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Trial profile: pilot study of the multicentre randomised trial of *H. pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality (the GISTAR Pilot study)

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Abstract – *Purpose:* The GISTAR Pilot study is part of a large multi-centre randomised trial conducted in Latvia with the main aim to evaluate preventive strategies to decrease mortality from gastric cancer in high-risk areas, especially in the Baltic States and Eastern Europe.

Participants: A total of 3,447 apparently healthy, asymptomatic participants (40-64 y/o) were recruited between 2013 and 2015 for the GISTAR pilot study. Participants were interviewed for socio-economic status, lifestyle, environmental and occupational exposures, medical history, family history of diseases, and dietary habits. Participants were randomly assigned to either Intervention (n=1,724) or Control (n=1,723) group. The intervention included *H. pylori* eradication of those positives and endoscopic examinations of those whose levels of pepsinogens and gastrin-17 were altered. Participants in the Control group received routine care. All the trial participants are followed up at least for 15 years.

Findings to date: The majority of the participants were Latvian, reported to have a professional training or higher level of education and to be either overweight or obese. Around 26% of the participants were current smokers. The main risk factors for *H. pylori* positivity were having a Russian nationality, heavy drinking, and spicy food consumption while higher income and consumption of food or drink at hot temperature were associated with the absence of the infection.

Future plans: The GISTAR Pilot study investigates a wide range of epidemiological questions related to gastric cancer and its precursors in an Eastern European country, where the burden of this disease remains high, but epidemiological data to develop a preventive strategy are limited. A series of publications on gastric cancer aetiology and prevention using the Pilot study data are under preparation. GISTAR will add to the current evidence whether *H. pylori* eradication and endoscopic examination of those with serological evidence of atrophic gastritis would reduce the gastric cancer burden in high-risk areas in Europe.

Keywords: Gastric cancer prevention, *H. pylori* infection, Pepsinogen testing, East Europe, GISTAR.

INTRODUCTION

Gastric cancer is an important global public health problem with more than one million new cases and an estimated 800,000 deaths each year[1]. It occurs mainly in East Asia and Central and Eastern Europe, while the lowest rates are observed in Africa and North America[1]. The geographical differences in incidence rates in men are as extreme as more than 10-fold, e.g., age standardised rate (ASR) of gastric cancer incidence in the Republic of Korea being higher than 60 per 100,000 *vs.* several African and USA populations, not exceeding 5 per 100,000[2]. Despite the declining trends observed in many countries, gastric cancer remains a substantial global burden due to population growth and aging[3].

There is sufficient epidemiological and experimental evidence that supports a causal link between chronic infection with *Helicobacter pylori* (*H. pylori*) and gastric cancer[4]. A recent estimate suggested that 89% of non-cardia gastric cancers worldwide are attributable to this infection[5]. However, there is still limited evidence from clinical trials (mainly from East Asia) to indicate whether *H. pylori* eradication with antimicrobial therapy is the approach of choice at the population level or only in selected groups to reduce risk of gastric cancer[6]. In addition, whether *H. pylori* eradication at an advanced stage of gastric atrophy is still effective in reducing cancer development is not known, although eradication has been shown to be effective in preventing metachronous gastric cancer after endoscopic treatment of the initial malignancy[7], i.e., in patients that have developed either precancerous lesions or cancer.

Currently available international guidelines suggest that serological tests of pepsinogens, which is a marker for atrophic gastritis, as well as *H. pylori* antibodies, may be useful to identify individuals at an increased risk of gastric cancer[8,9]. However, the effectiveness of these tests, especially combined with an endoscopic follow-up strategy of those with premalignant lesions has not yet been evaluated, particularly in an organised cancer screening setting.

We therefore aim to conduct a large multi-centre randomised trial in several countries from the Baltic States and Eastern Europe, areas with high burden of gastric cancer, to evaluate preventive strategies to decrease mortality from gastric cancer in high-risk areas (Multicentric randomized study of *H. pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality, the GISTAR study). The primary objective is to investigate if *H. pylori* screening followed by treatment in participants with positive result and endoscopic follow-up of those with serological evidence of atrophic gastritis can reduce gastric cancer mortality. The design of the main GISTAR study has been described in detail elsewhere[10]. Prior to the initiation of the large-scale intervention with the trial, a pilot study was conducted and completed in Latvia (the GISTAR Pilot study) to evaluate the trial assumptions, performance and appropriateness of the chosen tools. The GISTAR Pilot study therefore includes a wider range of laboratory methods compared to the main GISTAR study and features different strategies on, for example, recruitment and follow-up as the main study has been tailored according to the results obtained from the Pilot study. The large sample size of this pilot study allows investigation of multiple ancillary studies to generate hypotheses which could later be evaluated in the main trial. This study profile describes the GISTAR Pilot study and the baseline data.

The GISTAR Pilot study was conducted from October 9, 2013 to December 18, 2015 in four centres in Latvia: Cēsis, Alūksne, Ludza, and Saldus. The study was funded in part by the National Program for Research in Latvia: Biomedicine 2014-2017. This work was supported by project number lzp-2018/1-0135 "Research on implementation of a set of measures for prevention of gastric cancer mortality by eradication of *H. pylori* and timely recognition of precancerous lesions" of the Latvian Council of Science.

The study was approved by the Ethics Committee of the International Agency for Research on Cancer (IARC), reg. No. IEC 12-36 (original approval on 26/03/2013, related updates approved on 02/10/2015), the Ethics Committee of the Riga East University Hospital Support foundation has approved the protocol 03/10/2013, reg. No. 14-A/13, and the Central Medical Ethics Committee in Latvia has approved the protocol 09/12/2013, reg. No. 01-29.1/11. The trial is registered in the clinicaltrials.gov database (NCT02047994).

TRIAL DESCRIPTION

Participants

Figure 1 describes the study design. Eligible men and women between 40-64 years of age at entry who were residents in Cēsis, Alūksne, Ludza, and Saldus were invited to participate in the trial by visiting one of the study clinics set up specifically for this study. The target population was selected from the general practitioner (GP) registries. Whenever telephone contacts were available to the GPs, potential participants were approached by phone. If these contacts were not available, the subjects were approached by an invitation letter.

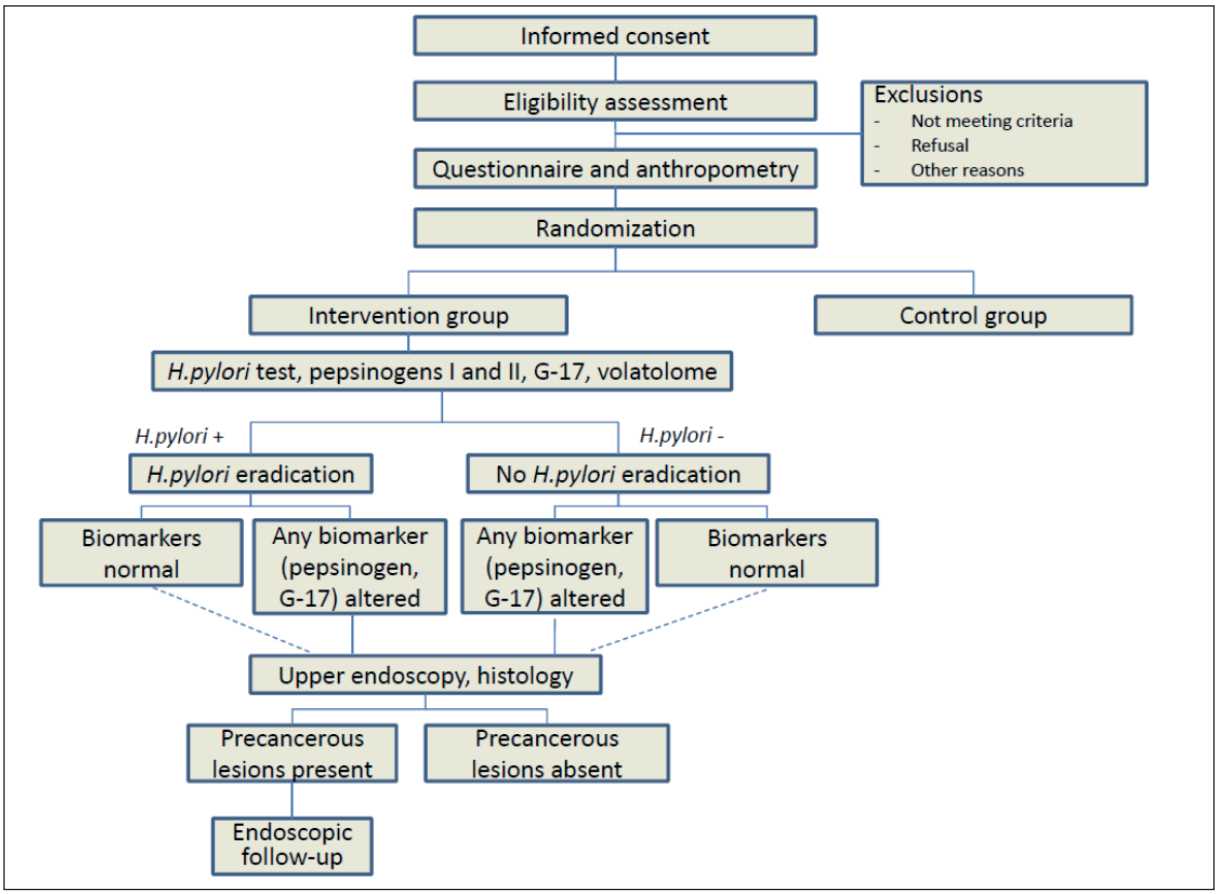

Figure 1. GISTAR Pilot study design.

To assure equal participation of both genders, a more intense invitation strategy for men was established in which men were selected with priority and actively approached from the list of the GP registries as women tended to participate more willingly. Only in one GP in Cēsis both genders were invited from the registration list, which enabled us to estimate the difference in participation rate between the genders. Participants were excluded from the trial when they had any of the following: personal history of gastric cancer prior to enrolment; gastric resections due to benign disease (participants with ulcer suturing and vagotomy were eligible); *H. pylori* eradication therapy within 12 months prior to inclusion (irrespective of the treatment result); presence of alarm symptoms for digestive or any other diseases; pathological findings at medical history and physical exam suggestive of a serious disease requiring immediate management; factors otherwise limiting the participation according to the protocol; serious psychological conditions/psychiatric disease limiting the possibilities to understand the requirements for diagnostic and/or medical interventions; or low expectations on the compliance for the diagnostic work-up, treatment or follow-up.

For eligible participants who agreed to participate and signed informed consent, a comprehensive questionnaire with a wide range of potential risk factors was administered. We developed a centralised multiple-language web-based electronic data-capture system and

data management facilities dedicated for the study. The questionnaire and investigation data were recorded in a standardised way and the system provided the primary data source.

Participants were randomly assigned to either intervention (50%) or control (50%) group. Among those assigned to the Intervention Group, *H. pylori* screening by detecting IgG group antibodies in plasma using an enzyme-linked immunosorbent assay (ELISA) was performed. Those participants who were *H. pylori* positive received *H. pylori* eradication treatment. In addition, pepsinogens and gastrin-17 (G-17) were measured as markers for detecting gastric atrophy.

Participants who met the pre-defined referral criteria underwent upper endoscopy with appropriate biopsy sampling. In addition, a subgroup of participants with normal biomarkers was randomly selected to undergo endoscopy to verify the referral bias, evenly selected in each batch of the blood samples to avoid batch effects. The size of this subgroup was chosen to be half of those in the altered biomarker group.

Participants assigned to the other group constituted the Control Group, after having had a medical evaluation at the time of recruitment. During the follow-up period this group is referred to consult a specialist when required due to clinical symptoms.

Both groups were offered fecal immunochemical test (FIT) as a benefit of study participation. Any participants who show a positive FIT result were referred to colonoscopy.

A centralized biorepository for the study was established by the University of Latvia and supervised by IARC. The reference endoscopy centre has been established at Digestive Diseases Centre GASTRO, Riga, Latvia. Pathology services and archiving of formalin-fixed and paraffin-embedded materials were handled by the Academic Histology Laboratory in Riga, Latvia.

Recruitment for the pilot study was initiated in October 2013 and completed in December 2015. The first site, Cēsis recruited 757 participants while the second site Alūksne recruited 599 participants. The third site was Ludza and 1,016 participants were recruited. The last site was opened in Saldus where 1,075 participants were recruited.

Out of 3,498 participants whose eligibility was assessed, 51 were excluded due to alarm symptoms and screening failures (Figure 2). A total of 3,447 participants were included in the pilot study cohort (n=1,724 and 1,723 in Intervention and Control Groups, respectively).

How Often Have They Been Followed-Up?

All the study participants, including the Control Group, are followed up at least for 15 years to collect systematic information on medical conditions, in particular gastric cancer and cause of death. A follow-up telephone call or alternative means of communication are planned to be made every five years for outcome assessment, until the end of the study. Whenever possible, participants will be invited to the study centres to obtain follow-up data including demographic information, socio-economic status, physical examination, as well as biological samples (plasma, serum and stool samples). The first record linkage to the National Cancer and Mortality Registry database of Latvia was made in January 2018 to ascertain cases of and deaths from gastric cancer and this record linkage will be made on a yearly basis.

In the Intervention Group, those participants identified with abnormalities during endoscopic and consequently histological examinations were referred to appropriate medical treatment according to the local practice. Further endoscopic surveillance for individuals with atrophic gastritis and/or intestinal metaplasia without dysplasia or patients with dysplasia are made according to the MAnagement of Precancerous conditions and lesions in the Stomach (MAPS) guidelines[11]. During the follow-up period participants in the Control Group will be offered to consult a specialist when required due to any clinical symptoms.

What Has Been Measured?

Information collected from all participants before randomisation

Socio-demographic, lifestyle, and dietary factors

Country of origin, ethnicity, marital status, education, family income, and employment data with detailed questions about occupational exposures were captured. In addition, smoking habits, alcohol consumption, physical activity, and a wide range of dietary factors were assessed with detailed questions and visual aids (Table 1).

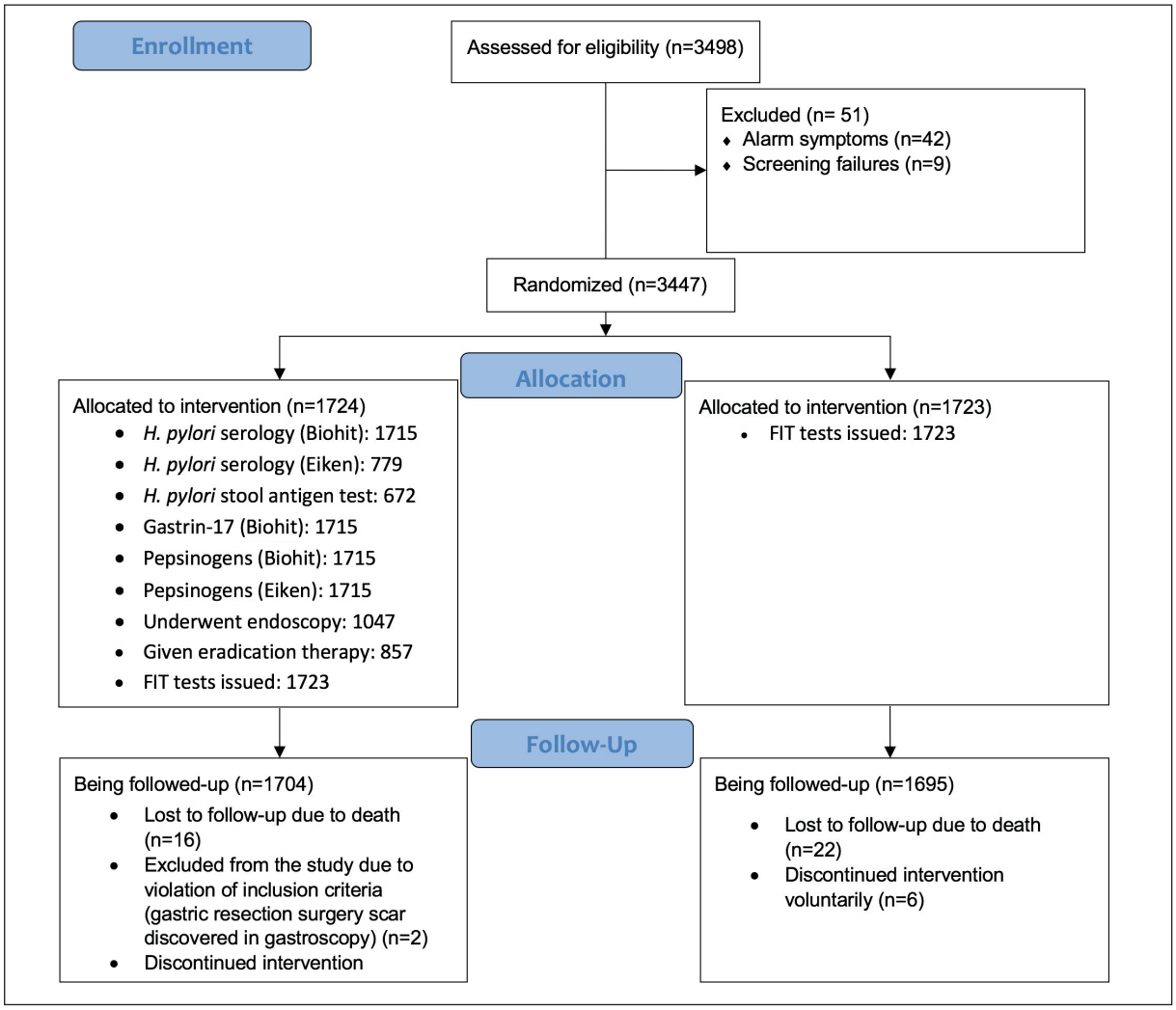

Figure 2. CONSORT study diagram: GISTAR Pilot.

TABLE 1. OVERVIEW OF MEASUREMENTS TAKEN AT BASELINE AND PLANNED TO BE TAKEN AT FOLLOW-UPS – GISTAR PILOT STUDY.

Phase	Measurements
Baseline 2013-2015	• Blood samples taken, *H. pylori* infection, pepsinogen I and II, gastrin-17 measured, serum and plasma aliquots stored at –70°C • Volatile markers • Stool samples collected for FIT with the potential to be used in microbiome testing • Gastric biopsies taken for histological assessments and microbiome testing, including *H. pylori* • Self-reported socio-economic status, lifestyle factors, environmental exposures • Anthropometric measures: weight, height, waist & hip circumference • Blood pressure
Follow-up (planned every 5 years)	• Repeat of the biological sample collection (serum, plasma and gastric biopsies), whenever possible • Questionnaires: Self-reported major diseases and treatment Self-reported socio-economic position and behaviours
Ongoing	• All participants have been flagged with routine data sources providing deaths since baseline and cancer registry entries since 2015

Medical History and Anthropometric Data

Detailed medical history, with a particular emphasis on gastrointestinal conditions was assessed together with related treatment history. From women, the questions were also included to obtain information on menopause, pregnancy, use of oral contraceptives, and hormone replacement therapy. Anthropometric data including height, weight, waist, and hip circumferences were measured by trained nurses. Blood pressure was also measured.

Faecal Immunochemical Test

As an incentive for participation, all participants were offered faecal occult blood testing by a laboratory-based immunochemical test (FIT) OC-Sensor (Eiken Chemical Co., Tokyo, Japan, Figure 2), and whenever positive (cut-off at 10 µg/g faeces from a single faecal sample), referred for colonoscopy to be followed-up according to routine care.

Measurements taken and interventions provided to participants assigned to the Intervention Group

Biological materials including serum, plasma, as well as stool and gastric biopsies, were collected from the participants assigned to the Intervention Group to investigate the study objectives.

Assessment and management of *H. pylori* infection

As per the study protocol and the standard operating procedures (SOPs), *H. pylori* infection seropositivity was assessed by IgG antibodies measured with an enzyme-linked immunosorbent assay (ELISA, Biohit Plc., Helsinki, Finland, n=1,715, Figure 2). Participants who tested *H. pylori* positive received a conventional triple therapy for 10 days: esomeprazole 40 mg, clarithromycin 500 mg, amoxicillin 1000 mg, each administered twice a day.

In addition, in subgroups of participants latex-agglutination (Eiken Chemical Co., Tokyo, Japan, n=779) and stool antigen test (Premier Platinum HpSA PLUS, Meridian Diagnostics Inc., Cincinnati, OH, USA, n=672) were also used to investigate performance of different test strategies for *H. pylori* detection against histology as a gold standard[12]. The stool antigen test was made using frozen stool samples which were stored at -70°C.

In study subjects undergoing upper endoscopy, the presence of *H. pylori* was assessed based on the results of modified Giemsa staining method using the gastric biopsy samples, but in questionable cases immunohistochemistry was used (see further below for more details).

Gastric biopsies being collected in a special transport/storage medium were made available for *H. pylori* culture and sensitivity testing to antibiotics, as well as for amplification methods, if required.

Pepsinogen I and II, Gastrin 17

In addition, the following biomarker tests for detecting gastric atrophy were measured in the Intervention Group; pepsinogen I (PgI) and pepsinogen II (PgII) tests using both ELISA (Biohit Plc. Helsinki, Finland, n=1,715) and latex-agglutination (Eiken Chemical Co. Tokyo, Japan, n=1,715), and gastrin-17 (G-17) test using ELISA (Biohit Plc., Helsinki, Finland, n=1,715). Participants who met the following criteria (Biohit: Pg I/II ratio <3 and/or Eiken: Pg I/II ratio<3 and PgI <70 ng/ml and/or G-17 <1 pmol/l) were referred to upper endoscopy with appropriate biopsy sampling.

Endoscopies and histological assessment of gastric biopsies

Participants with serological evidence of atrophic gastritis from the pepsinogen testing underwent upper endoscopic examinations using a standard video-endoscope with monitor and light source. Altogether, 1,047 upper endoscopies were performed, including 274 endoscopies in the group with all normal levels of pepsinogens and G-17.

During the endoscopy, five non-targeted gastric biopsies were obtained for histology: two from the corpus, one from greater curvature and the other from lesser curvature; one from the *incisura angularis*; and two from the antrum, one from greater curvature and the other from lesser curvature, according to the updated Sydney System[13], and two additional biopsies from antrum greater curvature and corpus greater curvature were obtained for microbiome analyses. Biopsies were stained with Haematoxylin and eosin, modified Giemsa, as well as Alcian blue as routine methods, while high-diamine alcian blue (HID-AB) method was applied to biopsies with intestinal metaplasia.

Volatile breath markers

Two breath samples for measuring breath volatolome were collected from each of the study participants in the Intervention Group. One of the samples was used for gas chromatography with mass-spectroscopy (GC-MS), while the other was assessed with laboratory-based sensor technology by using a nanomaterial-based sensor array. ORBO™ 402 Tenax® TA sorbent tubes (Sigma-Aldrich, Steinheim, Germany) were used for trapping and storing the exhaled volatile markers. Altogether 1,447 subjects were included to the GC-MS analysis, and 726 study subjects to the sensor analysis.

FINDINGS TO DATE

Baseline characteristics of the Pilot study participants aged 40-64 are described in Table 2. As expected, there was no significant difference between the intervention and Control Group in terms of participants' characteristics due to randomisation. The majority of the participants

TABLE 2. BASELINE CHARACTERISTICS OF THE GISTAR PILOT STUDY PARTICIPANTS.

Characteristics	Control Group N=1723 (%)	Intervention Group N=1724 (%)
Sex		
Women	922 (53.5)	916 (53.1)
Men	801 (46.5)	808 (46.9)
Center		
Cēsis	378 (21.9)	379 (22.0)
Aluksne	300 (17.4)	299 (17.3)
Saldus	539 (31.3)	536 (31.1)
Ludza	506 (29.4)	510 (29.6)
Age (years)		
39-45	397 (23.0)	402 (23.3)
46-51	477 (27.7)	464 (26.9)
52-57	445 (25.8)	464 (26.9)
58-64	404 (23.5)	394 (22.9)
Nationality		
Latvian	1372 (79.6)	1333 (77.3)
Russian	211 (12.2)	244 (14.2)
Others *	140 (8.2)	147 (8.5)
Education level		
<Lower-upper secondary education	409 (23.7)	364 (21.1)
Professional training	782 (45.4)	821 (47.6)
Higher education	523 (30.4)	533 (30.9)
Net monthly family income level		
<100 euros	121 (7.0)	97 (5.6)
100-<250 euros	563 (32.7)	521 (30.2)
250-<500 euros	692 (40.2)	737 (42.8)
≥500 euros	205 (11.9)	221 (12.8)
BMI (kg/m²)		
Underweight-normal	407 (23.6)	434 (25.2)
Overweight	665 (38.6)	657 (38.1)
Obese	651 (37.8)	633 (36.7)
Waist/hip ratio		
Mean (SD)	0.89 (0.093)	0.89 (0.089)
Smoking status		
Never	873 (50.7)	896 (52.1)
Former	400 (23.2)	380 (22.1)
Current	449 (26.1)	445 (25.9)

*Others include Armenian, Belarrussian, Estonian, German, Hebrew, Lithuanian, Pole, Tatar, Ukrainian, Buryat, Kazakh, Uzbek, Georgian, Romanian, Finnish, Hungarian, and Moldovan.

were Latvian, reported to have professional training or higher level of education, more than 250 euros of monthly family income, and to be either overweight or obese. Around 26% of the participants were current smokers.

In a subgroup of participants whose *H. pylori* information is available in the Intervention Group (n=1,715), the Pilot study suggested that having a male gender, Russian nationality, lower income, being a current smoker, heavy drinker, and not consuming food or drink at hot temperature, and eating spicy food were significantly associated with higher *H. pylori* prevalence (Table 3). Figure 3 suggests an inverse association between monthly income level and *H. pylori* prevalence (p=0.04). The *H. pylori* prevalence was comparable across the four

TABLE 3. CHARACTERISTICS OF THE GISTAR PILOT PARTICIPANTS IN THE INTERVENTION GROUP AND THEIR ASSOCIATION WITH *H. PYLORI* INFECTION.

Factors	Categories	Total		*H. pylori* positivity	*p*
		N	n	% (95% CI)	
Overall		1,715	1,164	**67.9 (65.6-70.0)**	
Gender	Women	911	595	65.3 (62.2-68.3)	**0.02**
	Men	804	569	70.8 (67.5-73.8)	
Age (years)	39-45	397	278	70.0 (65.3-74.3)	0.61
	46-51	463	306	66.1 (61.6-70.3)	
	52-57	461	309	67.0 (62.6-71.2)	
	58-64	394	271	68.8 (64.0-73.2)	
Nationality	Latvian	1,327	889	67.0 (64.4-69.5)	**0.008**
	Russian	241	183	75.9 (70.1-80.9)	
	Others *	147	92	62.6 (54.5-70.1)	
Net monthly family income	<100 euros	96	77	80.2 (71.0-87.0)	**0.04**
	100-<250 euros	518	352	68.0 (63.8-71.8)	
	250-<500 euros	733	501	68.3 (64.9-71.6)	
	≥500 euros	221	138	62.4 (55.9-68.6)	
Education level	Lower-upper secondary	363	251	69.1 (64.2-73.7)	0.13
	Professional training	814	567	69.7 (66.4-72.7)	
	Higher education	532	341	64.1 (59.9-68.1)	
Living conditions	Lives alone	332	229	69.0 (63.8-73.7)	0.86
	Lives with the family	1,369	926	67.6 (65.1-70.1)	
Employment status	Unemployed	159	112	70.4 (62.9-77.0)	0.47
	Employed or self-employed	1,355	912	67.3 (64.8-69.8)	
	Retired	132	88	66.7 (58.2-74.2)	
	Disabled person	69	52	75.4 (63.8-84.2)	
BMI (kg/m²)**	Underweight-normal range	434	288	66.4 (61.8-70.7)	0.64
	Overweight	653	451	69.1 (65.4-72.5)	
	Obese	628	425	67.7 (64.0-71.2)	
Smoking status	Never	893	588	65.9 (62.7-68.9)	**0.001**
	Former	377	243	64.5 (59.5-69.1)	
	Current	442	330	74.7 (70.4-78.5)	
Alcohol consumption	Never	105	67	63.8 (54.2-72.5)	0.12
	Ever	1,602	1,094	68.3 (66.0-70.5)	
Heavy drinker	No	750	474	63.2 (59.7-66.6)	**<0.001**
	Yes	965	690	71.5 (68.6-74.3)	
Eating or drinking hot food/drink	No	1,221	846	69.3 (66.6-71.8)	**0.05**
	Yes	493	317	64.3 (60.0-68.4)	
Eating spicy food	No	1,216	800	65.8 (63.1-68.4)	**0.004**
	Yes	498	363	72.9 (68.8-76.6)	

*Others include Armenian, Belarrussian, Estonian, German, Hebrew, Lithuanian, Pole, Tatar, Ukrainian, Buryat, Kazakh, Uzbek, Georgian, Romanian, Finnish, Hungarian, and Moldovan.
**BMI= Body Mass Index classified as underweight-normal weight (<25.0), overweight (25.0-29.99), and obese (≥30).

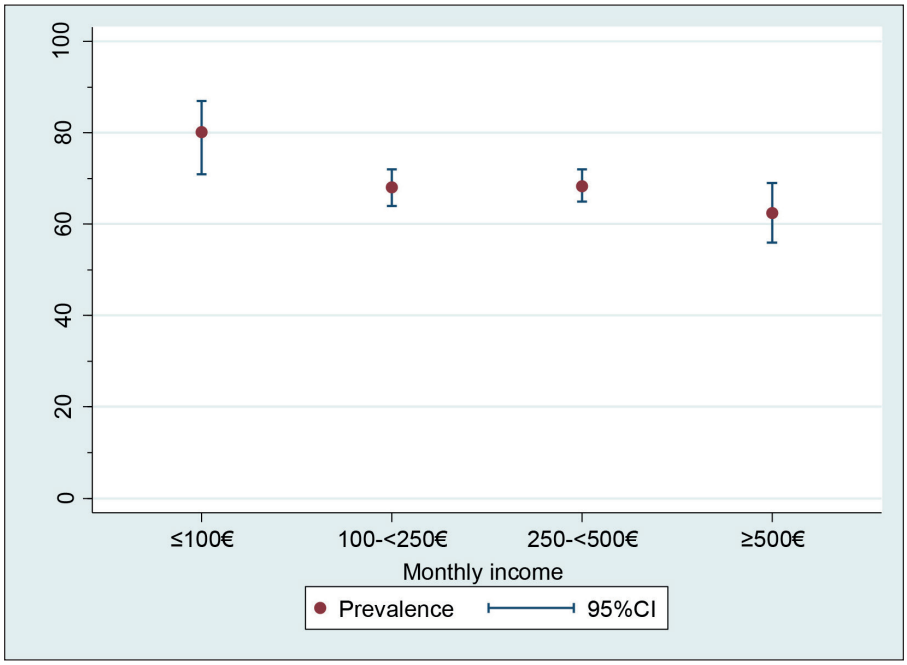

Figure 3. *H. pylori* prevalence according to levels of monthly family income.

study centres (Table 4). The final multivariable model of the factors associated with *H. pylori* positivity in the Intervention Group indicated that the main risk factors for having *H. pylori* infection were Russian nationality, heavy drinking habit, and spicy food consumption while higher income and consumption of food or drink at hot temperature were associated with absence of the infection (Figure 4).

TABLE 4. *H. PYLORI* PREVALENCE IN THE FOUR STUDY CENTRES.

		Total		*H. pylori* positivity	*p*
		N	n	% (95% CI)	
Local centres	Cesis (n=757)	377	255	67.6 (62.7-72.2)	0.65
	Aluksne (n=599)	297	201	67.7 (62.1-72.8)	
	Saldus (n=1075)	536	355	66.2 (62.1-70.1)	
	Ludza (n=1016)	505	353	69.9 (65.7-73.8)	

From the GISTAR Pilot study, we were able to evaluate and adjust the study assumptions, methods, tools, and infrastructure based on the following main findings:

We found that *H. pylori* serology, which was the method chosen for detecting the infection in the Intervention Group had a suboptimal accuracy compared with histology as a gold standard (12). The study team concluded that clinical decisions for *H. pylori* treatment cannot be solely based on antibody test results. This has led to the change that ^{13}C-urea breath test (UBT) would be the primary test for *H. pylori* detection for the general GISTAR study.

We found that G-17 provided little additional benefit to identify higher risk group which needs endoscopic surveillance (manuscript under preparation) and will not be used in the general GISTAR study as one of the referral criteria for endoscopy.

The efficacy of the *H. pylori* eradication regimen used in the study (10 day triple therapy containing clarithromycin) ascertained by UBT was investigated in Cēsis two years after the eradication. The eradication success rate was 87% according to the intention-to-treat analysis (manuscript under preparation). Further investigations on the efficacy of alternative treatment regimens will be conducted within the general study.

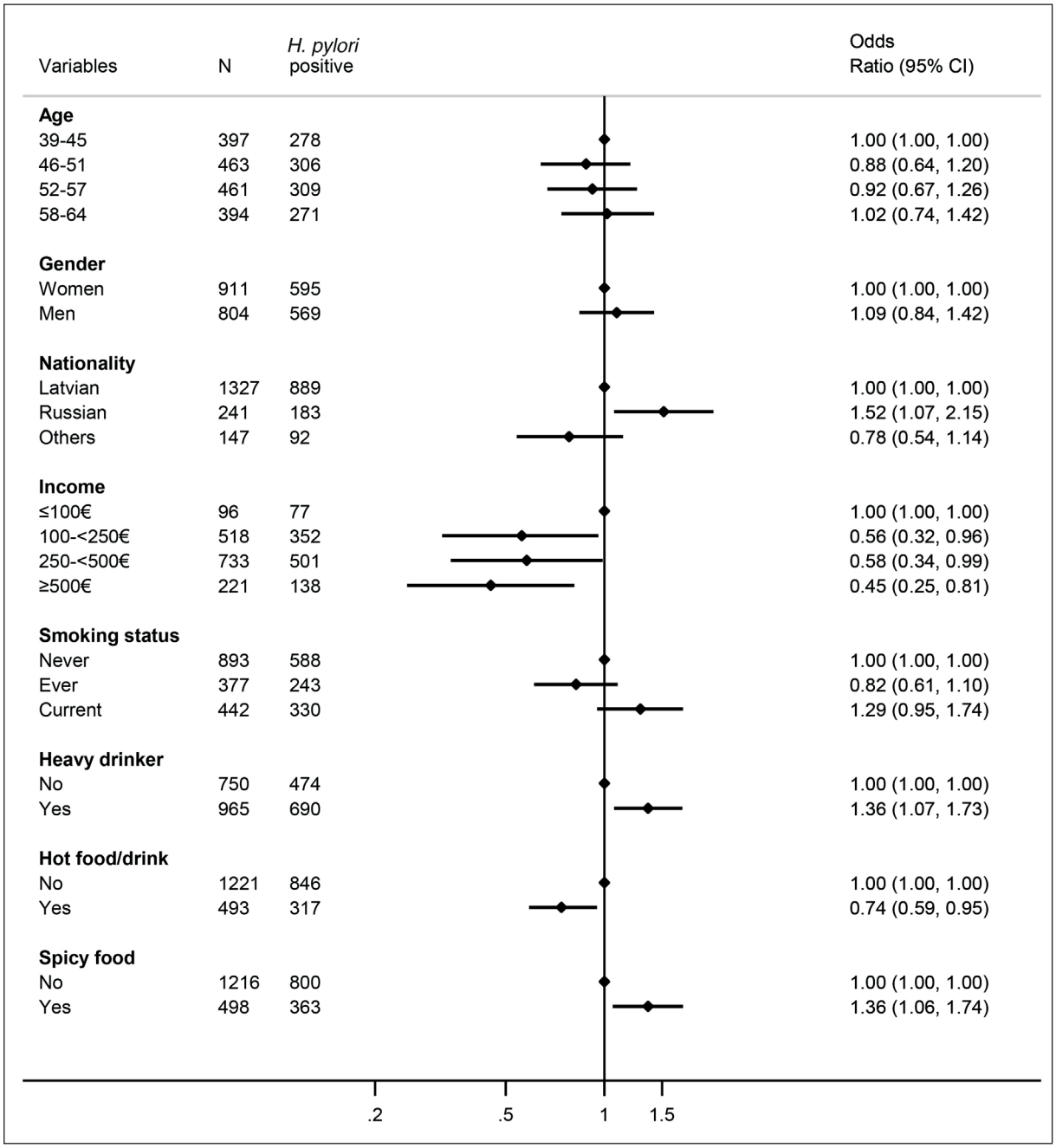

Figure 4. Forest plot of the factors associated with *H. pylori* positivity in the Intervention Group.

STRENGTHS AND LIMITATIONS

The GISTAR Pilot study investigates a wide range of epidemiological questions related to gastric cancer and its precursors in an Eastern European country, where the burden of disease remains high but epidemiological data to develop a preventive strategy are limited.

The follow-up results of the study will add to the currently available evidence whether population-based eradication of *H. pylori* is acceptable and reduces gastric cancer burden in high risk regions in Europe. In addition, the study evaluates the strategy of combining population-based *H. pylori* eradication with pepsinogen testing with endoscopic surveillance of participants in whom precancerous lesions have been detected, which has not been evaluated before.

This is a unique study including extensive endoscopic data with complete histological information which will provide important information on the precursors of gastric cancer in middle aged men and women. This pilot trial is also a great resource to conduct a number of unique ancillary

studies including microbiome analyses. Furthermore, this study will provide additional insight on the important questions not yet answered in European population: 1) if detection of early gastric cancer precursors (e.g., atrophic gastritis) can select subjects who require *H. pylori* treatment to achieve reduction in gastric cancer incidence and mortality, which lowers the burden of unnecessary antibiotic use, and 2) if detection and appropriate clinical managements of advanced premalignant lesions or early gastric cancers reduces gastric cancer mortality. Ultimately, this study will have the potential to find effective prevention strategies by identifying appropriate target groups that could get most benefits from the *H. pylori* treatment and clinical managements.

The GISTAR study is currently being continued as a main (general) study by including four additional study sites in Latvia. One of the weaknesses of the study is that the Pilot was conducted only in one country, i.e., Latvia when the main study aims to expand the study to the neighbouring countries in Baltic States and Eastern Europe. Another limitation is potential self-selection of individuals with clinical symptoms or health-seeking behaviour, limiting the study to be truly population-based.

COLLABORATION

The Pilot study data are initially available to the principal investigators, study statisticians, and to the members of the Data Safety and Monitoring Board (DSMB), which has been specifically set up for this study to safeguard the interests of the study participants and to ensure the scientific validity of the study. Although the GISTAR Pilot data are not currently available to external investigators, we would welcome specific proposals relevant to the study objectives for future collaboration, while we develop data access policy in the near future. Such requests should be addressed to the GISTAR study investigators. Data from the Pilot study are currently being analysed in detail to be presented in forthcoming publications. Information on the study progress, gastric cancer, and *H. pylori* infection, study publications and collaboration policy are available at: https://www.gistar.eu.

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Contributors:

JYP, ML, LD, and RH conducted the data analysis and wrote the manuscript. ML, JYP, and RH have been involved in initial design of the protocol. JYP, SP, ILK, SI, IK, DR, AK, AV, JA, DS, ID, and VF committed to developing particular specialised parts of the protocol and data collection. JYP, RM, IP, and RH committed to improve the initial study protocol and LD, JYP and RM to the statistical evaluations. All authors reviewed, critically revised, and approved the manuscript.

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Competing Interest:

None declared.

Disclaimer:

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Data Sharing Statement:

Researchers interested in collaboration are invited to submit a request with specific proposals relevant to the study objectives. The requests can be submitted to gistar@gistar.eu and will be reviewed by the GISTAR Central Coordinating Group.

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