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Stroke risk associated with cold spells occurring during the warm season☆

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A B S T R A C T

Background: Recent climate changes have resulted in a rising frequency of extreme cold events that take place during the warm season. Few studies have investigated the impact of these warm-season cold spells on cardiovascular health. Here, we aimed to investigate the potential relationship between exposure to relatively low temperature exposure during the warm season and stroke risk.

Methods: We conducted a time-stratified case-crossover study using a validated, complete, and detailed registration of all stroke cases in the city of Augsburg, Germany, from 2006 to 2020 to assess the association between the occurrence of stroke and exposure to cold spell events during the warm season (May–October). Six cold spell definitions were created using different relative temperature thresholds (1st, 2.5th, and 5th percentiles) and durations (more than 1–2 consecutive days). Conditional logistic regression with distributed lag models was then applied to assess the accumulated effects of these warm-season cold spells on stroke risk over a lag period of 0–6 days, with adjustments for daily mean temperature.

Results: Results confirmed that warm-season cold spells were significantly linked to an elevated risk of stroke with effects that could persist three days after exposure. The cumulative odds ratio (OR) estimates for the cold spells using the 2.5th percentile as air temperature threshold reached 1.29 (95% confidence interval (CI): 1.09–1.53) and 1.23 (95%CI: 1.05–1.44) for durations more than one and two days, respectively. Warm-season cold spells also had significant associations with both transient ischemic attacks and ischemic strokes. The stratified analysis showed that the elderly population (aged $\geq$ 65 years), females, and stroke cases characterized by minor symptoms demonstrated a significantly increased stroke risk of the effects of warm season cold spells.

Conclusions: This study presents strong evidence for an overlooked association between warm-season cold spells and an increased risk of stroke occurrence. These findings further highlight the multifaceted ways in which climate change can affect human health.

1. Introduction

Global warming has made the occurrence of extreme temperature fluctuations more frequent, particularly in the mid-to-high latitudes of the Northern Hemisphere (Bathiany et al., 2018). This phenomenon is attributed to a combination of factors. On a local scale, the decrease in soil moisture and the significant expansion of impervious urban surfaces diminishe the localized atmospheric regulatory effect on extreme air masses from external sources (Seneviratne et al., 2006). On a global scale, the instability in Arctic circulation, driven by the extreme warming in high latitudes, leads to the escape of colder air masses from the Arctic Circle (Cohen et al., 2018). This shift in climate significantly has a notable impact, especially during the boreal summer (Bathiany et al., 2018). As a result, there has been a noticeable increase in relatively low temperature exposures occurring beyond the traditional winter months (Twardosz et al., 2021). Some studies suggested the long-

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term change to a warmer climate holds the potential for even higher vulnerability to cold extreme outside the winter period (Barcikowska et al., 2019; Brunner et al., 2017). Given that these warmer months generally lack widespread central heating and a generally lower public awareness regarding protection against such unexpected cold conditions pose unique challenges to public health.

The recent Global Burden of Disease report has underscored the inclusion of low temperatures within the top ten risk factors for mortality among the elderly population (Murray et al., 2020). Numerous epidemiological studies have shown a compelling link between cold exposure and escalated mortality and morbidity (Alahmad et al., 2023; Fan et al., 2023). Furthermore, various cardiovascular (CVD) health outcomes have been directly linked to the influence of low temperatures (Gao et al., 2019; Guo et al., 2013). A recent systematic review indicated that cold spells were associated with an approximately 11% increase in CVD mortality rates worldwide (Ryti et al., 2016). Notably, for stroke occurrences, the impact of cold exposure is multifaceted and significant. Cold exposure can lead to the elevation of platelet counts, red blood cells, blood viscosity, plasma cholesterol, fibrinogen, and blood pressure (Dong et al., 2013; Kattlove and Alexander 1971; Xu et al., 2019), all of which are potential risk factors for stroke. In addition, compared to other cardiovascular diseases, stroke often has a more acute onset and can lead to more severe consequences, making it a critical focus for research. Cold spells, typically recognized as extended intervals of unusually cold weather during colder seasons, have conclusively demonstrated a substantial association with increased stroke risk (Chen et al., 2013; Gao et al., 2019). However, the current understanding of the health impact of cold spells outside the winter remains limited (Ryti et al., 2022), particularly concerning their effect on cerebro- and cardiovascular diseases. While it's noteworthy that the burden of moderate cold throughout the year is significantly greater than that of extreme cold (Chen et al., 2018), and in some tropical regions, where there is no distinct cold season, exposure to cold still notably increases the risk of emergency cardiovascular hospital admissions (Qiu et al., 2013). In this tropical study, "cold" temperatures were relatively higher, often higher than 10 °C, highlighting the impact of relative low temperature rather than absolute low temperatures. However, this aspect remains underemphasized in research, particularly for regions in mid to high latitudes where temperature fluctuations during the warmer seasons are more pronounced.

In order to bridge these knowledge gaps, we conducted a time-stratified case-crossover study using a validated, complete, and detailed registration of all stroke cases in the city of Augsburg, Germany, from 2006 to 2020 to assess the association between the occurrence of stroke and exposure to cold spell events that happened during the warm season. Subgroup analyses by stroke subtype, including transient ischemic attacks, ischemic strokes, and hemorrhagic strokes, age group, sex, and stroke severity, were performed to pinpoint specific subsets of the population displaying an increased vulnerability to cold spells during the warmer season.

2. Methods

2.1. Study population

In this study, we encompassed individuals who had been admitted to the Department of Neurology at the University Hospital Augsburg. As a prominent stroke center in Germany, the hospital holds a notable position as a dedicated facility for stroke care, serving a population of more than 750,000 residing in the city of Augsburg, with a yearly admission rate of around 2000 stroke cases. It stands as one of the largest stroke centers in the country. The present analysis incorporated data from 22,284 recorded stroke cases between January 2006 and August 2020. Concurrently, we excluded cases of recurrent ($n = 2{,}764$) and fatalities ($n = 109$), focusing our analysis on the impacts of initial stroke occurrences. All these stroke cases were recorded with their specific hospital admission time at an hourly scale and can be categorized into three subtypes by using the ICD-10 code system: transient ischemic attacks (G45), ischemic strokes (I63), and hemorrhagic strokes (I60, I61, and I62). The severity of each case was assessed during the initial admission using the National Institutes of Health Stroke Scale (NIHSS), a standardized tool to evaluate stroke symptoms' severity. This NIHSS has been extensively used in prior research to evaluate stroke severity and the effectiveness of novel stroke treatments (Kwah and Diong, 2014). All this information for each case was further verified by the medical controlling unit of the University Hospital Augsburg and has been previously used in our prior research (Ertl et al., 2019; He et al., 2024).

2.2. Meteorological and air quality exposure data

Data on meteorological variables, including air temperature, relative humidity, and barometric pressure, were gathered on an hourly basis, and obtained from the official urban background monitoring site located on the premises of the Bavarian Environment Agency (LfU, Bayerisches Landesamt für Umwelt), approximately 4 km south of the city center. For all variables, the 24-hourly records within a day were averaged to derive the daily mean value for analysis. This particular site was selected for its meteorological data as it effectively represents the climatic conditions of Augsburg, especially in terms of air temperature fluctuations, which have already been utilized in our previous assessments of temperature-related health risks (Chen et al., 2019). The data quality was high, with a missing value rate below 0.1% during the study period. To ensure completeness, we addressed these rarely missing data through linear interpolation. This imputation method did not compromise the validity of our findings regarding the health effects of temperature fluctuations, as this dataset has been employed and rigorously validated in numerous prior studies on temperature exposure and its health impacts, demonstrating its robustness and reliability (Chen et al., 2019; He et al., 2024).

Daily concentrations of particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) and daily maximum 8-hour average ozone (O_3) levels were obtained from local air quality monitoring stations in Augsburg. More explanations regarding the specifics of these exposure data can be found in the Supplementary Material.

2.3. Definition of unusual cold during warm season

This study aimed to investigate unusual relative low temperature exposures during the warm season. To identify these cold spell events, we first focused on the hottest six consecutive months in Germany (May to October). We then estimated the relative thresholds (5th, 2.5th, and 1st percentiles) based on the daily mean temperature distributions during these six months from 2006 to 2020. These selected thresholds aligned with previous studies' criteria for cold spell events (Lei et al., 2022; Ni et al., 2022). In addition, we considered two different durations of cold spells, including one or more consecutive days (≥1d) and two or more consecutive days (≥2d). We did not include longer threshold of days because cold spells during the warm season typically do not persist for extended periods (Alexander et al., 2006). Overall, we included a total of six cold-spell definitions comprising combinations of the three thresholds and two durations. According to the established definitions, we classified each day within the selected six adjacent months as either a cold-spell day or a non-cold-spell day.

2.4. Statistical analyses

We employed an individual-level, time-stratified, case-crossover design (Janes et al., 2005) to estimate the association between warm-season cold spell events and stroke risk. Specifically, by using conditional logistic regression models, we investigated the potential relationship between stroke and warm-season cold spell events. Each stroke case's exposure on the day of occurrence ('case' day) was compared with exposures on other days within the same month and the day of the week ('control' days) preceding the event. This study design was chosen for its ability to effectively account for long-term time trends, seasonal variations in underlying stroke rates, and time-invariant confounding, and to mitigate potential biases arising from exposure-related time trends (Chen et al., 2019).

To account for the lag effect of cold spells, we implemented distributed lag models (DLMs) (Gasparrini and Leone 2014). Existing studies have demonstrated that the estimated associations of cold exposure may persist for more than several days (Ni et al., 2022). Due to the time-stratified case-crossover design, we set a 7-day lag period to prevent overlap between exposure and control days while capturing both immediate and delayed effects, including potential mortality displacement (harvesting effect). The exposure-response function of cold spells and strokes was modeled by DLM with a linear function of cold-spell days (as a binary variable). The lag-response curve was set with a natural cubic spline with four degrees of freedom (df) and two internal knots placed at equally spaced values in the log scale (Jiang et al., 2023; Yin et al., 2018). In addition, to control for the confounding effect of daily temperature, our main model also included a distributed lag non-linear model (DLNM) for daily mean temperature by establishing a cross-basis function of temperature with the same lag period as cold spells. Referring to related studies (Jiang et al., 2023; Vicedo-Cabrera et al., 2021), the DLNM for daily mean temperatures with the same 7 lag days included a quadratic B-spline with 2 df and two internal knots placed at equally spaced values in the log scale and a lag–response curve with a natural cubic spline with three internal knots (plus an intercept) placed at equally spaced values in the log scale. Our main model also included natural cubic B-splines with three degrees of freedom for relative humidity and barometric pressure on the same day, and a categorical variable of the holidays to control for their potentially confounding effects (Chen et al., 2019). To facilitate the interpretation of the odds ratios (ORs) associated with cold spell events during warm-season months, we selected non-cold spell days as the reference. We reported the ORs of stroke, accompanied by their 95% confidence intervals (CIs), during the cold spell days with different definitions. Furthermore, to compare the main temperature effect of daily mean temperature and the additional effect of cold spells during the warm season, referring to a related study (Gasparrini and Armstrong, 2011), we also examined the impact of daily mean temperature on stroke risk, calculating ORs for warm-season months based on the same primary model setting but adjusting for cold spell effects. Here, the reference day was chosen as the day with the minimum stroke ratio temperature during the warm season. The main effects were estimated from the variation in ORs corresponding to the daily mean temperature that defines the threshold for cold spells in comparison to the minimum mortality temperature days, while the additional effects represent the ORs of cold spell days after adjusting for the mean temperature effect, compared to non-cold spell days.

Moreover, to provide a more nuanced understanding of the impact of cold exposure, we conducted subgroup analyses for different stroke subtypes, including transient ischemic attacks, ischemic, and hemorrhagic strokes, using the same analytical methods. In addition, we performed stratified analyses on total stroke events to investigate potential effect modification by sex (male vs. female), age (<65 vs. ≥65 years), and the NIHSS scale (≤4 which indicates the symptoms are less severe vs. >4 which indicates the symptoms are identified as moderate to severe. This cutoff point effectively distinguishes between patients with favorable and less favorable prognoses (Inoa et al., 2014). It is also consistent with our previous study, enhancing the comparability of our results (He et al., 2024). To test the statistically significant difference between these sub-groups, we adopted the multivariate Wald test; a *P*-value < 0.05 was considered statistically significant (Chen et al., 2019; He et al., 2024).

2.5. Sensitivity analyses

In order to test the robustness of our findings, we conducted a series of sensitivity analyses from several aspects. Analyses included potential modifications in the estimated associations when additionally adjusting for air pollution, including $PM_{2.5}$ and O_3, and changing the setting in the knots for the exposure-response function in our main analysis model.

3. Results

3.1. Stroke cases and cold spell exposure during the warm season

During the study period, the daily mean temperature averaged 14.7 °C, with an interquartile range of 7.1 °C. In addition, the temperature value corresponding to the 1st, 2.5th and 5th percentile of daily mean temperature are 6.8 °C, 8.1 °C and 9.3 °C respectively. We identified a range of cold-spell days varying from 6 to 115 days within the six warm months, applying six cold-spell definitions as presented in Table 1. As shown in Fig. S1, the annual total of cold-spell days for each definition did not exhibit an obvious declining trend from 2006 to 2020. However, there was a noticeable increase in average temperature from the period 2006–2012 to 2013–2020, as indicated in Table S1. In terms of air quality parameters, the mean concentrations of 24-hour $PM_{2.5}$ and 8-hour O_3 were 9.50 ± 4.95 μg/m^3 (mean ± standard deviation) and 60.2 ± 17.9 μg/m^3, respectively.

Regarding the stroke cases included in this study, as presented in Table 2, a total of 11,037 cases of first hospitalization for each individual that did not result in death during the study period were included. The average age of this study's cases was 71.3 years, with a standard deviation of 13.2 years. In terms of stroke subtypes, our dataset encompassed 2947 cases of transient ischemic attacks, 642 cases of hemorrhagic strokes, and 7430 cases of ischemic strokes. Notably, a significant proportion (52.5%) of these stroke cases were categorized as moderate (NIHSS >4 and ≤15).

3.2. Association between warm-season cold spells and stroke occurrences

Fig. 1 illustrates the estimated lag pattern of the relationships between cold spells during the warm season and the occurrences of total stroke cases. It indicates that warm-season cold spells were significantly linked to an elevated risk of stroke and showcased a nonlinear lagged association. The significant effect of warm-season cold spells could persist up to three days after exposure. In most definitions, the effect tended to diminish after two days.

In comparison, the patterns of associations were comparable across

Table 1
Summary statistics of annual cold days during the warm season with different definitions in Augsburg, Germany, from 2006 to 2020.

	Name	Definition	No. of cold spells per year during the warm season Mean	SD	Total days
P1* (6.8 °C)**	P1 ≥ 1d	≤P1 with ≥ 1d duration	1.5	1.6	23
	P1 ≥ 2d	≤P1 with ≥ 2d duration	0.4	0.9	6
P2.5 (8.1 °C)	P2.5 ≥ 1d	≤P2.5 with ≥ 1d duration	3.9	2.9	58
	P2.5 ≥ 2d	≤P2.5 with ≥ 2d duration	1.9	2.1	28
P5 (9.3 °C)	P5 ≥ 1d	≤P5 with ≥ 1d duration	7.8	4.5	115
	P5 ≥ 2d	≤P5 with ≥ 2d duration	4.6	3.5	69

* P1: 1st percentile; P2.5: 2.5th percentile; P5: 5th percentile; 1d: 1 day; 2d: 2 days.
** The temperature value in the brackets correspond to the value at the respective percentile.

Table 2
Summary statistics of stroke cases in Augsburg, Germany, during the months of May–October from 2006 to 2020, focusing on the hottest six consecutive months as our study period.

	No. of cases (proportion%)
Total strokes	11,037
Transient ischemic attacks	2947 (26.7%)
Hemorrhagic strokes	642 (5.8%)
Ischemic strokes	7430 (67.3%)
Not specified strokes	18 (0.2%)
Sex	
male	3600 (32.6%)
female	4799 (43.5%)
Unknown	2638 (23.9%)
Age (years), mean (SD)	71.3 (13.2)
<65	3010 (27.3%)
≥65	8027 (72.7%)
NIHSS at admission *	
Minor stroke (1–4)	3737 (33.9%)
Moderate stroke (5–15)	5792 (52.5%)
Moderate to severe stroke (16–20)	285 (2.6%)
Severe stroke (21–42)	107 (1.0%)

* NIHSS: National Institutes of Health Stroke Scale.

different definitions of cold spells. Within the same temperature threshold categories, the lag patterns tended to remain consistent across varying durations of cold spells. Notably, cold spells with shorter durations often yielded more pronounced lag patterns and higher OR estimates. Cold spells defined using the 2.5th percentile exhibited higher OR estimates in different temperature threshold categories than the other two relatively temperature-based definitions.

Overall, as shown in Fig. 2, the cumulative OR estimates for the cold spells under the definition using the 2.5th percentile temperature reached 1.29 (95%CI: 1.09–1.53) and 1.23 (95%CI: 1.05–1.44) for durations more than one day (2.5th percentile ≥ 1d) and two days (2.5th percentile ≥ 2d), respectively. In addition, a lower cumulative OR was estimated for the 5th percentile ≥ 1d (1.13 (95%CI: 1.01–1.30)), and notably, the OR estimates derived from the definition of 5th percentile ≥ 2d became statistically insignificant (1.10 (95%CI: 0.96–1.26)). Furthermore, as shown in Table 3 and Fig. 3, compared to the main effects of the daily mean temperature under different cold spell definitions, the additional effects of the cold spells were almost comparable, or even slightly exceeded.

As shown in Supplemental Fig. S2–S4, the lag patterns for the estimated associations of cold spells on different causes of stroke were also generally consistent. The association between warm-season cold spells on transient ischemic attack and ischemic stroke was mainly positive and statistically significant across different definitions. In comparison, among different definitions, cold spells using the definition of the 2.5th percentile temperature were associated with higher cumulative OR estimates and prolonged effect duration. Furthermore, transient ischemic attack cases were associated with higher OR estimates, while hemorrhagic strokes displayed insignificant associations with all definitions of cold spells.

3.3. Stratified analysis

Fig. 4 shows the cumulative OR estimates of different cold-spell definitions and total stroke by sex, age, and severity. Across most cold spell definitions, cumulative OR estimates for females displayed the most positivity and statistical significance. However, significant statistical results were only observed under the definitions of 2.5th percentile

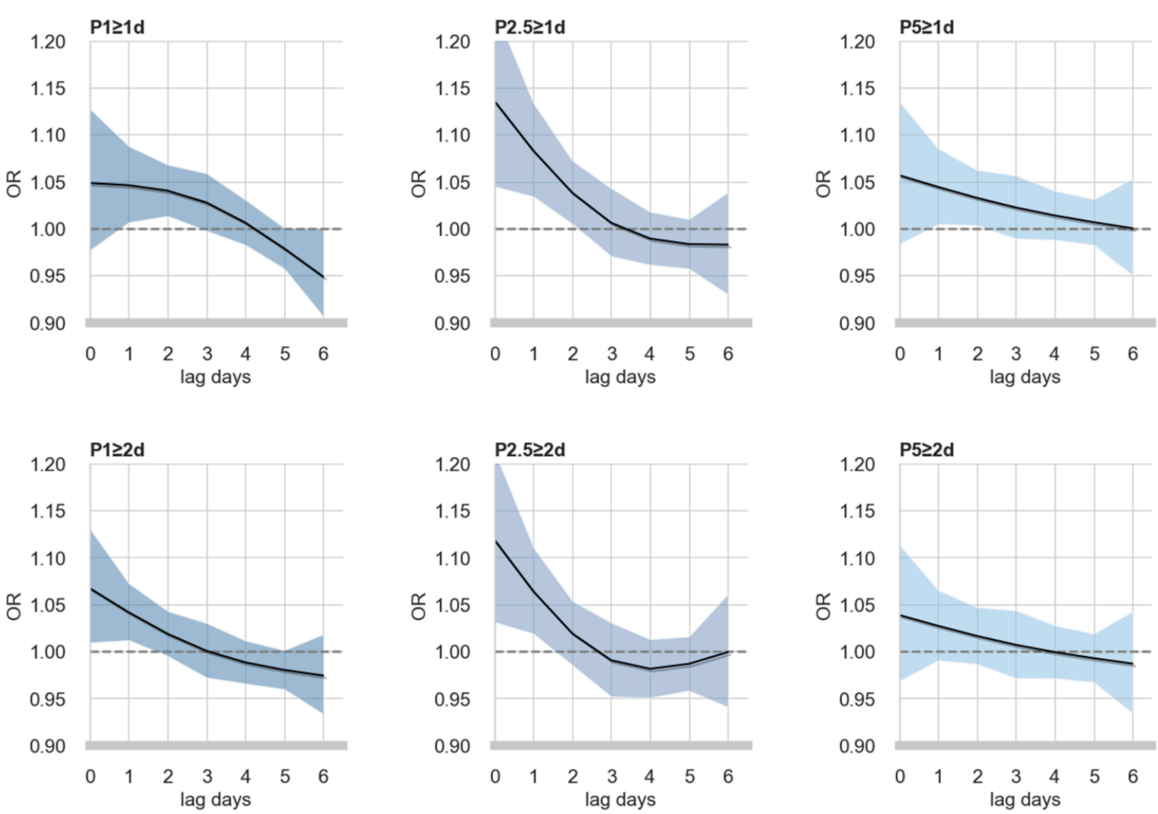

Fig. 1. Lag structures for the associations of total stroke occurrence with warm-season cold spells using different definitions. The solid black lines represent lag-specific odds ratios of stroke associated with warm-season cold spells, and the colored areas are their 95% confidence intervals. The cold spell definitions include a range of combinations with temperatures lower than different percentiles (P1, P2.5, and P5) of daily temperature distributions and duration of no less than 1 and 2d. P1, 1st percentile of the daily mean temperature distribution; P2.5, 2.5th percentile of the daily mean temperature distribution; P5, 5th percentile of the daily mean temperature distribution.

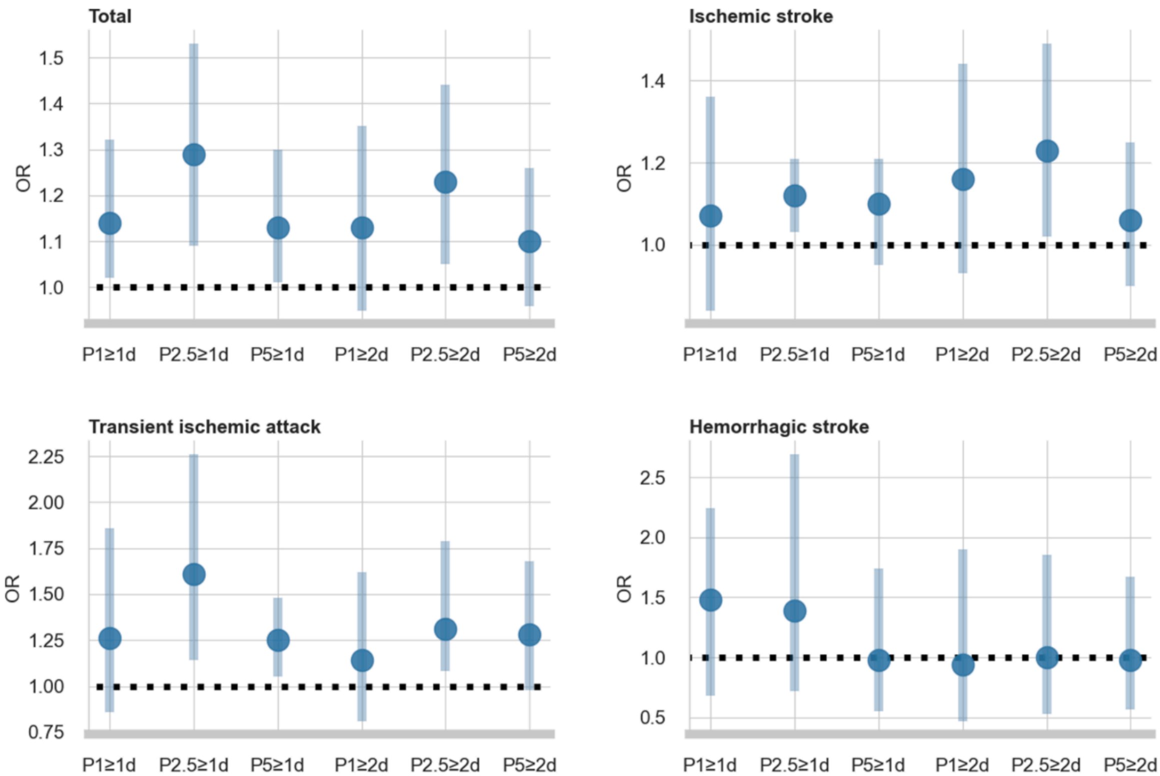

Fig. 2. Cumulative odds ratios (ORs) and 95% CIs of stroke occurrence associated with warm season cold spells among different subtypes of stroke over lags 0–6 d in Augsburg, Germany, during the months of May–October from 2006 to 2020. Points represent the estimated ORs of stroke risk (cold-spell days vs. non–cold-spell days); lines represent the 95% CIs. CIs, confidence intervals; P1, 1st percentiles of the daily mean temperature distribution; P2.5, 2.5th percentiles of the daily mean temperature distribution; P5, 5th percentiles of the daily mean temperature distribution. The months of May and October were selected as we focused on the hottest six consecutive months as our study period.

Table 3
Cumulative odds ratios (ORs) and 95% CIs of stroke occurrence associated with the main and added effects of warm season cold spells over lags 0–6 d in Augsburg, Germany, during May–October from 2006 to 2020. The main effects were estimated from the variation in ORs corresponding to the daily mean temperature that defines the threshold for cold spells.

No. Days	Percentile	Main Effect	Added Effect
≥1	≤1th	1.20 (1.02–1.45)	1.14 (1.02–1.32)
	≤2.5th	1.20 (1.03–1.41)	1.29 (1.09–1.53)
	≤5th	1.21 (1.06–1.41)	1.13 (1.01–1.30)
≥2	≤1th	1.28 (1.12–1.49)	1.13 (0.95–1.35)
	≤2.5th	1.21 (1.06–1.39)	1.23 (1.05–1.44)
	≤5th	1.16 (1.04–1.31)	1.10 (0.96–1.26)

≥ 1d and 2.5th percentile ≥ 2d for males. Among individuals aged 65 years and above, the cumulative OR estimates exhibited predominance in positivity and statistical significance for cold spells defined under different definitions. However, within the younger population (below 65 years), there were not statistically significant OR estimates across different definitions of cold spells. Furthermore, cumulative OR estimates in stroke cases characterized by minor symptoms (NIHSS ≤ 4) were positive and statistically significant across most cold spell definitions. In contrast, stroke cases identified with moderate to severe symptoms (NIHSS > 4) did not yield any significant estimates.

3.4. Sensitivity analysis

In the sensitivity analysis, the cold spell with the definition of 2.5th percentile ≥ 1d was used in models after controlling for the associations of $PM_{2.5}$ and O_3 concentrations. As shown in Table S2, the pooled cumulative OR of total stroke risk associated with warm-season cold spells were not appreciably changed by this adjustment. In addition, our results were also robust to changed degrees of freedom for lag days (3–5 df).

4. Discussion

Our study investigated the association between cold spells during the warm season and stroke occurrences, using a time-stratified case-crossover study based on a validated, complete, and detailed registration of all stroke cases in the city of Augsburg. Results of this study revealed significant associations between cold spells during the warm season and an increased risk of stroke occurrences, with a lagged association over two days after exposure. Notably, cold spells under definitions of 2.5th percentile ≥ 1d and 2.5th percentile ≥ 2d displayed robust influences. These cold spells exhibited substantial correlations with both transient ischemic attacks and ischemic strokes, while the impacts on hemorrhagic strokes did not achieve statistical significance. These additional effects of cold spell events were found to be comparable to the main effects of daily mean temperature corresponding to cold spell thresholds. So, if we neglect the additional health effects of these types of cold spells, we will overlook a significant portion of the health impacts of low temperatures during the warm season. Results of the stratified analysis showed that the elderly population (aged ≥65 years), females, and stroke cases characterized by minor symptoms (NIHSS ≤ 4) demonstrated increased vulnerability to the effects of cold spells. To our knowledge, this is the first case-crossover study to assess the relationships of warm season cold spells with cardiovascular diseases based on individual cases.

While low temperature has been extensively considered as a risk factor for cardiovascular diseases (Alahmad et al., 2023), the impacts of relative low temperature exposure during the warm season have not

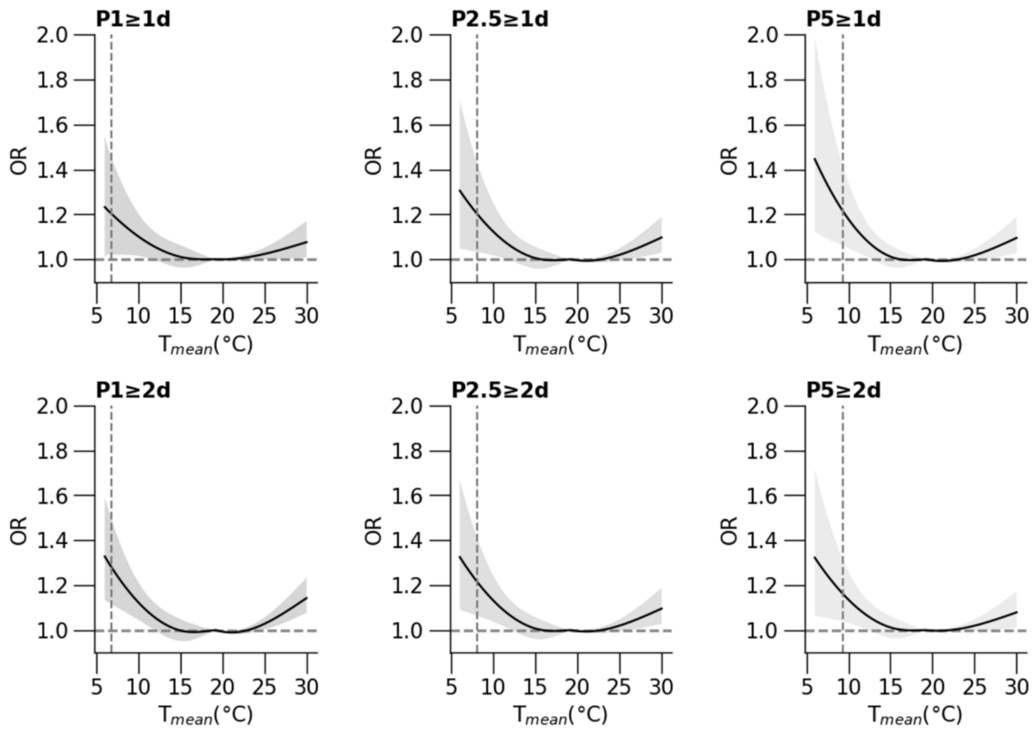

Fig. 3. Cumulative exposure–response relationships between daily mean temperature and stroke risk over lag 0–6 days with corresponding 95% confidence intervals (colored areas), after the adjustment for the effects of cold spells as defined by various criteria. The vertical dashed line indicates the main effect of daily mean temperature in the context of these variously defined cold spell events. The reference day was selected as the lowest stroke ratio temperature during the warm season, which pinpointed the daily mean temperature that corresponded with the lowest stroke risk, which, according to our database, is 19.2 °C. The months of May and October were selected as we focused on the hottest six consecutive months as our study period.

received enough attention. In our study, we focused on relatively low temperatures of 6.8 °C, 8.1 °C, and 9.2 °C during the warm season. Existing research has predominantly centered on cold spells within the typical winter months (Jiang et al., 2023; Lei et al., 2022). Only a limited number have explored the effects of low temperature exposure outside winter months (Ryti et al., 2022). Furthermore, divergent findings emerge as some studies document a significant rise in mortality or morbidity linked to cold spells (Davídkovová et al., 2014; Lei et al., 2022), while others detect no associations (Huang et al., 2012; Shaposhnikov et al., 2014). These discrepancies in outcomes can be traced back to differences in study design, the specific health outcomes (including symptom onset, hospitalization, or mortality), as well as the diverse definitions used to classify instances of cold spells. In addition, studies based on hospitalizations or mortality may face challenges related to the potential temporal mismatch between exposure and disease occurrence. Utilizing individual-level data can help mitigate this potential misclassification issue. However, only a few case-crossover studies have delved into the health effects of cold spells (Jiang et al., 2023; Vaičiulis et al., 2021). In contrast, by adopting the registry-based time-stratified case-crossover study design, the present study considered various cold spell definitions and adjustments for the cumulative effects of daily temperature over multiple lag days. Consistent with previous epidemiological studies (Jiang et al., 2023; Lei et al., 2022), our study found the impact was significant to several days afterward but more transient than that on mortality (e.g., two to four weeks), as reported in the related research (Lei et al., 2022). This difference is conceivable, given that there generally exists a time span (typically ranging from several days to a few weeks) between the onset of disease symptoms and the eventual occurrence of death, except in cases of sudden death. Moreover, our study revealed that contrary to expectations, extending the duration of cold spells for the same temperature threshold did not correspond to larger OR estimates. This phenomenon may be attributed in part to the fact that relatively low-temperature exposure occurring during the warm season tends to be of very short duration compared to typical cold spell events happening during winter, leading to fewer case days available to demonstrate a stronger effect. Additionally, shorter cold spells imply more rapid temperature fluctuations, which may pose a greater challenge to the population's ability to adapt during the warm season. Additionally, we compared the results using the same database and the same series of definitions but focusing on the traditional winter period (November, December, and January). As shown in Table S3, we found that, during the winter, the stroke incidence risk associated with cold spells at temperatures corresponding to the 1st, 2.5th, and 5th percentiles (−9.80 °C, −6.56 °C, and −4.16 °C, respectively) was comparable to the results observed in the warm season. Under some definitions, the risks were even lower, though the differences were not statistically significant.

The influence of warm-season cold spells on strokes holds biological plausibility. The correlation between cold weather and its effects on health primarily stems from the direct consequences of cold exposure (Fan et al., 2023), especially during warm season when the protective effect of heating systems diminishes, rendering cold exposure more direct (Ryti et al., 2022). Moreover, the sudden temperature variability associated with cold spells during the warm season may play a crucial role in stroke induction. This temperature variability can cause rapid physiological changes that the body may struggle to adapt to quickly enough (Guo et al., 2016). During the warm season, the body's response to unusual cold includes autonomic nervous system reactions such as shivering and vasoconstriction, which may alter blood pressure and increase the risk of stroke (Dong et al., 2013; Xu et al., 2019). A recent study suggested that unusual cold exposure can lead to thermoregulatory fatigue, resulting in attenuated shivering and vasoconstriction responses, further compromising the body's defense against cold stress (Zhao et al., 2024). Unusual low temperatures can prompt vasoconstriction, which narrows blood vessels, redirecting blood flow towards vital central organs, and consequently, blood pressure often rises (Chen

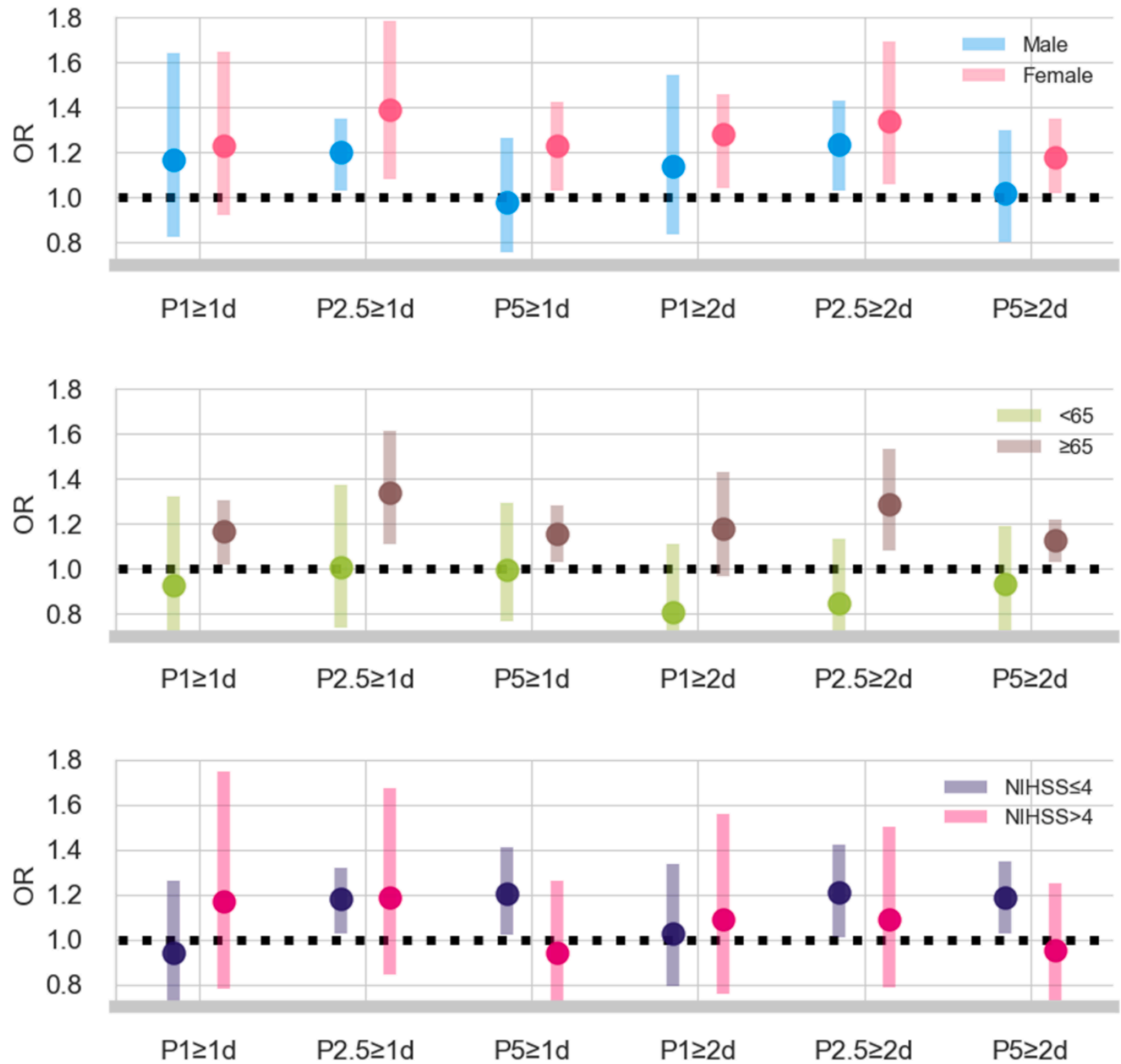

Fig. 4. Cumulative odds ratios (ORs) and 95% CIs of total stroke occurrence associated with warm season cold spells among sex, age, and severity over lags 0–6 d in Augsburg, Germany, during the months of May–October from 2006 to 2020. Points represent the estimated ORs of stroke risk (cold-spell days vs. non-cold-spell days); lines represent the 95% CIs. CIs, confidence intervals; P1, 1st percentiles of the daily mean temperature distribution; P2.5, 2.5th percentiles of the daily mean temperature distribution; P5, 5th percentiles of the daily mean temperature distribution. NIHSS: National Institutes of Health Stroke Scale.

et al., 2022). Furthermore, the cold spells of the warm season are less likely to induce the immune responses typically triggered by cold, dry winter air. Moreover, unusual low cold exposure has the potential to increase the brain's demand for oxygen, potentially triggering an excessive cerebral blood flow that could exacerbate brain ischemia (Chen et al., 2022). Additionally, exposure to unusual cold can trigger the elevation of various thrombogenic factors, including increased blood cell counts, higher plasma cholesterol levels, elevated concentrations of C-reactive protein, fibrinogen, and heightened platelet reactivity (Wolf et al., 2009), all of which may eventually lead to stroke. It is also important to note that, unlike in winter, the activation of irritant receptors in the lungs by cold air is not expected during the warm season (Turmel et al., 2012). During the warm season, when the protective effect of heating systems might be insufficient, the general population could be exposed directly to lower temperatures, thereby increasing the risk of cold-related stroke.

The observed increase in ischemic strokes can be attributed to similar factors, including dehydration, elevated blood viscosity, and alterations in blood vessel function (Chen et al., 2022). Cold exposure can potentially exacerbate these factors, increasing the propensity for clot formation, and thereby contributing to the elevated risk of ischemic strokes (Qi et al., 2021). On the other hand, the impact of unusual cold exposure on hemorrhagic strokes seems less prominent, which may be caused by its limited total cases during the warmer season and also may be in line with other research findings indicating that hemorrhagic strokes are generally less susceptible to cold exposure (Luo et al., 2018). Additionally, milder stroke cases tend to be more responsive to temperature changes. In contrast, the impact of cold spells on more severe stroke cases is less pronounced, as severe stroke cases are often driven by pathological factors rather than being triggered by environmental conditions (Boehme et al., 2017). Regarding specific demographic groups, the elderly population emerged as a particularly vulnerable group, with a notable rise in ORs compared to younger individuals. This heightened susceptibility can be attributed to several age-related factors. Aging is associated with a decline in thermoregulatory capacity, including reduced peripheral vasoconstriction and decreased shivering response (Florez-Duquet and McDONALD 1998). These physiological changes impair the body's ability to maintain core temperature during cold exposure. Furthermore, older individuals often have pre-existing health conditions such as hypertension, diabetes, or cardiovascular diseases, which can exacerbate the impact of cold stress on the body (Assar et al., 2016). Compared to males, females are more vulnerable to warm-season cold spells. This gender disparity in cold susceptibility can be explained by several factors. Women undergoing menopause often experience thermoregulatory dysfunction, affecting their ability to adapt to sudden temperature changes (Gupta et al., 2000). This hormonal transition can increase sensitivity to temperature fluctuations. Moreover, women generally possess a higher body fat percentage than men, which can hamper their unusual cold dissipation capacity (Graham 1988). While body fat provides insulation, it may also slow the body's ability to adjust to rapid temperature changes.

The findings from this study carry several implications for stroke prevention. Firstly, there is a significant need to design more resilient public infrastructures, such as advocating for adopting effective personal protective measures against cold temperatures even outside the winter months. This becomes especially pertinent considering that most preventive measures against the cold focus on the winter season. Moreover, given the escalating intensity of temperature fluctuations during the summer and autumn months, addressing cold exposure during these periods becomes increasingly essential. Second, the results about the temporal patterns of the associations between warm season cold spells and stroke risk help develop warning systems and establish appropriate durations for implementing preventive measures in response to unusual cold days during the warm seasons. Lastly, particular attention should be directed towards vulnerable population groups, notably elderly individuals. Tailored preventive strategies should be developed to safeguard their health and mitigate their increased susceptibility to the impacts of cold spells.

The main strengths of this study are listed as follows. First, a notable strength of this study lies in its reliance on a validated, exhaustive, and comprehensive registry of recorded stroke cases. The time of stroke cases was validated against the medical records, instead of using the patient's self-reported time upon arrival of hospital admission or time of receiving the emergency call. The considerable sample size (11,037) and extended observation period (15 years) ensured adequate statistical power of analysis. Second, the study benefits from the inclusion of detailed information about each stroke case. This rich dataset enhanced the depth of the study's findings in identifying specific sensitive population groups.

Potential limitations of this study should also be noted. First, as done in most previous studies(Lei et al., 2022; Ni et al., 2022; Wolf et al., 2009), we evaluated the exposure to cold spells relying on fixed-site measurements of temperature, which would lead to inevitable exposure measurement errors. However, given the study's focus on the warm season (May to October), it's worth noting that the distinction between indoor and outdoor temperatures may be less noticeable compared to the colder months. Secondly, our study findings are specific to a singular hospital in Germany. Although this hospital has a substantial number of cases and a large patient base, which strengthens the internal validity of our study, the results may not be applicable to diverse cities or counties characterized by differing climatic, demographic, and socioeconomic conditions. To extend the generalizability of our conclusions, further research employing similar study designs within varied geographical contexts is warranted. Thirdly, although the study design effectively controlled for time-invariant risk factors, transient confounders that fluctuate within a short period—such as short-term stress and physical activity—could still have potential impacts. Moreover, it is important to note that a significant proportion of cases (23.9%) had missing gender information. This data limitation could potentially affect the reliability of our observed gender differences. Finally, it is important to highlight that our examination was limited to stroke occurrences, and the findings may not necessarily extend to stroke-related fatal events.

In conclusion, this case-crossover study conducted over a prolonged time period provides compelling evidence regarding the links between warm season cold spells and an elevated risk of total stroke incidence. The risk is significant for transient ischemic attacks and ischemic strokes, particularly among the elderly population and females. In light of the recently escalating temperature fluctuations during the warm season, especially in urban area, our findings further underscore the complexity of climate change's health implications. Moreover, these results hold the potential to enhance the cold spell alert systems beyond the winter season and guide the development of personalized preventive measures in the context of global climate change and urbanization.

CRediT authorship contribution statement

Cheng He: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Susanne Breitner:** Methodology, Investigation, Formal analysis, Conceptualization. **Siqi Zhang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation. **Markus Naumann:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration. **Claudia Traidl-Hoffmann:** Validation, Supervision, Project administration, Methodology. **Gertrud Hammel:** Writing – original draft, Visualization, Validation, Supervision. **Annette Peters:** Supervision, Project administration. **Michael Ertl:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources. **Alexandra Schneider:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation.

Declaration of competing interest

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109514.

Data availability

The authors do not have permission to share data.

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