

Shift Work and the Risk of Peptic Ulcer: A Systematic Review

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Abstract

Background: Recent studies show that the prevalence of gastrointestinal problems among shift workers is much higher than that of day workers. The present study was conducted to summarize the findings of previous related studies regarding shift work and peptic ulcers.

Methods: This is a systematic review study in which observational studies with English full text were included. Three international databases including PubMed, Web of Science (Clarivate analytics) and Scopus were searched to find relevant articles. Searches were done on August 04, 2023. Related studies were identified, and then the required data were extracted and qualitatively synthesized.

Results: The total number of potentially eligible articles retrieved was 73. Fifty-three titles, abstracts, and full text remained for further screening after the removal of duplicate records. Of these, 45 did not meet the inclusion criteria; finally, 8 articles were selected for qualitative synthesis. Of the eight included studies, five revealed a significant positive association between shift work and peptic ulcer. The difference in peptic ulcer prevalence was more than twice as high between shift workers and daytime workers in some studies.

Conclusion: This systematic review identified a higher incidence of peptic ulcers among shift workers than day workers. It is necessary to provide a counseling system such as anti-inflammatory dietary recommendations, modify food habits, highly support the job, and modify work structures to improve coping skills that may weaken the peptic ulcer disease prevalence among shift workers.

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Introduction

Shift work is defined as working at unusual times of the day, which is expanding due to the need for more production nowadays.¹ Shift work is the performance of duties outside the normal daily working hours, i.e., the hours between 7 am and 6 pm, which is common in industry. In developed countries, production and service sectors rely on shift work.² Shift work is known as a harmful occupational factor that can cause adverse effects by disrupting the biological rhythms, especially

the circadian rhythm and its effect on hormone secretion and regulation.^{3,4}

Studies indicate that shift work has various complications such as sleep disorders, digestive diseases and complications, cardiovascular diseases, personal, family and social problems, high blood pressure, diabetes, and cancer risk.⁴⁻⁶ Recent studies show that the prevalence of gastrointestinal problems among shift workers is much higher than that of day workers.⁷⁻⁹ Rotating shift workers are likely to vary the timing, frequency, and content of their

meals. Gastrointestinal dysfunction is more common among rotating shift workers than day workers. For example, constipation due to change in bowel habits or functional indigestion, the symptoms of which include upper abdominal pain, abdominal bloating, loss of appetite, nausea and vomiting, and peptic ulcers.^{4,10}

After waking up, the motility of the digestive system increases and stimulates the need for stool. However, long shift work often disrupts these physiological rhythms, which strongly affects the biological clock and is associated with intestinal incompatibility, resulting in unpleasant symptoms such as diarrhea, bloating, constipation, and abdominal pain.^{3,11} On the other hand, the tendency toward unhealthy lifestyle habits are more common in shift workers compared to day workers. Shift work is associated with higher alcohol consumption, inadequate sleep, and smoking.¹² In addition, shift work can change the pattern of food consumption and is related to low diet quality, irregular eating patterns, and delayed meal timing.¹³⁻¹⁵

The prevalence of gastrointestinal symptoms is widespread in the world and has economic, social, and psychological consequences; in the United States, 11% of the population has chronic gastrointestinal disease, and its prevalence reaches 35% in people over 65 years of age.^{16,17}

Irritable bowel syndrome (IBS), peptic ulcers, constipation, and indigestion were the most common gastrointestinal problems suffered by rotating shift workers.¹⁸ The impact of rotating shift work on the health of workers has been the focus of researchers in recent years.^{14,19} Gastrointestinal problems likely contribute to decreased levels of alertness and increased irritability, which have previously been shown to negatively affect the behavior of shift workers.²⁰ According to the contradictory findings, the present study was conducted to perform a systematic review to summarize the findings of related studies regarding shift work and the risk of peptic ulcer.

Methods

Study Design

This systematic review study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This study retrieved and reviewed articles related to shift work and peptic ulcer from international databases using relevant keywords.

Eligibility Criteria

The inclusion criteria included observational studies (cross-sectional, case-control, and cohort studies) as well as articles with English full text. The exclusion criteria included articles other than original articles (letter to the editor, commentary, etc.) and lack of access to the full text of the article. The time limit

was not applied in searching articles.

Information Sources

To find relevant articles, we searched three international databases including PubMed, Web of Science (Clarivate Analytics), and Scopus. All the studies were done until August 04, 2023. To find more relevant articles, we manually checked Google Scholar as well as the reference list of the articles entered in the systematic review.

Search Strategy

The previously mentioned databases using various and relevant keywords were searched to find the articles. The keywords included “Peptic Ulcer”[Mesh], “Peptic Ulcer”[tw], “gastroduodenal ulcer”[tw], “Marginal Ulcer”[tw], “peptic Ulcers”[tw], “Shift Work Schedule”[Mesh], “Shift Work Schedule”[tw], “Night Shift Work”[tw], “Rotating Shift Work”[tw], and “Irregular Work”[tw]. Different tags such as text word (tw) and Medical Subject Heading (MeSH) were used in search.

Selection Process

The retrieved articles were first entered into the Endnote software. Then, duplicate articles were removed, and in the next step, the titles and abstracts of the remaining articles were screened and irrelevant articles were removed. Then, the full text of the remaining articles was screened and related articles were included in the systematic review. Two authors independently did all these steps.

Data Collection Process and Data Items

The extracted variables included the name of the first author, year of article publication, study design, study population, exposure (job characteristics), diagnostic methods, confounding control, and the main results. All these steps were done by two authors independently and disagreements between the authors were solved by discussion with the third author.

Risk of Bias Assessment

To check the methodological risk of bias, Newcastle-Ottawa scale was used, and the included studies were categorized into three groups: low, moderate, and high-risk studies.

Results

The process of study selection is summarized in Figure 1 as a flowchart. The total number of potentially eligible articles retrieved was 73. Fifty-three titles, abstracts, and full text remained for further screening after the removal of duplicate records. Of them, 45 did not meet the inclusion criteria, so they were excluded; finally, 8 articles were selected for qualitative synthesis (Table 1).

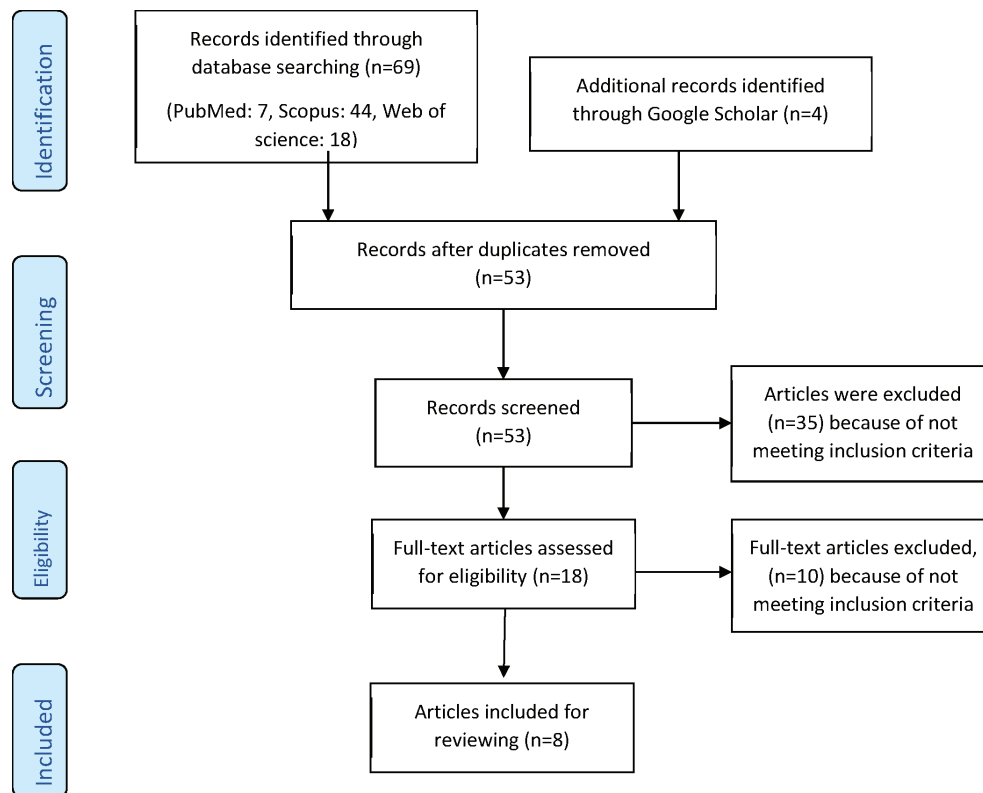


Figure 1: Flow diagram of the literature search for studies included in the systematic review

Of the 8 included studies, 5 revealed a significant positive association between shift work and peptic ulcer.

A cohort study consisted of 122116 men in Denmark in different occupations in which at least one fifth did not experience daytime work, and a reference cohort of 593281 employers with exclusively daytime work was followed after discharge with a gastric ulcer as the main diagnosis. A standardized hospitalization ratio (SHR) for gastric ulcers was calculated among different groups of workers. Increased risk of gastric ulcer was observed in various forms of non-day work. A significant SHR of 130 (90% CI: 118–142) was found for all individuals in groups with non-daytime work.²¹

Zober et al. investigated the prevalence of helicobacter pylori infection in a large company and its relationship with gastrointestinal tract complaints among day and shift workers. The results showed that positive immunoglobulin G serology was considerably more prevalent among shift workers than day workers (46.1% vs 34.6%). The two studied groups did not show any significant difference in terms of ulcer disease occurrence.²²

In a study done by Pietroiusti et al., among participants with similar sex, age, family history, and additional risk factors for peptic ulcers, such as helicobacter pylori infection, the risk of duodenal ulcer development was higher among shift workers than day workers (OR=3.92, 95% CI 2.13-7.21). Additionally, the likelihood of duodenal ulcer development was higher among shift workers who worked more than

seven nights/month compared to workers who worked fewer nights/month (OR=3.13, 95% CI 1.14-8.54).²³

In another study to investigate sleep disorders with the etiology of peptic ulcer, the prevalence of this disease in day and shift workers in banks, factories, or schools was investigated by photographing the upper part of the digestive tract. The results showed that the prevalence of gastric and duodenum ulcers in shift workers was 2.38% and 1.37%, respectively. In contrast, these values for day shift workers were 1.03 and 0.69 %, respectively.²⁴

In a prospective study, Japanese male workers aged 30 to 59 were followed up to 18 months to identify the risk factors associated with peptic ulcer in those without a previous history of the disease. The results of this study showed that the risk of developing peptic ulcers was higher in workers who had a lot of life-related stress than people who did not experience any stress. The relative risk for peptic ulcer in people who experienced night work 10-12 times a month was significantly higher than in other workers (relative risk:2.00, 95%CI 1.49-2.67).²⁵

A study by Mark et al. was designed to answer whether shift work enhances the potential for peptic ulcer by H pylori infection or not. In this study, 615 day and shift workers were included, and information related to upper gastrointestinal disease, medications, job characteristics, and experience of various stresses were collected from these people. Presence or absence of H pylori infection was also analyzed using blood and stool tests.

Table 1: Characteristics of the included studies

Author/year	Design	Risk of bias score	Study population	Exposure (job characteristics)	Diagnostic methods	Confounding control	Results
Tuchsen et al., 1994 ²¹	Cohort study	Low risk	A group of men with full-time jobs (n=112116) and a reference cohort of employers (n=593 281)	Different types of shift work including late evening work and 24- hour service centers providing	SHR was calculated after being discharged from the hospital with the diagnosis of gastric ulcer	Results were compared based on age and various types of shift work with similar occupation status	SHR of late evening work (236, 90% CI 184-299) SHR of 24-hour service-providing centers (147, 90% CI 116-183) SHR of other types of non-daytime job (114, 90% CI 101-128) SHR of all individuals in groups with non-daytime work (130, 90% CI: 118–142)
Zober et al., 1998 ²²	Cross sectional study	Low risk	Personnel of a chemical production company (n=6143)	Shift work as 12-hour rotating system	H pylori infection was determined by serology. Any specific symptom was examined by a physician for certain diagnosis	Nationality, age and recruitment group were adjusted	Higher positive immunoglobulin G serology among shift workers than day workers (46.1% vs 34.6%, RR=1.20 95% CI 1.10-1.32) without any significant difference in terms of ulcer disease occurrence
Pietroiusti et al., 2006 ²³	Cross sectional study	Low risk	Active shift workers (n=101) and day workers (n=247) with persistent dyspepsia at least for one year	shift workers defined as either rotating shifts or night shifts at least four nights/month during the last year and day workers without being on shift work	First assessment of H pylori with non-invasive techniques, further examination with a physician in case of a positive test	Adjusted for age, sex, smoking and family history	Higher prevalence of duodenal ulcer in shift workers than in day-time workers (29 of 101 v 23 of 247; OR = 3.96 95% CI 2.10 to 7.47)
Segawa et al., 1987 ²⁴	Cross sectional study	Low risk	Personnel of banks, factories, or schools (n=11657)	Former shift workers, day workers and night shift workers	Initial screening by x-ray, further examination by endoscopy and x-ray among those with abnormal results	-	Higher prevalence of gastric ulcer among current shift workers than day workers (2.38% vs 1.37%, p<0.001), that of duodenal ulcer (1.37% vs 0.69, p<0.01)
Sugisawa et al., 1998 ²⁵	Prospective study	Low risk	male workers in different occupations (n=12127)	Exclusively day workers, exclusively night workers, shift workers without night work, shift workers with night work, permanent day and night shift, and irregular shifts	Questionnaire with a question about any treatment for peptic ulcer during the past one year	Adjusted for age	A positive significant correlation between permanent shift work and peptic ulcer (RR= 2.00, 95%CI 1.49- 2.67)
Mark et al., 2010 ²⁶	Descriptive study	Moderate risk	Employees of an automotive plant (n= 615)	Day time workers, shift workers with and without night work	Reporting in medical history or questionnaire	age, sex, smoking habits, partnership status, number of children, and the shift work status	higher prevalence of H pylori infection in shift workers (34.6%) than in all workers including day workers (27.6%) without any significant positive relationship between shift work and increased incidence of ulcer disease

Author/year	Design	Risk of bias score	Study population	Exposure (job characteristics)	Diagnostic methods	Confounding control	Results
Lin et al., 2019 ²⁷	Cross-sectional quantitative study	Low risk	Full-time firefighters (n=9328) and policemen (n=42,798)	On-call workers, shift workers, fixed or non-fixed schedules	Peptic ulcer examination by a physician or self-report of currently physician diagnosed	Different groups, marital status, educational level, job duration, manager, levels of employing government, alcohol, smoking, and betel nut chewing	The prevalence of peptic ulcer among firefighters and policemen (5.5% and 6.5%, respectively). The chance of peptic ulcer incidence was not higher among shift workers.
Chadoli et al., 2017 ²⁸	Cross-sectional study	Low risk	891 consecutive subjects, who attended the Endoscopy unit of an institution (2014-2015)	Various occupational parameters including shift work	Standard gastroscopy and colonoscopy	Alcohol, smoking, and caffeine intake	A significant direct relationship between peptic ulcer and shift work (OR= 2.463, 95% CI 1.058-5.731)

CI: Confidence Interval, OR: Odds Ratio, SHR: standardized hospitalization ratio, RR: Risk Ratio, H pylori: Helicobacter Pylori

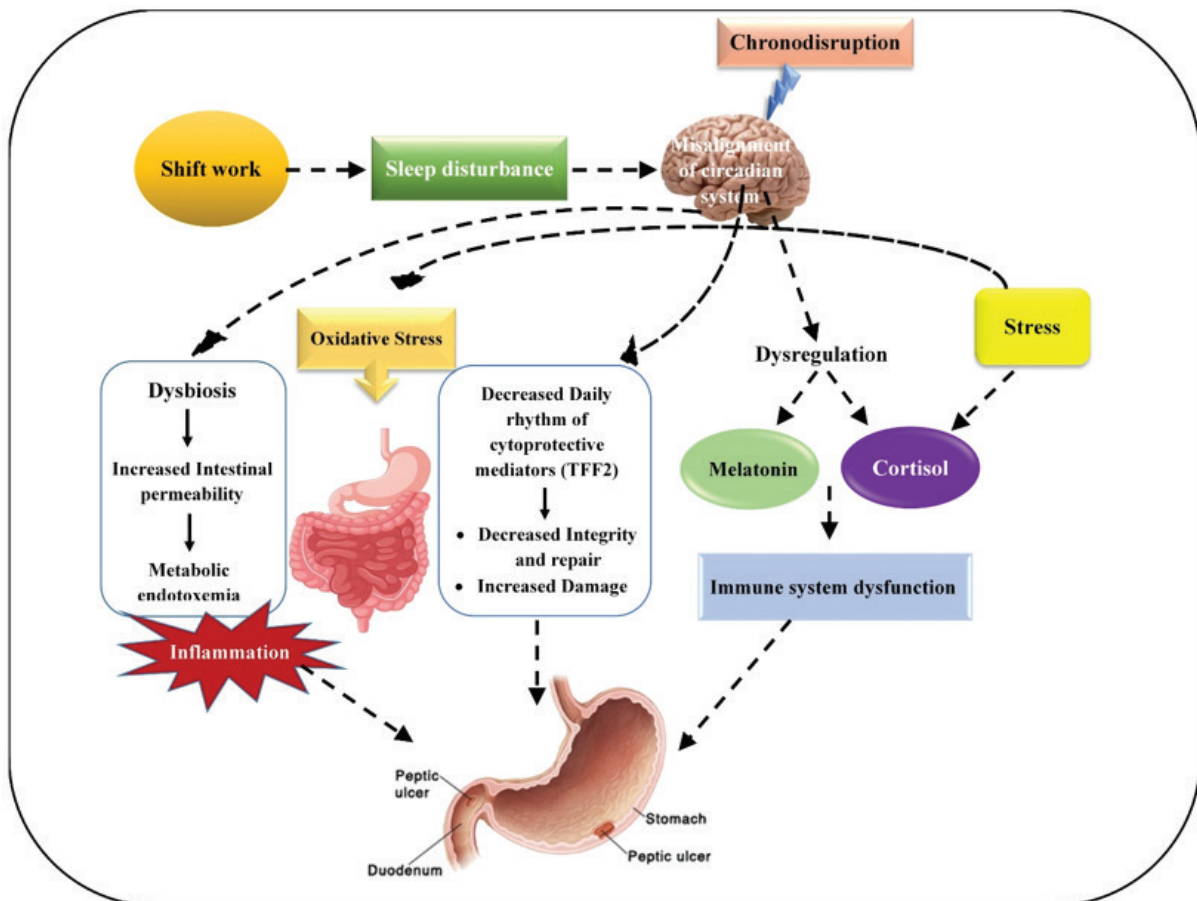


Figure 2: Possible links between shift work, circadian system misalignment, and peptic ulcer (This figure was designed by the authors)

The results showed a higher prevalence of H pylori infection in shift workers (34.6%) than in all workers including day workers (27.6%). However, any significant positive relationship was not observed between shift work and increased incidence of upper gastrointestinal diseases.²⁶

In another cross-sectional study on firefighters and policemen, the relationship between job support and peptic ulcer disease was investigated. In this study, 9,328 firefighters and 42,798 policemen participated. Information was collected through interviews and e-mails and by completing relevant questionnaires.

Diagnosis of peptic ulcer disease was made by physician examination or reported by individuals. The prevalence of peptic ulcers among firefighters and policemen was 5.5% and 6.5%, respectively. A 53% increase in the chance of peptic ulcer was observed in people with low job support and high job burnout, but the chance of peptic ulcer incidence was not higher among shift workers.²⁷

In Chadolias et al.'s study, the relationship between occupational factors and digestive disorders was examined. In this study, 891 working people underwent colonoscopy and endoscopy and were interviewed about their occupational exposures, and necessary information was collected. After analyzing the data, it was observed that peptic ulcer had a significant direct relationship with shift work (OR: 2.463, 95% CI: 1.058-5.731).²⁸

Some possible mechanisms used to clarify the relationship between shiftwork, circadian rhythm misplacement, and the occurrence of peptic ulcers are discussed below (Figure 2).

Discussion

The present systematic review indicated that peptic ulcer was more prevalent among shift workers than in daytime workers. The difference in peptic ulcer prevalence was more than twice as high between shift workers and daytime workers in some studies,²⁴ signifying the importance of the mechanism exploration and of why shift workers have more functional gastrointestinal symptoms. However, the exact mechanisms of this phenomenon are poorly documented.

Shift work may lead to disruption of circadian rhythm by alterations in sleep time and its quality. The circadian system has a strong effect on major GI functions including gut motility, acid secretion, maintenance of mucosal barrier integrity, and immunologic function of the GI tract.²⁹ Therefore, misalignment of the circadian system may exert deleterious effects on proper GI function, leading to GI disorders such as peptic ulcers.

1. Night Sleep Disturbance

Based on previous data, gastrointestinal (GI) function is affected by work-related factors such as time of work (day/night) and constancy of the schedule higher than over time.³⁰ Sleep time is disturbed by working at night and consequently leads to misalignment of the circadian system and thus biological rhythm.³¹ Inappropriate time of sleep and wake among shift workers have been documented in several studies.^{32, 33} One of the main outcomes of interrupted sleep is a marked vulnerability toward neurological conditions, which may cause a peptic ulcer. As a result, there is a reciprocal association between sleep disturbances and peptic ulcer.²⁰

The disrupted circadian system may also influence the daily rhythm of cytoprotective mediators including human trefoil protein (TFF2) in the GI mucosa. TFF2 prevents damage to the GI mucosa and has a role in its repair. In the elderly and in the case of infection by *H. pylori*, the daily rhythm of TFF2 is remarkably weakened, implying that aging and chronic inflammatory response may strongly impact the protective mechanisms of the GI mucosa. Based on this observation, it is indicated that misalignment of the circadian clock due to shift work and poor sleep quality causes similar adverse effects on the integrity of the GI mucosa. The clarification of the exact association between cytoprotective factors and clock genes in the GI tract demands further investigation.²⁹

Deregulation of the circadian system by shift work may also influence melatonin and cortisol daily rhythm.³⁴ Melatonin is produced by the pineal gland in the brain and contributes to controlling the sleep cycle. Melatonin reaches its highest level in the plasma during the dark time of light-dark cycle.³⁵ According to evidence, shift work disturbs the daily melatonin levels. The association of poor sleep quality with peptic ulcer may be due to disturbed and/or decreased melatonin synthesis with shift work.³⁴ Additional studies suggest that melatonin may protect against peptic ulcer recurrence or ulcer healing by antioxidative properties and nitrous oxide system, elevation of growth factors secretion, gastric mucosal microcirculation, and promoting cell proliferation and angiogenesis, whereas the poor sleep quality due to shift work leads to lack of melatonin, resulting in destroyed protective effect of melatonin against peptic ulcer.^{29, 36}

Cortisol, as a stress-responsive hormone, shows a unique daily rhythm with high levels in the active phase (early morning) and low levels in the passive phase (evening).³⁴ Several studies have reported that the daily profile of cortisol is disturbed during shift work.^{37, 38} Niu et al. indicated in a systematic review that cortisol levels were higher during daytime sleep than during night time sleep.³⁹ In other words, elevated cortisol levels may inhibit the occurrence of slow wave sleep or deep sleep.⁴⁰

Given that the GI system has a circadian rhythm, and the gastric emptying process varies during awaking, rapid eye movement (REM), and non-REM sleep, this phenomenon may also contribute to the association between troubled sleep and peptic ulcer. Based on evidence, because of anticholinergic activity in the REM sleep stage, gastric emptying is stronger during REM sleep and awaking than non-REM sleep during night sleep in patients with esophagitis.²⁴ Hence, interrupted sleep may cause functional gastrointestinal symptoms by overactivation of the autonomic nervous, consequently increasing the tendency toward a peptic ulcer.

Additionally, it has been confirmed that gastric acid secretion profile was low in the morning and high in the evening.⁴¹ Gastrin is a hormone that stimulates the secretion of gastric acid; pepsinogen, as an enzyme, is released from the stomach cells and transformed to pepsin in the presence of hydrochloric acid. Pepsin can cause peptic ulcers by acting as an aggressor.⁴² Based on the results of a study done by Tarquini et al., shift work may cause a significant elevation in the secretion of gastrin/acid/pepsin. The results indicated that shift workers had increased the levels of serum gastrin and pepsinogen.⁴³

2. Gut Microbiota Imbalance

The gut microbiota are considered as a barrier that plays an important role in human health and disease.⁴⁴ Recently, it has been shown that the gut microbiome varies daily and are influenced by meal times and disturbed by circadian misplacement.⁴⁵ Disturbed rhythmicity in the gut flora may be responsible for a direct and frequently reported effect of shift work, namely, GI discomfort.⁴⁶ Dysfunction of the GI tract may also explain the considerably higher rate of peptic ulcers in shift workers compared to fixed-day workers.⁴⁷

As mentioned above, sleep displacement disturbs the composition of the gut microbiota. Additionally, *H. pylori*-positive subjects are susceptible to digestive disorders including peptic ulcers, chronic gastritis, and gastric cancers.⁴⁸ Zober et al.²² reported that infection by *H. pylori* was more prevalent among shift (46.1%) than day workers (34.6%). Moreover, a study by Pietroiusti et al.²³ showed that the prevalence of peptic ulcer was higher among *H. pylori*-infected shift workers (28.7%) than infected day workers (9.3%). A potential explanation for these results could be that shift work weakens the natural defense against an *H. pylori* infection.

Several pieces of evidence showed that *H. pylori* in the gastric system altered the microbiota flora in infected patients.^{49, 50} Wang et al. demonstrated that some gut microbial species and functions in Chinese population with *H. pylori* infection were different from healthy individuals.⁵¹ Extended exposure to *H. pylori* infection in the gastric system of rodents has also been shown to alter the composition of the microbiota in the stomach,⁵² suggesting that there is an interaction between *H. pylori* and the gastric microbial community. However, the exact mechanism of *H. pylori* in inducing dysbiosis in the gastric system remains unclear; possibly, host antimicrobial peptides including cecropin-like peptides or β -defensin 2 might directly destroy other microbiota.⁵³

Recently, it has been speculated that there is a reciprocal link between the gut-brain axis and gut microbiota which is modulated by the immune

system.⁵⁴ Exposure to stress causes changes in the composition of the microbiota and may cause dysbiosis, increasing intestinal permeability and exerting a phenomenon named metabolic endotoxemia. This condition is related to increases in the inflammatory tone and alterations in proinflammatory cytokine and neurotransmitter levels by stimulating the innate immune system,⁴⁴ all of which could have impressive effects on developing different gastrointestinal diseases including peptic ulcers. Therefore, shift work may contribute to peptic ulcer through causing a disturbance in sleep schedule, leading to dysbiosis or weakening the immune system, subsequently promoting susceptibility toward *H. pylori* infection.

3. Stress, Inflammation, and Immune System Dysfunction

Shift workers may experience more stressful conditions than fixed-day workers.²³ Stress provokes adaptive responses to protect the stability of the internal environment (1). The immune system and the gastrointestinal tract are mainly responsive to diverse stressors. It has been recently reported that psychosocial and environmental stressors influence the pathogenesis of the gastrointestinal disorders including peptic ulcers.⁵⁴ Therefore, there is a strong relationship between stress and gastrointestinal disorders.²⁸ It is speculated that the gut-brain axis exerts a main role in the modulation of stress and gastrointestinal diseases.⁵⁴ One of the outcomes of the endocrine and immune response to stress is the elevation of plasma cortisol levels. Misleading regulation of cortisol levels could disrupt immune system functions and consequently exert health-related problems.³⁸ Also, poor sleep quality may cause stressful conditions, elevating cortisol levels and subsequently gastric acid secretion levels. The increased levels of cortisol and gastric acid may prevent the normal inflammatory responses in the gastrointestinal tract.⁵⁵

Another harmful effect of stress is the induction of oxidative stress, which may lead to the breakage of GI tract mucosal barriers and the development of mucosal lesions and ultimately ulcerations.⁵⁶ Under the condition of oxidative stress, the sympathetic nervous system is overstimulated, and the activity of the parasympathetic nervous system reduces; subsequently, digestive tract motility increases, resulting in gastric mucosal ischemia and hypoxia. This condition gives rise to the generation of radical species, and lipid peroxidation, resulting in the reduction of membrane fluidity, loss of membrane integrity and cellular functions. It is of interest that stress may lead to the inactivation of the antioxidant enzymes, especially gastric peroxidase (GPx) in the gastric mucosa by extreme generation of OH producing GPx oxidative damage. This phenomenon

also appears to play an important role in the induction of gastric ulceration by stress.⁵⁷

Conclusion

This systematic review identified a higher incidence of peptic ulcers among shift workers than day workers. It is necessary to provide a counseling system such as dietary recommendations to improve the gut flora, promote the immune system, overcome inflammation, and modify food habits to experience highly qualified sleep and subsequently align the circadian system and provide high job support. Additionally, it is recommended work structures should be modified to improve coping skills that may reduce the prevalence of peptic ulcer disease among shift workers.

Limitations and Future Directions

As a main limitation of the study, we could not carry out a meta-analysis due to a high level of heterogeneity among studies. The analysis method of studies, definition of shift work, the participant's different jobs, and years of shift work experience were the main reasons of heterogeneity. Lifestyle-related factors such as body mass index, calorie intake, job, and physical activity may influence the association between shift work and peptic ulcer, which were not considered or controlled in no study. Therefore, more robust studies are needed to clarify the exact effect of shift work on gastrointestinal health.

Authors' Contribution

FG, HJV, SSG, and AAH conceived the study. FG and SSG contributed to the title, full-text screening, and data extraction. All authors contributed equally to the initial draft of the manuscript, and all authors have read and approved the final version of the manuscript.

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Conflict of Interest: None declared.

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