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Japanese Encephalitis and Associated Environmental Risk Factors in Eastern Uttar Pradesh: A time series analysis from 2001 to 2016

Himangi Singh[a,b], Nidhi Singh[a], R K Mall[a,*]

[a] DST-Mahamana Centre of Excellence in Climate Change Research, Institute of Environment and Sustainable Development, Banaras Hindu University, Varanasi, India
[b] University Grant Commission, Ministry of Human Resource Development, New Delhi, India

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ABSTRACT

India and other Southeast Asian countries are severely affected by Japanese encephalitis (JE), one of the deadliest vector-borne disease threat to human health. Several epidemiological observations suggest climate variables play a role in providing a favorable environment for mosquito development and virus transmission. In this study, generalized additive models were used to determine the association of JE admissions and mortality with climate variables in Gorakhpur district, India, from 2001–2016. The model predicted that every 1 unit increase in mean (Tmean;°C), and minimum (Tmin;°C) temperature, rainfall (RF; mm) and relative humidity (RH; %) would on average increase the JE admissions by 22.23 %, 17.83 %, 0.66 %, and 5.22 % respectively and JE mortality by 13.27 %, 11.77 %, 0.94 %, and 3.27 % respectively Conversely, every unit decrease in solar radiation (Srad; MJ/m^2/day) and wind speed (WS; Kmph) caused an increase in JE admission by 17% and 11.42% and in JE mortality by 9.37% and 4.88% respectively suggesting a protective effect at higher levels. The seasonal analysis shows that temperature was significantly associated with JE in pre-monsoon and post-monsoon while RF, RH, Srad, and WS are associated with the monsoon. Effect modification due to age and gender showed an equal risk for both genders and increased risk for adults above 15 years of age, however, males and age groups under 15 years outnumbered females and adults. Sensitivity analysis results to explore lag effects in climate variables showed that climate variables show the strongest association at lag 1 to 1.5 months with significant lag effect up tp lag 0-60 days. The exposure-response curve for climate variables showed a more or less linear relationship, with an increase in JE admissions and mortality after a certain threshold and decrease were reported at extreme levels of exposure. The study concludes that climate variables could influence the JE vector development and multiplication and parasite maturation and transmission in the Gorakhpur region whose indirect impact was noted for JE admission and mortality. In response to the changing climate, public health interventions, public awareness, and early warning systems would play an unprecedented role to compensate for future risk.

1. Introduction

Japanese encephalitis poses a major public health concern in consideration of its most common and deadly mosquito-borne encephalitis in Asia, Australia, and the western Pacific (Le Flohic et al., 2013; Simon and Kruse, 2018). China and India alone account for about 86–95% of the total cases or even more due to underreporting (IAP, 2013; Wang and Liang, 2015; Muniaraj and Rajamannar, 2019). The JE annual incidence varies from <1 to >10 per 100 000 individual resulting approximately 68 000 cases annually (Houle and Eurich, 2019) with overall 20% to 30% mortality that increased to 50– 80% in children (Vasanthapuram et al., 2019; Simon and Kruse, 2020). About 30 to 50% of JE cases who survive will have significant neurologic and psychiatric sequelae (Simon and Kruse, 2020). The disease mainly affects the central nervous system and can cause severe complications, seizures, and even death. (Tian et al., 2015). JE is caused by Japanese Encephalitis Virus (JEV) from the Flaviviridae family transmitted mainly by *Culex tritaeniorhynchus* as a primary vector, that feeds on pigs (Ampliflying host) and wading birds (intermediate hosts for virus amplification) and prefers to breed in irrigated rice paddies. A human being is a dead-end host in the JE transmission cycle due to the inability to produce sufficient viremia (Tian et al., 2015; Simon and Kruse, 2020). The regions with paddy dominant cultivation offer ideal environmental conditions for increasing mosquito population density and JEV transmission (Kumari and Joshi, 2012).

There is increasing evidence that climate variables, play an

* Corresponding author.
E-mail address: rkmall@bhu.ac.in (R.K. Mall).

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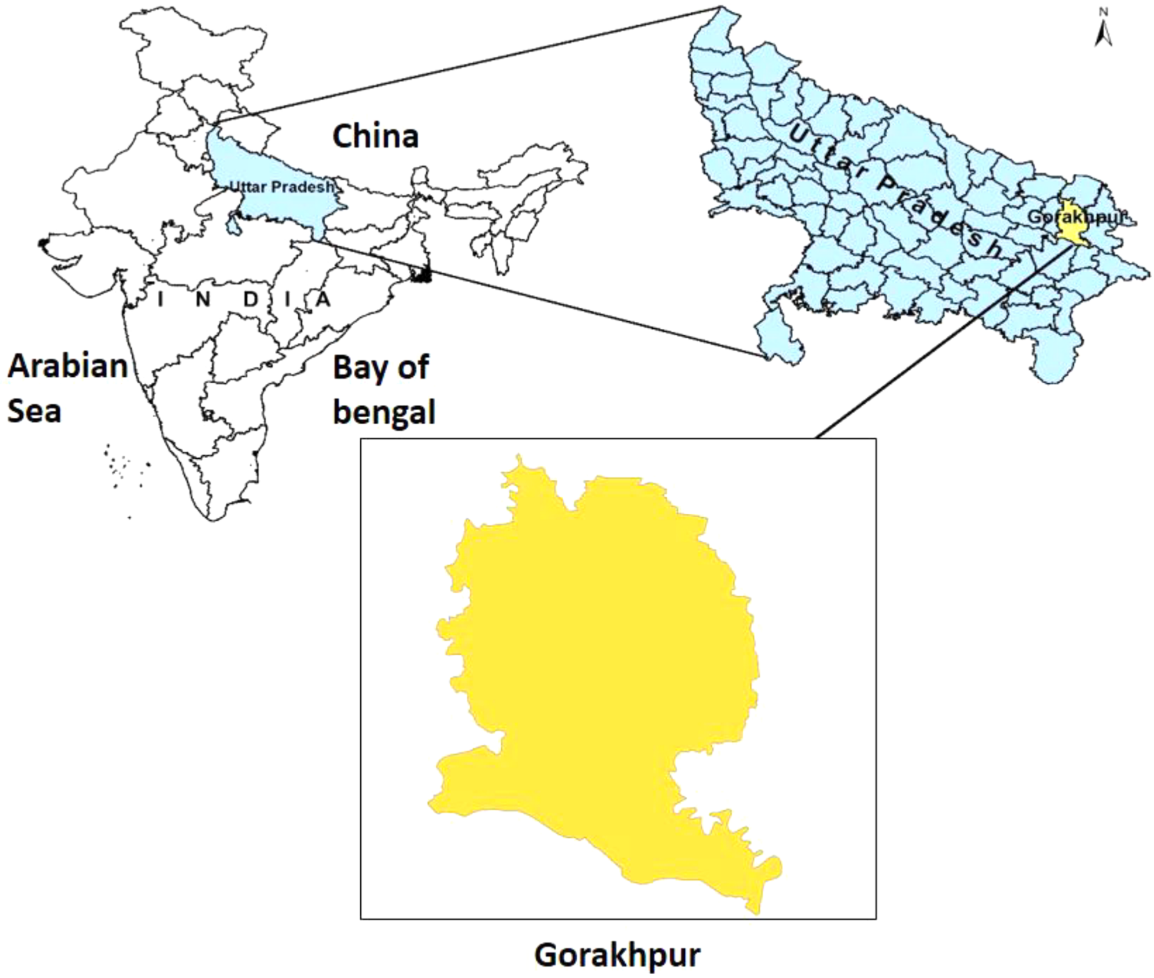

Fig 1. Map of Gorakhpur showing its location in India and Uttar Pradesh.

important role in the incidence of JE disease worldwide (Bi et al 2007; Borah et al., 2013; Tian et al., 2015; Lee et al., 2017). Studies from China, Taiwan, Vietnam, Nepal, and India showed a significant association of climate variables such as temperature, rainfall, relative humidity, and solar radiation to Japanese encephalitis cases (HSU et al., 2008; Impoinvil et al., 2011; Borah et al., 2013; Tian et al., 2015; Lee et al., 2017; Kumar et al., 2017a). These climate factors, influence the JE transmission by affecting the mosquito life cycle in terms of larval development time and mosquito population density (Reisen et al., 1976; Olson et al., 1983; Gingrich et al., 1992; Murty et al., 2010). The warmer temperature may increase virus replication and dissemination rates (Kilpatrick et al., 2008), thus reducing the duration of viral transmission to humans (Takahashi, 1976). However, other factors such as ecological heterogeneity, rice-growing techniques, public health intervention, vaccine coverage, population immunity, socioeconomic status play an important role in defining the scale of endemicity.

In Gorakhpur, the Japanese encephalitis virus (JEV) is the leading cause of maximum and sustained AES outbreaks between 1978 and 2010 (Mathur et al., 1982, Kakkar et al., 2013, Murrhekar et al., 2018). Between 2008 and 2012, out of the 10,175 AES cases reported, 8.4% (95% CI: 7.898.9) were due to JEV, with a case fatality ratio of 20% (Ranjan et al. 2014). The survivors often suffer neurologic impairment and require long-term treatment and care due to psychiatric symptoms (Kumari and Joshi, 2012). Among the survivor's around 30% may suffer permanent intellectual, behavioral or neurologic damage that includes paralysis, recurrent seizures, difficulty in speech, and inefficiency to independently perform daily activities (Caldwell et al., 2018; O'Leary and Kimberlin 2018; Simon and Kruse 2019). Given there was no effective antiviral therapy for Japanese encephalitis in 2006, the government of India started its first vaccination program in JE endemic areas. However, the increase in JE incidence did not cease, rather it has been increasing at an alarming rate, questioning the efficacy of the vaccine (NHP, 2012; Ranjan et al., 2014; Singh et al., 2015). In 2014, the Ministry of Health and Family Welfare (MoHFW) Government of India launched Mission Indradhanush to immunize 90% of children under two years and pregnant women by 2020 (UIP, 2014; Policy Note, 2017; Muniaraj and Rajamannar, 2019). Gorakhpur, due to its low and flat topography, is a flood-prone area, heavily impacted by rainfall and silting river beds. This offers favorable vector breeding conditions and associated JEV transmission (Kumari and Joshi, 2012). Apart from these factors, the presence of a large number of pigs that serve as a JEV reservoir and high mosquito populations also impact JEV transmission in Gorakhpur (Murrhekar et al., 2018).

The motivation for the present study is the realization of the complex association between JE prevalence and climate variables. The previous studies in India have mostly focussed on the association of JE risk with climate parameters, much of which was focused on temperature, precipitation, and humidity due to their well-characterized effects on primary vector *Culex tritaeniorhynchus.* Moreover, other climatic factors, including solar radiation and wind speed, may show subtle yet important influence, the association of which was poorly studied. Furthermore, a systematic and advanced approach to study the lagged relations in terms of distributed lag modeling and cumulative lag exposure with climate parameters and the exposure-response function was lacking in previous studies in particular for the study region.

Because, effect of increase in exposure parameter on single day will be distributed over several days. Therefore, the use of distributed lag model will have benefit over using single lag day model, that captures the effect of only particular day. This study aims to determine the relationship between climate variables and JE admissions and mortality as surrogate determinants of mosquito density and JE virus development dynamics in the Gorakhpur region in an attempt to give some insights on the risk associated with variation in climate variables on change in the JE epidemic. As Gorakhpur is among the most vulnerable areas of the JE epidemic this study can be helpful for a local health or administrative authorities in identifying early warning signs for management of JE in this area.

2. Materials and methods

2.1. Study Area

Gorakhpur district is located in the North-Eastern part of the State of Uttar Pradesh, between latitudes 26°13′N and 27°29′N and longitudes 83°05′E and 83°56′E (Fig. 1) with an area of 3,483.8 km^2. The district is situated on the bank of river Rapti and Rohini, responsible for causing recurrent and severe floods (Terai area) (Verma and Gupta 2014). In 2011, Gorakhpur had a total population of 44, 40,895 of which 51% were males and 49% were females with a decadal growth rate of +17.81%. The district Gorakhpur is divided into 7 tehsils (An administrative boundary in which a district is further divided into sub-districts) (Government of India, 2001) and 19 blocks (Government of Uttar Pradesh, 2020). Gorakhpur is known for extensive paddy cultivation that has led to the vast expansion of the irrigation system which supports mosquito breeding. District experience a humid subtropical climate with Four broad seasons – winter (Dec to Feb), Premonsoon (March to May), Monsoon (Jun to Sep), and Post Monsoon (Oct-Nov). The year-round average maximum temperature varies from 22 to 38°C and the average minimum temperature varies from 9 to 26°C. The average annual rainfall is 1200 mm and relative humidity varies 30 to 80%.

2.2. Data

As per guidelines of the National Vector Borne Disease Control Programme (NVBDCP), 2006 for surveillance of acute encephalitis syndrome (with special reference to Japanese encephalitis), suspected JE cases are now reported as follows: "Clinically, a case of AES is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence, or abnormal behavior greater than that seen with usual febrile illness. The clinical confirmation of the presence of the Japanese Encephalitis Virus (JEV) is done by testing the serum and cerebrospinal fluid samples of suspected AES cases by IgM enzyme-linked immunosorbent assay (ELISA) by the respective medical officers of the health centers and hospitals. Any admission/death due to the presence of clinically confirmed JEV is reported as JE admission/mortality (Kumari and Joshi, 2012). The daily JE admissions and mortality data between January 1, 2001, and December 31, 2016, were collected from the office of chief medical Officer, Gorakhpur. These data were classified by age (≤1, 2-5, 6-14, and ≥15 years), gender (male/female), and place of death (blocks). Climate data, including mean temperature (Tmean; degree celcius,°C) maximum (Tmax; degree celcius,°C), and minimum temperature (Tmin; degree celcius,°C), relative humidity (RH; percent,%), rainfall (RF, milimeter, mm), solar radiation (Srad; megajoue/meter^2/day, MJ/m^2/day), and wind speed (WS; kilometre/hour, Kmph) was obtained from the India Meteorological Department, New Delhi for the same period (IMD 2019).

2.3. Data analysis

2.3.1. Correlation analysis

The relationship between daily JE admission and mortality and climatic variables was examined using Pearson's correlation. The values were considered significant if $p < 0.05$.

2.3.2. Statistical Analysis

The semi-parametric quasi-Poisson regression model was used taking into account the autocorrelation and multicollinearity. Due to the high correlation between mean temperature (Tmean), maximum temperature (Tmax), and minimum temperature (Tmin), separate multivariate models were developed. Tmax was not used in the present study as daily mortality didn't show a significant correlation with Tmax, and to maintain uniformity, Tmean, and Tmin was used both for admission and mortality. Intuitively each model was selected after running multiple iterations taking into account multicollinearity between covariates, autocorrelation, R^2 AIC score, significance level ($p < 0.05$). The core model was adjusted for the potential confounding effect of long term time trend and seasonality. The models were run separately for JE admissions and JE mortality. The following generalized additive model was used:

$$\mathrm{Log}\{\mathrm{E}[(JE_t)]\} = \alpha + \beta_1 X1_t + \beta_2 X2_t + \ldots + \beta_5 XN_t + f(Time_t) \quad (1)$$

where $\mathrm{E}[JE_t]$ denotes the JE admissions and mortality at time t (in days), β is the regression coefficients over time't'; X denotes climate parameters like Tmean, Tmin, RF, RH, Srad, and WS, f is the smoothed function (penalized cubic smoothing spline) of nonlinear confounding factors such as time.

The above equation was fitted separately for age and gender to account for effect modification due to individual characteristics. To test the independence across the group, we used the Wald $\chi 2$- test to compare the group regression coefficients (Diggle et al., 1994).

Besides, we developed an exposure-response curve of JE admissions and mortality and different climate variables to observe the changes in JE admissions and mortality at different levels of exposure. We applied the penalized cubic spline function of the climate variables in the above equation to generate the dose-response curves.

To test the robustness of our model, it was also tested whether lag effects of the climatic variables were associated with JE admissions and mortality. To test this, sensitivity analyses were undertaken to establish the time lag effects of climate variables using a distributed lag model up to 60 days' lag with a polynomial of degree two with equation 1 (Schwartz, 2000).

$$Log(E(Y)) = covariates = \eta_0 \mathrm{W}_0 + \ .. + \eta_d \mathrm{W}_\mathrm{d} \quad (2)$$

Where η represent the parameters of the polynomial and W_d is represented as

$$W_d = Z_1 + 2^d Z_2 + q^d Z_q \ and \ W_0 = Z_0 + Z_1 + \ .. + Z_q \quad (3)$$

W_d is the weighted sums of the exposure variable Z and its lags, with "q" lags and degree "d"

In this study, the lag associations were shown as distributed lag effects as well as cumulative lag exposure. Distributed lag modeling shows the distribution of the effect of an increase in the current day level of a climate variable over subsequent days. Whereas, cumulative lag exposure is a sort of aggregation that takes into account the risk associated with all prior lags and the current day. Thus the cumulative lag 010 will add the risk associated with lag 0, lag 1…lag 10, and will combine all the risks in a single value. As maximum JE admissions and mortality were limited to a few months, the admissions and mortality from Jul to Dec were used to explore the lag effect.

The results for all the performed analyses were represented as the percent change in JE admission and mortality or as relative risk (RR) per unit change in climatic variables with 95% confidence intervals (CI). All the analyses were done using statistical software R version

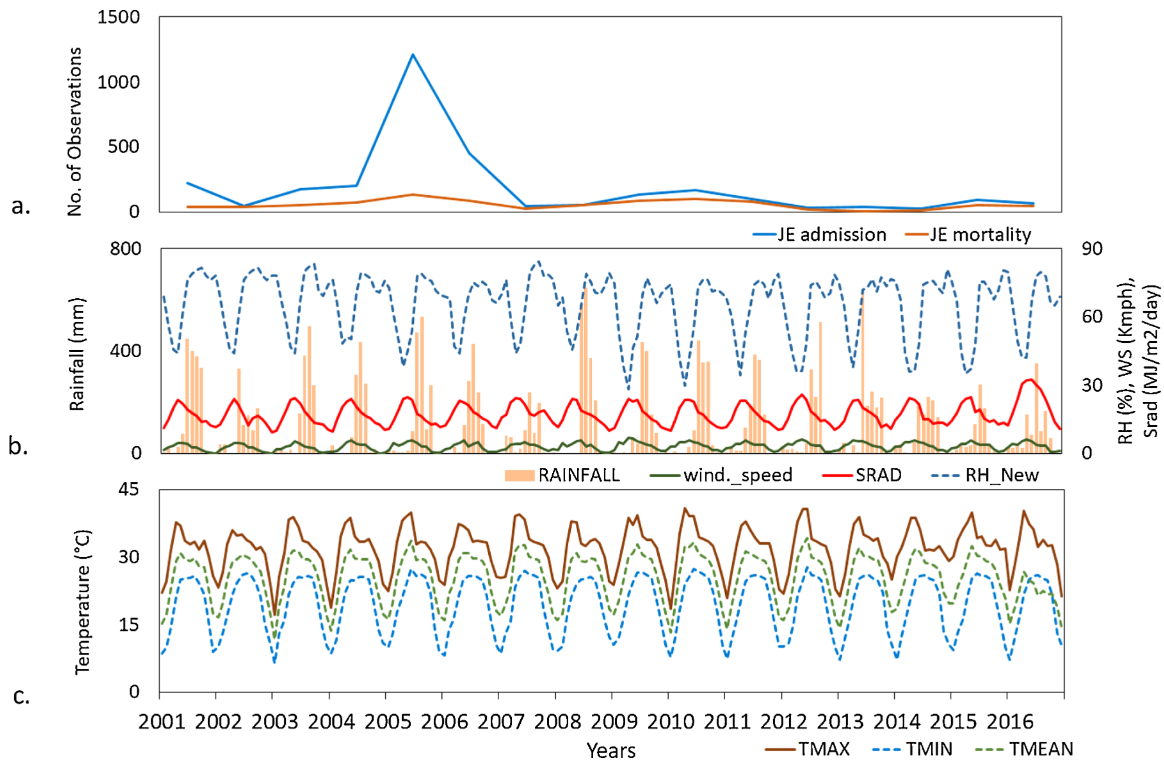

Fig 2. Distribution of yearly (a) JE cases and JE mortality in Gorakhpur (b) rainfall, relative humidity, Solar radiation and wind speed and, (c) Maximum, minimum and mean temperature.

3.5.1 (R Core Team, 2018); R -package "mgcv" (version 1.8–18.) (Wood, 2006), and "dlnm" (version 2.3.2.) (Gasparrini, 2011). All statistical tests were two-tailed and p-value < 0.05 were considered significant.

3. Results

Descriptive statistics of daily JE admissions and mortality classified by age, gender, and daily meteorology are summarized in Table S1. There were a total of confirmed 2764 JE admissions and 1025 JE mortality in Gorakhpur district during the study period. Mean (± SD) daily JE admissions and mortality for 2001-2016 were 0.47 (± 2.02) and 0.18 (± 0.58) respectively, among which 58% admissions were for males and 83% admissions were for children under 15 years of age. Time series for JE admissions and mortality and different climate variables are presented in Fig. 2(a-c). Fig. 2a shows the JE admissions and JE mortality in Gorakhpur. A large upsurge in JE admissions and mortality was noted in the year 2005 and a decline was noted in recent years with peaks observed every 2 to 3-year intervals (Fig. 2a). Figure S1 confirms the general seasonal trend of JE admissions and mortality with an initial increase of transmission from June followed by a peak from August to October and a decrease thereafter. The seasonal distribution revealed higher admissions during monsoon (JJAS; 58%) and post-monsoon (ON; 30%) season. Similar was the case for JE mortality. The long-term trend of climate variables was visualized as smoothed curves over time using penalized cubic spline (Fig. 3). Over the period, a clear increasing trend of the Tmean (0.4°C), Tmax (2.9°C), and Tmin (0.7°C), Srad (6MJ/m^2/day), and WS (1Kmph) was observed from 2001 to 2016. RH (3.7%) and RF (700 mm) have shown a decrease in recent years.

Correlation analysis was conducted between weather variables and daily JE admissions and mortality (Table S2). The results indicate that Tmean, Tmin, RH, and RF were positively correlated while Srad and WS were negatively but significantly related to JE admissions and mortality.

3.1. Multivariate analysis

The annual and seasonal results for the multivariate generalized additive model considering Tmean and Tmin separately are given in Table 1. Every 1°C increase in Tmean and Tmin was associated with 22.23 % (95% CI: 20.1, 24.4), and 17.83 % (95% CI: 16.14, 19.52%) increase in JE admissions respectively while an increase by 13.27% (95% CI: 11.15, 15.40%) and 8.77% (95% CI: 3.18, 14.35%) was noted respectively for JE mortality (Table 1). RF accounted for 0.66% (95% CI: 0.36, 0.96%) and RH about 5.22% (95% CI: 4.66, 5.79%) to JE admissions at every 1 unit increase. Srad and WS had a negative association with JE admissions and mortality, with every 1 unit decrease in srad, and WS caused about 17 % (95% CI: 14.57, 19.44%) and 11.42 % (95% CI: 8.20, 14.63%) rise in JE admissions respectively (Table 1).

Seasonal analysis shows that increase in Tmean and Tmin is reported to significantly increase the JE admission in pre-monsoon (Tmean; 9.66%, 95% CI: 1.41, 17.91%) and post-monsoon (Tmean; 22.62%, 95% CI:18.54, 26.71%) season whereas, JE mortality is mainly influenced by temperature in winter (Tmean; 11.24%, 95% CI: 5.84,16.65%) and post-monsoon (Tmean; 10.15%, 95% CI: 4.93,15.38%). RF and RH were found to influence the JE mainly in monsoon. While WS and Srad were negatively but significantly associated with JE in monsoon.

The effect modification due to age and gender show a much clear picture in terms of increased vulnerability in children in all the age groups, however, the age group of 15 and above in most of the cases show increased and significant vulnerability compared to others (Fig. 4 and Fig. S2). Males and females were found to be equally affected but more admissions and mortality were noted for males. Moreover, no significant between-group differences were established using the Wald $\chi 2$- test (Table S3).

3.2. Sensitivity analysis

It was believed that the JE admissions and JE mortality are not

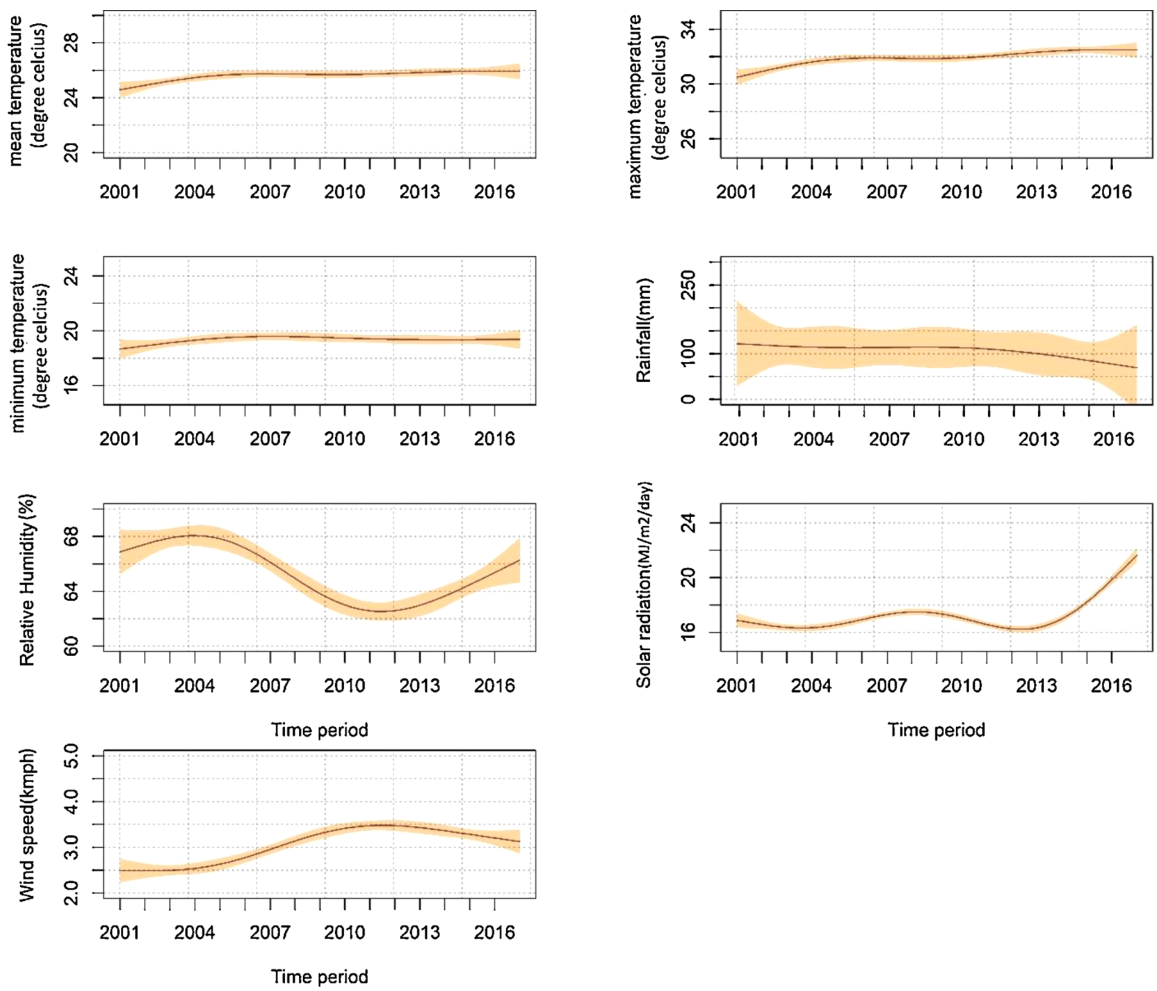

Fig. 3. Distribution of daily mean, maximum and minimum temperature, rainfall, relative humidity, solar radiation and wind speed over time.
Note. The colour shade represents the 95% confidential intervals.

necessarily associated with the same day exposure (climate) variable but with the previous day's exposure too. The same was reflected in the sensitivity analysis results. The distributed lag effect for temperature on JE admission and mortality showed an increase in risk with an increase in lag and reached maximum effect at lag 30 and decreased thereafter (Fig. 5 and Fig. S3). RF showed maximum effect at lag 40 and RH and WS showed maximum effect at lag 50 and decreased thereafter. Srad showed a delayed effect by 15 days and showed maximum association at lag 35. This shows that the lag effects vary differently for different climate parameters between one month to 1.5-month. The cumulative lag results showed a significant increase from lag 01 days and showed maximum association at lag 060 days for all the meteorological parameters compared to current day exposure (Table 2 and 3). The magnitude of the lag effect remained the same for JE admissions and mortality except for variation in RH and WS.

3.3. *Exposure-response Relationship*

Fig. 6 and S4 indicates the exposure-response curves for different climate variables associated with JE admissions and mortality respectively with a 95% confidence interval. In general, a linear association was observed between climate exposure and JE risk. The exposure-response curve for temperature class shows an increase in RR with an increase in temperature but higher temperature leads to a decrease in associated risk. Increases in Tmean between 12-32°C and minimum temperature, 7-27°C seem to provide the most suitable climatic conditions for JE transmission and related risk. The JE admission and mortality rate shows an increased risk with an increase in RF however, the associated risk decreased at much higher rainfall. Similar was the case with Srad and RH where Srad shows an increase in risk above 10 MJ/m^2/day but decrease above 30 MJ/m^2/day and RH shows an increase in JE risk between 50-70% and decreases thereafter. WS on the other hand shows an almost linear decrease in associated JE risk with its increase.

4. Discussion

JE is one of the most important causes of viral encephalitis in UP (Jain et al., 2016) though the present study as well as another study from West Bengal showed a decline in JE cases and associated mortality after 2011 (Bandyopadhyay et al. 2013) conversely study from Bihar showed an increasing trend in JE cases (Kumar et al., 2017b). Intensive mass vaccination programm in children, herd immunity, and awareness programs could be attributed to the declining trend. Some studies also suggest that cross-protection by other flavivirus infections, like dengue, may also account for the subtle decline in JE cases. (Roy et al., 2006; Kakkar et al., 2013; Jain et al., 2016). Climate change is likely to increase temperature and bring erratic shifts in rainfall patterns that can further influence mosquito and virus development, and humanistic behavior as well (Ciota and Keyel 2019, Kumar et al., 2020). Therefore, it is important to understand the present impact of climate on the transmission of JE to predict future changes. This study found that Tmean and Tmin, RF, RH, Srad, and WS significantly affected the JE associated admission and mortality in Gorakhpur, a humid subtropical

Table 1
Effect of different metrics on JE admissions and mortality overall and for different seasons

Parameters	Season	% Change in admission/ unit change in the weather variable	% Change in mortality/ unit change in the weather variable
Tmean (adjusted for Srad and WS)	Overall	**22.23 (20.1,24.4)**	**13.27 (11.15, 15.40)**
	Winter	2.84(-6.9,12.59)	**11.24(5.84,16.65)**
	Pre monsoon	**9.66(1.41,17.91)**	**7.83(0.77,14.89)**
	Monsoon	-4.97(-10.05,0.12)	-2.72(-7.33,1.89)
	Post-Monsoon	**22.62(18.54,26.71)**	**10.15(4.93,15.38)**
RF (adjusted for Tmean)	Overall	**0.66 (0.36,0.96)**	**0.94(0.54,1.33)**
	Winter	-7.8(-32.6,16.99)	4.26(-4.81,13.33)
	Pre-monsoon	-1.85(-10.4,6.71)	0.09(-5.5,5.67)
	Monsoon	**0.33(-0.03,0.69)**	**0.4(-0.05,0.85)**
	Post-Monsoon	**-1.64(-3.14,-0.14)**	-3.41(-9.75,2.93)
RH (adjusted for Tmean)	Overall	**5.22(4.66,5.79)**	**3.27(2.72,3.82)**
	Winter	-1.16(-4.2,1.88)	0.22(-1.44,1.87)
	Pre-monsoon	-0.95(-3.4,1.5)	-1.46(-3.55,0.63)
	Monsoon	**4.37(3.33,5.41)**	**2.97(1.91,4.02)**
	Post-Monsoon	0.36(-1.46,2.18)	**-2.33(-4.4,-0.26)**
Tmin (adjusted for Srad and WS)	Overall	**17.83 (16.14, 19.52)**	**11.77 (10.08, 13.46)**
	Winter	-4.93(-15.52,5.65)	**8.77(3.18,14.35)**
	Pre monsoon	**8.48(0.92,16.04)**	4.7(-1.69,11.09)
	Monsoon	-5.69(-13.92,2.53)	-2.15(-11.42,7.12)
	Post-Monsoon	**14.8(11.8,17.8)**	**6.92(3.19,10.65)**
Srad (adjusted for Tmin and WS)	Overall	**-17 (-19.44, -14.57)**	**-9.37 (-11.56, -7.19)**
	Winter	-8.32(-19.87,3.23)	-1.25(-7.82,5.31)
	Pre-monsoon	**-11.09(-21.47,-0.72)**	-7.02(-14.63,0.59)
	Monsoon	**-17.39(-20.43,-14.35)**	**-8.88(-11.56,-6.21)**
	Post-Monsoon	1.25(-5.44,7.94)	5.65(-1.9,13.19)
WS (adjusted for Tmin and Srad)	Overall	**-11.42 (-14.63, -8.20)**	**-4.88 (-8.41, -1.34)**
	Winter	-7.08(-21.89,7.74)	
	1.75(-7.16,10.67)		
	Pre-monsoon	-6.13(-18.5,6.24)	-1.38(-11.58,8.83)
	Monsoon	**-8.18(-12.05,-4.31)**	**-5.89(-10.48,-1.3)**
	Post-Monsoon	**-12.77(-23.59,-1.95)**	1.5(-9.24,12.24)

Note. The abbreviations used in the table are: Tmean = Mean temperature; Tmin = Minimum Temperature; RF = Rainfall; RH = Relative Humidity; Srad = Solar radiation; WS = Wind speed. Values in bold are significant at $p < 0.05$.

city of India. The study is the first attempt to use the distributed lag model, cumulative lag, and exposure-response function together for analyzing the association of JE with climate variables. Modeling the association of the JE admissions and mortality with climate as an indirect estimation of vector prevalence provides useful information in disease-endemic areas and to predict the impact on disease prevalence with anthropogenic changes to the environment in climate change scenarios (Selvey et al., 2014; Ciota and Keyel 2019).

The marked increase in JE admissions and mortality from July to November is mainly attributed to high rainfall contemporary to paddy cultivation (breeding ground of Culex) and hot weather that favors the mosquito breeding (Bi et al., 2007; Sarkar et al., 2012; Mutheneni et al., 2014; Murhekar et al., 2018). Tmean, Tmin, WS, and Srad showed significant association both at overall and seasonal analysis. However, RF and RH showed a significant association only in seasonal analysis. Some previous studies provide evidence of the role of climatic variables on JE incidence/JE cases. For example, in a study by Lee et al., 2017 shows that for every 1°C rise in average monthly temperature, the viral encephalitis incidence rose by 4 % to 9% provided a very high relative humidity above 80%. The study by Pisudde et al., 2017, bring forth that relative humidity and rainfall were positively associated with the number of JE cases in Bihar, India. A similar observation was reported from Changsha, a subtropical city of China where, maximum and minimum temperatures and absolute humidity have increased mosquito density and thus JE transmission (Tian et al., 2015). Besides, sunshine duration, absolute humidity, and wind speed were also found to influence the JE transmission (Murty et al., 2014; Lee et al., 2017; Tian et al., 2015). Temperature is known to regulate the mosquito's extrinsic incubation period (EIP), frequency of biting, blood-feeding, mating behavior, and adult longevity, and efficiency of the mosquito to transmit the virus (Takahashi, 1976; Leake and Johnson; 1987; Impoinvil et al., 2011; Tian et al., 2015). The present study shows no association of JE admission with Tmean or Tmin during winter owing to the explanation as at lower temperatures the multiplication of the virus slowed down (Takahashi 1976), whereas higher temperature is known to decrease the mosquito longevity (Gunay et al., 2010; Ciota and Keyel 2019). However, in this study, we found an increased association during pre-monsoon when the temperature is high. This may be explained due to increased agricultural activities and preparation for paddy crop cultivation, swimming, or other outdoor activities to get relaxation from high temperatures thus increasing the exposure to mosquitoes (Peng et al., 2007). Furthermore, an increased association of JE mortality with Tmean and Tmin was observed during winter as higher minimum temperature might assist larvae survival in winter (Peng et al., 2007). High precipitation during the monsoon period provides a suitable breeding ground for mosquito development and proliferation, and subsequent increase in virus activity and human to mosquito contact (Impoinvil et al., 2011; Kumari and Joshi, 2012). Apart from the monsoon, a certain amount of precipitation during summer and winter would develop a certain amount of humidity, fulfilling the essential requirement for mosquito development and propagation (Sarkar et al., 2012; Khan et al., 1996; Sen et al., 2014; Mutheneni et al., 2014; Impoinvil et al., 2011). RH has shown a positive and significant association with JE mortality during monsoon. Humidity is known to influence mosquitoes' mating and feeding behavior, adult longevity, mosquito dispersal, and oviposition and subsequent JE

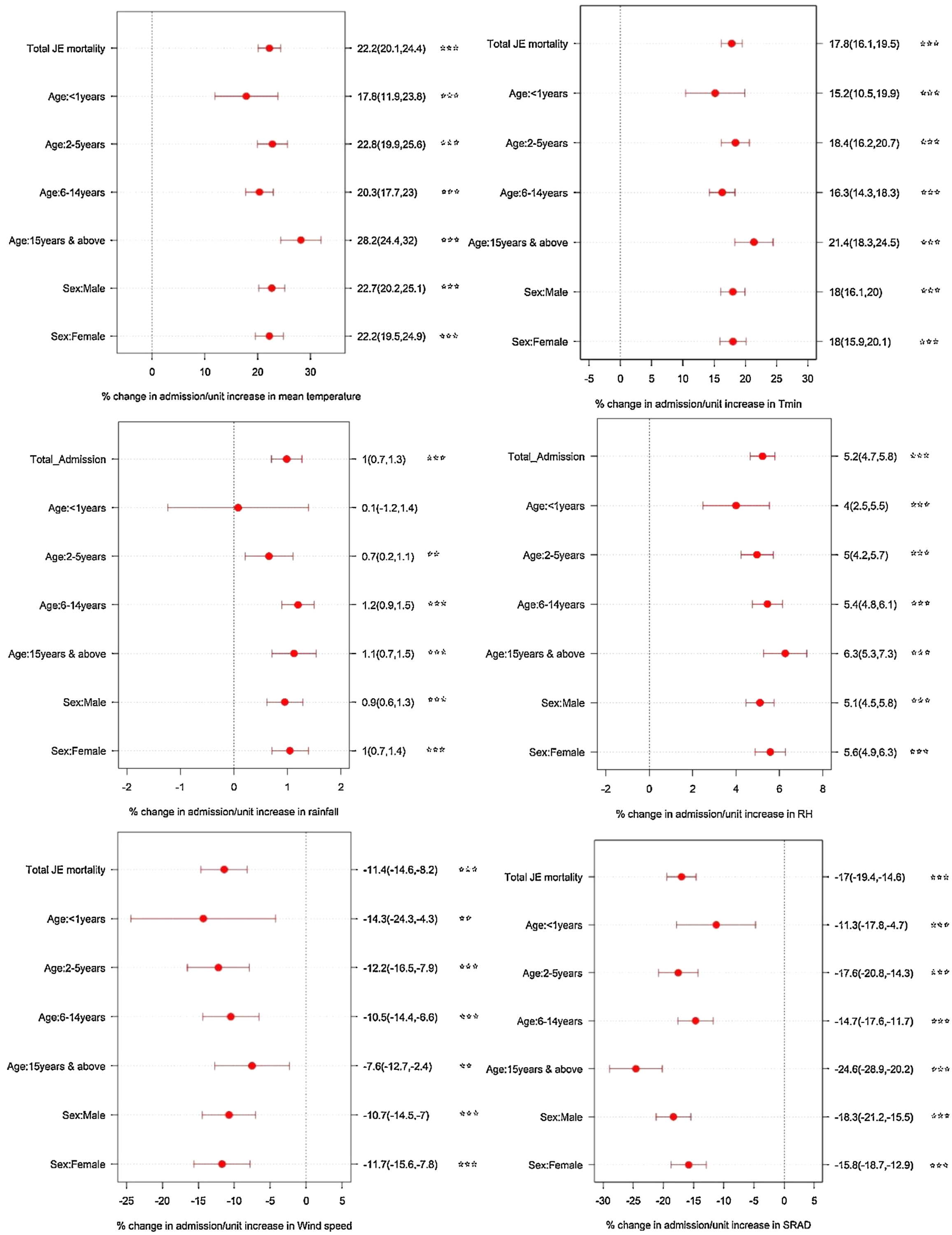

Fig 4. Percent change in JE admission by total, age and sex associated with change in mean and minimum temperature, rainfall, relative humidity, solar radiation and wind speed.
Note. The filled circle represent the average percent change and whiskers represent the 95% confidence intervals. Star indicates level of significance. **** <0.001, ** <0.01, * <0.05.

transmission (Peng et al., 2007). Within the present study, the inverse association of WS with JE admissions and related deaths is explained as with increasing WS the mosquito flight is suppressed this may lead to reductions in blood-feeding and oviposition and thus a reduction in their reproductive capacity (Service 1980). Similarly, an inverse association with Srad is possible because of significantly lower vector survival in high solar radiation (Villena et al., 2018).

JE is predominantly known to be a disease of children under 15 years of age due to their lower immunological response (Sen et al., 2014. Kakkar et al. 2013, Kumari and Joshi 2012). About 83% of the mortality in the study is contributed by children below 15 years of age. The presence of neutralizing antibodies with increasing age along with natural exposure and subclinical infections may decrease the risk rate (Kumari and Joshi 2012). But it is important to note that despite a

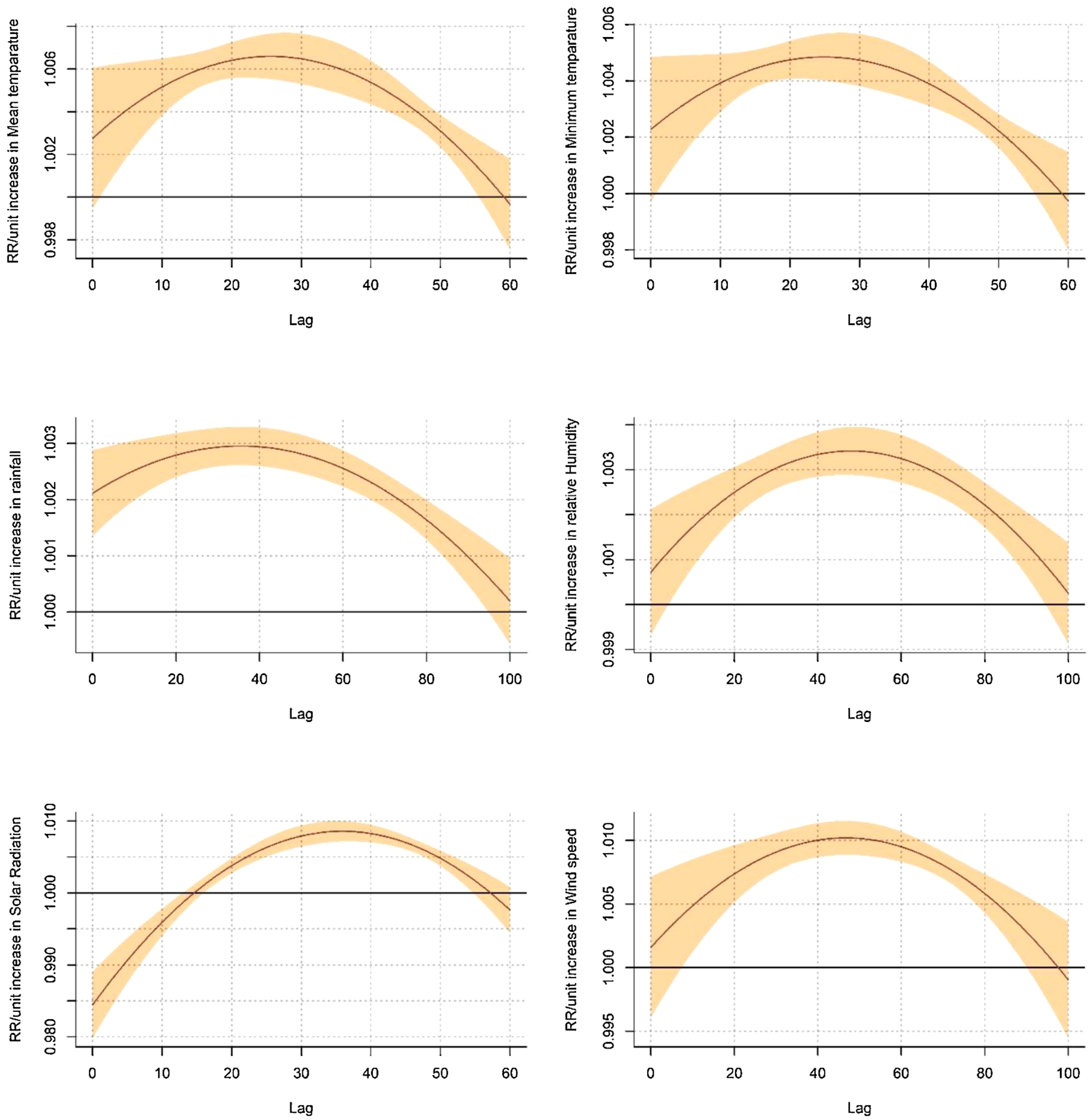

Fig. 5. Lag patterns mean and minimum temperature, rainfall, relative humidity and solar radiation and wind speedeffect on JE admissions
Note. The coloured shade represents the 95% confidential intervals. The SI unit for variables are: "°C" for temperature, "mm" for rainfall, "%" for relative humidity, "MJ/m2/day" for solar radiation and "Kmph" for wind speed.

Table 2
Relative risk (RR) in JE admissions per unit change in climatic parameters at cumulative lag 01 to 060.

Lag Choices	Tmean RR (95% CI)	Tmin RR (95% CI)	RF RR (95% CI)	RH RR (95% CI)	Srad RR (95% CI)	WS RR (95% CI)
Lag 01	1.026(0.962,1.094)	**1.165(1.143,1.186)**	**1.003(1,1.006)**	**0.988(0.979,0.998)**	**0.916(0.892,0.941)**	**0.895(0.867,0.924)**
Lag 010	**1.067(1.006,1.132)**	**1.179(1.157,1.202)**	**1.013(1.006,1.02)**	**1.026(1.01,1.042)**	**0.912(0.882,0.943)**	**0.804(0.759,0.852)**
Lag 020	**1.113(1.053,1.177)**	**1.195(1.17,1.22)**	**1.018(1.007,1.029)**	**1.053(1.031,1.075)**	0.965(0.93,1.001)	**0.883(0.827,0.944)**
Lag 030	**1.135(1.08,1.193)**	**1.21(1.185,1.236)**	**1.038(1.023,1.052)**	**1.082(1.056,1.109)**	1.022(0.984,1.061)	1.03(0.957,1.11)
Lag 040	**1.169(1.116,1.224)**	**1.219(1.194,1.245)**	**1.073(1.056,1.091)**	**1.121(1.093,1.151)**	**1.082(1.041,1.125)**	**1.136(1.045,1.234)**
Lag 050	**1.224(1.17,1.281)**	**1.242(1.216,1.269)**	**1.13(1.11,1.151)**	**1.173(1.142,1.204)**	**1.141(1.092,1.193)**	**1.306(1.197,1.426)**
Lag 060	**1.204(1.152,1.259)**	**1.234(1.206,1.263)**	**1.164(1.141,1.187)**	**1.21(1.176,1.245)**	**1.134(1.079,1.192)**	**1.522(1.383,1.673)**

Note. Values in bold are significant at $p < 0.05$.

fewer number of cases in adults (above 15 years), the association of JE admissions and mortality with temperature and Srad was the highest. The plausible explanation for this is the presence of transient immune status within a community population with high and effective childhood vaccination programs, so that majority of JE cases are in nonimmune adults (Arai S, et al. 2008; Jain et al., 2016). It was found that males and females were equally affected, but the number of males outnumbered females. The more outdoor activities associated with the nature of the work and more exposed body parts are mainly attributed to the high biting rate in males whereas, women generally tend to keep

Table 3
Relative risk (RR) in JE mortality per unit change in climatic parameters at cumulative lag 01 to 060.

Lag Choices	Tmean RR (95% CI)	Tmin RR (95% CI)	RF RR (95% CI)	RH RR (95% CI)	Srad RR (95% CI)	WS RR (95% CI)
Lag 01	1.02(0.961,1.082)	**1.106(1.078,1.134)**	1.003(0.998,1.008)	0.997(0.984,1.01)	**0.944(0.915,0.974)**	0.978(0.933,1.024)
Lag 010	1.042(0.98,1.108)	**1.109(1.081,1.137)**	**1.02(1.008,1.032)**	1.008(0.988,1.028)	**0.959(0.926,0.993)**	1.089(0.997,1.188)
Lag 020	**1.072(1.012,1.137)**	**1.115(1.087,1.143)**	**1.026(1.009,1.043)**	1.015(0.989,1.042)	0.98(0.945,1.017)	**1.253(1.127,1.394)**
Lag 030	**1.104(1.043,1.169)**	**1.121(1.093,1.149)**	**1.036(1.014,1.058)**	1.006(0.976,1.038)	1.011(0.973,1.051)	**1.416(1.264,1.585)**
Lag 040	**1.128(1.066,1.194)**	**1.13(1.103,1.159)**	**1.058(1.032,1.084)**	1.02(0.986,1.055)	**1.047(1.004,1.092)**	**1.499(1.325,1.696)**
Lag 050	**1.148(1.083,1.216)**	**1.133(1.104,1.163)**	**1.085(1.058,1.114)**	**1.039(1.001,1.078)**	**1.074(1.025,1.125)**	**1.64(1.437,1.872)**
Lag 060	**1.1(1.04,1.164)**	**1.119(1.09,1.149)**	**1.1(1.07,1.132)**	1.039(0.998,1.083)	**1.043(0.991,1.098)**	**1.945(1.682,2.249)**

Note. Values in bold are significant at $p < 0.05$.

their bodies fully covered and thus at comparable lower risk (Kumari and Joshi, 2012).

The distributed lag effect of climate variables on the JE admissions and mortality were found to vary between 1 to 3 months but highest at a lag of 1 to 1.5 months. It is emphasized that lags in temperature, rainfall, and RH are consistent with the total time required by the virus to complete its infection process to biting to the development of symptoms, like, the time required for virus development, the growth of vector, duration of the incubation period of Japanese encephalitis virus within mosquitoes, and the virus within the host (Peng et al., 2007; Tian et al., 2015). In an study from Assam, the average time from the onset of illness till visit to the hospital varied between between 1 to 12 days (Kakoti et al., 2013). The cumulative lag exposure and associated risk showed a consistent increase in cumulative risk with an increase in lag days that reach to a maximum at cumulative lag 050 to 060 days. A study by Borah et al., 2013 and Bi et al., 2007 and Pisudde et al., 2017

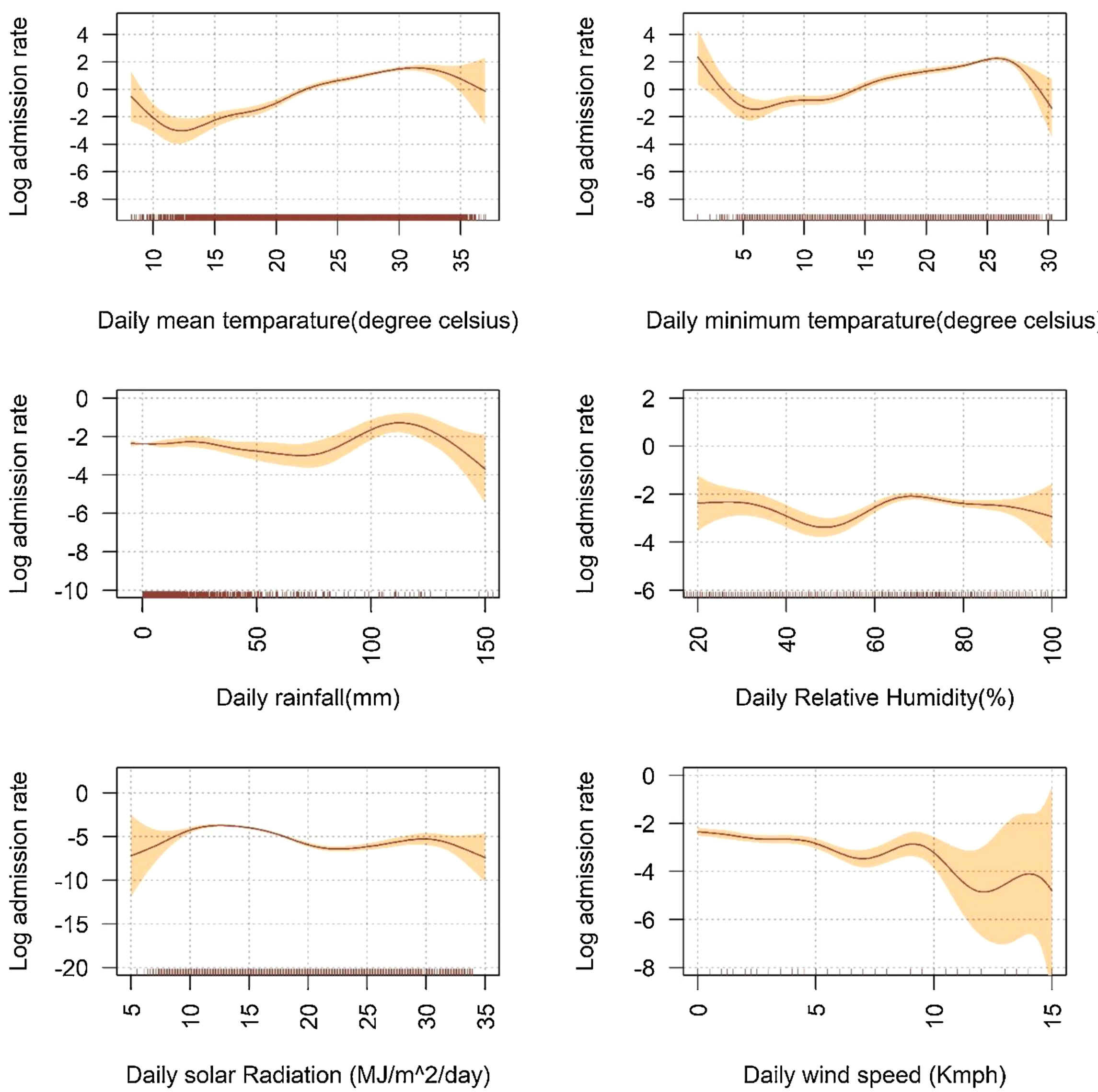

Fig. 6. Exposure-response relationship of mean and minimum temperature, rainfall, relative humidity, solar radiation and wind speed with JE admissions Note. The colour shade represents the 95% confidential intervals.

also reported similar lag choices of 1-month lag to 3-month lag (Kumari and Joshi, 2012).

The exposure-response curve shows the detrimental impact of increasing temperature in association with increasing humidity and appropriate solar radiation. Within the study, Tmean between 12-32°C and Tmin between 7-27°C provides the most suitable temperature for JE transmission and the related JE admissions and deaths. However, Heavy rainfall days above 100mm rainfall within a single day reduced the admissions and deaths. Also, it can be seen from the curve for WS that JE cases and admission decreased with an increase in WS making the movement of vectors restricted. Other studies (Murty et al., 2010; Impoinvil et al., 2011; Mutheneni et al., 2014; Miller et al., 2012; Tian et al., 2015) have shown that the optimal temperature (22 to 34°C) and relative humidity (42.7 to 69.6%) provide a suitable condition for larval development and adult survival, to facilitate the higher mosquito density as well as JE virus replication and occurrence of JE cases. Increasing temperature increases the digestion rate of blood meal thus increasing the ovarian development, egg-laying process, reduced time of the gonotrophic cycle, and increased likelihood of blood-feeding and subsequently increase the probability of transmission (Martens et al. 1995). A rise in minimum temperature, in particular, may enhance the rate of virus development and vector that would accelerate the JEV transmission yet higher temperatures may increase larval mortality (Ciota and Keyel 2019) and could decrease feeding rates (Ciota et al., 2014). It is expected that under the climate change scenario, vector and virus distribution and development, and host susceptibility, will all be affected (Ciota and Keyel 2019). Similarly, very high rainfall can create a flushing effect causing increased vector mortality. It is apparent that apart from climate there are additional risk factors such as, population immunity, disease transmission rate, intervention practices, agricultural practices, water management systems, human behavior, and socio-economic development play an important role in the transmission of the disease that should be taken into consideration (Kumari and Joshi, 2012; Ciota and Keyel 2019).

Some limitations of the study should be acknowledged. Factors such as social and economic status, population immunity (including vaccination), control measures, virulence, and the virus-carrying rate of the mosquitoes were not taken into consideration. The absence of block-wise meteorological parameters restricted us to do spatial-temporal analysis. Therefore, the result of this study can only be generalized to areas with similar geographic locations. However, the results of this study provide some evidence and understanding of the relationship between JE admissions and JE mortality and climate in Gorakhpur.

5. Conclusion

The present study estimates the effects of climatic parameters for the Gorakhpur district. The main findings of the study bring forth evidence that daily Tmean and Tmin, RH, Srad, and WS were strongly associated with JE admissions and mortality annually and seasonally. Effect modification based on gender and age showed males and children under 15 years of age contributed to maximum cases. Both the genders show equal association while age groups above 15 years of age were more vulnerable. The lag effect for all the parameters was significant up to lag 60 days but highest at lag 1 – 1.5 months and the cumulative lag response showed increased risk with an increase in the lag that reached the maximum at lag 050 days. The exposure-response curve explored the linear relation between JE admissions and mortality and different meteorological metrics where certain thresholds increased JE risk. Given the exposure range that has much influence on the JE vector and the associated admission and deaths in Gorakhpur, research outcomes from this study may be used by local and national governing bodies, epidemiologists, virologists keeping in mind the endemicity of the area for robust public health decisions, efficient environmental health risk management and promoting community health education that will help prevent additional outbreaks of JE. The study presents the impact of a diverse set of climatic parameters on JE risk. Moreover, the study is the first of its kind to add new knowledge to the existing but limiting information on JE admissions and JE mortality together. The use of the distributed lag model, cumulative lag exposure, and exposure-response function to study the JE risk associated with climate variables add value to the research over use of single lag model. As it is likely that global warming will impact temperature and rainfall patterns that may directly or indirectly influence the virus and vector's various intrinsic and extrinsic properties, it is important to study the complex association between climate and JE under the present scenario so that a reliable future prediction of the disease prevalence could be made. Thus, this study with some confidence establishes the adverse impact of change in climatic parameters on increasing JE risk. However, addressing detailed ecological and epidemiological studies, confounding factors, monitoring of virus infection in vector mosquitoes will help better predict disease outbreaks, and the development of an early warning system.

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Ethical Approval

None, as it was not needed.

Author's Contribution

R K Mall conceptualize, overall supervised and provided the resources for this study. Material preparation, data collection and analysis were performed by Nidhi & Himangi. The first and final draft of the manuscript was prepared by Nidhi & Himangi. RKM reviewed and edited the manuscript at different stages. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.actatropica.2020.105701.

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