The prevalence of *Helicobacter Pylori* infection in patients with obstructive sleep apnea having metabolic syndrome and its relation to both disorders

Laila A.H. Banawan[a], Rasha G.A. Daabis[a], Wafaa H. Elsheikh[b], Mona M. Tolba[c], Amira M. Youssef[d]

Introduction Obstructive sleep apnea hypopnea syndrome (OSAHS) is a highly prevalent respiratory disorder and is associated with metabolic syndrome (MS). *Helicobacter pylori* (*H. pylori*) infection (Hp-I) may be involved in the pathogenesis of both obstructive sleep apnea (OSA) and gastroesophageal reflux disease (GERD); the latter is also associated with OSAHS. An association between Hp-I and OSA has been reported as well as a potential association between Hp-I and insulin resistance, which represents the pathogenetic basis of MS.

Objective To study the prevalence of Hp-I in patients with OSAHS having MS and its relation to both OSAHS and MS and to asses GERD symptoms in the studied groups and its relation to the severity of OSA and to Hp-I.

Patients and methods This study included 28 patients with confirmed OSAHS by overnight polysomnography, with half of them having MS. Demographic, comorbidities, anthropometric, and clinical data were collected. Stool analysis for *H. pylori* antigen was done.

Results Patients with OSAHS with MS had significantly more severe OSA ($P \leq 0.001$*). The prevalence of both Hp-I and GERD was significantly higher in the MS group ($P=0.023$ and 0.018, respectively). GERD was significantly associated with *H. pylori* infection in the studied groups ($P<0.001$). The prevalence of Hp-I and GERD increased with the severity of OSAHS, but it did not reach statistical significance, as in patients with mild, moderate, and severe OSAHS, the prevalence of Hp-I and GERD was 16.7, 50, and 64.3%, respectively, and 12.5, 25, and 62.5%, respectively.

Conclusion *H. pylori* infection can be considered as a potential confounder involved in OSAHS and GERD pathophysiology associated with MS.

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Keywords: gastroesophageal reflux disease, *Helicobacter pylori* infection, metabolic syndrome, obstructive sleep apnea hypopnea syndrome, obstructive sleep apnea hypopnea syndrome severity

[a]Departments of Chest diseases, [b]Internal Medicine, Faculty of Medicine, [c]Department of Parasitology, Medicine Research Institute, Alexandria University, [d]Department of Chest Diseases, Shobrakhit Central Hospital, Alexandria, Egypt

Correspondence to Rasha G.A. Daabis, MD, Department of Chest Diseases, Faculty of Medicine, Alexandria University, Alexandria, 21524, Egypt; Tel: 01224582538;
e-mail: rgdaabis@yahoo.com

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Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) is an important medical condition whose prevalence is estimated to range from 3 to 7%, which can increase in some subgroups of population. It is an important cause of morbidity and mortality worldwide. It is characterized by episodes of complete or partial pharyngeal obstruction during sleep [1].

The metabolic syndrome (MS) is an emerging public health concern [2]. It includes several interrelated risk factors of metabolic origin that increase the risk for developing coronary artery disease (CAD), stroke, and diabetes, owing to its underlying associated proinflammatory and prothrombotic states [3].

In the sleep literature, the term Syndrome Z has been used to describe such interrelated diseases. It includes the typical features of the MS (Syndrome X), which are central obesity, diabetes, hypertension, and dyslipidemia, with the addition of obstructive sleep apnea (OSA) [4].

Helicobacter pylori (*H. pylori*) infection (Hp-I) is highly prevalent worldwide. Despite its high prevalence, *H. pylori* seroprevalence has been found to be more increased in OSAHS. It has recently been linked to OSAHS by the effect of inflammation, which contributes to autonomic reflexes, upper airway collapsibility, and inspiratory pharyngeal muscle dysfunction [5].

Moreover, Hp-I has been also linked to MS as it leads to a chronic, low-grade inflammation of the gastric mucosa. Moreover, systemic inflammation is present in Hp-I through the production of high levels of tissue and circulatory cytokines by different cell types. This can further affect metabolic processes through local, central, and peripheral actions and thus can be an underlying risk factor for chronic gastritis, atherosclerosis, MS, obesity, insulin resistance, and type 2 diabetes [6].

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Therefore, our aim was to study the prevalence of Hp-I in patients with OSAHS having MS and its relation to both OSAHS and MS and also to assess the gastroesophageal reflux disease (GERD) symptoms in the studied groups and its relation to the severity of OSA and to Hp-I.

Patients and methods

This study included 28 patients with OSAHS admitted to Alexandria Main University Hospitals, Alexandria, Egypt. They were divided into two groups: group I included patients with OSAHS having MS and group II included patients with OSAHS only without the criteria of MS [7].

The patients' inclusion criteria were an age of greater than 18 years and a confirmed diagnosis of OSAHS based on the apnea–hypopnea index (AHI): AHI up to 15 events per hour or AHI up to 5 and 14 or less events per hour with documented sleep symptoms or documented hypertension, ischemic heart disease, or a history of stroke.

Exclusion criteria

Prior *H. pylori* eradication therapy, consumption of acid suppressive drugs or antibiotics preceding 6 months, coexistent or pre-existing systemic illness, a history of vagotomy or operation of the upper gastrointestinal tract, COPD, or any lung parenchymal disease were the exclusion criteria.

All participants were enrolled in the study after a written informed consent was obtained according to the protocol approved by the ethics committee of the hospital.

The severity of OSAHS in the studied patients was classified according to AHI into mild: 5–15 events per hour, moderate: 15–30 events per hour, and severe: greater than 30 events per hour.

All patients were subjected to the following:

(1) History taking and physical examination stressing on symptoms of OSAHS like loud snoring, witnessed apnea, and excessive day sleepiness (EDS). Symptoms of GERD were assessed using the validated GerdQ questionnaire, which is a simple, patient-centered questionnaire including six items. It asks patients to score the number of days with symptoms and use of over-the-counter medications during the previous 7 days. It uses a four graded scale (0–3) to score the frequency of four positive predictors of GERD (heartburn, regurgitation, sleep disturbance owing to reflux symptoms, or use of over-the-counter medications for reflux symptoms) and a reversed scale (3–0) for two negative predictors of GERD (epigastric pain and nausea) giving a total GerdQ score range of 0–18 (Table 1). Patients having a score of up to 9 were considered as having GERD symptoms [8].
(2) Anthropometric data were recorded, including BMI, neck circumference (NC), and waist circumference (WC).
(3) The Epworth sleepiness scale (ESS) was used for assessing daytime sleepiness [9].
(4) Routine laboratory investigations were done, including lipid profile [serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein, and serum triglycerides] and fasting blood sugar.
(5) Stool analysis for *H. pylori* antigen.
(6) Full overnight polysomngraphy for diagnosis of OSA.

The results were automatically analyzed and manuallyrevised using AASM 2012 criteria [10], and the following parameters were documented: AHI, oxygen desaturation index (ODI), sleep efficiency, minimum SpO_2, average SpO_2, and SpO_2 less than 90.

Statistical analysis

Data were analyzed using IBM statistical package for the social sciences software package version 20.0 (SPSS;

Table 1 The GerdQ questionnaire

Question	Frequency score (points) for symptom			
	0 day	1 day	2–3 days	4–7 days
How often did you have a burning feeling underneath your breastbone (heartburn)?	0	1	2	3
How often did you have stomach contents (liquid or food) moving upward to your throat or mouth (regurgitation)?	0	1	2	3
How often did you have pain in the center of the upper stomach?	3	2	1	0
How often did you have nausea?	3	2	1	0
How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take such as Tums, Rolaids, Maalox?	0	1	2	3

SPSS Inc., Chicago, Illinois, USA). Qualitative data were presented using number and percentage. Quantitative data were presented using mean and SD. Significance of the obtained results was judged at the 5% level. χ^2-Test was used for categorical variables to compare between different groups. Fisher's exact or Monte Carlo correction was used for χ^2-test when more than 20% of the cells have expected count less than 5. For normally quantitative variables, Student's *t*-test was used to compare between the two studied groups. For abnormally quantitative variables, Mann–Whitney test or Kruskal–Wallis test was used to compare between groups. Spearman's coefficient was used to correlate between two abnormally quantitative variables.

Results

Baseline characteristics of the two studied groups

BMI, NC, WC, and witnessed apnea were significantly higher in patients with OSAHS with MS (P=0.019*, 0.001*, 0.021*, and 0.001*, respectively) in comparison with those without MS as presented in Table 2.

Respiratory sleep parameters and Epworth sleepiness scale in the studied groups

ESS, AHI, and ODI were significantly higher in the metabolic group ($P \leq 0.001$*, $P \leq 0.001$* and P=0.003*, respectively) as presented in Table 3.

Comparison of the severity of obstructive sleep apnea hypopnea syndrome in the studied groups

Patients with OSAHS with MS had significantly more severe OSA ($P \leq 0.001$*) as presented in Table 4 and Fig. 1.

Prevalence of *Helicobacter pylori* infection and gastroesophageal reflux disease in the studied groups

The prevalence of both Hp-I and GERD was significantly higher in the metabolic group (P=0.023*and 0.018*, respectively) as presented in Table 5 and Fig. 2.

Table 2 Comparison between the two studied groups according to baseline characteristics

	OSAHS		*P*
	Nonmetabolic (*n*=14)	Metabolic (*n*=14)	
Sex [*n* (%)]			NS
Male	6 (42.9)	6 (42.9)	
Female	8 (57.1)	8 (57.1)	
Age	49.71±8.98	55.36±9.55	NS
BMI	32.85±10.63	40.90±5.85	0.019*
NC	40.43±3.13	45.86±4.66	0.001*
WC	110.14±11.75	122.43±14.50	0.021*
Loud snoring [*n* (%)]	14 (100.0)	14 (100.0)	NS
Witnessed apnea [*n* (%)]	3 (21.4)	12 (85.7)	0.001*

Results are presented as mean±SD unless otherwise specified. NC, neck circumference; OSAHS, obstructive sleep apnea hypopnea syndrome; WC, waist circumference. *$P \leq 0.05$, statistically significant.

Table 3 Comparison between the two studied groups according to respiratory sleep parameters and Epworth sleepiness scale

	OSAHS		*P*
	Nonmetabolic (*n*=14)	Metabolic (*n*=14)	
ESS	15.07±3.27	19.29±1.90	<0.001*
Sleep efficiency (%)	71.87±11.39	74.89±8.84	NS
AHI	16.83±6.37	49.79±17.48	<0.001*
ODI	17.97±31.87	37.95±26.20	0.003*
Min SpO_2	80.57±10.52	76.79±9.74	NS
Average SpO_2	91.0±4.15	88.79±6.09	NS
SpO_2>90	24.67±39.49	36.36±34.65	NS

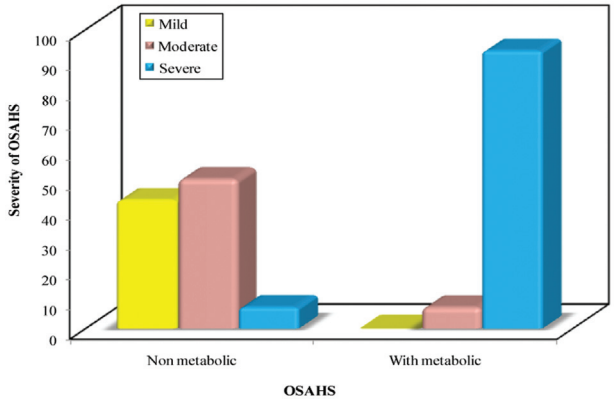
Results are presented as mean±SD. AHI, apnea hypopnea index; ESS, Epworth sleepiness scale; ODI, oxygen desaturation index; OSAHS, obstructive sleep apnea hypopnea syndrome. *$P \leq 0.05$, statistically significant.

Table 4 Comparison between the two studied groups according to severity of obstructive sleep apnea hypopnea syndrome

	OSAHS		*P*
Severity of OSAHS	Nonmetabolic (*n*=14)	Metabolic (*n*=14)	
Mild	6 (42.9)	0	<0.001*
Moderate	7 (50)	1 (7.1)	
Severe	1 (7.1)	13 (92.9)	

Results are presented as number and percentage. OSAHS, obstructive sleep apnea hypopnea syndrome. *$P \leq 0.05$, statistically significant.

Figure 1



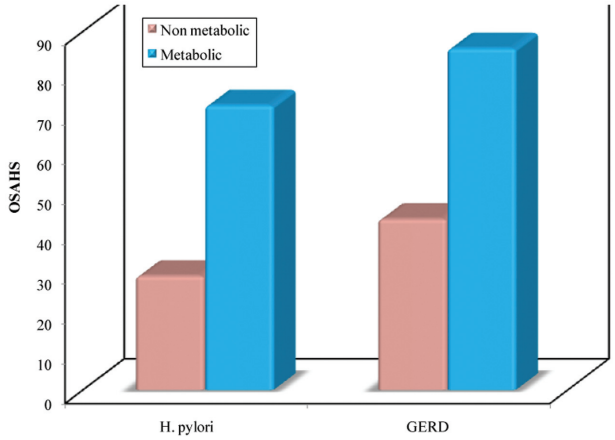
Comparison between the two studied groups according to severity of obstructive sleep apnea hypopnea syndrome (OSAHS)

Table 5 Comparison between the two studied groups according to *Helicobacter pylori* and gastroesophageal reflux disease

	OSAHS		*P*
	Nonmetabolic (*n*=14)	Metabolic (*n*=14)	
H. pylori	4 (28.6)	10 (71.4)	0.023*
GERD	6 (42.9)	12 (85.7)	0.018*

Results are presented as number and percentage. *H. pylori*, *Helicobacter pylori*; GERD, gastroesophageal reflux disease; OSAHS, obstructive sleep apnea hypopnea syndrome. *$P \leq 0.05$, statistically significant.

Figure 2



Comparison between the two studied groups according to *Helicobacter pylori* and gastroesophageal reflux disease. OSAHS, obstructive sleep apnea hypopnea syndrome; GERD, gastroesophageal reflux disease

The prevalence of *Helicobacter pylori* infection and gastroesophageal reflux disease in patients with different comorbidities

There was a high prevalence of Hp-I in diabetic patients and patients with IHD (P=0.002*and ^{FE}P=0.013, respectively) as shown in Table 6. Also, there was high prevalence of GERD in diabetic patients and patients with IHD (P=0.022* and ^{FE}P=0.039*, respectively) as shown in Table 7.

Table 6 Relation between *Helicobacter pylori* and comorbidities

Comorbidity	*N*	*H. pylori*		*P*
		Negative (*n*=14)	Positive (*n*=14)	
HTN	11	4 (36.4)	7 (63.6)	0.246
DM	14	3 (21.4)	11 (78.6)	0.002*
IHD	9	1 (11.1)	8 (88.9)	^{FE}P=0.013*

Results are presented as number and percentage. DM, diabetes mellitus; FE, Fisher's exact test; HTN, hypertension; IHD, ischemic heart disease. *$P \leq 0.05$, statistically significant.

The relationship between gastroesophageal reflux disease and *Helicobacter pylori* infection

GERD was significantly associated with Hp-I in the studied groups ($P \leq 0.001$*) as presented in Table 8.

The relation of *Helicobacter pylori* infection and gastroesophageal reflux disease with the severity of obstructive sleep apnea hypopnea syndrome

The prevalence of Hp-I increased with increase in severity of OSAHS, where in patients with mild, moderate, and severe OSAHS, it was 16.7, 50, and 64.3%, respectively, but it did not reach statistical significance (χ^2=3.649 and ^{MC}P=0.160).

Similar trend was seen with GERD, which was also increasing with increased severity of OSAHS, as in mild, moderate, and severe OSAHS, the prevalence of GERD was 12.5, 25, and 62.5%, respectively, but this increase did not reach statistical significance as well (χ^2=2.691 and ^{MC}P=0.253).

Discussion

This study revealed that BMI, NC, and WC were significantly higher in patients with OSAHS having MS. As obesity is associated with insulin resistance and MS, it contributes to hypertension, high serum cholesterol, low HDL-cholesterol, and hyperglycemia [11]. Moreover, the excess of body fat in the abdomen, which was measured by waist circumference, is more indicative of the MS profile than BMI [12]. In agreement with our study, Preis *et al.* [13] found that NC was positively associated with risks of type 2 diabetes, hypertension, decreased HDL-cholesterol, and increased triglycerides.

MS was related to more severe OSAHS. This may be because of increasing abdominal obesity, which is the main feature of MS and causes decrease in lung volumes and in turn decreases the caudal traction on

Table 7 Relation between gastroesophageal reflux disease with comorbidities

Comorbidity	*N*	GERD		*P*
		No (*n*=12)	Yes (*n*=16)	
HTN	11	3 (27.3)	8 (72.7)	^{FE}P=0.253
DM	14	3 (21.4)	11 (78.6)	0.022*
IHD	9	1 (11.1)	8 (88.9)	^{FE}P=0.039*

Results are presented as number and percentage. DM, diabetes mellitus; FE, Fisher's exact test; HTN, hypertension; IHD, ischemic heart disease. * $P \leq 0.05$, statistically significant.

Table 8 Relation between gastroesophageal reflux disease and *Helicobacter pylori* infection

H. pylori	GERD		*P*
	No (*n*=12)	Yes (*n*=16)	
Negative	12 (100.0)	2 (12.5)	<0.001*
Positive	0 (0.0)	14 (87.5)	

Results are presented as number and percentage. GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*. *$P \leq 0.05$, statistically significant.

the upper airway during lung inflation, causing lesser longitudinal tension on the pharyngeal walls, especially in the supine position, which can further predispose to upper airway collapse. This was in line with multiple studies that have shown an epidemiologic relationship between OSA and MS, with an increasing association of MS with OSA severity [14,15].

Witnessed apnea was significantly higher in patients with OSAHS with MS as MS is associated with more severe OSAHS and a higher BMI. Moreover, all cases complained of loud snoring, which is the most frequent symptom of OSAHS, occurring in 70–95% of patients. However, it was found that none of the common presenting symptoms alone has sufficient discriminatory value to make an accurate diagnosis of OSAHS [16]. In addition, in a large study of 5000 participants, those reporting habitual loud snoring and frequent witnessed apneas were three to four times more likely to have an AHI of up to 15 than those who did not report these symptoms [17].

ESS was significantly higher in the MS group. As MS contributes to more severe OSAHS, EDS, which is considered a cardinal sign of sleep apnea, was more prevalent in this group, which was demonstrated by higher ESS. In addition, the strong association between EDS and diabetes adds further support for the association of EDS with the MS. This finding is clinically significant because it would suggest that diabetes should be considered whenever a complaint of EDS is stated. Supporting our results, a study that evaluated the potential risk factors associated with EDS in a general population sample found that the presence of EDS is more strongly associated with depression and metabolic factors than with sleep-disordered breathing or sleep disruption, suggesting that patients complaining of EDS should be thoroughly assessed for depression and obesity/diabetes independent of whether sleep-disordered breathing is present [18].

ODI was significantly higher in MS group, as the severity of OSAHS was higher in this group, and was increasing significantly with increase of AHI in this study. This was in line with Fietze *et al.* [19], who recorded the ODI for 35 patients over seven nights. Their patients were classified into three categories: normal, mild OSAHS, and moderate to severe OSAHS. They found that ODI was increasing with increasing OSAHS severity (<5, 5≤ODI≤15 and ODI>15, respectively) [19].

The prevalence of Hp-I was significantly higher in the MS group (P=0.023)]. *H. pylori* may affect MS through the elevations in inflammatory markers such as C-reactive protein and interleukin-6. In agreement with our results, a few epidemiological studies supported a significant association between *H. pylori* infection, insulin resistance, and MS [20,21].

Moreover, our study revealed a high prevalence of Hp-I in diabetic patients (78.6%) (P=0.002*). This may be explained by the inflammation induced by Hp-I, which has been implicated in the pathogenesis of diabetes through insulin resistance. Gentile *et al.* [22] found that the prevalence of Hp-I was significantly higher in the diabetic patients compared with a control group.

On the contrary, some studies detected that fasting plasma glucose was lower in HP-infected diabetics than in noninfected controls. The explanation was that both basal and meal-stimulated glucose levels are decreased as antral gastrin release is increased by Hp-I and this, in turn, inhibits glucose absorption in the small intestine and augments glucose-stimulated insulin release in females but not in males [23]. Most of these studies were done on female patients, and similar findings were not seen in male patients. However, in this study, 43% of the patients were males, which might explain the difference in our results.

Also, our study revealed a high prevalence of Hp-I in patients with IHD (88.9%) (^{FE}P=0.013*) which may be because of stimulation of inflammatory cytokines by *H. pylori* which can further predispose to endothelial damage and atherosclerosis, thereby causing microvascular damage and triggering premature development of atherosclerosis. Supporting our study, Tousoulis *et al.*

[24] first proposed an inflammatory mechanism for endothelial dysfunction. C-reactive protein and inflammatory adhesion molecule such as intracellular adhesion molecule-1 are elevated in patients with *H. pylori* infection, suggesting a possible link between infection and endothelial dysfunction [25].

However, Niemelä *et al.* [26] showed that the association between CAD and Hp-I was not strong. This may be explained by the different inclusion criteria of patients and controls used in the various studies.

This study found that the prevalence of Hp-I increased with increase in severity of OSAHS, but it did not reach statistical significance owing to small sample size. This may be explained by OSAS-related poor gastric circulation which may be a causative factor for Hp-I, or it may further confirms the underlying relation between Hp-I and the pathogenesis of OSAHS through different inflammatory pathways [27].

On the contrary, inflammation caused by Hp-I may contribute to autonomic reflexes, upper airway collapsibility, and inspiratory pharyngeal muscle dysfunction. These unfavorable processes may increase the severity of OSAS, setting up a vicious cycle. This was in agreement with Unal *et al.* [28] who found a significant positive correlation between Hp-I and severity of OSAHS.

In this study, we found that the prevalence of GERD was significantly higher in metabolic group, and this may be explained by the increase in the gastroesophageal pressure gradient causing the development of hiatal hernia, precipitated by high intra-abdominal pressure owing to excess abdominal fat and obesity [29], which are more evident in the metabolic group.

Our study revealed a high prevalence GERD in diabetic patients (78.6%). Diabetes mellitus and GERD share similar risk factors such as obesity, and as diabetes mellitus affects autonomic nerve functions, a higher prevalence of GERD is to be expected in those patients [30]. In agreement with our results, Nishida *et al.* [31] demonstrated a significantly higher prevalence of GERD in diabetic patients compared with controls.

Moreover, this study revealed a high prevalence of GERD in patients with IHD (88.9%). This is may be explained by cardiac drugs commonly used to treat IHD, particularly antiplatelet drugs, which may either predispose patients with IHD to GERD or aggravate pre-existing GERD, or by the underlying Hp-I [32]. In agreement with our study, Garcia-Pulido *et al.* [33] reported that 55% of patients with CAD have acid reflux, and 65% of those with acid reflux have chest pain related to acid reflux.

In the current study, GERD was related to OSAHS and also increased with increasing severity of OSAHS, though it did not reach statistical significance.

Many pathophysiological mechanisms have been proposed for the association between gastroesophageal reflux and OSAHS

Pharyngeal spasm and mucosal exudative neurogenic inflammation that occur because of nocturnal proximal migration of gastric acid and prolonged acid clearance could render the upper airway dysfunctional and prone to collapse during sleep [34]. Additionally, nocturnal GERD can cause arousal during sleep leading to sleep fragmentation and upper airway edema promoting the expression of OSA. On the contrary, OSAHS may cause or aggravate GERD. At night-time, gastric acid production is increased, gastric emptying and esophageal clearance are delayed, and upper esophageal sphincter pressure diminishes significantly [35].

In agreement with our study, Tanaka *et al.* [36] showed a significant association between the prevalence of GERD and the severity of OSAS as assessed by AHI score.

In the current study, GERD was significantly associated with Hp-I in the studied groups as all cases of Hp-I were complaining of GERD; this is may be because of their sharing many combined factors favoring both conditions such as chronic inflammation, obesity, and metabolic disorders. Both conditions may occur either independently or concomitantly. Hp-I produces an increase in basal and stimulated gastric acid output through the secretion of gastrin, somatostatin, and inflammatory mediators, which are possible causes of GERD [37]. Moreover, *H. pylori* eradication has been found to cause better control of GERD symptoms and improve esophagitis [38].

Therefore, GERD and OSA, Hp-I and GERD, and *H. pylori*-associated mucosal disruption of the upper aerodigestive tract could be interrelated phenomena.

In accordance with our study, Masjedizadeh *et al.* [39] found high prevalence of *H. pylori* (88.2%) among patients with GERD. However, there are many controversies regarding the relation between GERD and Hp-I.

In contrast to our study, Brazowski *et al.* [40] found that the prevalence of Hp-I in patients with GERD was lower than patients without GERD. Their explanation was that colonization of gastric mucosa by *H. pylori* results in hypochlorhydria in patients with diffuse gastritis and gastric atrophy and therefore seems to be at less risk of developing GERD [41].

The limitation of our study is that we did not perform an upper gastrointestinal endoscopy or esophageal manometry to confirm the diagnoses of GERD.

In conclusion, OSAHS, MS, Hp-I, and GERD share interacting pathogenetic risk factors. It is unclear whether the co-occurrence of these conditions represents a causal relationship or is simply a reflection of shared risk factors such as obesity and systemic inflammation. More studies are needed to clarify the pathogenetic mechanisms underlying these associations.

Moreover, in this study, Hp-I was associated with both OSA and GERD; the latter was also associated with OSAHS. Therefore, the association between Hp-I and OSAHS as well as the potential association between Hp-I and MS indicates that Hp-I can be considered a potential confounder in OSAHS and GERD pathophysiology associated with MS.

Therefore, further studies should be undertaken to investigate the effect of *H. pylori* eradication on improving OSAHS and if this will further affect its association with MS.

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Conflicts of interest
There are no conflicts of interest.

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