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Effect of Ambient Temperature on Daily Hospital Admissions for Upper Gastrointestinal Bleeding in Nanchang, China: A Time-Series Analysis

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1. Abstract

1.1. Background: Hospital admission for upper gastrointestinal bleeding (UGB) increased in cold months indicate that ambient temperature might be associated with UGB.

1.2. Methods: We performed a time-series study of 3990 patients admitted with a first episode of UGB in Nanchang from May 2017 to June 2020. A generalized additive model with a distributed lag non-linear model was used to assess the association between temperature and UGB. Long-term time trends, seasonality, and the effect of day of week and public holidays were controlled in the model.

1.3. Results: We found a non-linear association of daily average temperature with UGB, with cold temperatures tending to increase the risk of esophageal and gastric variceal bleeding (EGVB), acute nonvariceal UGB, and total UGB. The effect of low temperatures (5.1°C, 2.5th percentile and 11.9°C, 25th percentile) on total UGB was evident at a lag of 1 day, with relative risk (RR) 1.43 (95% confidence interval [CI], 1.09–1.89) at the 2.5th percentile and 1.29 (95% CI, 1.05–1.59) at the 25th percentile. The association of acute nonvariceal UGB and EGVB with low temperatures was evident at a lag of 6 days, with RR 1.52 (95% CI, 1.03–2.23) and 1.91 (95% CI, 1.11–3.29) at the 2.5th percentile and RR 1.44 (95% CI, 1.07–1.93) and 1.54 (95% CI, 1.01–2.33) at the 25th percentile, respectively. Associated elevated risk was extended to a maximum lag of 7 days.

1.4. Conclusion: These findings suggest that cold temperature is an important contributor to the risk of UGB in Nanchang, China.

2. Introduction

Upper gastrointestinal bleeding (UGB) is a common medical emergency with an incidence of 48 to 160 per 100,000 people per year in the United States, Europe, and China [1-3]. UGB has heavy morbidity and mortality burdens worldwide, especially in low- and middle-income countries. As one of the largest developing countries, China has experienced a heavy disease burden owing to UGB, with an estimated UGB-specific death rate of 4% to 14% [1]. Hypothermia alone may cause an imbalance between gastric acid secretion and the mucosal defense system of the gastric mucosa, leading to the formation of UGB. A rat model of cold restraint stress-induced gastric ulceration showed that when the body has been restrained with cold-water immersion for 6 hours, hemorrhage or erosions of the gastric mucosa appear [4]. One study showed that hospital admission for UGB in cold months (December to April) was significantly higher than that in warm months (June to September) [5, 6]. These findings indicate that ambient temperature might be associated with UGB.

Previous evidence suggests that ambient temperature may have a significant impact on diseases of different systems, including cerebro-cardiovascular diseases, kidney injury, premature rupture, mental disorders, respiratory disease, and some digestive diseases [7-14]. Cold ambient temperature has been proven to be associated with ischemic stroke, myocardial infarction, respiratory symptoms, premature death, and gastroenteritis [8, 15-18]. High ambient temperature could have an impact on oxygen-consuming organs and cause diseases such as cardiovascular diseases, stroke, male reproductive function, mental disorders, premature rupture, and pancreatitis [7, 9-11, 14, 15]. One study showed that each 2.9°C decrease in temperature during a 24-hour period resulted in an 11% increase in the risk of cerebral stroke (95% confidence interval [CI], 1.01–1.22) [8]. Another study in 15 Chinese megacities from 2007 to 2013 showed that among cardiovascular disease-related deaths attributable to ambient temperature, 15.8% (95% CI, 13.1%–17.9%) were attributable to cold temperatures [15]. Morral-Puigmal et al [18], used a distributed lag non-linear model (DLNM) to estimate the effects of meteorological factors on hospitalizations for gastroenteritis in Spain and found that both high and low temperatures increased the risk of such hospitalizations (relative risk [RR], 1.21; 95% CI, 1.09–1.34 and RR, 1.07; 95% CI, 1.00–1.15, respectively]. However, evidence regarding the effects of temperature on UGB is relatively scarce, especially in low- and middle-income countries.

Nanchang is a representative rapidly developing city in inland southeastern China, with an area of 7195 km^2 and a permanent population of 5.5 million [14]. Because both cold and hot air can stagnate on the ground owing to its climate and geographic characteristics, Nanchang has relatively cold winters and extremely hot summers. A wide range of temperatures can be observed in Nanchang throughout the year, with the highest recorded temperature being 40.9°C and the lowest being −15.2°C [19]. Therefore, Nanchang provides an ideal setting to investigate the associations between ambient temperature and UGB in developing regions. Using hospitalization data from the provincial hospital, we aimed to investigate the associations between different types of UGB and ambient temperature to clarify whether climate contributes to the onset of UGB.

3. Materials and Methods

3.1.Study Design and Setting

Nanchang, the capital of Jiangxi Province, is located inland in southeastern China at the middle–lower reaches of the Yangtze River (Figure 1). Owing to its low latitude (at the 28th parallel) and distance from the sea (450 kilometers), Nanchang has a subtropical monsoon climate. The annual temperature and precipitation of Nanchang are approximately 18°C and 1600 mm, respectively. To investigate the association between ambient temperature and UGB, in this study, we recorded daily temperatures from May 2017 to June 2020 in Nanchang city and observed the incidence of UGB hospitalization among residents in the central part of the city. Daily ambient records in the city were provided by the Jiangxi Meteorological Ecology Center. UGB hospitalization data of residents in the city were obtained from the electronic medical records for inpatients of the First Affiliated Hospital of Nanchang University, the Second Affiliated Hospital of Nanchang University, and Jiangxi Provincial People's Hospital.

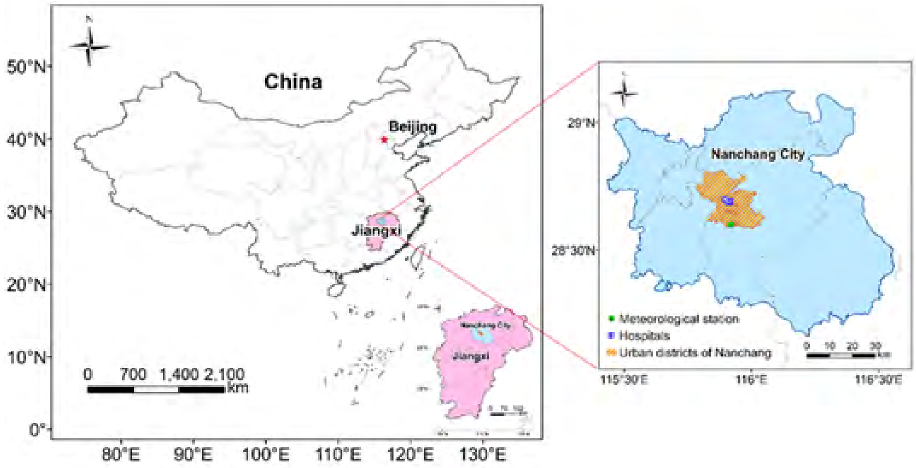


Figure 1: Location of Nanchang city in China and geographic distribution of hospitals and meteorological station.

3.2. Participants

Study participants were residents living in the central area of Nanchang city, who were admitted to provincial hospitals for UGB from May 2017 to June 2020. Most patients were hospitalized in The First Affiliated Hospital of Nanchang University, the Second Affiliated Hospital of Nanchang University and Jiangxi Provincial People's Hospital. A total of 3990 patients were finally included in the analysis.

3.3. Variables

3.3.1. Outcomes: The dependent variable was UGB hospitalization and the hospitalization risk among residents in the central area of Nanchang. The electronic medical system recorded the date of UGB hospitalization and daily UGB hospitalizations for most residents of central Nanchang during the observation period. On this basis, we calculated the cumulative relative risk (RR) and 95% confidence interval (CI) of UGB hospitalization with temperatures at the 2.5th, 25th, 75th, and 97.5th percentiles for lags of 0–2 to 0–7, 0–14, 0–21 days. The etiological type of UGB was a dichotomous variable, divided into esophageal and gastric variceal bleeding (EGVB) and acute nonvariceal upper gastrointestinal bleeding (ANVUGIB).

3.3.2. Predictors: The independent variables were meteorologic data of Nanchang. Hourly ambient temperature, relative humidity, precipitation, and atmospheric pressure in Nanchang were obtained from the China Meteorological Data Sharing Service System (http://data.cma.cn). Daily median temperatures at the 2.5, 25, 75 and 97.5 percentiles were obtained from the Jiangxi Ecological Meteorology Center.

3.3.3. Covariate: Individual-level variables were divided into sex (male, female), age (<15, 15–44, 45–64, ≥65 years) and etiology of UGB. The etiology of UGB was classified using the International Classification of Diseases Tenth Revision (ICD-10). The ICD-10 codes of gastro-esophageal laceration-hemorrhage syndrome, esophagorrhagia, gastric ulcer with hemorrhage, duodenal ulcer with hemorrhage, peptic ulcer with hemorrhage, acute hemorrhagic gastritis, esophageal varices with bleeding, gastric varices with bleeding, and esophageal and gastric variceal bleeding are K22.6, K22.8, K25.0, K26.0, K27.0, K29.0, K74.615, K74.618, and K74.617, respectively [3, 20].

3.4. Statistical Analyses

On the basis of previous studies on the effect of ambient temperature on adverse health outcomes [10, 11, 21], we used a generalized additive model (GAM) with a quasi-Poisson distribution and DLNM to assess the association of ambient temperature and UGB, as in the following equation:

$$Log[E(Y_t)] = s(time, 7df/year) + s(humidiy, 3df) + cb(temp, 3df, lag = 7, 4df) + DOW + PH + intercept \quad (1)$$

in which $E(Y_t)$ refers to the estimated number of UGB hospitalizations on day t; s() is the penalized spline function in GAM to account for the non–linear variables (i.e., time trend and relative humidity); and *cb*() is the cross–basis function in DLNM and accounts for the non-linear and delayed effect of daily mean temperature. The effects of day of the week (DOW) and public holidays (PH) were also adjusted, with the categorical variables DOW and PH recoded as dummy variables in the models. On the basis of previous studies [11, 14], the maximum lag for temperature with a significant effect on UGB was selected to be 7 days. To ensure comparability with recent studies [22, 23], we controlled the time trend with seven degrees of freedom (DFs) per year (i.e., 21 DFs). The DFs for climate conditions (i.e., humidity and temperature) were determined by minimizing the generalized cross validation score, which is suggested to be a better indicator than the quasi Akaike information criterion or partial auto-correlation functions of residuals for evaluating the performance of an over-dispersed Poisson model [24].

Given the non-linear exposure–response (E-R) relationship, the effect estimates of ambient temperature on UGB were reported as the cumulative RRs and 95% CIs of hospitalization for UGB at the 2.5th, 25th, 75th, and 97.5th percentiles of temperature relative to median temperature for lags of 0–7 days. The predicted associations on the grid of predictor-lag values between temperature and UGB hospitalization risks over lags and the overall E-R relationship curves were further visualized. The E-R relationship was estimated using a natural cubic spline function with the reference level set to the median and three equally spaced knots placed across the temperature range [15]. To explore potential modifiers, we conducted stratified analyses by age and sex.

To test the robustness of our estimates, we conducted a series of sensitive analyses by respecifying the model as follows: (1) we extended the maximum lag to 14 and 21 days for temperature effect to justify the 7-day maximum period; (2) we changed the DFs for temperature from 4 to 6; and (3) we changed the DFs for lag-response to 3, 5, and 6. Additionally, considering the potential confounding effects of air pollution on UGB as well as multicollinearity, we further included the main air pollutants in Nanchang—particulate matter with an aerodynamic equivalent diameter less than 2.5 μm ($PM_{2.5}$) and ozone (O_3)—with a natural spline function of three equally spaced knots in the model [25-27].

All statistical analyses were conducted in R software version 4.0.3 (The R Project for Statistical Computing, Vienna, Austria) using the "mgcv" and "dlnm" packages. All tests were two-sided, with effects at $p<0.05$ considered significant.

4. Results

4.1. Baseline Characteristics of Study Participants and Variables

In this study, 3090 (77.4%) participants were male patients and 900 (22.6%) participants were female patients (Table 1); the average age was 51 years (range 11–93 years). The proportion of patients aged 45–64 years was the highest at 45.1%, and the proportion of young patients aged 0–14 years was the lowest at only 0.6%. There were more patients with ANVUGIB than those with EGVB. Men aged 45–64 years accounted for the highest proportion of ANVUGIB, and there was only one case of EGVB in a female patient under 15 years old. Significantly more cases of UGB were caused by ANVUGIB (69.6%) than by EGVB (30.4%). The median daily average temperature and relative humidity in Nanchang during the study period was 20.9°C and 76.0%, with ranges of −1.3°C to 34.6°C and 31.3% to 97.3%, respectively.

4.2. Multilevel Analysis for the Effect of Temperature on UGB Hospitalization

The effects of temperature on different types of UGB, including total UGB, ANVUGIB, and EGVB, over different lags are shown in Figure 2. Total UGB, ANVUGIB, and EGVB at a lag of 0 days had an obvious "low temperature effect." In other words, when the air temperature was low, its effect on UGB, ANVUGIB, and EGVB was high. When the air temperature decreased to a certain threshold (approximately 20°C), the risk of bleeding significantly increased with a decline in temperature, and the change trend was abrupt.

To analyze the lag effect of different temperature ranges on UGB, typical temperatures at the 2.5th (5.1°C), 25th (11.9°C), 75th (25.7°C), and 97.5th (32.1°C) percentiles were chosen to explore the RR of UGB with lag-time change. Table 2 shows the cumulative RR and 95% CI of the daily average temperature on total UGB, EGVB, and ANVUGIB at these four percentiles over specific lags: 0, 0–1, 0–2, 0–3, 0–4, 0–5, 0–6, and 0–7 days. Compared with the median temperature (20.9°C), lower temperatures were associated with higher RRs of total UGB. The effect of low temperature (5.1°C, 2.5th percentile and 11.9°C, 25th percentile) was evident at a lag of 1 day, with an RR of 1.43 (95% CI, 1.09–1.89) at the 2.5th percentile and 1.29 (95% CI, 1.05–1.59) at the 25th percentile. There were increasingly apparent associations between daily average temperature and the occurrence of total UGB at the 2.5th to 97.5th percentiles of temperature along lag 0–1 to lag 0–7 days. Similar to total UGB, lower temperatures were associated with higher RRs of EGVB and ANVUGIB. A lower daily average temperature significantly increased the occurrence of EGVB and ANVUGIB at all four temperature percentiles (2.5th, 25th, 75th, and 97.5th) at a lag of 0–7 days. The association of the occurrence of ANVUGIB and EGVB with low temperatures (5.1°C, 2.5th percentile and 11.9°C, 25th percentile) was evident at a lag of 6 days, with an RR of 1.52 (95% CI, 1.03–2.23) and 1.91 (95% CI, 1.11–3.29) at the 2.5th percentile and an RR of 1.44 (95% CI, 1.07–1.93) and 1.54 (95% CI, 1.01–2.33) at the 25th percentile, respectively. There were increasingly apparent associations between daily average temperature and the occurrence of ANVUGIB and EGVB at the 2.5th to 97.5th percentiles of temperature from lag 0–6 to lag 0–7 days.

To clearly demonstrate the E-R relationship between daily average temperature and the RR of daily hospital admissions for UGB, we plotted E-R curves at lags of 0–7 days for different UGB hospitalizations: total UGB, ANVUGIB, and EGVB (Figure 3). A declining association between daily average temperature and the occurrence of UGB, ANVUGIB, and EGVB was apparent at a lag of 0–7 days. A decrease in the daily average temperature significantly increased the risk of different types of UGB at a lag of 0–7 days. Exposure to cold and heat was associated with an increased and decreased risk of different types of UGB, respectively.

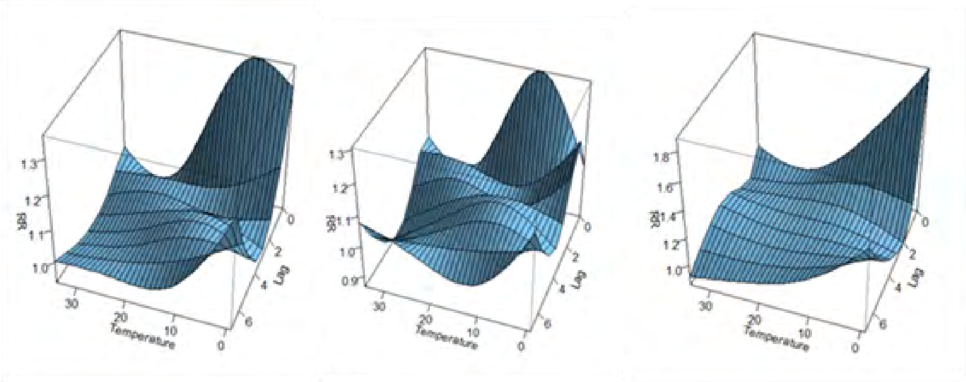
Table 3 presents the results of analysis for the effects of temperature on hospital admissions for different types of UGB over a lag of 0–7 days, stratified by age and sex. The cumulative RR over a lag of 0–7 days for UGB associated with cold temperature, especially for ANVUGIB, was generally higher among female patients and patients aged ≥65 years. For example, a significantly elevated risk of ANVUGIB occurrence owing to cold temperature was observed at a lag of 7 days in patients with advanced age. Compared with the median temperature (20.9°C), the RR for ANVUGIB associated with low temperature (5.1°C, 2.5th percentile and 11.9°C, 25th percentile) was 1.47 (95% CI, 1.09–1.98) and 1.20 (95% CI, 1.01–1.51), respectively. The RR (11.9°C, 25th percentile) for total UGB and ANVUGIB in female patients was 1.57 (95% CI, 1.03–2.40) and 1.65 (95% CI, 1.07–2.54), respectively, at a lag of 7 days.

Sensitivity analyses showed that the elevated risks of different kinds of UGB associated with cold temperature tended to disappear when the maximum lag days was extended to 14 and 21 days (Figure S1). The E-R curves for temperature and different kinds of UGB in the respecified model were generally similar to our main results, with a robustly elevated risk of UGB associated with cold temperature exposure, especially for EGVB (Figure S2). Additionally, the overall E-R relationships of temperature and different kinds of UGB, additionally adjusted for air pollution, did not substantially change, with cold temperature still being consistently associated with elevated risks of UGB (Figure S3).

Table 1: Summary of daily hospital admissions for UGB in Nanchang from May 2017 to June 2020 (n=3990)

Etiology	ANVUGIB	EGVB	Total	Percent (%)
Sex				
Male	2178	912	3090	77.4
Female	600	300	900	22.6
Age				
<15	25	1	26	0.6
15–44	949	339	1288	32.3
45–64	1097	703	1800	45.1
⩾65	707	169	876	22
Frequency(n)	2778	1212	3990	/
Percent (%)	69.6	30.4	/	/

Abbreviations: UGB, upper gastrointestinal bleeding; ANVUGIB, acute nonvariceal upper gastrointestinal bleeding; EGVB, esophageal and gastric variceal bleeding



(a) Total UGB (b) ANVUGIB (c) EGVB

Figure 2: Three-dimensional plots of predicted effect on different types of UGB using grids of temperature–lag values.

Table 2: Cumulative RRs (95% CIs) of UGB associated with daily mean temperature among selected cutoff points

	UGB				ANVUGIB				EGVB			
Lag effects	2.5th	25th	75th	97.5th	2.5th	25th	75th	97.5th	2.5th	25th	75th	97.5th
Lag 0	1.36 (0.97,1.90)	1.28 (1.00,1.63)	0.94 (0.84,1.06)	0.99 (0.72,1.35)	1.24 (0.84,1.83)	1.28 (0.97,1.68)	0.94 (0.82,1.07)	0.99 (0.68,1.43)	1.58 (0.90,2.75)	1.27 (0.84,1.91)	0.97 (0.81,1.17)	1.04 (0.64,1.
Lag 0-1	1.43(1.09,1.89)*	1.29(1.05,1.59)*	0.94 (0.85,1.05)	0.98 (0.74,1.29)	1.29 (0.94,1.78)	1.24 (0.98,1.58)	0.95 (0.84,1.09)	1.01 (0.72,1.39)	1.70 (0.99,2.67)	1.37 (0.97,1.94)	0.93 (0.79,1.11)	0.97 (0.63,1.
Lag 0-2	1.41(1.06,1.87)*	1.26(1.01,1.57)*	0.94 (0.84,1.05)	0.94 (0.71,1.26)	1.30 (0.94,1.79)	1.19 (0.93,1.53)	0.95 (0.84,1.09)	0.96 (0.68,1.36)	1.60 (1.00,2.56)	1.38 (0.96,2.00)	0.92 (0.77,1.10)	0.95 (0.60,1.
Lag 0-3	1.42(1.07,1.87)*	1.30(1.04,1.61)*	0.91 (0.82,1.02)	0.89 (0.68,1.18)	1.33 (0.97,1.82)	1.24 (0.97,1.58)	0.91 (0.80,1.04)	0.86 (0.62,1.20)	1.53 (0.96,2.43)	1.38 (0.96,1.99)	0.93 (0.78,1.11)	0.98 (0.64,1.
Lag 0-4	1.47(1.09,1.97)*	1.37 (1.09,1.72)*	0.88 (0.79,0.99)*	0.85 (0.63,1.13)	1.39 (0.99,1.94)	1.33 (1.03,1.72)	0.86 (0.75,0.98)	0.76 (0.54,1.07)	1.53 (0.94,2.50)	1.40 (0.96,2.04)	0.94 (0.78,1.14)	1.04 (0.66,1.
Lag 0-5	1.56 (1.11,2.17)*	1.45 (1.12,1.87)*	0.86 (0.76,0.98)*	0.81 (0.59,1.11)	1.45 (0.99,2.13)	1.41 (1.05,1.89)*	0.82 (0.71,0.96)*	0.70 (0.48,1.01)	1.65 (0.95,2.86)	1.44 (0.94,2.21)	0.95 (0.77,1.17)	1.08 (0.66,1.
Lag 0-6	1.69 (1.22,2.36)*	1.50 (1.16,1.94)*	0.85 (0.75,0.97)*	0.79 (0.58,1.08)	1.52(1.03,2.23)*	1.44(1.07,1.93)*	0.82 (0.70,0.95)*	0.68(0.47,0.99)*	1.91* (1.11,3.29)*	1.54* (1.01,2.33)*	0.94 (0.76,1.16)	1.07 (0.65,1.
Lag 0-7	1.89(1.36,2.63)*	1.52 (1.17,1.96)*	0.86 (0.75,0.98)*	0.80 (0.58,1.10)	1.58 (1.08,2.32)*	1.38 (1.02,1.87)*	0.85 (0.72,1.00)	0.73 (0.50,1.06)	2.42* (1.42,4.13)*	1.69* (1.11,2.57)*	0.90 (0.72,1.13)	0.99 (0.59,1.

*Significant at p<0.05; 2.5th percentile, 5.1°C; 25th percentile, 11.9°C; 50th percentile (median), 20.9°C; 75th percentile, 25.7°C; and 97.5th percentile, 32.1°C.

Abbreviations: RR, relative risk; CI, confidence interval; UGB, upper gastrointestinal bleeding; ANVUGIB, acute nonvariceal upper gastrointestinal bleeding; EC esophageal and gastric variceal bleeding.

Table 3: Cumulative RR (95% CI) of UGB associated with daily mean temperature among selected cutoff points at lag of 0–7 days, stratified by age and sex

Subgroup	Total UGB				ANVUGIB				EGVB			
	2.5th	25th	75th	97.5th	2.5th	25th	75th	97.5th	2.5th	25th	75th	97.5th
Age (years)												
15–44	1.31 (0.84,2.07)	1.22 (0.87,1.71)	0.95 (0.80,1.13)	0.97 (0.60,1.55)	0.98 (0.69,1.39)	1.06 (0.82,1.37)	0.89 (0.79,1.00)	0.73 (0.48,1.11)	1.85 (0.68,5.05)	1.46 (0.67,3.16)	1.18 (0.80,1.73)	2.13 (0.81,5.58)
45–64	1.45 (0.90,2.34)	1.19 (0.84,1.70)	0.89 (0.74,1.07)	0.76 (0.47,1.23)	0.97 (0.65,1.43)	1.07 (0.81,1.41)	0.96 (0.84,1.09)	0.94 (0.61,1.43)	2.42 (0.96,6.12)	1.56 (0.78,3.13)	0.70 (0.50,1.00)	0.42 (0.17,1.00)
≥65	1.39 (0.90,2.16)	1.22 (0.88,1.70)	0.99 (0.84,1.17)	1.10 (0.71,1.72)	1.47 (1.09,1.98)*	1.20 (1.01,1.51)*	1.03 (0.92,1.15)	1.20 (0.84,1.71)	0.91 (0.35,2.34)	0.97 (0.49,1.94)	1.14 (0.80,1.63)	1.51 (0.60,3.79)
Sex												
Male	1.37 (0.99,1.88)	1.10 (0.87,1.40)	0.99 (0.87,1.12)	0.99 (0.71,1.36)	1.17 (0.94,1.45)	1.17 (0.94,1.45)	0.99 (0.92,1.07)	0.96 (0.74,1.23)	1.35 (0.66,2.75)	1.11 (0.64,1.92)	1.09 (0.83,1.43)	1.36 (0.68,2.71)
Female	1.30 (0.72,2.34)	1.57 (1.03,2.40)*	0.84 (0.68,1.05)	0.85 (0.47,1.52)	1.20 (0.66,2.17)	1.65 (1.07,2.54)*	0.88 (0.71,1.10)	1.06 (0.57,1.95)	2.08 (0.66,6.56)	1.57 (0.69,3.56)	0.71 (0.46,1.07)	0.44 (0.15,1.26)

*Significant at $p<0.05$; 2.5th percentile, 5.1°C; 25th percentile, 11.9°C; 50th percentile (median), 20.9°C; 75th percentile, 25.7°C; and 97.5th percentile, 32.1°C. **Abbreviations:** RR, relative risk; CI, confidence interval; UGB, upper gastrointestinal bleeding; ANVUGIB, acute nonvariceal upper gastrointestinal bleeding; EGVB, esophageal and gastric variceal bleeding.

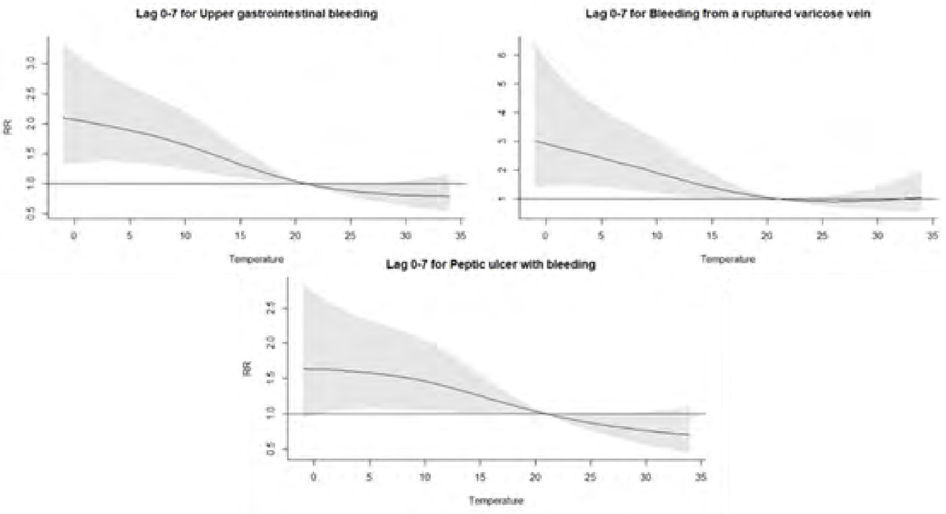


Figure 3: Exposure–response curves of daily average temperature and RR for different types of UGB at a lag of 0–7 days. **Abbreviations:** UGB, upper gastrointestinal bleeding; RR, relative risk.

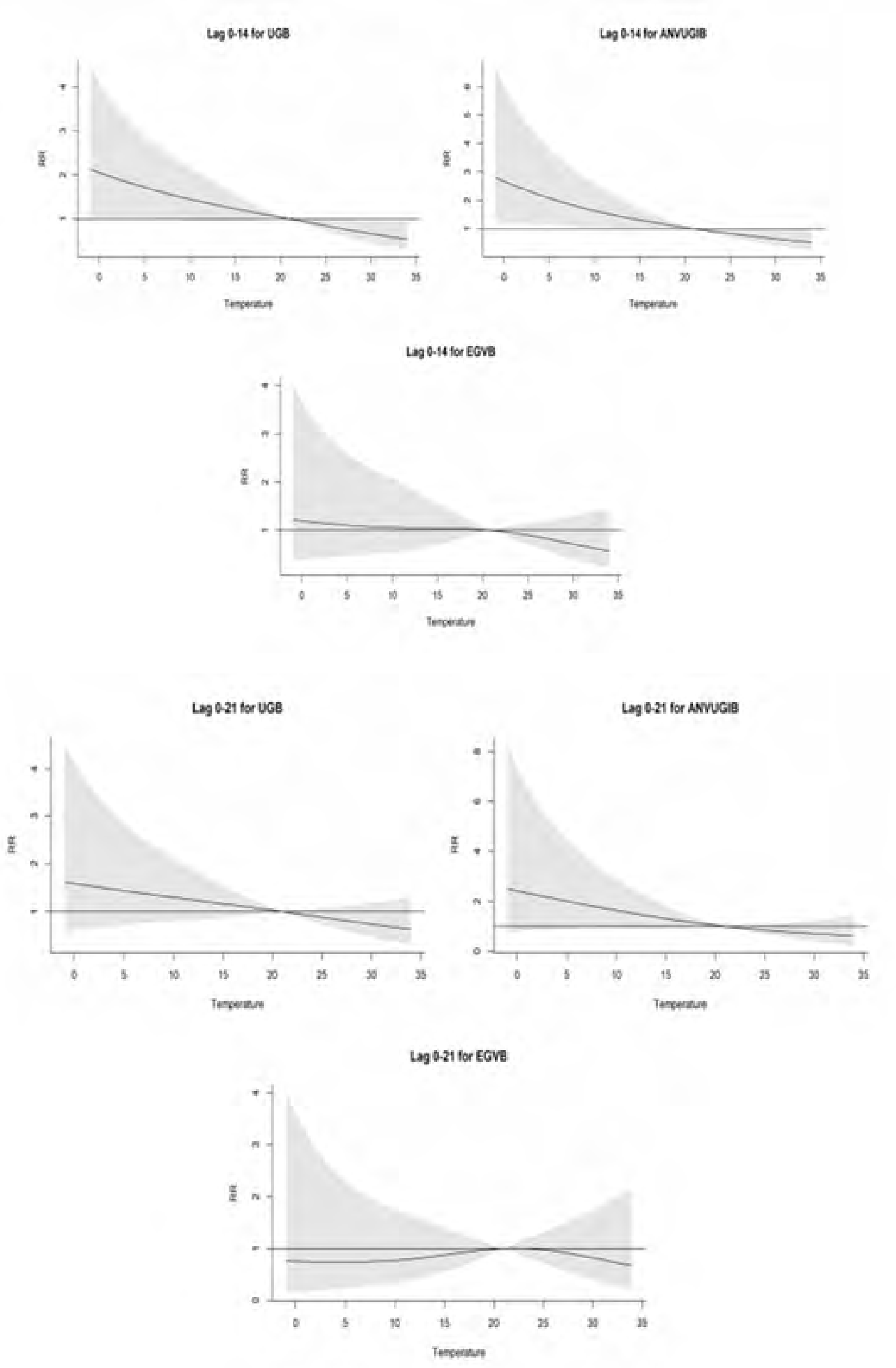
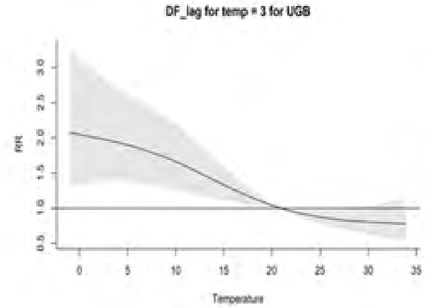
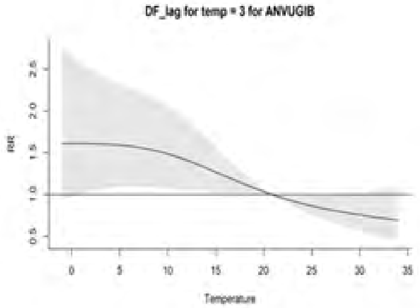
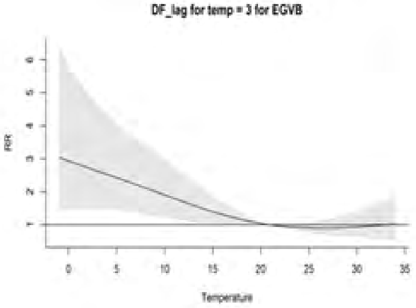


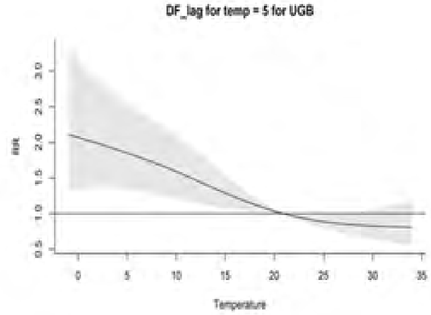
Figure S1: Exposure–response curves of daily average temperature and RR of different types of UGB at a lag of 0–14 days and 0–21 days.

Abbreviations: RR, relative risk; UGB, upper gastrointestinal bleeding; ANVUGIB, acute nonvariceal upper gastrointestinal bleeding; EGVB, esophageal and gastric variceal bleeding.


DF_lag for temp = 3 for UGB


DF_lag for temp = 3 for ANVUGIB


DF_lag for temp = 3 for EGVB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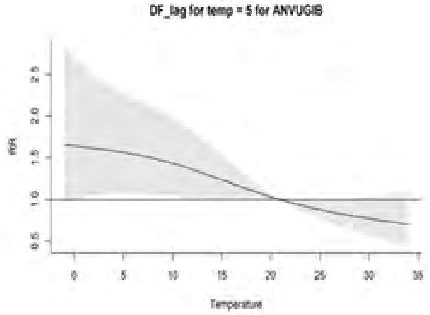
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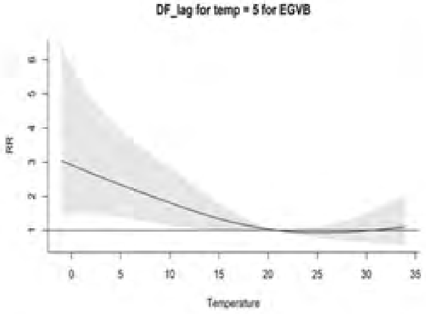
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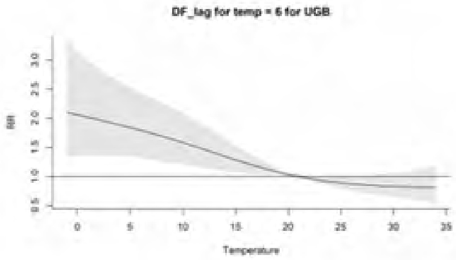
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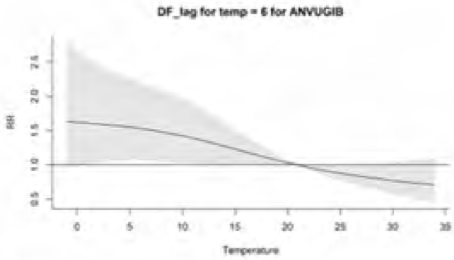
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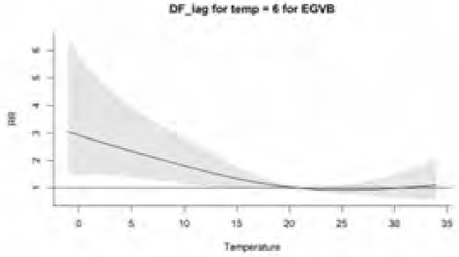
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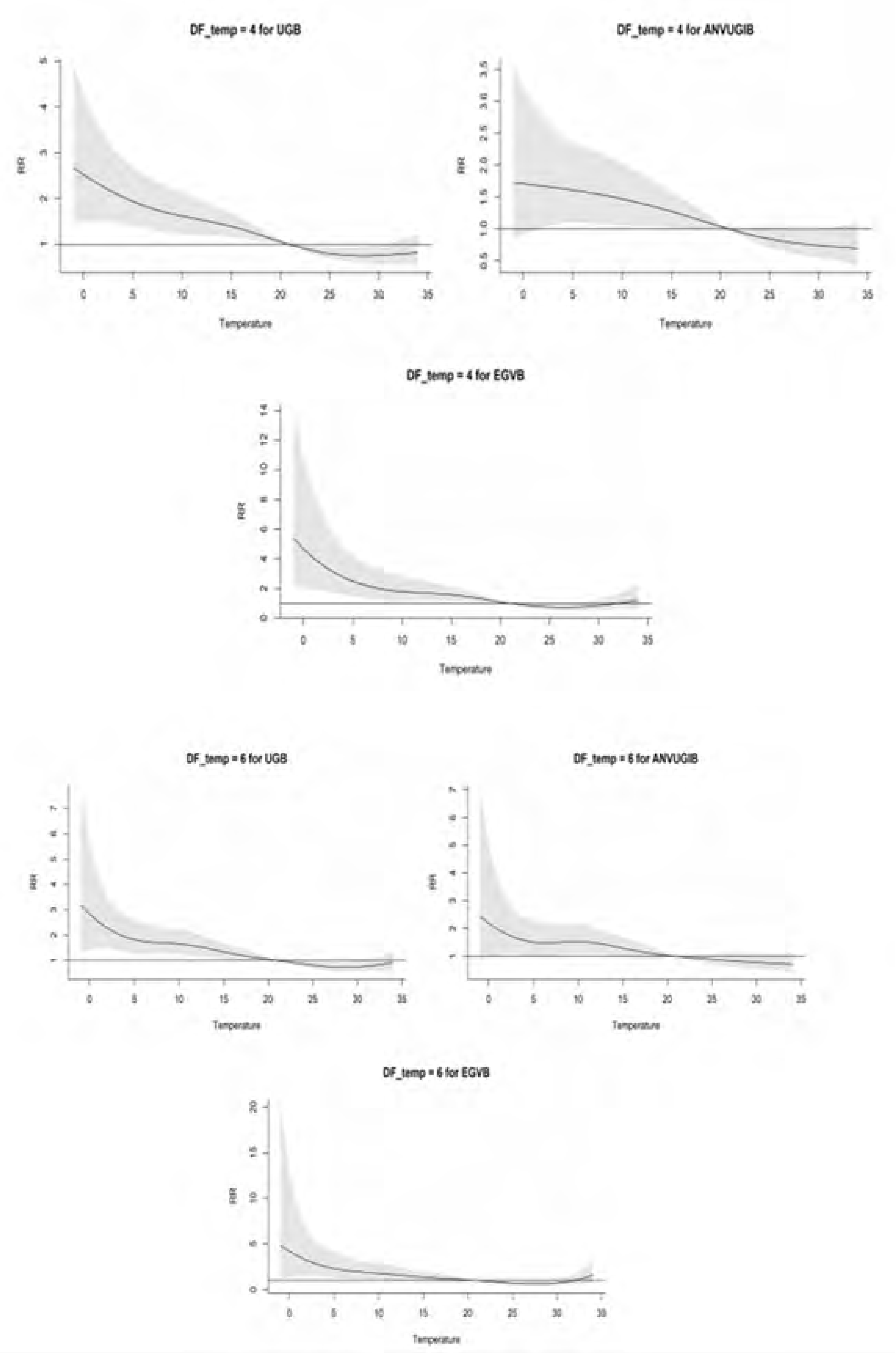

Figure S2: Exposure–response curves of daily average temperature and RR of different types of UGB of different degrees of freedom at a lag of 0–7 days.

Abbreviations: RR, relative risk; UGB, upper gastrointestinal bleeding; ANVUGIB, acute nonvariceal upper gastrointestinal bleeding; EGVB, esophageal and gastric variceal bleeding.

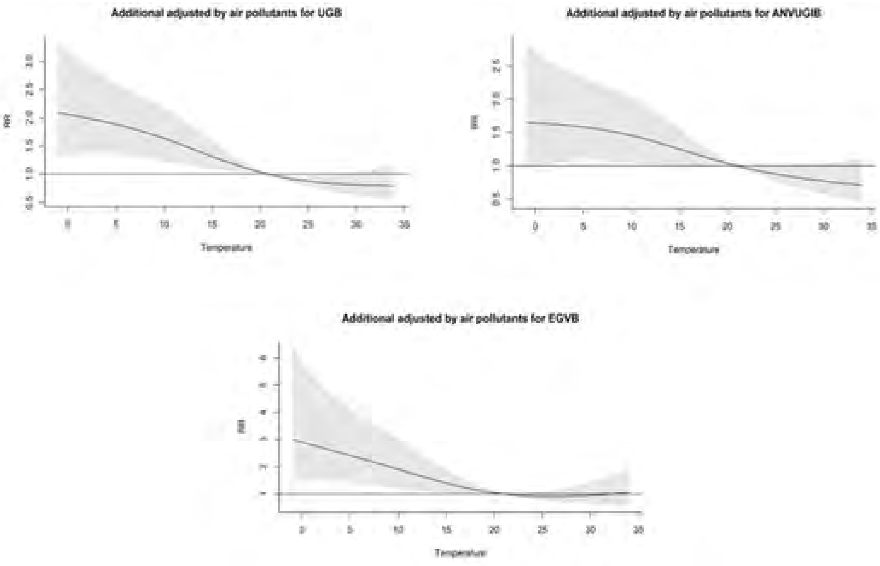

Figure S3: Exposure–response curves of daily average temperature and RR of different types of UGB at a lag of 0–7 days adjusted by air pollution. **Abbreviations:** RR, relative risk; UGB, upper gastrointestinal bleeding; ANVUGIB, acute nonvariceal upper gastrointestinal bleeding; EGVB, esophageal and gastric variceal bleeding.

5. Discussion

Owing to its high morbidity and mortality, UGB is the most frequent medical emergency among digestive diseases. According to its etiology (whether it is triggered by portal hypertension), UGB can be divided into ANVUGIB and EGVB; ANVUGIB includes peptic ulcers with bleeding, gastroesophageal laceration-hemorrhage syndrome, acute hemorrhagic gastritis, and esophageal bleeding. To our knowledge, this was the first study using time-series analysis to investigate the association between climatic factors and UGB. Unlike our previous research on acute pancreatitis, the number of hospital admissions for UGB in cold months was significantly higher than that in warm months5 6. With a focus on the associations of cold temperature with UGB, we found non-linear associations of ambient temperature with UGB of different etiologies, with cold temperature exposure consistently associated with an elevated risk of UGB, especially EGVB. Female and elderly people tended to have higher risks of UGB associated with cold temperature.

The present study showed an adverse association between cold temperature exposure and UGB, with lower temperatures associated with a higher risk of hospitalization for UGB. However, consistent with our findings, other evidence has suggested a higher risk of UGB in cold months (December to April) than in warm months [5, 6, 28, 29]. Additionally, in experimental studies of rat models, ulceration or hemorrhage of the gastric mucosa appeared when the body had been restrained with cold-water immersion for 6 to 7 hours [4, 30]. These findings imply that cold weather may play an important role in the pathogenesis of UGB.

Similar to our findings regarding the strong adverse effects of cold temperature exposure, previous studies have shown that exposure to ambient cold increases the risk of other diseases. Morral-Puigmal et al [18], found that cold temperatures were associated with hospitalizations for gastroenteritis, which was mainly caused by rotavirus infection. Wang et al [31], used a DLNM to estimate the effects of ambient temperature on hospital admissions for ischemic stroke in Jinan city and found that low temperature might be a risk factor for ischemic stroke (0°C: RR, 1.43; 95% CI, 1.10–1.85) at a lag of 0 days. Stjernbrandt et al [13], evaluated cold exposure and airway symptoms in the general population of northern Sweden and concluded that occupational cold exposure was associated with wheezing (odds ratio [OR], 1.3; 95% CI, 1.1–1.4], chronic cough (OR, 1.2; 95% CI, 1.1–1.4), and productive cough (OR, 1.3; 95% CI, 1.1–1.4). Gasparrini et al [17], estimated premature deaths attributable to ambient temperature in 384 locations in 13 countries and regions and found that much of the premature mortality burden (7.29%; 95% CI, 7.02%–7.49%) was caused by low ambient temperature. Grjibovski et al [32], studied associations between air temperature and the number of ambulance calls for asthma in Nur-Sultan, the capital of Kazakhstan; they found that a 1°C decrease in the minimum apparent temperature was associated with a 1.7% increase (95% CI, 0.1%–3.3%) in the number of calls for patients aged ≥60 years.

We found that adverse associations of ambient temperature with UGB may be stronger among female and elderly patients. Other groups that are similarly vulnerable to cold temperatures have been found in previous studies. Stjernbrandt et al [13], evaluated cold exposure and airway symptoms in the local general population and suggested that cold-related respiratory symptoms are more common among women and generally increase with age. Deng et al [33], applied a quasi-Poisson model combined with a DLNM to estimate the association of ambient temperature and non-accidental mortality. Those authors found a trend for the risk of increased death owing to ambient temperatures with increasing age, and the cold-related burden was greater for female individuals. However, these findings must be interpreted with cautious owing to the overlap of 95% CIs; the results need to be further verified in future studies with a larger sample.

Cold temperature exposure was associated with elevated risks of UGB, ANVUGIB, and especially EGVB. The cumulative elevated risks owing to cold temperature exposure may persist for up to 7 days. Although ambient cold markedly increased the risks of ANVUGIB and EGVB at the same lag of 0–6 days in our study, the underlying mechanisms were different. ANVUGIB is a type of hemorrhage induced by ulcers or erosion of the upper gastrointestinal mucosa. Research has shown that when rats' bodies are restrained with cold-water immersion (20ºC±1ºC), gastric erosions and robust ulceration occur. Additionally, cold stress induces acidification by activating gastric H+/K+ ATPase pumps and promoting pepsin C release through the induction of progastricsin expression in the gastric mucosa, leading to tiny hemorrhages or erosions of the gastric mucosa that manifest as Wischnewski spots in fatal hypothermia4. Moreover, exposure to cold causes a significant increase in inflammatory cytokines and methane dicarboxylic aldehyde and a decline in superoxide dismutase and glutathione peroxidase activity, attenuating the mucosal defensive abilities of acid [34]. EGVB is characterized by stress-related variceal rupture caused by high pressure in the portal vein among patients with progressive portal hypertension. Cold stress activates the renin–angiotensin system and reduces nitric oxide production, which can lead to increased portal pressure and resultant EGVB [35, 36]. Cold exposure is thought to increase blood pressure, cardiac output, and peripheral resistance [37]. It has also been suggested that in cold temperatures, the blood volume may shift from the body circulation to the portal circulation, consequently increasing the severity of portal hypertension. The gastric mucosal defense system involves mucus secretion, self-healing, and microcirculation, counteracting the acid effect and mitigating the contribution of low temperature to UGB [4, 38].

This study had several limitations. First, many patients with melena or mild UGB were cured in the outpatient service and could not be recruited to our study. Second, because of the ecological nature of this time-series study, the lack of personal exposure measures might have resulted in exposure misclassification. Additionally, we cannot ignore the possibility of misclassification bias owing to different types of UGB being assigned according to ICD-10 codes on the patients' disease certificates. Owing to the characteristics of southern China, there are few extreme cold events, and no data were available concerning this condition.

In conclusion, we found that cold temperature exposure tended to increase the risk of hospitalization for UGB of different etiologies. Associated cumulative elevated risks may persist to a maximum of 7 days. Female patients and elderly patients may be more vulnerable to the adverse effects of cold temperature exposure. Our findings provide epidemiological evidence to fill the current knowledge gap regarding the adverse effects of temperature on UGB, possibly helping clinicians and researchers to understand the pathogenesis. Further clinical and/or mechanistic studies are needed to reveal the underlying mechanisms.

6. Contributors

WZ and CJ conceived and designed the study. HY collected the data. LB and ZM analyzed and interpreted the data. WZ, CJ, HY, LB, ZM, and IB contributed substantially to study conception and design, acquisition of data, and analysis and interpretation of data. WZ and CL drafted the manuscript. All authors read, edited, and approved the final manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. WZ is responsible for the overall content of the manuscript, and serves as the guarantor.

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8. Competing Interests

The authors have no potential conflicts of interest to disclose.

9. Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

References

1. Wang J, Cui Y, Wang J. Clinical epidemiological characteristics and change trend of upper gastrointestinal bleeding over the past 15 years. Zhonghua Wei Chang Wai Ke Za Zhi. 2017; 20(4): 425-31.
2. Abougergi MS. Epidemiology of Upper Gastrointestinal Hemorrhage in the USA: Is the Bleeding Slowing Down? Digestive Diseases and Sciences. 2018; 1-3.
3. Ahmed A, Armstrong M, Robertson I, Morris AJ, Blatchford O, Stanley A. Upper gastrointestinal bleeding in Scotland 2000-2010: Improved outcomes but a significant weekend effect. World J Gastroenterol. 2015; 21(38): 10890-7.
4. Yang C, Sugimoto K, Murata Y, Hirata Y, Kamakura Y, Koyama Y, et al. Molecular mechanisms of Wischnewski spot development on gastric mucosa in fatal hypothermia: an experimental study in rats. Sci Rep. 2020; 10(1): 1877.
5. Du T, Lewin MR, Wang H,Ji X, Bohn HH, Xu T, et al. Circadian and seasonal rhythms of acute upper gastrointestinal bleeding in Beijing. Emerg Med J. 2010; 27(7): 504-7.
6. Sezgin O, E Altintaş, Tombak A. Effects of seasonal variations on acute upper gastrointestinal bleeding and its etiology. Turkish Journal of Gastroenterology the Official Journal of Turkish Society of Gastroenterology. 2007; 18(3): 172.
7. Mohammadi D, Zadeh MZ, Sakhvidi MJZ. Short-term exposure to extreme temperature and risk of hospital admission due to cardiovascular diseases. International Journal of Environmental Health

Research. 2021; (3): 344-54.

8. Rakers F, Schiffner R, Rupprecht S, Brandstädt A, Witte O W, Walther M, et al. Rapid weather changes are associated with increased ischemic stroke risk: a case-crossover study. Eur J Epidemiol. 2016; 31(2): 137-46.
9. Hoang-Thi AP, Dang-Thi AT, Phan-Van S, Nguyen-Ba T, Truong-Thi PL, Le-Minh T, et al. The Impact of High Ambient Temperature on Human Sperm Parameters: A Meta-Analysis. Iran J Public Health. 2022; 51(4): 710-23.
10. Peng ZX, Wang Q, Kan HD, Chen RJ, Wang WB. Effects of ambient temperature on daily hospital admissions for mental disorders in Shanghai, China: a time-series analysis. Sci Total Environ. 2017; 590: 281-6.
11. Song J, Lu JG, Wang EH, Lu MG, An Z, Liu Y, et al. Short-term effects of ambient temperature on the risk of premature rupture of membranes in Xinxiang, China: a time-series analysis. Sci Total Environ. 2019; 689: 1329-35.
12. Leddin D, Macrae F. Climate Change: Implications for Gastrointestinal Health and Disease. J Clin Gastroenterol. 2020; 54(5): 393-7.
13. Stjernbrandt A, Stenfors N, Liljelind I. Occupational cold exposure is associated with increased reporting of airway symptoms. International Archives of Occupational and Environmental Health. 2021; 94(8): 1945-52.
14. Li B, Huang W, Chen P, Chen J, Biviano I, Wang Z. Effect of ambient temperature on daily hospital admissions for acute pancreatitis in Nanchang, China: A time-series analysis. International Journal of Environmental Health Research. 2021; (2): 1-11.
15. Yang J, Yin P, Zhou MG, Ou CQ, Guo YM, Gasparrini A, et al. Cardiovascular mortality risk attributable to ambient temperature in China. Heart. 2015; 101(24): 1966-72.
16. Braga AL, Zanobetti A, Schwartz J. The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. Environ Health Perspect. 2002; 110(9): 859-63.
17. Xu R, Zhao Q, Coelho MSZS, Saldiva PHN, Abramson MJ, Li S, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. Lancet. 2015; 386(9991): 369-75.
18. Morral-Puigmal C, Martínez-Solanas È, Villanueva CM, Basagaña X. Weather and gastrointestinal disease in Spain: A retrospective time series regression study. Environ Int. 2018; 121: 649-57.
19. Chen JH, Jiang H, Wu L, Liao X, Lu Y, Tao XQ, et al. Association of ischemic and hemorrhagic strokes hospital admission with extreme temperature in Nanchang, China-A case-crossover study. J Clin Neurosci. 2017; 43: 89-93.
20. Weissman S, Sharma S, Aziz M, Ehrlich D, Perumpail M, Sciarra M, et al. Impact of Readmission for Variceal Upper Gastrointestinal Bleeding: A Nationwide Analysis. Dig Dis Sci. 2022; 67(6): 2087-93.
21. Entezari A, Mayvaneh F. Applying the Distributed Lag Non-Linear Model (DLNM) in Epidemiology: Temperature and Mortality in Mashhad. Iran J Public Health. 2019; 48(11): 2108-11.
22. Xu R, Zhao Q, Coelho MSZS, Saldiva PHN, Abramson MJ, Li S, et al. Socioeconomic inequality in vulnerability to all-cause and cause-specific hospitalisation associated with temperature variability: a time-series study in 1814 Brazilian cities. Lancet Planet Health. 2020; 4(12): 566-7.
23. Kriit HK, Andersson EM, Carlsen HK, Andersson N, Ljungman PLS, Pershagen G, et al. Using Distributed Lag Non-Linear Models to Estimate Exposure Lag-Response Associations between Long-Term Air Pollution Exposure and Incidence of Cardiovascular Disease. Int. J. Environ. Res Public Health. 2022; 19, 2630.
24. Bai L, Ding GQ, Gu SH, Bi P, Su BD, Qin DH, et al. The effects of summer temperature and heat waves on heat–related illness in a coastal city of China, 2011–2013. Environ Res. 2014; 132: 212-9.
25. Wang Y, Li M, Wan X, Sun Y, Cheng K, Zhao X, et al. Spatiotemporal analysis of PM2.5 and pancreatic cancer mortality in China. Environ Res. 2018; 164: 132-139.
26. Liu XZ, Liang Y, Guo JM. Heavy metal pollution in Nanchang City and its health implication on traffic policemen. Environ Sci Pollut R. 2019; 26(18): 17885-90.
27. Sherafati L, Zanjirabad HA, Behzadi S. Spatio-Temporal Modeling of Ozone Distribution in Tehran, Iran Based on Neural Network and Geographical Information System. Iran J Public Health. 2022; 51(1): 196-204.
28. Sato G, Matsutani S, Maruyama H, Saisho H, Fukuzawa T, Mizumoto H, et al. Chronobiological analysis of seasonal variations of variceal hemorrhage. Hepatology. 1998; 28(3): 893-5.
29. Manfredini R, De Giorgio R, Smolensky MH, Boari B, Salmi R, Fabbri D, et al. Seasonal pattern of peptic ulcer hospitalizations: analysis of the hospital discharge data of the Emilia-Romagna region of Italy. BMC Gastroenterol. 2010; 10: 37.
30. Landeira-Fernandez J. Analysis of the cold-water restraint procedure in gastric ulceration and body temperature. Physiol Behav. 2004; 82(5): 827-33.
31. Wang Q, Gao C, Wang H, Lang L, Yue T, Lin H. Ischemic stroke hospital admission associated with ambient temperature in Jinan, China. PLoS One. 2013; 8(11): e80381.
32. Grjibovski AM, Adilbekova B, Omralina E, Imangazinova S, Akhmetova Z, Ainabai A, et al. Effects of air temperature on the number of ambulance calls for asthma during cold season in Nur-Sultan- the second coldest capital in the world. Int J Circumpolar Health. 2021; 80(1): 1978228.
33. Deng CY, Ding Z, Li LJ, Wang YF, Guo P, Yang SY, et al. Burden of non-accidental mortality attributable to ambient temperatures: a time series study in a high plateau area of southwest China. BMJ Open. 2019; 9(2): e024708.
34. Tuo BX, Li CM, Peng LJ, Ye MX, Liu W, Zhong XL, et al. Analysis of differentially expressed genes in cold-exposed mice to investigate the potential causes of cold-induced hypertension. Exp Ther Med. 2014; 8(1): 110-114.
35. Brzozowski T, Ptak-Belowska A, Kwiecien S, Krzysiek-Maczka G, Strzalka M, Drozdowicz D, et al. Novel concept in the mechanism of injury and protection of gastric mucosa: role of renin-angiotensin system and active metabolites of angiotensin. Curr Med Chem. 2012; 19(1): 55-62.

36. Coskun T, Yeğen BC, Alican I, Peker O, Kurtel H. Cold restraint stress-induced gastric mucosal dysfunction. Role of nitric oxide. Dig Dis Sci. 1996; 41(5): 956-963.
37. Saeki K, Obayashi K, Iwamoto J, Tone N, Okamoto N, Tomioka K, et al. Stronger association of indoor temperature than outdoor temperature with blood pressure in colder months. Hypertens. 2014; 32(8): 1582-9.
38. Hagen SJ. Mucosal defense: gastroduodenal injury and repair mechanisms. Curr Opin Gastroenterol. 2021; 37(6): 609-14.