Quantifying the lagged effects of non-optimal temperature exposure on risk of cause-specific mortality through distributed lag non-linear modeling and mixed-effects meta-regression

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Abstract

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Background: Exposure to high and low ambient temperature is associated with increased risk for mortality from a variety of causes. Previous analyses have shown that elevated risk persists for a period of time following a temperature exposure; however, no analysis has yet explored these lagged effects on the cause-specific level. We therefore assessed the relationship between non-optimal temperature exposure and mortality by creating cause-specific relative risk curves incorporating lagged effects.

Methods: We matched International Classification of Diseases-coded cause of death data with administrative unit identifiers to daily and mean annual temperature estimates from the ERA5 global temperature dataset. For each administrative unit, we modelled cause-specific relative risks incorporating lagged effects for 17 communicable, non-communicable, and external causes using a distributed lag non-linear modeling framework. We meta-regressed the resulting relative risks using a Bayesian, two-dimensional spline surface specified by daily temperature and 23 mean temperature zones to predict a set of globally-applicable, cause-specific risk curves.

Results: We included 52.7 million individual mortality observations from 12,641 administrative units across 8 countries for the years 1980 – 2016. For non-external causes (ischemic heart disease, stroke, cardiomyopathy and myocarditis, hypertensive heart disease, diabetes, chronic kidney disease, lower respiratory infection, and chronic obstructive pulmonary

disease) we observed J-shaped relationships between daily temperature exposure and risk of mortality, while external causes (homicide, suicide, drowning, and related to disasters, mechanical, transport, and other unintentional injuries) displayed monotonically increasing relationships. For non-external causes, lagged effects existed for both heat and cold, though lagged effects for cold were more pronounced and occurred across almost all causes and temperature zones. Lagged effects for heat appeared primarily and moderate and warmer temperature zones for most non-external causes. A lag period of 21 days resulted in the highest RRs for non-external causes for cold, but for heat, lag periods of 7 or 14 days sometimes observed higher RRs than a 21-day lag period. Compared to non-external causes, external causes displayed more heterogeneous lagged effects.

Conclusion: Exposure to extreme cold and heat presents substantial risks to human health, but exposure-response relationships vary by cause. Lagged effects for both temperature extremes indicate that increased risk of mortality is not limited to the single day on which an extreme temperature event occurs for most causes. Burden assessments should incorporate lagged effects to avoid underestimating non-optimal temperature's disease burden. Medical, public health, and structural decision making must consider sustained effects of extreme temperature exposure across time when designing strategies to address climate change and extreme weather events.

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Introduction

Exposure to extreme temperature has long been linked with adverse impacts on human health.[1] We define non-optimal temperature as ambient temperature above or below the temperature exposure associated with the lowest disease burden for a given location-year.[2] Non-optimal temperature encompasses both high and low temperature extremes. Exposure to non-optimal ambient temperature is associated with diverse impacts on the cardio-respiratory and metabolic systems and with altered cognition and behavior.[3]

Several recent publications have examined the large and heterogeneous body of evidence to characterize exposure-response relationships and quantify disease burden. Recently, Gasparrini and colleagues evaluated all-cause disease burden due to non-optimal temperature globally, based on mortality data from 384 locations in 13 countries spanning Asia, Australia, Europe, and North America.[4] Additional work by Burkart and colleagues identified seventeen causes of death linked to exposure to non-optimal temperature, estimated exposure-response curves, and characterized cause-specific global disease burden by incorporating non-optimal temperature as a risk factor in the Global Burden of Disease Study.[2,3] These causes encompass communicable (lower respiratory infections), non-communicable (ischemic heart disease, stroke, hypertensive heart disease, cardiomyopathy and myocarditis, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease), and external (road injuries, other transport injuries, drowning, exposure to mechanical forces, animal contact, exposure to forces of nature, other unintentional injuries, self-harm, and interpersonal violence) causes of death and disability.[3] Recent literature highlights the current and growing importance of ambient temperature as a determinant of human health and matter of health justice, and indicates that taking action to mitigate the disease impact of non-optimal temperature is a growing public health priority.

Despite the growing body of recent disease burden analyses, gaps remain in the characterization of the effects of non-optimal temperature on cause-specific disease burden. Specifically, Burkart and colleague's 2021 analysis and the GBD Study currently do not incorporate the lagged effects of high and low temperature on mortality and therefore likely underestimates the cumulative burden of non-optimal temperature on human health.[2,3] Lagged effects of heat and cold embody excess risk caused by exposure to these risk factors that extends beyond a single day, into a lag period.[4] Much literature suggests that heat effects are more immediate and confined to a few days, while cold effects extend over a longer period of weeks.[4,5] However, other studies found that, in some warmer locations, the lagged effects of cold last only between 2 to 6 days.[6–8] The distributed lag nonlinear modeling (DLNM) framework, introduced by Gasparrini and colleagues in their 2011 publication, presents a way to characterize these lagged effects.[9] While DLNMs have been used extensively to model the relationship between ambient temperature and all-cause mortality, to our knowledge this framework has not yet been applied to estimates of relative risk for cause-specific mortality at a granular level. The structure of lagged effects (if any exist) for the 17 causes listed above remains unclear.

Here, we aim to expand understanding of the relationship between exposure to non-optimal temperature and cause-specific human health impacts, with a particular focus on assessing potential lagged effects of temperature exposure on excess risk of mortality. We employ a two-phase modeling approach by combining the DLNM framework for estimating lagged effects[9] with mixed-effects metaregression.[3,10] We use this approach to 1) develop a set of globally-applicable exposure-response incorporating lagged effects, 2) compare estimated

relative risks (RRs) for non-optimal temperature encompassing the entire lag period with those produced by Burkart et al., 2021 which do not include lagged effects,[3] and 3) compare RRs for non-optimal temperature exposure and causes-specific mortality outcomes across different lag periods.

Methods

Input data

For ambient temperature estimates, we used the ERA5 gridded reanalysis dataset, produced by the European Center for Medium Range Weather Forecasts.[11] Using temperature estimates from January 1, 1980 to December 31, 2019, we calculated the temperature zone, defined as the mean temperature experienced across all days used in the analysis, for each grid cell according to methods developed by Burkart and colleagues.[3] For our analysis, we included only the zones between the 1st and 99th percentiles of the input data distribution to avoid modeling challenges from limited data availability at extremes. These are zones with mean annual temperatures ranging from 6 to 28 degrees Celsius.

Outcome input data for this project comprises cause-specific mortality data (with information on ICD code, administrative unit, and day) from eight countries compiled from publicly available datasets or through the GBD collaborator network. Countries included are Brazil, Chile, Colombia, Guatemala, Mexico, New Zealand, South Africa, and the United States of America. Data was matched to GBD causes, temperature zone, daily mean temperature, and location as described in Burkart et al, 2021.[3]

Distributed lag non-linear modeling

All stages of the analysis were conducted independently for each of the 17 causes of interest: lower respiratory infections, chronic obstructive pulmonary disease, ischemic heart disease, stroke, hypertension, diabetes, cardiomyopathy and myocarditis, chronic kidney disease (non-external causes); and self-harm, interpersonal violence, animal contact, drowning, exposure to forces of nature, exposure to mechanical forces, road injuries, other transport injuries, and other unintentional injuries (external causes).

In the first stage of the analysis, we applied a distributed lag non-linear modeling (DLNM) framework to estimate RRs for each cause of interest from data for each most-detailed administrative unit. To obtain RR estimates from mortality observations, we conducted a first-stage regression using a natural cubic B-spline on a trend variable with 8 degrees of freedom per year to capture secular trends (encompassing seasonal and long-term temporal variation), a log-transformed population offset, an indicator for day of the week, and an indicator for zone code (a more granular administrative identifier available for some administrative units). We incorporated lagged effects using DLNMs, which comprise two functions: an exposure-response function and a lag-response function.[4] These model components together estimate the distribution of an exposure's excess risk across time, generating a distribution that can be reduced to the overall (or "cumulative") exposure-response association by cumulating the risk across the chosen lag period.[4] In this analysis, we used a maximum lag period of 21 days to encompass varying proposed length of lagged effects for heat and cold, as well as mortality advancement, which has been observed in several temperature exposure-response analyses.[4,12–14] Mortality advancement, or harvesting, is the displacement of mortality in which deaths are advanced by a few days due to an extreme weather event. We specified the exposure-response function as a cubic spline with four degrees of freedom and three internal knots places at the 10th, 75th, and 90th percentiles. For the lag dimension, we used a cubic spline with four degrees of freedom with three internal knots that were equally-spaced on the log scale.

We truncated input data to only that between the 1st and 99th percentiles of temperature exposure experienced by each administrative unit's temperature zone. Truncating input data was also implemented in RR analyses for Burkart et al., 2021 to prevent outliers from producing

implausible trends in the risk curve tails (such as sharp increases or decreases that deviate from other regions of the curves). After fitting DLNMs for each administrative unit and cause of interest, we cross-reduced model output to obtain cumulative RRs of mortality. The cumulative RR expresses the summary RR for a given daily temperature exposure encompassing effects across a specific lag period. We calculated cumulative RRs for each cause and administrative unit for lag periods of 7, 14, and 21 days (the maximum lag period).

Mixed effects metaregression

In the analysis's second stage, we meta-regressed cumulative RRs from all administrative units to produce globally-applicable exposure response curves. We used the MetaRegression—Bayesian, Regularized, Trimmed (MR-BRT) framework, a meta-regression framework used widely across GBD risk factor teams,[10] to fit a two-dimensional spline surface on RR predictions. This approach predicts log-transformed RRs for each outcome from both daily mean temperature and temperature zone. We implemented random effects on administrative unit identifiers and priors to constrain curves for outcomes with expected J-shaped curves (non-external causes) to decrease or increase beyond the theoretical minimum risk exposure level (TMREL). For external causes, we used a monotonicity constraint.[3] From these predicted surfaces, we derived a set of cause-specific RR curves for each of the 23 temperature zones.

Results

We used 52,700,000 individual mortality observations from 12,641 administrative units in 8 countries as input data for the first stage of our analysis. These data spanned January 1, 1980 to December 31, 2016 across 23 temperature zones with mean annual temperatures ranging from 6°C to 28°C. Daily mean temperatures for these data ranged from -29°C to 33°C.

For non-external causes, we observed J-shaped curves for which elevated risk of mortality for temperatures below the curve's minimum (cold effects) was readily apparent across almost all temperature zones for all causes of interest. In contrast, increased risk of mortality for temperatures beyond the curve's minimum (heat effects) often emerged at temperate to warmer temperature zones only (those beyond 12° C for some causes). Interestingly, we found lack of evidence for cold effects for the coldest temperature zones (zones 6 and, in some cases 8) for all non-external causes except LRI. This may result from more limited data in these zones, or from the presence of human adaptation to extreme cold that attenuates the exposure-response relationship. RR curves for external causes were monotonically increasing, with elevated risk more pronounced at moderate temperature zones and less pronounced at extremes. Curves for temperature zone 18 for all causes are shown in Figure 1; those for all temperature zones appear in Figure S1.

Compared to results shown in Burkart et al. 2021 (Figure 2), we found notable presence of 21-day lagged effects for both heat and cold for most non-external causes, though magnitude of these effects varied by zone, evidencing the presence of human adaptation to temperature extremes. As with the underlying shape of the RR curves, we found that lagged effects due to cold were readily apparent for almost all temperature zones for all causes, but that lagged effects due to heat were observed primarily at warmer temperature zones. For external causes we found evidence for pronounced lagged effects for drowning, exposure to forces of nature, other unintentional injuries, and self harm; evidence for moderate or no lagged effects for interpersonal violence and road injuries; and no compelling evidence for lagged effects for animal contact, exposure to mechanical forces, or other transport injuries. Comparisons between curves with no lagged effects from Burkart et al. 2021 and curves from this analysis incorporating 21-day lags are displayed for temperature zone 18 in Figure 2. Plots for all temperature zones appear in Figure S2.

When comparing curves across different lag periods, we observed that, for non-external causes, cold effects displayed longer lag periods than heat effects. For most outcomes, using a lag periods of 21 days resulted in a higher RR for cold effects than using lag periods of 0, 7, or 14 days. For heat effects, however, the 21-day lag period often produced lower estimated RRs than 7- or 14-day lag periods, though the differences in predicted RRs between 7-, 14-, and 21-day lag periods were generally less pronounced for heat effects than for cold effects. Differences in excess risk between lags were more heterogeneous for external causes. Some causes (drowning, exposure to mechanical forces, other unintentional injuries) displayed little difference between non-zero lags. Others (interpersonal violence, self-harm, and road injuries) observed the highest estimated RR for the 7-day lag period. Finally, the remaining causes (animal contact, exposure to forces of nature, other transport injuries) displayed the highest elevated risk for the full 21-day lag period. Figure 3 compares curves with 7-, 14-, and 21-day lagged effects for all causes for temperature zone 18, and curves for all other zones are available in Figure S3.

We also found evidence of harvesting for some mortality outcomes. For cardiomyopathy and myocarditis, COPD, diabetes, HHD, IHD, and stroke, many moderate and warm temperature zones displayed harvesting for heat effects, wherein RRs for 7- or 14-day lag periods were higher than those for the 21-day lag period. Harvesting for cold effects was less pronounced, though some moderate temperature zones displayed evidence of harvesting for exposure to cold for diabetes, cardiomyopathy and myocarditis, and stroke. Harvesting may also occur for some external causes, such as interpersonal violence, self-harm, and road injuries, where using the 7-day lag period produces higher estimated RRs than the total lag period. Figures 4, 5, and 6 display comparisons between lag periods for LRI, drowning, and stroke as examples of a non-external cause, external cause, and cause with evidence of harvesting, respectively. Lag comparisons for all other causes are available in the appendix (Figures S3).

Discussion

This study analyzed a large, cause-specific mortality dataset of 52.7 million observations from 12,641 administrative units in 8 countries through a two-step approach. We first derived RRs, incorporating lagged effects, from raw mortality input data for each administrative unit. We then meta-regressed these RR predictions to generate globally-applicable, cause-specific risk curves for each of the 23 global temperature zones. These findings supported previous evidence that the shape of exposure-response relationships for non-optimal temperature exposure varies between external and non-external causes: non-external causes display J-shaped relationships, with elevated risk at both extreme heat and cold, while elevated risk for external causes of death monotonically increases with rising temperature.

We also gained new insight into the structure of lagged effects for cause-specific mortality outcomes. We found that lagged effects for heat and cold exist for all causes included in this analysis, but that the distribution of lagged effects varies by cause and temperature zone. For non-external causes, lagged effects for heat were generally shorter than those for cold. Lagged effects for heat often emerged only at moderate and warmer temperature zones, while lagged effects for cold occurred across almost all temperature zones. Harvesting was also more pronounced for heat effects for non-external causes, though diabetes, cardiomyopathy and myocarditis, and stroke also displayed harvesting for cold for some moderate temperature zones. Our findings on the presence of harvesting suggest that including a longer lag period of 21 days may be beneficial for future risk and burden assessments to avoid artificially-elevated RR predictions due to mortality advancement. External causes displayed more variable patterns of lagged effects, ranging from limited evidence for lagged effects beyond the day of temperature exposure to evidence for effects 21 days after initial exposure.

Previous studies of cardiovascular and respiratory mortality (excluding external causes) found evidence that heat effects last for shorter time periods of 1,[15] 3,[5] or 5 days,[16] while cold effects can persist for up to 7,[15] 12,[16] and 21 days.[5] Other studies on all-cause mortality have also found evidence for shorter lagged effects for heat than for cold.[4,17] Results from this analysis largely corroborate these previous findings, though our analysis suggests that lagged effects for heat may last longer than previously demonstrated, especially for non-external causes of death in warmer temperature zones. These added findings render climate change mitigation strategies all the more critical, especially for locations that already experience extreme heat exposure and high burden from non-external causes. Further, variability in the magnitude and pattern of lagged effects between causes and temperature zones indicates that all-cause mortality analyses may mask varying time-dependent relationships between temperature exposure and mortality that appear on the cause-specific level. This finding is of particular importance for designing clinical and public health interventions for specific populations with varying disease burden composition. Finally, as previously discussed, our analyses indicate that cause-specific curves, such as those presented by in the Global Burden of Disease Study 2019 and our previous analysis, likely underestimate the disease burden for most non-external causes and many external causes.[2,3] This is especially true for locations exposed to cold temperatures; lagged effects for cold were largest in magnitude and most prevalent across varying temperature zones.

The strength of these findings is supported by the large, globally comprehensive mortality dataset used for primary analyses. These input data represent approximately 95% of temperature zones inhabited by humans and also cover a large range of sociodemographic and development characteristics. We further expanded the applicability of our estimates by meta-regressing RR predictions using a 2D spline interface that draws strength from areas rich in observations to produce informed estimates for those with limited or missing data. Conducting all steps of the analysis on the cause-specific level also enhances the utility of our results for public health decision making and policy action.

Though the 2D spline meta-regression framework allows inferences to be made about RR distributions for regions with limited data, the complexity of this framework also renders is less flexible and robust. For some causes, at temperature extremes, the 2D spline framework demonstrated a lack of flexibility in fitting relationships that deviated from J-shaped curves due to priors implemented based on trends in other regions of the surface. One example is the RR curve for temperature zone 28 for diabetes, which appears to deviate from the exposure-response relationship suggested by input observations (figures S1 and S3). We also observed a lack of cold effect for the coldest temperature zones for all non-external causes except LRI. This may result from lack of data at the coldest temperature zones or from adaptive measures to extreme cold, but clearly indicates the need for rich data sources to inform this complex modeling process. For this reason, and because we currently lack data from many parts of the world, this analysis is also hindered by limited data availability. We included data from 8 countries encompassing a wide range of mean annual temperatures and sociodemographic characteristics; however, we have no data from Europe, Asia, or the Middle East, and have data from only a single country in Sub-Saharan Africa (South Africa). Incorporating more cause-specific mortality data is critical to deepening our understanding of how extreme temperature exposure affects human health.

Though we incorporated differences between temperature zones into our modeling approach via a 2D spline meta-regression, we did not directly adjust for any measure of human adaptability in our analysis. Such adaptations, including insulated housing, urban planning, air conditioning, and other infrastructural and behavioral adaptations modify the association between daily temperature and elevated risk of mortality.[18–20] As more data on adaptive behaviors becomes available, incorporating such variables into our analysis is a key priority. We also did not explore any interactive effects between temperature and air pollution, though recent

evidence indicates that heat effects and air pollution from various sources display synergistic effects on increasing risk for mortality.[21,22] Finally, because our analysis is ecological in nature, we were unable to match mortality observations with daily and mean temperatures experienced by individuals. These limitations indicate clear directions for future research.

Despite limitations, evidence presented here on the presence of lagged effects for heat and cold suggests that non-optimal temperature is responsible for a larger share of human mortality than previously estimated in cause-specific analyses.[2,3] Climate change will exacerbate temperature-related health disparities in places that are already vulnerable to the effects of extreme heat.[3] Lagged effects of heat for non-external causes may further widen the mortality gap between locations who are able to mitigate the effects of extreme temperature and those who are unable to do so. These findings provide strong evidence that action must be taken to pursue medical interventions, infrastructure development, and systemic action to mitigate climate change and non-optimal temperature's disease burden, and that these strategies should consider varying exposure-response relationships between causes.

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Figure 1. Log-transformed relative risk (RR) of mortality incorporating lagged effects over a 21-day lag period for the 18 °C temperature zone, faceted by cause of death. Gray shaded regions indicate uncertainty. Blue points indicate cumulative RR input data from DLNM stage.

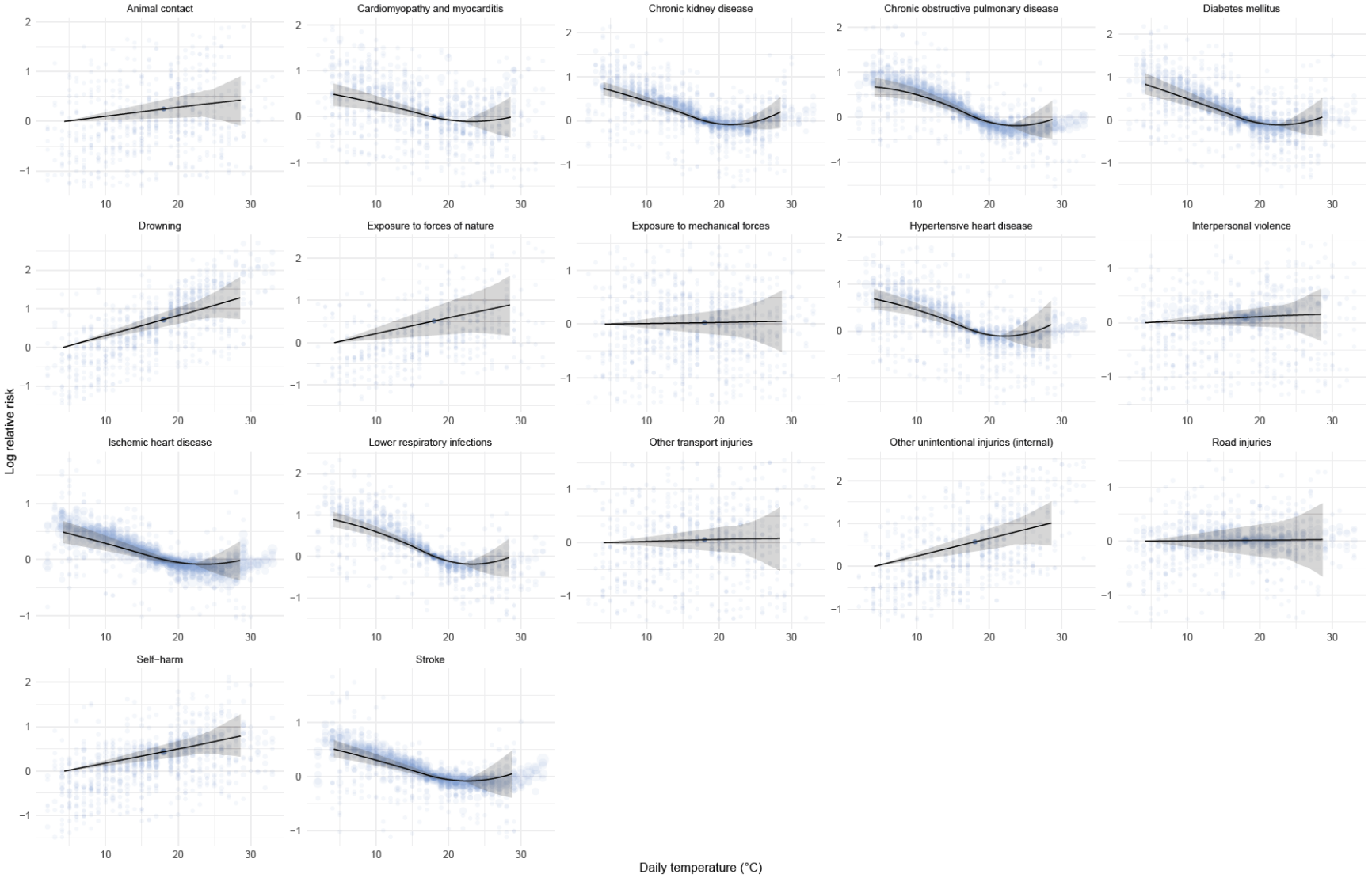

Figure 2. Log-transformed RR of mortality for the 18 °C temperature zone, faceted by cause of death. Green curves are those estimated by Burkart et al., 2021 and do not incorporate any lagged effects. Pink curves are those estimated with cumulative RRs across a 21-day lag period.

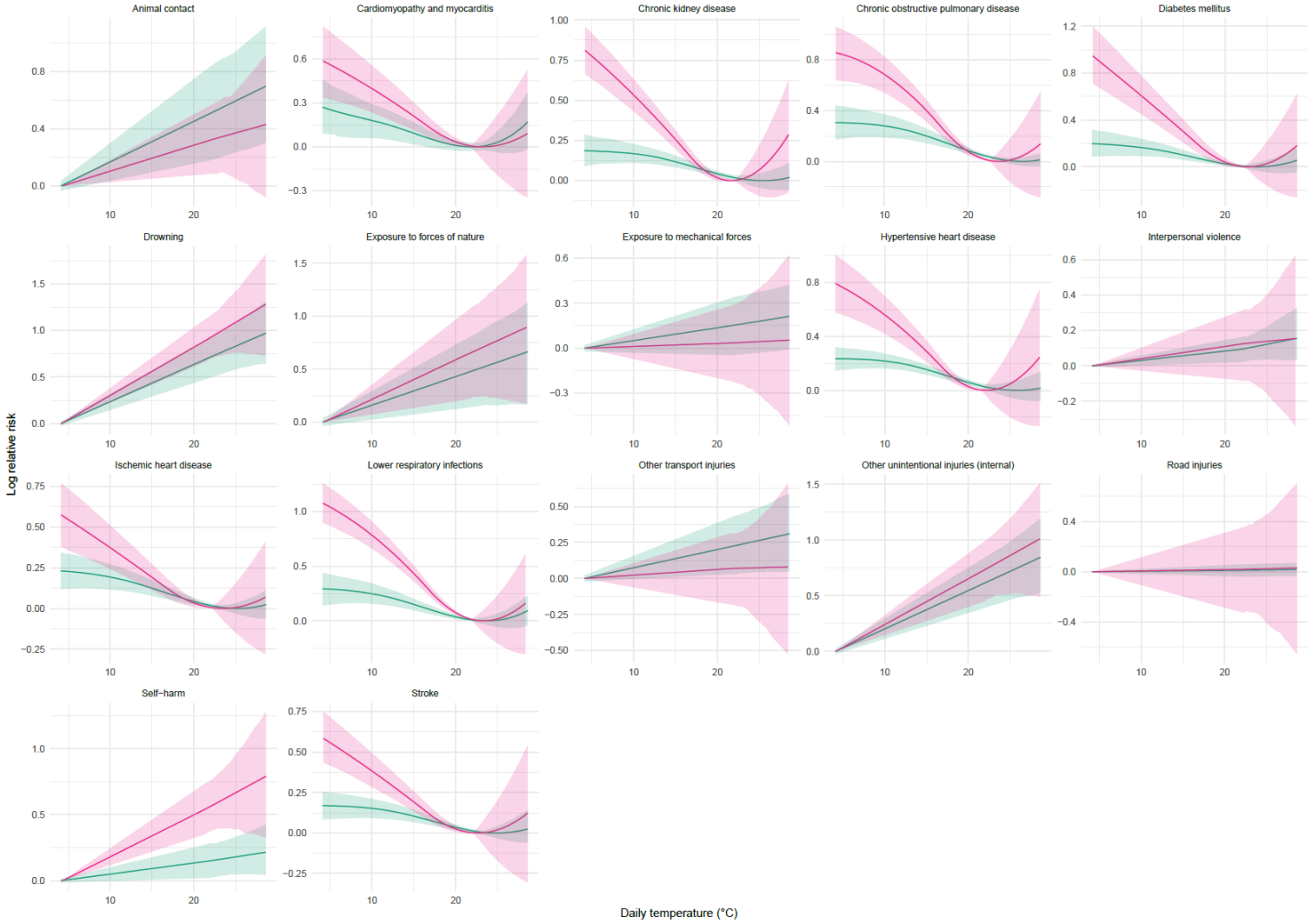

Figure 3. Log-transformed RR of mortality for the 18 °C temperature zone, faceted by cause of death. Colors denote lag periods (varying between 0, 7, 14, and 21 days) used to estimate the represented RR curves.

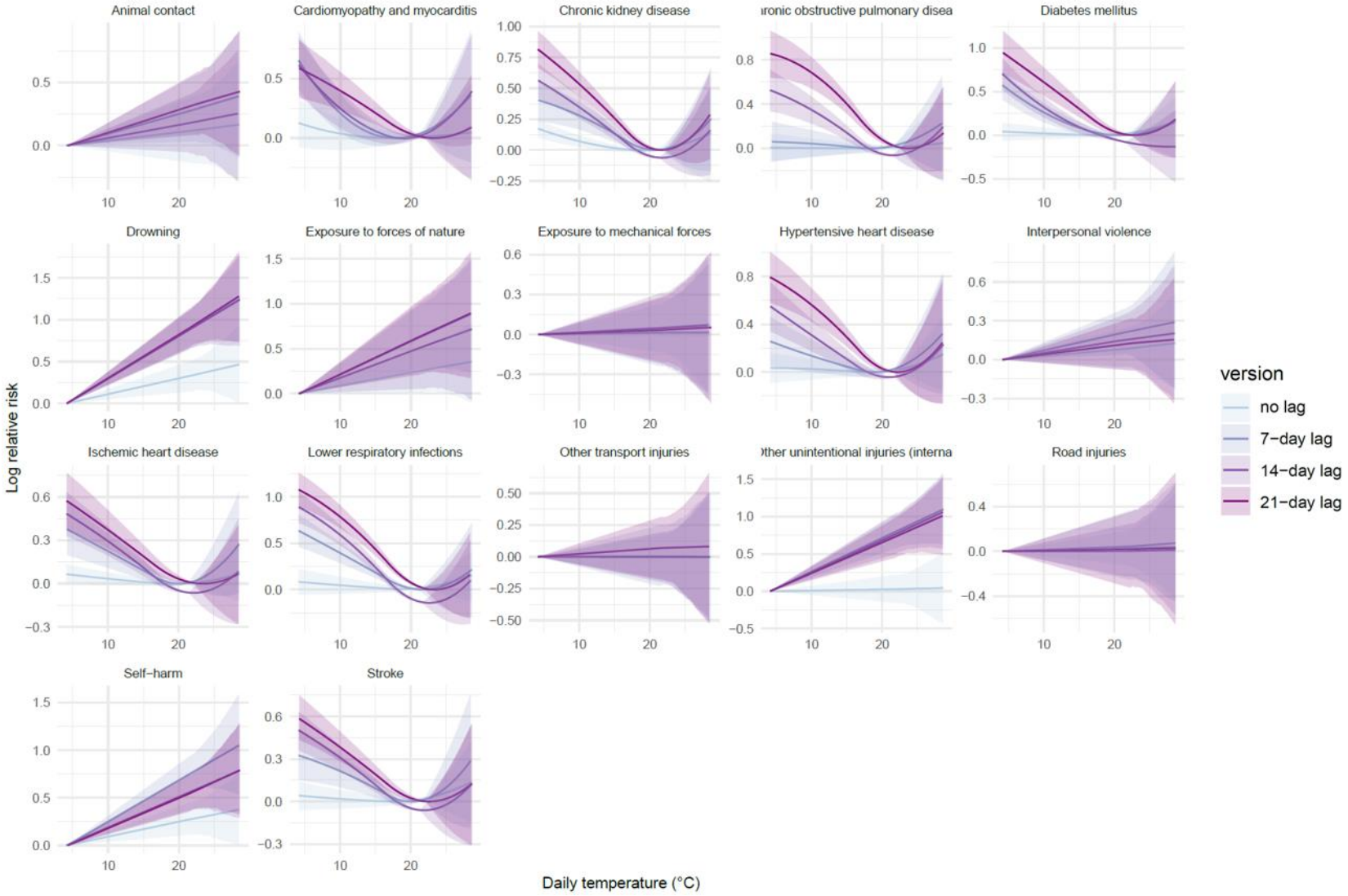

Figure 4. Log-transformed RR of mortality for lower respiratory infections, faceted by temperature zone. Colors denote the lag periods used to estimate the represented RR curves. Note that predictions were generated only for the range of daily temperature exposures for each zone's input observations.

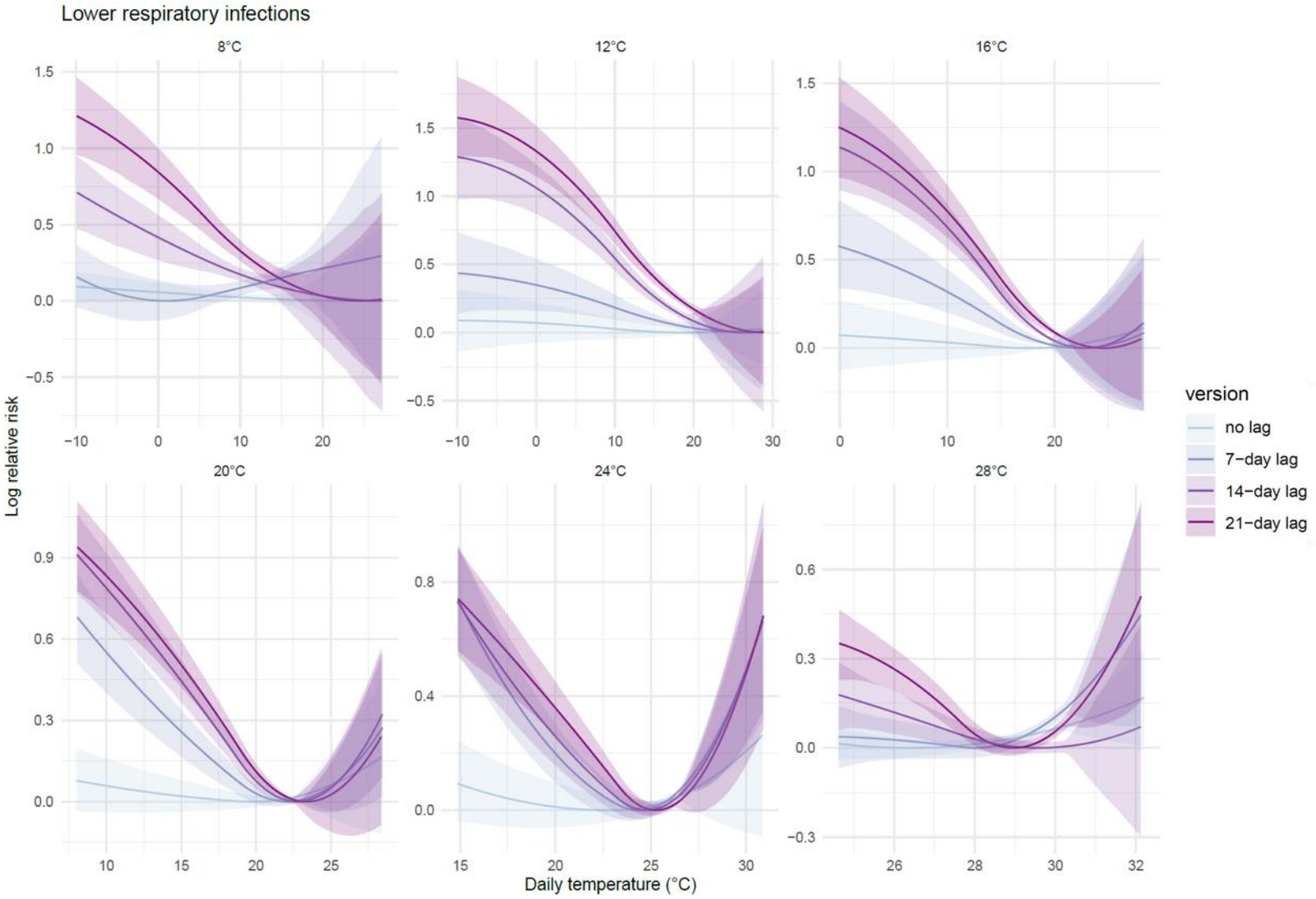

Figure 5. Log-transformed RR of mortality for drowning, faceted by temperature zone. Colors denote the lag periods used to estimate the represented RR curves. Note that predictions were generated only for the range of daily temperature exposures for each zone's input observations.

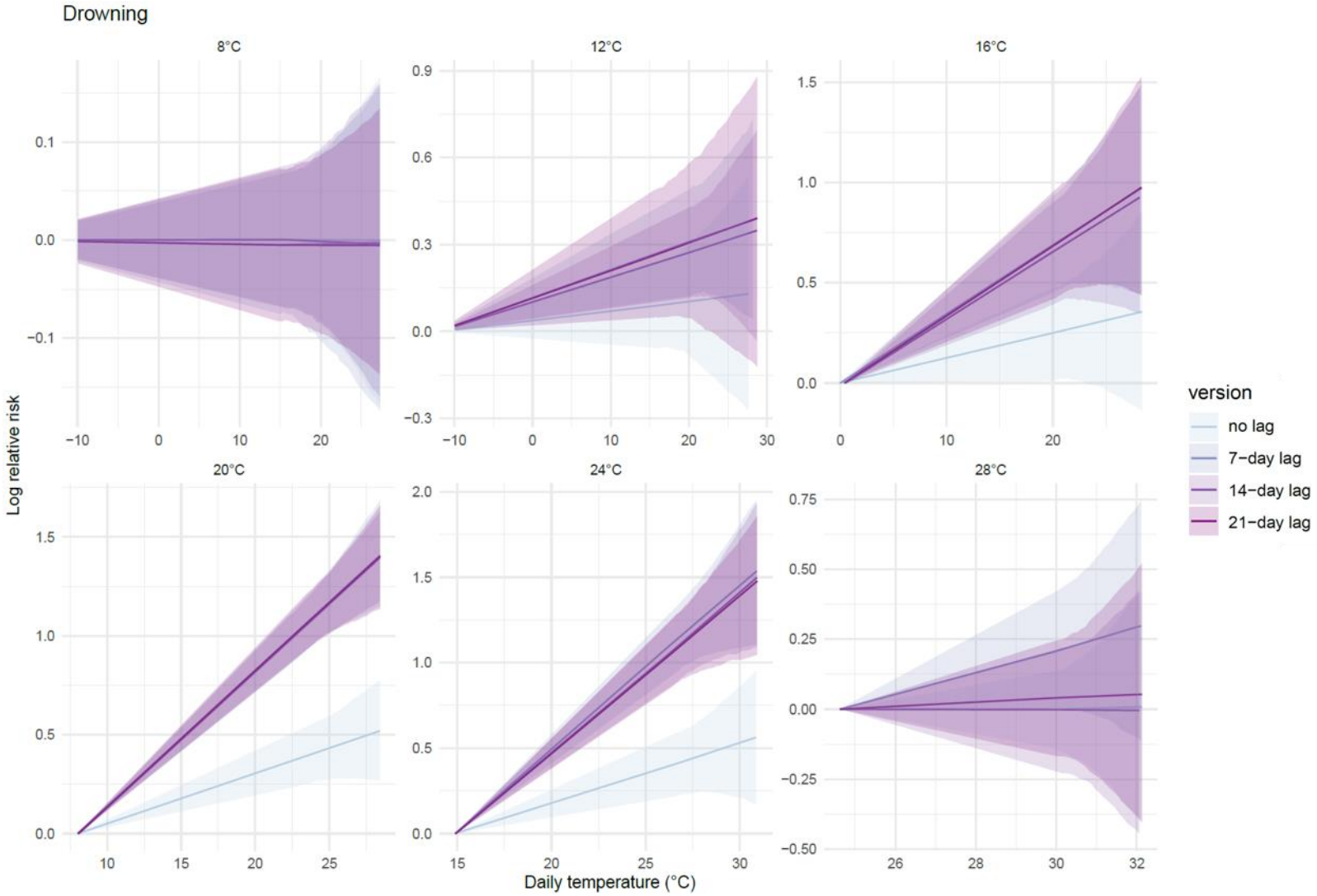

Figure 6. Log-transformed RR of mortality for stroke, faceted by temperature zone. Colors denote the lag periods used to estimate the represented RR curves. Note that predictions were generated only for the range of daily temperature exposures for each zone's input observations.