Delayed positive association between air temperature and covid-19 incidence in Italy

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Abstract

The association between air temperature and covid-19 incidence is unclear, particularly regarding lag effects. Here we address this research gap using high resolution data from Italy. We obtained daily covid-19 cases, populations at risk, and mean daily air temperature from 97 Italian cities for the period 24 February through 21 September 2020. We fitted a mixed-effects distributed lag non-linear model, presenting the effects as relative risks (RR) and cumulative relative risks (RR_{cum}).

Negative increments in mean daily temperature produced approximately inverted U- shaped lag-responses, though for large positive increments in temperature, the peak RR occurred at the maximal lag of 14 days. The temperature exposure response curves generally showed an increased RR with increasing temperature, though the shape varied according to the lag period. Positive and negative increments in temperature caused increases and decreases in the RR_{cum} respectively, though the plateau effect for negative increments was not observed above small positive increments in temperature.

We postulate that latent variables correlated with temperature, such as frequency and duration of social activities, are the underlying cause of our observed trends. Nonetheless, our statistical model can be utilised to forecast cumulative covid-19 incidence rates assuming specified air temperature increments at the city level.

1. Introduction

As of July 2020, more than 10 million cases of COVID-19 infections have been confirmed worldwide, and the global death toll has now exceeded 500,000 people (World Health Organization, 2020). Other than the direct impact of COVID-19, healthcare in other fields unrelated to infectious disease have also suffered from its knock-on effects. Woolf et al. (2020) reported a higher number of deaths in the United States than expected when comparing data from previous years, and it is estimated that 35% of the excess mortality is due to conditions not directly attributed to COVID-19. Though difficulty in seeking medical treatment due to movement restriction measures and reluctance to risk exposure in healthcare settings are speculated reasons for the excess mortality, an overwhelmed healthcare system likely played a significant role, especially in the formative stages of the outbreak. Italy was among the worst affected countries near the start of the pandemic, with daily new confirmed cases peaking at

the end of March 2020. Italy remained within the top ten countries with the highest cumulative number of confirmed cases by June 2020, at more than 240,000 cases, with a recorded case fatality rate exceeding 10% (Worldometer, 2020).

The association between climate and infectious diseases has been long established (Grassly and Fraser, 2006). Among respiratory viruses, one of the most prominent examples is the influenza virus, with cases spiking during winter months (Moriyama et al., 2020). Similarly, there is evidence to suggest that classical human coronavirus infections, as well as the Middle Eastern respiratory syndrome coronavirus (MERS-CoV) infections, peak around winter and early spring (Killerby et al., 2018; Cherrie et al., 2018; Kasem et al., 2018). Mechanisms behind the seasonality of these infections are incompletely understood, though various hypotheses have been proposed. Changes in meteorological parameters through the seasons likely affect the stability of coronaviruses on external surfaces, with increased rates of virus inactivation in environments with a higher temperature and higher relative humidity (RH) (Casanova et al., 2010; Chan et al., 2011).

Experiments on SARS-CoV-2 have demonstrated a temperature-dependent effect on the stability of virus particles on smooth surfaces (Chin et al., 2020). Since SARS-CoV-2 is shown to be capable of surviving in aerosols for at least 3 hours, airborne transmission is highly plausible (van Doremalen et al., 2020). Aerosol dynamics, and subsequently disease transmission, are affected by weather conditions, as a combination of low humidity and low temperature results in smaller infected droplet nuclei that can travel further, linger for a longer duration in the air, and cause delayed virus inactivation (Chen, 2020; Moriyama et al., 2020). Experimental evidence for the effects of climate on transmission dynamics using influenza virus in a guinea pig model lends credence to this hypothesis (Lowen et al., 2007). However, not all experimental studies agree that stability of SARS-CoV-2 is greatly affected by temperature, so caution is warranted in drawing definite conclusions (Kratzel et al., 2020).

Seasonal changes not only affect the biology of viruses, but human physiology, immunology, and behaviour will likely also influence COVID-19 transmission (Moriyama et al., 2020). Since the beginning of the outbreak, a number of studies have investigated the relationship between climate and COVID-19 transmission by examining epidemiological data from different regions worldwide. As highlighted by Yuan et al. (2020), these studies found contradictory results, even when analysing similar data for similar regions. In the case of Italy, a preliminary analysis using moving averages from five provinces showed a negative association between relative humidity and daily incidence, but a positive association between daily temperature and daily incidence in three of five provinces (Passerini et al., 2020). The

latter finding does not align with predictions based on our prior understanding. Another study focusing on time-series data in the city of Milan alone also found a positive correlation between temperature and COVID-19 (Zoran et al., 2020). In contrast, one study using multivariate analyses for three regions in Italy that compared climatic factors in relation to daily COVID-19 confirmed cases demonstrated an inverse correlation of temperature with daily incidence (Pirouz et al., 2020). A number of studies have also attempted to model lag effects of climatic predictors, though these have so far been limited to select regions (Runkle et al., 2020), relatively narrow temperature ranges (Passerini et al., 2020; Bashir et al., 2020; Tosepu et al., 2020), relatively short time series (Shi et al., 2020) and lag periods (Tobías and Molina, 2020), all of which may induce significant biases.

The objective of this contribution is to utilise high resolution data from a large number of Italian cities to quantify the lag effects of air temperature on COVID-19 incidence at the country level. To this end, we employ a mixed-effects distributed lag non-linear model (DLNM), which accounts for the trajectory of the epidemic in each city, as well as public health measures. We aim to provide further insight to predict if an increase in severity of the outbreak will occur during the winter months and to help us understand the potential seasonality of COVID-19.

2. Materials and Methods

We obtained daily confirmed COVID-19 cases, corresponding populations at risk, and public health interventions for the period of 24 February through 21 September, from 97 Italian cities across 21 regions, extracted from the COVID-19 R package (Guidotti and Ardia, 2020). Corresponding daily mean temperatures were obtained by overlaying the city coordinates on a geo-spatial grid (0.50 - degree latitude x 0.50 - degree longitude) obtained from the National Oceanic and Atmospheric Administration Physical Sciences Laboratory (https://psl.noaa.gov/data/gridded/data.cpc.globaltemp.html). The range of temperature in our dataset spanned from -7.55 to 30.62 °C.

In order to model the temporal dependency between mean daily temperature and daily COVID-19 cases, we employed a Distributed Lag Non-linear Model (DLNM) (Gasparrini et al., 2010). Our model took the form:

$$Y_{it} \sim Negative\ Binomial\ (\mu_{it}),$$

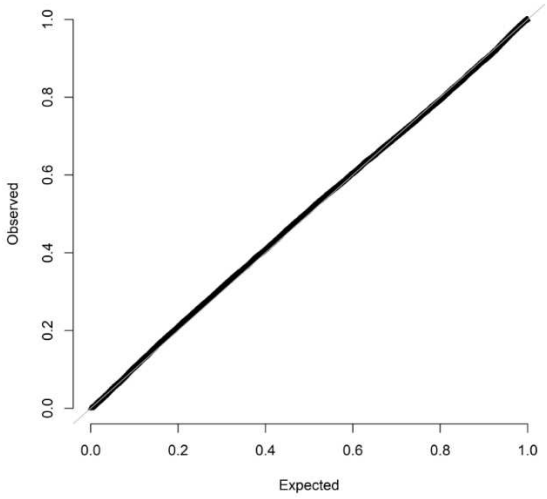
$$log(\mu_{it}) = \alpha + log(P_{it}) + \beta T_{it}, l + \lambda D_{it} + \tau R_{it} + C_0 + (\nu + C_1).ns(t), \qquad \text{eq. 1}$$

where Y_{it} is the mean COVID-19 cases in city i at time (day) t, P_{it} is the population at risk, T_{it}, l is a cross-basis matrix representing the daily lag (l) effect of mean daily temperature (T_{it}), D_{it} and R_{it} are fixed effect dummy variables for school closure, transport closure, day of week and region respectively, and α, β, λ, τ and ν denote model parameters to be estimated. C_0 and C_1 represents random intercept and slope terms for city i respectively. To model the trajectory of the epidemic over time (t), we used natural splines (ns) with 7 pre-specified degrees of freedom, which were allowed to vary by city. A redundancy analysis (Harrell, 2015) was performed on other potential public health control measures, including school and workplace closure, cancellation of public events, restrictions of mass gatherings, closing of public transports, movement and stay-at-home restrictions, information campaigns, as well as testing policies. These variables were found to be adequately explained by the above terms and thus not included in this model. The cross-basis matrix was constructed using natural splines with 3 pre-specified degrees of freedom for both the lag and exposure (i.e. mean temperature) bases. We specified an AR1 covariance structure in order to model temporal autocorrelation (Kristensen, 2020). The maximal lag period was pre-specified to 14 days. We applied a constraint in the model by excluding the intercept in the lag dimension of the cross-basis term. This had the effect of fixing the RR to 1 at lag 0, implying no immediate effect of any increment in T on the same day. The natural logarithm of P constitutes the model offset to account for varying populations at risk. Estimates of parameters were performed using full maximum likelihood. To check the assumptions of our model, we computed scaled (quantile) residuals using a simulation-based approach (Hartig, 2020) and produced plots to assess autocorrelation in the residuals (van Rij et al., 2020).

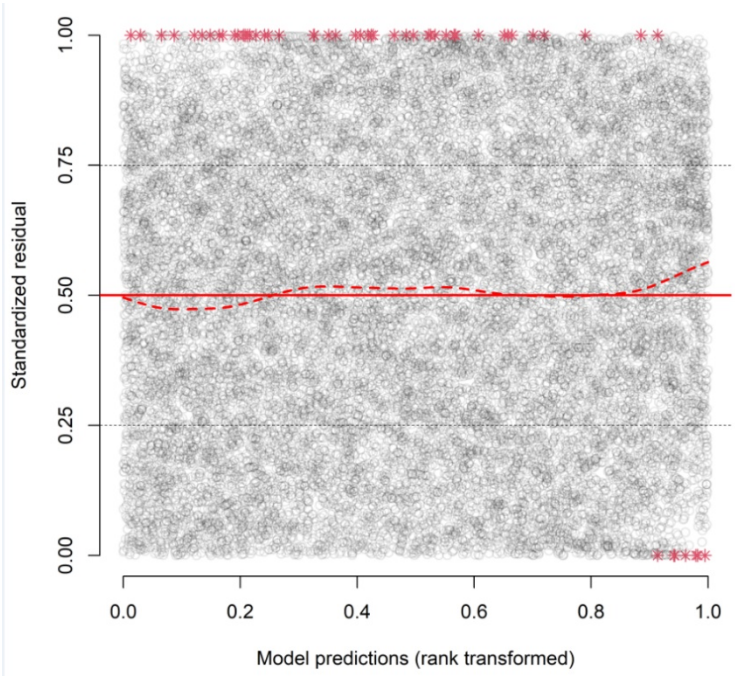
We computed the Relative Risk (RR) (±95 % confidence intervals) to quantify the direction and magnitude of the temperature exposure- and lag- response respectively. For interpretability, predictions were centred at the reference level of the mean temperature. The RR represents the ratio of the probability of contracting COVID-19 in the 'exposed group' (i.e. specified increment in temperature compared to the reference level) to the probability of COVID-19 in the 'non-exposed group' (temperature at the reference level). We also computed cumulative Relative Risks (RR_{cum}) at each lag by summing the individual RR's from previous lags. All statistical analyses were performed in R version 3.6.1 (R Core Team, 2013), relying heavily on the packages dlnm (Gasparrini, 2011) and glmmTMB (Brooks et al., 2017). The fully reproducible R code is included in the supplementary material.

3. Results

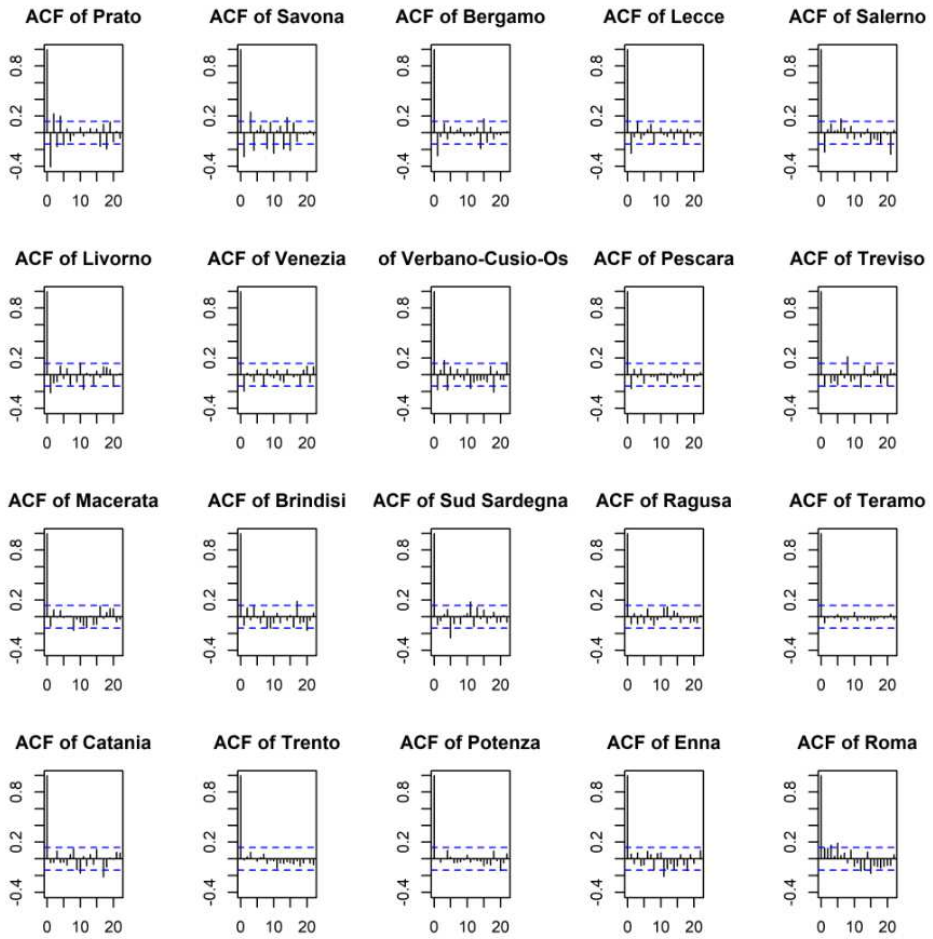
Our model fits the data well, as verified by a number of model checking plots (supplementary information figs1-3).



Supplementary information Figure 1. Quantile-Quantile plot of our statistical model computed using a simulation-based approach.



Supplementary information Figure 2. Fitted vs standardised residuals plot of our statistical model computed using a simulation-based approach.



Supplementary information Figure 3. Autocorrelation diagnostic plots for 20 random cities from our statistical model.

A bidimensional surface plot of the model predictions shows a twisted plane, intimating that the response to incremental changes in mean temperature was dependant on the lag time and vice versa (fig 1).

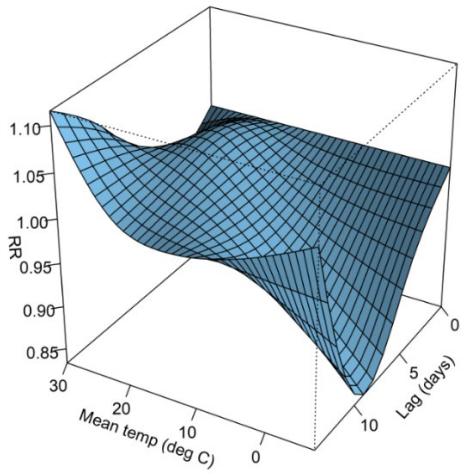


Figure 1. Bi-dimensional exposure lag response surface showing joint effect of lag time (days) and increments in temperature (°C) on predicted relative risk (RR). Increments in temperature are relative to the reference level of mean temperature 15 °C (i.e. the mean across all lags and cities).

The direction and magnitude of the lag-response varied according to the direction and magnitude of the increment in mean temperature compared to the reference level (i.e. 15 °C) (fig 2). Small positive increments in mean temperature produced a lag response whereby the RR gently increased above 1 at lag 0 to peak at approx. lag 5 days, before declining towards the null at the end of the lag period. Greater positive increments in mean temperature caused the peak RR to occur at later lags. For larger increments in temperature, the RR did not tend toward the null at the end of the lag period. Negative increments in temperature produced approximately U - shaped curves, which appeared greater in magnitude relative to positive increments in temperature. RR declined from 1 at lag 0 to the lowest RR (approx. 7-9 days lag) before rising again at the end of the lag period. In contrast to positive increments in temperature, the trough RR is relatively consistent across different negative increments in temperature.

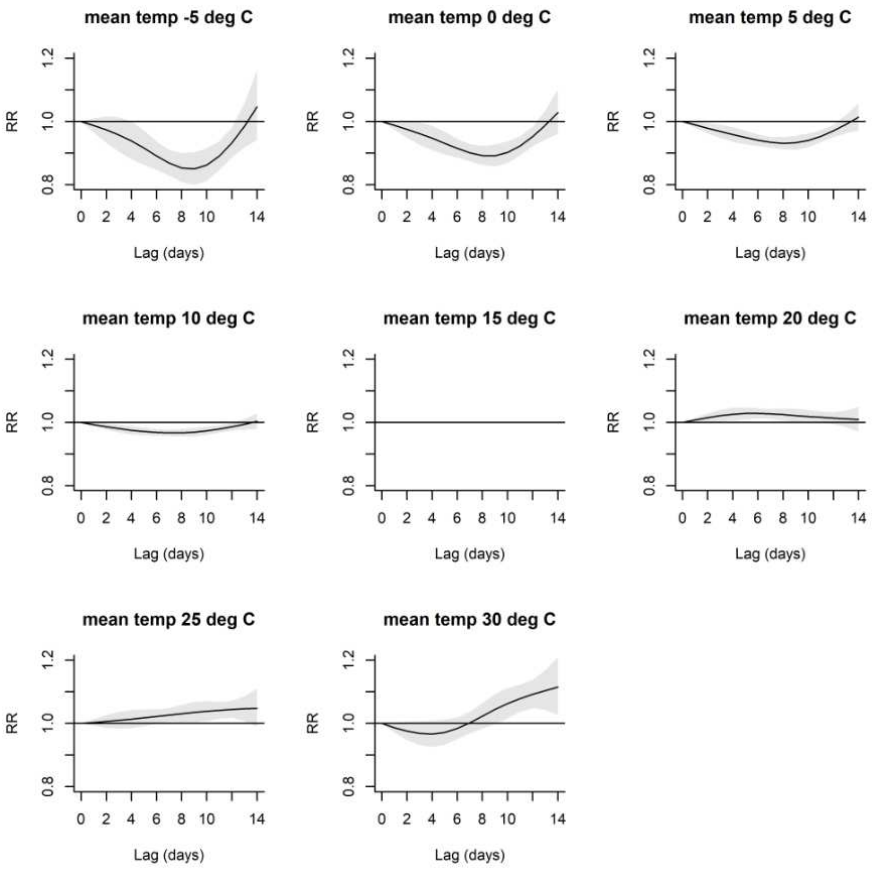


Figure 2 Estimated lag response of the Relative Risk (RR) and 95 % confidence intervals for specified increments in mean temperature (°C). RR>1 indicates a positive association whilst RR<1 indicates a negative association. Increments in temperature are relative to the reference level of mean temperature 15 °C (i.e. the mean across all lags and cities). For example, for the panel entitled mean temperature 20 °C, implies a 5 °C increase in the mean temperature.

The exposure response curves generally show an increased RR with increasing temperature relative to the reference temperature, though the shape varied according to the lag period (fig 3). Over much of the temperature range, RR increases approx. linearly with increasing temperature. However, at higher temperatures (20-30 °C), the shape transitioned from a slight decline (e.g. lag = 2, 4 and 6 days) to a plateau (lag = 8 days) to further increases (lag = 10, 12 days) in the RR. The exposure response at lag 14 days shows a slight decrease in the RR between -7 and 15 °C, though confidence intervals are wide and always include the null over this range.

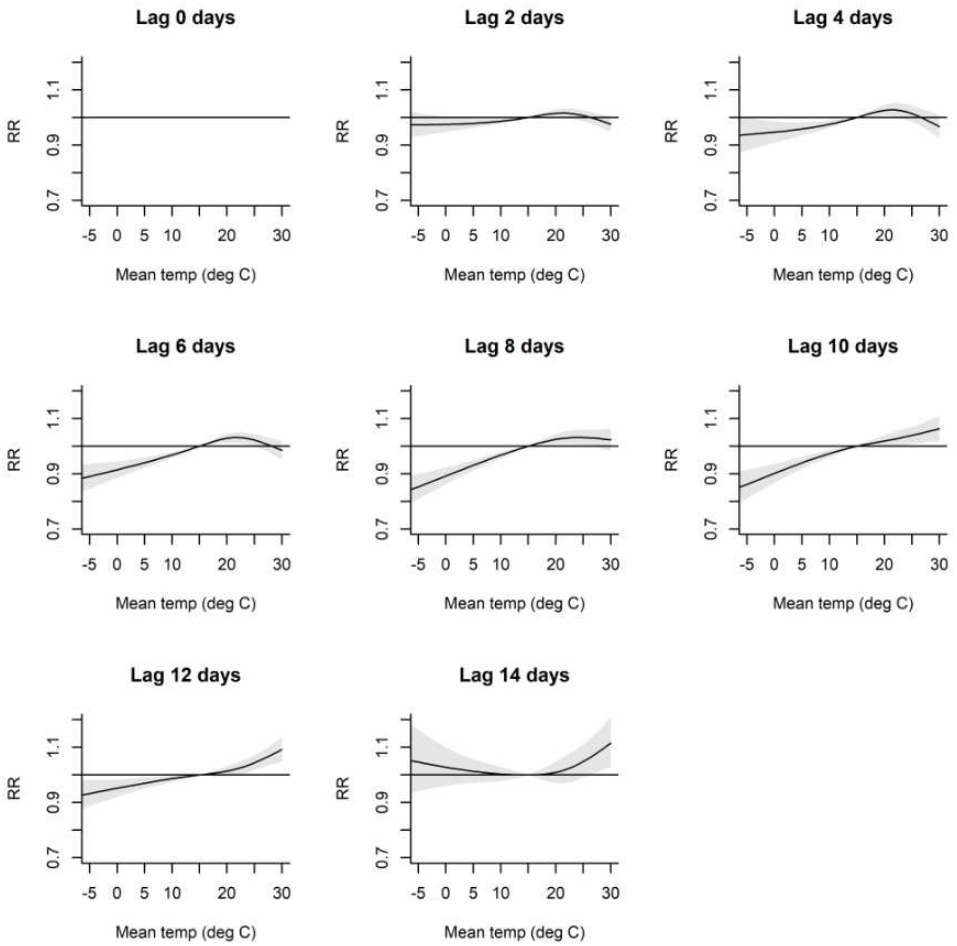


Figure 3 Estimated temperature response of the Relative Risk (RR) and 95% confidence intervals for specified lag periods (years). Increments in temperature are relative to the reference level of mean temperature 15°C (i.e. the mean across all lags and cities). Accordingly, the RR = 1 at temperature = 15°C for all panels on the plot.

Reductions in mean temperature relative to the reference level causes the RR_{cum} to decline over the lag period, reaching a plateau at later lags (fig 4). For relatively small positive increments in temperature, the RR_{cum} increases over the lag period, but plateaus at later lags. For greater positive increments in temperature the $RR_{cum\ lag}$ response resembles an exponential curve, though confidence intervals are wide for large positive increments.

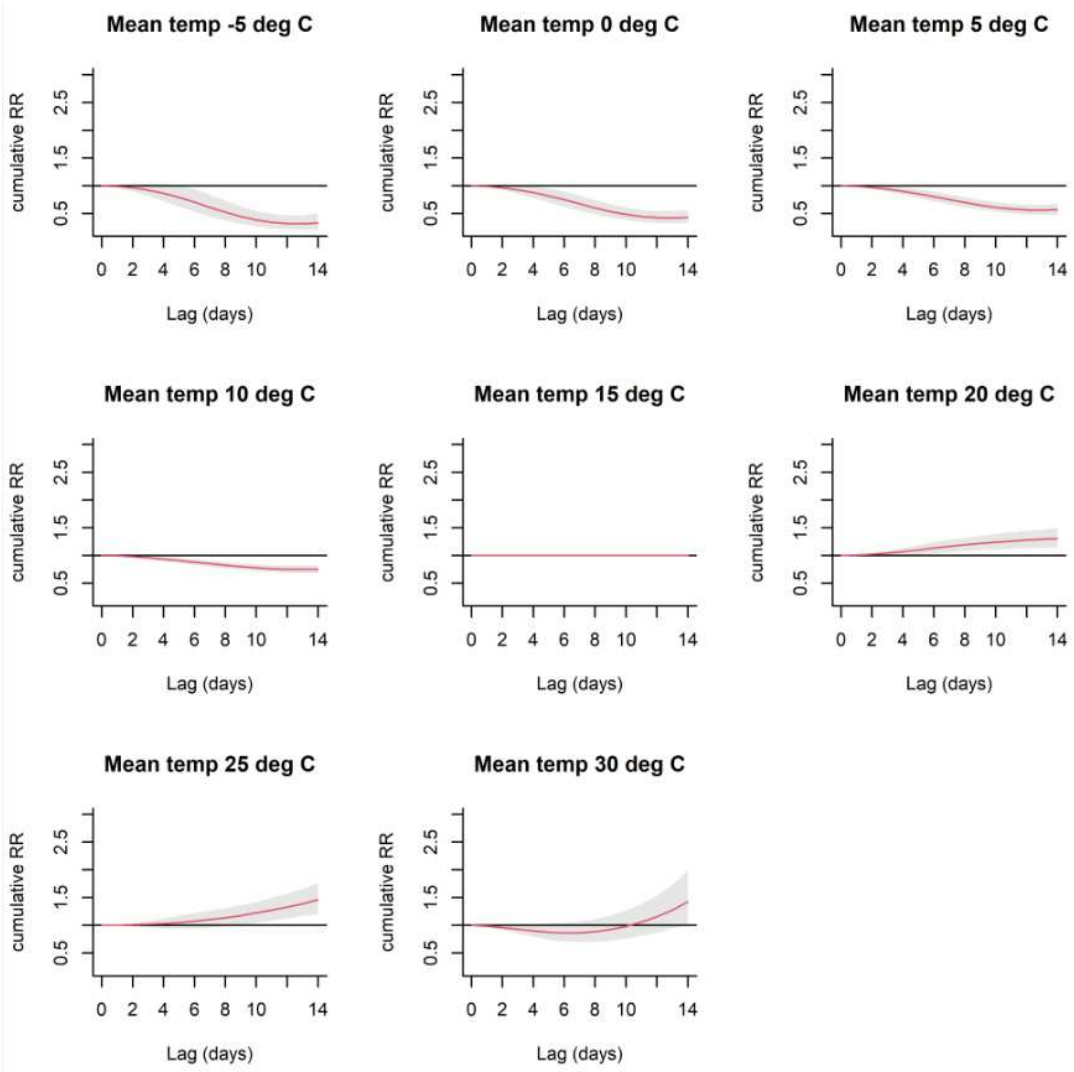


Figure 4 Estimated lag response of the cumulative Relative Risk (RR_{cum}) for specified increments in mean temperature (°C). Increments in temperature are relative to the reference level of mean temperature 15°C (i.e. the mean across all lags and cities). For example, for the panel entitled mean temperature 20 °C, implies a 5 °C increase in the mean temperature.

4. Discussion

To our knowledge, our study is the first to show the non-linear lag effects of daily temperature on daily COVID-19 cases at the country level by pooling the effects across 97 cities. Our analysis incorporated a wider temperature range (-7.55 to 30.62 °C), longer lag period (14 days), and longer time series (24 February through 21 September 2020) compared with previous studies. Overall, our results suggest a positive non-linear relationship between mean daily temperature and COVID-19 incidence, though the shape and magnitude of the curves vary according to the lag period.

The positive association between air temperature and COVID-19 incidence reported herein is in agreement with several observational studies (Bashir et al., 2020; Tosepu et al., 2020; Wang et al., 2020b) including two in Italy (Passerini et al., 2020; Zoran et al., 2020), though others have reported negative associations (Islam et al., 2020; Wang et al., 2020a; Liu et al., 2020; Luo et al 2020; Pirouz et al., 2020). Meteorological variables (Grassly and Fraser, 2006), control measures (Prem et al., 2020), and cultural practices (Bruns et al., 2020) are all plausible confounders which might account for these apparent disparities. Negative associations are more in line with the majority of experimental studies suggesting that low temperature is more favourable for virus transmission (Chen, 2020; Moriyama et al., 2020), though there is ongoing discourse as to the magnitude of the effect (Kratzel et al., 2020). However, assuming such an effect exists at the individual level, it would be fallacious to assume the equivalent at the population level.

One quite plausible explanation for our reported positive association between air temperature and COVID-19 transmission is that as temperature becomes warmer, so too will people be willing to go outside and congregate, increasing the risk of COVID-19 transmission. This seems particularly plausible since Italy has a culture of outdoor dining. Although lockdown measures were enforced in Italy, they were not very stringent, and anything less than the strictest lockdown (i.e. from 8 Mar to at least mid-April) did not seem to be very effective in limiting mobility (Vinceti et al., 2020). However, even during this period, outdoor exercise and pet walking were still permitted (Denti and Amante, 2020; Balmer and Pollina, 2020), and it is plausible that these activities would occur more frequently and / or for longer duration in warmer temperatures. Moreover, the surge in cases in August might reasonably be attributed to the complete lifting of the lockdown in early June, as opposed to higher temperatures during this time.

The peak and trough of the lag response curves represent the lagged day on which any increment in temperature has the strongest effect on COVID-19 incidence in the current day. These peaks (positive increments in T) or troughs (negative increments in T) fall between approx. 5 and 14 days depending on the direction and magnitude of the increment in mean daily temperature. This is slightly longer than the mean incubation period of 5.8 days (McAloon et al., 2020), though this might reflect a reporting delay. A noteworthy feature is that for large positive increments in T, the lag response curve does not reach a plateau at later lags. This might be suggestive of a longer lag period beyond 14 days and is worthy of further inquiry.

The RR returning back to approx. 1 at the end of the lag period translates to a plateauing effect in most of the cumulative effect plots. This is suggestive that any increment in temperature >14 days ago has no bearing on incidence in the current day. However, for larger positive increments in temperature e.g. 30°C, the RR does not fall back to the null, but increases exponentially. As a result, the corresponding RR_{cum} appears to be increasing at the end of the lag period, though again, the wide confidence bands do not rule out a plateauing effect. This could imply that the lags beyond 14 days might still influence COVID-19 incidence in the current day.

Using a forward perspective, our model can be used to forecast RR_{cum} for given increments in mean daily temperature over desired future time periods. Approximate RR_{cum} point estimates and confidence intervals can be obtained from fig 4, though exact values are easily obtained from our model predictions (R code in supplementary material). For example, a 5°C increase in mean T for a period of 10 days hence will produce a 24 [11,39] % increase in the incidence of COVID-19 (RR_{cum} = 1.24 [1.11 , 1.39])

Whilst this work offers a significant contribution to the literature, specifically with regards to the lag effects of temperature, the work is not without limitations. The first concerns the accuracy of the estimated daily counts of COVID-19. Notwithstanding the rate of testing, it is postulated that estimates are biased low due to undocumented infections (Li et al., 2020) or other reporting errors (De Natale et al., 2020). Secondly, our study is limited to the lag effects of mean temperature. A recent study (Babin, 2020) reported that min/max temperature might actually be a better predictor of COVID-19 incidence; this would be a worthy avenue for future research. Third, our results suggest the lag effect may extend longer than 14 days and so future work should consider this. Finally, although we have incorporated data from a large number of cities across a wide time frame, the trends reported herein cannot, as it stands, be generalized beyond Italy. Further work might consider a multicounty approach in order to estimate the temperature lag effect with greater precision or make inter-country comparisons.

Conflicts of interest

None

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Figures

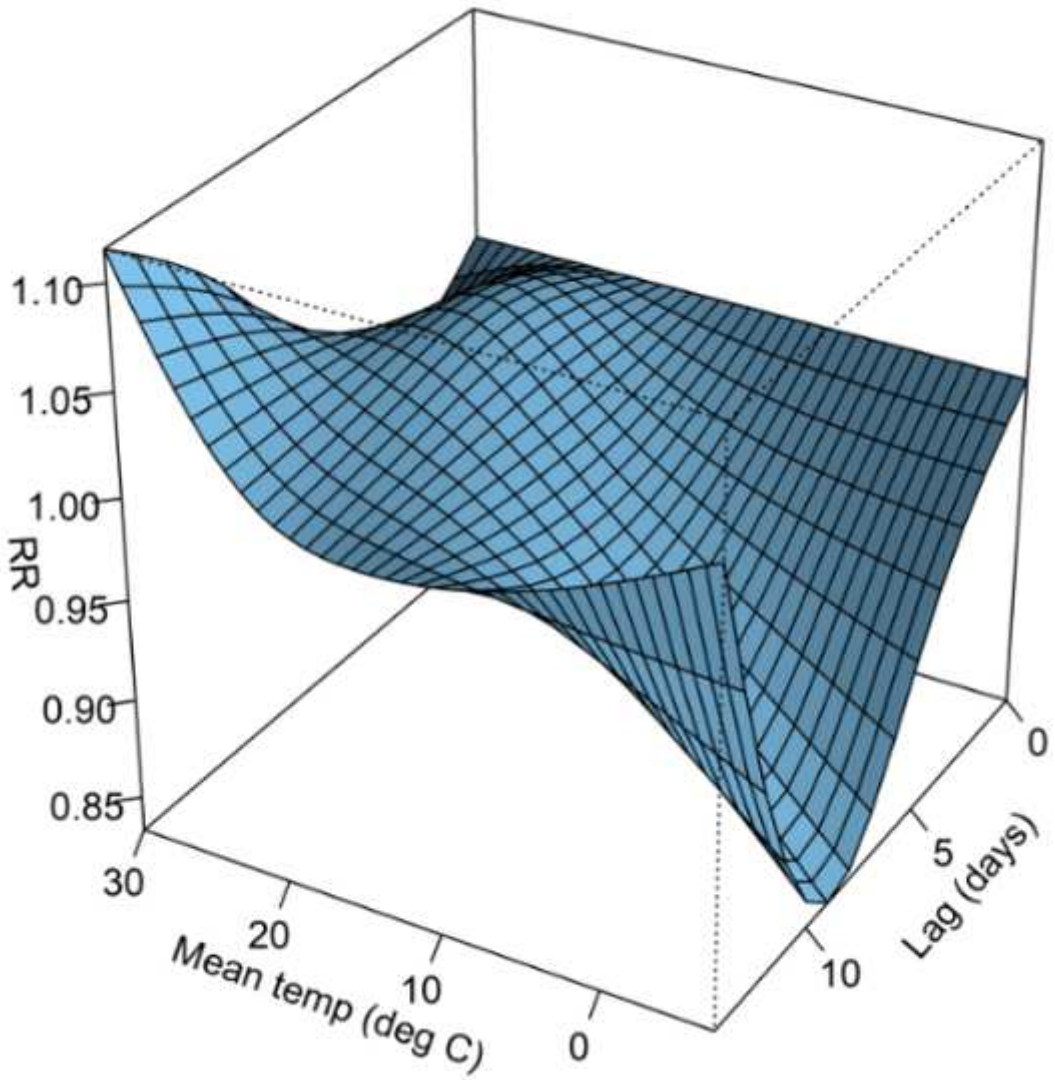

Figure 1

Bi-dimensional exposure lag response surface showing joint effect of lag time (days) and increments in temperature (°C) on predicted relative risk (RR). Increments in temperature are relative to the reference level of mean temperature 15 °C (i.e. the mean across all lags and cities).

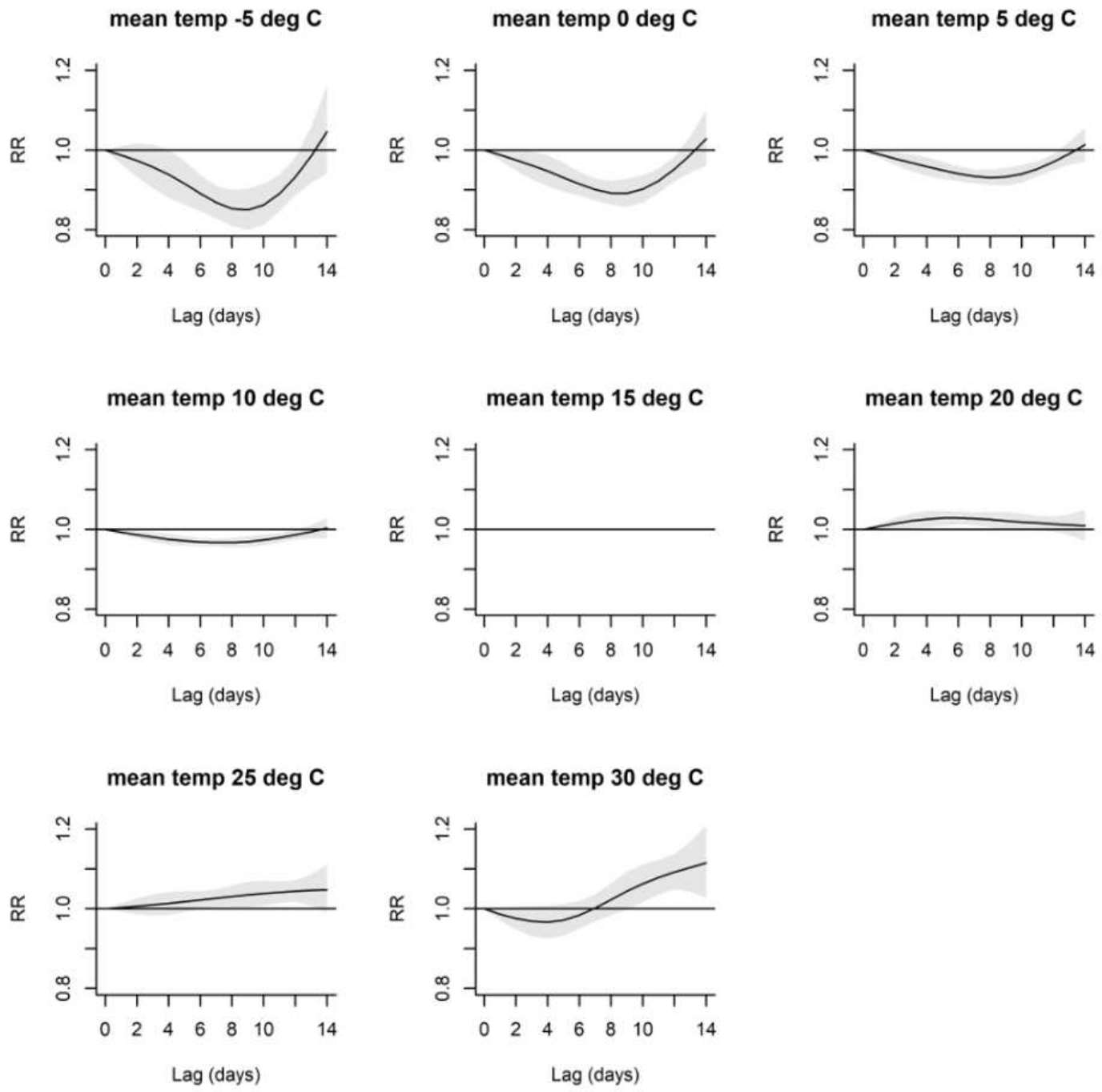

Figure 2

Estimated lag response of the Relative Risk (RR) and 95 % confidence intervals for specified increments in mean temperature (°C). RR>1 indicates a positive association whilst RR<1 indicates a negative association. Increments in temperature are relative to the reference level of mean temperature 15 °C (i.e. the mean across all lags and cities). For example, for the panel entitled mean temperature 20 °C, implies a 5 °C increase in the mean temperature.

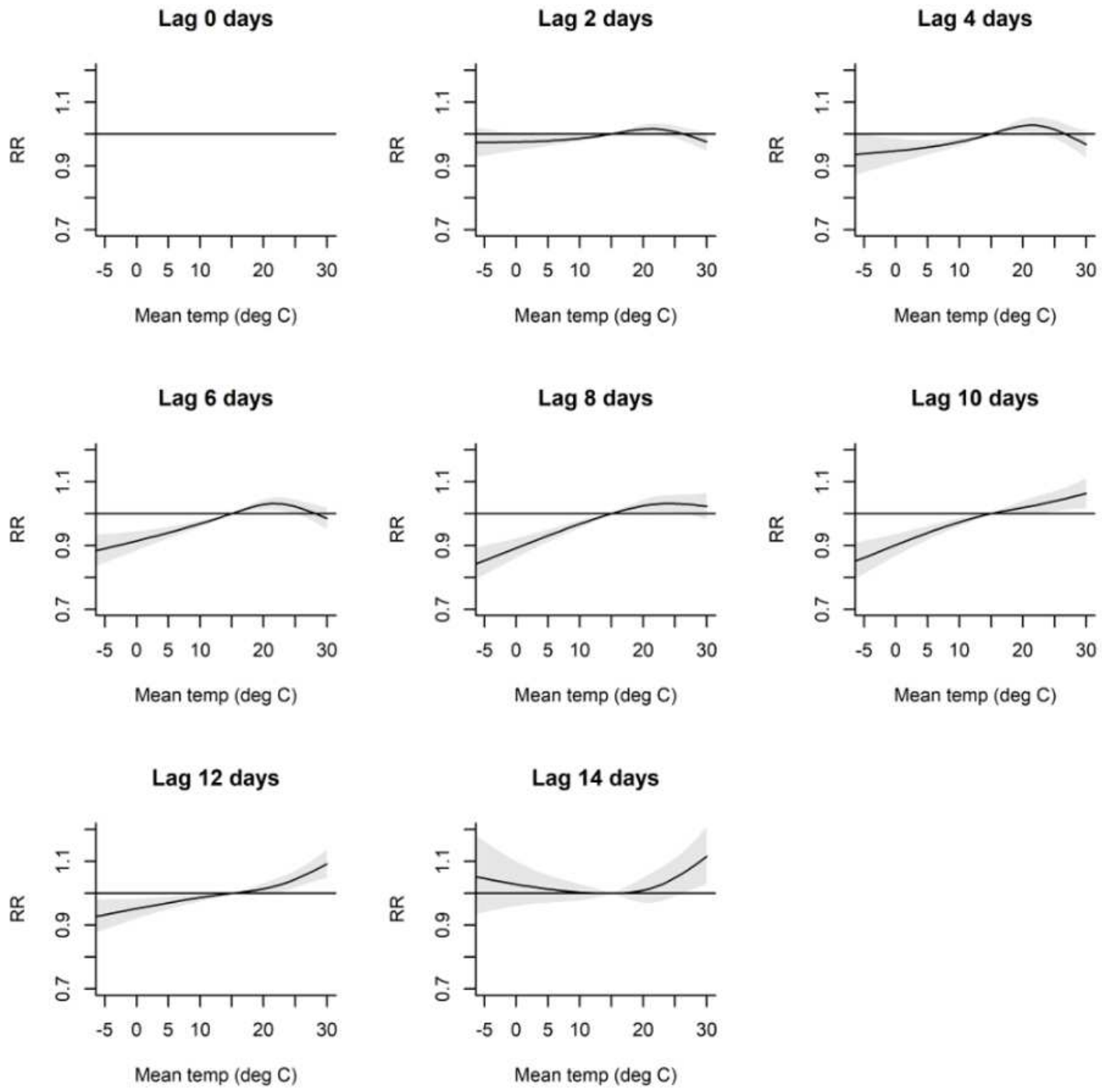

Figure 3

Estimated temperature response of the Relative Risk (RR) and 95% confidence intervals for specified lag periods (years). Increments in temperature are relative to the reference level of mean temperature 15°C (i.e. the mean across all lags and cities). Accordingly, the RR = 1 at temperature = 15°C for all panels on the plot.

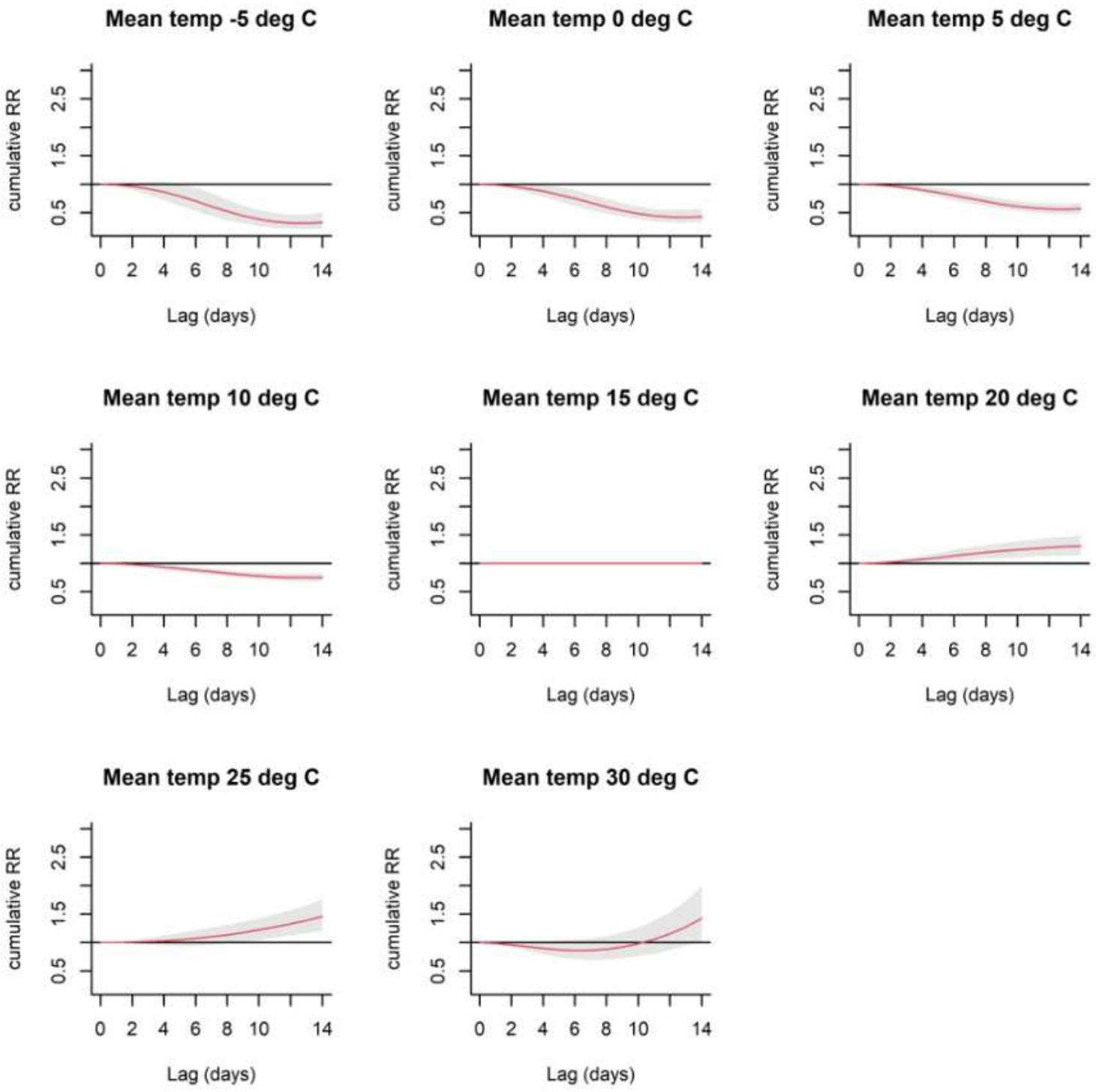

Figure 4

Estimated lag response of the cumulative Relative Risk (RRcum) for specified increments in mean temperature (°C). Increments in temperature are relative to the reference level of mean temperature 15°C (i.e. the mean across all lags and cities). For example, for the panel entitled mean temperature 20 °C, implies a 5 °C increase in the mean temperature.

Supplementary Files

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- Fongetal2020Rcode02Nov2020.r