Environmental–life style related factors

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Summary

The prevalence of Gastro Esophageal Reflux Disease (GERD) has been increasing worldwide. This increase is likely associated with the increased prevalence of obesity, the aging of the population and the decreased prevalence of *Helicobacter pylori* (Hp) infection. These different environmental factors interact with GERD pathogenesis in a potentially negative way. Esophago-gastric junction competence, esophageal clearance mechanisms and reflux causticity are involved in GERD pathophysiology. Obesity alters GERD pathogenesis by disrupting the EGJ and increasing intragastric pressure. Additionally, the number of transient lower esophageal sphincter relaxations is potentially increased in obese patients. The potential effect of obesity on esophageal peristalsis and the implication of impaired esophageal clearance in GERD pathogenesis are still to establish. Aging also plays an important role in GERD pathogenesis by decreasing lower esophageal sphincter pressure and impairing esophageal clearance. However a link between these abnormalities and an increased acid esophageal exposure has not yet been demonstrated in the elderly. The role of Helicobacter pylori and its eradication remain controversial. The type of Hp gastritis may explain the controversial effect. Hp with antral predominant gastritis is responsible for an increase gastric acid secretion and thus promotes GERD. On the opposite spectrum, Hp with diffuse gastritis induces a gastric atrophy and in this particular case, the Hp eradication may restore acid secretion and lead to a more caustic refluxate in patients with predisposing conditions for GERD. The association of GERD and the type of Hp gastritis remains to be confirmed.

Keywords

GERD; physiopathology; obesity; age; helicobacter pylori

Gastro-esophageal reflux is defined by the movement of gastric content into the esophagus. It could be associated with evocative symptoms such as heartburn or regurgitation or with extra-esophageal symptoms (cough, sore throat…). This phenomenon is physiologic, however, it becomes pathological when symptoms associated with reflux events impair a patient's quality of life or when they are responsible for esophageal (esophagitis, Barrett's mucosa…) or extra-esophageal lesions. Nevertheless, even if GERD impairs quality of life, it does not increase the long term mortality [1-2].

Commonly twice weekly reflux over several months is used to define Gastro-Esophageal Reflux Disease (GERD) as it is associated with impairment of quality of life [3]. Based on these criteria 10-20% of individuals in Western countries have pathological GERD [4-5].

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This is higher than what is observed in Asia (5-7%) [4, 6-8]. Different factors may explain the variable prevalence among the countries [9]. The understanding of heartburn is not the same in the different languages. For example there is no translation for the word heartburn in most Asian languages [10]. Cultural differences in diagnostic practices and in physician recognition modify GERD reporting among the population. Finally the lifestyle, the environmental factors and the genetic backgrounds may influence GERD variations among the various geographic areas.

GERD physiopathology is complex and involves an interplay between many different aggressive and defensive forces promoting or retarding reflux: esophago-gastric junction (EGJ) competence, esophageal clearance and acid secretion are involved in determining the amount of gastric content refluxed into the esophagus. The GERD epidemiological risk factors interplay with these mechanisms at many different levels.

Despite the geographical variations, the prevalence of GERD is also increasing all over the world. This increase is associated with an increased prevalence of obesity, an aging population and a decreased prevalence of *Helicobacter pylori* (*Hp*) infection. This suggests that these factors could play a role in GERD occurrence. Moreover they interact with the different GERD mechanisms.

The aims of this review are to explore the different mechanisms involved in GERD pathogenesis and to determine how environmental and lifestyle risk factors interact with these mechanisms.

How may environmental factors and lifestyle influence GERD occurrence?

GERD Pathogenesis

The pathophysiology of GERD focuses on an interaction between an incompetent antireflux barrier, a default of esophageal clearance and/or the causticity of the gastric reflux (Figure 1).

The esophago-gastric junction (EGJ)—The EGJ is synonymous with the antireflux barrier and is composed of the lower esophageal sphincter (LES), the crural diaphragm and the flap valve. An alteration of this anti-reflux barrier will promote opening of the EGJ; which is a prerequisite for reflux.

Transient LES relaxations (tLESRs) represents the main mechanism of GERD and these long duration LES relaxations are triggered by gastric distension, some food components (fat) or medications. Although the overall number of tLESRs is not increased in GERD, the number of acid reflux associated tLESRs is increased in GERD patients [11].

A hypotensive LES is also a favorable factor in promoting GERD symptoms and complications, such as esophagitis and stricture. Multiple studies have shown a relationship between severe erosive esophagitis and lower basal LES pressure [11-13].

Finally an anatomic disruption of the EGJ inclusive of, but not limited to hiatus hernia are also a major contributor to GERD occurrence [5, 14]. The flap valve formed by a musculomucosal fold created by the entry of the esophagus into the stomach along the lesser curvature could play a role in the EGJ competence [15-17].

The esophageal clearance—The efficacy of esophageal clearance depends on the vigor of esophageal peristalsis and the acid buffering property of saliva. An alteration of these

mechanisms leads to an increased contact time between noxious acid content and esophageal mucosa.

Ineffective esophageal motility is frequently encountered in GERD patients [18] and it is a risk factor for developing esophagitis [19]. In healthy volunteers and GERD patients, severe ineffective esophageal motility (>80% ineffective contractions) is also associated with prolonged clearance and acid exposure, especially in supine position [20-21].

Saliva contains bicarbonate that helps buffer the acidity of gastric juice during reflux events and increasing the volume of saliva secretion shortens esophageal acid clearance [22]. Epidermal growth factor is also present in saliva and may promote the healing mechanisms of esophageal mucosa [23-24].

The gastric content—The different components of the gastric refluxate are toxic for the esophageal mucosa. Acid is the main component and induces not only symptoms when it is in contact with esophageal mucosa but also esophageal ulcerations. The incidence of GERD is particularly high (around 80%) in patients with acid hypersecretion (with or without Zollinger-Ellison syndrome) [25].

The other components of gastric juice, pepsin but also bile acids and pancreatic enzymes are also harmful to esophageal epithelium [26-28]. Their toxicity is dependant on the background pH: pepsin is activated in an acidic environment; bile acids can penetrate through the cell membrane in a weakly acidic medium (pH 3-5) [29].

Lifestyle and Environmental risks for GERD

Obesity

The incidence of obesity in Western countries has dramatically increased [30] and this has occurred in concordance with an increase in the number of patients suffering from GERD [31] (Figure 2). Multiple epidemiological studies clearly demonstrate an association between obesity and GERD and physiologic investigations support a biologically plausible relationship between obesity and GERD.

Epidemiological data

Epidemiological studies point to obesity as a major risk factor for GERD in adults [32-33] and in children [34]. This association exists not only for the symptoms occurrence but also for the complications of GERD.

Different studies have shown an association between higher body mass index (BMI) and GERD [7, 35-38] and both obesity (BMI > 30 kg/m^2) and overweight (BMI 25-30 kg/m^2) are associated with GERD [1, 39-40]. Studies from Asia utilize a different cut off to define obesity (BMI > 25 kg/m^2) due to different fat composition according to the race. In these studies, BMI is also a risk factor for GERD [7, 41-42]. Interestingly, in a prospective study in Korea a BMI > 25 was associated with erosive esophagitis whereas a BMI < 23 was associated with non erosive reflux disease [43]. A meta-analysis underlines the association between Barrett's esophagus and being overweight (odds ratio (OR) 1.33, 95% confidence intervals (CI) 1.07 to 1.64, p=0.01) and obese (OR 1.70, 95% CI 1.36 to 2.12, p<0.01) [44].

The effects of BMI on GERD occurrence seems to be independent of total caloric intake, dietary intake of fiber, fruits and vegetables, or other macro or micronutrients [33]. Weight gain facilitates also GERD occurrence [42] and GERD symptoms may improve after weight loss [45] and bariatric surgery [46-47].

Controversies exist concerning the association between hiatus hernia (HH), GERD and obesity. Some studies reveal a positive association [42, 48]. El Serag noted that obesity and HH were independent risk factors for severe esophagitis [49]. Lee *et al* confirmed that BMI and HH were independent risk factors for erosive esophagitis [50]. On the contrary, Wu failed to find an association between BMI and HH [51].

Inter-relation between obesity and GERD mechanisms

Obesity may modify EGJ morphology and function. First, obesity generates a mechanical disruption of EGJ by promoting an axial separation between the LES and the extrinsic crural diaphragm [52]. LES incompetence has also been observed in obese patients [46, 53-54] and among morbidly obese patients a higher esophageal acid exposure was significantly associated with a lower LES pressure [55].

The distribution of fat may also play a role in GERD pathogenesis as GERD is also associated with an increased waist circumference [14, 33, 56]. Moreover a higher mean visceral fat area evaluated by computed tomography was found in patients with erosive esophagitis compared to controls [50]. It is possible that adipose tissue surrounding the stomach creates an extrinsic gastric compression which in turn leads to increasing intra gastric pressures and therefore a permissive gastro-esophageal pressure gradient. Finally an increasing number of tLESRs in obese patients has been observed in 2 studies [57-58]. Wu *et al* showed that, obese and overweight patients had an increase of tLESR number compared to patients with normal weight during the post-prandial period [57]. The proportion of tLESRs with acid reflux was also higher in overweight and obese patients as well as the gastro-esophageal pressure gradient. Schneider *et al* also noted a significantly increased frequency of tLESRs in obese patients compared to healthy volunteers, but not compared to GERD patients [58]. Theoretically, abdominal obesity could lead to more intense stimulation of both stretch and tension mechanoreceptors in the proximal stomach which will in turn provoke more post-prandial tLESRs.

An alteration of esophageal clearance is also suspected in obese patients. Esophageal motility disorders are encountered in 25 to 60% of obese patients [54, 59-61] and impaired bolus transit is more frequent in morbidly obese GERD patients than in GERD patients with normal weight [62]. However the prevalence of defective LES and abnormal peristalsis among obese patients with GERD is low in comparison with non obese patients with GERD [47, 54, 63-64]. This could reflect a physiologic compensatory response to increased gastric pressure.

Hormonal status could interplay with GERD and obesity [33]. Indeed upper GI symptoms and increased weight were found more frequently in perimenopausal and menopausal women than in premenopausal women [65]. In a large cohort of menopausal women receiving estrogen alone, estrogen plus progestin or placebo, Zheng et al. observed a trend toward a higher incidence of symptomatic GERD after one year of estrogen therapy whereas the combined hormonal therapy did not affect GERD occurrence [45]. In this study no association between BMI and hormonal treatment was observed.

Age

Studies support that the incidence of GERD increases with age. In a systematic review of the UK General Practice Research Database, El Serag noted that the incidence of GERD was highest in the 60-69 year range and decreased slightly thereafter [1]. This association with age was also found in studies from Asia [6]. Older patients, however, often complain of less severe or frequent heartburn than their younger cohorts [66] but the elderly have more complications including esophagitis [67], peptic strictures and Barrett's esophagus [68]. The

existence of prolonged acid exposure over many years could explain the prevalence of complicated GERD and an alteration of the sensorimotor response is also suspected to play a role in this blunted perception in older patients [69].

Higher frequency of hiatal hernia [67], impaired esophageal motility [70-71], and decreased saliva volume and bicarbonate concentration are involved in GERD occurrence in the elderly. The high prevalence of hiatal hernia may be related to the presence of kyphosis in elderly people [72]. Additionally, the use of medications that may interfere with LES pressure and esophageal peristalsis may also explain the higher frequency of GERD in elderly.

Helicobacter pylori

Since the discovery of the role of *Helicobacter pylori* (*Hp*) in the pathogenesis in ulcer disease, multiple studies have focused on the role of *Hp* in different gastrointestinal diseases. While the incidence of *Hp* decreased, the percentage of patients suffering from GERD has increased. Conflicting results exist concerning the influence of *Helicobacter pylori* and its eradication on GERD symptoms and complications.

In a meta-analysis of 20 case controls studies, the average prevalence of *Hp* infection in patients with GERD was 38.2% (95% CI 20.0-82.0%) compared to 49.5% (95% CI 29.0-75.6%) in non GERD patients (OR 0.58) [73]. In a systematic review of studies and trials extending up to September 2003, the same author concluded that successful eradication of *Hp* in patients with duodenal ulcer disease did not increase the risk of provoking *de novo* esophagitis [74]. Moreover there was a trend towards diminished prevalence of heartburn following eradication, successful or failed. The absence of an association between *Hp* eradication and development of new cases of GERD in dyspeptic patients was also observed in a meta-analysis recently published [75]. However, in the cohort studies for the subgroup of patients with peptic ulcer disease the odds ratio for GERD in *Hp* eradicated group versus persistent *Hp* was 2.04 (1.08-3.85, p=0.03). These heterogeneous results could be explained by the choice of control group (patients addressed for endoscopy with potential link between dyspepsia and *Hp*), the tools to diagnose *Hp* infection (serology, biopsies, urease test…) and GERD (heartburn score, pH studies, endoscopy).

Another possible explanation for the heterogeneous results regarding the relationship between GERD and Hp may be related to the variable effect of Hp on acid gastric. Helicobacter pylori infection has a major effect on somatostatin secreting D-cells in the gastric antrum. Thus the feedback inhibition by luminal acid on gastrin release is interrupted [76-77]. The gastrin levels are higher in subjects infected by Hp and do not exhibit normal feedback [78]. This lack of inhibition may be responsible for the increased acid secretion found in patients with Hp-induced duodenal ulcer or predominant antral gastritis. In the case of Hp-induced corpus gastritis, the gastrin levels are also increased, however, the local inflammation associated with increased levels of cytokines alters the parietal cell function [79]. This leads to hypochlorhydria and gastric atrophy. Reversal of Hp-induced corpus gastritis has the potential to increase gastric acid secretion [80]. Based on these effects, eradicating Hp in duodenal ulcer predominant antral gastritis patients may improve GERD symptoms whereas eradication in patients with predominant corpus gastritis may worsen GERD. Thus absence of gastric atrophy (diagnosed by a pepsinogen I/II ratio greater than 6) was found to be associated with a higher incidence of newly-developed GERD as well as negative Hp antibodies in Japanese population [81].

Finally some differences could be explained by the *Hp* strains and the genetic backgrounds of the patients. In a study conducted in Malaysia, an increased prevalence of Hp and Cag A

positive strains was associated with reduced severity of GERD in Indian patients but not in Malaysian patients or Chinese patients [82]. The Indian patients had a higher prevalence of corpus atrophy and were more likely HLAB27 positive suggesting a higher predisposition to reduced acid secretion.

Other related GERD factors

Eating and lifestyle—Eating habits and lifestyle issues may interact with key factors involved in GERD physiopathology and thus, they are commonly implicated as risk factors for GERD occurrence.

Eating habits: Different foods may influence the occurrence of reflux events. An Italian study revealed less esophageal reflux events detected by pH-impedance monitoring in healthy volunteers [83] than what it was previously observed in American and Europeans cohorts [84-85]. One explanation given by the authors was the consumption of a Mediterranean diet (pasta or rice, meat or fish, vegetables and fruits). Foods listed in table 1 are associated with GERD through their presumed effects on reducing LES pressure and slowing gastric emptying.

High dietary fat intake is associated with an increased risk of GERD and erosive esophagitis [86]. In GERD patients, the consumption of carbonated soft drink is a predictor of heartburn during sleep [38]. Coffee may also be associated with an increase in heartburn occurrence [87]. However in a Norwegian case control study a negative association was found between GERD and coffee (OR 0.5 (95% CI 0.4-0.6) among subjects who drank 4-7 cups per day compared to those who didn't drink coffee) [88]. In the same study, consumption of dietary fibers was found to be a protective factor whereas extra table salt use was considered a risk factor.

Alcohol consumption: Alcohol consumption is a risk factor for GERD symptoms and complications [14, 35, 89-90]. Alcohol facilitates hydrogen ion penetration into the esophageal mucosa [91] and thus increase the risk of mucosal injuries. It can also decrease LES pressure and esophageal motility [92-93] resulting in an alteration of esophageal clearance [94]. In a study including 463 Japanese males, the OR for esophagitis was 1.88 in moderate drinkers (25 to 50 g alcohol per day) (p=0.04) and 1.99 in heavy drinkers (more than 50 g alcohol per day) (p<0.01). The risk to develop Barrett's esophagus was also shown to be elevated in heavy drinkers (OR=1.91, p<0.01). However, in this study age and smoking could be confounding factors since heavy drinkers were older and more likely smokers than the other subjects included. In an Irish case-control study, only binge drinking and high liquor intake were associated with esophagitis (2 fold increase risk) while wine consumption tended to reduce the risk of reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma.

Smoking: Smoking increases the risk of GERD occurrence [14, 35, 37, 50, 88, 90, 95]. In a Norwegian case control study, the odds ratio for GERD symptoms was 1.7 (95% CI 1.5 to 1.9) among people who had smoked daily for more than 20 years compared with non-smokers [88]. Smoking reduces the LES pressure and then promotes the reflux of gastric content into the esophagus [96]. Moreover it may diminish salivary base secretion and thus impair acid esophageal clearance [97].

Physical exercise: Physical exercise has been found to be a protective factor against reflux [88]. However esophageal acid exposure increases significantly in healthy volunteers and GERD patients during the exercise periods compared to the non exercise periods [17]. The intensity of exercise-induced reflux was correlated with the EGJ morphology in this study

and thus, the integrity of the EGJ may be a key protective factor in preventing strain-induced reflux during exercise.

Medications—Table 2 summarizes different medications that may interfere with the EGJ function. These medications have been reported to promote GERD occurrence [81, 98]. Unfortunately, well done studies are lacking to truly assess the role on the different medications on GERD occurrence and controversy data exist. Some confounding factors limit the interpretation of the epidemiologic studies that underlies the relationship between medication and GERD occurrence. Thus, the association might be drug related or a result of the underlying condition. In case-control studies, asthma medication use was associated with Barrett's esophagus [99] and esophageal adenocarcinoma [100]. The use of other medications known to have an effect on LES pressure (nitrates, calcium channel blockers , benzodiazepines) was not associated with Barrett's mucosa or esophageal adenocarcinoma occurrence. Asthma has also been reported to be associated with GERD [1] and it is difficult to separate the role of the underlying condition from the role of the medication. Moreover, a randomized study focusing on the effect of theophylline failed to find any effect on GERD occurrence [101].

A case-control study focusing on the potential role of tricyclic antidepressants on the occurrence of reflux esophagitis revealed that only clomipramine was associated with esophagitis [102]. NSAIDs are also associated with GERD [35-37, 90, 103] and it is postulated that they act by reducing the protective mechanisms against acid, however, they should also be considered to be an increased risk factor for pill esophagitis.

Underlying conditions—The association of GERD with other health conditions is frequent and typically is associated with some abnormality in esophageal or gastric motility [104].

Diabetes mellitus could be associated with GERD occurrence [105], however, different confounding factors could exist such as the BMI [106]. One Australian study noted that diabetes mellitus and high blood pressure were associated with GERD but were not independent risk factors while high cholesterol was independently associated with GERD [95]. A study reported a higher prevalence of GERD in diabetic patients with neuropathy than in those without [107]. And it is possible that the neuropathy associated with diabetes may facilitate reflux by delaying gastric emptying or impairing esophageal motility.

Cardiovascular diseases are also associated with GERD. In a case control study based on a large Norwegian health survey conducted in 1995-97, a positive association was noted between GERD and angina pectoris (OR 1.9, 95% CI 1.6-2.2) [108].

Finally, an interaction exists between pulmonary disease and GERD. For example chronic pulmonary diseases and asthma were associated with new GERD diagnosis in a study using the UK General Practice Research Database [1]. GERD may also be one of the contributing factors of interstitial lung disease in patients with scleroderma [109-111].

Genetic backgrounds—Data suggest that genetic background could be associated with GERD symptoms and complications occurrence. Some polymorphisms of interleukin-1gene (*IL-1B*) and *IL-1RN* (gene coding for an interleukin-1 antagonist receptor) are associated with GERD. Thus the *IL-1B*-511 CC genotype and C allele are associated with higher risk of GERD than the TT genotype (OR 2.0, 95% CI 1.12-3.57, p=0.01). In contrast, the *IL-1B*-511*T/*IL-1RN*-*1haplotype is associated with a lower risk of GERD particularly among patients with *Hp*infection [112]. This haplotype is associated with higher gastric

mucosal IL-1β levels and inflammatory response. This status may decrease the level of acid secretion and explain the protective effect on GERD occurrence.

The incidence of GERD complications could differ with race. Wang *et al* used the Clinical Outcomes Research Initiative database to evaluate ethnic trends in esophagitis and Barrett's esophagus among various racial groups in USA [113]. This database included 280,075 patients with upper endoscopy from 2000 to 2005. Hispanics were found to be more likely to have esophagitis (prevalence 19.6% in Hispanics, 17.3% in Whites, 15.8% in Blacks and 9.5% in Asian/Pacific Islanders) whereas Whites were more likely to have Barrett's esophagus (prevalence 5% in Whites, 2.9% in Hispanics, 1.8% in Asian/Pacific Islanders and 1.5% in Blacks). Although these differences are statistically significant, they are marginal and should not alter treatment or management strategies.

Conclusion

Gastro-esophageal reflux disease is frequently encountered in Western countries; however, its prevalence is increasing all over the world. Its complex physiopathology lays the foundation for numerous interactions with environmental and lifestyle risk factors. Obesity is one of the main risk factors and interacts not only with esophago-gastric junction integrity but also with the mechanisms of esophageal clearance and promoting a preferential pressure gradient. Aging also plays an important role by impairing LES function, esophageal peristalsis and saliva secretion. The role of Helicobacter pylori and its eradication remain controversial and clarifications are required before global management strategies can be supported.

Acknowledgments

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Abbreviations

GERD	Gastro Esophageal Reflux Disease
EGJ	Esophago-Gastric Junction
Hp	*Helicobacter pylori*
LES	Lower Esophageal Sphincter
tLESR	transient Lower Esophageal Sphincter Relaxation
BMI	Body Mass Index
OR	Odds Ratio
CI	Confidence Intervals
HH	Hiatus Hernia

Practice Points

- GERD prevalence is increasing worldwide

- Obesity, age, absence of Helicobacter pylori infection are the main risk factor for GERD

- The different risk factors alter esophago-gastric junction integrity, esophageal clearance and/or enhance acid gastric secretion

Research agenda

- The effects of obesity on esophago-gastric junction and esophageal peristalsis have to be linked with increased acid esophageal exposure

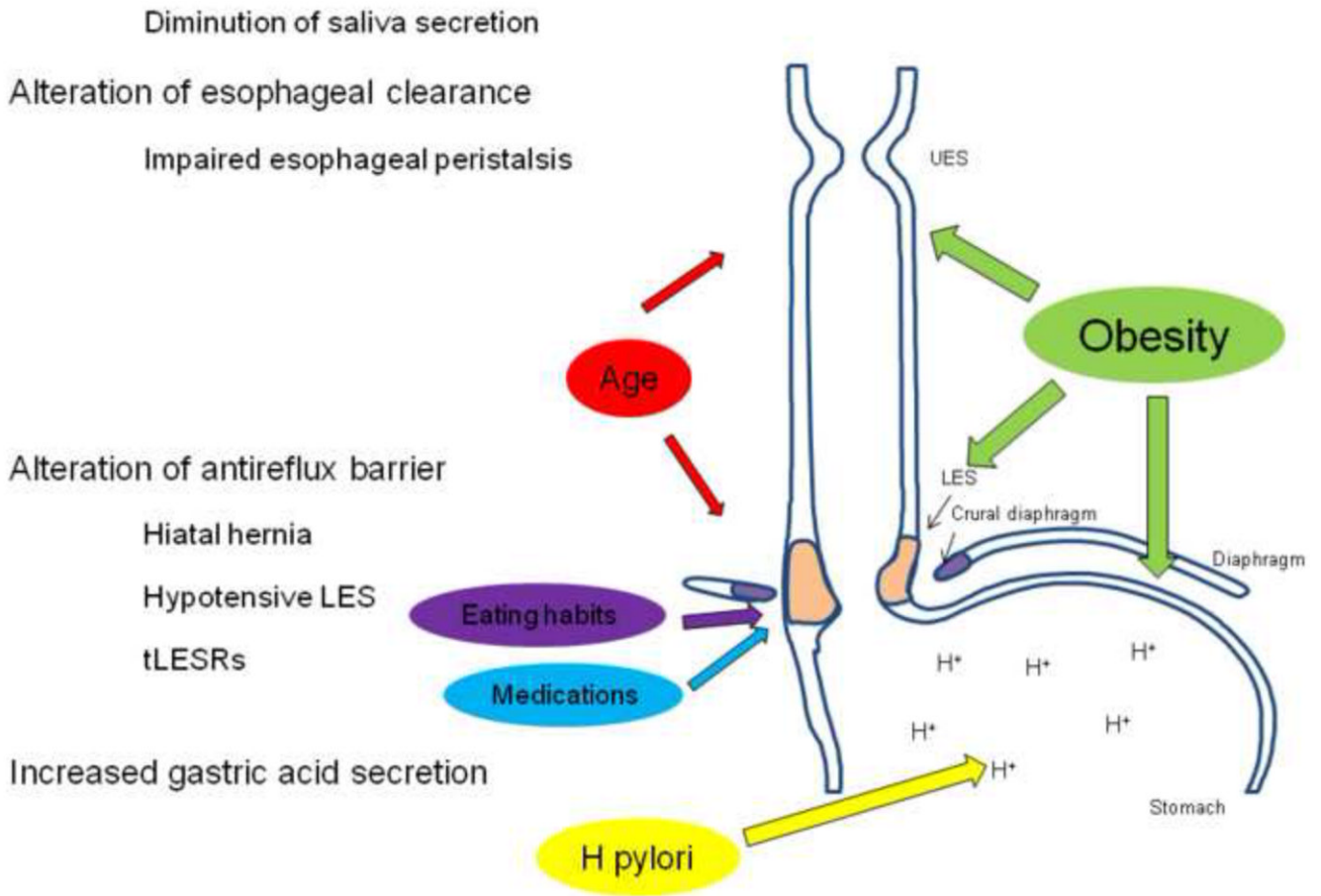- The role of Helicobacter pylori and its eradication in GERD occurrence need to be clarified

Figure 1.
The environmental factors interact with the different mechanisms involved in GERD pathogenesis. Obesity alters esophago-gastric junction (EGJ) integrity, esophageal peristalsis and increases intra-gastric pressure. Age modifies EGJ integrity and impairs esophageal clearance by altering esophageal peristalsis and decreasing saliva secretion. Eating habits and medications decrease lower esophageal sphincter pressure (LES), increase the number of transient LES relaxations and delay gastric emptying. Helicobacter pylori modifies acid gastric secretion.
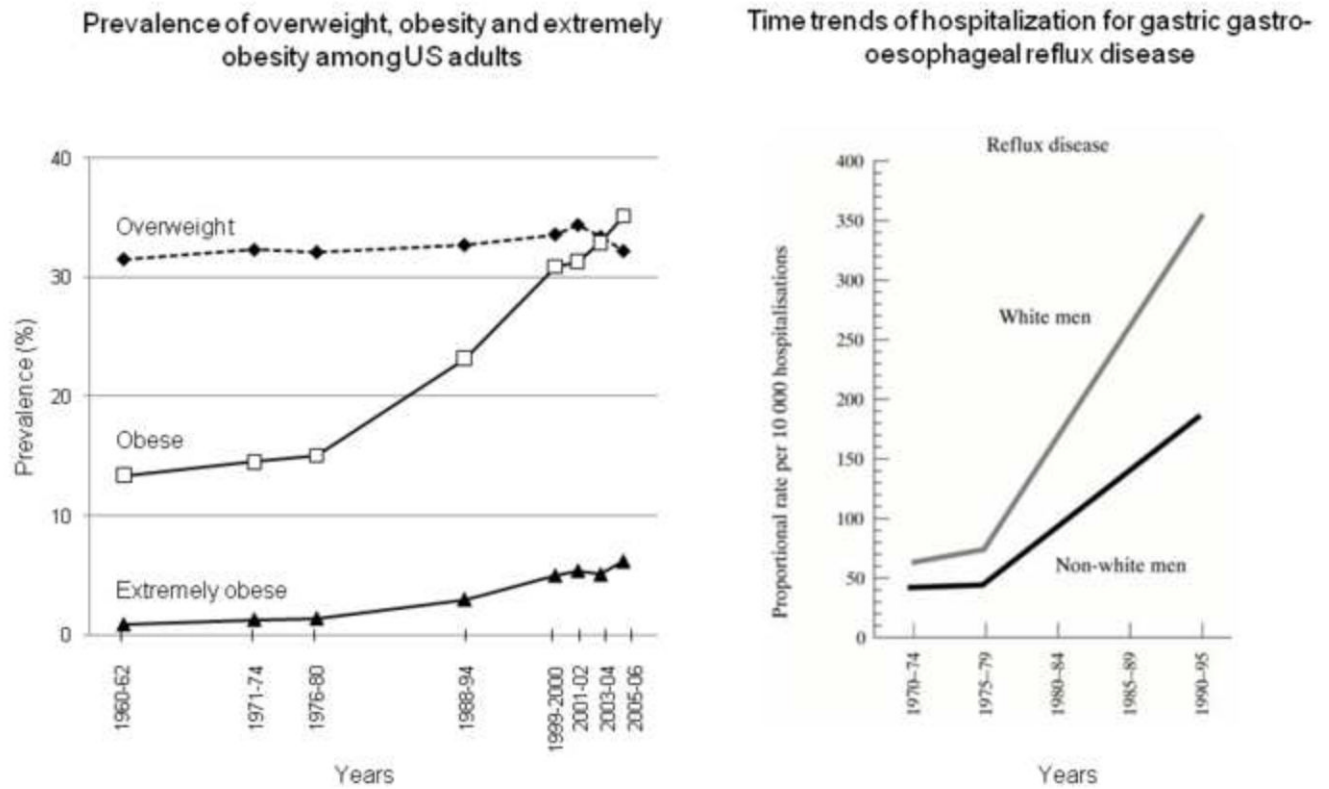
Prevalence of overweight, obesity and extremely obesity among US adults

Time trends of hospitalization for gastric gastro-oesophageal reflux disease

Figure 2.
Increased prevalence of Obesity (left panel) and GERD (right panel) among US adults. The age-adjusted prevalence of overweight (BMI 25-30 kg/m^2, black diamond, dashed line), obesity (BMI > 30 kg/m^2, white square, black line) and extremely obesity (BMI > 40 kg/m^2, black triangle, black line) increased from 1960 to 2006. This survey includes subjects aged from 20 to 74 years (source: Department of Health and Human Services. Centers for Disease Control and Prevention.http://www.cdc.gov/nchs/data/hestat/overweight/overweight_adult.htm [30]). The time trends of hospitalization for gastro-esophageal reflux disease also increased in the US Department of Vetrans Affairs from 1970 to 1995 [31].

Table 1

Foods and effect on LES and gastric emptying

Effects	Foods
Decrease lower esophageal sphincter pressure	Fat food
	Alcohol
	Chocolate
	Peppermint
Slower gastric emptying	Fat food

Table 2

Medications and effect on esophago-gastric junction functions

Effects	Medications
Decrease lower esophageal sphincter pressure	Nitrates
	Calcium channel blockers
	Anticholinergics
	β adrenergic agonists
	Theophylline
	Morphine
	Benzodiazepins
Increase transient lower esophageal sphincter	Sumatriptan