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Original Article

Impact of weather factors on *Mycoplasma pneumoniae* pneumonia

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ABSTRACT

Background: Although multiple combinations of weather factors may contribute to an increased incidence of *Mycoplasma pneumoniae* (*M. pneumoniae*) pneumonia, few studies have investigated the association between weather factors and cases of *M. pneumoniae*.

Methods: We acquired data for *M. pneumoniae* pneumonia cases and weather factors in Fukuoka, Japan, from 1999 to 2007 and used time-series analysis to assess the effects of weather variables on *M. pneumoniae* pneumonia cases, adjusting for confounding factors. A total of 13,056 *M. pneumoniae* pneumonia cases were reported during the nine-year study period, of which 12,234 (93.7%) were under 15 years of age.

Results: The weekly number of *M. pneumoniae* pneumonia cases increased by 16.9% (95% CI: 11.3–22.8) for every 1°C increase in the average temperature and by 4.1% (95% CI: 2.7–5.5) for every 1% increase in relative humidity.

Conclusions: From 1999 to 2007, *M. pneumoniae* pneumonia cases increased significantly with increased average temperature and relative humidity in Fukuoka, Japan.

Keywords: *Mycoplasma pneumoniae*; Weather; Temperature; Humidity; Epidemiology

INTRODUCTION

Mycoplasma pneumoniae (*M. pneumoniae*) is a common respiratory pathogen that affects both upper and lower respiratory tract infections in all age groups.[1,2] This agent is estimated to be responsible for 15–20% of all cases of community-acquired pneumonia (CAP), and as many as 40% of cases among children.[2,3] An estimated 30% or more of *M. pneumoniae* infections in children 5–15 years of age result in pneumonia, and as many as 18% of these cases require hospitalization.[4,5]

M. pneumoniae infections can occur worldwide, with outbreaks occurring cyclically every 3–7 years.[6,7] A study has shown that *M. pneumoniae* infection did not show seasonal variations;[8] in contrast, however, recent studies have shown that *M. pneumoniae* infection peaks in winter[9] or spring,[10] and this etiology should be considered first when it occurs in the summer and fall months.[11] The clear cyclical and seasonal occurrence suggests that climatic factors could play a role. Moreover, other study has indicated that the most important factor explaining the variance in CAP is the direct and indirect effects of meteorological variables.[12] However, few quantitative studies have investigated the impact of weather factors and variability on the incidence of *M. pneumoniae* pneumonia, allowing for the mutual confounding between weather factors and potential confounding by other seasonally varying factors. The objective of this study was to investigate a relationship between weather variations and the weekly incidence of *M. pneumoniae* pneumonia between 1999 and 2007 in Fukuoka, Japan, using time-series methodology.

METHODS

Data sources

In Japan, systematic infectious disease surveillance began in 1981 under the Infectious Disease Control Law. This system, organized by the Ministry of Health and Welfare, involves about 3,000 sentinel medical institutions accounting for approximately 8% of the total number of pediatric hospitals and clinics throughout the country.[13] A case of *M. pneumoniae* pneumonia is defined by positive serology in combination with clinical factors. Clinical manifestations of upper respiratory tract symptoms include sore throat, hoarseness, fever, cough, headache, chills, coryza, myalgias, earache, and general malaise. Infections of the lower respiratory tract generally manifest with a cough, sometimes with dyspnoea, adenopathy, wheezing, and, rarely, with respiratory failure. *M. pneumoniae* respiratory tract infections are also associated with a wide range of extrapulmonary manifestations, including neurological, cardiac, dermatological, musculoskeletal, haematological, and gastrointestinal symptoms.[2,14] Serological methods include passive agglutination, complement fixation, and ELISA; in addition, a combination of PCR and serology is recommended for reliable diagnosis.[15-17]

The number of *M. pneumoniae* pneumonia patients is reported on a weekly basis from 120 sentinel medical institutions within Fukuoka Prefecture, southwest of Tokyo, Japan. The number of sentinels is based on the population of the area in which the health center is located: A health center with a population of < 30,000 would have one sentinel, an area with a population of 30,000–75,000 would have two, and an area with a population of > 75,000 would have three or more according to the formula ((population – 75,000)/50,000).[18] Clinical data are recorded and reported by sentinel volunteers to the Fukuoka Prefectural Government and the Fukuoka Institute of Health and Environmental Sciences (the municipal public health institute of Fukuoka Prefecture).

We analyzed the data of 13,056 *M. pneumoniae* pneumonia cases and the meteorological data from 1999 to 2007 for Fukuoka Prefecture. We also obtained data on the daily average temperature and relative humidity in Fukuoka Prefecture from the Japan Meteorological Agency. The weekly means for average temperature and relative humidity were calculated from the daily records.

Statistical analysis

We examined the relationship between the number of weekly *M. pneumoniae* pneumonia cases and temperature or humidity using generalized linear Poisson models allowing for over-dispersion.[19] We used mean temperature and humidity as they were better predictors of temperature and humidity relationships when compared with either maximum or minimum temperature by the maximum likelihoods for the models. To account for the seasonality of *M. pneumoniae* pneumonia cases not due directly to weather factors, Fourier terms up to the sixth harmonic were included in the model. Fourier terms can capture repeated periodic (e.g. seasonal) patterns comprising a combination of pairs of sine and cosine terms (harmonics) of varying wavelength.[20] Indicator variables for each year were incorporated into the model to allow for long-term trends and other variations occurring over the nine years of the study. To allow for autocorrelations, an autoregressive term at order one was incorporated into the models.[21] Plots of model residuals, predicted and observed time series plots, and partial autocorrelation function of the residuals (Supplementary Data, Fig. S1) suggested that this was an adequate amount of adjustment for seasonal trends.

Temperature models

Based on the results of exploratory analyses, existing literature,[22,23] and considerations of interpretational difficulty with very long lag periods, we considered lag periods (delays in effect) of up to 8 weeks for the influence of temperature on the number of *M. pneumoniae* pneumonia cases. In the initial analyses designed to identify the broad shape of any association, we fitted a natural cubic spline (3 *df*)[24] to the average over lag periods of 0 to 8 weeks. We also included humidity as a natural cubic spline (3 *df*) in the model to control for the effects of confounding, with a lag of 0 to 8 weeks.

The choice of model (linear or threshold) was based on comparing the deviance of the models derived from likelihood ratio tests.[25] The model with the smallest deviance was preferred. When a difference in values of deviance between linear and the best-fit threshold models was less than 3.84 (chi square value for one degree of freedom at the $P = 0.05$ level), the linear model was chosen for simplicity. Likelihood profiles suggested that the deviance between the linear and threshold models changed little; thus, we assumed that linear models without a threshold were appropriate for assessing the effects of weather variability on *M. pneumoniae* pneumonia cases.

Using the simple linear model, we then examined lag effects in greater detail by fitting linear unconstrained distributed lag models comprising temperature terms at each lag period that could be as long as 8 weeks.

Humidity models

Humidity was analyzed because we hypothesized that, along with temperature, humidity is a potential causal factor of a multiple factor pathway for the incidence of *M. pneumoniae* pneumonia cases. Specifically, we fitted a natural cubic spline (3 *df*) to the average humidity over lag periods of 0 to 8 weeks and incorporated this into a model comprising the same confounders included in the temperature model. As in the temperature models, the lag period was set at 0 to 8 weeks.

Because the plots of the smoothed relationships with humidity suggested a broadly linear positive relationship and the deviance between the linear and threshold models changed little, we fitted a linear model to estimate the effect (slope).[25] With the simple linear model, we examined lag effects in more detail by fitting linear unconstrained distributed lag models comprising humidity terms at each lag period that could be as long as 8 weeks.

We then examined whether the association still held if the two epidemics in 2001 and 2006 were removed from the analysis, because the large number of cases during two epidemics coinciding with high temperature and humidity may have skewed the data. In addition, to investigate whether the results were sensitive to the levels of control for seasonal patterns, the sensitivity analyses were conducted using different degrees of seasonal control (3 and 12 harmonics). All statistical analyses were carried out using Stata 10.1 (Stata Corporation, College Station, TX, USA).

RESULTS

We analyzed a total of 13,056 (100%) *M. pneumoniae* pneumonia cases from 1999 to 2007, of which 211 (1.6%) were infants younger than 12 months of age, 1,966 (15.1%) were 1–2 years of age, 3,081 (23.6%) were 3–4 years of age, 5,346 (40.9%) were 5–9 years of age, 1,630 (12.5%) were 10–14 years of age, and 822 (6.3%) were 15 years of age or older. Descriptive statistics for the number of patients and weather variables are displayed in Table 1. Analysis of the weekly reported cases of *M. pneumoniae* pneumonia revealed that the seasonal peak in cases was not identical from year to year (Fig. 1). We have analyzed our data to look for synergy between temperature and humidity.

Relationship with temperature

The relationships between the relative risk of *M. pneumoniae* pneumonia cases and temperature are shown in Figure 2. In the crude relationship, the potential risk of *M. pneumoniae* pneumonia increased as temperature increased from the lowest temperatures (Supplementary Data, Fig. S2). A significant positive relationship was found between the relative risk of *M. pneumoniae* pneumonia cases and the presence of higher temperatures during a lag of 0 to 8 weeks after adjusting for seasonal, between-year, and humidity variations (Fig. 2). For a 1°C increase, the number of *M. pneumoniae* pneumonia cases increased by 16.9% (95% CI: 11.3–22.8) and the temperature effect was significant for lag periods of 7 weeks using the distributed lag model. Little effect was observed for the other lag periods (Fig. 3).

Relationship with humidity

The relationships between the relative risk of *M. pneumoniae* pneumonia cases and humidity are shown in Figure 4. In the crude relationship, the potential risk of *M. pneumoniae* pneumonia increased as relative humidity increased from the lowest relative humidity (Supplementary Data, Fig. S3). After adjusting for seasonal, between-year, and temperature variations, we observed a significant increase in the number of cases of *M. pneumoniae* pneumonia with a 1% increase in relative humidity for lag periods between 0 and 8 weeks, as indicated by the positive linear slope with high humidity (Fig. 4). For a 1% increase in humidity, the number of *M. pneumoniae* pneumonia cases increased by 4.1% (95% CI: 2.7–5.5). The effect of humidity was significant at the lag periods of 3, 4, 5, 6, 7, and 8 weeks using the distributed lag model. Little effect was observed for the other lag periods (Fig. 5).

As the result of analysis without the two epidemics in 2001 and 2006, the weekly number of *M. pneumoniae* pneumonia cases increased by 8.4% (95% CI: 2.3–14.9) for every 1°C increase in the average temperature and by 4.1% (95% CI: 2.6–5.7) for every 1% increase in relative humidity. In sensitivity analyses, when the degree of seasonal control was halved (3 harmonics) or doubled (12 harmonics), the estimates of the effect of temperature and humidity changed little.

DISCUSSION

Several notable points are concluded from our findings. Most importantly, our results suggest that, after adjusting for potential confounding by temperature (only in the *humidity models*), humidity (only in the *temperature models*), seasonal patterns, and between-year variations, there was evidence for an increase in the number of *M. pneumoniae* pneumonia cases with either increase in temperature or relative humidity. Moreover, these positive associations still held after removing the two strong epidemics in 2001 and 2006. A laboratory-based study suggested that the survival of airborne *M. pneumoniae* was found to be a function of both temperature and relative humidity, however, the temperature response was mediated by humidity in that the effects of temperature could be observed only if some water vapor was present.[26] In addition, at all temperatures, survival of *M. pneumoniae* in aerosols was found to be best at extremes of relative humidity and the effects of temperature were such that irrespective of relative humidity an increase in temperature resulted in a decreased airborne survival time.[26] However, the result of epidemiological longitudinal study suggested that the survival and spread of *M. pneumoniae* were highly favored during the spring and early fall seasons and there might be a positive relationship between *M. pneumoniae* infections and temperature, which was only indirectly inferred from interannual observations or seasonal variations.[27] Thus, the positive relationship between *M. pneumoniae* pneumonia cases and increased temperature in this study is broadly consistent with the previous finding.

Our study also found that the number of *M. pneumoniae* pneumonia cases was increased with increase in relative humidity independent of ambient temperature. With respect to an association between the prevalence of *M. pneumoniae* pneumonia cases and humidity, a laboratory-based study has suggested that the survival of the airborne *M. pneumoniae* found to be best at 27°C and <25 or 90% relative humidity, whereas the most lethal relative humidity levels were at 60 and 80%.[28] Another laboratory-based study indicated that the biological stability of airborne *M. pneumoniae* might be easily modified by a sudden change in the relative humidity, such as occurs in natural atmospheres.[29] On the other hand, some epidemiological studies have indicated that there was little relationship between *M. pneumoniae* infections and relative humidity.[10,30] However, the former findings were studied at variable relative humidity with a controlled temperature, and the latter were studied by descriptive analysis. The discrepancy could be due to the effects of seasonally varying factors and mutual confounding between weather factors; these were controlled in the current study, but not in the previous one. In any case, our combined temperature and humidity results demonstrate the importance of weather factors on the prevalence of *M. pneumoniae* pneumonia infections.

Using the distributed lag model, the temperature effects appeared immediately at shorter lag periods (0–1 weeks), and were generally positive at later lags. In contrast, the humidity effects seemed to be delayed by a week or two, and were significantly positive throughout the lag periods around 3–8 weeks. These results may be related to the fact that *M. pneumoniae* has long incubation period of the organism and late detection of outbreaks.[31] Because of these characteristics of *M. pneumoniae*, public health officials and health-care providers struggle, often with little success, to detect *M. pneumoniae* pneumonia infections. This may also indicate that a need for more precise modeling of any lag effects of temperature and humidity on disease risk and further discussion of disease-specific issues would be important.

There may be concerns that not all cases in the community are represented in surveillance data. This under-reporting can occur anywhere in the reporting chain, from the initial tendency of a patient to seek health care to the recording of the case in the disease registry. *M. pneumoniae* infections commonly occur in closed or semi-closed communities,[32,33] and most people with *M. pneumoniae* infections have relatively mild disease symptoms,[34] such as a cough or sore throat, or no symptoms at all.[35] Thus, containing *M. pneumoniae* infections is difficult. However, we find no reason to believe this would result in substantial bias because the degree of under-reporting is not likely to vary over time. Another concern may be related to the fact that sentinel medical institutions were recruited on a voluntary basis, but this does not pose a threat to validity of the comparisons over time, which is the subject of this study.

The short term associations reported here cannot be directly extrapolated to changes in climate over decades. While it remains uncertain how increases in warmer temperatures could affect *M. pneumoniae* infections, the results of this study suggest that hot-related *M. pneumoniae* pneumonia cases would likely increase with climate change in Fukuoka, Japan.

Finally, we would like to refer to the practical implications of the present findings. Understanding the effects of weather variability on the epidemiology of infectious diseases is important for planning health services. These observed associations of weather variability with adverse health effects could represent a possible model or analog for health impacts of future climate changes. Health services may need to prepare for the effects of climate change on the epidemiology of *M. pneumoniae* pneumonia through the implementation of preventive public health interventions. Such interventions might include alerting health workers, intensive community-based campaigns, weather forecasting for early warning, and planning additional control programs for *M. pneumoniae* pneumonia. In accordance with these interventions, we might have a change in behavior, such as people coming into closer contact with each other and thereby increasing the chance of person-to-person transmission.

In conclusion, this study found quantitative evidence that the number of *M. pneumoniae* pneumonia cases increased with higher temperature and relative humidity in the weeks preceding disease onset for a large number of cases over a nine-year period.

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COMPETING INTERESTS

None declared.

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Tables

Table 1. Characteristics of the weekly number of *M. pneumoniae* pneumonia cases and meteorological data in Fukuoka, Japan, 1999–2007.

Variable (unit)	Minimum	Percentile			Maximum
		25	50	75	
Number of *M. pneumoniae* pneumonia cases	4	15	24	36	96
Average temperature (°C)	2.9	10.6	17.5	24.4	30.5
Average humidity (%)	43.9	60.1	65.5	70.7	83.9

Figure legends

Figure 1. Seasonal variations in the weekly number of *M. pneumoniae* pneumonia cases, temperature, and humidity in Fukuoka, Japan, 1998–2007.

Figure 2. Relationship adjusted for relative humidity, seasonal variations, and between-year variations between relative risk (RR) of *M. pneumoniae* pneumonia cases (scaled to the mean weekly number of *M. pneumoniae* pneumonia cases) and temperature over lag periods of 0 to 8 weeks (shown as a 3 *df* natural cubic spline). The center line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits.

Figure 3. Percent change (and 95% CIs) in the number of *M. pneumoniae* pneumonia cases for temperature (per 1°C increase) at each lag (unconstrained distributed lag models).

Figure 4. Relationship adjusted for temperature, seasonal variations, and between-year variations between relative risk (RR) of *M. pneumoniae* pneumonia cases (scaled to the mean weekly number of *M. pneumoniae* pneumonia cases) and relative humidity over lag periods of 0 to 8 weeks (shown as a 3 *df* natural cubic spline). The center line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits.

Figure 5. Percent change (and 95% CIs) in the number of *M. pneumoniae* pneumonia cases for humidity (per 1% increase) at each lag (unconstrained distributed lag models).

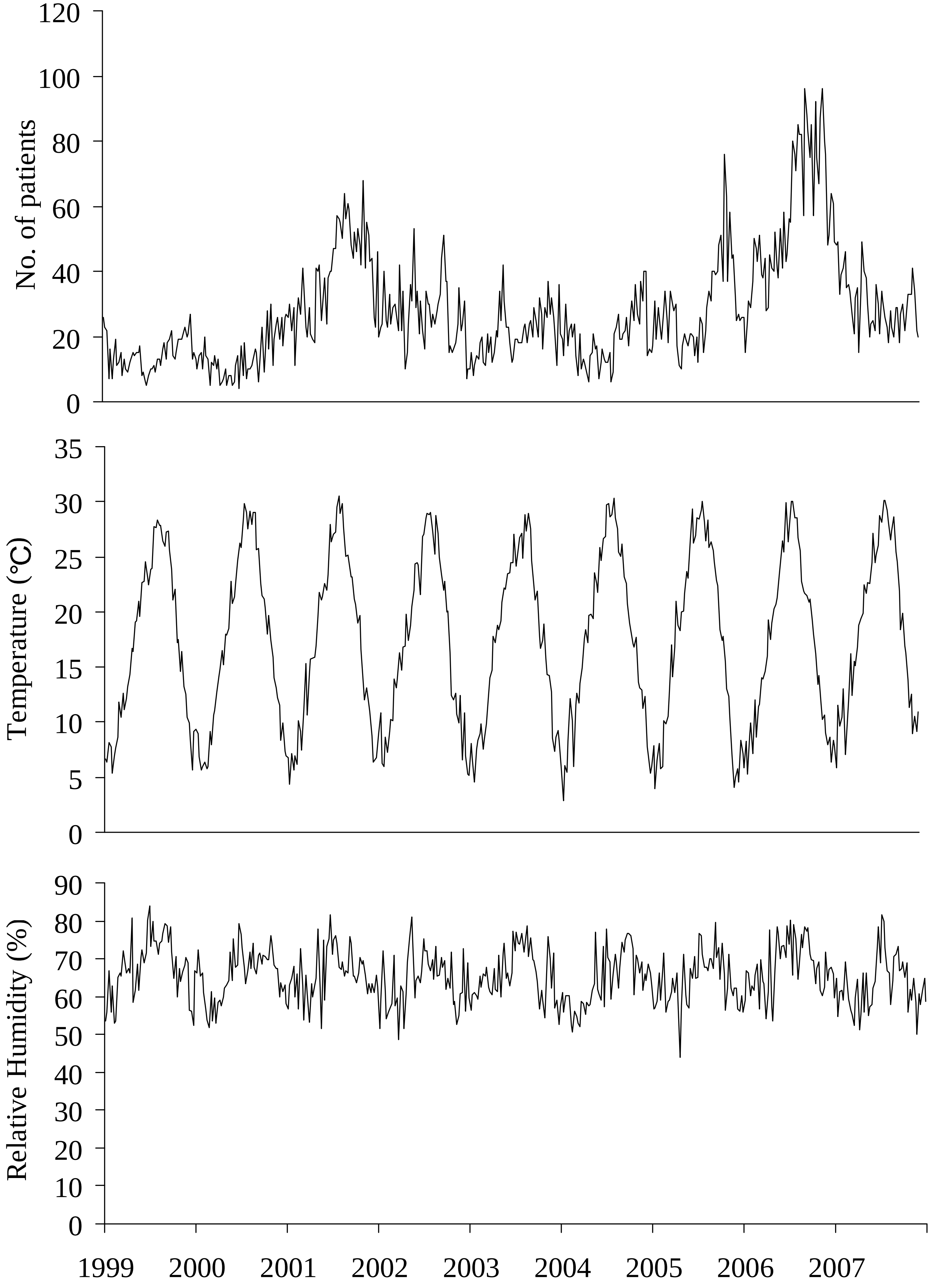
Supplementary Data

Figure S1. Diagnostics of models: (a) plots of model residuals, (b) predicted and observed time series plots, (c) partial autocorrelation function of the residuals.

Figure S2. Crude relationship between relative risk (RR) of *M. pneumoniae* pneumonia cases (scaled to the mean weekly number of *M. pneumoniae* pneumonia cases) and temperature over lag periods of 0 to 8 weeks (shown as a 3 *df* natural cubic spline). The center line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits.

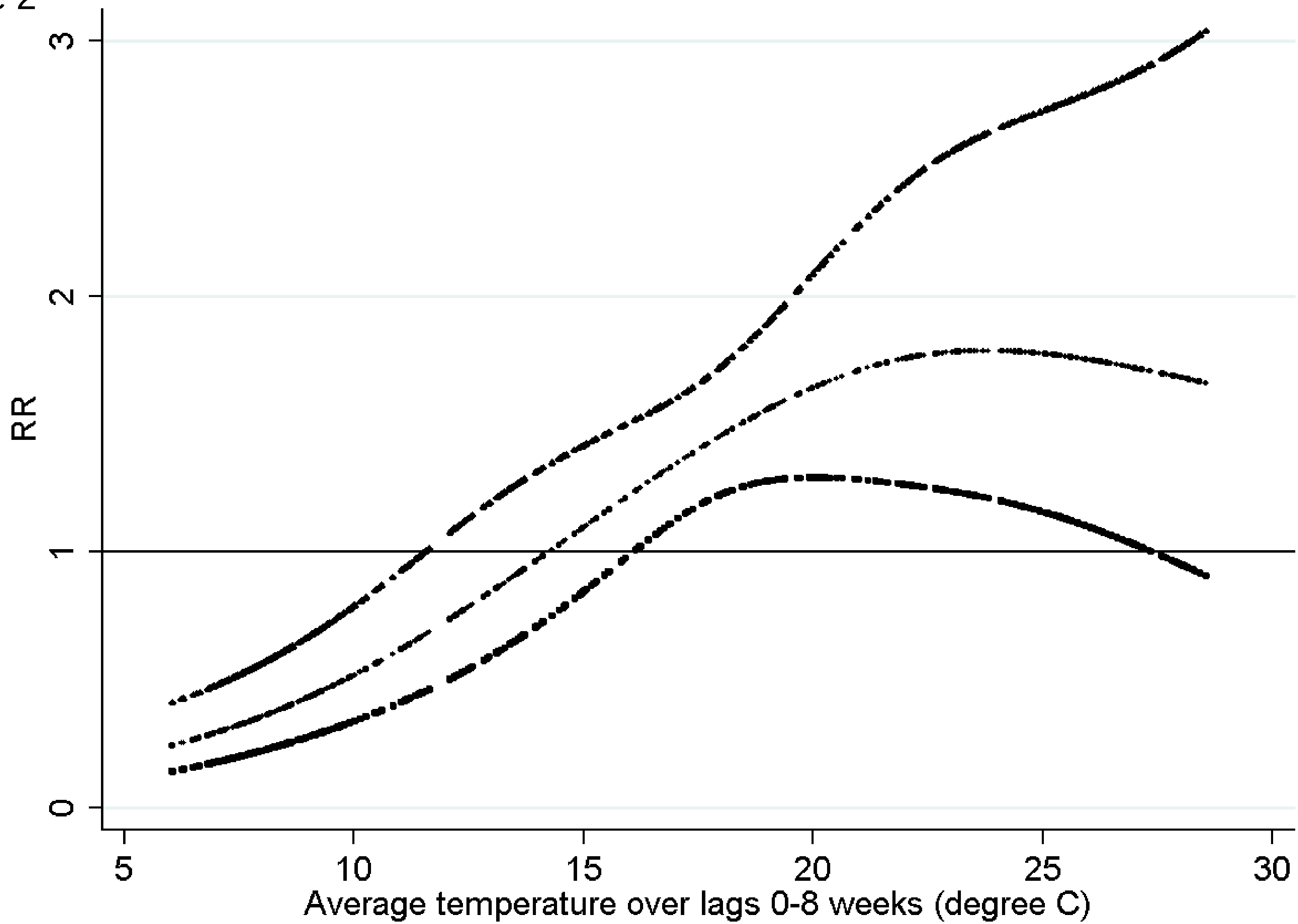
Figure S3. Crude Relationship between relative risk (RR) of *M. pneumoniae* pneumonia cases (scaled to the mean weekly number of *M. pneumoniae* pneumonia cases) and relative humidity over lag periods of 0 to 8 weeks (shown as a 3 *df* natural cubic spline). The center line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits.

Figure 1



No. of patients
0
20
40
60
80
100
120
Temperature (°C)
0
5
10
15
20
25
30
35
Relative Humidity (%)
0
10
20
30
40
50
60
70
80
90
1999
2000
2001
2002
2003
2004
2005
2006
2007

Figure 2



RR
0
1
2
3
5
10
15
20
25
30
Average temperature over lags 0-8 weeks (degree C)

Figure 3

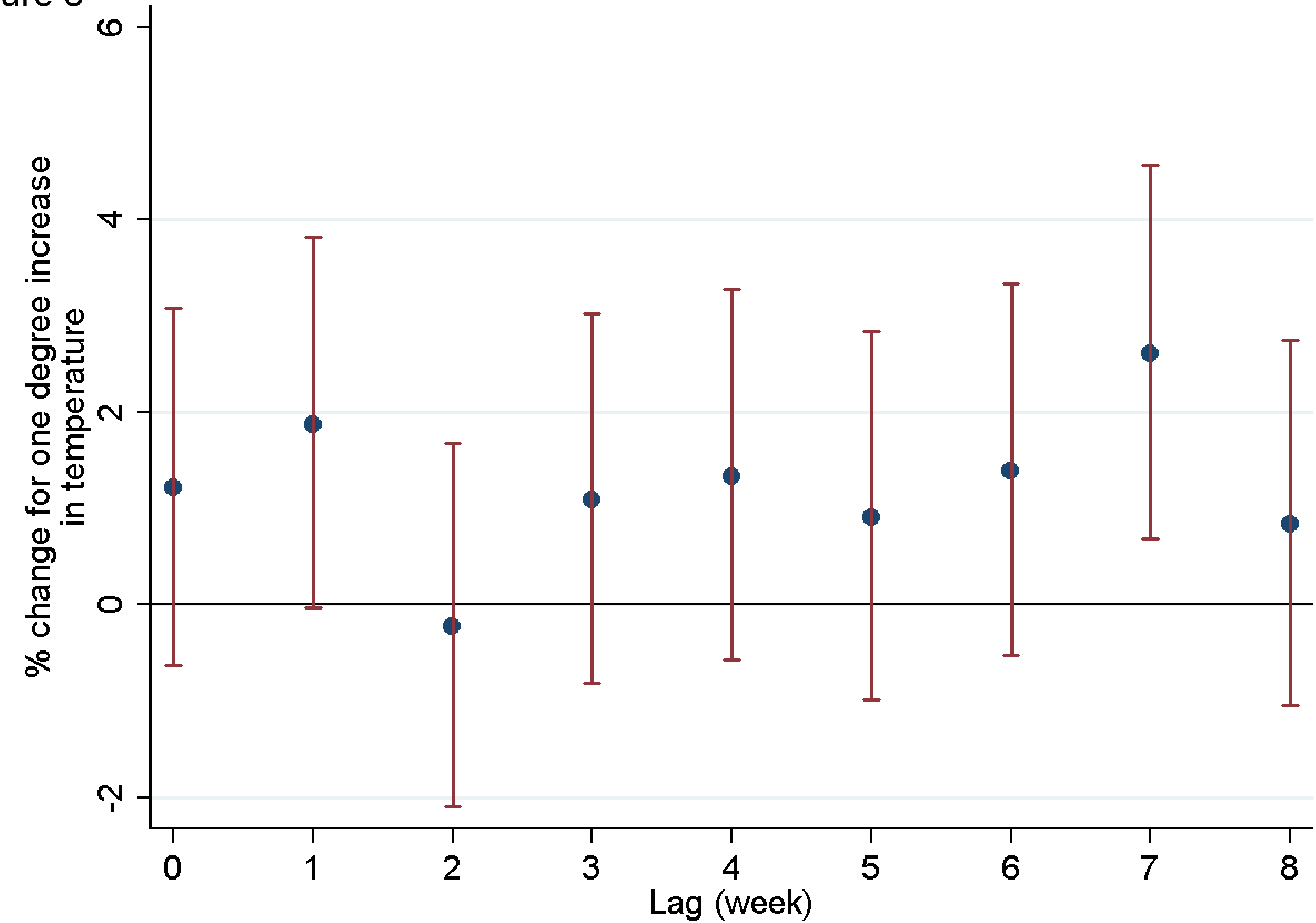

% change for one degree increase in temperature
-2
0
2
4
6
0
1
2
3
4
5
6
7
8
Lag (week)

Figure 4

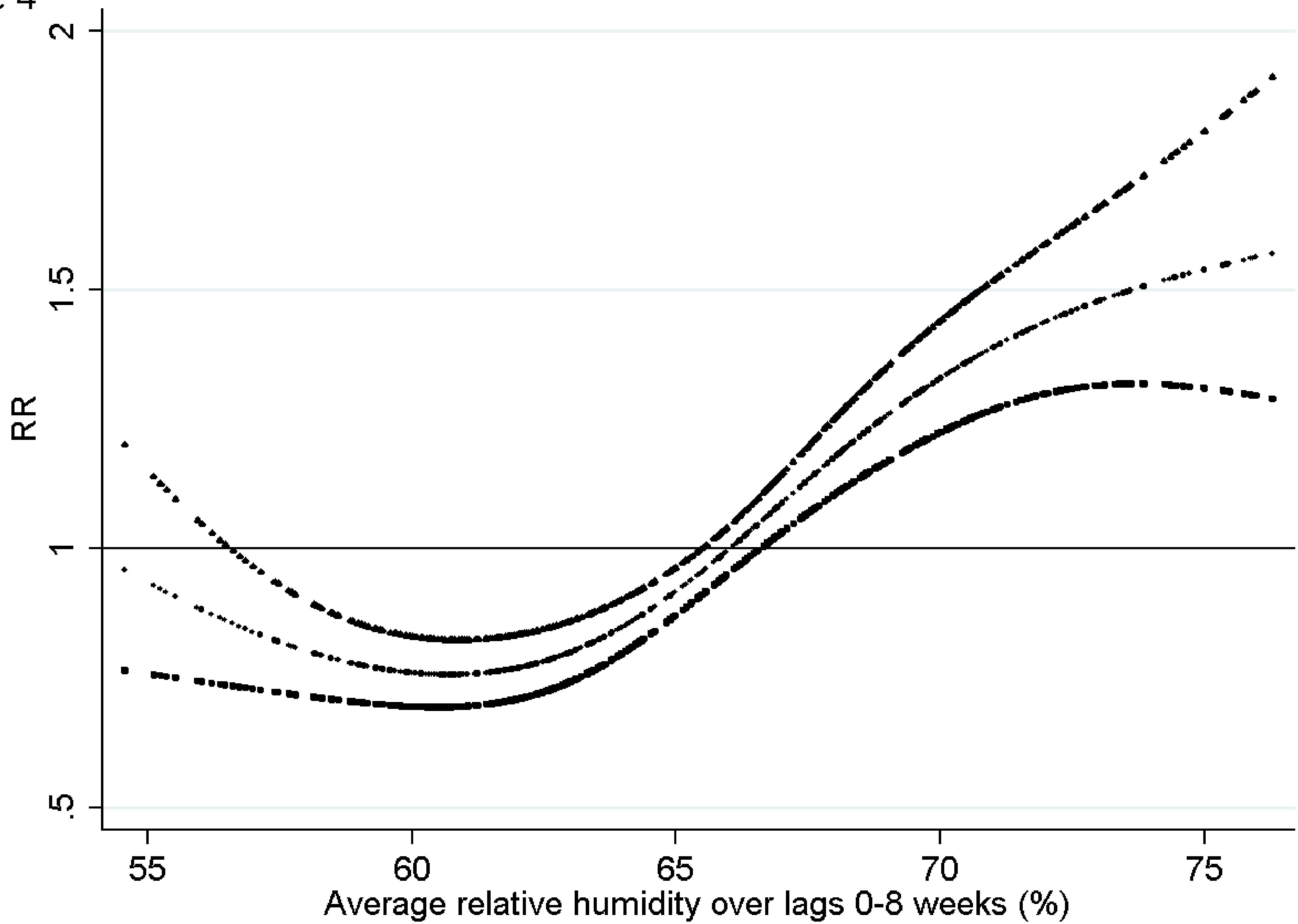
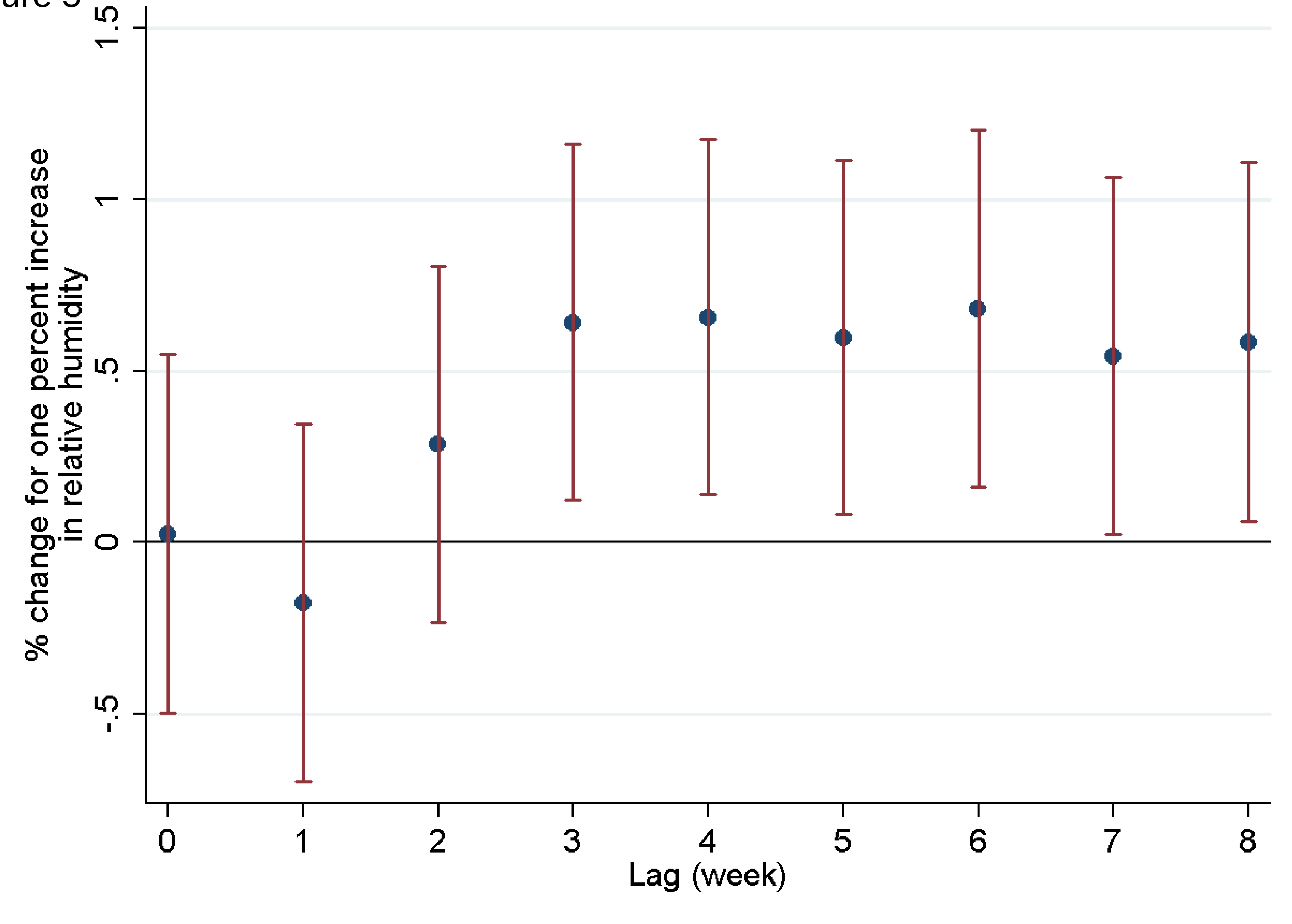

RR
2
1.5
1
.5
55
60
65
70
75
Average relative humidity over lags 0-8 weeks (%)

Figure 5



% change for one percent increase
in relative humidity
1.5
1
.5
0
-.5
0
1
2
3
4
5
6
7
8
Lag (week)

Figure S1
(a)

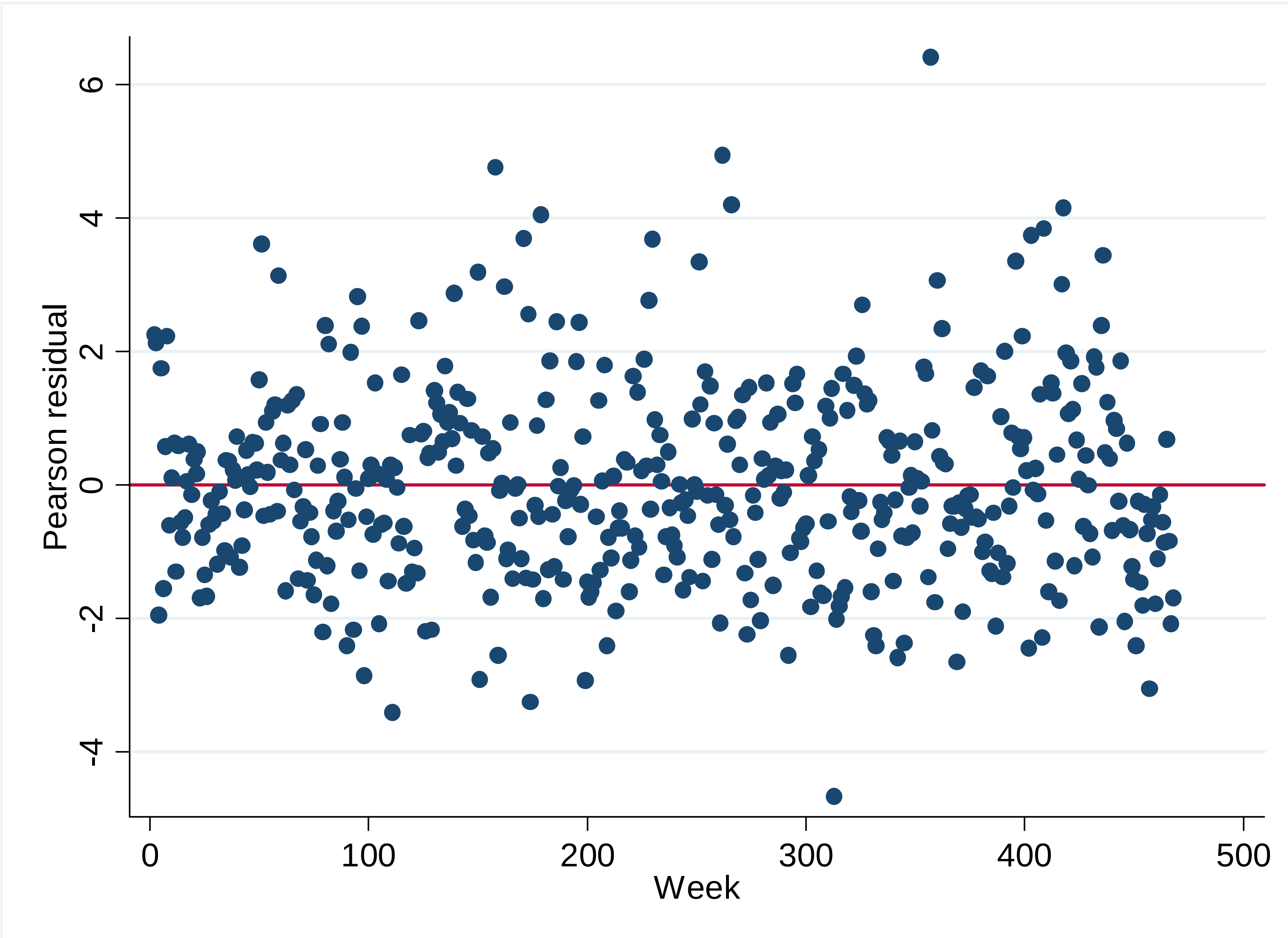


Figure S1
(b)

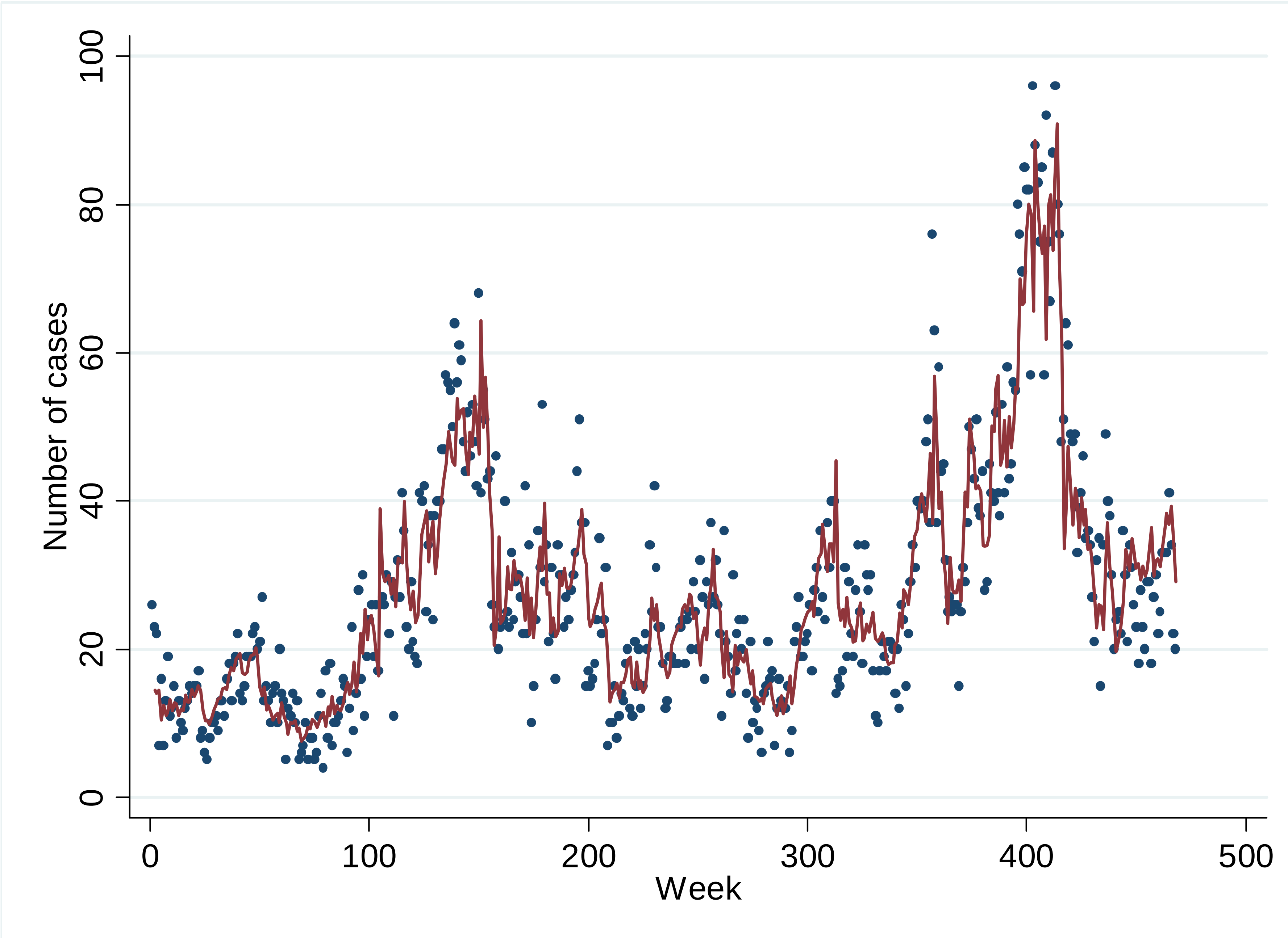
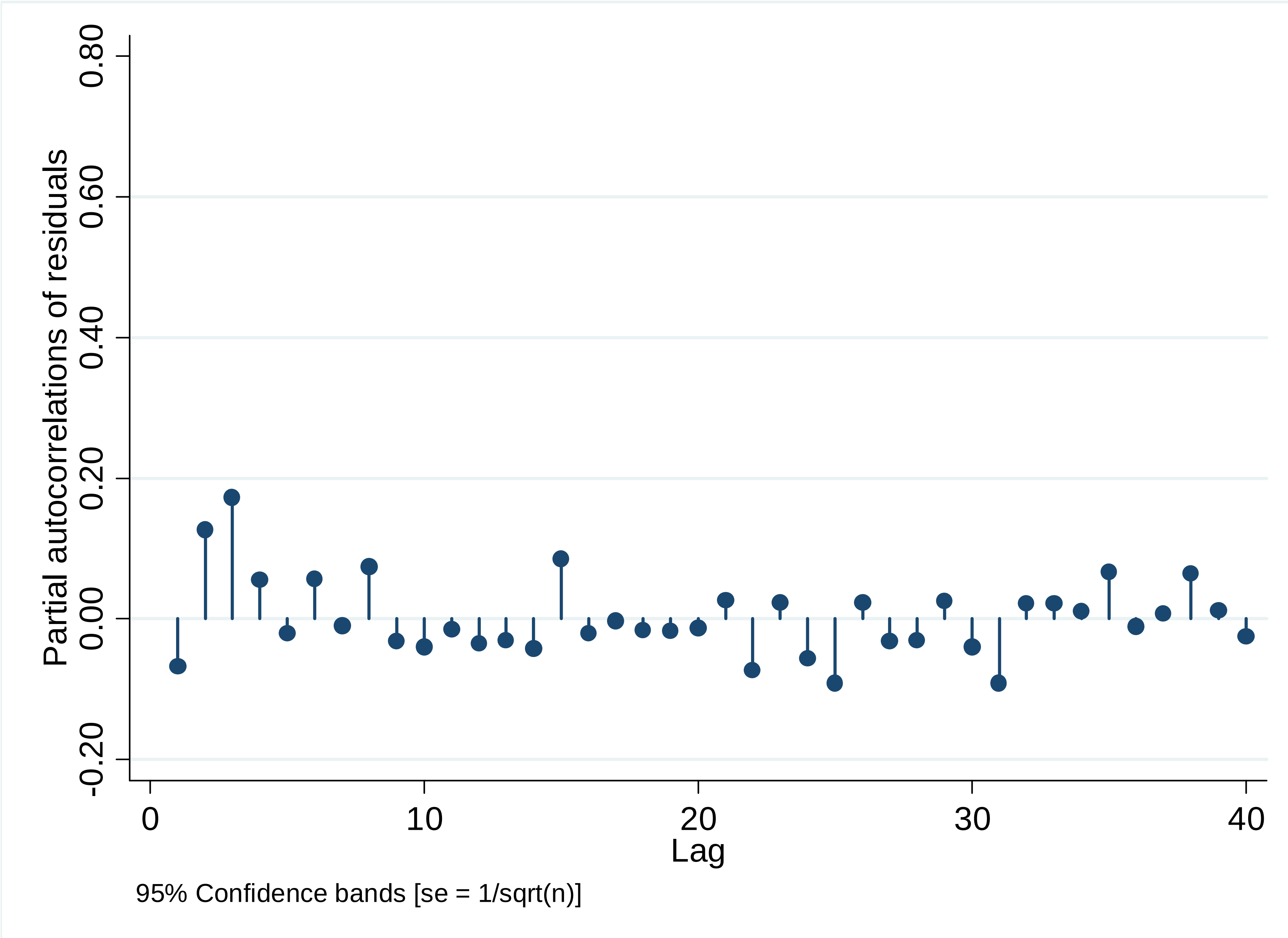


Figure S1

(c)



Partial autocorrelations of residuals
0.80
0.60
0.40
0.20
0.00
-0.20
0
10
20
30
40
Lag
95% Confidence bands [se = 1/sqrt(n)]

Figure s1

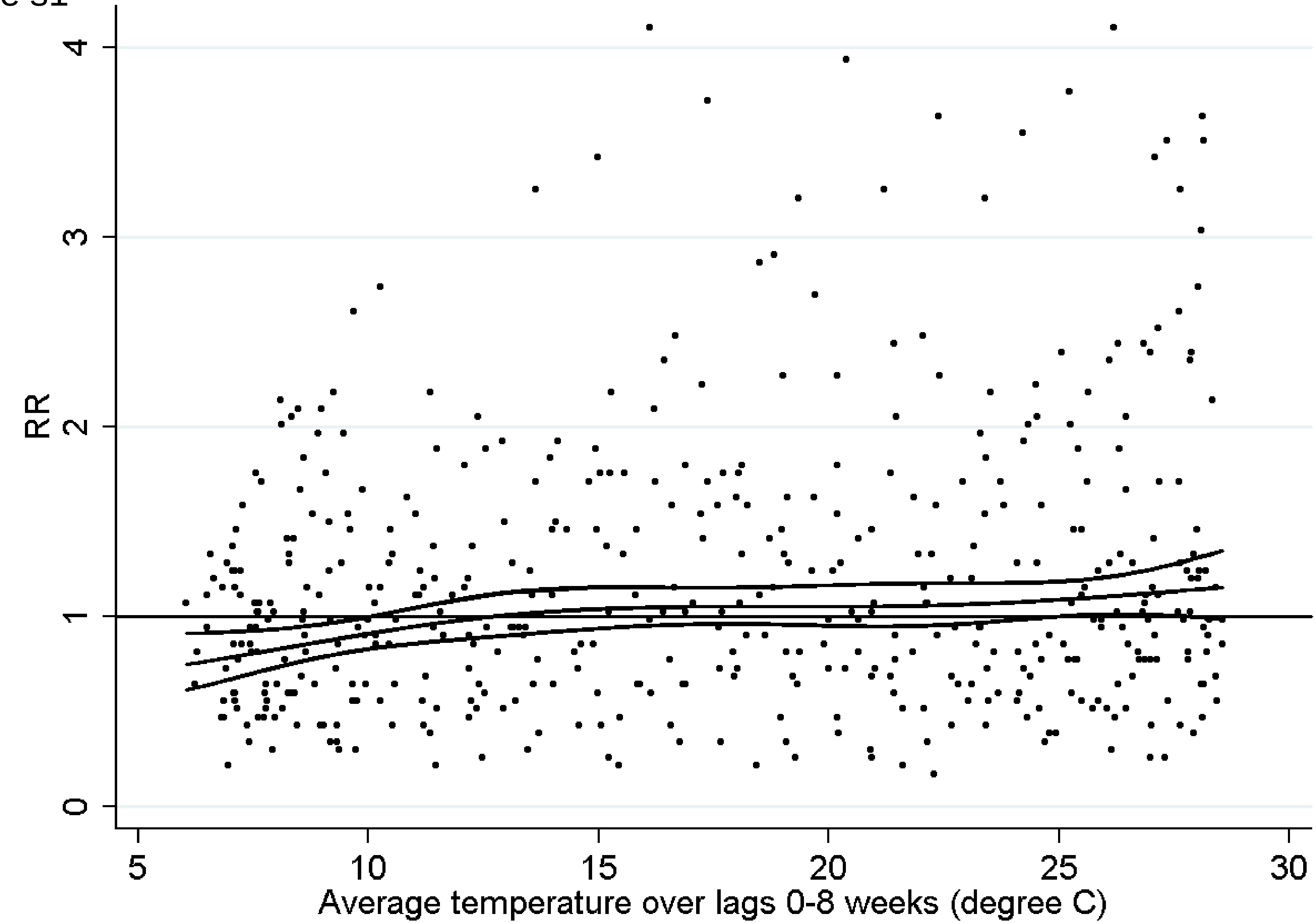
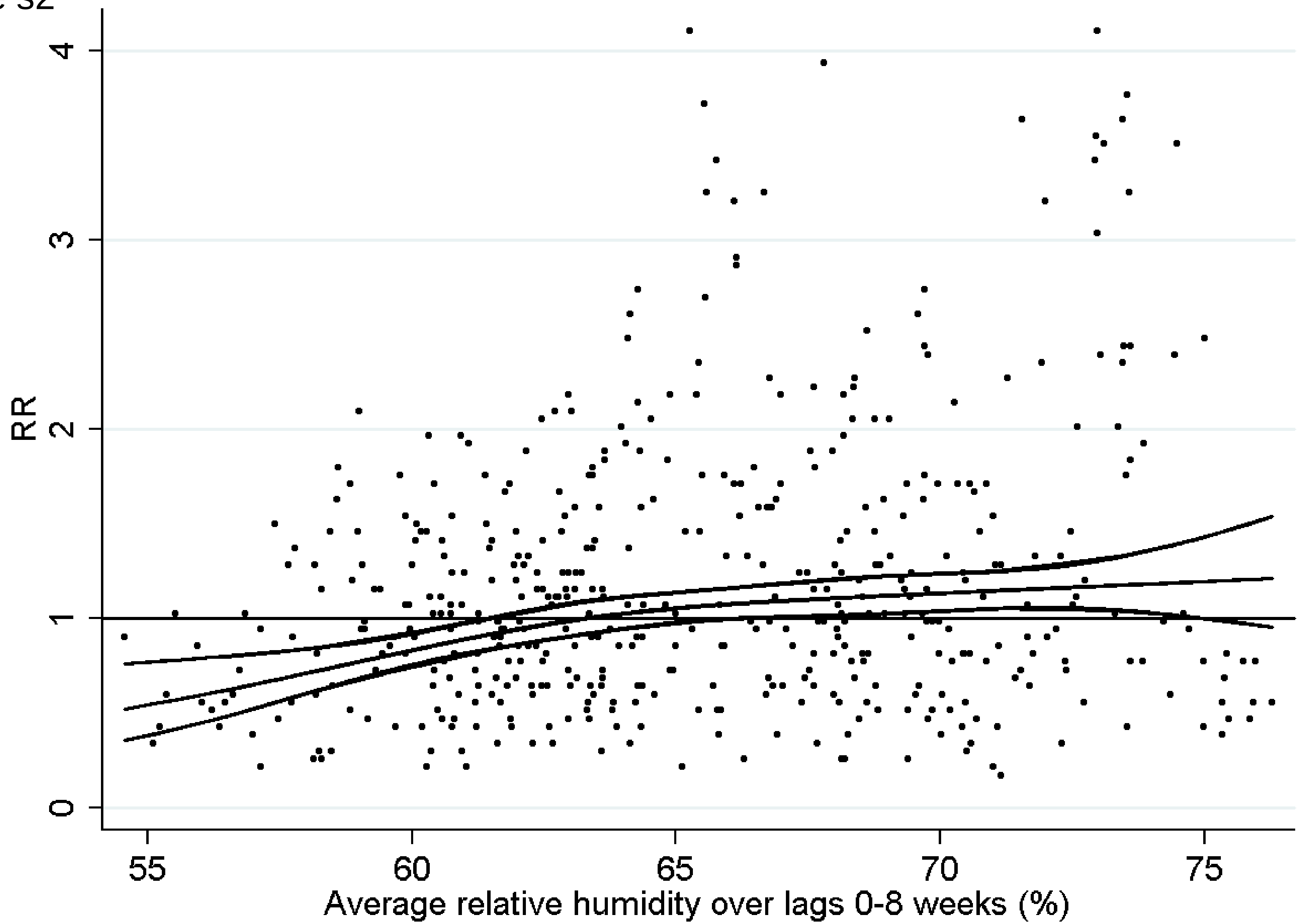

RR
0
1
2
3
4
5
10
15
20
25
30
Average temperature over lags 0-8 weeks (degree C)

Figure s2



RR
0
1
2
3
4
55
60
65
70
75
Average relative humidity over lags 0-8 weeks (%)