EPIDEMIOLOGIC CHARACTERISTICS OF HELICOBACTER PYLORI INFECTION AND SOCIODEMOGRAPHIC FEATURES OF REFLUX-RELATED SYMPTOMS IN SOUTHEAST HUNGARY

Ph.D. Thesis

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2022

1. LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS

I. **Bálint L**, Tiszai A, Kozák G, Dóczi I, Szekeres V, Inczefi O, Ollé G, Helle K, Róka R, Rosztóczy A. Epidemiologic characteristics of Helicobacter pylori infection in southeast Hungary. World Journal of Gastroenterology. 2019 Nov 14;25(42):6365-6372. doi: 10.3748/wjg.v25.i42.6365. PMID: 31754296; PMCID: PMC6861848.

IF: 3.665 (Gastroenterology Q1, Medicine Q1)

II. Helle K, **Bálint L**, Szekeres V, Ollé G, Rosztóczy A. Prevalence of reflux-related symptoms in South-Hungarian blood donor volunteers. PLoS One. 2022 Mar 15;17(3):e0265152. doi: 10.1371/journal.pone.0265152. PMID: 35290403; PMCID: PMC8923446.

IF: 3.752 (Multidisciplinary Q1)

Cumulative IF: 7.417

2. LIST OF FULL PAPERS NOT RELATED TO THE SUBJECT OF THE THESIS

I. Rosztóczy A, Laczkó D, **Bálint L**. Az esomeprazol szerepe a gyomorsav okozta betegségek terápiájában. Háziorvos Továbbképző Szemle. 2013; 18: D5-9.

II. Rosztóczy A, **Bálint L**, Laczkó D. Az esomeprazol szerepe a gyomorsav okozta betegségek terápiájában. Metabolizmus. 2013; 11: L5-8.

III. **Bálint L**, Rosztóczy A. Szimptomatikus diverticulosis, irritábilis bél szindróma (IBS) vagy kivizsgálást igénylő szövődményes állapot? Háziorvos Továbbképző Szemle. 2014; 19: 412-416.

IV. **Bálint L**, Rosztóczy A. Szimptomatikus diverticulosis, irritábilis bél szindróma (IBS) vagy kivizsgálást igénylő szövődményes állapot? Gyógyszerész továbbképzés. 2014; 8(5): 162-166.

3. TABLE OF CONTENTS

4. SUMMARY

Background: Helicobacter pylori (H. pylori) infection is one of the most common chronic human bacterial infections worldwide, affecting up to half of the world's population. H. pylori is a Gram-negative, spiral-shaped pathogenic bacterium, that is uniquely adapted to colonize the gastric mucosa. The infection is predominantly acquired in childhood and usually persists throughout life. The transmission mechanism of H. pylori is not completely understood, but person-to-person spread through the oral-oral and fecal-oral routes seems to be the most likely. This bacterium is the main cause of gastritis, gastroduodenal ulcer, gastric adenocarcinoma, and mucosa-associated tissue lymphoma. International Agency for Research on Cancer (IARC) has classified H. pylori in the first group of carcinogenic agents in 1994. Therefore, the eradication of H. pylori remains a public health concern. The prevalence of H. pylori has declined worldwide, although wide variation has been observed. It varies according to geographical location, ethnicity, age, and socioeconomic factors: high in developing countries and lower in the developed parts of the world. The proposed risk factors for H. pylori infection included male sex, higher age, lower body height, tobacco use, lower socioeconomic status, obesity, and lower educational status of the parents.

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders worldwide, which develops when frequent regurgitation of the gastric acid irritates the esophagus, mouth, and/or respiratory system. GERD is a common clinical problem potentially decreasing quality of life. Large epidemiological studies have shown a global variation in the prevalence of symptomatic GERD. Several important sociodemographic and socioeconomic factors are strongly related to both GERD symptoms and its complications.

Aims: Recent epidemiologic studies have revealed decreases in the prevalence of H. pylori in Western Europe, in the United States, and have shown a global variation in the prevalence of symptomatic GERD. Conversely, little is known regarding the prevalence of H. pylori, and GERD-related symptoms in Central Europe, especially in Hungary, where a substantial population resides in rural areas, presumably with lower socio-economic conditions.

Study I aimed to obtain data regarding H. pylori prevalence in Csongrád-Csanád and Békés counties in Hungary, evaluate differences in prevalence between urban and rural areas, and establish factors associated with positive seroprevalence. Study II aimed to identify sociodemographic factors for the presence of GERD-related symptoms in Southeast Hungary and compare the data with the known epidemiologic studies.

Methods: In study I, one-thousand and one healthy blood donors [male/female: 501/500, mean age: 40 (18–65) years] were consecutively enrolled in Csongrád-Csanád and Békés counties. Data collection was performed using an anonymous questionnaire including 26 questions associated with demographic parameters, and medical status.

In study II, a total of two-thousand and two blood donor volunteers [male/female: 1156/846, mean age: 39 (18–65) years] were consecutively enrolled, blood donors completed detailed questionnaires related to demographic data, presence and frequency of typical and atypical GERD-related symptoms.

Results: In study I, the overall seropositivity of H. pylori was 32% in the studied healthy subjects. A significant positive association was observed between age and H. pylori positivity. According to childhood residence, the prevalence of H. pylori was significantly higher in rural areas than in urban areas ($p = 0.0051$). Furthermore, residence in rural areas for at least one year was associated with a significantly higher H. pylori prevalence than continuous urban residency ($p = 0.0003$). Parameters related to occupation were also associated with H. pylori infection. A higher prevalence was established for industrial workers and agricultural workers compared to office workers and non-agricultural workers, respectively. Coffee consumption, pet or domesticated animal rearing, and positive family history of gastric cancer were associated with H. pylori infection as well. To rule out the strong effect of age, three age groups were formed for further analysis. In the youngest group, the presence of epigastric pain was an independent risk factor for H. pylori positivity. By contrast, animal rearing was a risk factor for the middle age group, and male sex and living in rural areas for at least one year were risk factors in the oldest age group.

In study II, among blood donors who had GERD-related symptoms at least monthly, we found significant correlations between typical GERD complaints and living on a farm currently or during childhood. An increased prevalence of GERD-related typical and/or atypical symptoms was shown among housewives and retired blood donors or individuals living on a farm currently. In the group of blood donors who had GERD-related symptoms daily, significant correlations were found between typical and/or atypical GERD complaints and living on a farm during childhood.

Conclusion: We proved that in line with the global trends, the prevalence of H. pylori infection has decreased in Southeast Hungary with changes in society, including improvements in socioeconomic status and living standards, during recent decades. Meanwhile, the prevalence remains high in the middle-aged and older rural populations. Generally accepted risk factors for H. pylori positivity appeared valid for the studied population, whereas the presence of dyspeptic symptoms was identified as an independent risk factor in the young population.

The association between the prevalence of GERD-related symptoms among Southeast Hungarian blood donor volunteers and their sociodemographic features could not be as clear as in Western countries.

5. INTRODUCTION

H. pylori infection is one of the most common chronic human bacterial infections worldwide, affecting up to half of the world's population. Isolation and identification of H. pylori by Warren and Marshall in 1982 led to a better understanding of gastric pathophysiology. H. pylori is a Gram-negative, spiral-shaped pathogenic bacterium, that is uniquely adapted to colonize the gastric mucosa. The infection is predominantly acquired in childhood and usually persists throughout life. The transmission mechanism of H. pylori is not completely understood, but person-to-person spread through the oral-oral and fecal-oral routes seems to be the most likely. This bacterium is the main cause of gastritis, gastroduodenal ulcer, gastric adenocarcinoma, and mucosa-associated tissue lymphoma. International Agency for Research on Cancer (IARC) has classified H. pylori in the first group of carcinogenic agents in 1994. Therefore, the eradication of H. pylori remains a public health concern. Given the high frequency of H. pylori-associated diseases, knowledge about its epidemiology, antibiotic resistance, diagnosis and treatment is necessary. Its prevalence varies according to geographical location, ethnicity, age, and socioeconomic factors: high in developing countries and lower in the developed parts of the world[1-10].

The prevalence of H. pylori has declined worldwide, although wide variation has been observed. In Japan, the prevalence of H. pylori was 90% among individuals born before 1950, but with a subsequent decreasing trend, reaching less than 2% among subjects born after the 2000s. According to a 2017 and a 2018 meta-analysis, the countries with the lowest H. pylori prevalence were Switzerland (13.1-24.7%), Denmark (17.8-26.5%), New Zealand (21.4-26.5%), Australia (17.2-32.1%), and Sweden (18.3-34.1%) in the former meta-analysis, while Indonesia (10.0%), Belgium (11.0%), Ghana (14.2%), and Sweden (15.0%) in the latter. Countries with the highest prevalence were Nigeria (83.1-92.2%), Portugal (84.9-87.9%), Estonia (75.1-90.0%), Kazakhstan (74.9–84.2%), and Pakistan (75.6-86.4%) in the former study, and Serbia (88.3%), South Africa (86.8%), Nicaragua (83.3%), and Colombia (83.1%) in the latter. The former study used two periods to analyze the prevalence trend over time. The H. pylori prevalence after 2000 was lower than before 2000 in Europe (48.8% vs 39.8%), North America (42.7% vs 26.6%), and Oceania (26.6% vs 18.7%). In contrast, the prevalence was similar in Asia (53.6% vs 54.3%), Latin America and the Caribbean (62.8% vs 60.2%)[11-13]. Detailed data are shown in Table 1[11].

Table 1. Prevalence of H. pylori in Europe[11]

Country	No. of reporting studies	No. of participants	Prevalence estimates, % (95% CI)
Eastern Europe (n=10)			
Czech Republic	3	4644	41.2 (24.8-57.6)
Poland	3	7806	66.6 (56.4-76.7)
Romania	1	960	68.5 (65.6-71.5)
Russian Federation	3	4771	78.5 (67.1-89.9)
Northern Europe (n=22)			
Denmark	2	37741	22.1(17.8-26.5)
Estonia	2	2198	82.5 (75.1-90.0)
Finland	1	896	56.8 (46.5-67.0)
Iceland	2	834	36.0 (32.7-39.2)
Ireland	1	1000	43.0 (39.9-46.1)
Latvia	1	3564	79.2 (77.9-80.05)
Norway	3	4068	30.7 (20.5-40.8)
Sweden	5	7149	26.2 (18.3-34.1)
United Kingdom	5	15098	35.5 (14.5-56.5)
Southern Europe (n=22)			
Albania	1	101	53.5 (43.7-63.2)
Croatia	3	6538	52.7 (42.5-62.8)
Greece	3	1571	52.1 (40.2-64.0)
Italy	5	9055	56.2 (46.9-65.4)
Portugal	1	2067	86.4 (84.9-87.9)
San Marino	2	3765	47.5 (40.5-54.5)
Spain	7	2721	54.9 (48.6-61.1)
Western Europe (n=16)			
Belgium	3	27845	32.7 (22.4-43.0)
France	1	64	46.9 (34.7-59.1)
Germany	8	19015	35.3 (31.2-39.4)
The Netherlands	3	8592	35.5 (30.1-41.0)
Switzerland	1	175	18.9 (13.1-24.7)

Abbreviations: CI = Confidence interval.

In the absence of new, extended multicenter studies with a large number of patients from Central Europe and Hungary, this area's H. pylori prevalence is little known. Four groups of authors from West and North Hungary investigated the prevalence of H. pylori between 1990 and 2000. Their results were similar throughout the country (58.6-63.3%) excluding the capital, in which the prevalence was only 47.3%. In Southeast Hungary, the H. pylori workgroup of our institute conducted a retrospective analysis in 2005 and 2010 among patients with dyspepsia and gastroduodenal ulcer disease. The rate of seropositivity decreased from 46% to 38%[14-19]. Detailed data are shown in Table 2[14-17].

Table 2. The prevalence between 1990 and 2000 throughout the country[14-17]

Date	**1993**	**1999**	**2000**	**1998-2000**
County	Tolna	Vas	Szabolcs-Szatmár-Bereg	Pest
Authors	Tamássy K. et al	Lakner L. et al	Iszlai É. et al	Prónai L. et al
Method	Serology	Serology	Serology	13C-UBT
Population	Blood donors	Blood donors	Healthy volunteers	Symptomatic patients
No. of participants	400	533	756	1027
Prevalence of Hp (%)	**63.3**	**62.3**	**58.6**	**47.3**

Abbreviations: Hp = Helicobacter pylori; 13C-UBT = 13C urea breath test.

The proposed risk factors for H. pylori infection included male sex, higher age, lower body height, tobacco use, lower socioeconomic status, obesity, and lower educational status of the parents. According to a previous Hungarian study, the major risk factors for H. pylori infection are socioeconomic status and the household hygiene of the patient and family during childhood. This study revealed greater seropositivity among undereducated subjects, in persons living without sewers, those living in crowded homes or having three or more brothers and sisters, and those with high alcohol consumption. Moreover, they observed significant differences in prevalence between industrial and office workers. A Russian study reported that 88% of the Moscow working population is infected with H. pylori, of whom 78% is younger than 30 years, and 97% is older than 60 years[10,14,20-22].

A study from Szabolcs-Szatmár-Bereg county (2000) examined the seroprevalence of H. pylori infection and the risk factors among adult volunteers from East Hungary. H. pylori seropositivity increased statistically with age ($p < 0.001$), which was 45.2% in those aged 18-29 and 69.6% in those aged 50-59. Seropositivity was significantly higher in the rural population ($p < 0.001$), in individuals who shared a bed in childhood ($p < 0.001$), and who had manual workers parents ($p < 0.001$). The authors of this study found a significant inverse correlation between H. pylori infection and educational level ($p < 0.001$), income ($p < 0.005$), absence of water supply and sanitation (childhood: $p < 0.001$, adulthood: $p < 0.05$)[16]. Detailed data are shown in Table 3-6[16].

Table 3. Parents' occupation associated with H. pylori prevalence in Szabolcs-Szatmár-Bereg county (2000)[16]

Factors	**Total**	**Hp positive**				
	n	n	%	p	Odds ratio	CI (95%)
Parents' occupation						
Father						
Intellectual	128	53	41.4			
Physical	628	390	62.1	<0.001	2.32	[1.58-3.41]
Mother						
Intellectual	85	29	34.1			
Physical	671	414	61.7	<0.001	3.11	[1.94-4.98]
Both parents						
Intellectual	62	19	30.6			
Physical	605	380	62.8		3.82	[2.19-6.68]
Mother: physical + father: intellectual	66	34	51.5			
Mother: intellectual + father: physical	23	10	43.5	<0.001	1.38	[0.54-3.58]

Abbreviations: Hp = Helicobacter pylori; CI = Confidence interval.

Table 4. Hygienic factors associated with H. pylori prevalence in Szabolcs-Szatmár-Bereg county (2000)[16]

Factors	Total	Hp positive				
	n	n	%	p	Odds ratio	CI (95%)
Hygiene in childhood						
Running water						
Positive	307	151	49.2			
Negative	449	292	65.0	<0.001	1.92	[1.43-2.58]
Sewage disposal						
Positive	312	157	50.3			
Negative	444	286	64.4	<0.001	1.79	[1.33-2.40]
Type of toilet						
Western-style toilet	184	76	41.3			
Both	85	52	61.2		2.24	[1.33-3.78]
Pit latrine	487	315	64.7	<0.001	2.60	[1.84-3.68]
Both-pit latrine					1.16	[0.73-1.86]
Hygiene in adulthood						
Running water						
Positive	742	434	58.5			
Negative	14	9	64.3	0.249	2.13	[0.62-7.32]
Sewage disposal						
Positive	725	426	58.8			
Negative	31	17	54.8	0.19	0.85	[0.42-1.73]
Type of toilet						
Western-style toilet	589	329	55.9			
Both	143	99	69.2		1.78	[1.20-2.62]
Pit latrine	24	15	62.5	<0.05	1.32	[0.58-2.99]
Both-pit latrine					0.74	[0.31-1.78]

Abbreviations: Hp = Helicobacter pylori; CI = Confidence interval.

Table 5. Sociodemographic and socioeconomic factors associated with H. pylori prevalence in Szabolcs-Szatmár-Bereg county (2000) I.[16]

Factors	Total	Hp positive				
	n	n	%	p	Odds ratio	CI (95%)
Age						
18-29	155	70	45.2			
30-39	153	80	52.3		1.33	[0.85-2.08]
40-49	220	140	63.6		2.13	[1.40-3.23]
50-59	135	94	69.6		2.78	[1.72-4.51]
60-69	93	59	63.4	<0.001	2.11	[1.25-3.56]
Adult residence						
Urban	420	220	52.4			
Rural	336	223	66.4	<0.001	1.79	[1.33-2.41]
Childhood residence						
Urban	242	117	48.4			
Rural	514	326	63.4	<0.001	1.85	[1.36-2.52]
Adult migration						
Within the city	226	109	48.2			
Moved to the city	194	111	57.2		1.44	[0.98-2.11]
Within the village	320	215	67.2	<0.001	2.20	[1.55-3.12]
Moved to the city-Throughout in village					1.53	[1.06-2.21]
Education						
University/college	191	87	45.6			
High school	240	136	56.7		1.56	[1.07-2.29]
Vocational school	160	104	65.0		2.22	[1.44-3.42]
Primary school	144	101	70.1		2.81	[1.78-4.43]
< Primary school	21	15	71.4	<0.001	2.99	[1.14-7.78]

Abbreviations: Hp = Helicobacter pylori; CI = Confidence interval.

Table 6. Sociodemographic and socioeconomic factors associated with H. pylori prevalence in Szabolcs-Szatmár-Bereg county (2000) II.[16]

Factors	Total	Hp positive				
	n	n	%	p	Odds ratio	CI (95%)
No. of siblings						
0	44	28	63.6			
1	278	148	53.2			
2	197	110	55.8		1.11	[0.77-1.60]
>3	237	157	66.2	<0.05	1.72	[1.21-2.46]
2-3					1.55	[1.05-2.29]
Separated room						
Positive	180	91	50.6			
Negative	576	352	61.1	<0.05	1.54	[1.10-2.15]
Sleeping habits in childhood						
Alone	442	235	53.2			
Not alone	314	208	66.2	<0.001	1.73	[1.28-2.33]
Family income during childhood						
High	55	26	47.3			
Medium	454	250	55.1		1.37	[0.78-2.38]
Low	247	167	67.6	<0.005	2.33	[1.29-4.19]
Medium-low					1.70	[1.23-2.35]
Family income during adulthood						
High	148	66	44.6			
Medium	409	254	62.1		2.04	[1.39-2.98]
Low	199	123	61.8	<0.005	2.01	[1.31-3.10]
Medium-low					0.98	[0.70-1.40]

Abbreviations: Hp = Helicobacter pylori; CI = Confidence interval.

GERD is one of the most common gastrointestinal disorders worldwide, which develops when frequent regurgitation of the gastric acid irritates the esophagus, mouth, and/or respiratory system. It is well known that a wide range of symptoms is associated with this chronic condition: typical such as heartburn and acid regurgitation, and atypical symptoms like chronic cough and other respiratory symptoms, chest pain, dysphagia, globus sensation, nausea, vomiting. GERD is a common clinical problem potentially decreasing quality of life and having a relevant impact on health care costs. Early recognition of symptoms is essential in the prevention of esophageal and extraesophageal complications of GERD[23-30].

Large epidemiological studies have shown a global variation in the prevalence of symptomatic GERD. According to a review from 2005, when defined GERD as at least weekly heartburn and/or acid regurgitation, the prevalence in the Western world generally ranged between 10% and 20%, whereas in Asia, the prevalence was reported to be less than 5%. There is a trend for the prevalence in North America to be higher than in Europe, and this trend is also suggested for a higher prevalence in Northern over Southern European countries[31] . Detailed data are shown in Table 7[31].

A latter study (2020) conducted a systematic review and meta-analysis on GERD prevalence and risk factors at a global level. During the study selection, GERD was defined as the following: heartburn and/or acid regurgitation at least once a week regardless of the severity of symptoms. The review identified the countries with the highest and the lowest pooled prevalence of GERD as Turkey (22.4%) and China (4.16%), respectively. The region with the highest pooled prevalence of GERD was North America (19.55%) and the lowest rates were found in Latin America and the Caribbean (South America) (12.88%)[32]. Detailed data are shown in Table 8[32].

Several important sociodemographic and socioeconomic factors are strongly related to both GERD symptoms and its complications, including age, sex, marital status, residence, education level, occupation, obesity, tobacco use, and inversely with H. pylori infection. According to some authors, two major factors could explain the increasing prevalence of GERD symptoms in the Western world: obesity epidemic and the decreasing prevalence of H. pylori-associated gastritis. Studies evaluating the presence or absence of H. pylori in GERD have often given conflicting results. The opposing time trends of gastroduodenal and esophageal diseases are consistent with the hypothesis that the declining prevention of H. pylori has led to a rise in GERD disease and associated esophageal adenocarcinoma. In support of this, a systematic review reported a significantly lower prevalence of H. pylori among patients with GERD than among individuals without the disease. On the contrary, according to another meta-analysis (2010), there is no association between H. pylori eradication and the development of new cases of GERD among dyspeptic patients[32-38].

Table 7. Population studies of the prevalence of GERD[31]

Reference	Country	No. of participants	Prevalence of heartburn (%)	Prevalence of acid regurgitation (%)	Prevalence of heartburn and/or acid regurgitation (%)
Locke, 1997	USA	2073	17.8	6.3	19.8
Locke, 1999	USA	2118	17.4	6.6	20
Talley, 1992	USA	1021	13.2	6.5	
El-Serag, 2004	USA	915	Black people: 27 White people: 23	Black people: 16 White people: 15	Black people: 29 White people: 28
Mohammed, 2003	UK	8960			18
Isolauri, 1995	Finland	2500	15	15	
Terry, 2000	Sweden	1123			16.7
Valle, 1999	Italy	768	7.7	6.6	
Diaz-Rubio, 2004	Spain	8686			9.8
Hu, 2002	China	2640			4.8
Wong, 2003	China	3605			2.5
Pan, 2000	China	5000	3.1		

Table 8. Pooled prevalence of GERD according to geographical location[32]

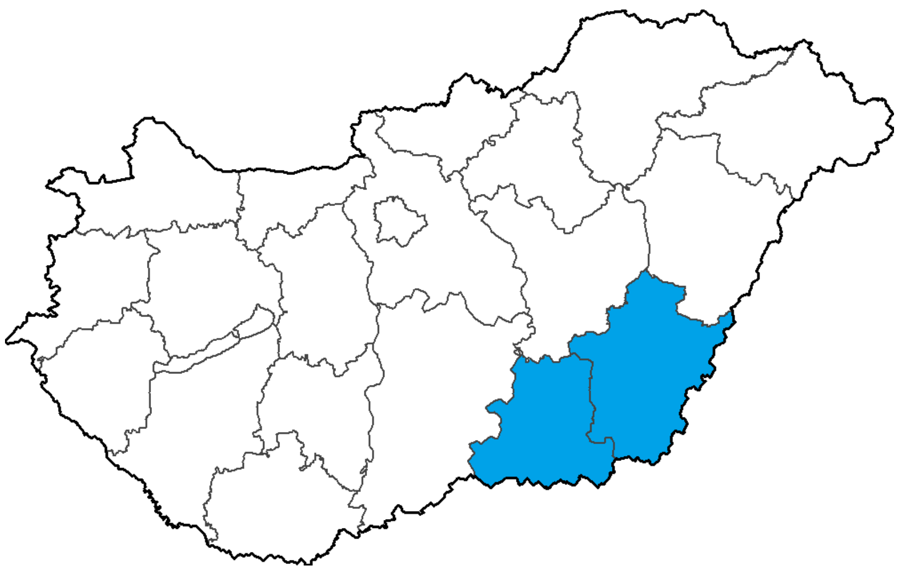
Geographical location	No. of studies	No. of participants	GERD prevalence (%)
GLOBAL			
Overall	102	469899	13.98
Male	50	122849	15.69
Female	50	138435	17.17
CONTINENTS			
Asia	54	240451	12.92
Europe	29	190057	14.12
North America	9	20525	19.55
Latin America and the Caribbean	4	12756	12.88
Oceania	4	3760	13.78
COUNTRIES			
China	10	36887	4.16
Japan	7	27912	13.81
South Korea	7	43897	5.84
Iran	16	102295	18.43
Turkey	4	13332	22.40
Sweden	4	8120	16.15
UK	4	12467	14.53
USA	8	19489	21.04

6. AIMS

Recent epidemiologic studies have revealed decreases in the prevalence of H. pylori in Western Europe and the United States, and have shown a global variation in the prevalence of symptomatic GERD. Conversely, little is known regarding the prevalence of H. pylori, and GERD-related symptoms in Central Europe, especially in Hungary, where a substantial population resides in rural areas, presumably with lower socio-economic conditions. Detailed demographic data are shown in Figure 1[39-41].

Therefore, study I aimed to obtain data regarding H. pylori prevalence in Csongrád-Csanád and Békés counties in Hungary, evaluate differences in prevalence between urban and rural areas, and establish factors associated with positive seroprevalence. Study II aimed to identify sociodemographic factors for the presence of GERD-related symptoms in Southeast Hungary and compare the data with the known epidemiologic studies.

Figure 1. Geographical location of Csongrád-Csanád and Békés counties [39-41]



7. PATIENTS AND METHODS

In study I, one-thousand and one healthy blood donors [male/female: 501/500, mean age: 40 (18–65) years] were consecutively enrolled in Csongrád-Csanád and Békés counties. Detailed demographic data are shown in Table 9[39-41].

Data collection was performed using an anonymous questionnaire including 26 questions associated with demographic parameters (sex, age, place of birth, childhood residence, marital status, current residence, household crowding, educational status) and medical status (symptoms associated with H. pylori infection and gastroduodenal ulcer disease, smoking habits, alcohol consumption, and family history of H. pylori infection, gastroduodenal ulcer disease, and gastric malignancy) (Table 10).

Table 9. Detailed demographic data regarding Csongrád-Csanád and Békés counties[39-41]

	Hungary	**Csongrád-Csanád county**	**Békés county**
Population			
Total	9,909,000 (M/F: 4,716,000/5,193,000)	410,000 (M/F: 193,000/216,000)	359,000 (M/F: 172,000/188,000)
Urban	6,936,000 (70%)	307,000 (75%)	270,000 (75%)
Rural	2,972,700 (30%)	102,000 (25%)	89,000 (25%)
Population density	106/km^2	96/km^2	63/km^2
Work			
Employment rate	58.4%	50.3%	48.8%
Unemployment rate	10.3%	12.3%	11.1%
Physical work	-	55%	61%
Intellectual work	-	45%	39%

Abbreviations: M = Male; F = Female.

Table 10. Questionnaire of study on the prevalence of H. pylori

Question	**Answer**				
Sex	Male	Female			
Date of birth					
Family structure	Alone	Adults only	Adults and children		
Current residence	Capital	County seat	City	Village	Farm
Place of birth	Capital	County seat	City	Village	Farm
Childhood residence	Capital	County seat	City	Village	Farm
Min. one year in rural environment	Negative	Positive			
Occupation	Student	Office	Industrial	Agricultural	Housewife
Agricultural work	Negative	Positive			
Domestic animals	Negative	Positive			
Smoking status	Non-smoker	Smoker	Former smoker		
Coffee consumption	Never	1	More than 1		
Alcohol consumption	Never	Occasional	Regular		
Family history of Hp	Negative	Positive			
Family history of GI ulcer	Negative	Positive			
Family history of gastric cancer	Negative	Positive			
Abdominal pain	Negative	Positive			
		Min. 1 daily	Min. 1 weekly	Min. 1 monthly	Rare
Epigastrial pain	Negative	Positive			
		Min. 1 daily	Min. 1 weekly	Min. 1 monthly	Rare
Endoscopy in lifetime	Negative	Positive			
Test for Hp	Negative	Positive			
Result of Hp test		Negative	Positive		
Eradication	Negative	Positive			
Result of eradication		Negative	Positive		

Abbreviations: Hp = Helicobacter pylori; GI = Gastrointestinal.

Data were collected using a questionnaire at the Hungarian National Blood Transfusion Service in Szeged or Békéscsaba, and at external blood donations in villages of Csongrád-Csanád or Békés county. In Hungary, blood donation is allowed for individuals weighing more than 50 kg and aged 18-65 years. Blood donors are allowed to have some diseases in a well-controlled form [42].

Based on the childhood residence of the subjects, the following four groups of 250 subjects were established: urban males, urban females, rural males, and rural females. Groups were matched by age. Subgroup analysis was performed according to living circumstances, residence in Békés or Csongrád-Csanád county, smoking habits, alcohol and coffee consumption, occupation, intermittent agricultural work, pet or domestic animal rearing, gastrointestinal complaints, and family history of H. pylori infection, gastric ulcer, and gastric cancer.

All subjects were tested for H. pylori IgG antibody positivity using a Platelia H. pylori IgG enzyme-linked immunosorbent assay, which reportedly has 100% sensitivity and 90% specificity according to the manufacturer. In the validation study of Burucoa et al (Bio-Rad), these values were 95.6% and 85.1%, respectively[43].

For the statistical analysis of different variables related to H. pylori infection, the chi-squared test or two-sample t-test was applied. The association between H. pylori infection and potential risk factors was established via univariate analysis, and odds ratios and 95% confidence intervals were calculated. In addition, a stratified analysis according to age (18–35, 35–50, and 50–65 years) was performed. The final model was developed using a generalized linear regression model via stepwise regression, with inclusion and exclusion criteria set at significance levels of 0.05 and 0.10, respectively. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using MATLAB (Mathworks, Natwick, MA, United States). The study received ethical approval.

In study II, a total of two-thousand and two blood donor volunteers [male/female: 1156/846, mean age: 39 (18–65) years] were consecutively enrolled. As a number of studies have used questionnaire components to investigate factors possibly associated with GERD, in this study, blood donors completed detailed questionnaires related to demographic data (childhood residence, current residence, family structure, occupation) (Table 11).

The presence and frequency of typical (heartburn, acid regurgitation) and atypical GERD-related symptoms (nausea, vomiting dysphagia, globus sensation, chest pain, and respiratory symptoms such as chronic cough, shortness of breath, hoarseness, new or worsening asthma) were assessed. Four symptom-frequency categories were used: at least once a day, at least once a week, at least once a month, and less than once a month.

Subgroup analysis was conducted by sociodemographic factors (childhood residence, current residence, family structure, occupation) and the prevalence of symptoms. All statistical analyses were performed using R software. Chi-square test was applied as required, and p-value < 0.05 was considered statistically significant. The study received ethical approval.

Data were collected using a questionnaire at the Hungarian National Blood Transfusion Service in Szeged, and at external blood donations in settlements of Csongrád-Csanád county.

Table 11. Questionnaire of study on the prevalence of GERD-related symptoms

Question	Answer				
Family structure	Alone	Adults only	Adults and children		
Current residence	Capital	County seat	City	Village	Farm
Childhood residence	Capital	County seat	City	Village	Farm
Occupation	Student	Office	Industrial	Agricultural	Housewife
Epigastrial pain, heartburn, acid regurgitation	Negative	Positive			
		Min. 1 daily	Min. 1 weekly	Min. 1 monthly	Rare
Medication for heartburn or acid regurgitation	Negative	Positive			
		Min. 1 daily	Min. 1 weekly	Min. 1 monthly	Rare
		Effective	Not effective		
Nausea, vomiting, dysphagia, globus sensation, chest pain, upper respiratory symptoms, dyspnea, typical symptoms during the night, abdominal pain	Negative	Positive			
		Min. 1 daily	Min. 1 weekly	Min. 1 monthly	Rare
Endoscopy in lifetime	Negative	Positive			
Test for Hp	Negative	Positive			
Result of Hp		Negative	Positive		
Eradication	Negative	Positive			
Result of eradication		Negative	Positive		

Abbreviations: Hp = Helicobacter pylori.

8. RESULTS

In study I, the overall seropositivity of H. pylori was 32% in the studied healthy subjects. There was no statistically significant difference in prevalence between males and females ($p = 0.0521$) in our study. A significant positive association was observed between age and H. pylori positivity. According to childhood residence, the prevalence of H. pylori was significantly higher in rural areas than in urban areas ($p = 0.0051$). Furthermore, residence in rural areas for at least one year was associated with a significantly higher H. pylori prevalence than continuous urban residency ($p = 0.0003$). Parameters related to occupation were also associated with H. pylori infection. A higher prevalence was established for industrial workers and agricultural workers compared to office workers and non-agricultural workers, respectively. Coffee consumption, pet or domesticated animal rearing, and positive family history of gastric cancer were associated with H. pylori infection as well. All the other results of our study (current residence, smoking habits, alcohol consumption, family structure, family history of H. pylori infection, and family history of gastrointestinal ulcer, abdominal pain, epigastrial pain) were not statistically significant. Detailed data are shown in Table 12, Table 13, and Table 14.

A significant positive association was observed between age and H. pylori positivity (Table 12). To rule out this strong effect of age, three age groups were formed for further analysis. In the youngest group, the presence of epigastric pain was an independent risk factor for H. pylori positivity. By contrast, animal rearing was a risk factor for the middle age group, and male sex and living in rural areas for at least one year were risk factors in the oldest age group (Table 15).

A higher H. pylori seropositivity was found among blood donors in Békés county compared to those in Csongrád-Csanád county. This finding could be explained by the differences in living standards between the two counties. According to data from the Hungarian Central Statistical Office in Csongrád-Csanád county, the average annual number of death and the proportion of disadvantaged children in kindergartens and primary schools are lower, while life expectancy at birth is higher than in Békés county. The difference in the prevalence of H. pylori infection between the two counties is not significant[40,41]. Detailed data are shown in Figure 2.

Table 12. Sociodemographic factors associated with H. pylori prevalence

Sociodemographic factors	Hp positive		Hp negative					
	n	%	n	%	Total	p	Odds ratio	CI (95%)
Sex						0.0521		
Female	146	29.2	354	70.8	500		1.0	
Male	175	34.9	326	65.1	501		1.3016	[0.9973, 1.6987]
Age						0.000**		
	44.5638	10.7693	37.3599	11.9457			0.9484	[0.9363, 0.9606]
18-25	25	14.9	143	85.1	168			
25-35	32	16.9	157	83.1	189			
35-45	97	34.4	185	65.6	282			
45-55	106	43.6	137	56.4	243			
55+	61	51.3	58	48.7	119			
Current residence						0.0809		
Urban	185	30.0	431	70.0	616		1.0	
Rural	136	35.3	249	64.7	385		1.2725	[0.9706, 1.6683]
Childhood residence						0.0051**		
Urban	140	27.9	361	72.1	501		1.0	
Rural	181	36.2	319	63.8	500		1.4631	[1.1201, 1.9110]
Min. 1 year in rural environment						0.0003**		
Negative	104	25.6	303	74.4	407		1.0	
Positive	217	36.5	377	63.5	594		1.6770	[1.2695, 2.2153]

*: $p < 0.05$, compared to the respective group; **: $p < 0.01$, compared to the respective group

Abbreviations: Hp = Helicobacter pylori; CI = Confidence interval.

Table 13. Socioeconomic and lifestyle factors associated with H. pylori prevalence

Socioeconomic+lifestyle factors	Hp positive		Hp negative					
	n	%	n	%	Total	p	Odds ratio	CI (95%)
Smoking status						0.1121		
Non-smoker	169	29.5	403	70.5	572		1.0	
Smoker	91	34.2	175	65.8	266		1.2400	[0.9090, 1.6915]
Former smoker	61	37.4	102	62.6	163		1.4261	[0.9904, 2.0534]
Alcohol consumption						0.1420		
Never	95	36.0	169	64.0	264		1.0	
Occasional	216	30.3	497	69.7	713		0.7731	[0.5740, 1.0413]
Regular	10	41.7	14	58.3	24		1.2707	[0.5434, 2.9715]
Coffee consumption						0.0390*		
Never	82	26.7	225	73.3	307		1.0	
1	94	36.3	165	63.7	259		1.5632	[1.0929, 2.2358]
More than 1	145	33.3	290	66.7	435		1.3720	[0.9943, 1.8931]
Family structure						0.1649		
Alone	51	39.2	79	60.8	130		1.0	
Adults only	135	31.5	294	68.5	429		0.7113	[0.4736, 1.0683]
Adults and children	135	30.5	307	69.5	442		0.6812	[0.4538, 1.0224]
Occupation						0.0000**		
Physical	186	38.4	299	61.6	485		1.0	
Intellectual	135	26.2	381	73.8	516		0.5696	[0.4355, 0.7450]
Agricultural work						0.0012**		
Negative	140	27.4	371	72.6	511		1.0	
Positive	181	36.9	309	63.1	490		1.5523	[1.1882, 2.0279]
Domestic animals						0.0015**		
Negative	54	23.5	176	76.5	230		1.0	
Positive	267	34.6	504	65.4	771		1.7266	[1.2301, 2.4236]

*: $p < 0.05$, compared to the respective group; **: $p < 0.01$, compared to the respective group

Abbreviations: Hp = Helicobacter pylori; CI = Confidence interval

Table 14. Factors in patient history associated with H. pylori prevalence

Patient history	Hp positive		Hp negative					
	n	%	n	%	Total	p	Odds ratio	CI (95%)
Family history of HP						0.8829		
Negative	161	32.5	335	67.5	496		1.0	
Positive	18	31.0	40	69.0	58		0.9363	[0.5205, 1.6844]
NA	142	31.8	305	68.2	447			
Family history of GI ulcer						0.3810		
Negative	217	33.3	435	66.7	652		1.0	
Positive	57	29.7	135	70.3	192		0.8464	[0.5965, 1.2009]
NA	47	29.9	110	70.1	157			
Family history of GI cancer						0.0014**		
Negative	277	32.1	587	67.9	864		1.0	
Positive	17	63.0	10	37.0	27		3.6025	[1.6284, 7.9701]
NA	27	33.8	53	66.3	80			
Abdominal pain						0.8108		
Negative	264	32.2	555	67.8	819		1.0	
Positive	57	31.3	125	68.7	182		0.9586	[0.6784, 1.3547]
Epigastrial pain						0.1105		
Negative	214	30.5	487	69.5	701		1.0	
Positive	107	35.7	193	64.3	300		1.2617	[0.9481, 1.6789]

*: $p < 0.05$, compared to the respective group; **: $p < 0.01$, compared to the respective group

Abbreviations: Hp = Helicobacter pylori; CI = Confidence interval; NA = not applicable; GI = gastrointestinal.

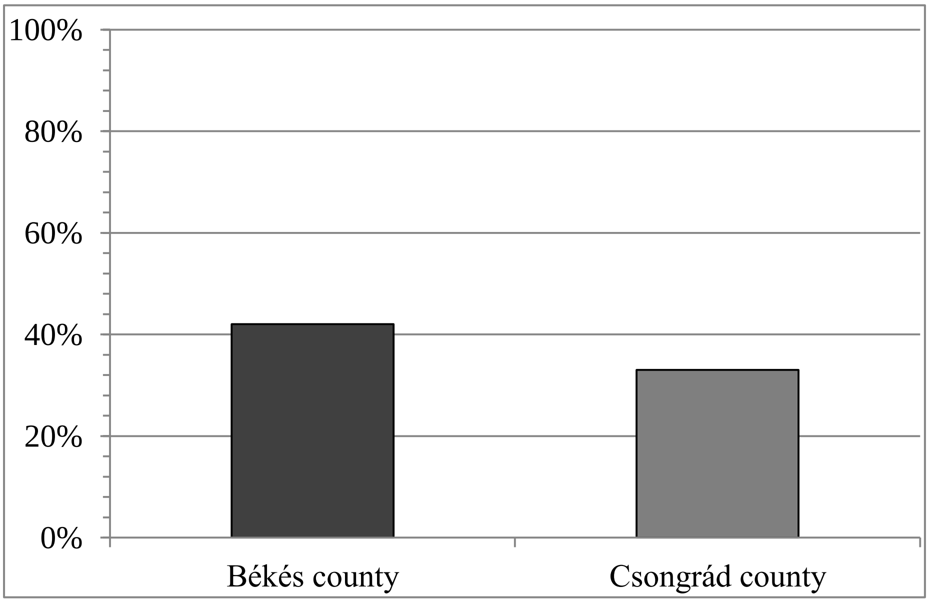
Table 15. Independent risk factors associated with H. pylori prevalence

	Age 18-35	Age 35-50	Age 50-65
Male sex	Not significant	Not significant	p = 0.0389*; OR: 0.5847; CI=[0.0753, 1.0940]
Rural residence in childhood	Not significant	Not significant	p = 0.0246*; OR: 1.8537; CI=[1.3154, 2.3920]
Domestic animals	Not significant	p = 0.0036; OR: 2.0855; CI=[1.5897, 2.5812]	Not significant
Epigastrial pain	p = 0.0026**; OR: 2.5514; CI=[1.9422, 3.1606]	Not significant	Not significant

*: p < 0.05, compared to the respective group; **: p < 0.01, compared to the respective group

Abbreviations: OR = Odds ratio; CI = Confidence interval.

Figure 2. Prevalence of H. pylori infection in Csongrád-Csanád and Békés counties



In study II, associations between the prevalence of typical and typical and/or atypical GERD-related symptoms occuring at least once a week, or at least once a month, and certain sociodemographic factors are discussed.

Among blood donors who had GERD-related symptoms at least weekly, significant correlations were not found between typical GERD complaints and childhood residence, current residence, family structure, and occupation. Among blood donors who had GERD-related symptoms at least weekly, significant correlations were not found between typical and/or atypical GERD complaints and the examined sociodemographic factors (Tables 16, and 17).

Conversely, among blood donors who had GERD-related symptoms at least monthly, we found significant correlations between typical GERD complaints and living on a farm currently or during childhood. An increased prevalence of GERD-related typical and/or atypical symptoms was shown among housewives and retired blood donors or individuals living on a farm currently. All the other results of our study were statistically non-significant (Tables 16 and 17).

In the group of blood donors who had GERD-related symptonorms daily, significant correlations were found between typical and/or atypical GERD complaints and living on a farm during childhood (Tables 16 and 17).

Table 16. Sociodemographic factors and GERD-related symptoms

		GERD-related symptoms (typical / atypical) (n = 871)			
	Asymptomatic (n=1,131)	**< 1 / month (n=286)**	**≥ 1 / month& < 1 / week (n=254)**	**≥ 1 / week& < 1 / day (n=191)**	**≥ 1 / day (n=140)**
Family structure					
Alone	161 (14.2%)	37 (12.9%)	36 (14.2%)	17 (8.9%)	14 (10.0%)
Adults only	446 (39.4%)	112 (39.2%)	109 (42.9%)	74 (38.7%)	59 (42.1%)
Adults and children	524 (46.4%)	137 (47.9%)	109 (42.9%)	100 (52.4%)	67 (47.9%)
Current residence					
Capital	12 (1.1%)	4 (1.4%)	5 (2.0%)	1 (0.5%)	1 (0.7%)
City	849 (75.1%)	226 (79.0%)	169 (66.5%)	136 (71.2%)	97 (69.3%)
Village	257 (22.7%)	50 (17.5%)	76 (29.9%)	51 (26.7%)	39 (27.9%)
Farm	13 (1.1%)	6 (2.1%)	4 (1.6%)*	3 (1.6%)	3 (2.1%)
Childhood residence					
Capital	16 (1.4%)	4 (1.4%)	4 (1.6%)	1 (0.5%)	2 (1.4%)
City	732 (64.7%)	226 (79.0%)	150 (59.1%)	119 (62.3%)	80 (57.1%)
Village	360 (31.9%)	50 (17.5%)	94 (37.0%)	68 (35.6%)	50 (35.8%)
Farm	23 (2.0%)	6 (2.1%)**	6 (2.4%)	3 (1.6%)	8 (5.7%)*
Occupation					
Student	159 (14.1%)	38 (13.3%)	54 (21.3%)	34 (17.8%)	18 (12.9%)
Office	493 (43.6%)	119 (41.6%)	108 (42.5%)	88 (46.1%)	55 (39.3%)
Agricultural	42 (3.7%)	11 (3.8%)	12 (4.7%)	9 (4.7%)	7 (5.0%)
Industrial	396 (35.0%)	108 (37.8%)	75 (29.5%)	58 (30.4%)	54 (38.6%)
Housewife/retired	41 (3.6%)	10 (3.5%)	5 (2.0%)*	2 (1.0%)	6 (4.3%)

*: $p < 0.05$, compared to the respective group; **: $p < 0.01$, compared to the respective group

Table 17. Sociodemographic factors and GERD-related typical symptoms

		GERD-related typical symptoms (n =559)			
	Asymptomatic (n=1,131)	**< 1 / month (n=229)**	**≥ 1 / month& < 1 / week (n=194)**	**≥ 1 / week& < 1 / day (n=101)**	**≥ 1 / day (n=35)**
Family structure					
Alone	161 (14.2%)	28 (12.2%)	21 (10.8%)	14 (10.3%)	6 (17.2%)
Adults only	446 (39.4%)	95 (41.5%)	79 (40.7%)	57 (41.9%)	16 (45.7%)
Adults and children	524 (46.4%)	106 (46.3%)	94 (48.5%)	65 (47.8%)	13 (37.1%)
Current residence					
Capital	12 (1.1%)	4 (1.7%)	1 (0.5%)	1 (0.7%)	1 (2.9%)
City	849 (75.1%)	173 (75.5%)	126 (64.9%)	106 (77.9%)	28 (80.0%)
Village	257 (22.7%)	49 (21.4%)	63 (32.5%)	27 (19.9%)	6 (17.1%)
Farm	13 (1.1%)	3 (1.4%)	4 (2.1%)*	2 (1.5%)	0 (0.0%)
Childhood residence					
Capital	16 (1.4%)	6 (2.6%)	2 (1.0%)	1 (0.7%)	1 (2.9%)
City	732 (64.7%)	158 (69.0%)	105 (54.1%)	90 (66.2%)	21 (60.0%)
Village	360 (31.9%)	58 (25.3%)	79 (40.8%)	42 (30.9%)	12 (34.3%)
Farm	23 (2.0%)	7 (3.1%)	8 (4.1%)*	3 (2.2%)	1 (2.9%)
Occupation					
Student	159 (14.1%)	34 (14.8%)	31 (16.0%)	14 (10.3%)	4 (11.4%)
Office	493 (43.6%)	88 (38.4%)	82 (42.3%)	65 (47.8%)	14 (40.0%)
Agricultural	42 (3.7%)	9 (3.9%)	13 (6.7%)	6 (4.4%)	0 (0.0%)
Industrial	396 (35.0%)	95 (41.5%)	63 (32.5%)	47 (34.6%)	14 (40.0%)
Housewife/retired	41 (3.6%)	3 (1.3%)	5 (2.6%)	4 (2.9%)	3 (8.6%)

*: $p < 0.05$, compared to the respective group

9. DISCUSSION

H. pylori infection is still the most common human infection worldwide, although on a global scale, its prevalence is decreasing with high geographical variability. The 2017 meta-analysis used two periods to analyze the changes in prevalence trend. The H. pylori prevalence after 2000 was lower than before 2000 in Europe (48.8% vs. 39.8%), North America (42.7% vs 26.6%), and Oceania (26.6% vs 18.7%)[13].

A significant decrease in the prevalence of H. pylori infection was also reported in developed European countries like Germany. The overall H. pylori prevalence was nearly 30% among blood donors in 2016 in Saxony-Anhalt, which is lower in comparison to previous study (2010) conducted at the emergency department in the same area (28.9% vs 44.4%), respectively[44,45].

In the surrounding Central European countries, such as the Czech Republic and Slovakia, the prevalence of H. pylori infection followed the global trend, decreased from 42% to 23% after 10 years (2001-2011) in the former, from 62% to 35% after 15 years (1992-2007) in the latter. A decrease in the prevalence of H. pylori was also found in other former communist countries such as Estonia, it has significantly decreased among children during an 11-year period (42.2% in 1991 vs 28.1% in 2002) of profound socioeconomic changes[46-51].

This prospective study proved that the prevalence of H. pylori infection in Hungary has followed international trends, falling to 32% over the last two decades. The prevalence between 1990 and 2000 was similar throughout the country (58.6-63.3%) excluding the capital, where it was only 47.3% (Table 2). Although the Southeastern region of the country was not investigated prospectively before this study, the H. pylori workgroup of our institute conducted a retrospective analysis in 2005 and 2010 among patients with dyspepsia and gastroduodenal ulcer disease. The rate of seropositivity decreased from 46% to 38%[14-19].

Having examined the potential factors associated with a higher H. pylori prevalence, our results were in concordance with previous observations revealing a positive linear association with age. An epidemiological survey (2013) from the southern Netherlands reported overall H. pylori seroprevalence of 31.7% in blood donors born between 1935 and 1987. The authors could prove an age-specific decline: the seroprevalence of 48% for donors born between 1935 and 1946 decreased to 16% for those born between 1977 and 1987[52].

Furthermore, our study supported findings that rural subjects are more likely to be H. pylori-positive than urban residents. However, we could not establish a significant effect of sex on the seroprevalence, it is impressive that older rural males have an approximately sixfold higher risk of H. pylori positivity than young urban females (61.29% vs 11.11% $p < 0.0001$). Such results are most commonly explained by differences in socioeconomic status and household hygiene of the family during childhood. Furthermore, a new original finding is that people who lived in rural conditions for at least one year also had an increased risk for H. pylori seropositivity. An evaluation of the occupations of the subjects provided further proof that socioeconomic factors can influence H. pylori infection risk. Meanwhile, the lack of difference in risk between urban and rural residence can be explained by the general improvement of living standards in our country over the last two decades, as most rural people currently have access to water supply and sanitation[10,14,16,17,49,50,53,54].

Several other studies highlighted the importance of hygienic conditions in childhood. A prospective, cross-sectional, population-based study was undertaken in asymptomatic Czech children in the period 2003-2005. The overall H. pylori prevalence was 7.1%. It was higher in subjects who had never breast-fed (12.4%) and showed a negative relationship with the duration of breast-feeding. There was a significant inverse association between H. pylori prevalence and the highest educational level of the parents. A higher risk for the infection was found in families with a higher number of children (2 or more). H. pylori infection was much more frequent (80.8%) among institutionalized children. The study from Szabolcs-Szatmár-Bereg county (2000) reported significantly higher H. pylori seropositivity in individuals who shared a bed in childhood, had manual workers parents, had disadvantaged hygienic conditions in childhood, and lived in the rural area. The authors found a significant inverse correlation between H. pylori infection and the absence of water supply and sanitation[16,55]. Detailed data are shown in Table 3, Table 4, Table 5, and Table 6[16].

The infection could not be acquired in only childhood. A meta-analysis (2011) reported a higher risk of H. pylori infection among endoscopy personnel based on a pooled analysis of 24 retrospective prevalence studies. This occupational risk was evident for gastroenterologists and their assistants[56].

According to some epidemiologic studies, smoking could be another independent risk factor for H. pylori infection in adults. In a study from the Czech Republic in 2001, smoking habits were strongly related to the risk of H. pylori positivity: heavy smokers with the lowest education were at the highest risk of the infection. Surprisingly, there was no evidence of an increased risk of H. pylori infection among current or former smokers neither in the latter study (2012) of this workgroup, nor in our study[46,49].

One of the four workgroups from West and North Hungary reported a significantly greater number of seropositive individuals among alcoholics in 1999. The prevalence of H. pylori infection was significantly higher among participants who consumed alcohol daily compared to abstinent ones. A very contested subject is the role of domestic animals in the development of H. pylori infection, however, most epidemiological studies could not find an association between them. Besides other authors found an increased prevalence of infection in subjects keeping a cat in their household, in children "playing with sheep", and in Sardinian and Polish shepherds who come into direct contact with sheep. Our prospective study could not prove an explicit connection between H. pylori prevalence and alcohol consumption, merely coffee consumption habits and pet or domestic animal rearing[14,16, 57-60].

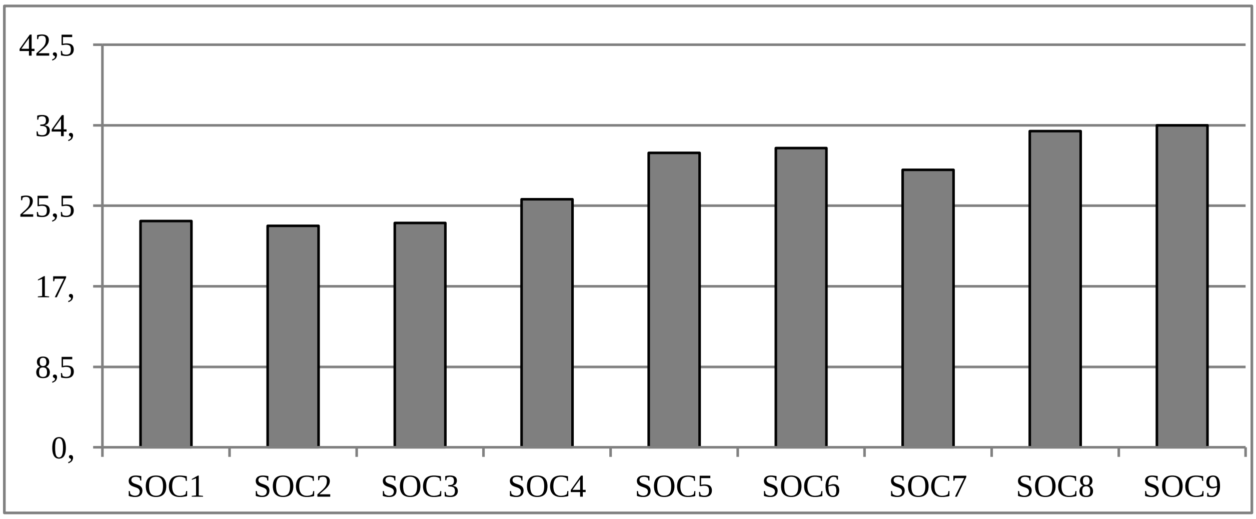
It is well known that H. pylori infection and family history of gastric cancer are the main risk factors for gastric cancer. We have shown that the prevalence of H. pylori infection was significantly higher among blood donors with a family history of gastric cancer. However, the association between family history of gastric cancer and the risk for H. pylori infection has not been previously widely reported. Cameroonian data showed that 80.39% of patients with a family history of gastric cancer were seropositive, while 19.6% were seronegative ($p = 0.001$). According to German data, the prevalence of H. pylori was much higher among subjects with a parental history of gastric cancer (69% vs 44%)[61,62].

The link between epigastric pain and H. pylori seropositivity among young subjects supports the currently accepted, Rome IV diagnostic protocol for functional dyspepsia, which states that excluding H. pylori infection (known as "H. pylori-associated dyspepsia") should be the first step in the presence of such symptoms. Conversely, improved household hygiene in recent decades likely explains the lack of a relationship between socioeconomic status and H. pylori prevalence in this group. The findings further supported the hypothesis that hygiene differences between urban and rural areas were more significant in their childhood than nowadays. In addition, young males had poorer hygiene, than young females at that during childhood[63].

Our Southeast Hungarian population-based study was the first to establish the sociodemographic features of GERD-related symptoms in Central Europe. Some of the large epidemiological studies and meta-analyses from highly developed countries reported associations between several sociodemographic, and socioeconomic factors and GERD.

A study in the UK, which enrolled 3,179 patients, reported an association between GERD and socio-economic status: GERD was more common among the socially disadvantaged ($p < 0.005$). Each patient provided their occupation and the occupation of their partner, and nine major occupational groups, according to the Standard Occupational Classification (SOC), were assigned[38]. Detailed data are shown in Figure 3[38].

Figure 3. Prevalence of GERD symptoms by socioeconomic groups in the UK[38]



A study conducted in Spain reported that the frequency of GERD symptoms showed an inverse association with educational level. This relationship has been described by American authors too, and probably reflects the action of certain unhealthy lifestyles, habits, or less ability to modify such habits. The other study conducted in the USA detected that heartburn prevalence survey respondents who were not college-educated were more likely to report frequent symptoms compared to individuals with heartburn who were college-educated. On the contrary, logistic regression modeling identified a higher level of education and frequent vs infrequent heartburn as significant predictors of whether patients told a physician about their heartburn symptoms[64,65].

A systematic review and meta-analysis investigated the prevalence of GERD according to education level, marital status, and residence. The prevalence of GERD was significantly higher in those with low education compared to those with medium and high education levels. When the pooled prevalence of GERD was stratified according to marital status, divorced/separated/widowed and married individuals were significantly more complainant compared to single ones. Residence also had a significant effect on this connection. The pooled prevalence of GERD in subjects living in urban areas was higher compared to subjects living in rural areas[32]. Detailed data are shown in Table 18[32].

Table 18. Pooled prevalence of GERD according to risk factors[32]

Risk factor	No. of studies	No. of participants	GERD prevalence (%)
Education level			
Low	21	24609	16.78
Medium	15	23428	11.52
High	18	16159	8.98
Income level			
Low	6	11034	11.69
Medium	4	7704	8.42
High	6	2615	7.68
Marital status			
Single	12	11657	12.85
Married	12	28768	15.98
Divorced/separated/widowed	6	1538	22.95
Residence			
Rural	8	12387	11.70
Urban	8	11528	13.43

As our findings show, there was no evidence of an increased prevalence of GERD-related symptoms among physical workers, individuals living in urban circumstances - neither currently nor in childhood -, and blood donors living in a family compared to single people.

In contrast, among the blood donors who had GERD-related symptoms at least monthly, significant correlations were found between typical GERD complaints and living on a farm currently or during childhood. An increased prevalence of GERD-related typical and/or atypical symptoms was shown among individuals living on a farm currently.

Both studies have limitations. In Hungary, blood donors are unpaid, relatively healthy, and conscious volunteers; therefore, they may not completely represent all segments of the population of Southeast Hungary.

The decreasing prevalence of H. pylori infection in developed countries has been paralleled by increased recognition of GERD and its complications. These epidemiological observations do not support the role of H. pylori in the pathogenesis of GERD but could suggest a protective role of H. pylori infection against the development of esophageal diseases. Studies about the exact association between H. pylori and GERD are divisive. Neither in study I: Epidemiologic characteristics of H. pylori infection nor in study II: Sociodemographic features of GERD-related symptoms, typical GERD symptoms were not related to lower prevalence of H. pylori or urban residence with presumably lower infection rate. On the contrary, rural residence has shown an association with GERD-related symptoms, where H. pylori infection is more common. Fundamentally, the evidence for differences in the prevalence of H. pylori infection between patients with or without GERD remains uncertain[31-37,66].

10. CONCLUSIONS

In conclusion, we proved that in line with the global trends, the prevalence of H. pylori infection has decreased in Southeast Hungary with changes in society, including improvements in socioeconomic status and living standards during recent decades. Meanwhile, the prevalence remains high in the middle-aged and older rural populations.

The global decrease in the prevalence of H. pylori infection could not be explained only by one specific reason. The experts explain this trend mostly by improving socioeconomic status, increasing standard of living conditions, the birth-cohort phenomenon, the "screen and treat" project, and the widespread use of antibiotics for various indications.

Generally accepted risk factors for H. pylori positivity appeared valid for the studied population, whereas the presence of dyspeptic symptoms was identified as an independent risk factor in the young population.

As the prevalence of H. pylori infection is decreasing in Southeast Hungary, an ongoing decline in the age-standardized incidence of gastric cancer may be expected.

The association between the prevalence of GERD-related symptoms among Southeast Hungarian blood donor volunteers and their sociodemographic features could not be as clear as in Western countries. The findings of risk factors are important to developing GERD prevention and improving the quality of life. Knowledge of these factors can greatly assist clinicians in recognizing the symptoms of GERD in patients who are most at risk of developing complications.

11. NEW RESULTS ESTABLISHED IN THE THESIS

1. The prevalence of H. pylori infection has decreased in Southeast Hungary in line with the global trends.

2. A significant positive association was observed between age and H. pylori positivity.

3. According to childhood residence, the prevalence of H. pylori was significantly higher in rural areas than in urban areas. Furthermore, residence in rural areas for at least one year was associated with a significantly higher H. pylori prevalence than continuous urban residency.

4. Parameters related to occupation, coffee consumption, pet or domesticated animal rearing, and positive family history of gastric cancer were associated with H. pylori infection.

5. The presence of dyspeptic symptoms was identified as an independent risk factor in the young population.

6. Among blood donors who had GERD-related symptoms at least monthly, we found significant correlations between typical GERD complaints and living on a farm currently or during childhood. In the group of blood donors who had GERD-related symptoms daily, significant correlations were found between typical and/or atypical GERD complaints and living on a farm during childhood.

12. ACKNOWLEDGEMENTS

I would like to extend my sincere thanks to all people who have helped and inspired me during my doctoral studies.

First of all, I would like to extend my deepest gratitude to my supervisor **Dr. András Rosztóczy** for all his support and guidance, as well as for his valuable ideas, remarks and supervision of my scientific research.

I am deeply grateful to **Dr. Andrea Tiszai**, who made it possible for me to conducting research at the clinic, and I would like to thank all of her assistance and practical suggestions.

Furthermore, I would like to recognize the assistance that I received from the members and colleagues of the Motility Workgroup: **Dr. Richárd Róka, Dr. Orsolya Inczefi, Dr. Georgina Ollé, Dr. Krisztina Helle,** and **Klára Vadászi**, who encouraged me throughout my work.

I am grateful to **Prof. Dr. Tibor Wittmann**, **Prof. Dr. György Ábrahám and Prof. Dr. Csaba Lengyel**, former and current heads of the First Department of Medicine, and Department of Medicine, University of Szeged who gave me the opportunity to work in their departments.

In addition, I would like to thank **Dr. Ilona Dóczi** and her colleagues at the Department of Clinical Microbiology, University of Szeged, **Dr. Gábor Kozák** at the Department of Physiology, University of Szeged, and **Dr. Veronika Szekeres** and her colleagues at Hungarian National Blood Transfusion Service, Szeged, who all helped me in my research work.

Lastly, I would like to thank my **family** and **friends** for all their support, endless patience and encouragement.

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14. FIGURES

15. TABLES

ANNEXES

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World J Gastroenterol 2019 November 14; 25(42): 6365-6372

DOI: 10.3748/wjg.v25.i42.6365

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Epidemiologic characteristics of *Helicobacter pylori* infection in southeast Hungary

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Author contributions: Bálint L, Rosztóczy A designed research, performed research, and wrote the paper; Tiszai A performed research; Kozák G designed research and analyzed data; Dóczi I contributed analytic tools; Szekeres V performed research; Inczefi O performed research; Ollé G performed research; Helle K performed research; Róka R performed research.

Institutional review board statement: The study was approved by the institutional review board of University of Szeged.

Informed consent statement: The institutional review board of University of Szeged waived the requirement to obtain informed consents from patients.

Conflict-of-interest statement: The authors have no conflict of interest to disclose.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

Epidemiologic studies have revealed a decrease in the prevalence of *Helicobacter pylori* (*H. pylori*) infection in Western Europe.

AIM

To obtain data regarding the prevalence of *H. pylori* in Csongrád and Békés Counties in Hungary, evaluate the differences in its prevalence between urban and rural areas, and establish factors associated with positive seroprevalence.

METHODS

One-thousand and one healthy blood donors [male/female: 501/500, mean age: 40 (19–65) years] were enrolled in this study. Subjects were tested for *H. pylori* IgG antibody positivity *via* enzyme-linked immunosorbent assay. Subgroup analysis by age, gender, smoking habits, alcohol consumption, and urban *vs* non-urban residence was also performed.

RESULTS

The overall seropositivity of *H. pylori* was 32%. It was higher in males (34.93% *vs* 29.2%, P = 0.0521) and in rural areas (36.2% *vs* 27.94%, P = 0.0051). Agricultural/industrial workers were more likely to be positive for infection than office workers (38.35% *vs* 30.11%, P = 0.0095) and rural subjects in Békés County than those in Csongrád County (43.36% *vs* 33.33%, P = 0.0015).

STROBE statement: This study adopted the guidelines of the STROBE Statement.

Manuscript source: Unsolicited manuscript

Received: September 2, 2019
Peer-review started: September 2, 2019
First decision: September 19, 2019
Revised: October 10, 2019
Accepted: October 18, 2019
Article in press: October 18, 2019
Published online: November 14, 2019

P-Reviewer: Boyanova L, Mihara H, Reshetnyak VI, Triantafillidis JK
S-Editor: Tang JZ
L-Editor: A
E-Editor: Zhang YL

CONCLUSION

Although the prevalence of *H. pylori* infection decreased in recent decades in Southeast Hungary, it remains high in middle-aged rural populations. Generally accepted risk factors for *H. pylori* positivity appeared to be valid for the studied population.

Key words: *Helicobacter pylori*; Epidemiology; Prevalence; Central Europe; Healthy volunteers; Enzyme-linked immunosorbent assay; Differences in urban and rural population

Core tip: Whereas a decrease in the prevalence of *Helicobacter pylori* (*H. pylori*) has been confirmed in Western Europe, its prevalence in Central Europe, which has a substantial rural population, is unclear. Therefore, this study analyzed the prevalence of *H. pylori* among healthy volunteers in two Hungarian counties. The results of the study illustrated that the seropositivity of *H. pylori* in this area was 32%. The prevalence was higher in males, among people living in rural areas. Agricultural/industrial workers were more likely to be positive for infection than office workers. Meanwhile, rural subjects in Békés County had higher prevalence than those in Csongrád County.

Citation: Bálint L, Tiszai A, Kozák G, Dóczi I, Szekeres V, Inczefi O, Ollé G, Helle K, Róka R, Rosztóczy A. Epidemiologic characteristics of *Helicobacter pylori* infection in southeast Hungary. *World J Gastroenterol* 2019; 25(42): 6365-6372
URL: https://www.wjgnet.com/1007-9327/full/v25/i42/6365.htm
DOI: https://dx.doi.org/10.3748/wjg.v25.i42.6365

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is one of the most common chronic human bacterial infections worldwide, affecting up to half of the world's population. It is the main cause of gastritis, gastroduodenal ulcer, gastric adenocarcinoma, and mucosa-associated tissue lymphoma. Its prevalence is variable in relation to geography, ethnicity, age, and socioeconomic factors[1,2,3].

The prevalence of *H. pylori* has declined worldwide, although wide variation has been observed.

According to a 2017 and a 2018 meta-analysis, the countries with the lowest *H. pylori* prevalence were Switzerland (13.1%-24.7%), Denmark (17.8%-26.5%), New Zealand (21.4%-26.5%), Australia (17.2%-32.1%), and Sweden (18.3%-34.1%) in the former meta-analysis, Indonesia (10.0%), Belgium (11.0%), Ghana (14.2%), and Sweden (15.0) in the latter, whereas those with the highest prevalence were Nigeria (83.1%-92.2%), Portugal (84.9%-87.9%), Estonia (75.1%-90.0%), Kazakhstan (74.9%–84.2%), and Pakistan (75.6%-86.4%) in the former study, Serbia (88.3%), South Africa (86.8%), Nicaragua (83.3), and Colombia (83.1%) in the latter. The former study used two periods to analyze the prevalence trend over time. The *H. pylori* prevalence after 2000 was lower than that before 2000 in Europe (48.8 *vs* 39.8), North America (42.7% *vs* 26.6%), and Oceania (26.6% *vs* 18.7%)[4,5].

The major risk factors for *H. pylori* infection include socioeconomic status and the household hygiene of the patient and family during childhood. A previous Hungarian study revealed greater seropositivity among undereducated subjects, in persons living without sewers, those living in crowded homes or having three or more brothers and sisters, and those with high alcohol consumption, and they observed significant differences in prevalence between industrial and office workers. A Russian study reported that 88% of the Moscow working population is infected with *H. pylori*, 78% in people younger than 30 years, 97% in individuals older than 60 years. Recent epidemiologic studies revealed decreases in the prevalence of *H. pylori* in Western Europe and the United States. Conversely, little is known regarding the prevalence of *H. pylori* in Central Europe, in which a substantial population resides in rural areas[6,7,8,9,10].

The aims of this study were to obtain data regarding *H. pylori* prevalence in Csongrád and Békés Counties in Hungary, evaluate differences in prevalence between urban and rural areas, and establish factors associated with positive seroprevalence.

MATERIALS AND METHODS

One-thousand and one healthy blood donors [male/female: 501/500, mean age: 40 (18–65) years] were consecutively enrolled in Csongrád and Békés Counties. Detailed demographic data are shown in Figure 1[11,12,13].

In Hungary, blood donation is allowed for individuals weighing more than 50 kg and aged 18–65 years. Data collection was performed using an anonymous questionnaire including 26 questions associated with demographic parameters (gender, age, place of birth, childhood residence, marital status, current residence, crowding in family, and educational status) and medical status (symptoms associated with *H. pylori* infection and gastroduodenal ulcer disease, smoking habits, alcohol consumption, and family history of *H. pylori* infection, gastroduodenal ulcer disease, and gastric malignancy).

On the basis of the childhood residence of the subjects, the following four groups of 250 subjects were established: Urban males, urban females, rural males, and rural females. Groups were matched by age. Subgroup analysis was performed according to living circumstances, residence in Békés or Csongrád County, smoking habits, alcohol and coffee consumption, occupation, intermittent agricultural work, pet or domestic animal rearing, gastrointestinal complaints, and family history of *H. pylori* infection, gastric ulcer, and gastric cancer.

All subjects were tested for *H. pylori* IgG antibody positivity using a Platelia *H. pylori* IgG enzyme-linked immunosorbent assay, which reportedly has 100% sensitivity and 90% specificity according to the manufacturer. These values were 95.6% and 85.1% in the validation study of Burucoa *et al*[14] respectively (Bio-Rad).

For the statistical analysis of different variables related to *H. pylori* infection, the chi-squared test or two-sample *t*-test was applied. The association between *H. pylori* infection and potential risk factors was established *via* univariate analysis, and odds ratios and 95% confidence intervals were calculated. In addition, a stratified analysis according to age (18–35, 35–50, and 50–65 years) was performed. The final model was developed using a generalized linear regression model *via* stepwise regression, with inclusion and exclusion criteria set at significance levels of 0.05 and 0.10, respectively. A two-sided P value < 0.05 was considered statistically significant. All statistical analyses were performed using MATLAB (Mathworks, Natwick, MA, United States).

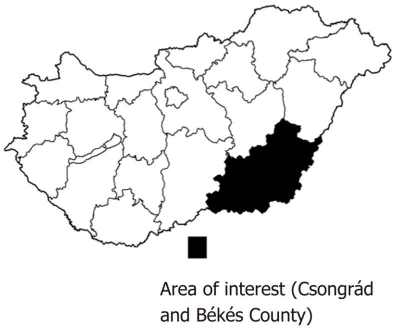
RESULTS

The overall seropositivity of *H. pylori* was 32% in the studied healthy subjects. There was no statistically significant difference in prevalence between males and females (P = 0.0521) in our study. According to residence, the prevalence of *H. pylori* was significantly higher in rural areas than in urban areas (P = 0.0051). Furthermore, residence in rural areas for at least one year was associated with a significantly higher *H. pylori* prevalence than continuous urban residency (P = 0.0003). Parameters related to occupation were also associated with *H. pylori* infection. A higher prevalence was established for industrial workers and agricultural workers than for office workers and non-agricultural workers, respectively. Coffee consumption and pet or domesticated animal rearing were associated with *H. pylori* infection, whereas the rate of *H. pylori* positivity was similar for the remaining parameters. Detailed data are shown in Table 1-3.

A significant positive association was observed between age and *H. pylori* positivity (Table 1). To rule out this strong effect of age, three age groups were formed for further analysis. In the youngest group, the presence of epigastric pain was an independent risk factor for *H. pylori* positivity. By contrast, animal rearing was a risk factor for the middle age group, and male sex and living in rural areas for at least one year were risk factors in the oldest age group (Table 4).

DISCUSSION

This prospective study proved that the Hungarian prevalence of *H. pylori* infection has followed international trends, falling to 32% over the last two decades. The prevalence between 1990 and 2000 was similar throughout the country (58.6%–63.3%) excluding the capital, in which the prevalence was only 47.3% (Table 5). Although the



Local demographics

	Hungary	Csongrád County	Békés County
Population			
Total	9.909.000 (Male/Female: 4.716.000/5.193.000)	410.000 (Male/Female: 193.000/216.000)	359.000 (Male/Female: 172.000/188.000)
Urban	6.936.000 (70%)	307.000 (75%)	270.000 (75%)
Rural	2.972.700 (30%)	102.000 (25%)	89.000 (25%)
Population density	106/km^2	96/km^2	63/km^2
Work			
Employment rate	58.4%	50.3%	48.8%
Unemployment rate	10.3%	12.3%	11.1%
Physical work	-	55%	61%
Intellectual work	-	45%	39%

Figure 1 Csongrád and Békés Counties and detailed demographic data regarding Csongrád and Békés Counties.

Southeastern region of the country was not studied prospectively before this study, the *H. pylori* Workgroup of our institute conducted a retrospective analysis in 2005 and 2010 among patients with dyspepsia and gastroduodenal ulcer disease. The rate of seropositivity decreased from 46% to 38%. The 2017 meta-analysis used two periods to analyze the changes of prevalence trend. The *H. pylori* prevalence after 2000 was lower than that before 2000 in Europe (48.8 *vs* 39.8), North America (42.7% *vs* 26.6%), and Oceania (26.6% *vs* 18.7%). In the surrounding Central European countries, such as the Czech Republic and Slovakia, the prevalence of *H. pylori* infection followed the trends of our region, decreasing from 42% to 23% after 10 years in the former from 62% to 35% after 15 years in the latter[4,6,15-21].

Having examined the potential factors associated with a higher *H. pylori* prevalence, our results were in concordance with previous observations revealing a positive linear association with age. Furthermore, our study supported findings that rural subjects are more likely to be *H. pylori*-positive than urban residents. Although we could not establish a significant effect of gender on the seroprevalence, it is impressive that older rural males have an approximately sixfold higher risk of *H. pylori* positivity than young urban females (61.29% *vs* 11.11% $P < 0.0001$). Such results are most commonly explained by differences in socioeconomic status and household hygiene of the family during childhood. Furthermore, a new original finding is that people who lived in rural conditions for at least one year also had an increased risk for *H. pylori* seropositivity. An evaluation of the occupations of the subjects provided further proof that socioeconomic factors can influence *H. pylori* infection risk. Meanwhile, the lack of difference in risk between urban and rural residence can be explained by the general improvement of living standards in our country over the last two decades, as most rural people currently have access to water supply and sanitation[6-8,16,20-23].

The link between epigastric pain and *H. pylori* seropositivity among young subjects supports the currently accepted, Rome IV diagnostic protocol for functional dyspepsia, which states the excluding *H. pylori* infection (known as "*H. pylori*-associated dyspepsia") should be the first step in the presence of such symptoms. Conversely, improved household hygiene in recent decades likely explains the lack of a relationship between socioeconomic status and *H. pylori* prevalence in this group. The findings further supported the hypothesis that hygiene differences between urban and rural areas were more significant at their childhood than nowadays. In addition, young males had poorer hygiene, than young females at that during childhood[24].

This study has a limitation. In Hungary, blood donors are unpaid, healthy, and conscious volunteers; therefore, they may not completely represent all segments of the population of Southeast Hungary.

In conclusion, we proved that in line with the worldwide trends, the prevalence of *H. pylori* infection has decreased in Southeast Hungary with changes of society, including improvements in socioeconomic status and living standards, during recent decades. Meanwhile, the prevalence remains high in the middle-aged and older rural populations. Generally accepted risk factors for *H. pylori* positivity appeared valid for the studied population, whereas the presence of dyspeptic symptoms was identified as an independent risk factor in the young population.

Table 1 Sociodemographic factors associated with *Helicobacter pylori* prevalence

Socio-demographic factors	*H. pylori* positive		*H. pylori* negative		Total	*P* value	Odds ratio (univariate)	95%CI
	n	%	*n*	%				
Sex						0.0521		
Female	146	29,2	354	70,8	500		1.0	
Male	175	34,9	326	65,1	501		1.3016	[0.9973, 1.6987]
Age						0.000		
	44.5638	10.7693	37.3599	11.9457			0.9484	[0.9363, 0.9606]
18-25	25	14,9	143	85,1	168			
25-35	32	16,9	157	83,1	189			
35-45	97	34,4	185	65,6	282			
45-55	106	43,6	137	56,4	243			
55 +	61	51,3	58	48,7	119			
Residence						0.0809		
Urban	185	30,0	431	70,0	616		1.0	
Rural	136	35,3	249	64,7	385		1.2725	[0.9706, 1.6683]
Childhood						0.0051		
Urban	140	27,9	361	72,1	501		1.0	
Rural	181	36,2	319	63,8	500		1.4631	[1.1201, 1.9110]
Min. one year in rural enviroment						0.0003		
Negative	104	25,6	303	74,4	407		1.0	
Positive	217	36,5	377	63,5	594		1.6770	[1.2695, 2.2153]

H. pylori: *Helicobacter pylori*; CI: Confidence intervel.

Table 2 Socioeconomic and lifestyle factors associated with *Helicobacter pylori* prevalence

Socio-economic + lifestyle factors	*H. pylori* positive		*H. pylori* negative		Total	*P* value	Odds ratio (univariate)	95%CI
	n	%	*n*	%				
Smoking						0.1121		
Non-smoker	169	29,5	403	70,5	572		1.0	
Smoker	91	34,2	175	65,8	266		1.2400	[0.9090, 1.6915]
Former smoker	61	37,4	102	62,6	163		1.4261	[0.9904, 2.0534]
Alcohol consumption						0.1420		
Never	95	36,0	169	64,0	264		1.0	
Occasional	216	30,3	497	69,7	713		0.7731	[0.5740, 1.0413]
Regular	10	41,7	14	58,3	24		1.2707	[0.5434, 2.9715]
Coffee						0.0390		
Never	82	26,7	225	73,3	307		1.0	
1	94	36,3	165	63,7	259		1.5632	[1.0929, 2.2358]
More than 1	145	33,3	290	66,7	435		1.3720	[0.9943, 1.8931]
Household population						0.1649		
Alone	51	39,2	79	60,8	130		1.0	
Adults only	135	31,5	294	68,5	429		0.7113	[0.4736, 1.0683]
Adults and children	135	30,5	307	69,5	442		0.6812	[0.4538, 1.0224]
Work						0.0000		
Industrial	186	38,4	299	61,6	485		1.0	
Office	135	26,2	381	73,8	516		0.5696	[0.4355, 0.7450]
Agricultural work						0.0012		
No	140	27,4	371	72,6	511		1.0	

Yes	181	36,9	309	63,1	490		1.5523	[1.1882, 2.0279]
Domestic animals						0.0015		
No	54	23,5	176	76,5	230		1.0	
Yes	267	34,6	504	65,4	771		1.7266	[1.2301, 2.4236]

H. pylori: *Helicobacter pylori*; CI: Confidence intervel.

Table 3 Factors in patient history associated with *Helicobacter pylori* prevalence

Patient history	*H. pylori* positive		*H. pylori* negative		Total	*P* value	Odds ratio (univariate)	95%CI
	n	%	*n*	%				
Familiy history of *H. pylori*						0.8829		
Negative	161	32,5	335	67,5	496		1.0	
Positive	18	31,0	40	69,0	58		0.9363	[0.5205, 1.6844]
NA	142	31,8	305	68,2	447			
Family history of GI ulcer						0.3810		
Negative	217	33,3	435	66,7	652		1.0	
Positive	57	29,7	135	70,3	192		0.8464	[0.5965, 1.2009]
NA	47	29,9	110	70,1	157			
Family history of GI cancer						0.0014		
Negative	277	32,1	587	67,9	864		1.0	
Positive	17	63,0	10	37,0	27		3.6025	[1.6284, 7.9701]
NA	27	33,8	53	66,3	80			
Abdominal pain						0.8108		
Negative	264	32,2	555	67,8	819		1.0	
Positive	57	31,3	125	68,7	182		0.9586	[0.6784, 1.3547]
Epigastrial pain						0.1105		
Negative	214	30,5	487	69,5	701		1.0	
Positive	107	35,7	193	64,3	300		1.2617	[0.9481, 1.6789]

H. pylori: *Helicobacter pylori*; CI: Confidence intervel; NA: Not applicable; GI: Gastrointestinal.

Table 4 Independent risk factors associated with *Helicobacter pylori* prevalence

	Age 18-35	Age 35-50	Age 50-65
Male sex	Not significant	Not significant	*P* = 0.0389; OR = 0.5847; CI: [0.0753 1.0940]
Rural residence in childhood	Not significant	Not significant	*P* = 0.0246; OR = 1.8537; CI: [1.3154 2.3920]
Animal rearing	Not significant	*P* = 0.0036; OR = 2.0855; CI: [1.5897 2.5812]	Not significant
Epigastrial pain complaint	*P* = 0.0026; OR = 2.5514; CI: [1.9422 3.1606]	Not significant	Not significant

OR: Odds ratio; CI: Confidence intervel.

Table 5 The prevalence between 1990 and 2000 throughout the country

Date	1993	1999	2000	1998-2000
Region	Tolna	Vas	Szabolcs-Szatmár-Bereg	Pest
Authors	Tamássy *et al*[15]	Lakner *et al*[6]	Iszlai *et al*[16]	Prónai *et al*[19]
Method	Serology	Serology	Serology	13C-UBT
Population	Blood donors	Blood donors	Healthy volunteers	Symptomatic patients
n =	400	533	756	1027
Prevalence of *H. pylori* (%)	63, 3	62, 3	58, 6	47, 3

H. pylori: *Helicobacter pylori*.

ARTICLE HIGHLIGHTS

Research background

Epidemiologic studies have revealed a decrease in the prevalence of *Helicobacter pylori* (*H. pylori*) infection in Western Europe. Conversely, little is known regarding its prevalence in Central Europe, in which a substantial population resides in rural areas.

Research motivation

The last Hungarian epidemiologic studies on *H. pylori* were carried out approximately two decades ago and showed high seroprevalence rates. Therfore we aimed to obtain new data and to test whether it decreases similarly to the Western European tendencies.

Research objectives

The aims of the present study were to obtain data regarding the prevalence of *H. pylori* in Csongrád and Békés Counties in Hungary, evaluate the differences in its prevalence between urban and rural areas, and establish factors associated with positive seroprevalence.

Research methods

One-thousand and one healthy blood donors were enrolled. Data collection was performed using an anonymous questionnaire including 26 questions associated with demographic parameters and medical status. All subjects were tested for *H. pylori* IgG antibody positivity using IgG enzyme-linked immunosorbent assay.

Research results

The overall seropositivity of *H. pylori* was 32%. The prevalence of *H. pylori* was significantly higher in rural areas than in urban areas. Residence in rural areas for at least one year was associated with a significantly higher *H. pylori* prevalence than continuous urban residency. A significant positive association was observed between age, occupation, coffee consumption, pet or domesticated animal rearing and *H. pylori* positivity. Three age groups were formed for further analysis, in the youngest group, the presence of epigastric pain was an independent risk factor for *H. pylori* positivity.

Research conclusions

The prevalence of *H. pylori* infection decreased in recent decades in Southeast Hungary, it remains high in middle-aged rural populations. Generally accepted risk factors for *H. pylori* positivity appeared to be valid for the studied population. Furthermore, a new original finding is that people who lived in rural conditions for at least one year also had an increased risk for *H. pylori* seropositivity.

Research perspectives

The results of this study seems to consider the subsequent changes in seropositivity of *H. pylori* in Hungary. It would be interesting to test whether the significant positive association between age and *H. pylori* positivity continuous observed after 10 or 15 years or rather not, “new” infected will appear, or in the older age will stay low seropositivity. The other experience of this study is the link between epigastric pain and *H. pylori* seropositivity among young subjects, which supports the recommendation in countries with high *H. pylori* seropositivity, that patients with dyspeptic symptoms should be examined for *H. pylori* infection (Rome IV diagnostic protocol).

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PLOS ONE

RESEARCH ARTICLE

Prevalence of reflux-related symptoms in South-Hungarian blood donor volunteers

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Abstract

Background/Aim

Population-based studies on the prevalence of GERD-related symptoms are still missing in Eastern Europe, therefore, we aimed to obtain such data in South-East Hungarian subjects.

Methods

A total of 2,002 apparently healthy blood donor volunteers were consecutively enrolled and completed detailed questionnaires related to general factors, demographic data, socioeconomical factors, and the presence and frequency of typical and atypical GERD-related symptoms.

Results

Among 2,002 study participants, 56.5% were completely asymptomatic. The prevalence of typical GERD symptoms appearing at least monthly or weekly was 16.5% and 6.8%, respectively. Two-thirds (209/330) of the patients experienced at least monthly occurring typical GERD symptoms and also had associated atypical symptoms and this was even more pronounced when comparing subgroups with higher symptom frequencies. Significant correlations were found between monthly GERD-related complaints and height, body mass index (BMI), coffee consumption, and smoking. Positive family history was another significant factor in all the symptom-frequency categories. GERD-related symptom frequency showed a linear association with sex ($R^2 = 0.75$, P = 0.0049). Typical and atypical GERD symptoms were significantly more common in those with chronic diseases than those without. Heartburn was observed in 12.5% and 4.4% ($P<0.05$) and acid regurgitation was seen in 6.9% and 1.8% ($P<0.05$), respectively.

Conclusion

The prevalence of GERD-related symptoms in South Hungary was significantly lower than that in Western countries and was closer to Eastern values. The presence of mild, non-exclusionary chronic diseases significantly increased the prevalence of GERD-related

Citation: Helle K, Bálint L, Szekeres V, Ollé G, Rosztóczy A (2022) Prevalence of reflux-related symptoms in South-Hungarian blood donor volunteers. PLoS ONE 17(3): e0265152. https://doi.org/10.1371/journal.pone.0265152

Editor: Giannicola Iannella, Sapienza University of Rome, ITALY

Received: November 15, 2021

Accepted: February 23, 2022

Published: March 15, 2022

Data Availability Statement: All relevant data are within the paper.

Funding: Publication is supported by University of Szeged Open Access Fund, No. 5569. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

symptoms, as well as positive family history of GERD, height, BMI, coffee consumption, and smoking.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal diseases worldwide. It is a chronic condition in which frequent regurgitation of the gastric acid into the esophagus, mouth, and/or respiratory system causes typical (heartburn, regurgitation) and atypical (chronic cough, other respiratory symptoms, chest pain, dysphagia, globus sensation, nausea, vomiting) symptoms and/or esophageal/extraesophageal complications. These symptoms are common in the general population and have an impact on quality of life; however, only a few people consult a doctor about them [1–4].

The prevalence of GERD has been determined according to the presence of typical GERD symptoms in many epidemiological studies, although symptom-oriented diagnosis of GERD has at least two issues. First, these "typical symptoms" are also present in patients with functional esophageal disorders (e.g., functional heartburn), which cannot be subjectively distinguished from those caused by acidic reflux. This is supported by the recommendation of the Rome Foundation, as the presence of symptoms alone is not sufficient to diagnose functional esophageal disorders, and a more detailed evaluation is required [5, 6]. Second, many patients have not typical symptoms of GERD (mostly in Barrett's esophagus or asthma), therefore a symptom-oriented diagnosis cannot be carried out at all, and detailed clinical evaluation is needed [7–13].

With the exception of these limitations, large epidemiological studies have shown that the prevalence of symptomatic GERD is around 20% to 25% in the Western world and 10% in Eastern countries [14–16]. Little, if anything, is known about the prevalence in central Europe, which is located between the west and east, and is where a substantial part of the population lives outside of the larger cities.

The present study aimed to obtain population-based data on the prevalence of GERD-related symptoms in South-East Hungary to identify potential risk factors for the presence of GERD-related symptoms and compare the data with the known Western and Eastern values.

Patients and methods

A total of 2,002 apparently healthy, health-conscious, unremunerated blood donor volunteers [1,156 (42.1) males and 846 (57.9%) females; mean age, 39 (18–65) years] were consecutively enrolled, after given informed consent in written form. Data were collected by means of a questionnaire at the Hungarian National Blood Transfusion Service in Szeged and in the settlements of Csongrád-Csanád county. In Hungary, blood donation from healthy people who weigh >50 kg and are aged between 18 and 65 years is permitted. Volunteers are allowed to have the following diseases in initial and/or mild/well-controlled form: hypertension (at target value with antihypertensive monotherapy), diabetes mellitus (normal serum glucose and HbA1c levels with diet ± metformin), obesity, hypothyroidism/hyperthyroidism (normal thyroid gland function with therapy), hypercholesterolemia (at normal value with diet ± statin), hyperuricemia, asthma bronchiale (normal respiratory function test with long and short-acting bronchodilator inhalers, and/or with other medication), allergy (intermittent antihistamine therapy), GERD, osteoporosis, tachycardia/arrhythmias, polycystic ovary syndrome, coeliac disease, eczema, Gilbert's syndrome, and some musculoskeletal disorders [17]. These conditions were confirmed by the physician of the Hungarian National Blood Transfusion Service.

Participant donors completed detailed questionnaires related to general factors [age, sex, body mass index (BMI) calculated from height and weight], demographic data (place of childhood, current place of residence, composition of the family, occupation), socioeconomical factors (smoking habits, alcohol and coffee consumption, family history of GERD, patient history of chronic diseases). The presence and frequency of typical (heartburn, acid regurgitation) and atypical GERD-related symptoms (nausea, dysphagia, globus sensation, respiratory symptoms as chronic cough, shortness of breath, hoarseness, new or worsening asthma, and chest pain) were also assessed. The following symptom-frequency categories were used: at least once a day, at least once a week, at least once a month, and less than once a month.

Subgroup analysis was performed by age, sex, height, weight, BMI, smoking habits, alcohol and coffee consumption, inheritance (GERD in the family), chronic diseases, and prevalence of symptoms. All statistical analyses were performed using R software. Chi-square test, unpaired *t* test, and linear regression were applied as required. The level of significance was set at 0.05. The study received ethical approval (ethical committee approval number: WHO 3345).

Results

Among the 2,002 consecutive blood donor volunteers, 56.5% (1,131/2,002) were completely asymptomatic. Among the remaining volunteers, 27.9% (559/2,002) had typical symptoms of GERD (heartburn and/or acidic regurgitation). However, symptoms that appeared at least monthly or weekly were significantly less common [16.5% (330/2,002) and 6.8% (136/2,002), $P < 0.05$, respectively]. The majority of participants with typical GERD symptoms [56.4% (315/559)] also had atypical symptoms (such as abdominal pain, nausea, vomiting, dysphagia, globus sensation, cough, respiratory symptoms, and chest pain). This difference was further and significantly increased and showed a linear correlation with symptom frequency ($R^2 = 0.9748$, $P < 0.0001$) (Fig 1). Atypical symptoms were also seen in participants that had typical GERD symptoms at least monthly [63.1% (209/330)], weekly [79.4% (108/136)], and daily [88.6% (31/35)] (Table 1).

Detailed symptom analysis showed that the prevalence of heartburn was higher than that of acidic regurgitation in all symptom-frequency categories.

Among the atypical (esophageal and extraesophageal) symptoms, respiratory symptoms were the most prevalent (19%), although only 13% of the participants had respiratory symptoms at least monthly. Globus sensation occurred in 6% and other atypical symptoms were reported by <5% of the participants (Table 2).

Among the blood donors who had GERD-related symptoms at least monthly, significant correlations were found between the complaints and some socioeconomical factors, such as height, BMI, coffee consumption, and smoking. The correlation between frequency of symptoms and sex of the volunteers was different. Females showed an increased frequency of GERD-related symptoms ($R^2 = 0.75$, $P = 0.0049$) (Fig 2). This linear association was observed when both typical and all symptoms were assessed (Fig 2). The remaining parameters (occupation, household population, current, and childhood residence) showed no correlation. Positive family history was a significant predictive factor in all studied symptom-frequency categories (Table 3). Analysis of typical GERD-related symptoms only showed the tendency was the same as in blood donors with any GERD-related symptoms (Table 4).

Associations between different chronic diseases and GERD-related symptoms were examined. Due to the rules of eligibility to donate blood, volunteers with mild, well-controlled, chronic diseases were not excluded. Therefore, 390 participants with non-exclusionary

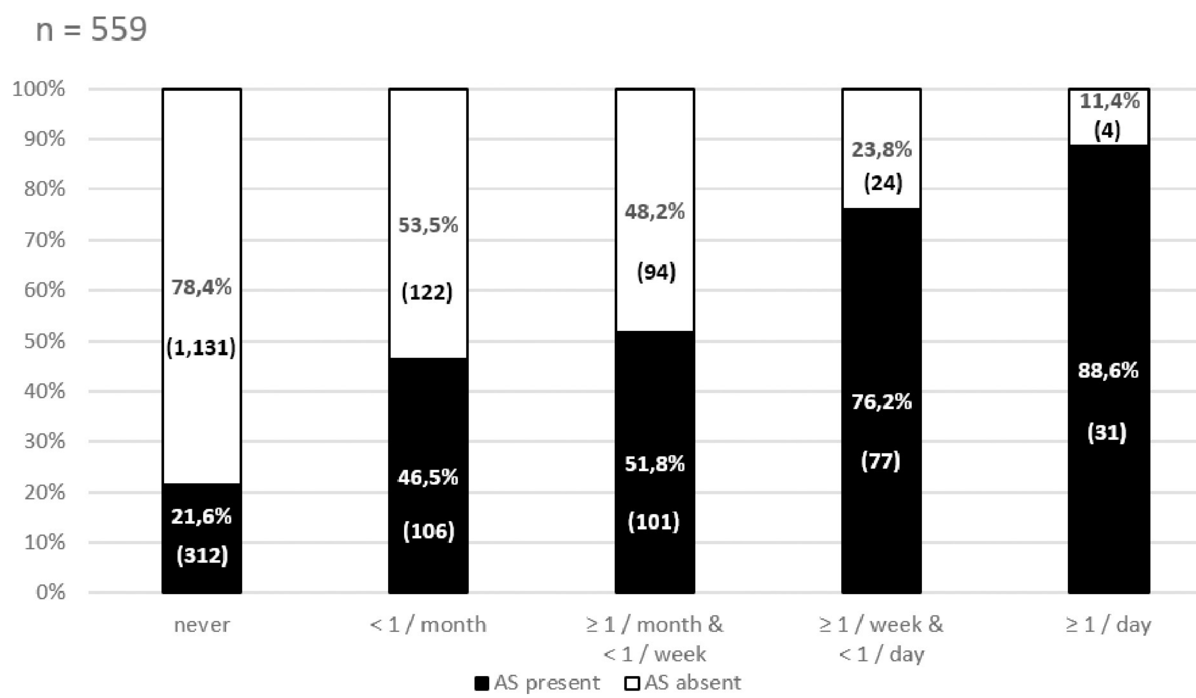

Fig 1. The occurrence of atypical symptoms in participants with typical GERD symptoms. There is a positive linear association between the frequency of the typical GERD-related symptom, and the presence of atypical symptoms (AS). (R^2 = 0.9748, P<0.0001).

https://doi.org/10.1371/journal.pone.0265152.g001

diseases were also enrolled. Among these, 93.3% (364/390) had only one disorder, whereas 6.7% (26/390) had two different chronic conditions.

Among blood donors with non-exclusionary chronic diseases (e.g., hypertension, hyperthyroidism/hypothyroidism, diabetes), those with typical GERD symptoms appearing at least weekly were significantly more common compared with those without non-exclusionary chronic diseases. Heartburn and acid regurgitation were reported by 12.5% and 6.9% of participants with chronic diseases, in contrast to 4.4% and 1.8% of completely healthy participants, respectively (for all categories $P < 0.05$).

Overweight or obesity without any further chronic diseases were detected in 925/2,002 (46.2%) participants and showed no relevant effects on the prevalence of GERD-related typical symptoms (Table 5).

On the contrary, blood donors with any GERD-related symptoms were more obese than asymptomatic participants and a linear correlation was observed between these two parameters (R^2 = 0.63, P = 0.0497) (Tables 3 and 4, Fig 3).

In participants with hypertension (173/2,002, 8.6%), heartburn (45/173, 26%, P = 0.0313), acidic regurgitation (35/173, 20.2%, P = 0.0055), nocturnal typical symptoms (14/173, 8.1%,

Table 1. The presence of the typical and/or atypical symptoms.

n = 2,002		ever	< 1 / month	≥ 1 / month & < 1 / week	≥ 1 / week & < 1 / day	≥ 1 / day
typical GERD symptoms	**atypical GERD symptoms**					
present (n = 559)	***present***	315 *(15.7%)*	106 *(5.3%)*	101 *(5.0%)*	77 *(3.8%)*	31 *(1.6%)*
	absent	244 *(12.2%)*	122 *(6.1%)*	94 *(4.7%)*	24 *(1.2%)*	4 *(0.2%)*
absent (n = 1,443)	***present***	312 *(15.6%)*				
	absent	1,131 *(56.5%)*				

https://doi.org/10.1371/journal.pone.0265152.t001

Table 2. The prevalence and frequency of different GERD-related symptoms.

n = 2,002	< 1 / month	≥ 1 / month & < 1 / week	≥ 1 / week & < 1 / day	≥ 1 / day
heartburn	168 *(8.4%)*	160 *(8.0%)*	93 *(4.6%)*	29 *(1.4%)*
acid regurgitation	163 *(8.1%)*	108 *(5.4%)*	44 *(2.2%)*	18 *(0.9%)*
typical symptoms during night	51 *(2.5%)*	32 *(1.6%)*	20 *(1.0%)*	5 *(0.2%)*
dysphagia	8 *(0.4%)*	12 *(0.6%)*	13 *(0.6%)*	4 *(0.2%)*
globus sensation	54 *(2.7%)*	33 *(1.6%)*	23 *(1.1%)*	9 *(0.4%)*
upper respiratory tract symptoms	121 *(6.0%)*	80 *(4.0%)*	80 *(4.0%)*	93 *(4.6%)*
dyspnea	35 *(1.7%)*	14 *(0.7%)*	16 *(0.8%)*	3 *(0.1%)*
chest pain	26 *(1.3%)*	40 *(2.0%)*	11 *(0.5%)*	4 *(0.2%)*
epigastric pain	66 *(3.3%)*	56 *(2.8%)*	60 *(3.0%)*	21 *(1.0%)*
abdominal pain	8 *(0.4%)*	19 *(0.9%)*	24 *(1.2%)*	11 *(0.5%)*
nausea, vomiting	37 *(1.8%)*	27 *(1.3%)*	20 *(1.0%)*	4 *(0.2%)*

https://doi.org/10.1371/journal.pone.0265152.t002

$P = 0.009$), and respiratory symptoms (42/173, 24.3%, $P = 0.0385$) were the most common complaints and were also significantly more prevalent compared with participants without chronic non-exclusionary disorders.

All typical and atypical symptoms were significantly more common in participants with known minor respiratory diseases [44/2,002 (2.2%); $P < 0.05$]. The low number of cases did

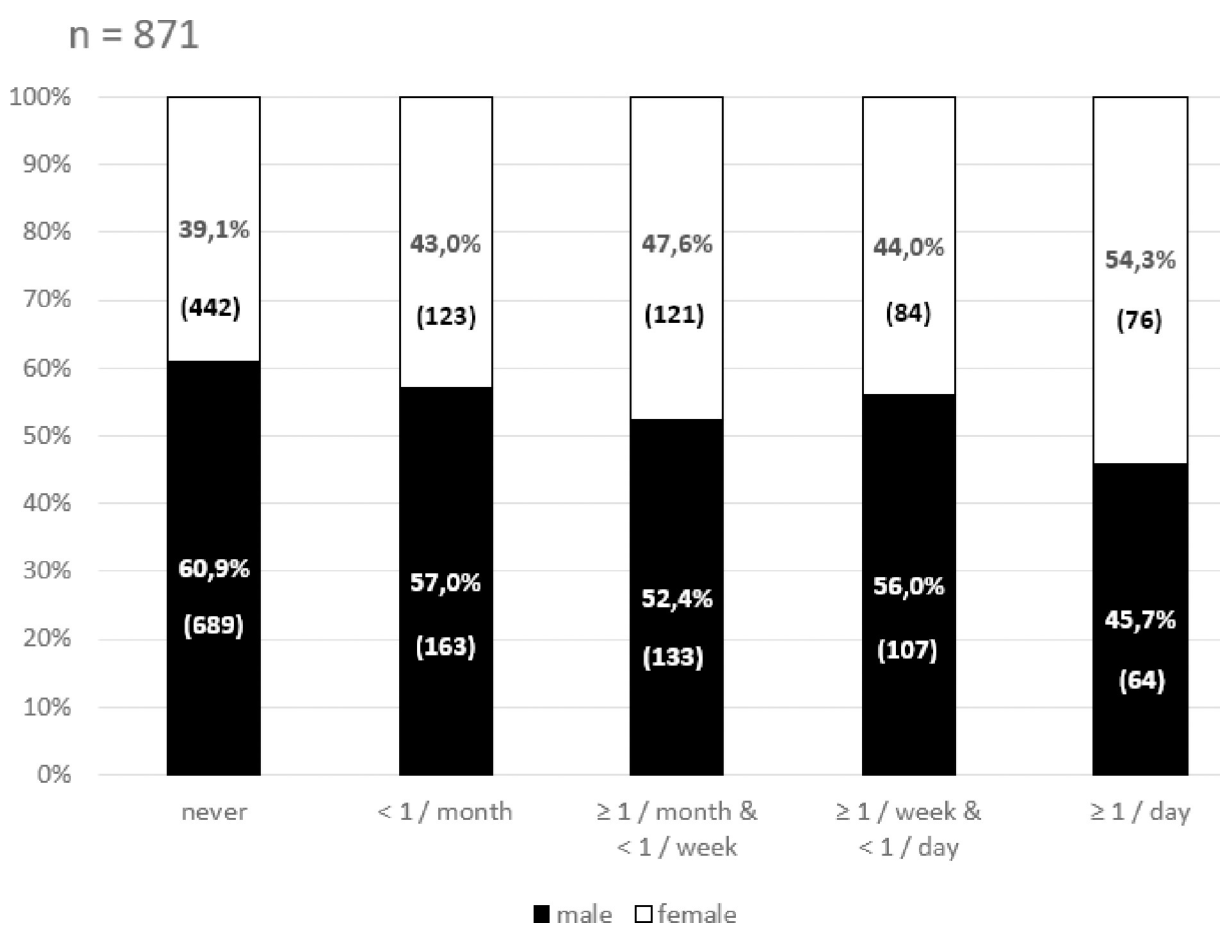

Fig 2. The frequency of GERD-related symptoms is positively associated to female sex ($R^2 = 0.75$, P = 0.0049). Similar association was found if only the typical symptoms were assessed.

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Table 3. Socioeconomical factors of blood donor volunteers with any GERD-related symptoms (typical and/or atypical). Age, weight, height and BMI are presented with mean ± SD and range.

	Asymptomatic (*n = 1,131*)	Any GERD-related symptoms (typical / atypical) (*n = 871*)			
		< 1 / month (*n = 286*)	≥ 1 / month & < 1 / week (*n = 254*)	≥ 1 / week & < 1 / day (*n = 191*)	≥ 1 / day (*n = 140*)
Sex					
Male	689 (60.9%)	163 (57.0%)	133 (52.4%)	107 (56.0%)	64 (45.7%)
Female	442 (39.1%)	123 (43.0%)	121 (47.6%) *	84 (44.0%)	76 (54.3%) **
Age (years)	39 ± 12.4 (17–66)	39 ± 12.7 (17–65)	38 ± 13.3 (18–65)	38 ± 12.3 (18–64)	41 ± 12.2 (18–64)
Weight (kg)	81 ± 15.8 (50–140)	81 ± 16.7 (52–135)	80 ± 17.2 (51–180)	81 ± 17.0 (52–130)	79 ± 16.9 (50–140)
Height (cm)	174 ± 9.2 (150–197)	173 ± 8.9 (155–198)	172 ± 9.5 (150–197) **	173 ± 9.1 (150–196)	171 ± 9.9 (150–200) **
BMI (kg/m^2)	26.6 ± 4.5 (16.9–52.7)	27.0 ± 4.8 (18.9–45.2)	27.0 ± 5.2 (17.7–52.6)	27.0 ± 4.8 (18–43.9)	26.9 ± 4.9 (17.0–45.2)
BMI categories					
1 –underweight	3 (0.3%)	0 (0.0%)	3 (1.0%)	2 (1.0%)	1 (0.7%)
2 –normal weight	444 (39.3%)	112 (39.2%)	96 (37.8%)	71 (37.2%)	57 (40.7%)
3 –overweight	455 (40.2%)	109 (38.1%)	99 (39.0%)	73 (38.2%)	43 (30.7%)
4 –obesity	169 (14.9%)	45 (15.7%)	39 (15.4%)	36 (18.8%)	32 (22.9%)
5 –extreme obesity	60 (5.3%)	20 (7.0%)	17 (6.7%)	9 (4.7%)	7 (5.0%) *
Smoking					
recent / previous	368 (32.5%)	102 (35.7%)	106 (41.7%)	84 (44.0%)	72 (51.4%)
never	763 (67.5%)	184 (64.3%)	148 (58.3%) **	107 (56.0%) **	68 (48.6%) **
Coffee					
yes	756 (66.8%)	195 (68.2%)	187 (73.6%)	132 (69.1%)	110 (78.6%)
no	375 (33.2%)	91 (31.8%)	67 (26.4%) *	59 (30.9%)	30 (21.4%) **
Alcohol					
regular	30 (2.7%)	8 (2.8%)	10 (3.9%)	9 (4.7%)	9 (6.4%)
never / occasional	1101 (97.3%)	278 (97.2%)	244 (96.1%)	182 (95.3%)	131 (93.6%)
GERD in the family					
yes	147 (13.0%)	54 (18.9%) **	63 (24.8%) **	54 (28.3%) **	39 (27.9%) **
no	825 (72.9%)	176 (61.5%)	154 (60.6%)	110 (57.6%)	77 (55.0%)
unknown	159 (14.1%)	56 (19.6%)	37 (14.6%)	27 (14.1%)	24 (17.1%)

*: $p < 0.05$, compared to the asymptomatic subjects

**: $p < 0.01$, compared to the asymptomatic subjects

https://doi.org/10.1371/journal.pone.0265152.t003

not allow for statistical confirmation of the association with a positive family history of GERD (10/44, 22.7% vs. 27/44, 61.4%).

Globus sensation was the only considerable symptom (4/23, 17.4% *vs* 5.7%, $P = 0.0434$) among participants with thyroid disorders (23/2,002, 1.2%). Any type of cardiac disease (58/2,002, 2.9%) was associated with nausea, vomiting, and chest pain ($P < 0.05$).

Patients with non-exclusionary chronic diseases were older than completely healthy participants (Table 6). However, age showed no correlation with prevalence of GERD-related symptoms (Table 2).

Discussion

Our South-East Hungarian population-based study is the first to establish the epidemiologic characteristics of GERD-related symptoms in Eastern Europe. Our results showed a significantly lower prevalence of these symptoms compared with those in Western countries.

Table 4. Socioeconomical factors of blood donor volunteers with any GERD-related typical symptoms. Age, weight, height and BMI are presented with mean ± SD and range.

	Asymptomatic *(n = 1,131)*	**GERD-related typical symptoms *(n = 559)***			
		< 1 / month *(n = 229)*	**≥ 1 / month & < 1 / week *(n = 194)***	**≥ 1 / week & < 1 / day *(n = 101)***	**≥ 1 / day *(n = 35)***
Sex					
Male	689 (60.9%)	145 (63.3%)	100 (51.5%)	54 (53.5%)	16 (45.7%)
Female	442 (39.1%)	84 (36.7%)	94 (48.5%) **	47 (46.5%)	19 (54.3%)
Age (years)	39 ± 12.4 (17–66)	39 ± 12.5 (18–65)	39 ± 12.9 (18–64)	41 ± 11.6 (18–64)	39 ± 10.9 (21–58)
Weight (kg)	81 ± 15.8 (50–140)	83 ± 16.7 (51–135)	83 ± 18.3 (51–180)	82 ± 15.7 (54–130)	82 ± 20.9 (50–140)
Height (cm)	174 ± 9.2 (150–197)	174 ± 9.4 (153–198)	172 ± 9.7 (150–200) **	172 ± 8.7 (150–190) *	172 ± 9.0 (153–187)
BMI (kg/m^2)	26.6 ± 4.5 (16.9–52.7)	27.2 ± 5.0 (17.7–45.2)	27.9 ± 5.4 (18.3–52.6) **	27.7 ± 4.5 (18.8–39.7) *	27.6 ± 5.7 (20.1–45.2)
BMI categories					
1 –underweight	3 (0.3%)	3 (1.3%)	1 (0.5%)	0 (0%)	0 (0%)
2 –normal weight	444 (39.3%)	84 (36.7%)	66 (34.0%)	33 (32.7%)	11 (31.4%)
3 –overweight	455 (40.2%)	84 (36.7%)	73 (37.6%)	39 (38.6%)	14 (40.0%)
4 –obesity	169 (14.9%)	40 (17.5%)	36 (18.6%)	26 (25.7%)	7 (20.0%)
5 –extreme obesity	60 (5.3%)	18 (7.9%) *	18 (9.3%)	3 (3.0%)	3 (8.6%)
Smoking					
recently/previously	368 (32.5%)	80 (34.9%)	77 (39.7%)	44 (43.6%)	14 (40.0%)
never	763 (67.5%)	149 (65.1%)	117 (60.3%) *	57 (56.4%) *	21 (60.0%)
Coffee					
yes	756 (66.8%)	151 (65.9%)	145 (74.7%)	77 (76.2%)	25 (71.4%)
no	375 (33.2%)	78 (34.1%)	49 (25.3%) *	24 (23.8%) *	10 (28.6%)
Alcohol					
regularly	30 (2.7%)	6 (2.6%)	9 (4.6%)	6 (5.9%)	2 (5.7%)
never/occasionally	1101 (97.3%)	223 (97.4%)	185 (95.4%)	95 (94.1%)	33 (94.3%)
GERD in the family					
yes	147 (13.0%)	52 (22.7%)	49 (25.3%)	43 (42.6%)	13 (37.1%)
no	825 (72.9%)	133 (58.1%)	107 (55.2%)	47 (46.5%)	17 (48.6%)
unknown	159 (14.1%)	44 (19.2%) **	38 (19.6%) **	11 (10.9%) **	5 (14.3%) **

*: $p < 0.05$, compared to the asymptomatic subjects

**: $p < 0.01$, compared to the asymptomatic subjects

https://doi.org/10.1371/journal.pone.0265152.t004

Although the studied population was likely healthier than the general population, GERD-related symptoms were detected and associated with different socioeconomic and other risk factors, such as positive family history, obesity, coffee consumption, and smoking.

Most population-based epidemiological studies have reported a high prevalence of GERD-related typical symptoms appearing at least monthly. In general, prevalence ranges from 20% to 30% in Western countries. A study in the UK, which enrolled 3,179 patients, reported GERD in 28.7% of the sample population and found it was more common among socially disadvantaged individuals ($P < 0.005$). Although we also examined these potential associations, we were unable to show a correlation between the presence of GERD-related symptoms and the different measurements of socioeconomical status of our participants. Another study conducted in the USA reported that the prevalence of heartburn and/or acid regurgitation experienced at least weekly was 19.8%. In that study, heartburn and acid regurgitation were associated with noncardiac chest pain, dysphagia, dyspepsia, and globus sensation but not

Table 5. The effect of coexisting, chronic diseases (including obesity) on the prevalence of GERD-related symptoms.

	with chronic diseases (*n* = 390)				without chronic diseases							
					BMI < 25 kg/m² (*n* = 687)				BMI > 25 kg/m² (*n* = 925)			
	< 1 / month	≥ 1 / month & < 1 / week	≥ 1 / week & < 1 / day	≥ 1 / day	< 1 / month	≥ 1 / month & < 1 / week	≥ 1 / week & < 1 /day	≥ 1 / day	< 1 / month	≥ 1 / month & < 1 /week	≥ 1 /week & < 1 /day	≥ 1 / day
heartburn	39 *(10.0%)*	33 *(8.5%)*	38 *(9.7%)* **	11 *(2.8%)* *	47 *(6.8%)*	47 *(6.8%)*	22 *(3.2%)*	8 *(1.2%)*	82 *(8.9%)*	80 *(8.6%)*	33 *(3.6%)*	10 *(1.1%)*
acid regurgitation	42 *(10.8%)* *	34 *(8.7%)* **	16 *(4.1%)* *	11 *(2.8%)* **	40 *(5.8%)*	28 *(4.1%)*	12 *(1.7%)*	1 *(0.1%)*	81 *(8.8%)*	46 *(5.0%)*	16 *(1.7%)*	6 *(0.6%)*
typical symptoms during night	18 *(4.6%)* **	8 *(2.1%)*	8 *(2.1%)* *	3 *(0.8%)*	5 *(0.7%)*	9 *(1.3%)*	4 *(0.6%)*	1 *(0.1%)*	28 *(3.0%)*	15 *(1.6%)*	8 *(0.9%)*	1 *(0.1%)*
dysphagia	4 *(1.0%)*	5 *(1.3%)*	7 *(1.8%)* *	2 *(0.5%)*	1 *(0.1%)*	4 *(0.6%)*	3 *(0.4%)*	1 *(0.1%)*	3 *(0.3%)*	3 *(0.3%)*	3 *(0.3%)*	1 *(0.1%)*
globus sensation	16 *(4.1%)* *	9 *(2.3%)*	7 *(1.8%)*	6 *(1.5%)* **	21 *(3.1%)*	15 *(2.2%)*	7 *(1.0%)*	3 *(0.4%)*	17 *(1.8%)*	9 *(1.0%)*	9 *(1.0%)*	0 *(0%)*
upper respiratory tract symptoms	28 *(7.2%)*	20 *(5.1%)*	20 *(5.1%)*	33 *(8.5%)* **	46 *(6.7%)*	24 *(3.5%)*	30 *(4.4%)*	23 *(3.3%)*	47 *(5.1%)*	36 *(3.9%)*	30 *(3.2%)*	37 *(4.0%)*
dyspnea	17 *(4.4%)* **	8 *(2.1%)* **	7 *(1.8%)* *	3 *(0.8%)* **	5 *(0.7%)*	2 *(0.3%)*	5 *(0.7%)*	0 *(0%)*	13 *(1.4%)*	4 *(0.4%)*	4 *(0.4%)*	0 *(0%)*
chest pain	11 *(2.8%)**	14 *(3.6%)* *	3 *(0.8%)* *	3 *(0.8%)* *	7 *(1.0%)*	13 *(1.9%)*	7 *(1.0%)* *	1 *(0.1%)*	8 *(0.9%)*	13 *(1.4%)*	1 *(0.1%)*	0 *(0%)*
epigastric pain	21 *(5.4%)**	11 *(2.8%)*	25 *(6.4%)* **	11 *(2.8%)* **	16 *(2.3%)*	22 *(3.2%)*	14 *(2.0%)*	3 *(0.4%)*	29 *(3.1%)*	23 *(2.5%)*	21 *(2.3%)*	7 *(0.8%)*
abdominal pain	2 *(0.5%)*	5 *(1.3%)*	10 *(2.6%)* **	6 *(1.5%)* *	5 *(0.7%)*	7 *(1.0%)*	9 *(1.3%)*	2 *(0.3%)*	1 *(0.1%)*	7 *(0.8%)*	5 *(0.5%)*	3 *(0.3%)*
nausea & vomiting	12 *(3.1%)*	8 *(2.1%)*	10 *(2.6%)* **	2 *(0.5%)*	11 *(1.6%)*	12 *(1.7%)*	4 *(0.6%)*	2 *(0.3%)*	14 *(1.5%)*	7 *(0.8%)*	6 *(0.6%)*	0 *(0%)*

*: $p < 0.05$, compared to the respective group of subjects without chronic diseases

**: $p < 0.01$, compared to the respective group of subjects without chronic diseases.

https://doi.org/10.1371/journal.pone.0265152.t005

with asthma, hoarseness, bronchitis, or history of pneumonia. A recent Italian study reported that the prevalence of gastro–esophageal reflux was 26.2% (792/3012). The authors found significant differences in frequency of the disorder according to sex, smoking habits, and BMI. GERD-related symptoms were more common among females, smokers, and those with higher BMI values [18–20].

In contrast, a study conducted in India reported a lower prevalence of GERD-related symptoms, with 7.6% of the 3,224 participants experiencing heartburn and/or acid regurgitation at least once a week. Older age and consumption of non-vegetarian, fried foods, aerated drinks, and tea/coffee were associated with GERD. Frequency of smoking and BMI were similar among participants with or without GERD [21].

A study conducted in Iran including 803 patients (age, 11–84 years) reported that GERD was more common in females than males. Furthermore, the disease became more prevalent with age. In the present study, there was an interesting association between sex and the presence of GERD-related symptoms. As the frequency of GERD-related symptoms increased, the blood donors were more likely to be female. In our participants, there was no difference according to age [22].

We identified only one study in the literature that was conducted in Japan that reported a positive relationship between the upper gastrointestinal symptoms and shorter height (in

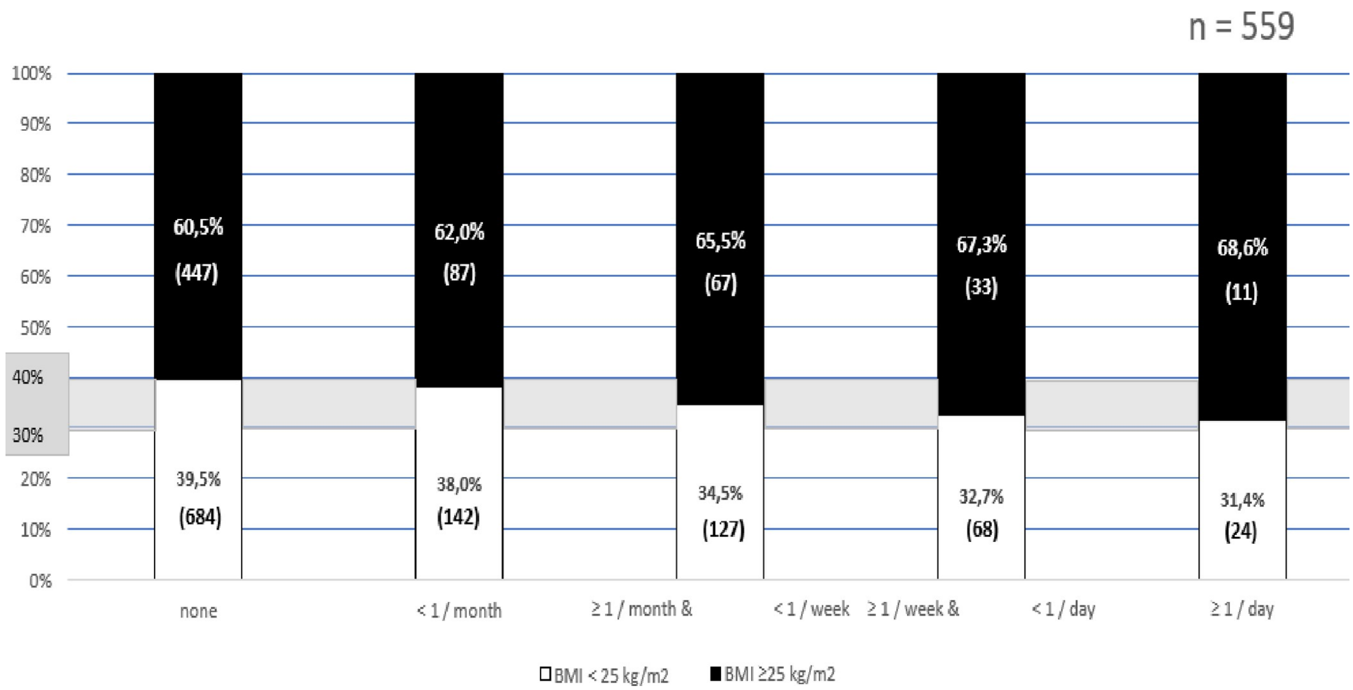

Fig 3. The frequency of GERD-related typical symptoms is positively associated to the presence of overweight (R^2 = 0.63, P = 0.0497). Similar association was found if all (typical + atypical) reflux related symptoms were assessed.

https://doi.org/10.1371/journal.pone.0265152.g003

elderly, mostly female Japanese participants). In our blood donor volunteers, this correlation was also detected, and the height became shorter as the frequency of GERD-related symptoms increased [23].

Obesity plays a role in the development of GERD symptoms as well as its complications (erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma) [24]. Obesity was a detected risk factor in this population but the presence of overweight or obesity alone was not associated with a higher prevalence of symptoms. Most recent epidemiological studies detected an association between BMI and GERD, for both the symptomatic form and various complications (e.g., erosive esophagitis, Barrett's esophagus). It should be also highlighted that obesity is one of the major risk factors of obstructive sleep apnea (OSA). The international literature demonstrates a high incidence of LPR (45.2%) in OSA patients. Moreover, a recent meta-analysis showed a significant correlation between OSA-hypopnea syndrome and GERD [25, 26]. Therefore, obesity has become a risk factor for these diseases. The present study examined this feature using two approaches. First, participants with mild, chronic, non-exclusionary diseases showed a greater frequency and prevalence of GERD-related (typical/atypical) symptoms than overweight/obese, otherwise healthy participants. Second, a positive linear correlation was found between the prevalence of GERD-related symptoms and the presence of obesity. In another study, the prevalence, frequency, and severity of symptoms of GERD increased with increasing BMI [27].

Smoking significantly exacerbates GERD via direct provocation of acidic reflux and a long-lasting reduction of lower esophageal sphincter pressure [28]. In our study, smoking was also a significant risk factor (Tables 3 and 4).

It remains unclear whether coffee consumption is a factor in the development of GERD. A recent study reported no association between coffee consumption and the symptoms or erosive esophagitis [29]. In another study, coffee (in contrast to tea) increased the prevalence of

Table 6. Socioeconomical factors of blood donor volunteers according to the presence of coexisting, chronic diseases. Age, weight, height, and BMI are presented with mean ± SD and range.

	with chronic diseases *(n = 390)*	without chronic diseases	
		BMI $<$ 25 kg/m^2 *(n = 687)*	BMI $>$ 25 kg/m^2 *(n = 925)*
Sex			
Male	205 (52.6%)	333 (48.5%)	618 (66.8%) **
Female	185 (47.4%)	354 (51.5%)	307 (33.2%)
Age (years)	45 ± 11.8 (18–66) **	34 ± 12.0 (18–65)	40 ± 12.0 (17–65)
Weight (kg)	85 ± 17.0 (52–134)	68 ± 9.1 (50–92)	89 ± 14.0 (58–180)
Height (cm)	172 ± 9.4 (150–198)	173 ± 8.9 (153–197)	174 ± 9.3 (150–200)
BMI (kg/m^2)	28.7 ± 4.9 (17.0–45.2)	22.5 ± 1.7 (16.9–24.9)	29.2 ± 3.8 (25.0–52.7)
BMI categories			
1 –underweight	2 (0.5%)	7 (1.0%)	0
2 –normal weight	100 (25.6%)	680 (99.0%)	0
3 –overweight	141 (36.2%)	0	638 (69.0%)
4 –obesity	110 (28.2%)	0	211 (22.8%)
5 –extreme obesity	37 (9.5%)	0	76 (8.2%)
Smoking			
recently / previously	139 (35.6%)	248 (36.1%)	345 (37.3%)
never	251 (64.4%)	439 (63.9%)	579 (62.6%)
Coffee			
yes	285 (73.1%) *	457 (66.5%)	638 (69.1%)
no	105 (26.9%)	230 (33.5%)	286 (30.9%)
Alcohol			
regularly	15 (3.8%)	16 (2.3%)	35 (3.8%)
never / occasionally	375 (96.2%)	671 (97.7%)	889 (96.2%)
GERD in the family			
yes	87 (22.3%) *	119 (17.3%)	151 (16.3%)
no	244 (62.6%)	475 (69.1%)	623 (67.4%)
unknown	59 (15.1%)	93 (13.6%)	150 (16.3%)

*: $p < 0.05$, compared to the respective group of subjects without chronic diseases

**: $p < 0.01$, compared to the respective group of subjects without chronic diseases).

https://doi.org/10.1371/journal.pone.0265152.t006

GERD. Therefore, factors other than caffeine may be responsible for the induction of GERD [30]. Coffee consumption was a significant risk factor in our study population (Tables 3 and 4).

A meta-analysis of 26 cross-sectional studies and three case–control studies showed a potential association between drinking alcohol and risk of GERD. Increased alcohol consumption and frequency showed a stronger correlation with GERD [31]. This association was not observed in the present study.

Taken together, these findings indicate that the prevalence of GERD-related symptoms in South-East Hungary was closer to the Eastern values. Interestingly, some of the detected risk factors supported previous results from Eastern studies while others supported the findings from Western studies.

Some chronic diseases may be associated with upper gastrointestinal motility disorders. However, epidemiological studies of symptomatic GERD have not evaluated their influence on the prevalence of GERD-related symptoms. In the present study, an association was found between GERD-related symptoms and chronic diseases. Furthermore, their prevalence was three times higher in individuals with mild, chronic non-exclusionary diseases compared with apparently healthy individuals. Therefore, primary GERD is likely less common based on the findings from epidemiological studies. This difference may be explained by upper gastrointestinal hypomotility associated with these disorders or their pharmaceutical treatment.

Many risk factors are common in cardiovascular diseases and GERD and GERD can be a risk factor for cardiovascular diseases (such as hypertension). A significant correlation was previously found between GERD and hypertension, as well in our study population [32]. Our findings support some well-known symptom–disease associations, such as coughing and respiratory disorders, chest pain and heart diseases, and globus sensation and thyroid problems. All typical and atypical symptoms were significantly more common ($P < 0.05$) in individuals with known minor respiratory diseases (44/2,002, 2.2%).

Positive family history of GERD has been examined in several studies, but these mostly occurred for the genetic markers. Epidemiological studies have not examined the positive family history of the disease in larger populations along with GERD-related symptoms. Our findings indicate that individuals with a higher frequency of typical GERD symptoms were more likely have a positive family history of GERD. While the prevalence was twice as high for those experiencing less than weekly symptoms, the likelihood of a positive family history was three times higher in individuals with at least weekly symptoms [33, 34].

The present study has some limitations. The study was limited to a questionnaire survey of symptoms and medical history. No instrumental examinations (e.g., endoscopy and esophageal function testing, such as the gold standard pHmetry) were performed in the participants. Therefore, only the prevalence value of the examined symptoms could be given and there was no data to state whether symptoms were caused by GERD (acidic/weakly acidic/non-acidic reflux) or functional disease (e.g., functional heartburn). In this study, the lack of RSI score is a limitation, which is mainly used for LPR but can be also performed for GERD patients for an evaluation of the symptoms [35, 36]. Patients with OSA and / or obesity were not observed in our study because there were no questions for sleeping disorder in the questionnaire.

Conclusion

In conclusion, the prevalence of GERD-related symptoms among South-East Hungarian blood donor volunteers was significantly lower than in the Western countries and closer to the Eastern values. In otherwise healthy, non-obese individuals, the prevalence of at least weekly occurring GERD-related symptoms was <5%. The presence of mild, non-exclusionary chronic diseases significantly increased the prevalence of GERD-related symptoms, as well as positive family history, coffee consumption, smoking, shorter height, and increased BMI.

Acknowledgments

I wish to record my thanks to support of the University of Szeged, including the financial support by following competition: EFOP 3.6.3-VEKOP-16-2017-00009 (2020/08).

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1.sz. melléklet

Társszerzői lemondó nyilatkozat

Alulírott……**Dr. Helle Krisztina**............(felelős társszerző) kijelentem, hogy …**Dr. Bálint Lenke**...(pályázó) PhD értekezésének tézispontjaiban bemutatott - közösen publikált - tudományos eredmények elérésében a pályázónak meghatározó szerepe volt, ezért ezeket a téziseket más a PhD fokozat megszerzését célzó minősítési eljárásban nem használta fel, illetve nem kívánja felhasználni.

....Szeged, 2022. augusztus 25... ……………………......................................

dátum szerző

A pályázó tézispontjaiban érintett, közösen publikált közlemények:

Helle K, Bálint L, Szekeres V, Ollé G, Rosztóczy A. Prevalence of reflux-related symptoms in South-Hungarian blood donor volunteers. PLoS One. 2022 Mar 15;17(3):e0265152. doi: 10.1371/journal.pone.0265152. PMID: 35290403; PMCID: PMC8923446.