THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

Associations of seasonal variations and meteorological parameters with incidences of upper and lower gastrointestinal bleeding

OPEN ACCESS

Associations of Seasonal Variations and Meteorological Parameters with Incidences of Upper and Lower Gastrointestinal Bleeding

Chuan-Guo Guo,[1] Linwei Tian,[2] Feifei Zhang,[3] Ka Shing Cheung,[1] Wai K Leung[1]

1 Department of Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

2 School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

3 Usher Institute, University of Edinburgh, Edinburgh, United Kingdom

Corresponding author: Wai K. Leung, MD, Department of Medicine, Queen Mary Hospital, University of Hong Kong, 102 Pokfulam Road, Hong Kong. Email: waikleung@hku.hk

ABSTRACT

Background: Previous studies have demonstrated the seasonal variations of non-variceal upper gastrointestinal bleeding (UGIB), but there is scanty data on lower gastrointestinal bleeding (LGIB) and the association with other meteorological parameters.

Methods: We included all patients hospitalized for UGIB and LGIB between 2009 and 2018 in Hong Kong. The monthly age- and sex-standardized GIB incidences were fitted to meteorological data including average temperature (AT), maximum temperature (MaxT), minimum temperature (MinT), temperature range (TR), average precipitation, average atmospheric pressure (AtomP) and average relative humidity after adjusting for prescriptions of aspirin, proton pump inhibitors and *Helicobacter pylori* eradication therapy using the autoregressive integrated moving average (ARIMA) model.

Results: Despite a gradual decline in UGIB incidences, the incidences of UGIB were still higher in winter months. The incidence and fluctuation of both UGIB and LGIB were higher in the older age groups, especially those ≥80 years. The seasonality was only identified in those ≥60 years for UGIB, and only in those ≥80 years for LGIB. UGIB incidence was inversely associated with AT, MaxT and MinT, but positively associated with TR and AtomP. LGIB was also significantly associated with AT, MaxT, MinT and AtomP.

Conclusion: Despite the changes in GIB incidences, the seasonal patterns of GIB were still marked in the elderly. With the ageing population, the impacts of seasonal variations on GIB incidences could be considerable.

INTRODUCTION

Meteorological and climatic parameters have been associated with various human diseases.[1-3] Ambient air temperature, for instance, has been shown to be inversely associated with incidences of myocardial infarction.[1] The seasonal variations of non-variceal upper gastrointestinal bleeding (UGIB), especially peptic ulcer bleeding (PUB), were also found to be more frequent in winter than summer.[4-13] Moreover, early studies showed that air temperature, temperature changes or atmospheric pressure may be associated with the incidences of PUB.[4, 6, 12] In contrast, some studies failed to show the seasonality of non-variceal UGIB, or the association between UGIB incidences and meteorological factors.[13-15] However, most of these studies were descriptive,[4, 6, 12] or based on regression analysis without controlling for data autocorrelations,[16] which may generate spurious association.[17]

Ageing is a major challenge faced by many countries and regions, including Hong Kong. It is estimated that the proportion of the world's population over 60 years will nearly double between 2015 and 2050.[18] While advanced age is a major risk factor for GIB, concomitant medical illness and its related treatment, particularly aspirin and other anti-coagulants, would further increase the risk of both upper and lower gastrointestinal bleeding (LGIB). However, eradication of *Helicobacter pylori* (*H. pylori*) and acid suppressive agents are effective preventive strategies for UGIB. The dynamic changes in demographic composition as well as prescription patterns are therefore rapidly changing the epidemiology of GIB. As such, it is generally reported that the incidences

4

of UGIB are falling while the incidences of LGIB are rising due to limited preventive strategies.[19, 20]

With these rapidly evolving changes, there are increasing uncertainties whether previously observed seasonal variations of UGIB still exist. There are also limited studies that examine the potential seasonality of LGIB and its association with various meteorological parameters. In this study, we investigate the seasonal patterns of UGIB and LGIB in Hong Kong over the recent 10-year period and the potential associations with various meteorological factors in different age groups.

METHODS

Data source

All clinical data were retrieved from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hong Kong Hospital Authority is the only public healthcare provider in Hong Kong, which serves a population of 6,972,800 in 2009 and 7,451,000 in 2018. The CDARS is an electronic healthcare database of the Hong Kong Hospital Authority, which captures all key clinical information including demographics, diagnoses, drug prescriptions, hospitalization, and death of patients from all local public hospitals and clinics. The database has been reported in details in previous studies.[21, 22] The coding system of diagnosis in CDARS follows the International Classification of Diseases, 9th Revision (ICD-9). The

accuracy of the coding for GIB in the CDARS has been verified in our previous study.[23]

We retrieved the numbers of GIB hospitalizations in public hospitals in Hong Kong between 2009 and 2018. The ICD-9 codes of all GIB events were listed in **Supplementary Table 1**. For the coding of hematemesis (578.0) and melena or black tarry stool (578.1) among other diagnoses of unspecified GIB were treated as UGIB, whereas hematochezia from 578.1 was taken as LGIB in this study. For other diagnoses with the code of 578.xx, the diagnosis would be updated if the description of the bleeding location was available subsequently. Moreover, if there were new specific diagnoses within 30 days, the diagnosis of unspecified GIB would be renewed using the specific one with the index date unchanged. In addition, new GIB events within 30 days after a GIB event with same diagnoses or a diagnosis of unspecified GIB were excluded. PUB included gastric ulcer, duodenal ulcer and peptic ulcer site unspecified with bleeding. Due to the concern on the accuracy of ICD code of 578.1,[24] a sensitivity analysis after excluding the diagnosis code of 578.1 was performed. The monthly incidence rates of GIB were expressed as number per 100,000 person-months.

All prescriptions of aspirin and proton pump inhibitors (PPIs: omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazole and rabeprazole), non-steroidal anti-inflammatory drugs (NSAIDs: ibuprofen, naproxen, diclofenac, indomethacin, mefenamic, piroxicam, celecoxib and etoricoxib), anticoagulants (warfarin, dabigatran, apixaban, edoxaban and rivaroxaban) and other antiplatelet drugs (clopidogrel,

dipyridamole, cilostazol, ticagrelor and ticlopidine) from all local public hospitals and clinics during the 10-year study period were retrieved from the CDARS. Drug prescriptions were organized into monthly data as prescription-days per 100,000 person-months, which was defined as cumulative sum of prescription durations in a single calendar month without considering the dosage. Moreover, the numbers of prescription for a course of clarithromycin-containing triple therapy during the 10-year period were retrieved.[25, 26] All *H. pylori*-infected patients, who had received their first course of clarithromycin-containing triple therapy between 2009 and 2018. Clarithromycin-containing triple therapy was the most commonly used empirical first-line therapy for *H. pylori* eradication in Hong Kong with high eradication rate during the study period. Clarithromycin-containing triple therapy was identified by the co-prescription of clarithromycin with a PPI and either amoxicillin or metronidazole with the same start date of prescriptions and overlapping duration of 7–14 days.

Monthly meteorological data, for the period of 2009 to 2018, were obtained from the Hong Kong Observatory,[27] including average temperature (AT, °C), maximum temperature (MaxT, °C), minimum temperature (MinT, °C), temperature range (TR: MaxT - MinT, °C), average precipitation (Prep, mm), average atmospheric pressure (AtomP, 100 Pa) and average relative humidity (RH, %).

Population demographics of Hong Kong during the study period were obtained from the Census and Statistics Department of Hong Kong.[28] Data of mid-year population and

population by age group were used in the analysis.

Outcomes and Statistical Analysis

The incidences of GIB were standardized by age and sex according to the distribution

of the local population in 2018. The median and corresponding interquartile range (IQR)

of age- and sex-standardized incidences of UGIB and LGIB in different months were

calculated. Incidences of UGIB or LGIB in winter months (Dec to Mar) were compared

to summer months (Jun to Sep) using Wilcoxon test. GIB data were decomposed into

long-term trend component and seasonal component to better present the characteristics

of the data using additive decomposition model. An overall seasonality test (WO-test

from "seastests" package in R) was used to test the seasonality of the GIB data. WO-

test combines the results of the QS-test and the kwman-test. If the P value of the QS-

test is below 0.01 or the P value of the kwman-test is below 0.002, the time series is

considered seasonal.

Autoregressive integrated moving average model (ARIMA) was used to fit the monthly

age- and sex-standardized UGIB or LGIB data, in which seasonal component would be

included if it was significant. Parameters (coefficient and 95% confidence interval [CI])

were estimated using maximum likelihood estimation (**Supplementary Methods**).[17, 29]

In the model on UGIB, prescriptions of aspirin, PPIs, and number of patients who

received *H. pylori* eradication were controlled. For LGIB, only prescription of aspirin

was included. Due to their non-significant effects on UGIB and LGIB (**Supplementary**

8

Table 2), NSAIDs, anticoagulants and other antiplatelet drugs were not included in the final model. When adjusting for covariates, including prescriptions of aspirin, PPIs, and number of patients who received *H. pylori* eradication, the model was fit with ARIMA errors. A sensitivity analysis on PUB was also performed. The final model was chosen from ARIMA models with different parameters based on Akaike's Information Criterion (AIC).[17]

The associations between meteorological factors and incidences of UGIB or LGIB was evaluated using ARIMA models adjusting for covariates. Specifically, meteorological factors were analyzed at different month-lags (0-3 months lag) to evaluate if current meteorological factor (lag 0) or meteorological factor in previous months (lag 1-3) would affect UGIB or LGIB. Subgroup analyses in population ≥80 years old were also performed. *P* values <0.05 were considered statistically significant. All statistical analyses were performed using the R software (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Seasonal patterns of UGIB and LGIB

A total of 53,911 UGIB and 67,276 LGIB events were identified in the 10-year period. There was an obvious decline in the incidence of UGIB, whereas the incidences of LGIB remain relatively stable (**Figure 1**). The monthly incidences of UGIB showed an

obvious seasonal pattern, especially after removing the long-term trend (**Figure 1**). The incidences of UGIB were higher in the winter months (Jan 7.57 [IQR 6.27-8.11], Feb 6.59 [IQR 6.12-7.97], Mar 6.63 [IQR 6.19-8.17] and Dec 6.71 [IQR 5.52-7.76]) than in the summer months (Jun 5.52 [IQR 5.11-5.56], Jul 5.94 [IQR 5.38-6.85], Aug 5.72 [IQR 5.15-6.88] and Sep 6.71 [IQR 4.80-6.27], $P = 0.005$, **Figure 2**). However, the seasonal pattern was however less obvious for LGIB (**Figure 1 and 2**).

The WO-test identified significant seasonality in UGIB (P for QS-test and kwman-test <0.001) and LGIB (P for QS-test = 0.002 and P for kwman-test <0.001; **Supplementary Table 3**). For PUB (P for QS-test and kwman-test <0.001) and LGIB after excluding diagnosis code of 578.1 (P for QS-test and kwman-test <0.001), significant seasonality was still observed. In the ARIMA model, a significant 12-month seasonal pattern was also detected when fitted to UGIB, including subgroup of PUB, in both unadjusted and adjusted models. However, seasonal component was only observed in unadjusted model in LGIB, but not in model adjusted for aspirin prescriptions, which was also consistent for LGIB after excluding diagnosis code of 578.1 (**Supplementary Table 4**).

Age-stratified GIB incidences

After stratified by age, the incidences of both UGIB and LGIB were higher in the older age groups, especially among those ≥80 years old (**Figure 3A**). At seasonal level, the variations were also more apparent in older subjects (**Figure 3B**). Based on WO-test,

seasonality was only identified in the two age groups (≥60 years old) for UGIB, and

only in those ≥80 years old for LGIB (**Supplementary Table 3**). In the ARIMA models

of UGIB after stratified by age, the seasonal components were also observed in the two

age groups (≥60 years) in the unadjusted models. However, it was only significant in

age groups of ≥80 years old after adjusting for aspirin, PPI and *H. pylori* infection. For

models on LGIB, the seasonality was only observed in the unadjusted model, but not

in the adjusted model (**Supplementary Table 5**).

Effects of meteorological parameters on UGIB and LGIB

All meteorological parameters collected over the 10-year study period are presented in

Figure 1. In ARIMA model, we found that the UGIB incidences were inversely

associated with AT, MaxT and MinT at lag 0 and lag 1 (month), but positively

associated with TR at lag 1 and AtomP at lag 0 and lag 1, even after adjusting for aspirin,

PPI and *H. pylori* eradication (**Figure 4A**). For LGIB, temperature parameters

including AT, Max T, Min T and AtomP were significantly associated with the

incidence of LGIB at lag 0 after adjusting for aspirin in ARIMA model (**Figure 4B**).

No significant associations were observed between other parameters and UGIB or

LGIB.

As seasonality was mainly observed in those ≥80 years old, we evaluated the

relationship between UGIB or LGIB and meteorological parameters in the subgroup of

≥80 years old using ARIMA model. The results were consistent with the overall

analyses, but larger absolute values of coefficients were observed in both UGIB and LGIB than that in the overall analyses (**Supplementary Figure 1**).

DISCUSSION

In this study that covered the recent 10-year period in Hong Kong, we showed that the incidences of UGIB were higher in winter months than that in summer months with a significant 12-month seasonal pattern detected, despite an overall decline in UGIB incidences. Subgroup analysis of UGIB showed consistent findings for PUB. On the other hand, the seasonal variations of LGIB were less obvious, which disappeared after controlling for population prescription of aspirin. The seasonality was particularly marked in older subjects who also had the highest incidences of GIB.

In this study, we demonstrated the marked seasonal variations of GIB in the elderly, particularly those older than 80 years. One hypothesis is that elderly is more sensitive to cold stress due to impaired ability to maintain core temperature during cold exposure.[30] It was also suggested that the thermal tolerance appears to be minimally compromised by age per se, but chronic diseases, sedentary lifestyle, body composition and physical fitness may contribute to impaired thermoregulatory response in the elderly.[31, 32] Therefore, the marked seasonal variations may also be accentuated by the higher background prevalence of comorbidities in the elderly. In rat model, it was shown that chronic cold stress damaged intestinal epithelial cell proliferation and

induced inflammation in the small intestine.[33] In the older subjects, the gastrointestinal mucosa may also be more prone to various damages such as aspirin. In particular, the seasonality of LGIB disappeared after adjusting for aspirin in both overall analysis and analysis of ≥80 years, suggesting that the wider use of aspirin in the older age groups may account for this observation.

Although the seasonal patterns remained in this period, the seasonal fluctuation actually reduced, which can be seen from the original data or age-stratified data. In particular, we showed that the increasing use of PPIs and *H. pylori* eradiation could reduce the seasonal variations of UGIB. Whether similar seasonality will persist in the future with anticipated further decline of UGIB remains to be determined.

Seasonal variation of non-variceal UGIB has been reported in previous studies but the results were sometimes conflicting.[4-12, 16] Tsai et al found that UGIB was more common from November to March.[9] Kapsoritakis et al also reported that the total number of patients with UGIB showed a lower prevalence in summer and PUB had two peaks, from October to December and from February to May.[34] Not only seasonal pattern, a circadian rhythm was also reported on emergency admissions for acute UGIB.[11, 16] For peptic ulcer bleeding, Nomura et al reported that the number of gastric ulcer bleeding decreased in summer but increased in autumn and winter.[12] Studies also showed seasonal variation in duodenal ulcer bleeding,[6, 8, 9] though some studies with limited number of cases reported negative results.[12, 35] Kapsoritakis et al showed that bleeding

from NSAIDs use was more frequent from December to April, which may explain the higher risk of UGIB in winter months.[34] In contrast, Thomopoulos et al found that the seasonal fluctuation of UGIB was not related to NSAIDs use.[8] Moreover, the increasing popularity of PPIs have not been taken into account in previous studies.

Among various meteorological factors, UGIB incidences were inversely associated with various temperature parameters including AT, MaxT and MinT, but positively associated with TR and AtomP. As AtomP was inversely associated with air temperature from meteorological perspective, its association with UGIB could be accounted. For LGIB, significant associations with AT, MaxT, MinT and AtomP were also demonstrated. The seasonality and the association with these meteorological parameters were particularly marked in those ≥80 years old, who also had the highest incidence of UGIB and LGIB.

In contrast, previous studies, based on descriptive statistics, investigated the impacts of meteorological factors on the incidences of UGIB with conflicting results. Westerman et al reported a very good agreement between temperature changes and numbers of duodenal ulcer bleeding.[4] Nomura et al found that gastric ulcer bleeding had an inverse relationship to temperature and vapor pressure and had a parallel relation to atmospheric pressure.[12] However, some studies did not support the correlation of meteorological factors with UGIB frequency,[15, 16] which may be related to the small sample size and different climatic variations of study locations. More importantly, none

14

of these studies addressed the issues of medications that would alter the incidences of GIB, particularly, aspirin, PPIs and *H. pylori* eradication. In addition, long-term trend or data autocorrelations was not controlled.

The mechanisms underlying the seasonal pattern of UGIB incidences are intriguing. Although some studies showed that gastric secretion and acidity are higher in spring and autumn,[36, 37] other studies revealed that there was no parallel seasonal fluctuation in duodenal ulcer and gastric acidity.[35, 38] Studies investigated the potential mechanism of the relationship between temperature and UGIB in human were also limited. Yuan et al reported that the expression levels of occludin, heat shock protein 70, nitric oxide synthase and epidermal growth factor receptor were significantly lower, whereas the gastric acid secretion was significantly higher, in the cold weather when compared to the hot weather. In addition, gastric mucus thickness was also reduced in the cold climate.[39] The reduced barriers and increased gastric acid secretion in cold weather may possibly contribute to the development of peptic ulcer and accounting for the seasonal patterns of PUB. Hence, elderly subjects may be most susceptible to these environmental changes.

Previous studies have also suggested that seasonal changes could influence the clinical manifestations of rheumatoid arthritis and osteoarthritis,[40, 41] and climate change also could alter cardiovascular mortality,[42] which may enhance the consumptions of NSAIDs and aspirin. The seasonal fluctuation of aspirin consumption was actually very

obvious in our data,[43] which could partly explain the seasonal variations of LGIB, as the seasonality of LGIB disappeared after controlling aspirin. However, prescriptions of NSAIDs, anticoagulants and other antiplatelet drugs did not show significant effects on the incidences UGIB or LGIB in this study, and hence, they were not included in the final model. We infer that it may be caused by the use of a population-level data to evaluate their effect on the overall GIB trend in the population, in which the study unit was the overall population in one month, instead of individual assessment. Moreover, consumption levels of these drugs were much lower than that of PPIs or aspirin.[43] Therefore, their effects on GIB trend may be less obvious to be detected in this population-level analysis.

The strengths of this study are the use of multiple large data sources including population prescriptions to demonstrate the association between meteorological parameters and incidences of GIB, including both upper and lower GIB. We have used the territory-wide electronic healthcare database which captures all hospitalization records, prescription and dispensing records. The well documented clinical data make it possible to perform this monthly time series analysis. The GIB incidences were also standardized to age and sex distribution of the whole population. ARIMA model was used to model the GIB data and investigate the impact of meteorological factors after adjusting for drug consumptions and *H. pylori* eradication. The ARIMA model was one of the most commonly used methods for time series analysis and addressed the effects of autocorrelation of the data.

There are limitations of our study. First, the ICD coding of the electronic health database failed to distinguish the source of GIB in some cases and were labelled as unspecified GIB, which were not included in this study. In this study, to further classify the unspecified GIB with code of 578.1, melena or black tarry stool (578.1) were treated as UGIB, whereas hematochezia from 578.1 was taken as LGIB. However, the diagnosis code of 578.1 may not be accurate enough to diagnose LGIB. As only about 7% of LGIB had this diagnosis code, we have performed additional sensitivity analysis after excluding this diagnosis code and the results were consistent. For UGIB, we have also performed sensitivity analysis on PUB, which yielded consistent results suggesting the validity of our data. The accuracy of the coding for GIB has also been validated in our previous studies.[23, 25] Second, for aspirin and PPIs consumptions, we have only included the prescription durations but not the dosage, which could also impact on the incidence of GIB. While prescription duration could better reflect the influence of time window, the primary dosage of aspirin or PPIs is usually stable on the population level. Third, all the analyses were based on data from Hong Kong, which may limit the generalization of the results to other regions with different climates and different ethnic origins.

CONCLUSION

Despite a decline in the incidences of UGIB in Hong Kong over this 10-year period, there was a still significant seasonal pattern in the incidences of UGIB, which was more

17

obvious in the elderly. The incidences of UGIB, including PUB, was more prevalent in winter months, which were associated with air temperature. LGIB also demonstrated a seasonal fluctuation, especially in the elderly, but it disappeared after adjusting for aspirin. With the ageing population and changing prescription patterns, the impacts of seasonal variations on GIB can be considerable and deserve further attention.

Declarations

Author contributions

CGG and WKL: Conceptualization, Writing- Original draft preparation. CGG and FZ: Methodology, Software. CGG and KSC: Data curation. LT and FZ: Visualization, Investigation. WKL: Supervision. LT and KSC: Writing- Reviewing and Editing.

Ethics approval and consent: This study was approved by Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (Reference Number: UW19-543). In this study, informed consent was not required by the local Institutional Review Board. Because all data in this study are from the health care system of the Hong Kong Hospital Authority and are anonymized to protect

patients' confidentiality.

REFERENCE

1. Wolf K, Schneider A, Breitner S, et al. Air Temperature and the Occurrence of Myocardial Infarction in Augsburg, Germany. *Circulation*. 2009;120(9):735–742. doi:10.1161/CIRCULATIONAHA.108.815860

2. Zhang F, Liu Z, Gao L, Zhang C, Jiang B. Short-Term Impacts of Floods on Enteric Infectious Disease in Qingdao, China, 2005-2011. *Epidemiology and Infection*. 2016;144(15):3278–3287. doi:10.1017/S0950268816001084

3. Tseng CM, Chen YT, Ou SM, et al. The Effect of Cold Temperature on Increased Exacerbation of Chronic Obstructive Pulmonary Disease: A Nationwide Study. *PloS One*. 2013;8(3):e57066. doi:10.1371/journal.pone.0057066

4. Boles RS, Westerman MP. Seasonal Incidence and Precipitating Causes of Hemorrhage from Peptic Ulcer. *Journal of the American Medical Association*. 1954;156(15):1379–1383. doi:10.1001/jama.1954.02950150001001

5. Breen FJ, Grace WJ. Bleeding Peptic Ulcer: Seasonal Variation. *American Journal of Digestive Diseases*. 1962;7:727–732.

6. Langman MI. The Seasonal Incidence of Bleeding from the Upper Gastrointestinal Tract. *Gut*. 1964;5:142–144. doi:10.1136/gut.5.2.142

7. William Beaumont Society. Seasonal Incidence of Upper Gastrointestinal Tract Bleeding. Report of the Standing Committee on Upper Gastrointestinal Bleeding, William Beaumont Society, US Army. *JAMA*. 1966;198(2):184–185.

8. Thomopoulos KC, Katsakoulis EC, Margaritis VG, Mimidis KP, Vagianos CE, Nikolopoulou VN. Seasonality in the Prevalence of Acute Upper Gastrointestinal Bleeding. *Journal of Clinical Gastroenterology*. 1997;25(4):576–579.

9. Tsai CJ, Lin CY. Seasonal Changes in Symptomatic Duodenal Ulcer Activity in Taiwan: A Comparison between Subjects with and without Haemorrhage. *Journal of Internal Medicine*. 1998;244(5):405–410.

10. Yen FS, Wu JC, Wang LM, Kuo BI, Hu SC, Lee SD. Seasonal Variation in the Incidence of Peptic Ulcer and Esophageal Variceal Bleeding in Taiwan. *Zhonghua Yi Xue Za Zhi Chinese Medical Journal (Taipei)*. 1996;57(1):22–27.

11. Du T, Lewin MR, Wang H, et al. Circadian and Seasonal Rhythms of Acute

Upper Gastrointestinal Bleeding in Beijing. *Emergency Medicine Journal*. 2010;27(7):504–507. doi:10.1136/emj.2009.075820

12. Nomura T, Ohkusa T, Araki A, et al. Influence of Climatic Factors in the Incidence of Upper Gastrointestinal Bleeding. *Journal of Gastroenterology and Hepatology*. 2001;16(6):619–623.

13. Prechter F, Burger M, Lehmann T, Stallmach A, Schmidt C. A Study on the Correlation of Gastrointestinal Bleeding and Meteorological Factors - Is There a Weather Condition for GI Bleeding? *Zeitschrift für Gastroenterologie*. 2019;57(12):1476–1480. doi:10.1055/a-1008-9863

14. Tzagournis M. Seasonal and Monthly Incidence of Peptic Ulcer. *JAMA*. 1965;193:972–975. doi:10.1001/jama.1965.03090110110039

15. Lopez-Cepero JM, Lopez-Silva ME, Amaya-Vidal A, et al. Influence of Climatic Factors on the Incidence of Upper Gastrointestinal Bleeding. *Gastroenterología y Hepatologia*. 2005;28(9):540–545.

16. Prechter F, Burger M, Lehmann T, Schmidt C, Stallmach A. The Influence of Meteorological Factors on the Incidence of Acute Upper Gastrointestinal Hemorrhage. *Gastroenterology*. 2017;152(5):S945–S946. doi:Doi 10.1016/S0016-5085(17)33219-5

17. Cryer JD, Chan K-S. *Time Series Analysis with Applications in R*. 2nd ed. Springer Texts in Statistics. Springer Science+Business Media, LLC; 2008.

18. World Health Organization. Ageing and Health. Accessed Aug 15, 2020. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

19. Lanas A, Garcia-Rodriguez LA, Polo-Tomas M, et al. Time Trends and Impact of Upper and Lower Gastrointestinal Bleeding and Perforation in Clinical Practice. *American Journal of Gastroenterology*. 2009;104(7):1633–1641. doi:10.1038/ajg.2009.164

20. Guo CG, Leung WK. Potential Strategies in the Prevention of Nonsteroidal Anti-Inflammatory Drugs-Associated Adverse Effects in the Lower Gastrointestinal Tract. *Gut Liver*. 2020;14(2):179–189. doi:10.5009/gnl19201

21. Leung WK, Wong IOL, Cheung KS, et al. Effects of Helicobacter Pylori Treatment on Incidence of Gastric Cancer in Older Individuals. *Gastroenterology*. 2018;155(1):67–75. doi:10.1053/j.gastro.2018.03.028

22. Guo CG, Cheung KS, Zhang F, et al. Risks of Hospitalization for Upper

Gastrointestinal Bleeding in Users of Selective Serotonin Reuptake Inhibitors after Helicobacter Pylori Eradication Therapy: A Propensity Score Matching Analysis. *Alimentary Pharmacology and Therapeutics*. 2019;50(9):1001–1008. doi:10.1111/apt.15507

23. Chan EW, Lau WC, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding with Gastroprotective Agents: A Population-Based Study. *Gastroenterology*. 2015;149(3):586–595 e583. doi:10.1053/j.gastro.2015.05.002

24. Goyal A, Shannon T, Chatterjee K, Katz P. Are Icd-9 Codes Accurate in Identifying Lower Gastrointestinal Tract Bleeding. *American Journal of Gastroenterology*. 2016;111:S100-S101. doi:Doi 10.14309/00000434-201610001-00208

25. Guo CG, Cheung KS, Zhang F, et al. Incidences, Temporal Trends and Risks of Hospitalisation for Gastrointestinal Bleeding in New or Chronic Low-Dose Aspirin Users after Treatment for Helicobacter Pylori: A Territory-Wide Cohort Study. *Gut*. 2020;69(3):445–452. doi:10.1136/gutjnl-2019-318352

26. Guo CG, Cheung KS, Zhang F, et al. Delay in Retreatment of Helicobacter Pylori Infection Increases Risk of Upper Gastrointestinal Bleeding. *Clinical Gastroenterology and Hepatology*. 2021;19(2):314-322 e312. doi:10.1016/j.cgh.2020.03.071

27. Hong Kong Observatory. Climatological Information Services. Accessed Jul 16, 2019. https://www.hko.gov.hk/en/cis/climat.htm

28. Census and Statistics Department Hong Kong Special Administrative Region. Hong Kong Annual Digest of Statistics. Accessed Oct 26, 2019. https://www.censtatd.gov.hk/hkstat/sub/sp20.jsp?productCode=B1010003

29. Hyndman RJ, Athanasopoulos G. *Forecasting: Principles& Practice*. 2nd Edition ed. OTexts; 2018.

30. Degroot DW, Kenney WL. Impaired Defense of Core Temperature in Aged Humans During Mild Cold Stress. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*. 2007;292(1):R103–108. doi:10.1152/ajpregu.00074.2006

31. Kenney WL, Munce TA. Invited Review: Aging and Human Temperature Regulation. *J Appl Physiol (1985)*. 2003;95(6):2598–2603.

doi:10.1152/japplphysiol.00202.2003

32. Young AJ, Lee DT. Aging and Human Cold Tolerance. *Experimental Aging Research*. 1997;23(1):45–67. doi:10.1080/03610739708254026

33. Kaushik S, Kaur J. Effect of Chronic Cold Stress on Intestinal Epithelial Cell Proliferation and Inflammation in Rats. *Stress*. 2005;8(3):191–197. doi:10.1080/10253890500245953

34. Kapsoritakis AN, Ntounas EA, Makrigiannis EA, et al. Acute Upper Gastrointestinal Bleeding in Central Greece: The Role of Clinical and Endoscopic Variables in Bleeding Outcome. *Digestive Diseases and Sciences*. 2009;54(2):333–341. doi:10.1007/s10620-008-0364-1

35. Savarino V, Mela GS, Zentilin P, et al. Are Duodenal Ulcer Seasonal Fluctuations Paralleled by Seasonal Changes in 24-Hour Gastric Acidity and Helicobacter Pylori Infection? *Journal of Clinical Gastroenterology*. 1996;22(3):178–181. doi:10.1097/00004836-199604000-00005

36. Markov, II. [Seasonal Variations of Gastric Secretion and Acidity in Normal Dogs and Human Subjects]. *Biulleten Eksperimentalnoi Biologii i Meditsiny*. 1959;47(5):33–38.

37. Umanskii S. [Seasonal Variations in Gastric Juice Acidity and in Uropepsin in Paractically Health Subjects]. *Voprosy Pitaniia*. 1972;31(1):35–38.

38. Hui WM, Lam SK. Monthly Variation in Frequency of Active Duodenal-Ulcer and Maximal Acid Output. *Journal of Gastroenterology and Hepatology*. 1988;3(5):457–463. doi:DOI 10.1111/j.1440-1746.1988.tb01401.x

39. Yuan XG, Xie C, Chen J, Xie Y, Zhang KH, Lu NH. Seasonal Changes in Gastric Mucosal Factors Associated with Peptic Ulcer Bleeding. *Experimental and Therapeutic Medicine*. 2015;9(1):125–130. doi:10.3892/etm.2014.2080

40. Mori H, Sawada T, Nishiyama S, et al. Influence of Seasonal Changes on Disease Activity and Distribution of Affected Joints in Rheumatoid Arthritis. *BMC Musculoskeletal Disorders*. 2019;20(1):30. doi:10.1186/s12891-019-2418-2

41. Craddock D. Seasonal Variations in Osteoarthritis. *Journal of the Royal College of General Practitioners*. 1986;36(291):473.

42. Bunker A, Wildenhain J, Vandenbergh A, et al. Effects of Air Temperature on Climate-Sensitive Mortality and Morbidity Outcomes in the Elderly; a

Systematic Review and Meta-Analysis of Epidemiological Evidence. *EBioMedicine*. 2016;6:258-268. doi:10.1016/j.ebiom.2016.02.034

43.   Guo CG, Zhang F, Wu JT, et al. Divergent Trends of Hospitalizations for Upper and Lower Gastrointestinal Bleeding Based on Population Prescriptions of Aspirin, Proton Pump Inhibitors and Helicobacter Pylori Eradication Therapy. *United European Gastroenterol J*. 2021 doi:10.1002/ueg2.12067

Figure Legends

Figure 1 Time trends of GIB and meteorological factors

Figure 2 Incidences of UGIB and LGIB by month of the year

Figure 3 The incidences of UGIB and LGIB (A) and the corresponding seasonal

components (B) after stratified by age

Figure 4 Coefficients of meteorological factors on UGIB (A) and LGIB (B) in ARIMA

models for lagged associations