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The Complex Interplay of Pathophysiological, Metabolic, and Behavioral Risk Factors in Gastroesophageal Reflux Disease (GERD) : A Literature Review

Yusuf Akmal Karim[1], Linda Dewanti[2]

[1]Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[2]Department of Public Health Sciences, Faculty of Medicine, Airlangga University Surabaya

E-mail: yusuf.akmal.karim-2022@fk.unair.ac.id; linda-d@fk.unair.ac.id

*Corresponding author details: Linda Dewanti; linda-d@fk.unair.ac.id

ABSTRACT

Gastroesophageal reflux disease (GERD) is a multifactorial gastrointestinal disorder characterized by heartburn, regurgitation, and potential complications such as esophagitis, Barrett's esophagus, and esophageal adenocarcinoma, arising from a complex interplay of metabolic, structural, behavioral, lifestyle, psychological, and socioeconomic factors. Obesity, particularly central or visceral adiposity, and components of metabolic syndrome, including insulin resistance, dyslipidemia, and abdominal fat, are strongly associated with GERD risk, with Mendelian randomization studies supporting a causal relationship. Anatomical anomalies, such as hiatal hernia, and genetic predisposition further increase susceptibility by impairing lower esophageal sphincter function, delaying gastric emptying, and compromising mucosal defenses. Behavioral and lifestyle factors, including irregular meal patterns, high-fat or processed diets, late-night eating, physical inactivity, smoking, alcohol use, and poor sleep, exacerbate reflux and elevate disease burden, while psychological stress, anxiety, and depression influence GERD via the gut-brain and hypothalamic-pituitary-adrenal axes, creating a bidirectional relationship between mental health and reflux. Socioeconomic status independently affects prevalence and outcomes, with lower income, education, and neighborhood deprivation linked to higher risk, reduced healthcare access, and increased complications. Understanding these interrelated determinants underscores the importance of comprehensive, multidisciplinary approaches that integrate metabolic, anatomical, behavioral, psychological, and socioeconomic considerations, enabling targeted interventions to prevent disease, optimize symptom management, reduce long-term complications, and enhance quality of life for individuals with GERD.

Keywords: gastroesophageal reflux disease; obesity; metabolic syndrome; lifestyle factors; gut-brain axis; socioeconomic status

INTRODUCTION

Heartburn and regurgitation are common symptoms of gastroesophageal reflux disease (GERD), a multifactorial gastrointestinal disorder that can lead to esophagitis, Barrett's esophagus, and esophageal adenocarcinoma [3,5]. GERD has a significant worldwide impact, with regional variations in prevalence rates and an increasing incidence seen in both Western and Asian populations. This is mostly due to food and lifestyle changes, as well as rising rates of obesity and metabolic syndrome [4,3,7]. Anatomical, physiological, metabolic, and behavioral variables interact in the complicated pathophysiology of GERD. Lower esophageal sphincter (LES) dysfunction, temporary LES relaxations, decreased esophageal motility, delayed gastric emptying, and structural changes such as hiatal hernia are important pathophysiological causes [5,6,3]. Gastric acid and other refluxate components can harm the esophageal mucosa as a result of these changes, which impair the barrier function of the esophagogastric junction [6,3].

GERD risk has been found to be significantly influenced by metabolic variables, especially obesity and elements of the metabolic syndrome (such as insulin resistance, dyslipidemia, and abdominal fat). Metabolic disorders can worsen esophageal motility and mucosal defenses, and obesity raises intra-abdominal pressure and encourages LES dysfunction [4,7,9]. Recent genetic and epidemiological studies underscore the causal role of adiposity, diabetes, and lipid abnormalities in GERD development [1,7].

The development and course of GERD are also significantly influenced by behavioral and lifestyle

factors, such as eating habits, meal scheduling, physical inactivity, smoking, alcohol intake, and psychological stress [2,12,15,8]. Healthy eating habits and frequent exercise seem protective against GERD, but irregular eating patterns, high-fat diets, and late-night meals are consistently linked to an elevated risk [2,10,8].

Given the heterogeneity of GERD's clinical presentation and the diversity of its risk factors, a comprehensive understanding of the complex interactions among pathophysiological, metabolic, and behavioral determinants is essential for effective prevention, diagnosis, and management. This literature review aims to synthesize current evidence on these interrelated factors, providing a foundation for personalized and multidisciplinary approaches to GERD care.

REVIEW CONTENT

2.1 Metabolic and Structural Risk Factors

(1) *Obesity and Fat Distribution*

Obesity is a powerful, independent, and well-established risk factor for GERD, as both general and central (abdominal/visceral) adiposity dramatically raise the risk. Increases in body mass, whether assessed by body mass index (BMI), waist circumference, or other adiposity indices, are directly associated with increased susceptibility to GERD, according to a wealth of epidemiological and genetic evidence. This causal relationship is further supported by Mendelian randomization analyses, which show that the relationship is biologically driven rather than just correlational, with each standard deviation increase in BMI raising the risk of GERD by about 50% [11,22,18]. Crucially, the distribution of fat is important. Reflux is made worse by the mechanical and metabolic effects of visceral or central adiposity, especially the buildup of fat inside the abdominal cavity. Central fat is more harmful than subcutaneous fat, as evidenced by the fact that even people who are not considered obese but have high visceral fat have a significantly higher risk of developing erosive esophagitis, increased acid exposure, and more frequent reflux symptoms. Mechanistically, visceral fat increases intra-abdominal pressure, which disrupts the normal function of the lower esophageal sphincter (LES), promotes transient LES relaxations, and facilitates the upward movement of gastric contents into the esophagus. This mechanical load may also impair gastric emptying and increase gastroesophageal pressure gradients, further amplifying reflux episodes [16,19,20]. The association persists regardless of metabolic health. Research demonstrates that metabolically healthy obesity (MHO), a phenotype defined by excess adiposity despite normal metabolic markers, still confers a significantly increased risk of GERD, suggesting that the adverse effects of adiposity extend beyond metabolic disturbances alone. Factors such as mechanical strain from increased abdominal fat mass, adipose-derived inflammatory mediators, hormonal dysregulation, and structural changes in thoracoabdominal anatomy collectively contribute to GERD development across diverse populations. These findings reinforce that adiposity itself, rather than metabolic dysfunction, is a key driver of GERD risk [19].

(2) *Metabolic Comorbidities*

Insulin resistance, low HDL cholesterol, hypertension, abdominal obesity, and hypertriglyceridemia are among the specific components of metabolic syndrome that are intimately linked to GERD. A dose-response association between metabolic dysfunction and reflux risk is shown by large-scale population studies that show a positive correlation between the number and presence of metabolic syndrome components and a steady rise in GERD prevalence [17,14,21]. Among the elements, hypertriglyceridemia and low HDL-C seem to have especially strong correlations with GERD, possibly due to mechanisms involving delayed gastric emptying, changes in gastrointestinal motility, and chronic systemic inflammation, which can increase exposure of the esophageal mucosa to acidic gastric contents [17,21]. Additionally, esophageal defense mechanisms, such as mucosal integrity and peristaltic function, may be compromised by metabolic diseases, rendering the esophagus more vulnerable to damage. Diabetes mellitus and insulin resistance are two conditions that worsen gastric dysmotility and decrease neuromuscular control of the lower esophageal sphincter, both of which raise the risk of GERD [11,22,25].

(3) *Genetic and Anatomical Factors*

Genetic predisposition has a major impact on GERD risk; estimations of heritability show that inherited variables account for about 31% of an individual's vulnerability to GERD [18,23]. Evidence from twin and family studies, which demonstrate a higher prevalence of GERD among first-degree relatives, supports this genetic contribution and suggests that both common and uncommon genetic variations contribute to disease vulnerability. Numerous risk loci linked to GERD, such as FOXF1, MHC, and CCND1, as well as particular genetic polymorphisms like IL-1β and CYP2C19, have been found by genome-wide association studies (GWAS). These polymorphisms are linked to the development of GERD as well as its progression and complications, such as erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma [13,31]. By altering esophageal mucosal defense, acid secretion, inflammatory responses, and drug metabolism, these genetic variants may impact the pathophysiology of GERD, changing a person's vulnerability and response to treatment [31,27].

2.2 Behavioral and Lifestyle Risk Factors

(1) *Diet*

Nutrition is a highly modifiable risk factor for GERD since dietary habits, meal composition, and timing of food consumption have a significant impact on GERD risk and symptom severity [29,26,30]. Increased GERD prevalence and more severe reflux symptoms have been repeatedly linked to consumption of high-fat, fried, spicy, salty, and highly processed meals as well as carbonated drinks, chocolate, citrus, and caffeinated beverages.

While hot foods and acidic drinks may irritate the esophageal mucosa and sensitize nociceptors, resulting in increased symptom perception, high-fat and processed meals can slow gastric emptying, increase gastric volume, and cause temporary relaxations of the lower esophageal sphincter (LES). On the other hand, diets like the Mediterranean or vegan diet, which are high in fruits, vegetables, whole grains, fiber, and plant-based meals, are associated with a decreased prevalence of GERD and milder symptoms [29,28,40]. The preventive benefits are multifactorial: antioxidants and bioactive substances have anti-inflammatory and mucosal-protective properties, while fiber enhances stomach emptying and lowers intra-abdominal pressure. On the other hand, regular alcohol drinking and excessive salt intake raise the risk of GERD by decreasing esophageal clearance, delaying stomach emptying, increasing gastric acid production, and affecting LES function [29, 28, 36]. Meal timing and quantity size are also important; late-night, large, or quick meals aggravate reflux, whereas frequent, smaller meals and avoiding triggers close to bedtime help lessen the frequency and intensity of symptoms [29,26,30,28,40].

(2) *Eating Habits*

Meal habits and eating behaviors have a significant impact on GERD; irregular eating patterns, fast eating, overeating, midnight snacking, and eating less than three hours before bed are all linked to an increased risk of reflux [29,28,38]. These actions can assist the retrograde passage of stomach contents into the esophagus by raising intra-abdominal pressure, delaying gastric emptying, and encouraging brief relaxations of the lower esophageal sphincter (LES). Furthermore, eating extremely hot foods can irritate the mucosa of the esophagus, and skipping breakfast can interfere with the regular rhythm of the stomach and worsen reflux later in the day, hence raising the risk of GERD [29,34]. On the other hand, the frequency and intensity of GERD symptoms can be considerably decreased by adopting organized and conscious eating practices. For reflux sufferers, maintaining regular meal times, eating slowly, and avoiding late-night eating promotes correct gastric emptying, stabilizes LES function, and lowers esophageal acid exposure, all of which improve symptom control and quality of life. A holistic approach to controlling GERD and reducing symptom load can be achieved by combining these behavioral techniques with dietary changes, such as avoiding high-fat or acidic foods [28,38,32].

(3) *Substance Use*

Smoking and alcohol use are well-known behavioral risk factors for GERD since they both directly increase acid exposure and decrease esophageal function. [29,26,28,33]. Alcohol can delay gastric emptying, lower esophageal sphincter (LES) pressure, and decrease esophageal motility, all of which promote the retrograde passage of stomach contents into the esophagus. The esophagus is particularly susceptible to damage from gastric reflux because smoking predominantly impairs LES function, esophageal acid clearance, and mucosal defense mechanisms. Higher levels of alcohol consumption and smoking are associated with more frequent and severe reflux episodes, and the risk and intensity of GERD symptoms are dose-dependent. Furthermore, it has been demonstrated that shisha or hookah usage and passive smoking raise the incidence of GERD, emphasizing that even indirect exposure to tobacco smoke can negatively impact esophageal function and worsen acid symptoms [33,37].

(4) *Activity and Sleep*

The risk of GERD and the intensity of its symptoms are significantly influenced by lifestyle choices and physical exercise. Physical inactivity is a major risk factor for reflux, even though regular moderate exercise, defined as at least 30 minutes, three times per week, has been demonstrated to be protective. Weight gain, elevated abdominal pressure, and decreased stomach motility are all consequences of sedentary activity that can exacerbate gastroesophageal reflux. Frequent exercise may lessen the frequency and severity of GERD symptoms by increasing overall gastrointestinal function, lowering intra-abdominal pressure, and improving esophageal clearance [29,35,33]. GERD is also strongly associated with postural habits and sleep patterns. Increased reflux episodes, especially nocturnal reflux, are linked to poor sleep quality, insufficient sleep duration, and late bedtimes. This can exacerbate mucosal damage and impair quality of life. By encouraging stomach emptying and reducing nocturnal reflux episodes, behavioral techniques, including walking after dinner and raising the head of the bed during sleep, can lower esophageal acid exposure and enhance symptom control [43,32]. In the therapy and prevention of GERD, regular exercise and good sleep, and posture practices are crucial non-pharmacological interventions [29,46,43,43,32].

2.3 Psychosocial Risk Factor

(1) *Stress and the Gut-Brain Axis*

Anxiety, depression, and long-term stress are psychological variables that are strongly linked to a higher risk of GERD and more severe symptoms. The gut-brain axis, a bidirectional communication network that links the enteric nervous system and the central nervous system and controls gastrointestinal motility, secretion, and visceral perception, plays a major role in mediating these effects. Activation of the hypothalamic-pituitary-adrenal- adrenal (HPA) axis in response to stress leads to elevated cortisol levels, which can alter gastrointestinal motility, enhance visceral hypersensitivity, and compromise the esophageal mucosal barrier, thereby facilitating reflux [41,39,45,42]. Stress can worsen GERD mechanistically by lowering the pressure of the lower esophageal sphincter (LES), increasing the release of gastric acid, and changing the gut flora. These changes may further compromise the function of the esophageal barrier and increase the perception of symptoms [41,44,45]. Probiotics, cognitive-behavioral therapy, stress reduction, and

other psychological therapies are examples of non-pharmacological treatments that target the gut-brain axis and have demonstrated encouraging results in lowering GERD symptoms and enhancing general gastrointestinal and mental health outcomes [41,47].

(2) *Socioeconomic Factors*

The prevalence and severity of GERD are influenced by socioeconomic status (SES), which is a significant and independent predictor of GERD risk. Household income, educational attainment, and neighborhood-level disadvantage are all included in SES and have been demonstrated to have both causative and independent effects on GERD. Evidence from Mendelian randomization studies indicates that lower income, greater socioeconomic deprivation, and lower educational levels are strongly associated with an increased risk of developing GERD [48,41,49]. Low SES is also associated with lower rates of endoscopic screening, delayed diagnosis, and restricted access to healthcare, all of which raise the risk of problems such as esophageal cancer and Barrett's esophagus [35]. The risk and severity of GERD may be increased in people from lower socioeconomic backgrounds because they may find it difficult to adopt healthy lifestyle habits, get timely medical attention, and follow long-term management plans. These findings underscore that GERD prevalence, symptom burden, and adverse outcomes are significantly shaped by socioeconomic inequalities, highlighting the need for targeted public health interventions and equitable healthcare access to reduce disease burden [4,1].

CONCLUSION

A complex interaction of metabolic, structural, behavioral, lifestyle, psychological, and socioeconomic factors can cause gastroesophageal reflux disease (GERD). Mendelian randomization studies show a causal relationship between increased GERD risk and obesity, especially central or visceral adiposity, and metabolic syndrome components such as insulin resistance, dyslipidemia, and abdominal fat. Anatomical anomalies, such as a hiatal hernia, and genetic predisposition also increase vulnerability, while behavioral factors, including poor sleep habits, smoking, alcohol consumption, irregular eating patterns, nutrition, and physical inactivity, intensify symptoms. Increased acid exposure and reflux-related problems result from these factors' combined disruption of lower esophageal sphincter function, delay of stomach emptying, elevation of intra-abdominal pressure, and impairment of esophageal mucosal defenses.

There is a reciprocal association between mental health and reflux, as psychological stress, worry, and depression exacerbate GERD symptoms through the gut-brain axis and HPA activation. GERD prevalence and outcomes are independently influenced by socioeconomic position; poorer income, education, and neighborhood disadvantage are associated with higher risk, less access to care, and more problems such as esophageal cancer and Barrett's esophagus. Comprehensive management of GERD, therefore, requires an integrated approach that addresses metabolic health, anatomical factors, dietary and lifestyle behaviors, mental well-being, and socioeconomic determinants. By targeting these interconnected factors through multidisciplinary strategies, prevention, symptom control, and long-term complication reduction can be optimized, supporting personalized care and improved quality of life for patients.

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