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County-level heterogeneity in the associations between meteorological factors and varicella incidence in Guangxi, China: a multicounty time-series study

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Abstract

Varicella incidence shows pronounced seasonality, but the nonlinear and lagged associations between meteorological factors and varicella incidence, as well as their heterogeneity at the county level, remain incompletely understood. We analysed daily varicella case and meteorological data from 111 county-level administrative units in Guangxi, China, from 2010 to 2024. County-specific associations of temperature, relative humidity, rainfall, sunshine duration, and wind speed with varicella incidence were estimated using distributed lag non-linear models and pooled using multivariate random-effects meta-analysis. Best linear unbiased predictions were used to characterise county-specific exposure-response relationships. A total of 473,676 varicella cases were included. All five meteorological factors showed nonlinear associations with varicella incidence and distinct cumulative lag patterns. High temperature (95th percentile, 29.02°C) was associated with an increased cumulative risk over lag 0–6 days (RR 1.281, 95% CI 1.229–1.335), whereas the association with high relative humidity strengthened over longer lag periods and reached an RR of 1.180 (95% CI 1.092–1.275) over lag 0–21 days. Significant heterogeneity was observed across counties for all factors (I^2, 52.4%–65.0%). County-specific temperature and humidity exposure-response relationships differed substantially in direction, magnitude, and turning points. These findings may support geographically tailored varicella risk assessment and surveillance.

Introduction

Varicella (chickenpox) is a highly contagious disease caused by varicella-zoster virus (VZV), primarily affecting children and adolescents; some cases may develop serious complications, including pneumonia, encephalitis, and secondary bacterial infections [1,2]. Although vaccination has significantly reduced varicella incidence and outbreak risk, immunization strategies and coverage levels still vary across countries and regions [3–5]. In China, the disease burden of varicella remains high [6], and schools and childcare institutions remain important settings for varicella outbreaks[7,8]. Therefore, further identification of environmental factors associated with varicella transmission remains important for public health prevention and control.

Climatic and meteorological conditions may influence infectious disease risk by affecting pathogen survival, transmission processes, human behavior, and host susceptibility[9,10]. Varicella exhibits pronounced seasonality, and its associations with meteorological conditions have been documented across diverse climatic settings. For example, studies in Japan have linked temperature and school holidays to seasonal varicella transmission[11], while studies in Colombia and Europe have also reported associations of local climatic conditions with varicella seasonality and geographic distribution[12,13]. Multicity studies in southern China and Yunnan Province further identified nonlinear and lagged associations of temperature and relative humidity with varicella incidence[14,15], while a nationwide time-series study in Japan reported associations with multiple meteorological factors[16]. However, the reported exposure–response relationships, directions of association, and relevant exposure ranges vary across settings[16–18], suggesting geographic variation in the meteorological sensitivity of varicella.

Currently, multicity studies of meteorological associations with varicella in China have mainly been conducted at the city level, including studies in South China and Yunnan Province[14,15], whereas long-term county-level evidence remains limited. Multisite studies of other infectious diseases have also found that, even when similar analytical methods are used, meteorological–disease associations may show substantial spatial heterogeneity across locations. For example, a multicounty study in western China reported between-county differences in the temperature–hand, foot, and mouth disease association[19], while a nationwide multicity study identified marked spatial heterogeneity in the relative humidity–hand, foot, and mouth disease association[20]. These findings suggest that local climatic conditions and other regional characteristics may contribute to geographic variation in meteorological exposure–response relationships. Previous studies, which were mostly conducted at the prefecture-level city or larger spatial scales, may have obscured finer-scale variation in meteorological exposures and disease responses within the same region. Therefore, county-level studies are needed to further characterize meteorological associations with varicella incidence and their geographic heterogeneity.

Located in southern China, Guangxi Zhuang Autonomous Region is a multi-ethnic border region characterized by extensive mountainous and hilly terrain and well-developed karst landscapes. It borders the Nanling Mountains to the north, the Yunnan–Guizhou Plateau to the west, and the Beibu Gulf to the south. The combined influences of complex topography, the land–sea setting, and monsoon circulation ,contribute to marked between-county variation in the long-term distributions of temperature, relative humidity, rainfall, sunshine duration, and wind speed across Guangxi, providing an appropriate setting for investigating geographic heterogeneity in meteorological associations with varicella incidence. A previous study reported significant county-level spatial clustering of varicella incidence in Guangxi, with high-incidence areas and high–high clusters located mainly in northwestern Guangxi, suggesting that Guangxi-wide averages may obscure local epidemiological patterns[21]. However, previous studies in Guangxi have primarily described the spatiotemporal distribution of varicella incidence; they have not systematically quantified the nonlinear and lagged associations between multiple meteorological factors and varicella incidence or further characterized county-specific exposure–response relationships.

This study combined distributed lag non-linear models (DLNMs) with multivariate random-effects meta-analysis to examine the nonlinear and lagged associations between varicella incidence and temperature, relative humidity, rainfall, sunshine duration, and wind speed across 111 county-level administrative units in Guangxi[22,23]. Best linear unbiased predictions (BLUPs) were further used to estimate county-specific exposure–response relationships[22,24]. This study aimed to identify location-specific meteorological responses that may be masked by Guangxi-wide pooled estimates and to inform region-specific varicella risk assessment, meteorology-informed surveillance, and county-specific prevention and control strategies in Guangxi.

Results

Descriptive statistics

From January 1, 2010, to December 31, 2024, a total of 473,676 varicella cases were reported across 111 counties and districts in Guangxi, with a mean daily case count of 86.45 (SD, 82.23). Descriptive statistics for varicella cases and the major meteorological factors are presented in Table 1.

Table 1
Descriptive statistics of varicella cases and meteorological factors in Guangxi, China, 2010–2024.

Variable	Mean	SD	P25	P50	P75	Min	Max
Varicella cases	86.45	82.23	28	58	118	0	545
Temperature (°C)	20.7	6.69	15.83	22.23	26.31	−3.88	33.2
Relative humidity (%)	75.62	11.77	69.06	77.98	84.21	24.28	98.96
Rainfall (mm)	5.72	11.25	0.11	1.43	6.33	0	289.44
Sunshine duration (h)	9.96	3.31	8.3	10.97	12.48	0.15	13.65
Wind speed (m/s)	1.65	0.71	1.14	1.51	2.01	0.04	10.37

During the study period, varicella cases and the major meteorological factors exhibited clear temporal variation and seasonal patterns (Fig. 1). Varicella cases exhibited a bimodal seasonal pattern, with the major peak occurring from November to January of the following year and a secondary peak from May to June. The annual incidence rate fluctuated over time, reaching a relatively high level in 2019, declining markedly in 2020, and increasing again thereafter (Supplementary Figures S2–S3). Spearman correlations between daily varicella case counts and concurrent meteorological factors were generally weak (Supplementary Figure S1).

Pooled cumulative exposure–response associations and between-county heterogeneity

Figure 2 illustrates the pooled cumulative exposure–response relationships between the five meteorological factors and varicella incidence over lag 0–21 days, using the median value of each factor as the reference.

Temperature showed a distinct nonlinear association with varicella incidence (Fig. 2A). Using 22.23°C as the reference, the RR initially increased and then decreased as temperature increased, remaining relatively high within the moderate-temperature range and gradually declining at higher temperatures. The cumulative RR reached its maximum near 22.59°C but did not differ significantly from the null (RR = 1.001, 95% CI: 0.997–1.005). Cumulative RRs were significantly below 1 at temperatures of 4.40–19.63°C and 25.43–30.21°C, with the lowest RR observed at 4.40°C (RR = 0.502, 95% CI: 0.449–0.561).

Relative humidity also showed a nonlinear association with varicella incidence (Fig. 2B). The RR fluctuated with increasing relative humidity and increased again at higher humidity levels. Using 77.98%

as the reference, the cumulative RR was generally lower at low relative humidity and reached its minimum at 42.00% (RR = 0.678, 95% CI: 0.627–0.734). Above approximately 86.02%, the cumulative RR was significantly greater than 1 and reached its maximum at 94.41% (RR = 1.309, 95% CI: 1.163–1.473).

Rainfall showed a nonlinear association with varicella incidence, with greater uncertainty at higher exposure levels (Fig. 2C). Using 1.43 mm/day as the reference, the cumulative RR initially increased with rainfall and peaked at 3.06 mm/day (RR = 1.030, 95% CI: 1.016–1.044). Cumulative RRs were significantly greater than 1 between 1.67 and 4.72 mm/day. The RR subsequently decreased with further increases in rainfall and was significantly below 1 between 10.84 and 55.58 mm/day. Under no-rainfall conditions, the cumulative RR was 0.890 (95% CI: 0.853–0.930).

Sunshine duration and wind speed also showed nonlinear associations with varicella incidence (Figs. 2D, E). Using 10.97 h/day as the reference, sunshine duration was associated with the highest cumulative RR at 6.44 h/day (RR = 1.264, 95% CI: 1.164–1.373), and cumulative RRs were significantly greater than 1 between 2.15 and 10.97 h/day. Using 1.51 m/s as the reference, wind speed was associated with the highest cumulative RR at 1.00 m/s (RR = 1.073, 95% CI: 1.034–1.112). Above approximately 1.51 m/s, the cumulative RR decreased steadily with increasing wind speed and reached its minimum at 3.85 m/s (RR = 0.460, 95% CI: 0.399–0.531).

The corresponding two-dimensional exposure–lag–response surfaces for the five meteorological factors are presented in Supplementary Figure S4. Random-effects meta-analysis further showed significant heterogeneity in the associations for all five meteorological factors across county-level administrative units. The I^2 values were 62.1% for temperature, 64.0% for relative humidity, 52.4% for rainfall, 65.0% for sunshine duration, and 64.0% for wind speed, with all Cochran's Q-test p-values < 0.001 (Table 2), indicating moderate-to-substantial heterogeneity in the association estimates across counties and districts.

Table 2
Heterogeneity statistics for county-specific associations between meteorological factors and varicella incidence. I^2 indicates between-county heterogeneity.

Meteorological factor	Q	df	*P*	I^2 (%)
Temperature	2444.45	330	< 0.001	62.1
Relative humidity	2262.01	330	< 0.001	64
Rainfall	1756.32	330	< 0.001	52.4
Sunshine duration	2487.66	330	< 0.001	65
Wind speed	2175.23	330	< 0.001	64

Cumulative lag effects of extreme meteorological exposures

Figure 3 further illustrates the cumulative lag associations at the P5 and P95 levels of each meteorological factor over lag 0–21 days. The P5 and P95 levels of each meteorological factor were selected, with P50 serving as the reference (Supplementary Table S1).

Extreme temperature exposure showed a pronounced time-dependent pattern. At high temperature (P95, 29.02°C), the cumulative RR increased as the lag window lengthened during the early period, reached its maximum over lag 0–6 days (RR = 1.281, 95% CI: 1.229–1.335), and remained significantly above 1 through lag 0–13 days. The cumulative RR subsequently declined, became significantly lower than 1 from lag 0–18 days onward, and reached 0.816 (95% CI: 0.748–0.889) over lag 0–21 days. At low temperature (P5, 8.23°C), the cumulative RR remained significantly below 1 throughout the lag period and generally declined as the lag window lengthened, reaching 0.629 (95% CI: 0.577–0.684) over lag 0–21 days.

Relative humidity also showed a pronounced cumulative lag association. At high relative humidity (P95, 90.98%), the cumulative RR remained close to 1 during the early lag period and subsequently increased as the lag window lengthened. It became significantly greater than 1 from lag 0–12 days onward and reached its maximum over lag 0–21 days (RR = 1.180, 95% CI: 1.092–1.275). At low relative humidity (P5, 52.34%), the cumulative RR remained significantly below 1 throughout the lag period, reached its minimum over lag 0–11 days (RR = 0.845, 95% CI: 0.818–0.874), and was 0.888 (95% CI: 0.842–0.936) over lag 0–21 days.

Cumulative RRs were generally below 1 at both low and high rainfall levels. Under no-rainfall conditions (P5, 0 mm/day), the cumulative RR declined as the lag window lengthened, reached its minimum over lag 0–16 days (RR = 0.882, 95% CI: 0.853–0.912), and then increased slightly to 0.892 (95% CI: 0.854–0.931) over lag 0–21 days. At high rainfall (P95, 25.38 mm/day), the cumulative RR was significantly below 1 from lag 0–2 days onward, reached its minimum over lag 0–15 days (RR = 0.823, 95% CI: 0.782–0.866), and was 0.889 (95% CI: 0.828–0.954) over lag 0–21 days.

The cumulative associations with sunshine duration strengthened as the lag window lengthened. At low sunshine duration (P5, 2.71 h/day), the cumulative RR was significantly greater than 1 from lag 0–9 days onward, peaked over lag 0–18 days (RR = 1.157, 95% CI: 1.076–1.245), and remained significantly elevated over lag 0–21 days (RR = 1.140, 95% CI: 1.050–1.237). At high sunshine duration (P95, 13.38 h/day), the cumulative RR reached its maximum over lag 0–14 days (RR = 1.200, 95% CI: 1.116–1.291) and subsequently declined. By lag 0–21 days, the cumulative RR was 1.055 (95% CI: 0.947–1.176) and was no longer statistically significant.

The cumulative lag pattern for wind speed differed by exposure level. At low wind speed (P5, 0.78 m/s), the cumulative RR increased during the middle and later lag periods, remained significantly greater than 1 from lag 0–10 to lag 0–20 days, and peaked over lag 0–17 days (RR = 1.081, 95% CI: 1.022–1.143). By lag 0–21 days, the cumulative RR was 1.065 (95% CI: 0.994–1.141) and was no longer statistically significant. In contrast, at high wind speed (P95, 2.99 m/s), the cumulative RR remained significantly

below 1 throughout the lag period and declined steadily as the lag window lengthened, reaching 0.629 (95% CI: 0.581–0.680) over lag 0–21 days.

Overall, the associations between meteorological factors and varicella incidence showed distinct cumulative lag patterns. The direction of the high-temperature association changed as the cumulative lag window lengthened, high relative humidity showed a delayed and progressively stronger positive association, and high wind speed showed an increasingly pronounced inverse association.The RRs and 95% CIs for P5 and P95 exposures over selected cumulative lag periods are summarized in Supplementary Table S2.

County-specific exposure–response relationships based on BLUPs

Since temperature and relative humidity showed relatively consistent association patterns across the pooled exposure–response analysis, extreme-exposure analysis, and previous varicella studies, these two meteorological factors were selected for further county- and district-specific BLUP analyses. BLUP results for rainfall, sunshine duration, and wind speed were reported as supplementary results.

Figure 4 shows the county- and district-specific BLUP estimates and spatial distributions of cumulative RRs for temperature and relative humidity at the common Guangxi-wide P5 and P95 exposure levels.

For temperature, at low temperature (P5, 8.23°C), cumulative RRs were below 1 in 100 counties and districts, with 95% CIs entirely below 1 in 72. County- and district-specific RRs ranged from 0.127 to 1.602. Daxin County and Mashan County showed the strongest inverse associations, with cumulative RRs of 0.127 (95% CI: 0.083–0.196) and 0.210 (95% CI: 0.145–0.302), respectively.

At high temperature (P95, 29.02°C), cumulative RRs were below 1 in 94 counties and districts and above 1 in 17; 95% CIs were entirely below 1 in 49 locations and entirely above 1 in two. County- and district-specific RRs ranged from 0.105 to 2.108, indicating substantial geographic variation in both the direction and magnitude of the high-temperature association. Dahua Yao Autonomous County and Bama Yao Autonomous County showed the strongest inverse associations, with cumulative RRs of 0.105 (95% CI: 0.058–0.190) and 0.122 (95% CI: 0.060–0.249), respectively.

For relative humidity, the BLUP curves for the representative counties and districts differed markedly in shape and direction. Cumulative RRs increased sharply at high relative humidity in Liubei District and Daxin County, reaching 7.513 (95% CI: 3.465–16.288) and 6.006 (95% CI: 3.034–11.892), respectively, at 94.41%. In contrast, the curve for Ziyuan County declined substantially across the low-to-moderate humidity range and reached its minimum at 61.04% (RR = 0.395, 95% CI: 0.286–0.547). Liucheng County showed an elevated cumulative RR at the low-humidity end of the curve, reaching 2.272 (95% CI: 1.694–3.048) at 42.00%. These findings indicate that the county- and district-specific relative humidity–varicella associations differed not only in magnitude but also in direction and turning points.

Counties and districts were further ranked according to their BLUP-based cumulative RRs at the extreme temperature exposure levels. Representative locations showing the strongest inverse associations at P5 and P95 were selected for comparison with the pooled temperature exposure–response curve for Guangxi (Fig. 5). The corresponding curves differed in the locations of their risk peaks, curve shapes, and association magnitudes. Some counties and districts showed substantial changes in RR across the temperature range, whereas others exhibited relatively flat curves.

County-level administrative unit-specific BLUP results for rainfall, sunshine duration, and wind speed are presented in Supplementary Figure S5. Distributions of BLUP-based cumulative RRs for all five meteorological factors at the common Guangxi-wide P5 and P95 exposure levels are summarized in Supplementary Table S3.

Sensitivity analysis

To test the robustness of the model results, sensitivity analyses were conducted by varying the degrees of freedom (df = 2–4) for the exposure and lag dimensions of the cross-basis functions, the maximum lag period (14–28 days), and the degrees of freedom used to control for the long-term time trend (5–9 per year). The results showed that the cumulative exposure–response relationships and corresponding RR estimates for each meteorological factor remained materially unchanged across the alternative parameter settings (Supplementary Figures S6–S9). In particular, changing the maximum lag period did not alter the overall direction or pattern of the estimated associations. These findings indicate that the main results were robust to alternative model specifications.

Discussion

Based on daily surveillance data from 111 counties and districts in Guangxi from 2010 to 2024, this study found that temperature, relative humidity, rainfall, sunshine duration, and wind speed were all nonlinearly associated with varicella incidence and exhibited distinct cumulative lag patterns. The county- and district-specific association estimates for all five meteorological factors showed heterogeneity; the BLUP results for temperature and relative humidity further indicated that the exposure–response curves varied across counties and districts.

Temperature showed an overall inverted U-shaped association with varicella incidence, with higher RRs at moderate temperatures and progressively lower RRs at higher temperatures; the cumulative RR at P95 increased mainly over shorter lag windows, whereas that at P5 generally remained below the reference level. Relative humidity also showed a nonlinear association with varicella incidence, with the cumulative RR at P95 increasing with longer lag windows. Previous multiregional studies in China have likewise reported nonlinear and lagged associations of temperature and relative humidity with varicella incidence[14,15]; however, the exposure–response shapes and directions of association have varied among studies conducted in Wuxi, Guangzhou, and Japan[16–18]. Studies conducted in different climatic regions have also documented geographic variation in varicella seasonality and its associations

with meteorological conditions[13,14]. This variation may reflect regional differences in climate, exposure distributions, population behavior, and model specifications[25]. Temperature fluctuations may alter opportunities for varicella transmission by affecting viral stability in the external environment and altering human activity and contact patterns; stronger solar radiation at higher temperatures may also influence transmission[26,27]. Relative humidity may also influence respiratory virus transmission by modifying environmental conditions and the conditions under which hosts are exposed[28]. Accordingly, our findings should be interpreted in the context of Guangxi's climatic and epidemiological setting, and specific exposure levels should not be regarded as universally applicable risk thresholds.

Rainfall, sunshine duration, and wind speed also showed nonlinear associations with varicella incidence. Under rain-free conditions, the cumulative RR initially decreased as the lag window lengthened and then increased slightly, but remained below the reference level through lag 0–21 days. The association at P95 rainfall showed a non-monotonic pattern, while the associations with sunshine duration and wind speed also varied across exposure levels and lag windows. Previous studies have reported inconsistent associations for these meteorological factors. Studies conducted in Lu'an and Chongqing reported associations between multiple meteorological factors and varicella incidence, although the exposure–response patterns differed among factors[29,30]. A study in Hong Kong also reported associations of rainfall and wind speed with varicella incidence among children[31]. Regarding sunshine duration, previous studies have suggested that solar radiation and vapor pressure may help predict varicella outbreaks[32], although the direction of their associations may vary according to local climatic and seasonal conditions. These differences suggest that the associations of rainfall, sunshine duration, and wind speed with varicella incidence may vary across regions.

These meteorological factors may influence varicella transmission through several potential pathways. Rainfall not only alters environmental humidity but may also be associated with changes in indoor and outdoor activities and contact patterns. Previous varicella studies have also reported a nonlinear association between rainfall and incidence, suggesting that the observed association may vary according to local climatic conditions and population behavior[29,30]. Sunshine duration can serve as an indicator of solar radiation conditions. Previous studies have reported associations of solar radiation and vapor pressure with seasonal variation in varicella incidence[32]. A recent study in Shanghai also included sunshine duration, relative humidity, and rainfall in a comprehensive evaluation of natural environmental factors associated with varicella incidence, suggesting that varicella epidemiology may be related to multiple environmental and social factors[33]. Wind speed may modify conditions for transmission by influencing airflow, ventilation, and the dispersion of airborne particles. A study in Wuxi reported an inverse correlation between wind speed and varicella case counts and proposed that wind speed might influence the airborne dispersion and dilution of the virus[16]. These potential pathways may help explain differences in the exposure–response patterns across meteorological factors. However, the underlying processes require further investigation using data on individual behavior, indoor environments, and more detailed exposure assessments.

The cumulative associations of the meteorological factors showed distinct patterns across lag windows. Given the incubation period between varicella infection and symptom onset, the observed lag patterns may jointly reflect the timing of meteorological exposure and population contact, as well as the interval from infection through symptom onset to case reporting[34]. Previous climate–health studies have shown that associations between environmental exposures and health outcomes are often delayed and that their lag patterns and durations may vary by exposure and disease[35]. In this study, the positive association at P95 temperature was concentrated mainly within shorter cumulative lag windows, whereas the positive association at P95 relative humidity and the inverse association under rain-free conditions became more pronounced over longer cumulative lag windows. Sunshine duration and wind speed, by contrast, showed different temporal patterns. Similar factor-specific lag structures have been reported in other studies of meteorological factors and infectious diseases, with lagged associations differing in duration and magnitude across meteorological factors[36,37]. Therefore, the temporal variation in the cumulative association should be examined separately for each meteorological factor rather than assuming a common lag pattern across factors.

Varicella transmission may also be shaped by school schedules and patterns of social contact. A study in Japan reported that school holidays were associated with the seasonal transmission of varicella[11]. Research on VZV seasonality has also suggested that varicella transmission is not determined by meteorological conditions alone[27]. Therefore, the cumulative lag results are best interpreted as describing how meteorological associations change across lag windows and as providing information on potential priority periods for surveillance; they should not be reduced to a single, fixed lag day of elevated risk.

Heterogeneity across counties and districts was an important finding of this study. Statistical heterogeneity was observed in the county- and district-specific association estimates for all five meteorological factors, with I^2 values ranging from 52.4% to 65.0%. The county- and district-specific BLUP curves for temperature and relative humidity differed in shape, association magnitude, and peak location. Thus, although the pooled curves for Guangxi represented the average associations across the region, they did not fully characterize the meteorological association patterns in every county and district. Similar geographic variation has been reported in other multiregional studies of infectious diseases. A multicounty study in western China reported spatial heterogeneity in the temperature–HFMD association[19], while a nationwide multicity study similarly reported geographic variation in the relative humidity–HFMD association[20]. A multicity study in Shandong further showed that meteorological exposure–response relationships could vary among cities despite the use of common model specifications and might be modified by long-term environmental characteristics[38]. A multicity study in Sichuan also reported that long-term air pollution levels might modify associations between short-term meteorological exposures and infectious disease risk[39]. Together, these findings suggest that regional climatic conditions, long-term environmental exposures, and other location-specific characteristics may contribute to spatial heterogeneity in meteorological–disease associations[25,40]. Recent small-area exposure–lag studies have further highlighted the value of characterizing location-specific exposure–response relationships at finer spatial scales[41].

Counties and districts across Guangxi differ markedly in topography, inland or coastal location, and long-term meteorological conditions. This geographic variation provides context for the observed heterogeneity in meteorological associations across counties and districts. Similar regional heterogeneity has been reported in recent multiregional studies of other infectious diseases. A study of nine cities in Fujian fitted city-specific DLNMs and subsequently pooled the estimates using random-effects multivariate meta-analysis, identifying between-city heterogeneity in environmental–disease associations[42]. Another study covering 34 cities across seven Chinese provinces used a two-stage DLNM and multivariate meta-analysis and similarly reported spatial heterogeneity in meteorological associations with infectious disease risk[43]. Together, these studies indicate that meteorological–disease associations may vary across locations even when a common analytical framework is applied. In the present study, differences among counties and districts in climatic conditions, long-term environmental exposures, and other location-specific characteristics may partly explain the observed heterogeneity. Therefore, the pooled results for Guangxi should be interpreted alongside county- and district-specific characteristics, rather than assumed to apply uniformly to all 111 counties and districts.

This study provides location-specific epidemiological evidence to inform varicella surveillance in Guangxi. The distinct lag patterns of the meteorological factors may help identify potential periods for enhanced surveillance, while the county- and district-specific BLUP results may inform geographically differentiated risk assessments. When meteorological conditions associated with elevated varicella incidence occur in Guangxi, the corresponding lag patterns may provide temporal context for strengthening case surveillance and health education in schools and childcare facilities. Previous national and regional studies have consistently identified schools and childcare facilities as major settings for varicella outbreaks[7,8,44]. At the county and district levels, local meteorological distributions and location-specific exposure–response relationships could be considered jointly in regional risk assessments. Previous studies have also suggested that meteorological data may complement varicella surveillance and prediction[32,45]. However, we did not develop or validate a prediction model, and the identified exposure levels and lag windows should not be used directly as early-warning thresholds for varicella in Guangxi. Meteorological information should complement, rather than replace, vaccination, routine case surveillance, and school-based prevention and control. Previous surveillance studies in China have shown that immunization and public health measures remain central to varicella control[46,47].

This study included long-term surveillance data from 2010 to 2024 across all 111 counties and districts in Guangxi. The two-stage DLNM and multivariate meta-analysis allowed us to characterize nonlinear associations, lag patterns, and heterogeneity across counties and districts within a common analytical framework. The main findings were generally stable across the sensitivity analyses. Several limitations should be considered. First, county- and district-level average meteorological exposures may not accurately represent individual exposures. As an ecological time-series study, our analysis estimates population-level associations and does not support causal inference at the individual level[48]. Second, long-term, consistently measured county- and district-level data on vaccination coverage, school activities, population mobility, socioeconomic conditions, and air pollution were unavailable. Residual

confounding therefore remains possible, and the observed heterogeneity cannot be fully explained[38,39]. Finally, although BLUP provides relatively stable county- and district-specific estimates, it does not identify the sources of heterogeneity. Future studies could use reliable county- and district-level covariates in meta-regression to investigate potential sources of heterogeneity and assess the predictive value of meteorological information in independently developed and validated prediction models[49,50].

In summary, varicella incidence in Guangxi showed nonlinear and lagged associations with multiple meteorological factors, and the association patterns varied across counties and districts. These findings may inform the identification of potential priority surveillance periods and county- and district-specific risk assessments in Guangxi. However, their value for prediction and early warning requires further evaluation using additional long-term, consistently measured county- and district-level data and independent validation.

Methods

Study area

Guangxi Zhuang Autonomous Region, located in southern China (20°54'–26°23' N, 104°26'–112°03' E), covers approximately 237,600 km² and has a warm, humid subtropical monsoon climate with abundant rainfall. The study included 111 county-level administrative units in Guangxi and covered the period from January 1, 2010, through December 31, 2024.

Varicella case and population data

Daily varicella case data for 111 county-level administrative units in Guangxi were collected from January 1, 2010, to December 31, 2024. The case data were obtained from the China Information System for Disease Control and Prevention and provided by the Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention; cases were aggregated by date of onset and county-level administrative unit. Although varicella is not a nationally notifiable infectious disease in China, it is included among infectious diseases under key surveillance. County-level resident population data for the same period were obtained from the Guangxi Statistical Yearbook and the Guangxi Zhuang Autonomous Region Bureau of Statistics (https://tjj.gxzf.gov.cn/) and were used to calculate varicella incidence rates and adjust for population size in the time-series analyses. The Guangxi Statistical Yearbook provides population statistics and other basic information for counties, county-level cities, and districts.

Meteorological data

Daily meteorological data were obtained from the China Meteorological Science Data Sharing Service System (https://data.cma.cn/) and included mean temperature (°C), relative humidity (%), rainfall (mm), sunshine duration (h), and wind speed (m/s). Following spatial matching and data quality control, daily meteorological data for all 111 county-level administrative units in Guangxi were obtained for 2010–

2024. Missing values were imputed and obvious outliers were corrected according to the characteristics of each meteorological variable before subsequent analyses.

Statistical analysis

We first performed descriptive analyses of daily varicella case counts and meteorological variables. Continuous variables were summarized using the mean, standard deviation (SD), 25th percentile (P25), median (P50), 75th percentile (P75), minimum, and maximum. Temporal variations in varicella cases and the major meteorological variables were visualized using time-series plots. Spearman rank correlation analysis was used to assess correlations between daily varicella case counts and concurrent meteorological variables.

This study used a two-stage analytical approach to assess the associations between meteorological factors and varicella incidence and their heterogeneity across counties and districts. In the first stage, a distributed lag nonlinear model (DLNM) was fitted separately for each of the 111 county-level administrative units in Guangxi to estimate county-specific exposure–response relationships[23]. In the second stage, county-specific estimates were pooled using multivariate random-effects meta-analysis, and best linear unbiased predictions (BLUPs) were further derived to obtain county-specific exposure–response relationships.

Distributed lag non-linear models

To account for potentially nonlinear and lagged associations, DLNMs were used to separately examine the associations of mean temperature, relative humidity, rainfall, sunshine duration, and wind speed with daily varicella case counts[51]. Within the DLNM framework, a cross-basis function was constructed to simultaneously characterize the exposure–response and lag–response dimensions. Because daily varicella case counts were overdispersed count data, a quasi-Poisson regression model was specified.

The model was specified as:

$$[\mathrm{Y_{it}} \sim \mathrm{quasi-Poisson}(\mu_{\mathrm{it}})]$$

$$[\log[\mathrm{E}(\mathrm{Y_{it}})] = \alpha_{\mathrm{i}} + \mathrm{cb}(\mathrm{X_{it}}, \mathrm{l}) + \mathrm{ns}(\mathrm{time_t}, 6 \times \mathrm{years}) + \mathrm{DOW_t} + \mathrm{offset}[\log(\mathrm{Pop_{it}})].]$$

Here, $(\mathrm{Y_{it}})$denotes the number of varicella cases reported in county (i)on day (t), $(\mu_{\mathrm{it}})$is the expected number of cases, and (α_{i}) is the intercept. The term $(\mathrm{cb}(\mathrm{X_{it}}, \mathrm{l}))$ denotes the cross-basis function for meteorological exposure (X) over lag (l). A natural cubic spline of calendar time with 6 degrees of freedom per year was used to control for long-term trends and seasonality, $(\mathrm{DOW_t})$ denotes the day-of-week effect, and $(\mathrm{Pop_{it}})$ represents the corresponding population, whose natural logarithm was included as an offset.

For each meteorological factor, natural cubic splines with 3 degrees of freedom were specified for both the exposure–response and lag–response dimensions of the cross-basis function. Based on the incubation period of varicella and previous epidemiological studies, the maximum lag period was set to

21 days[15]. For each meteorological factor, the same basis-function specification was applied across all counties and districts to ensure the comparability of county- and district-specific effect estimates. After fitting the first-stage models, the two-dimensional exposure–lag associations were reduced using cross-reduction, yielding three-dimensional coefficient vectors representing the cumulative exposure–response relationships and the corresponding variance–covariance matrices for the second-stage multivariate meta-analysis.

Using the Guangxi-wide median (P50) of each meteorological factor as the reference, we estimated the cumulative exposure–response relationships across the P1–P99 exposure range and calculated relative risks (RRs) with 95% confidence intervals (CIs) for P5 and P95 relative to P50. At the P5 and P95 exposure levels, we estimated both lag-specific RRs and cumulative RRs over lags 0–21 days to characterize the lag patterns of the associations with each meteorological factor.

Multivariate random-effects meta-analysis and BLUP estimation

Following dimension reduction of the two-dimensional exposure–lag relationships from the first-stage county-level DLNMs, three-dimensional coefficient vectors and corresponding variance–covariance matrices representing the cumulative exposure–response relationship for each county and district were obtained. These estimates were then pooled using multivariate random-effects meta-analysis to obtain the overall cumulative exposure–response relationships between each meteorological factor and varicella incidence in Guangxi [24]. The random-effects model was estimated using restricted maximum likelihood (REML), and heterogeneity across counties and districts was assessed using Cochran's Q test and the I^2 statistic.

BLUPs were further derived from the second-stage meta-analysis model to obtain county- and district-specific cumulative exposure–response relationships[24]. Similar region-specific estimation methods have been used in multi-region studies of temperature-related health associations to assess regional heterogeneity. All county- and district-specific associations were centered at the Guangxi-wide median (P50) of each meteorological factor and compared at the common Guangxi-wide P5 and P95 exposure levels. To further illustrate differences in exposure–response relationships across counties and districts, counties and districts were ranked according to their BLUP-based cumulative RRs at the P5 and P95 exposure levels, and representative locations with relatively higher and lower estimates were selected for exposure–response curve comparisons.

Sensitivity analysis

To assess the robustness of the model results, we conducted sensitivity analyses by varying the degrees of freedom for the exposure–response and lag–response dimensions of the cross-basis functions (df = 2–4), the maximum lag period (14–28 days), and the degrees of freedom for long-term temporal trends (5–9 df per year). We then evaluated whether the cumulative exposure–response relationships and the estimates at P5 and P95 remained consistent across alternative model specifications.

All statistical analyses were performed using R software (version 4.5.3). DLNMs were fitted using the “dlnm” package, and multivariate meta-analyses were conducted using the “mvmeta” package. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant.

Declarations

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Author contributions

Zhang Linlin, Dong Aihu, Hua Yimeng: Writing – original draft, Writing – review & editing, Formal analysis. Lu Manyuan, Liao Tanfeng, Pan Guanxi: Investigation, Data curation. Lu Huaxiang, Qin Jian, Zhang Zhiyong: Conceptualization, Supervision, Project administration, Resources. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data used in the current study are available from the corresponding author upon reasonable request.

Ethics declarations

The study involving human participants was reviewed and approved by the Ethics Review Committee of the Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention (approval No.

GXCDCIRB2025-0030). The Ethics Review Committee of the Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention waived the requirement for informed consent. The study was conducted in accordance with the approved study protocol and relevant institutional ethical requirements.

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Figures

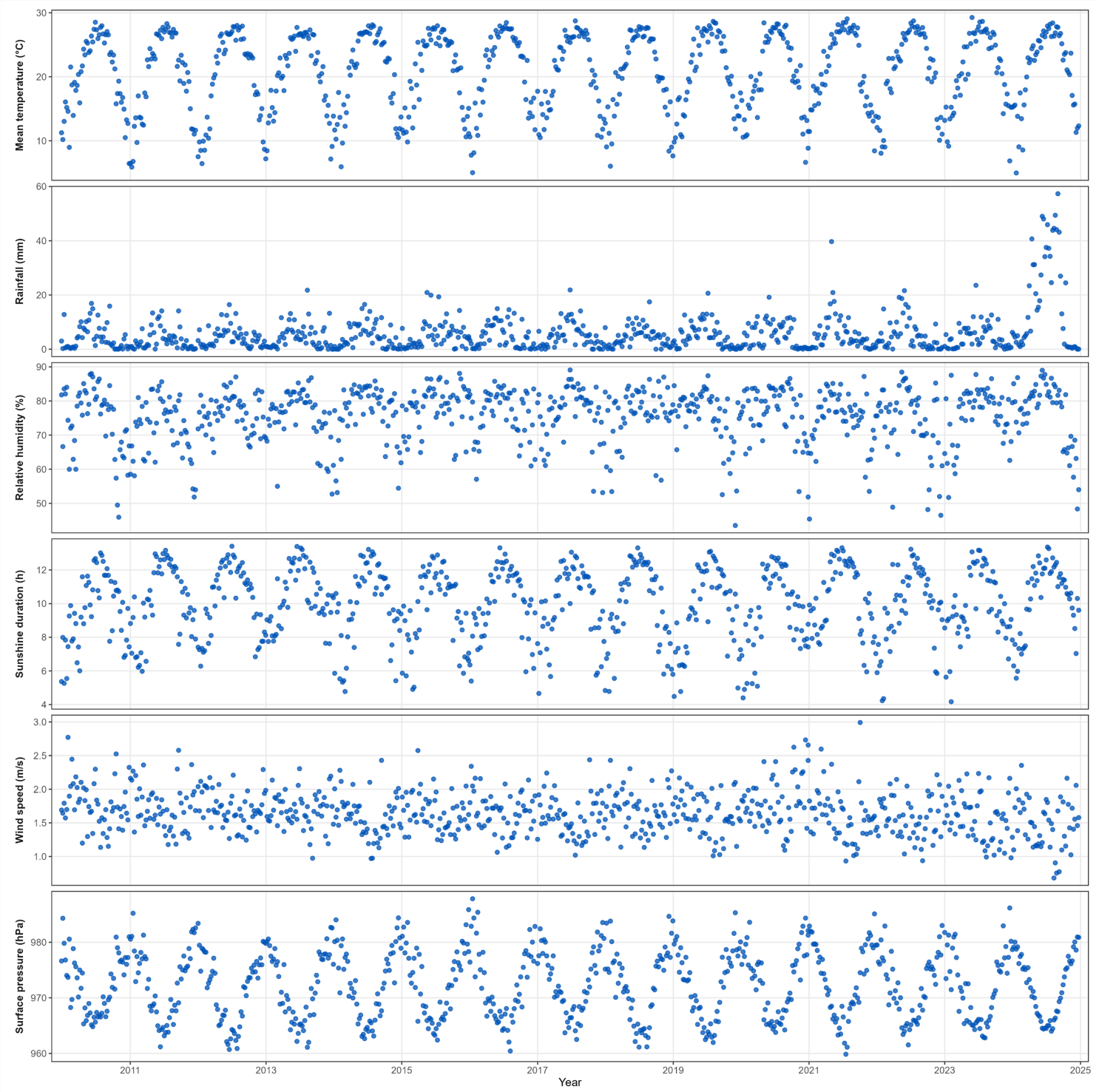


Figure 1

Temporal trends in daily varicella cases and meteorological factors in Guangxi, 2010–2024.

Notes: Panels show mean temperature (°C), rainfall (mm), relative humidity (%), sunshine duration (h), wind speed (m/s), and surface pressure (hPa), from top to bottom. Blue points represent monthly mean values.

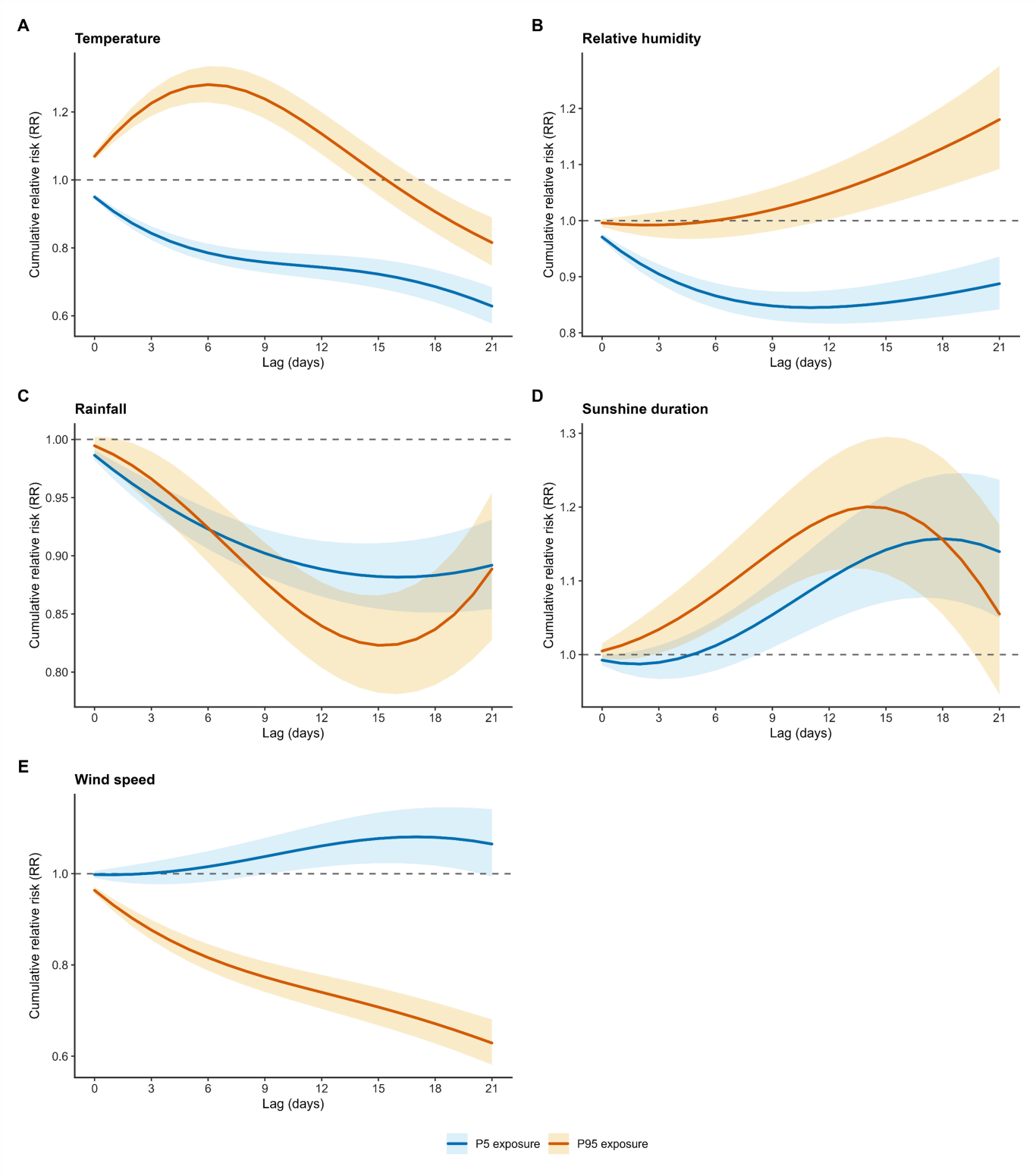


Figure 3

Cumulative lag associations between meteorological factors and varicella incidence at P5 and P95 exposure levels.

Notes: Panels A–E show temperature, relative humidity, rainfall, sunshine duration, and wind speed, respectively. Blue lines and light-blue shaded areas represent the P5 exposure and its 95% CI; orange lines and light-orange shaded areas represent the P95 exposure and its 95% CI. The P5/P95 values were 8.23/29.02 °C for temperature, 52.34/90.98% for relative humidity, 0.00/25.38 mm/day for rainfall, 2.71/13.38 h/day for sunshine duration, and 0.78/2.99 m/s for wind speed. Horizontal dashed lines indicate RR = 1; all estimates are relative to the corresponding Guangxi-wide median.

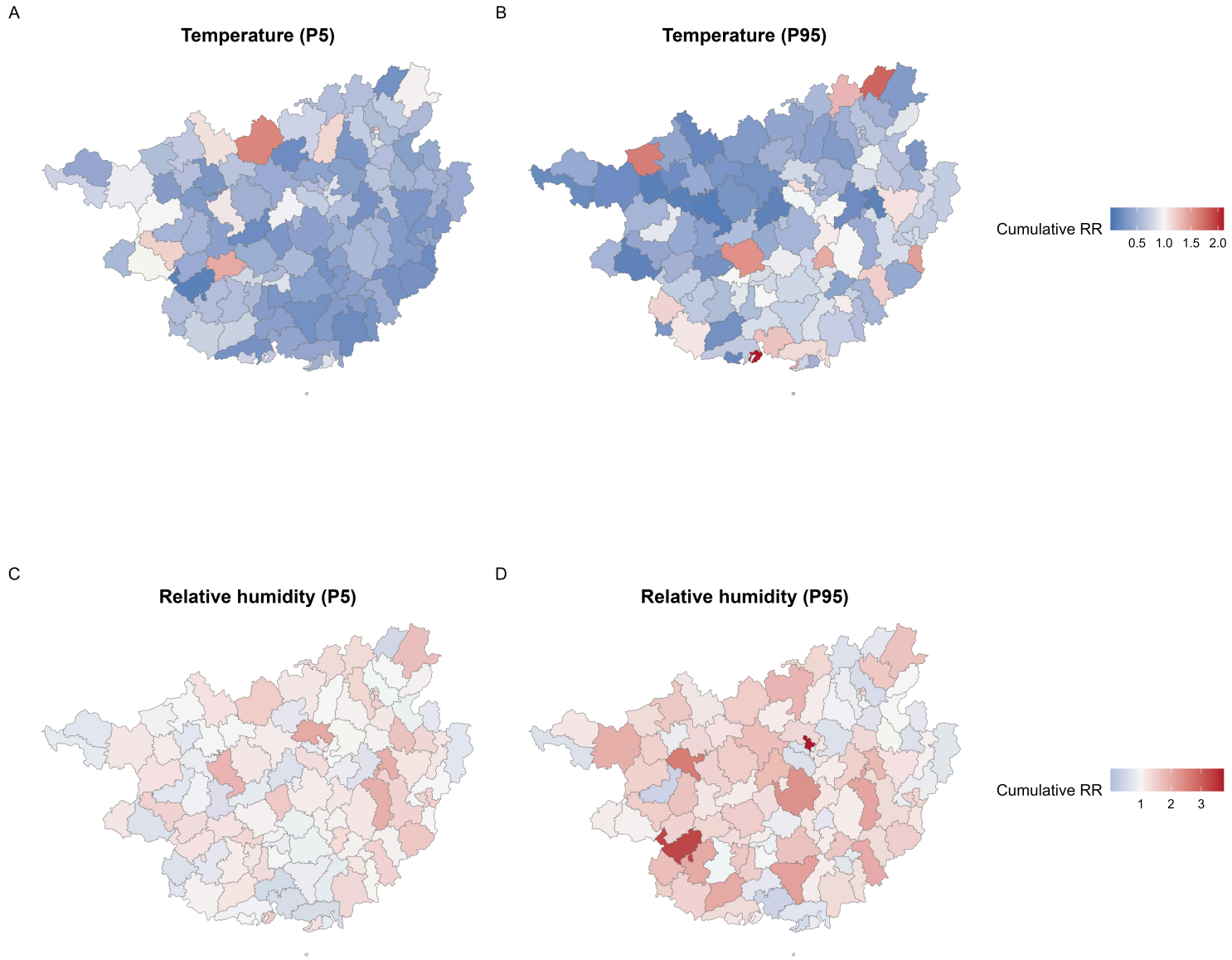


Figure 4

Spatial distribution of county-specific BLUP-based cumulative RRs for temperature and relative humidity at P5 and P95 exposure levels in Guangxi.

Notes: Panels A and B show cumulative RRs for temperature at P5 (8.23 °C) and P95 (29.02 °C), respectively; panels C and D show cumulative RRs for relative humidity at P5 (52.34%) and P95 (90.98%), respectively. Colours range from blue for lower RRs to red for higher RRs, with white indicating RR = 1. Estimates are BLUP-based cumulative RRs over lag 0–21 days, relative to the corresponding Guangxi-wide median.

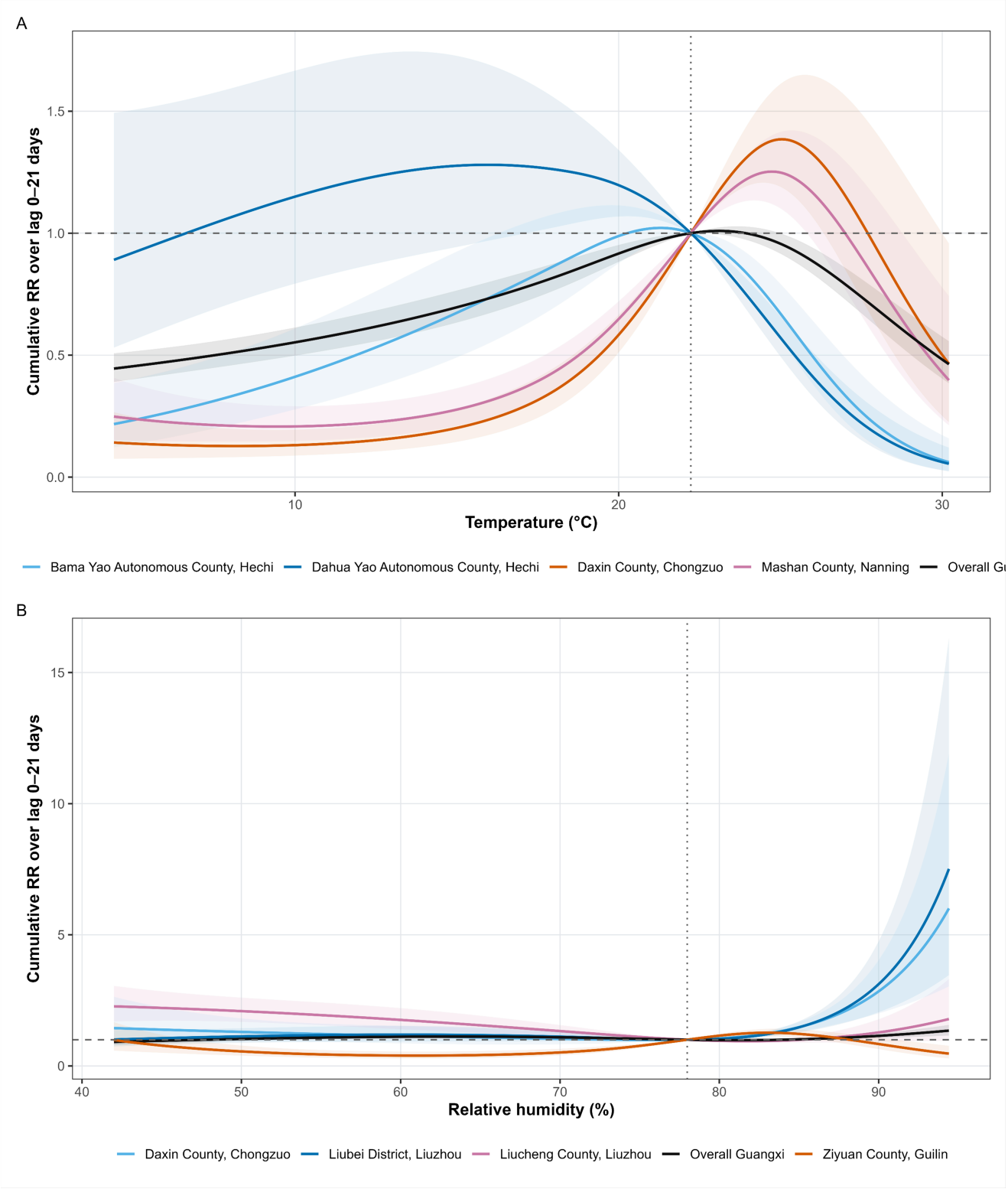


Figure 5

Comparison of county-specific BLUP exposure–response curves for temperature and relative humidity with the pooled Guangxi exposure–response curves.

Notes: Panel A shows temperature–varicella associations for Bama Yao Autonomous County, Hechi (light blue); Dahua Yao Autonomous County, Hechi (dark blue); Daxin County, Chongzuo (orange);

Mashan County, Nanning (purple); and the pooled Guangxi association (black). Panel B shows relative-humidity associations for Daxin County, Chongzuo (light blue); Liubei District, Liuzhou (dark blue); Liucheng County, Liuzhou (purple); Ziyuan County, Guilin (orange); and the pooled Guangxi association (black). Shaded areas in the corresponding colours indicate 95% CIs. Vertical dotted lines indicate the Guangxi-wide median reference values, and horizontal dashed lines indicate RR = 1.

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