strain in interaction with the specific host immune response will likely determine who will or will not develop stomach cancer.[10] Therefore, further studies are necessary to have more recent data on infection rates and to know the specific (possibly more carcinogenic) strains present by region for predicting the future burden of stomach cancer.

When comparing the infection rates, one should also take into account 1, the various detection methods used; 2, the different sample sizes studied; 3, the different inclusion and exclusion criteria used; and 4, the different age ranges. Serology is the most commonly used detection method for *H. pylori* infection in large epidemiological studies. According to region, it has a sensitivity and specificity of 80%-90%. The major disadvantage of the test is being unable to distinguish between active ongoing infection and previous exposure.[10] There were wide variations regarding the sample sizes between studies. In some instance, it was difficult to determining the representativeness of study with respect to the general population. Furthermore, not all studies were equally clear about the inclusion or exclusion criteria, for example, in specifying whether or not a specific subpopulation was enrolled. Health workers have been reported to be more frequently infected than others, which could be a selection bias.[73-75] In this review, studies of *H. pylori* infection among sick individuals or among health workers alone were excluded to avoid such overestimates as the aim of our review was to investigate the general adult population. Lastly, the groups studied had different age ranges and not all age groups were equally represented within the studies. However, selected studies had to be quite representative for a large part of an adult population; otherwise, they were excluded based on poor quality/representativeness (see exclusion criteria). This systematic review included study groups starting at 15 years old to represent an adult population.

The impact of lifestyle factors among infected subjects was systematically investigated to find the *H. pylori*-infected groups at highest risk of stomach cancer. Among infected individuals, a significantly increased risk was generally found among smokers, high salt consumers, and those eating larger amounts of (mainly processed) meat. This is in accordance with the recent report of the *World Cancer Research Fund International* (WCRF) reporting that there is strong evidence that consuming foods preserved by salting and consuming processed meat increases the risk of stomach cancer. However, that report did not focus on individuals testing positive for *H. pylori* infection and many studies were not adjusted for *H. pylori* status as confounding factor.[76] A median intake or more of fruit and vegetables decreased the risk among European *H. pylori*-infected individuals in two studies. Concerning other dietary components (vitamin A, vitamin C, vitamin E, β-carotene, flavonoids), the studies were inconclusive. Furthermore, no association was found for the remaining two lifestyle factors studied: alcohol consumption and physical activity.

Nevertheless, it should be noted that a healthy lifestyle, including increased intake of a diet rich in fruit and vegetables, reduced intake of salted and smoked food and red meat, and a reduction in alcohol intake as well as smoking cessation, remains a core recommendation in the prevention of gastric cancer, independent of *H. pylori* infection.[77]

Although the actual impact of lifestyle factors causing stomach cancer could be modified by host genetics and the characteristics of the bacterium,[78-80] studies using interaction terms in their models to show this relationship between these different factors were often showing conflicting results. High-quality studies among European populations are too scarce to draw any evidence-based conclusions in Europe. Studies usually investigate the independent impact of lifestyle factors on stomach cancer, but more research is needed on the impact of lifestyle in association with *H. pylori*. Knowing how this specific interaction affects disease progression to stomach cancer is important to define potential public health interventions. In addition, some studies applied different or more extended adjustments and inclusion/exclusion criteria. During the selection process, not all articles could be retrieved despite considerable efforts, which could have caused the omission of some relevant studies. Independent reviewers were involved in the selection process, and a methodological quality control was conducted for each selected study, which are strengths of this systematic review.

Some current eradication treatment shows a decrease in efficacy due to the increase in *H. pylori* resistance to clarithromycin.[11] Although recent guidelines recommend eradication in high-risk populations and subjects (Maastricht guidelines, attached), uncertainties remain about the potential impact and cost-effectiveness of routine screen-and-treat programs in European countries.[70] Adverse consequences such as an increase in antibiotic resistance are one of the concerns that have probably delayed the establishment of interventions. Moreover, *H. pylori* may have a protective role against atopic conditions which is also a major health problem in the industrialized countries.[81] Alternative options such as a vaccine have been investigated but still with limited success.[82] This systematic review summarizes recent insights on the impact of lifestyle factors on disease progression toward stomach cancer among infected individuals, which could be another interesting approach to elaborate preventive strategies against *H. pylori*-associated stomach cancer in Europe. Our findings suggest that even among infected individuals, some modifiable lifestyle factors such as smoking and the intake of salt; (processed) meat, fruits, vegetables, and vitamins should be evaluated as potential preventive interventions for stomach cancer reduction in high-risk areas.

DISCLOSURES OF INTERESTS

The authors have no conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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