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Gastrointestinal disorders among shift workers

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Objective Our aim was to review published literature on the association between shift work and gastrointestinal (GI) disorders.

Methods A systematic review of the literature was conducted of studies that have reported GI symptoms and diseases among shift workers. We used Medline to search for articles from 1966–2009. Next, we manually searched articles in the reference list of each article and previous reviews.

Results Twenty studies met the inclusion criteria. Four of six studies showed a significant association between shift work and GI symptoms, and five of six studies reported an association between shift work and peptic ulcer disease. Two of three studies showed an association between shift work and functional GI disease. Only a few studies have examined gastroesophageal reflux disease, chronic inflammatory bowel diseases, or GI cancers in relation to shift work.

Conclusions Our general judgment is that shift workers appear to have increased risk of GI symptoms and peptic ulcer disease. However, control for potential confounders (eg, smoking, age, socioeconomic status, and other risk factors) was often lacking or insufficient in many of the studies we examined.

Key terms cancer; Crohn's disease; *Helicobacter pylori*; intestinal disease; occupational health; peptic ulcer; review, ulcerative colitis.

Gastrointestinal (GI) diseases include diseases of the esophagus, stomach, duodenum, jejunum, ileum, large intestine, sigmoid colon, and rectum. GI symptoms are amongst the most frequent symptoms in primary health-care. Examples of GI diseases with structural changes are peptic ulcer disease (gastric and duodenal), chronic inflammatory bowel diseases (ie, Crohn's disease and ulcerative colitis), and malignancies. Functional disorders are those in which symptoms are present, but without structural changes to the GI system. Non-ulcer dyspepsia refers to pain and discomfort in the upper-abdominal region with no evidence of structural disease (eg, peptic ulcer).

Common causes of GI disorders are infections, unhealthy diet, stress, travelling over time zones, infection, and side effects of pharmaceutical agents (eg, non-steroidal, anti-inflammatory drugs). For some diseases of the GI system, substantial socioeconomic differences have been reported. Lower socioeconomic groups have a higher risk of acquiring a peptic ulcer and stomach and

colon cancer (1). Smoking is also a risk factor for peptic ulcer disease (2).

The lifetime risk of peptic ulcer disease is at least 10% (3). The prevalence of peptic ulcer varies in different studies. A recent study by Aro et al (4) showed the prevalence of peptic ulcer in northern Sweden to be 4.1% (20 gastric and 21 duodenal ulcers). A study carried out in the USA showed an incidence of self-reported peptic ulcer disease of 52.7 per 10 000 individuals (gastric 17.0, duodenal 6.1 and unspecified 30.4 per 10 000) (2). The long-term trend of peptic ulcer in Europe increased during the 19th century, reached a peak during the first half of the 20th century, and has since decreased (5).

In the 1980s the bacteria *Helicobacter pylori* was discovered as a possible causal factor of peptic ulcer disease. Later, it was also shown that *Helicobacter pylori* is associated with gastric cancer. A recent review concluded that *Helicobacter pylori* is present in the stomach in about half of the human population. Usually it does not cause any harm, but is associated with an

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increased risk of peptic ulcer, gastric carcinoma, and gastric lymphoma (6). A common opinion is that the association between the bacteria and duodenal ulcer is causal (7). However, the mechanism that links *Helicobacter pylori* infection to peptic ulcer and gastric cancer has not been fully explored. Hobsley et al (8) argue that *Helicobacter pylori* infection does not cause duodenal ulcer but prevents healing of an ulcer produced by hypersecretion of gastric acid. McCulloch (9) suggests that the bacterial infection is too common to be considered a direct precursor of cancer, but it gives rise to chronic inflammation, atrophy, and metaplasia, which in turn creates conditions for carcinogenesis.

In the literature, some studies have shown that other environmental factors could be risk factors for GI cancers. Both occupational and environmental exposures to asbestos are linked to peritoneal mesothelioma. A cohort study from France showed that a population exposed to occupational asbestos had increased incidence of digestive cancer, including mesothelioma, esophageal cancer, and cancer of the small intestine (10). Kjørheim et al (11) showed that workers exposed to asbestos in drinking water had an increased risk of stomach cancer. Koutros et al (12) reported that aromatic amino pesticides can cause colon cancer.

In reviews and textbooks from the 1950s and thereafter, it was generally agreed that peptic ulcer is more prevalent among shift workers. Thiis-Evensen (13) named peptic ulcer disease as “the occupational disease of shift workers” and Harrington (14) states in his influential review from 1978: “In summary, there is some epidemiological evidence which suggests that rotating shift work may play a part in either causing gastro-duodenal ulceration or at least exacerbating latent or pre-existent overt disease.” The evidence at that time, however, was mainly based on clinical experience or studies using only subjective symptoms. Sometimes X-ray examinations were used. Since then the development of diagnostic tools, especially endoscopy, has improved the quality of diagnosis. Endoscopy is a method for examining the body organs through an endoscope, which is a device with a camera mounted on a flexible tube. Using endoscopy, it is possible to get information by visual inspection and photography, and it is also possible to take biopsies. Fiberoptic endoscopes came into general clinical use in the 1960s and 1970s. The discovery of *Helicobacter pylori* as a pathogenic agent for peptic ulcer was made by Warren & Marshall in the early 1980s, but it was not until the mid-1990s that this knowledge altered treatment.

Many previous reviews on the association between shift work and GI disorders have focused on peptic ulcer disease or unspecific GI symptoms. We performed an updated systematic review of all studies that reported on the association between shift work and all types of GI disease.

Methods

Search strategy and selection criteria

We searched PubMed for manuscripts published between 1966–2009, thus the literature search covered the period from the inception of Medline. Search terms included: “shiftwork”, “shift work”, “nightwork”, “night work”, “gastrointestinal”, “gastroesophageal reflux disease”, “GERD”, “ulcus”, “ulcer”, “peptic”, “gastritis”, “dyspeptic”, “dyspepsia”, “heart burn”, “constipation”, “diarrhea”, “gastric pain”, “abdominal pain”, “inflammatory bowel disease”, “ulcerative colitis”, “Crohn’s disease”, “functional gastrointestinal disorders”, “irritable bowel syndrome”, “IBS”, “cancer”, and “malignancy”. We also did a manual search by reading articles in the reference lists of original and review articles and by contacting experts in the field.

The following inclusion criteria were used: (i) the paper should describe important characteristics of the study population; (ii) the shift work variable must be defined; (iii) the outcome variable must be described in terms of symptoms or diagnostic criteria – studies that used the term “GI disturbances” without further description were excluded; and (iv) the results must report figures of prevalence, incidence, or relative risk, including P-values or confidence limits, which makes it possible to compare shift and day workers.

Only articles in English published in peer-reviewed international journals were selected for this review. From each article, we extracted: study design, population size, exposure to shift work, outcome variables, and confounder control. Strengths and limitation were assessed.

Results

A major part of the articles found were concerned with GI symptoms and peptic ulcer disease. Six articles reported mainly GI symptoms (table 1) and three dealt with functional GI symptoms. Six papers reported original data on peptic ulcer disease among shift workers (table 2). Two studies dealt with chronic inflammatory bowel disease. Only two published studies reported an association between shift work and cancer in the GI system.

Studies in which mainly GI symptoms were reported

A number of studies on shift workers have collected data mainly on GI symptoms. Other kinds of diagnostic methods used were not reported, or reported in a way that makes it difficult to assess the quality of the diagnoses.

Dirken (15) carried out a survey study of around 2500 employees in several workshops and districts in the Netherlands. The aim of the study was to compare day and shift workers with respect to wellbeing. The questionnaire included 58 questions, of which 8 asked about GI symptoms, such as problems with appetite, pain, and bowel discomfort. The results did not show any significant differences between shift and day workers. The working time variable was not described in detail. The exposure variables were dichotomous shift work and non-shift work. No confounding control was done.

Koller et al (16) carried out a cross-sectional study of employees at an oil refinery in 1983. From 1260 male blue-collar workers, a random sample of 230 shift workers and 110 day workers was selected. The work schedule was described in detail. It included a clock-wise rotating schedule with morning, evening, and night shifts. The data were based on a questionnaire, interview, and medical check-up. The medical check-up included a medical history, doctor's consultations, sick absence, and information about treatments. The case histories were classified by a panel of physicians and coded according to the international classification of diseases (ICD). The results showed that the prevalence of diseases in the digestive system (ICD 520–579) was significantly more common among shift than day

workers (30.1% versus 13.2%). Figures for peptic ulcer disease were shown only in a graph, and figures were not reported for day and shift workers. The diagnostic criteria for the different ICD codes were not mentioned.

Alfredsson et al (17) studied GI symptoms among Swedish, male night-security guards (N=197). Data were collected by questionnaire. Comparison was made with data from the 1981 Swedish Standard of Living Survey. The results did not show any significantly increased risk of GI problems [standard morbidity ratio (SMR) 110, (95% confidence interval (95% CI) 82–143], nausea (SMR 118, 95% CI 77–173), or diarrhea (SMR 88, 95% CI 54–134) among the night working guards. The results were adjusted for marital status, smoking, socioeconomic group, and full-time, hectic, and monotonous work. A weakness of the study was that the national survey, which was used as the control population, was done in 1980, and the data collection among the guards many years later. If there has been a time trend in the GI problem in the population, the choice of control population could have created a bias in the results. This problem was not discussed in the paper.

Enck et al (18) carried out a survey study of 190 aircrew members of a German charter airline company. Ground-based employees of the same company were

Table 1. Characteristics of six epidemiological studies on shift work and gastrointestinal (GI) symptoms. [ICD = international classification of diseases; SMR = standard morbidity ratio, OR = odds ratio]

Author	Design	Population	Exposure	Diagnostic methods	Confounding control	Results
Dirken, 1966 (15)	Cross-sectional study	Employees in various workshops (N=2500)	Survey data; shift work and non-shift work	Questionnaire: 8 questions on GI symptoms	None	Prevalence of GI symptoms did not differ between day and shift workers
Koller et al, 1983 (16)	Cross-sectional study	Workers in oil refinery (N=340) (230 shift workers)	Shift schedule reported in detail; clock-wise rotating schedule, including night	Interview and medical records were assessed by a panel of physicians and ICD-coded	Not reported; population probably rather homogenous	Prevalence of GI diseases was significantly more common in shift than day workers (30.1% versus 13.2%)
Alfredsson et al, 1991 (17)	Cross-sectional study	Male night security guards (N=197); comparison with national survey data	Night work only	Questionnaire and interview: 6 questions on GI symptoms	Controlling by stratification: age, marital status, socioeconomic group, full-time work, monotonous work, place of residence	No significant differences between night workers and national control; SMR between 88–110 for various symptoms
Enck et al, 1995 (18)	Cross-sectional study	Employees in an airline company (N=290)	190 aircrew members were compared with 100 ground-based employees	Questionnaire: 9 questions on GI symptoms	Matching by age and gender; stratified analysis by: alcohol, smoking, fiber intake, laxative use, long-haul/short-haul flyers	Aircrew members had significantly more GI symptoms than ground staff
Prunier-Poulmaire et al, 1998 (19)	Cross-sectional study	Custom officers (N=302)	Shift schedule reported in detail; 3 rotating systems, which included night shifts, were compared with day shift	Questionnaire: 8 questions on GI symptoms	Adjustments were made for gender, age and work conditions; the choice of population indicates similar socioeconomic conditions	Shift system 4x6 hours had increased risk for 6 out of 8 symptoms; OR varied 2.6–3.6; shift system 3x8 hours had increased risk for 5 out of 8 symptoms (OR 2.7–3.7).
Caruso et al 2004, (20)	Cross-sectional study	Auto factory workers (N=343)	Permanent evening shifts (N=118) and permanent day shifts (N=225)	Questionnaire: 5 questions on GI symptoms	GI symptom index was used as outcome variable in linear and logistic regression, controlling for age, gender, trait anxiety	Evening shift work was associated with more GI symptoms, OR 3.30, 95% CI 1.35–8.07.

used as controls (N=100). The results showed that aircrew members, especially those on long-distance flights, had more upper-GI symptoms than ground staff. Lower-GI symptoms, such as constipation and diarrhea, were not differentiated between the groups. For both long- and short-haul flyers, the symptoms correlated with the total number of days on duty during the reported month.

Prunier-Poulmaire et al (19) performed a cross-sectional study on 302 male and female custom officers in France. The officers could be divided into four groups with different work schedules: (i) 4×6-hour shift system (N=94), which included morning (starting at 07.00 hours), afternoon, evening, and night shifts; (ii) 3×8-hour shift, including morning (starting at 05.00 or 06.00 hours), afternoon, and night shifts; (iii) 2×12-hour shift, including day and night shift, with the morning shift starting at 07.00 hours; (iv) day work starting at 07.00 or 08.00 hours (reference group). The study reported eight symptoms that could be related to GI problems: precordial pain, digestion difficulties, disturbed appetite, nausea, bloated stomach or flatulence, upset stomach, constipation, and use of antacid drugs. The results showed that employees who worked on the 4×6-hour shift system had significantly increased odds ratios for precordial pain, appetite problems, nausea, bloating, and constipation. Those on the 3×8-hour system had increased risk of digestive difficulties, appetite problems, bloating, constipation, and use of antacids. Those on the 2×12-hour rota had no significant effect on any GI health complaints. The results were adjusted for gender, age, and work conditions, including physically demanding job, relation with travelers, and monotony. A strength of the study was its good description of work schedules and confounding control.

Caruso et al (20) reported a cross-sectional study on auto factory workers in the USA. It included 343 participants who were assigned to permanent day or evening shifts. The work schedule for day shifts was 06:00–14:30 and 14:30–23:00 for the evening shifts. However, in reality the start times for the day shift could be from 01:00–13:00, with end times from 10:00–01:00 the next day. Start times for evening shift varied between 05:00–22:00 and end times ranged from 14:00–06:00 the next day. On average, day workers reported having worked 2.1 night hours, and evening workers 5.6 hours during the last 28-day period. The data were collected by questionnaire, which included five questions on GI symptoms. “Rate how often you have felt the following in the past 6 months: (i) nausea or being sick to your stomach; (ii) heartburn or indigestion; (iii) abdominal pain; (iv) loss of appetite; and (v) diarrhea or constipation.” It also asked for current GI diagnoses and medications in the past six months. Current GI symptoms were

added to a scale, which was treated as a continuous variable in multiple linear regression, controlling for age, gender, trait anxiety, and two interaction terms: smoking × noise and age × noise. **The results showed** that the evening shift was associated with more GI symptoms, but not the day shift. The total number of hours worked, number of night shifts, schedule variability, and interaction of shift by work were not significant. Evening shift was associated with a three-fold increase in the risk of a GI diagnosis.

Functional GI disease

Functional GI disorders include symptoms that are not explained by other pathologically-based disorders (21). According to the Rome III classification system, the functional GI disorders are classified into the following categories: (A) esophageal; (B) gastroduodenal; (C) bowel; (D) functional abdominal pain syndrome, (E) biliary; and (F) anorectal. Category C is subdivided into (C1) irritable bowel syndrome; (C2) functional bloating; (C3) functional constipation; and (C4) functional diarrhea. For many functional GI disorders, the etiology and pathogenesis are unclear. Altered autonomic function, immune activation, and altered activation of central nervous system circuits are possible mechanisms (22). In our search, we found three studies on functional GI disorders in relation to work schedules.

Westerberg & Theorell (23) reported on a study carried out in Sweden. The participants were primary care attendants seeking help for GI problems. After medical examination, endoscopy, and laboratory tests, only patients with functional GI disorders were included, totaling 615 subjects. Shift workers were overrepresented among dyspepsia patients (14.6% among men and 8.4% among women) compared with all employed persons in Sweden (5.7% among men, and 1.7% among women). A weakness of the study was the reference population, which did not cover the same geographical area as the cases. Another problem was the vague definition of shift work (“shift schedule or irregular working hours”).

Zober et al (24) see below.

Zhen Lu et al (25) studied functional bowel disorders among nurses in Singapore. Of these nurses, 60 worked during the daytime, and the rest had a rotating shift system, which included night work. The rotating shift nurses were younger than their daytime counterparts (median age 25 versus 32 years old). All subjects underwent a medical examination, and filled out questionnaires covering GI symptoms, sleep disturbances, irritable bowel syndrome, and a hospital anxiety/depression scale. A diagnosis of functional bowel disease was based on the Rome II criteria (26). No further investigations were done to rule out organic disease. The authors defended this because all participants who had been diagnosed as having organic

bowel disease were excluded from the study. In addition, they argued that inflammatory bowel disease was very uncommon in Singapore, and the prevalence of colon malignancies probably would be very low due to the relative youth of the participants. The results showed that the prevalence of functional bowel disease was significantly higher among shift than day nurses (38% versus 20%). The mean functional GI disorder score was also higher among shift than day nurses (3.0 versus 1.0, $P=0.002$). Dyspeptic symptoms, however, were not differentiated between the groups. Stepwise linear regression analysis demonstrated that sleep disturbance, decreased wellbeing, anxiety, somatic pain, younger age, and shift work were all associated with the functional bowel disorder score.

Peptic ulcer disease

In our tracking of papers, we found 26 epidemiological studies on peptic ulcer disease in relation to shift work. Of these, only six articles fulfilled our inclusion criteria as shown in table 2.

Segawa et al (27) carried out a cross-sectional study in Japan including 11 657 employees of factories, banks, and schools. The examinations were done over four years. The subjects were screened by means of barium meal X-ray examination. Those who had abnormal findings were further examined by X-ray and endoscopy. The doctors, who did the examinations and determined the diagnosis of peptic ulcer, did not know the work schedule of the subjects. The exposure assessment was based on the questionnaire data, in which the participants answered questions about work schedules (ie, night or day shift or former shift workers). The results showed that the prevalence of gastric ulcer was 2.38% among current shift workers and 1.93% among daytime workers. For duodenal ulcer, the corresponding figures were 1.36% and 0.69% respectively. Among former shift workers, the prevalence of gastric and duodenal ulcer was 1.52% and 0.62%, respectively. The relative risk for peptic ulcer, which can be calculated from the data, was 2.18 for current shift compared with day workers. The strength of this study was its good description of the population and the diagnostic methods used for detection of peptic ulcer. The exposure assessment, however, provided only a crude assessment of shift work. There was no information about shift work schedules (eg, prevalence of night work); no confounding control was done, nor was it clear whether there were age differences between shift and day workers.

Angersbach et al (28) performed a historical cohort study of workers in the chemical industry. The participants were followed between 1966–1977. The shift workers, who worked on a 12-hour shift rota were compared with 270 day workers undertaking “comparable work”. Of those who were shift workers at baseline, 210 remained

in shift work during the follow-up and 155 left shift work because of retirement, death, changing workplace, or transfer to day work. Of those who were day workers at baseline, 142 stayed in day work and 109 left due to changed workplace, retirement, or death. Thirteen changed to shift work. Sick records were obtained from the firm’s health insurance and the occupational health unit. This information was used for diagnostic coding (probably done by the authors of the article). The results showed that 9.7% of the shift workers had sickness absence due to peptic ulcer, compared with 5.1% of the day workers during the follow-up period. This difference was statistically significant. The strength of the study lay in its longitudinal design and good description of the shift schedule. Its limitations were weak diagnostic criteria and no adjustment for age or other confounding control. Person-years were not reported.

Higashi et al (29) undertook a study in Japan of 26 324 male manufacturing workers including 13 472 shift workers. All plants were members of the Japan Chemical Fibers and Textile Association. The cause of sickness absence was classified according to the ICD. A major part of the shift workers worked according to a 3-shift system, including nights. The results showed that shift workers on average had more episodes of sick leave due to peptic ulcer than day workers (0.72 versus 0.43 episodes/year), but the difference was not statistically significant. The limitations of the study were weak case criteria and the absence of confounding control.

Tüchsen et al (30) carried out a cohort study of 122 116 individuals in Denmark who were employed full-time in 1981. The outcome was obtained from hospital registries between 1981–1984 and based on the diagnosis of peptic ulcer disease (531, ICD-9). The shift work variable was an ecological variable constructed from an interview study carried out in 1976, which included information about job title and work hours. Four categories were defined: (i) groups in which at least 20% worked late in the evening, (ii) groups in which at least 20% covered 24-hour service, (iii) groups in which at least 20% had other forms of non-daytime work, and (iv) day workers. The standardized hospitalization ratio (SHR) was calculated by dividing the observed number of hospitalizations during 1981–1984 in a given subcohort by the expected number, which in turn was based on incidence rates for men economically active on 1 January 1981. The results showed that in the four employment groups with daytime work only, the SHR ranged from 42–129. Men in occupational groups with late evening work had a SHR of 236 (90% CI 184–299), those working in rosters covering 24-hour services had a SHR of 147 (90% CI 116–183), and those working on other non-daytime schedules had a SHR of 114 (90% CI 101–128). For all men in groups with non-daytime work, the SHR was 130 (90% CI 118–142). A strength

of the study was the good quality of the outcome assessment (hospital-based diagnoses). A limitation was the construction of the ecological exposure variable, which probably led to misclassifications.

Sugisawa & Uehata (31) performed a cohort study in Japan. Participants were men aged 30–59 years, working in various occupations and firms (N=12 127). Data were collected by questionnaires. Only subjects who had no prior history of peptic ulcer at baseline were included. Exposure to shift work was assessed by a question on working hours, and categorized into six groups; (i) day work, (ii) night work, (iii) shift work without night work, (iv) shift work with night work, (v) permanent day and night shift, and (vi) irregular shifts. They also constructed a dichotomized variable (“late night work” coded $\leq 9=0$, $\geq 10=1$). Occurrence of peptic ulcer disease was based on the question:

“Have you ever received medical treatment for stomach or duodenal ulcer within the past year?” The results showed the following age-adjusted relative risks for the different groups: (i) day work only (reference)=1.00, (ii) night work only=1.92 (95% CI 0.92–3.20), (iii) shift work without night work=1.12 (95% CI 0.73–1.71), (iv) shift work with night work=1.12 (95% CI 0.91–1.39), (v) permanent day and night shift work=2.00 (95% CI 1.49–2.67), and (vi) irregular shifts=1.15 (95% CI 0.76–1.73). Multiple logistic regression yielded significant odds ratio (OR) for “late night work”=2.34 (95% CI 1.02–1.75). Besides late night work, the logistic model included smoking habits, life event stress, and perceived work overload. The strengths of the study were its longitudinal design and confounding control. A limitation was its use of self-reported information on ulcer disease.

Table 2. Characteristics of six epidemiological studies on shift work and peptic ulcer disease. [RR = relative risk; ICD = international classification of diseases; SHR = standardized hospitalization ratio]

Author	Design	Population	Exposure	Diagnostic methods	Confounding control	Results
Segawa et al, 1987 (27)	Cross-sectional study	Employees in factories, banks, and schools (N=11 657)	Night shift workers, day shift, former shift workers	Screening by X-ray; those with abnormal findings were examined by X-ray and endoscopy	Not reported	Gastric ulcer prevalence was 2.38% in current shift workers and 1.93% in day workers (P<0.001); duodenal ulcer 1.36% in current shift workers and 0.69% in day workers (P<0.01)
Angersbach et al, 1980 (28)	Cohort study	Workers in chemical industry (N=635); follow-up time 11 years	Shift workers, day workers, and workers that transferred from one system to the other	Information from the firm's health insurance and the occupational health unit	Not reported; population probably rather homogenous with respect to socio-economic status	During follow-up 9.7% of shift workers and 5.1% of day workers had sick absence due to peptic ulcer; the difference was statistically significant
Higashi et al, 1988 (29)	Cross-sectional study	Workers in plants that were members of the Japan Chemical Fibers and Textile Association (N=26 324)	Rotating shift work, including night shift, was compared with day work	Cause and duration of sickness absence was obtained from company registries	Age-adjusted data; comparison showed that education, marital status, smoking, alcohol drinking, and wages were similar among shift and day workers	Short-term spells of ulcer were more frequent (P<0.05) among shift than day workers; long-term spells equally frequent; the RR was 1.6 for shift workers compared with day workers
Tüchsen et al, 1994 (30)	Cohort study	A cohort of 112 116 full-time employees were followed for 3 years	Shift work was defined as an ecological variable based on job title	First admission hospitalization with discharge diagnosis gastric ulcer (ICD-9:531) was used for calculation of SHR	Confounders were controlled by age standardization and by comparisons with occupational groups with similar employment status	Late evening work SHR=236 (90% CI 184–299), roster work SHR=147 (90% CI 116–183), other non-day-time SHR=114 (90% CI 101–128)
Sugisawa & Uehata, 1998 (31)	Cohort study	Employees in various occupations and firms (N=12 127); follow-up time 18 months	Day workers were compared with groups who worked (i) night shift, (ii) shift work without night shift, (iii) shift work with night shift, (iv) permanent day and night shift, and (v) irregular shift	Questionnaire, which included a question regarding receiving treatment for peptic ulcer within the last year	The results were controlled for age	Permanent night shift work was associated with ulcer disease (RR 2.00, 95% CI 1.49–2.67)
Zober et al, 1998 (24)	Cross-sectional study	Employees of a chemical company	Fast-forward rotating 12-hour shift system; comparison with day workers	Structured interview: antibodies to <i>Helicobacter pylori</i> were examined. In case of specific symptoms, the participant was referred to a physician for diagnosis	Adjustments were made for age, nationality, and recruitment group	Positive serology for <i>Helicobacter pylori</i> was more prevalent among shift than day workers (46.1% versus 34.6%; RR 1.20, 95% CI 1.10–1.32); occurrence of ulcer disease did not differentiate between groups

Zober et al (24) reported the prevalence of GI disorders among day and shift workers employed in chemical manufacturer BASF's production facilities in Ludwigshafen, Germany. Study subjects were recruited during occupational health clinic visits and through a communications campaign. Results were reported for male hourly employees (shift workers N=2230 and day workers N=990). A physician filled out a questionnaire based on the interview of each participant. A blood sample was collected to determine the presence of immunoglobulin (Ig) antibodies to *Helicobacter pylori*. If the titre of antibodies was increased or the participant reported specific upper-GI complaints, ulcer diagnoses, or family history of stomach cancer, he was referred to BASF's personal physicians or a gastroenterologist for further diagnostic measures. Six subgroups were identified: (i) non-ulcer dyspepsia alone, (ii) ulcer disease alone, (iii) family history of stomach cancer alone, (iv) non-ulcer dyspepsia and family history of stomach cancer, (v) ulcer and family history of stomach cancer, and (vi) free of findings for all three conditions. Individuals were diagnosed as non-ulcer dyspepsia if they had experienced ulcer-like or reflux symptoms in the absence of an ulcer diagnosis. The results showed that positive IgG serology was significantly more prevalent among shift than day workers (46.1% versus 34.6%). Occurrence of ulcer disease and non-ulcer dyspepsia was not significantly different between the two groups. The shift schedule at BASF is described in another report as being fast forward-rotating 12-hour shifts, with the day shift beginning at 06.00 hours and the night shift at 18.00 hours (32). A strength of the study was the case ascertainment procedure, which made it possible to discriminate between ulcer disease and functional dyspepsia. The statistical analysis included confounding control for age and nationality.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is caused by an insufficient sphincter function in the lower esophagus. This leads to the regurgitation of digestive juices to the esophagus. A typical symptom is heart burn. Established risk factors are hiatal hernia, obesity, smoking, and pregnancy. We found only one study reporting GERD in association with shift work.

Li et al (33) carried out a cross-sectional epidemiological investigation among outpatients at ten hospitals in China. The patients (N=15 283) completed a questionnaire, which included the Chinese version of the reflux disease questionnaire (RDQ), designed to assess the prevalence of GERD during the last month. The RDQ has been tested in a multicenter study in China, yielding a sensitivity of 94.1% and a specificity of 50%. The prevalence of GERD in this population was 7.28%. Multivariate logistic regression showed that night shift

work was significantly associated with GERD (OR 1.38, 95% CI 1.11–1.71). The authors adjusted for age, work burden, marital status, excessive eating, regular consumption of greasy food, regular consumption of sweet food, and constipation. A weakness of the study was that the night shift variable was not described. In addition, the population was not representative of a healthy working population.

Chronic inflammatory bowel diseases

Chronic inflammatory bowel diseases are characterized by inflammation of the large or small intestine, leading to pain and diarrhea and sometimes resulting in bleeding, structuring, and fistulas. The most common types of these diseases are ulcerative colitis and Crohn's disease. The causes are not known, but recently melatonin has been suggested as a mediator (34). Although the incidence of these diseases has been increasing in western societies, they are uncommon. We found two studies mentioning risk of chronic inflammatory bowel diseases in relation to shift work.

Sonnenberg (35) used occupational coding of rehabilitation cases in German insurance files and compared occupations for chronic inflammatory bowel diseases (12 014 patients) with the distribution of codes for the remaining diagnoses. The study is thus a case-control study, using prevalent occupation as exposure. OR for each occupation were calculated and, based on the results, it was suggested that extended and irregular shift work could be a risk for contracting chronic inflammatory bowel disease.

Bøggild et al (36) conducted two register-based cohort studies on Danes aged 20–59 years on 1 January 1981 and 1 January 1986, totaling 2 273 872 and 2 387 620 persons, respectively. They used occupational groups as exposure and identified hospitalization, with ICD codes for Crohn's disease and ulcerative colitis until 31 December 1990, as an outcome. The 10-year cohort had 6 296 first-time admissions. Eight male and five female occupational groups had statistically significant elevated SHR. The study specifically tested whether non-daytime jobs, identified from an independent survey of working conditions in 1976, were related to hospitalization for inflammatory bowel disease. Neither groups with predominately night and morning work, late evening work, and 24-hour services nor groups with other forms of irregular working hours had an elevated risk of hospitalization.

Cancer

We found only two studies analyzing the risk of cancer in the GI system. One did not demonstrate an increased risk, but the other reported an increased risk

of colo-rectal cancer among shift workers. Colo-rectal cancer is the second most common cancer in Sweden, striking around 6000 people per year. The risk increases with age. Smoking, a sedentary lifestyle, heavy alcohol use, obesity, and diabetes have been associated with colo-rectal cancer. In addition to that, a family history of colon cancer and polyps are also known risk factors.

Schernhammer et al (37) carried out an analysis of colo-rectal cancer in the nurses' health study, a cohort study that followed 78 586 women from 1988–1998. They found 602 incident cases of colo-rectal cancer. The results showed that women who worked 1–14 years or ≥ 15 years on rotating night shifts had relative risks of colo-rectal cancer of 1.00 (95% CI 0.84–1.19) and 1.35 (95% CI 1.03–1.77), respectively. A weakness of the study was that nurses who worked on permanent night shifts may have classified themselves as non-rotating night workers, and thus were treated as part of the non-exposed control cohort.

Taylor & Pocock (38) performed a mortality study of shift and day workers in England. The cohort study comprised 8603 male manual workers from 10 organizations. The total number of person-years was 37 962.8 among day workers, 39 581.0 among shift workers, and 4562.7 among former shift workers. The relative risk of stomach cancer was calculated from the data by dividing observed and expected cases in different exposure groups. Day workers' SMR was 1.24, shift workers' SMR was 1.43, and former shift workers' SMR was 1.14. Thus the shift workers had a greater risk than day workers, but the authors reported that the differences failed to reach significant levels. No other cancers in the GI tract were reported.

Mechanisms by which GI disturbances could be due to shift work

The GI system has a circadian rhythm. This has been demonstrated for bowel movement, secretion of gastric juices, bile acid synthesis, and immune activity. The circadian clock also influences appetite regulation. The biological rhythm of gastric movements was shown by Lindberg et al (39) in an experimental study on 30 healthy volunteers using electrogastrographic technique. The mean frequency of gastric electric activity peaked at midday and had its lowest level in the late night. Colonic motility has a strong circadian rhythm with increased activity during the day. The activity is also increased after meals. In a recent review article, Hoogerwerf (40) concluded that "it remains to be determined whether sleep-related motility changes are a direct consequence of sleep-induced changes in autonomic neural input or if changes in colonic motility are under circadian clock control." The work of Moore et al (41–43) demonstrated that gastric acid secretion profile was high in the evening

and low in the morning. Duane et al (44) showed that bile acid synthesis has a circadian rhythm with increased synthesis during daytime. This was confirmed in a recent study by Gälman et al (45). They showed that bile acid production had two distinct peaks during a 24-hour period. The first appeared at 13:00 and the second at 21:00 hours. The daytime peak persisted even when the study subjects fasted, which indicated that the circadian rhythm was governed by an intrinsic clock and not food intake.

Gastrin is a hormone that stimulates the secretion of gastric acid; pepsinogen is an enzyme that is released from cells in the stomach and transformed to pepsin in the presence of hydrochloric acid. Pepsin digests protein. Animal experiments have shown that pepsin can act as an aggressor and cause peptic ulcers (46). Tarquini et al (47) showed that shift work may cause a significant change in the gastrin/acidopepsin secretion system. They studied five adult male foundry shift workers with a work schedule that included day work (07:45–16:45 hours), morning shift (06:00–14:00 hours), afternoon shift (14:00–22:00 hours), and night shift (22:00–06:00 hours). Six adult males with working hours of 07:45–16:45 acted as the control group. The shift workers did not eat during the night shift. Blood samples were drawn on Monday and Friday of each week and were assayed for gastrin and pepsinogen. The results indicated that shift workers had increased levels of serum gastrin and pepsinogen. With cosinor analysis, it was not possible to detect circadian rhythm of these variables among shift workers.

Helicobacter pylori is a bacterium that contributes to the development of peptic ulcer. In a study by Zober et al (24), it was shown that infection by *Helicobacter pylori* was more prevalent among shift than day workers (46.1% versus 34.6%). In addition, a study by Pietroiusti et al (48) demonstrated that *Helicobacter pylori*-infected shift workers had higher prevalence of peptic ulcer than infected day workers (28.7% versus 9.3%). A possible explanation for these findings could be that shift work deteriorates the natural defense to a *Helicobacter pylori* infection.

Clock genes, which probably are crucial for the coordination of rhythmic functions, are present in cells in the GI tract (49). DNA synthesis in the epithelial cells peaks at different times. In mice, the peak DNA synthesis in the esophagus occurs at the end of the night, followed by the stomach 1–2 hours later, and then by the duodenum, jejunum, ileum, and finally the colon. The clock cells in the GI tract are entrained by the feeding time, and not by the master clock in the suprachiasmatic nucleus. As a consequence, varying eating times, which is common among shift workers, could lead to desynchronization between circadian biological clocks. However, it remains to be proven if this is a mechanism of GI diseases among shift workers. This special issue of the

Scandinavian Journal of Work, Environment & Health on shift work includes a discussion paper by Lowden et al (50) on food quality and timing of food intake.

Possible mechanisms that could explain increased cancer risks among shift workers are under debate. Some researchers argue that night work could lead to a suppression of the total melatonin secretion, which could increase the risk of cancer. This theory is supported by animal experiments.

Discussion

In this review, we have reported studies on GI disorders in relation to shift work. Twenty studies met our inclusion criteria. Four of six studies showed a significant association between shift work and GI symptoms, and five of six studies reported an association between shift work and peptic ulcer. Two out of three studies showed an association between functional GI disease and shift work. Only a few studies have studied gastroesophageal reflux disease, chronic inflammatory bowel diseases, or GI cancers in relation to shift work. We did not find any studies that have explored associations between shift work and diseases such as gall bladder disease, celiaci, polyps, or hemorrhoids.

Our general judgment is that shift workers appear to have an increased risk of GI symptoms and peptic ulcer disease. However, control for potential confounders (eg, smoking, age, socioeconomic status) was often lacking or insufficient in the studies we examined. In addition, only a few studies were cohort or case-control studies with a longitudinal design. Most studies were cross-sectional and could not be used for measuring incidence of disease.

Search strategy and selection bias in the studies

We decided to include all available studies, but only those in English and published in peer-reviewed publications. We found several, mostly older studies, in a variety of other languages and in proceedings and books. In general, the lower quality studies were published in a non-English language and non-peer-reviewed forms. Although the search strategy was wide and our judgment based on title and abstract, relevant studies may be missing. This suggests that while the estimated risk from the high quality studies remains valid, some research may have been omitted.

Even in the best longitudinal studies (28, 31), the exposed group was not followed from the time shift work was commenced, and if the GI disease was caused within the first years of shift work, selection bias might have caused a misclassification of shift workers into day work. The same selection problem occurred in all

of the cross-sectional studies. It has been described that 55% of the shift workers with ulcers reported having had symptoms before commencing shift work (13).

The prevalence of GI disease being a result of the product of the incidence and the average duration of the disease means that if shift workers were treated quicker for their disease (such as an ulcer), the prevalence may be lower than among day workers despite the same incidence.

Former shift workers were examined in several investigations. They appear to have a higher prevalence of ulcers than both day and current shift workers in cross-sectional studies. In general, the literature that included former shift workers was of a more limited quality. Part of the explanation for the higher prevalence is straightforward; sometimes shift workers experiencing ulcers are moved to day work; these results can be regarded as a "sick shift worker effect". In studies not separating the groups, a differential misclassification will result, underestimating the association if present.

Information bias in the studies

Diagnoses have been made in different ways. Peptic ulcers are mostly based on X-ray studies and, in recent years, in combination with endoscopy. In some studies, the diagnosis was based only on a physician's report. Questionnaire-based studies probably gravely overestimate the associations, as only 20% of dyspepsia cases are due to ulcers. If shift work is associated only with non-ulcer dyspepsia, but not with ulcers, screening with a questionnaire and the subsequent X-ray diagnosis will tend to inflate the risk estimate. Studies relying on existing X-rays are also subject to confounding by indication, as the physician may have referred shift workers due to suspicion, especially when corporate doctors have been aware of the alleged association.

A number of studies used sick leave as a proxy marker for disease, in some instances based on the diagnosis of the certifying doctor. It has repeatedly been shown that sick leave is not an unambiguous marker for disease, and shift workers may have a lower general absence rate as their colleagues often have to fill in.

Information on work schedule is mostly based on self-report, in some studies on company records and others on occupational codes. Bias in the exposure information will probably tend to be small and non-differential.

Confounding

Adjustment for potential confounders was not made or insufficiently made in a majority of the studies. As shift workers tend to be younger than day workers and GI diseases are related to age, the absent adjustment for

age would lead to an underestimation of the risk. Also, a lack of control of social class could be misleading, since educational level and income could differentiate between shift and day workers. Only three studies have controlled for social class (17, 30, 36), and, while others are restricted to a single factory or occupation, day workers may more often have been skilled than shift workers.

Use of drugs among shift and day workers are not well described, and especially use of non-steroidal anti-inflammatory drugs and low-dose aspirin, which are related to ulcers, may be higher among shift workers as they more often have heavy work.

Bias in the selection of studies for the review

A weakness of many studies was an insufficient description of work hours. Therefore, it was not possible to draw conclusions about which component in the work schedule is potentially harmful.

The causal pathways were unclear, and it is possible the mechanisms are different for various disorders.

Concluding remarks

Twenty studies met our inclusion criteria, fourteen of which showed an association between shift work and GI disorders. Eleven of fifteen studies on GI symptoms, peptic ulcer, and functional GI disease showed an association with shift work. The overall picture indicated that shift work is associated with GI disorders, even if the number of studies on each diagnostic group was small. A relevant concern, however, was the poor quality of many of the studies, especially insufficient confounding control. There is a need for new studies that use modern diagnostic methods. It is also important to diagnose infection with *Helicobacter pylori*.

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