

UiT

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# ***Helicobacter pylori* infection in the 21<sup>st</sup> century**

*Epidemiology, transmission and clinical aspects*

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*A dissertation for the degree of Philosophiae Doctor – 2016*



Cover photo: Tom Melby

## Acknowledgements

This project started back in 2003, when my main supervisor Jon Florholmen first created the idea of a *Helicobacter pylori* epidemiology study. Most of the work has been done in Bodø in late nights, week-ends, yearly periods off work and some holidays, and there have been many short trips to Tromsø for usually fruitful conversations and discussions. It is not possible for me to list all friends, colleges and relatives who have contributed directly and indirectly to fulfilment of this research. Nevertheless, I wish especially to thank

Jon, my main supervisor, for his never ending optimism and unstrained positive attitude  
Bjørn Straume, my co-supervisor, for valuable statistic and epidemiology insight.  
Eyvind Paulssen, for significant input in research thinking, academic writing and SPSS charts  
Anne Mette Asfeldt, for permitting me to work with her Sørreisa data, and for valuable advices  
Liisa Mortensen, for her priceless microbiology work in the start of the project  
Jan Magnus Kvamme, for fruitful input and encouraging discussions in the latter years

And

Bio engineer Jim Richard Ness, for his essential practical work in the microbiology laboratory  
Sissel Engan and Karin Harda Hansen for their secretarial work and for taking care of the many awkward inquiries.  
My very helpful colleges Randolf Hardersen, Knut Tore Lappegård and Terje Tollåli for willingly substituting for me in my final phase of writing  
Roger Steinbakk at the hospital library for speedy literature service  
Marianne Elvik and colleges for punching huge data sheets  
Head of Medical Clinic Olaug Kråkmo, for her positive attitude

The inhabitants of central Bodø community, for their remarkably positive attitude

Also

The Northern Norway Regional Health Authority for some initial financial support  
My employer Nordland Hospital for granting me leave and some salary in the project's closing stage

But most important

Gunvor, my beloved wife, who has supported me all the way in spite of her own heavy workload and lately disabling illness  
and our two excellent daughters Kaja and Silje, for taking responsibility for hard domestic work in my periods of absence, and for reminding me of the right priorities in life. Silje has also been research assistant in the start of the project and has given invaluable assistance in the very last writing phase

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## Abbreviations

BMI	Body Mass Index
Cag A	Cytotoxin-associated gene A
FB	Functional Bowel
GORD	Gastro-Oesophageal Reflux Disease
GSRS	Gastrointestinal Symptoms Rating Scale
<i>H. Pylori</i>	Helicobacter pylori
IBS	Irritable Bowel Syndrome
IgA	Immunoglobulin A
MLST	Multi-Locus Sequence Typing
NFκB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NHANES	National Health and Nutrition Examination Survey
NSAID	Non-Steroidal Anti-Inflammatory Drug
NUD	Non-Ulcer Dyspepsia
SSB	Statistisk Sentralbyrå (Statistics Norway)
UBT	Urea Breath Test
Vac A	Vacuolating Cytotoxin Gene

## List of papers

### *Paper I*

*Breckan RK, Paulssen EJ, Asfeldt AM, Mortensen L, Straume B, Florholmen J. The impact of body mass index and H. pylori infection on gastro-oesophageal reflux symptoms: A population-based study in Northern Norway. Scand J Gastroenterol. 2009, 10:1-7.*

### *Paper II*

*Breckan RK, Asfeldt AM, Straume B, Florholmen J, Paulssen EJ. Prevalence, comorbidity, and risk factors for functional bowel symptoms: a population-based survey in Northern Norway. Scand J Gastroenterol 2012, 47, 1274-82.*

### *Paper III*

*Breckan RK, Paulssen EJ, Asfeldt, AM, Kvamme JM, Mortensen L, Straume B, Florholmen J. The all-age prevalence of H. pylori infection and potential transmission routes in a population-based study. Submitted Helicobacter 2015.*

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## Summary in English

### ***Background***

More than half the world's population is colonized with *Helicobacter pylori* (*H. pylori*) in the gastric mucosa which is the major cause of chronic gastritis and peptic ulcer. Moreover, *H. pylori* has been associated with the development of non-cardia gastric cancer, the second leading cause of cancer-related deaths worldwide, and has been linked to extra-intestinal diseases, with unsettled causal relationships. The human host immune response is unable to clear the *H. pylori* infection, and the clinical phenotype is dependent on the interactions between the host immune response and the pathogenicity of the bacterium. The prevalence of *H. pylori* infection is greatly reduced in developed countries but can be as high as >90% in underdeveloped countries, and remains a great health problem world-wide.

### ***Aims***

In a population based study from two North Norwegian cohorts, we aimed to

- describe the association between *H. pylori* infection and reflux disease, functional bowel symptoms and obesity
- describe the all age prevalence of *H. pylori*
- describe potential transmission routes of *H. pylori*

### ***Results***

We found that *H. pylori* is protective against reflux symptoms in men but not in women, whereas obesity was an independent risk factor for reflux symptoms in women. Functional bowel symptoms are prevalent in the population, and female gender, high body mass index and low age, but not *H. pylori* infection, are risk factors for the condition. There was no association between *H. pylori* infection and body mass index including being obese. In our



populations with presently apparent high hygiene status, the transmission of *H. pylori* infection may start also in the adolescence, has a peak in adults, and potential transmission routes are out-door toilette, private well and farm animals but not as independent factors in multivariate analyses.

### ***Conclusion***

In the start of the 21<sup>st</sup> century it seems that the *H. pylori* infection may start also in the adolescents, and has its peak in adults, and the transmission is associated to low hygiene standards. *H. pylori* infection is associated with reflux symptoms in men, but not with functional bowel symptoms or obesity.

# Sammendrag på norsk

## ***Bakgrunn***

Over halvparten av verdens befolkning er infisert med bakterien *Helicobacter pylori* i magesekkens slimhinne. Denne bakterien er hovedårsaken til kronisk magekatarr og magesår. *Helicobacter pylori* er assosiert med utvikling av kreft i magesekken, og med utvikling av tilstander utenfor tarmsystemet hvor årsaksammenhengen er ukjent. Vertens immunrespons greier ikke å fjerne *Helicobacter pylori* infeksjonen, og de forskjellige sykdomstypene er derfor karakterisert ved interaksjoner mellom vertens immunrespons og bakteriens evne til å skape sykdom. Forekomsten av *Helicobacter pylori* infeksjonen er de siste tiår kraftig redusert i industrialiserte land, mens den er såpass høy som > 90 % i utviklingsland, og den er fortsatt et helseproblem verden over.

## ***Målsettinger***

I denne befolkningsbaserte studien fra to nordnorske kommuner er målsettingene å beskrive

- Sammenhenger mellom *Helicobacter pylori* infeksjonen og reflukssykdom, funksjonelle mageplager og overvekt
- Forekomsten av *Helicobacter pylori* i alle aldersgrupper
- Mulige smitteveier til *Helicobacter pylori*

## ***Resultater***

Studien viser at *Helicobacter pylori* virker beskyttende mot reflukssymptomer hos menn, men ikke hos kvinner, mens overvekt er en uavhengig risikofaktor for refluks symptomer hos kvinner. Funksjonelle tarmplager er utbredt hos unge voksne kvinner, men disse plagene har ikke sammenheng med *Helicobacter pylori*. Det var ingen sammenheng mellom *Helicobacter pylori* infeksjonen og kroppsmasseindeks inklusiv overvekt. I befolkninger med høy

hygienestandard, ser det ut som om smitte av *Helicobacter pylori* starter først i tidlig ungdomstid, mens forekomsten er størst hos voksne, og mulige smitteveier er via utedo, privat vannforsyning eller gårdsdyr, men ikke som uavhengige faktorer i statistiske multivarians analyser.

### ***Konklusjon***

I det 21 århundre viser våre data at *Helicobacter pylori* infeksjonen starter først i tidlig ungdomstid, forekomsten er størst blant voksne, og smitten er assosiert til ulike hygieniske faktorer. *Helicobacter pylori* infeksjonen er assosiert til reflukssymptomer hos menn men ikke til funksjonelle tarmlager eller overvekt

# 1. INTRODUCTION

Presently, over half the world's population is colonized with *Helicobacter pylori* (*H. pylori*), which is the major cause of chronic gastritis and peptic ulcer (1). *H. pylori* has also been associated with the development of non-cardia gastric cancer, which is the second leading cause of cancer-related deaths worldwide (2). *H. pylori* infection has also been linked to extra-intestinal diseases, yet with unsettled causal relationships (3). The host immune response is unable to clear the *H. pylori* infection, and the clinical phenotype is dependent on the interactions between the host immune response and the pathogenicity of the bacterium. The prevalence of *H. pylori* infection is greatly reduced in developed countries but can be as high as >90% in underdeveloped countries (4). The infection can be effectively cured by antibiotics combined with acid inhibitors (5), but still remains a challenge for gastroenterologists world-wide.

## ***1.1 H. pylori infection from ancient times to the final discovery***

Infection with *H. pylori* has co-evolved with mankind since the Paleolithic era (5). Thus, both humans and *H. pylori* migrated from East Africa around 58 000 years ago (6), (7).

The spiral-shaped microorganism later identified as *H. pylori* was noticed in the human stomach by the clinical researcher Jaworski at Krakow University, Poland in 1899 (8) after Bizzozero had found spiral organisms in dogs in 1893 (9). The main crucial events of our knowledge of *H. pylori* came in 1979-82 by the groundbreaking experiments of the two Australian scientists, the pathologist Robin Warren who identified the bacterium underneath the protecting lining mucus coat in the stomach, and Barry Marshall that finally, albeit accidentally, successfully cultured the bacterium (10), (11). In 1985, Marshall reported *H. pylori* to be the cause of gastritis (12). Finally, Borody in 1987 was the first to document that

*H. pylori* caused peptic ulcer disease by developing the triple therapy (bismuth, metronidazole and tetracycline) used in the eradication of *H. pylori* (13), (14). This has later been reported as “Marshall found the bug and Borody the drug”.

## ***1.2 H. pylori microbiology***

The *Helicobacter* genus includes more than 35 species. *H. pylori*, the most important human pathogen, is Gram-negative, spiral shaped, acid-resistant and microaerophilic. Research boomed heavily after 1997, when Tomb and co-workers published the entire *H. pylori* genome (15).

Thus, *H. pylori* can be described as a cross between a commensal and a pathogenic bacterium. Typically, all *Helicobacter* species express urease enzymes, an enzyme that is essential for microbial survival (16). Experimental deletion of the urease gene renders *H. pylori* unable to colonise gastric mucosa (17).(18). The function of urease is to increase pH in the microenvironment by the generation of ammonia (NH<sub>3</sub>) from urea and to secure the nitrogen supply for bacterial protein production (19). Urease is an intracellular enzyme that is bound to the outer membrane of other bacteria upon bacterial lysis. These non-covalently bound proteins may in turn impair the function of secretory IgA directed against *H. pylori* by antigen shedding. However, all clinical isolates produce urease and thus it cannot explain the occurrence of clinical disease.

Several pathogenic bacterial factors have been identified which may have impact on the clinical presentation, but the only factors with consistent impact in laboratory and clinical studies were cytotoxin-associated gene A (CagA) and vacuolating cytotoxin gene (VacA). Both of these factors can be detected in strains from asymptomatic carriers. However, their

contributions to *H. pylori*-related pathology are academically interesting, but the overall impact is small. Alternatively, the main determinant may be differences between immune phenotypes of the infected individuals.

Today the most thoroughly documented pathogenic factor of *H. pylori* is CagA (20). The functions of the CagA protein is not fully understood, but several lines of evidence indicate that the protein is a phosphatase capable of altering activation states of proteins and transcription factors like NF $\kappa$ B in the target cell (21).

All *H. pylori* strains contain the VacA gene, but five different genotypes exist rendering approximately 50% of the strains VacA protein negative. The VacA has been shown to induce vacuolization of epithelial gastric cell lines (16).

### ***1.3 The source and transmission routes of H. pylori***

The source or sources of *H. pylori* are so far unknown, and subsequently the knowledge of the transmission routes is limited. Faecal animal *H. pylori* has been one of the most frequent proposed sources (22), and the primary transmission route has been proposed to be via drinking water, and the secondary to be intra-familial *H. pylori* infection (23). The transmission routes have been proposed to be combinations of oral-oral, gastro-oral or faecal-oral transmission due to lack of access to clean drinking water and proper sanitation as proposed by Khalifa (24).

Both water and food have been proposed to be the primary source of *H. pylori* (for review, see (25)). *H. pylori* DNA can be detected in water using different methods (26), (27), and this has facilitated several studies dealing with water as a source of transmission. The animal source

for contamination drinking water has been proposed to be mice (22). Food has been suggested to be a vehicle rather than a source of *H. pylori* (28).

The understanding of intra-familial *H. pylori* infection was increased with the introduction of multi-locus sequence typing (MLST). This technology allows for the assessment of genomic profiles of *H. pylori* isolates from infected families. MLST can identify the original strain infecting the index person. In one report, a mother to child transmission could be detected in three of four families, and father-child and child-child transmission could also be documented (29). Transmission from mother to child and sibling to sibling has also been documented by Yokota (30). It is noteworthy that the oral cavity can be a reservoir of *H. pylori* (31), and it is also of interest that vaginal yeast is an important primary reservoir of *H. pylori*, thus explaining transmission to neonates (32).

The question of whether breast-feeding is a transmission route from mother to child, or the opposite: whether breast-feeding can protect from *H. pylori* infection, is unanswered. Most studies agree that the latter is the case. In a meta-analysis, breast feeding had a protective effect in a less economically developed setting (33). However, in one report, *H. pylori* DNA was found at a rate of 6.1% in breast milk, but there remained a question whether this was due to a contamination from the nipples (34).

#### **1.4 *H. pylori* diagnosis**

Various tests have been developed to diagnose *H. pylori* that display varying accuracy, specificity and feasibility for use in clinical practice or in research. This can be analytical tests for detection of HP antigen or antibodies, detection of urease production, histological detection or culture of the HP. The various tests have various advantages and disadvantages,

and the choice of test(s) to be used is dependent on many factors such as for clinical or research use. In general the tests need either an intervention such as a biopsy from an endoscopic examination, or a peripheral test such as blood tests for detecting HP antibodies, or antigen and/or antibodies tests from samples from saliva, urine and faeces, or detection of urea in expired breath air.

In clinical practice, a blood test for the detection of *H. pylori* antibody or the test for *H. pylori* antigen in feces are most often used, both being non-invasive. The former has the disadvantage that antibodies are present in blood also after eradication of the bacterium. The invasive tests mostly used in clinical practice are the rapid urease test and histological detection, both performed in biopsies from gastric mucosa. The former test can be false negative when bacterial growth is inhibited due to the use of acid suppression medication.

In clinical research, there is a need for extensive documentation of *H. pylori* using a combination of several tests, both invasive and non-invasive. For epidemiological studies, the serum *H. pylori* antibody tests are widely used. However, this has been challenged by the introduction of the fecal antigen test, which is more practical to perform and more reliable than the antibody test. For more details, see Chapter 1.5 (for review, see (35)).

### ***1.5 H. pylori epidemiology***

There is a marked difference in prevalence between developed and underdeveloped countries (36). Numerous epidemiological studies of *H. pylori* infection based on various registration methods such as cohort examinations exist, but only population-based studies will give a real estimate of the prevalence in a community. Only a few population-based prevalence studies in children and adolescents exist, in contrast to the larger number of studies in adults. Many of



the population studies have used serological testing (37), (38), a method with known limitations as described above. Lately, studies have also been published that use the urea breath test (UBT), which is practical for population studies (39), (40).

### **Studies in children**

Only a few population-based prevalence studies have been published that include children (41), (42), (43), and especially studies using modern precise methods are scarce. Serology-based studies from Europe have shown prevalence in children from 1.2% in the Netherlands (44) to 32% in Polish children (38). Reports from USA have revealed prevalence of 7.1% (45) up to 29% (46).

The UBT is more precise and feasible in children (47), and UBT-based studies from Europe have reported prevalence in Germany from around 6% (48) and 8.6% in Ireland. An American study revealed a prevalence of 17% in children (49). The highest occurrence of *H. pylori* infection have been reported from Asia, with prevalence found from 13.1% in Hong Kong (42) to around 50% in Turkey (50), and 64.2% in Iran (51).

Stool tests from asymptomatic subjects in Europe have revealed a prevalence of 27% in children of Turkish descent in Germany aged 1 to 4 (52), and 7.1% in children aged 0 to 15 in the Czech Republic (41). In Uganda, investigators found a prevalence of 44.3 in asymptomatic children aged 0 to 12 (53).

### **Studies amongst adolescents**

Prevalence studies in adolescents are harder to find. In Siberia, the seroprevalence in youths aged 14 to 17 was 56.3% (54), and in a follow-up study from Turkey in the age group 9 to 18,

the prevalence based on UBT was around 50% (55). A German study found a prevalence of 6.5% in 14-year old adolescents (56).

### **Studies in adults**

The prevalence of *H. pylori* infection in adults has been studied much more extensively. Most studies are based on serological tests. The first report from our region was that of Bernersen et al in 1987 (57), who used bacterial culture and found a prevalence of 41.8%. A follow-up study 17 years later reported 25% (58). In a North American study one found a seroprevalence of 17.1% in symptomatic patients (59), and studies from Iran (60) and Brazil (61) have found prevalence of 69% and 63%, respectively.

UBT-based prevalence studies are considered more precise than serology studies, but are more cumbersome to perform. European UBT-based studies have reported prevalences of 42% in all age groups 5-100 years in the Czech Republic (62) and 58% in Italy in age groups 18-80 (63). A study from Turkey found a prevalence of 82.5% in asymptomatic adults (64), and another study from USA found 52% (65).

Stool tests are not often used in adult studies, but a Japanese study using both serology and stool tests found a prevalence of approximately 40% (66). In Borneo, a stool test-based study revealed a prevalence of 37.7% (67). A Northern Norwegian methodology study found a prevalence of 44.3% in dyspeptics (68).

### ***1.6 H. pylori infection and gastric pathogenicity***

*H. pylori* typically colonizes the gastric mucosa with the development of histological gastritis in all infected subjects. However, the infection induces various clinical phenotypes depending on bacterial factors, host factors and environmental factors. It is of interest that only a

minority of the infected patients have symptoms, 10-20 % develops peptic ulcer disease, and less than 2% develop gastric cancer.

### **Acute and chronic gastritis.**

Colonization of *H. pylori* in the gastric mucosa induces inflammation, especially in the antrum and corpus part of the stomach. This chronic active gastritis is the pathophysiological mechanism of the *H. pylori*-associated disorders as described below.

There are only a few reports of acute gastritis, but some knowledge is based on established experimental human models (69). Thus, *H. pylori* infection is known to give some transient dyspeptic complaints, and transient hypochlorhydria, i.e. the reduction of acid secretion. Whether the acute gastritis can spontaneously be resolved is unknown.

When the *H. pylori* colonization becomes persistent, there is a more pronounced, lasting reduction of acid secretion, and the more extended the inflammation is, the greater is the reduction of secretion. There is a counteractive effect of acid secretion on the *H. pylori* growth. In patients with somewhat normal acid secretion, *H. pylori* colonization and the chronic gastritis is found in the gastric antrum where there is an absence of acid secreting parietal cells. In patients with more profound reduction of acid secretion, the gastritis moves proximally towards the gastric corpus, leading to pan-gastritis with the suppression of parietal cell function. The reduced acid secretion is counteracted initially by several mechanisms such as hypergastrinemia (for review, see (35))

### **Atrophic gastritis and gastric cancer**

The consequence of *H. pylori*-associated chronic gastritis may eventually be loss of normal gastric architecture, with the transformation of the gastric mucosa towards intestinal

metaplasia (intestinal-type epithelium) and fibrosis. Atrophic gastritis occurs in approximately 50% of *H. pylori*-infected patients, and especially in those with severe inflammation (70). The risk factors for developing atrophic gastritis beyond that of the intensity of *H. pylori* infection are not fully understood.

The association and causal relationship between *H. pylori*-associated atrophic gastritis, metaplasia and gastric cancer was first shown in studies of gastric cancer. Here, this pathophysiological sequence was more frequently seen when infection was present than in the uninfected controls (71). The causal relationship between *H. pylori* infection and gastric cancer has been established after extensive investigation (for review, see (35)). The risk of developing gastric cancer when infected by *H. pylori* is estimated to be increased by 10 fold compared to non-infected persons. Moreover, the extensive eradication of *H. pylori* the last decade in Western countries parallels the reduction of the incidence of gastric cancer. Yet a causal relationship is highly controversial, and even not documented in some studies (72).

### **H. pylori and peptic ulcer disease**

Before the nineteenth century, peptic ulcer disease – the common name for gastric and duodenal ulcer disease – was rare (73). From that time the prevalence of gastric ulcers increased, and around 1850 the first duodenal ulcers were reported. The diagnoses were based on physical examination, patient history and the presence of postprandial pain, as X-ray was not invented before 1895. Medical therapy was limited, and surgery was the main treatment up to the 1960s.

The cause of peptic ulcers remained a mystery for many decades, although several theories evolved. The Croatian physician Karl Schwartz published his theory of “no acid, no ulcer” (74) in 1910. Until the 1980s, the peptic ulcer disease was described as a multi-heterogeneous

disease with mucosal disturbances, vascular disturbances, infectious and/or toxic and psychogenetic as the most often reported causes (73).

The causal relationship between *H. pylori* infection and peptic ulcer disease was documented after extensive investigation subsequent to the discovery of the bacterium. In the first studies, *H. pylori* infection was found in 95% of patients with duodenal ulcer and in 85% in gastric ulcer patients. The life-time risk of developing peptic ulcer in *H. pylori* infected patients is 3 to 10 times higher than in non-infected patients (75). Finally, eradication of *H. pylori* became an efficient way to cure peptic ulcer disease (76).

One unexplained question is that why only some 10-20% of the infected patients develop peptic ulcer disease during a long term follow-up (77). This has been proposed to rely on bacterial and/or host factors.

### **H. pylori and non-ulcer dyspepsia**

Non-ulcer, or functional, dyspepsia (NUD), is defined as pain or discomfort from the upper gastrointestinal tract without documentable structural abnormalities. The association of *H. pylori* infection to non-ulcer dyspepsia has been extensively investigated. In a cohort of patients with dyspepsia, 30-60% will have *H. pylori* infection. However, the non-infected control group also has also a similar symptom rate (78). Therefore, there has been much debate of what will be the expected outcome of *H. pylori* eradication in patients with dyspepsia. In a meta-analysis of NUD, *H. pylori* eradication was associated with an 8% risk reduction compared to placebo, and the conclusion was that one had to eradicate *H. pylori* in 18 patients to achieve relief of dyspeptic symptoms in one patient (79). However, the Maastricht IV guidelines now recommend eradication in patients with functional dyspepsia, especially in high-prevalent regions (80).

### ***1.7 H. pylori and gastro-oesophageal reflux disease***

The prevalence of Gastro-Oesophageal Reflux Disease (GORD) is as high as 60% in many countries, and 10-20% have symptoms weekly (81). There are several potential risk factors for GORD, such as age, smoking, and life style factors with Body Mass Index (BMI) as the mostly proposed risk factor (82). Although extensively investigated, the contribution of overweight and obesity to GORD is still not clarified. When comparing the few strictly population-based studies, BMI was found to be independently associated to GORD in some studies (83), (84) but not in others (85), (86).

The role of *H. pylori* in GORD is also somewhat controversial, as both the presence and the absence of an association have been reported (87-89) A population-based study from 2007 has shown that *H. pylori* infection was not a risk factor for reflux symptoms (90). Finally, the interaction between BMI and *H. pylori* infection in the contribution to GORD is unsettled, as far as we know.

### ***1.8 H. pylori and functional bowel diseases***

Functional gastrointestinal disorders comprise a family of closely related symptom patterns describing pain or discomfort related to ingestion or digestion of food, often in the absence of a known organic cause. Functional bowel disease or Irritable Bowel Syndrome (IBS) according to the Rome criteria are possibly the most studied of these symptom patterns. IBS is a syndrome of constant or recurring abdominal pain or discomfort related to bowel movements, in the absence of biomarkers or endoscopic findings (91). IBS can be diagnosed according to the Rome II (92) or Rome III criteria (93). The prevalence of IBS is reported to be between 3% and 22%, with lower occurrence among males and in the elderly.

The cause of IBS is unclear, but etiological factors such as genetic, food intolerance and gut microbiology including post-infection IBS has been proposed, with visceral hypersensitivity as the common pathophysiological mechanism (94).

The association between *H. pylori* infection and IBS is not settled. *H. pylori* infection has been shown to be a risk factor for IBS in one study (95), but not in three other reports (96), (97), (98). There are, however, no larger, population-based studies that have addressed this issue.

### ***1.9 H. pylori and body weight***

The increasing prevalence of overweight and obesity from the 1980s in the developed world has a parallel in the decreasing prevalence of *H. pylori* and the increased use of antibiotics for its eradication. This has initiated a debate of a causal relationship between *H. pylori* infection and body mass index (BMI). Cross-sectional studies have shown an association between *H. pylori* infection and BMI (99), (100) whereas the the National Health and Nutrition Examination Survey (NHANES III) could not detect any association (101). In a large population-based, randomised controlled trial, significant weight gain (3 kg) was observed in the intervention group that underwent *H. pylori* eradication. Unfortunately, follow-up was only for 6 months. In an animal study, *H. pylori* colonization was shown to decrease weight gain (102). Finally, in a recent published review, the authors concluded that the increasing eradication of *H. pylori* during the last decade was a contributing causal factor to the obesity epidemic in the Western world (103). The *H. pylori* hypothesis explaining the obesity endemic is fascinating. Further support of this causal relationship is found in the report showing that eradication of *H. pylori* in non-dyspeptic patients caused an increase in plasma

ghrelin, the hunger hormone(104). In conclusion, there is some evidence of a causal relationship between *H. pylori* infection and BMI, but there is a need of further studies, especially population based, cross-sectional and prospective studies.

### ***1.10 Unresolved questions and challenges***

As described above, since the identification of *H. pylori* in 1970-80s, much knowledge has been gained of the epidemiology, pathophysiology and clinical phenotype of this infection. Maybe one of the most interesting unresolved questions is why only 10-20% of the *H. pylori*-infected patients develop peptic ulcer disease. Moreover, *H. pylori* behaves in some way as a commensal bacterium, and in other times as a pathogenic bacterium. Finally, the source and ways of transmission of the bacterium are still unsettled.

*H. pylori* infection is also associated to extra-gastroduodenal disorders, some of which have been described above. Further disorders that have been associated with *H. pylori* infection are coronary heart disease, dermatological disorders, autoimmune thyroid diseases and others (for review, see (35)). For these possible associations there are many controversies, and the associations may have several explanations. In general, association studies should be performed in large scale, population-based studies. Most of the discrepancies described above may be explained by the lack of such studies.

Therefore, major focus of *H. pylori* in the 21<sup>st</sup> century should be on the sources and transmission routes, and on potential association of the infection with extra-gastroduodenal disorders to find any existing causal relationships.



## 2. AIMS OF THE THESIS

Despite extensive investigations there are many unresolved questions and discrepancies in the understanding of *H. pylori* infection. Therefore, to gain more knowledge, I have in the my doctoral thesis focused on the following hypotheses:

1. There is an association between *H. pylori* infection and reflux disease
2. There is an association between *H. pylori* infection and functional bowel disease
3. There is an association between *H. pylori* infection and obesity
4. The low prevalence of *H. pylori* in the start of the 21<sup>st</sup> century is due to low transmission risk in young age groups.
5. *H. pylori* transmission is associated with low hygienic standards, i. e. animal contact, private water supply and out-door toilette.

### 3. SUMMARY OF RESULTS

#### 3.1 Paper I

*Breckan RK, Paulssen EJ, Asfeldt AM, Mortensen L, Straume B, Florholmen J. The impact of body mass index and H. pylori infection on gastro-oesophageal reflux symptoms: A population-based study in Northern Norway. Scand J Gastroenterol. 2009, 10:1-7.*

The aim of this study was to evaluate the effect of BMI and *H. pylori* on reflux symptoms in an adult population. For this cross-sectional, population-based study from Bodø and Sørreisa communities in Northern Norway, a total of 3927 adults were invited to complete a questionnaire on gastrointestinal symptoms and to provide stool samples for the assessment of *H. pylori*. Reflux symptoms were considered present when a reflux syndrome score was >2 according to the Gastrointestinal Symptom Rating Scale (GSRS).

The response rate was 44.2%, and 44.7% of the respondents were male. There were similar characteristics in the two populations studied, but in the more rural population in Sørreisa the prevalence *H. pylori* infection was slightly higher than in the urban population of Bodø (28.9 % versus 35.0 %, but not significant after Bonferroni correction). In logistic regression analyses, *H. pylori* and smoking were not risk factors for reflux symptoms, whereas male gender (OR 4.78 (95%CI 1.88; 12.1)), age (1.01 (1.00; 1.03)) and overweight (1.51 (1.14; 2.00)) were. When stratified by gender, overweight and age were independent risk factors for reflux symptoms in females only, whereas *H. pylori* infection was protective against such symptoms in men. Models including these parameters could only explain 3% of the variations in reflux symptoms.

The strength of this study is that it is population based , and that validated questionnaires have been used. It should be noted that a low-threshold definition of reflux symptoms (mean GSRS reflux symptom score) was chosen in order to compare our findings with those of other reports, as in the prevalence of 26% for reflux symptoms found in a Danish population(105)]. In a study from Italy, reflux symptoms were found in 44.3% of the participants (106), whereas in a Swedish population-based study there was a prevalence of 40.0% (107), both using different questionnaires. Our results may thus be somewhat conservative, yet comparable to a review that found at least monthly reflux symptoms in 25% of participants (108). In conclusion, BMI is an independent risk factor for gastro-oesophageal reflux symptoms among healthy female adults, but contributes only to a minor part of the variation in these symptoms. *H. pylori* is protective against reflux symptoms in men.

### **3.2 Paper II**

*Breckan RK, Asfeldt AM, Straume B, Florholmen J, Paulssen EJ. Prevalence, comorbidity, and risk factors for functional bowel symptoms: a population-based survey in Northern Norway. Scand J Gastroenterol 2012, 47, 1274-82.*

The objective was to assess the occurrence of functional bowel (FB) symptoms in Northern Norway, and to describe gender differences, comorbidity, and association to risk factors, including *H. pylori* infection.

Adult subjects (18–85 years) from the communities Bodø and Sørreisa were invited to complete a questionnaire on gastrointestinal symptoms, and to provide stool samples for assessment of *H. pylori*.

Of the 3927 invited subjects, 1731 (44.1%) returned the questionnaire and 1416 (36.0%) provided stool samples. Functional bowel symptoms were found in 25%, somewhat more frequent in females (28.6%). Symptom pattern differed between genders only with regard to constipation. Presence of FB symptoms was significantly associated with gastro-esophageal reflux symptoms, headache, dizziness, palpitations, sleep disturbances, and musculoskeletal symptoms. Psychometric traits were also more prevalent: feeling of low coping ability, feeling depressed, feeling of time pressure, and a low self-evaluation of health. In a multivariate regression model, factors that influenced the reporting FB symptoms were male gender (OR 0.71, 95% CI (0.52; 0.96)), age 50–69 years or ≥70 years (OR 0.49 (0.30; 0.80) and 0.40 (0.21; 0.79)), obesity (OR1.61 (1.05; 2.47)), NSAID use (OR2.50 (1.63; 3.83)), and previous abdominal surgery (OR1.54 (1.05; 2.26)). The presence of *H. pylori* was not associated with FB symptoms.

The strength of this study is the sampling of symptoms in a general population. Although invitation to participate in a study of a certain ailment is prone to select those who have such symptoms, we are aware of this and have taken measures to adjust for such a bias. The weakness is the use of a non-validated questionnaire for the assessment of symptoms that mimic irritable bowel syndrome. IBS is defined as a presence of traits with a duration sufficiently long to give it a chronic nature, whereas the questions in the GSRS form samples the severity of symptoms present in the last week. By transforming a symptom severity score into symptom prevalence we have extended the original intention of the GSRS form, thus the interpretation of our data on functional bowel symptoms in an IBS setting is not straightforward.

We conclude that functional bowel symptoms are prevalent, but our findings may be prone to self-selection bias. FB symptoms carry a significant burden of comorbidity. Female gender and low age are known risk factors for FB symptoms, NSAID use as a risk factor deserves further clarification, whereas *H. pylori* infection was not associated with FB symptoms.

### ***3.3 Paper III***

*Breckan RK, Paulssen EJ, Asfeldt, AM, Kvamme JM, Mortensen L, Straume B, Florholmen J. The all-age prevalence of H. pylori infection and potential transmission routes in a population-based study. Submitted Helicobacter 2015.*

Previous research on *H. pylori* epidemiology has mostly focused on adult populations. In this combined urban and rural community, population-based, and all-age prevalence study, the aim was to study *H. pylori* prevalence in all age groups including children, and to identify potential transmission routes of the bacterium. Subjects from all age groups (children 0-11 years, adolescents 12-17 years and adults 18->80 years of age) recruited from both an urban and a rural community in Northern Norway were invited to deliver stool samples for the diagnosis of *H. pylori* antigen and to fill in a questionnaire (adult and adolescents only) on gastrointestinal symptoms, lifestyle factors and biometric data.

A total of 1 624 (35.3%) of the invited subjects including 173 (39.3%) of the children, 45 (19.2%) in the adolescents group, and 1 416 (36.1%) in the adults group, responded to the invitation. *H. pylori* infection was nearly undetectable (0.6%) among the children and the prevalence increased from adolescents (20.0%) to adults towards 45% at the highest age group. A broad screening for potential transmission routes showed that ever having a private

water source, an outhouse toilet in childhood, or contact with farm animals, was significantly associated to *H. pylori* positivity in univariate analyses. However, no independent risk factor could be identified in the multivariate analyses. Our data indicate that the transmission routes in the 21<sup>st</sup> century may be related to life-style factors in adolescence.

The strength of this study is the population-based prevalence measurements including all age groups, from both an urban and a rural community. Moreover, we have based our data on an antigen-based *H. pylori* test, with known high sensitivity and specificity. Yet there are areas with some weakness. Firstly, the participation from the adolescence group was low. The prevalence data of *H. pylori* infection from this group thus remains uncertain, but the lowest possible prevalence would still be 3% if all the 205 non-participating subjects had tested negative. Therefore, we have evidence from this study that *H. pylori* infection first occurs at a very early age. Another weakness of our study is that more comprehensible data would have been available if a family-based prevalence study had been performed in the *H. pylori* positive subjects.

In conclusion, in our populations with presently apparent high hygienic status the transmission of *H. pylori* infection first starts not only in childhood, but also in the adolescence, where potential transmission routes may be out-door toilette, private well and farm animals. A mother cohort effect must also be considered.

## **4. GENERAL DISCUSSION**

### ***4.1 Methodological considerations***

This is a population based urban study from two communities in North Norway, The Bodø *Helicobacter* study and the Sørreisa Gastrointestinal Disorder Study address a general Norwegian, adult population.

#### ***4.1.1 Participation, questionnaire and sampling of stool test***

A representative sample from the urban part (population 24,625 in January 2005) of Bodø municipality was drawn by Statistics Norway (<http://www.ssb.no/english/>), consisting of 480 persons aged 18-29 years and 200 from each of five 10-year strata: 30-39, 40-49, 50-59, 60-69 and 70-79 years, all together 1480 individuals were invited to participate.

##### **4.1.1.1 Adults**

The study population from Sørreisa (population 3326) has been described previously (58). In short, 2447 persons (all adults aged 18 to 85 years in the community) were invited to participate in 2004.

Both populations were invited to answer the same questionnaire on gastrointestinal disorders, lifestyle factors and biometric data, as well as to provide stool samples. The questionnaire is presented in Appendix 1.

The participation and HP status are presented in Table 1.

**Table 1. Participation and HP status in the Bodø *Helicobacter* study and Sørreisa Gastrointestinal Disorder Study.**

Numbers (%)	Bodø	Sørreisa	Bodø + Sørreisa
Invited	1480	2447	3927
Responder questionnaire (%)	541 (36.6)	1193 (48.8)	1731 (44.1)
Responder stool test (%)	500 (33.8)	916 (37.4)	1414 (36.0)
Responder male %	41	46	44.7
Responder mean age	51.4	51.9	51.7
HP positive (%)	145 (29)	321 (35)	466 (33)

#### **4.1.1.2 Children and adolescents**

In addition, population-representative groups of 440 children between 0 and 11 years of age, and 240 adolescents 12-17 years old in Bodø were invited. The children - rather their guardians – were asked to provide a stool sample, whereas the adolescent subjects were asked to fill in a simplified questionnaire (Appendix 1) and to deliver a stool sample as for the adult subjects. No questionnaire was used among the children. One child (0,06%, a girl) and 7 adolescents (20%, 4 girls and 3 boys) tested *H. pylori* positive.



**Table 2. Response rates among children and adolescents in the Bodø Helicobacter Study.**

Age group	Invited		Stool samples		Questionnaires	
	N	M/F	n (%)	M/F	n (%)	M/F
0-11 years	440	220/220	173 (39.0)	92/81	n/a	n/a
12-17 years	240	120/120	35 (14.6)	18/17	45 (18.8)	22/23

Over-all and gender distribution of response rate (n, percent) to the invitation to fill in a questionnaire (adolescents only) and provide stool samples for the detection of *H. pylori* in the Bodø Helicobacter Study. An equal number of males (M) and females (F) were invited.

#### **4.1.2 Potential bias**

Statistical bias occurs when the results are distorted by systematic differences in the studied samples. I will concentrate on potential pitfalls in this thesis with focus on selection bias, information bias and confounding, especially as we have pooled data from two studies, and that very young participants (adolescents) were included.

##### **4.1.2.1 Selection bias**

Selection bias is defined as selecting individuals for analysis without achieving a representative selection – a selection that matches the population that the research aims to study. As the sample in this study was selected by Statistics Norway and not by the researcher, selection bias due to participant selection procedures is less likely. The Statistics Norway selection included an equal distribution of individuals of all ages, gender and of socioeconomic backgrounds. However, the individuals who chose to respond to the survey and submit stool samples may not fully represent the source population regarding these factors. This is accounted for by presenting the results in age, gender and socioeconomic

categories. As mentioned before, the attendance rates of the surveys ranged from 33.8% to 48.8% in the adult group (table 1) and from 14.6% to 39.3% for children and adolescents (table 2). These numbers are not as high as can be seen in plain questionnaire-based studies, but taking into consideration that the respondents were asked to submit their personal human waste, it is reconciling that so many individuals from rather small geographic areas chose to participate. In comparison, an *H.pylori* study from Leeds using the much less intimate Urea Breath Test ended up with a response rate of 25% (109). That being said, this project's study sample could favourably be larger.

#### **4.1.2.2 Information bias**

To avoid information bias, defined as measuring different samples using different methods, the same laboratory technicians examined all the stool samples, and the utilised techniques did not differ from sample to sample. Furthermore, the same questionnaire was sent to every subject. The quality or accuracy of the information gathered about the participants is therefore the same for the entire study sample. Information bias might also appear if the participants report incorrect information (110). Such a systematic error may result in misclassification. However, in the present studies, we do not think serious misclassification is a significant problem. Overall, we see no indications of serious differential misclassification in the included studies.

#### **4.1.3 Assessment of *Helicobacter pylori***

The presence of *H. pylori* was assessed by detection of bacterial antigen in stool samples with a monoclonal immunoassay amplification method ("Hp Star", Dako Cytomation, Glostrup, Denmark) strictly according to the manufacturer's instructions. This method has been shown to have a sensitivity and specificity of more than 90% in adults as well as children (47), (111)

, and 98% and 94%, respectively, in adult patients in our region where the test has been validated (68). Unfortunately, and as far as we know, the test is not validated in children in our region, has been so elsewhere (112), (113), (41). This test and the serological antibody test are the most commonly used non-interventional test for diagnosis of *H. pylori* in our country. Compared to the blood test the faecal antigen test can detect the bacterium, whereas the blood antibody test has the disadvantage that antibodies are present in blood also after eradication of the bacterium. The disadvantage of using a stool test is the psychological aspects of the sampling. This was apparently the main cause of the low participation rate in the study among adolescents, whereas in children the participation rate of stool sampling was high.

## 5 Discussion of main results

### 5.1 *H.pylori* and reflux disease

In our study we have documented that the presence of *H. pylori* independently protects against reflux symptoms in men but not in women. Moreover, BMI is an independent risk factor for gastro-esophageal reflux symptoms among healthy female adults, but contributes only to a minor part of the variation in these symptoms.

The issue of *H. pylori* and its role on reflux disease has been extensively studied with contradictory results (84). Unfortunately, there are few population based studies covering this issue. Our population based study is in contrast to a population-based study from Norway that could not find such an association (90). These discrepancies are hard to explain. A definite plausible explanation of this discrepancy could be differences in assessment of *H. pylori*: stool test versus serum antibody test. A protective effect of *H. pylori* has been proposed earlier but not documented, the proposed protective mechanism being that *H. pylori* attenuates the potency of the gastric reflux in patients with corpus predominant gastritis (84). Finally, the diverging results of *H. pylori* to protect reflux symptoms in men and women is surprising and also hard to explain.

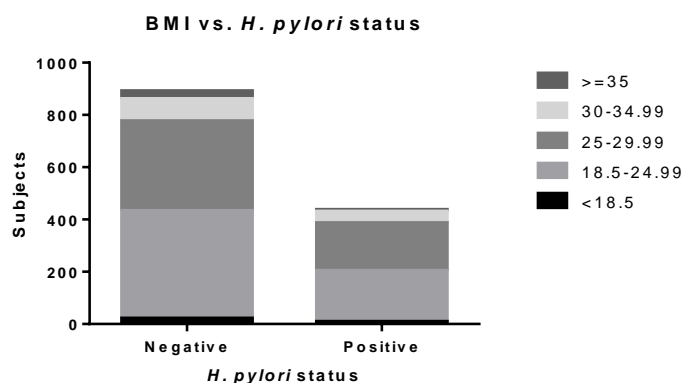
We also found that BMI was an independent risk factor for the development of gastro-esophageal reflux symptoms. BMI as an independent risk factor for reflux symptoms was only observed in younger adult women. Moreover, in agreement with a report by Nocon et al. (114), age was also an independent factor for reflux, although also only observed in women. As reported by Corley & Kubo (115), BMI-independent associations were observed in the white, but not in the black population. Therefore, the discrepancies observed in studies of

associations between reflux and BMI may be accounted for by differences in age, gender, ethnicity and geographical factors.

## 5.2 *H.pylori* and obesity

The distribution of infection in the various BMI classes is presented in Figure 1. There were no significant associations between the *H. pylori* status and the BMI classes among the females and among the males. It should be noted that the number of observations are low in the upper BMI classes, and most likely we have a statistical power problem.

**Figure 1. Relationships between *H. pylori* infection in the various BMI classes and the corresponding statistic analyses**



*H.pylori* status was not associated to any of the BMI classes ( $p=0.67$ ). This agrees with findings in another large population based study, the National Health and Nutrition Examination Survey (101). However, this is a controversial issue.

In a meta-analysis of 49 studies in Europe, Japan, US and Australia that found an inverse correlation between *H. pylori* infection and BMI (103). Moreover, this association to *H. pylori* infection is supported in an animal model (102).

Finally, in a recent published review, the authors concluded that the increasing eradication of *H. pylori* during the last decade was a contributing causal factor to the obesity epidemic in the Western world (103). There are no obvious explanations of the discrepancies between these studies. Obesity is a multifactorial condition, and it seems strange that *H. pylori* should play a pivotal role in the energy balance in humans. Therefore, there is need for more studies to elucidate a potential causal relationship between *H. pylori* infection and BMI, and at least there is still a need of further population based cross-sectional and prospective studies.

### ***5.3 H. pylori infection and functional bowel symptoms***

In our study of the testing various risk factors to functional bowel disease; *H. pylori* infection was not associated to this condition, whereas female and low age were positively associated. The cause of IBS is unclear, but etiological factors such as genetic, food intolerance and gut microbiology including post-infection IBS has been proposed with visceral hypersensitivity as the common pathophysiological mechanism (94). The association between *H. pylori* infection and IBS is not settled. *H. pylori* infection has been shown to be a risk factor for IBS in one study (95) but no association in three other reports (96), (97), (98). There are very few larger, population-based studies that have addressed this issue. In a Chinese population based study of 18000 subjects no association between *H. pylori* and IBS was found (116). It should however, be mentioned one 10 year prospective population based study of some 8500 subjects found that a *H. pylori* infection predicted the likelihood of a later IBS consultation (95). In conclusion, so far there is no good evidence for an association between *H. pylori* infection and functional bowel disease, but there is a need for more population based studies before a firm conclusion can be made.

#### ***5.4 H. pylori and prevalence***

In our population with apparent high hygiene status the transmission of *H. pylori* infection first starts in the young and with an apparent peak in the sixties. *H. pylori* infection was nearly not observed among children. Some few previous fecal antigen-based tests studies in children have been performed, finding prevalence figures from 7 % to 47 % (112), (113), (41), (52). Of interest is to note that our prevalence of 0,6% equals the serology based Dutch study in which the prevalence was 0.5% in children with two Dutch parents vs 2.6% in children with at least one non-Dutch parent (44).

The prevalence of *H. pylori* infection in the adolescents was 20 %. Prevalence studies from this age are harder to find in the literature. In Siberia, the prevalence in youths was 56.3% (54) and 42 % in an European multinational study (117), and around 50 % in Turkey (55). Our data indicate that in adolescence in the 21<sup>th</sup> century with high socio-economic and health standard, there is a so far unknown life-style factor(s) increasing the risk for transmission of *H. pylori*. It must be emphasized that a cohort effect cannot be ruled out, and if so, the mothers' prevalence must differ significantly in the two cohorts 0-11 and 12-17, which indeed was documented. Therefore, a follow-up study is needed to elucidate a potential transmission route from mother to child, which would be highly reduced with mothers of low rate of *H. pylori* infection.

Although our data from adolescents are weak due to low participation rate, we can hypothesise that if all the 233 non-respondent teenagers had tested negative, the prevalence would still be 3%. Moreover, there can be little doubt that the first positive tests of *H.bacter pylori* antigen in our all-age study occurs in the adolescents.

In our adult population the prevalence of *H pylori* was 33 % and lower than reported from most of the rest of the world with a range from 30 to > 50 % (118) review. The prevalence of *H pylori* in the adult populations is decreasing. Population studies from the community of Sørreisa showed a prevalence of 42 % in 1987 (57) to 33 % 17 years later (58). (see table 1). There is now well documented that the prevalence of the *H pylori* infection is decreasing worldwide in the start of the 21<sup>th</sup> century, especially in countries with high hygiene standards. It appears that the highest contribution to the decreasing prevalence is among children.

The strength of this study is the population-based prevalence measurements in all age groups, in two populations with similar socioeconomic background, and with a homogenous ethnicity. Moreover, we have based our data on an antigen-based *H. pylori* test with high sensitivity and specificity. Yet there are areas with some weakness. First, the participation from the adolescence group was low. The prevalence data of *H. pylori* infection from this group is uncertain, but the lowest possible prevalence would still be 3% if all the 205 non-participating subjects tested negative. Therefore, we have strong evidence from this study that *H. pylori* infection first occurs in the young. Another weakness of our study is that more comprehensible data would have been available if a family-based prevalence study had been performed in *H. pylori* positive subjects.

In conclusion, the world-wide tendency of reductions in the prevalence is most likely associated to increased hygiene standard. The very high hygiene standard in the mother-child care typical for the Westernized societies may contribute to the world-wide reductions in the prevalence of *H pylori* especially in childhood. According to our data, it remains unresolved what life style(s) in adolescent that contributes to increased risk of *H pylori* transmission.



### ***5.5 H. pylori and transmission routes***

In our study we searched for several potential transmission routes of the *H pylori* infection. In univariate analyses we found that risk factors for transmission were out-door toilette, private well and farm animals. These findings were as proposed from previous studies. Thus, faecal animal *H. pylori* has been one of the most frequent proposed sources (22), and the primary transmission route via drinking water and thereafter intrafamilial *H pylori* transmission (23). It should be mentioned that these risk factors were not independent of age. This may be explained by the fact that all potential risk factors tested are so tightly associated to age, that any independency cannot be expected. Despite this, our data indicate that *H pylori* comes from animal sources that may be of clinical importance associated to hygiene standards such as private water supply and tight contact with farm animals. Of interest to note was that the population without breast feeding as child was not associated to *H pylori* infection. Most studies agree that breast feeding has a protective effect in a less economically developed setting (33). Most likely, in populations with high hygiene standard there is no transmission whether or not breast feeding is practised. In conclusion, in our population with high hygiene standard the transmission of *H pylori* infection may come from animals, out-door toilets and private water supplies.

## 6. Conclusion and implications

### 6.1 Conclusions

In our study we have documented that the presence of *H. pylori* independently protects against reflux symptoms in men but not in women

We could not find any significant association between *H. pylori* infection and body weight classes according to BMI including obesity

We could not find any significant association between *H. pylori* infection and functional bowel symptoms

The prevalence of *H. pylori* is low in our population with high hygiene standard due to low transmission rate in young age groups.

*H. pylori* transmission is associated with low sanitary standards, such as animal contact, private water supply and out-door toilets but not as independent risk factors

## **6.2 Implications**

According to our conclusions, and if these are fully validated, the following implications can be proposed

1. In men in our region with HP *H. pylori* infection without any apparent symptoms due to the infection, there is no need to eradicate the bacterium - at worst case the patient can become suffering from reflux disease
2. Despite high hygienic conditions, there is an increased risk to be transmitted from *H. pylori* in young age, especially from adolescence on, where the environmental factors may be associated to animals, private water supply and out-door toilet

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# Bodø Helicobacter

Et forskningsprosjekt om mageplager i en nord-norsk bybefolkning

Ragnar K. Breckan

**Ungdom mellom 12 og 17 år !**

**Reg.nr.....**

## **Vil du delta i et forskningsprosjekt om mageplager?**

Mageplager er svært vanlige i befolkningen. Noen av disse mageplagene skyldes den såkalte "magesårsbakterien" *Helicobacter pylori*. Selv om det nå snart er 20 år siden man fant denne bakterien i magesekken hos pasienter med magesår, er det fortsatt mye man ikke vet om bakterien. Hos noen vil den forårsake sykdom, men hos de fleste vil den sannsynligvis ikke det. Forholdene omkring smitteveier og smittemåte er ikke ordentlig avklart. Antagelig smittes man allerede som barn fra familiemedlemmer eller lekekamerater, og beholder deretter bakterien i magesekken til voksen alder, men dette vet vi ikke sikkert. Vi håper at dette forskningsprosjektet skal kunne gi svar på noen av disse spørsmålene.

Den viktigste delen av prosjektet er å kartlegge forekomsten av bakterien *Helicobacter pylori* og andre mikrober hos friske personer i alle aldre. Til dette trenger vi en avføringsprøve slik det er angitt på vedlagte prøveglass, og som kan sendes inn i vedlagte ferdig frankerte konvolutt. I tillegg ønsker vi at vedlagte spørreskjema blir besvart og returnert.

Forskningsprosjektet er vurdert av Personvernombudet for forskning, Norsk samfunnsvitenskaplig datatjeneste AS. Regional Etisk Komité for Medisinsk Forskningsetikk har vurdert prosjektet og har ikke innvendinger mot gjennomføringen..

Det er frivillig å delta, og du kan trekke deg fra undersøkelsen til enhver tid uten begrunnelse. Om du ikke ønsker å delta, eller om du trekker deg senere, vil det ikke få noen betydning for ditt forhold til helsevesenet. Innsamlede data om din person vil da bli slettet.

Dataene som blir samlet inn, vil bli behandlet strengt fortrolig, og ingen utenom forskningsgruppen vil få vite hva du har svart. Resultatene vil bli oppbevart på isolert datasystem hvor personidentifikasjon er erstattet av registreringsnummer. Avføringsprøvene fryses og oppbevares med det samme registreringsnummeret. Dette nummeret viser til et personregister som oppbevares adskilt fra det øvrige materialet.

I tillegg til opplysningene om mageplager som du gir i spørreskjemaet, ønsker vi å kunne innhente opplysninger om mageplager som finnes i din journal på legekantorene hos fastlegene, og i eventuell sykehusjournal, f. eks. tidligere mageoperasjoner, røntgen-undersøkelser, magesårbehandlinger, andre vesentlige sykdommer.

Dette prosjektet vil vare til 1. januar 2015. Innen den tid kan noen av dere bli spurt om å delta i oppfølgingsprosjekter for å studere årsaksforhold for visse magesykdommer. Det er også mulig at dataene, i et evt. nytt delprosjekt, vil bli koblet til dataene i andre person- og helseregistre, for eksempel krefregistret eller folketellingen, for å få mer kunnskap om eventuelle sammenhenger mellom magebakterien og utvikling av annen sykdom. Hvis det ikke innhentes samtykke om noe annet, vil alle data anonymiseres i 2015.

All fremtidig bruk av opplysninger og prøver vil bare skje etter godkjenning fra Datatilsynet og såfremt Regional Etisk Komité for Medisinsk Forskningsetikk ikke har innvendinger mot det. Du har innsynsrett i de opplysninger som registreres om deg.

Forskningsresultatene vil bli publisert i medisinske tidsskrifter, og et sammendrag vil bli presentert i lokale medier, men ingen opplysninger vil her kunne etterspores til enkeltpersoner. Alle deltagere vil kunne få skriftlig beskjed om resultatet av testen på forespørsel til prosjektleder.

Vi ber deg bekrefte om du ønsker å delta i de forskjellige delene av prosjektet slik de er beskrevet på neste side.

Hvis du ikke ønsker å delta i prosjektet og vil unngå purring, kan du sette kryss i ruten her:  og returnere skjemaet på side 2. Du vil da ikke få purring senere.

Vennlig hilsen

Ragnar K. Breckan  
Prosjektleder



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NORDLANDSSYKEHUSET  
NORDLÁNDÁ SKIHPPJIVIESSO

## Samtykkeerklæring *Bodø Helicobacter*– sendes inn sammen med spørreskjemaet i hvit svarkonvolutt

Jeg har lest informasjonen i forespørselen og :

1. Samtykker i å delta i undersøkelsen ved å svare på spørreskjemaet.	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
2. Samtykker i å sende inn avføringsprøve til undersøkelse for mikrober	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
3. Samtykker i at opplysninger om mageplager og undersøkelser/ behandling for disse kan innhentes hos primær-/fastlege og hos sykehus.	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
4. Samtykker i å eventuelt bli kontaktet innen 1. januar 2015 med forespørsel om nye opplysninger eller undersøkelser	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
5. Samtykker i at resultatene mine (etter godkjenning fra datatilsynet) kan settes sammen med opplysninger om meg i andre registre til bruk i eventuelle nye delprosjekt/forskning om magelidelser. Det kan være registre om helse, trygd og sykdom. Det kan også være registre om inntekt, utdanning og yrke samt opplysninger fra tidligere helseundersøkelser. Eksempler på slike registre er Kreftregistret, Statistisk Sentralbyrå, Rikstrygdeverket. I disse tilfeller blir navnet og personnummeret mitt fjernet når dataene blir analysert	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei

Sted:\_\_\_\_\_

Dato:\_\_\_\_\_

Navn (blokkbokstaver):\_\_\_\_\_

Underskrift:\_\_\_\_\_

Foreldre/foresattes navn \_\_\_\_\_ og underskrift \_\_\_\_\_

*Sndes inn snarest mulig i vedlagte ferdig frankerte hvite svarkonvolutt*

Du kan ta vare på den andre kopien av forespørsel og samtykkeerklæring som din egen.  
Tusen takk!

Vennlig hilsen

Ragnar K. Breckan  
Seksjonsoverlege  
Nordlandssykehuset  
Bodø

Jon Florholmen  
Professor  
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Universitetet i Tromsø

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NORDLANDSSYKEHUSET  
NORDLÁNDA SKIHPPJIVIESO



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Samtykkeerklæring *Bodø Helicobacter* – ditt eksemplar

Jeg har lest informasjonen i forespørselen og :

1. Samtykker i å delta i undersøkelsen ved å svare på spørreskjemaet.	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
2. Samtykker i å sende inn avføringsprøve til undersøkelse for mikrober	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
3. Samtykker i at opplysninger om mageplager og undersøkelser/behandling for disse kan innhentes hos primær-/fastlege og hos sykehus.	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
4. Samtykker i å eventuelt bli kontaktet innen 1. januar 2015 med forespørsel om nye opplysninger eller undersøkelser	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei
5. Samtykker i at resultatene mine (etter godkjenning fra datatilsynet) kan settes sammen med opplysninger om meg i andre registre til bruk i eventuelle nye delprosjekt/forskning om magelidelser. Det kan være registre om helse, trygd og sykdom. Det kan også være registre om inntekt, utdanning og yrke samt opplysninger fra tidligere helseundersøkelser. Eksempler på slike registre er Kreftregistret, Statistisk Sentralbyrå, Rikstrykdeverket. I disse tilfeller blir navnet og personnummeret mitt fjernet når dataene blir analysert	<input type="checkbox"/> Ja	<input type="checkbox"/> Nei

Sted:.....

Dato:.....

Navn (blokkbokstaver):.....

Underskrift:.....

Du kan ta vare på denne kopien av forespørsel og samtykkeerklæring som din egen.  
Tusen takk!

Vennlig hilsen

Ragnar K. Breckan  
Seksjonsoverlege  
Nordlandssykehuset  
Bodø

Jon Florholmen  
Professor  
Institutt for klinisk medisin  
Universitetet i Tromsø

Bjørn Straume  
Førsteamanuensis  
Institutt for samfunnsmedisin  
Universitetet i Tromsø



Ungdom mellom 12 og 17 år

Registreringsnummer: .....

## PROSJEKT BODØ HP

### VEDLEGG TIL AVFØRINGSPRØVE – SENDES INN I VEDLAGTE FERDIG FRANKERTE BRUNE SVARKONVOLUTT

*Avføringsprøven tatt:*

*Dag:.....Måned:.....År:.....*



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**NORDLANDSSYKEHUSET**  
NORDLÁNDA SKIHPPIJVIESSO

## 1. Registreringsnr:

2. Er du født i Norge?

- 1  Ja  
2  Nei

3. Hvis du er født i annet land enn Norge?

Hvilket? \_\_\_\_\_

4. Er dine foreldre født i Norge?

- Mor 1  Ja  
2  Nei  
Far 3  Ja  
4  Nei

5. Hvis en av eller begge foreldrene dine er født i annet land enn Norge; hvilket?

Mor \_\_\_\_\_

Far \_\_\_\_\_

## Mageplager

6. Har du noen gang hatt smerter eller ”verk” i magen som har vart i minst 2 uker?  
(omgangssyke (reksjuka) regnes ikke med).

- 1  Ja  
2  Nei (hvis nei gå til pkt.9)

7. Hvis Ja i spørsmål 6, har du hatt smertene;  
(sett bare ett kryss)

- 1  Ukentlig ?  
2  Månedlig ?  
3  Årlig eller sjeldnere ?

8. Hvis Ja i spørsmål 6, hvor satt smertene eller ”verken”  
(sett bare ett kryss)

- 1  i øvre del av magen ?  
2  i nedre del av magen ?  
3  i hele magen ?

9. Har du noen gang hatt sure oppstøt, halsbrann eller  
brystbrann nesten daglig i minst en uke?

- 1  Ja  
2  Nei (Hvis Nei, gå til pkt 11)

10. Hvis Ja i spørsmål 9, har du hatt disse plagene  
(sett bare ett kryss)

- 1  Ukentlig?  
2  Månedlig?  
3  Årlig eller sjeldnere?

## Bruk av helsetjenester

11. Har du noen gang søkt fastlege på grunn av sure oppstøt,  
halsbrann, brystbrann, smerter eller ”verk” i magen?

- 1  Ja  
2  Nei  
g  Husker ikke

12. Har du noen gang vært henvist til, eller innlagt i sykehus  
på grunn av sure oppstøt, halsbrann, brystbrann, smerter eller  
”verk” i magen?

- 1  Ja  
2  Nei (Hvis Nei, gå til pkt 20)  
g  Husker ikke

13. Har du noen gang brukt syrenøytraliserende eller  
syrehemmende midler, daglig eller av og til?

- 1  Ja  
2  Nei  
g  Husker ikke

14. Er du operert i magen?

1  Ja

2  Nei (Hvis Nei, gå til pkt. 16)

15. Hvis Ja i spørsmål 14

Av hvilken årsak \_\_\_\_\_

Ved hvilket sykehus \_\_\_\_\_

I hvilket år \_\_\_\_\_

16. Oppgi din høyde og vekt nå:

Høyde uten sko \_\_\_\_\_ cm

Vekt uten klær \_\_\_\_\_ kg

### Slekt

17. Hvor mange søsken har du?

Antall \_\_\_\_\_

18. Hvilket nummer er du i rekken av søsken?

(Eksempel; Hvis søskenflokken består av 2 storebrødre, deg og lillesøster blir du nummer 3 av 4)

Nummer \_\_\_\_\_ av \_\_\_\_\_

19. Har noen av disse i din familie hatt magesår?

(Sett evt. flere kryss)

1  Ektefelle eller samboer

2  mor, far, søsken eller barn

3  Ingen

4  Vet ikke

20. Angi, såfremt du kan, om du som barn fikk:

(Sett bare ett kryss)

1  Brystmelk

2  Kunstig ernæring (flaske)

3  Begge deler

4  Vet ikke

### Fysisk aktivitet

21. Hvor ofte mosjonerer eller deltar du i fysisk trening av minst 20 minutters varighet og slik at du blir svett eller andpusten?

1  Sjelden eller aldri

2  Ukentlig

3  Flere ganger i uken

4  Daglig

### Medisin

22. Har du i løpet av de siste 3 måneder brukt penicillin eller andre antibiotika?

1  Ja

2  Nei (Hvis Nei, gå til pkt.24 )

23. Hvis Ja i spørsmål 22 angi dato;

(husker du ikke tidsrom eller navn skriv "???" på linjen)

fra \_\_\_\_\_ til \_\_\_\_\_

Navn på Medikament: \_\_\_\_\_

### Sosiale forhold

24. Hvor mange familiemedlemmer (deg selv medregnet) bor i din husstand?

Antall \_\_\_\_\_

25. Er noen i din husstand 11 år eller yngre?

1  Ja

2  Nei

## Dyrehold

26. Har du/din familie hatt noen form for husdyr/kjæledyr? 1  Ja  
2  Nei

27. Hvis ja i spørsmål 26 angi da hvilket dyr og i hvilken periode i forhold til din egen alder

f. eks Husdyr hest fra jeg var 5 til 8 år

Husdyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Husdyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Husdyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Husdyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Husdyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

f. eks Kjæledyr katt fra jeg var 6 til 12 år

Kjæledyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Kjæledyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Kjæledyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Kjæledyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

Kjæledyr \_\_\_\_\_ fra jeg var \_\_\_\_\_ til \_\_\_\_\_ år

(Nummereringen er ikke helt fortløpende av datatekniske årsaker).

