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Association between climate and infectious diseases among children in Varanasi city, India: A prospective cohort study

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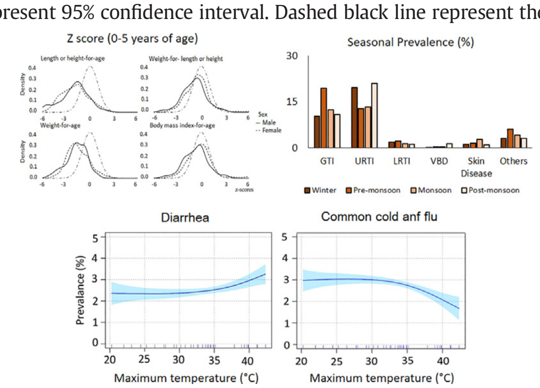
HIGHLIGHTS

- Morbidity link with climate, anthropometry and SES in children are reported.
- URTI and GIT constitute 78% of the cases of infectious diseases in children.
- Maximum temperature and humidity (absolute/relative) are important drivers.
- Family income/month, water source, and hand washing are important SES drivers.
- High proportion of children found in stunting, wasting, and underweight conditions
- Attributable Fraction (AFx) due to climate ranged from 9 to 18% for various diseases.

GRAPHICAL ABSTRACT

Nutritional status and exposure response relation of temperature and child morbidity in Varanasi.
Note: GIT represent Gastrointestinal Tract Infections, URTI represent Upper Respiratory Tract Infection
Blue shaded region represent 95% confidence interval. Dashed black line represent the optimum temperature.



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ABSTRACT

The effects of climate on infectious diseases could influence the health impacts, particularly in children in countries with the unfair socioeconomic conditions. In a prospective cohort of 461 children under 16-years-of-age in Varanasi city, India, the association of maximum-temperature (Tmax), relative humidity (RH), absolute humidity (AH), rainfall (RF), wind-speed (WS), and solar radiation (SLR) with prevalent infectious diseases (Diarrhea, Common cold and flu, Pneumonia, Skin-disease and Malaria, and Dengue) was examined using binomial-regression, adjusting for confounders and effect modifiers (socioeconomic-status; SES and child anthropometry), from January 2017 to January 2020. Attributable-fraction (AFx) was calculated due to each climate variable for each infectious disease. The result showed that each unit (1 °C) rise in Tmax was associated with an increase in diarrhea and skin-disease cases by 3.97% (95% CI: 2.92, 5.02) and 3.94% (95% CI: 1.67, 6.22), respectively, whereas, a unit decline in Tmax was associated with an increase in cold and flu cases by 3.87% (95% CI: 2.97, 4.76). Rise in humidity (RH) was associated with increase in cases of cold and flu by 0.73% (95% CI: 0.38, 1.08) and malaria (AH) by 7.19% (95% CI: 1.51, 12.87) while each unit (1 g/m^3) decrease in humidity (AH) observed increase in pneumonia cases by 3.02% (95% CI: 0.75, 5.3). WS was positively associated with diarrhea (14.16%; 95% CI: 6.52, 21.80) and negatively with dengue (17.40%; 12.32, 22.48) cases for each unit change (kmph). RF showed marginal association while SLR showed no association at all. The combined AFx due to climatic factors ranged from 9 to 18%. SES and anthropometric parameters modified the climate-morbidity association in children with a high proportion of children found suffering from stunting, wasting, and underweight conditions.

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Findings from this study draw the attention of government and policymakers to prioritize effective measures for child health as the present association may increase disease burden in the future under climate-change scenarios in already malnourished paediatric population through multiple pathways.

1. Background

A considerable number of studies have recognized and emphasized the climate change issues and their general and regional impacts given the projected global mean surface temperature (Tmean) is likely to increase by 4.8 °C (Representative Concentration Pathway, RCP 8.5) and by 3–5 °C during 2081–2100 in India (IPCC, 2013; Kumar et al., 2018). Moreover, northern India is expected to witness much of the increase in temperature and also an overall shift in rainfall patterns (Basha et al., 2017; Jha et al., 2021). Such as Uttar Pradesh (UP) observed a significant increase in annual mean (0–1.5%) and minimum temperature (1.5–3%) over 107 years (1901–2007) and a declining trend of diurnal temperature range during 1901–2016 (Mondal et al., 2015; Mall et al., 2021; Singh et al., 2021a). However, the rainfall observed a decrease by 0–8% (insignificant) in the eastern part of UP over 141 years (1871–2011) (Mondal et al., 2015).

Climate change presents unprecedented challenges to humankind through its impact on human-made and natural ecosystems, anthropocentric and economic activities (Singh et al., 2020). As per the Climate Risk Index, 2018, India was ranked fifth in the list of climate-vulnerable countries in the world (Germanwatch, 2018; Mall, 2019). The Lancet Climate Commission proposed climate change driven by anthropogenic activities may challenge the gains in public health over the past 50 years (Watts et al., 2017), and globally, it was estimated that children are to bear 88% of the burden of disease due to climate change, with the poorest disproportionately affected (Zhang et al., 2007; Perera, 2017). The higher risk associated with children is due to the combination of physiological vulnerability as well as the risk of exposure. According to the World Health Organization (WHO), under the scenario of no mitigation strategies being implemented, in 2030, there could be an additional 77,000–131,000 deaths among children under 5 years of age (Lloyd et al., 2014; Bhutta et al., 2019). Typical childhood maladies, such as diarrhea, pneumonia, malaria, and other infections associated with malnutrition, were identified as most sensitive to climate (Philipsborn and Chan, 2018).

The UP Burden of disease profile shows that in the year 2016, the percentage of disability-adjusted life years were highest among 1–19 years of age and, infectious diseases like diarrhea and lower respiratory tract infections (LRTI) account for about 40% of deaths (PHFI, 2018). Meteorological conditions aid the development and propagation of pathogens through their influence on the transport, reproduction, diffusion, and persistence thus aiding in defining the environmental reservoirs of pathogens and governing the intensity and timing of seasonal outbreaks (Moors et al., 2013).

As India is already witnessing climate change-related issues, it becomes imperative to address the link between climate variability and related health effects to improve the present capacity to prepare and respond, developing early warning systems and seasonal forecasts that would allow us to better address the challenges brought forth by climate change (Xu et al., 2012; Mall et al., 2017; Singh et al., 2019; Singh et al., 2021b). However, climate change related health impact studies particularly for children in India is at an early stage. And there exists a paucity of research-based empirical evidence that quantifies the impact of various climatic parameters on paediatric health and non-consideration of SES and anthropometric parameters. Any attempt to provide the epidemiological evidence associated with climate parameters over the poorly investigated regions of India will help the policymakers and the government to avert the risk that may arise due to climate change. Therefore, there is an urgent need to test the hypothesis of whether there exists an indirect and direct cause-and-effect relationship between climate variability and paediatric health.

In the light of the above, the present study aims 1) to provide insights on the current morbidity burden in children (0–16 years) 2) to study the association between climatic factors and infectious diseases (diarrhea (GIT), common cold, and flu (URTI), pneumonia (LRTI), malaria and dengue (VBD), and skin diseases), taking into account comprehensive SES and anthropometric variables, 3) to estimate the AFx due to climate variables that contribute to disease proportion among paediatric. For the present study, Varanasi, a city in UP, India was selected. The study will be able to advance our understanding of the environmental impact of different climate variables on paediatric health and how the association is influenced by different SES conditions and child anthropometry. The evidence from the present study will help in anticipation of adverse health effects and strengthen plans for preventive policies, priorities, and adaptive strategies.

2. Methodology

A community-based "Longitudinal" cohort was established within the boundaries of the Municipal Corporation of Varanasi among children from 0 to 16 years of age. The study was conducted in 26 wards, of 10 subzones and 5 zones for the period of 3 years; Jan 2017–Jan 2020. The list of selected wards, subzones, and zones, along with the subzone and zone population is mentioned in table S1 and the demographic profile of Varanasi city is given in table S2. Fig. 1 shows the geographical location of the study site (25°16′N, 82°59′E; 82 m MSL).

2.1. The eligibility criteria

The sample of children aged less than or equal to 16 years living in the selected wards of Varanasi city at the start of the survey was included in the present study.

2.2. Sample size estimation

The sample size of the study was determined using an equation by Daniel (1999), considering an estimate of 66.3% prevalence of the respiratory disease among children younger than 5 years old (at 95% CI; Kansal et al., 2008) for Varanasi. Assuming any particular outcome to be at absolute precision of 5% and a 95% confidence interval of certainty, the final sample size with a 20% non-response rate was determined to be 431 children up to 16 years old. To eliminate any chance of reduced power for statistical analysis, the sample size was further increased to 527.

2.3. Study settings and data collection

2.3.1. Household recruitment and sample selection

A multistage random sampling technique was used to select the study participants. From 90 wards, 26 wards were selected by a simple random sampling technique representing 5 zones and 10 subzones. The calculated sample size was allocated into randomly selected wards, proportional to the size of the population. From each ward, a simple random sampling technique was employed to obtain the respondents from the number of households with children younger than 16 years old. If within the household the target population was absent, we moved to the next household again selected through simple random sampling. Finally, 288 households and 527 children were selected.

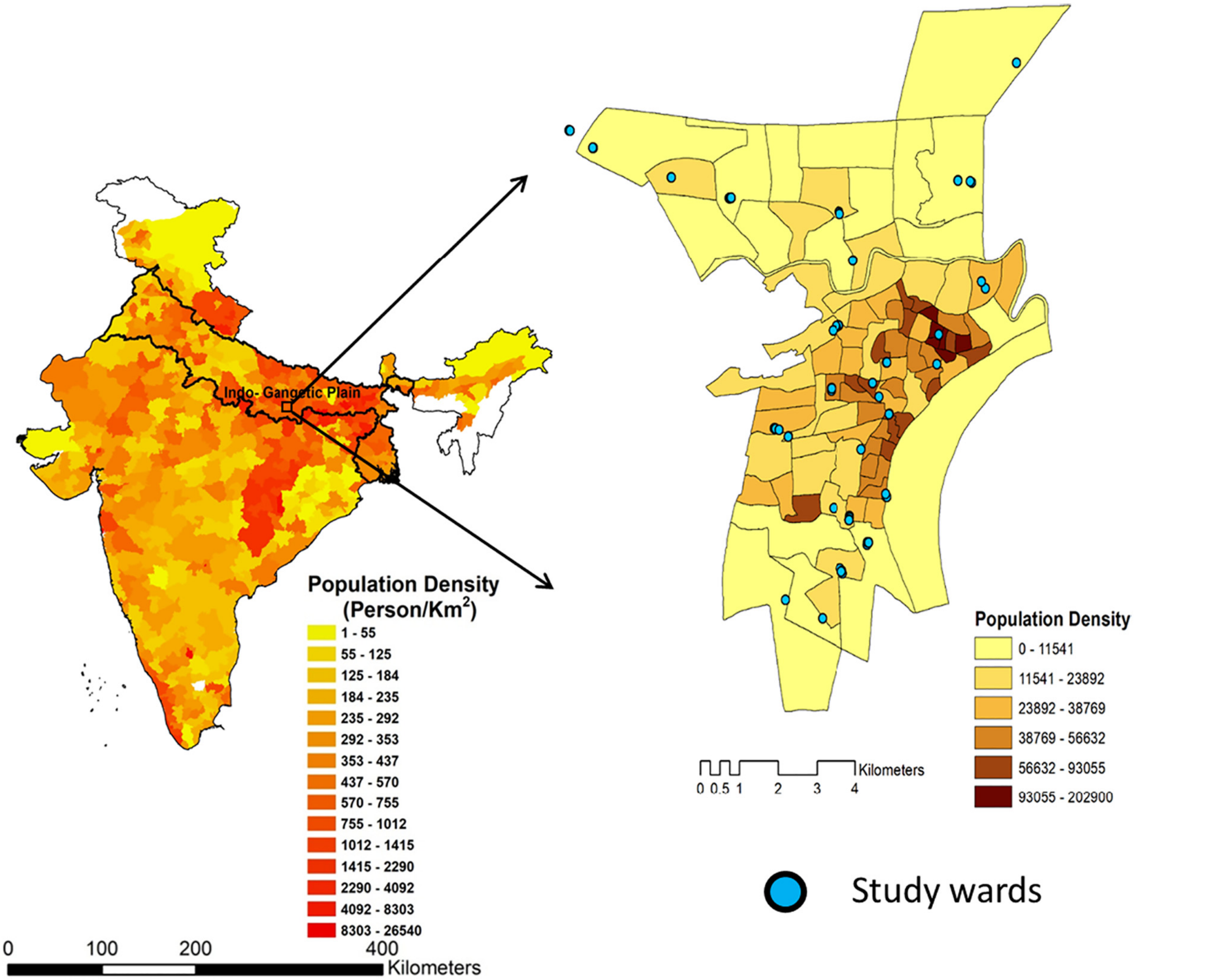

Fig. 1. (a) Map of India showing the location of study site and population density of India, (b) Map of Varanasi city showing sampling sites and population density of different wards.

After excluding the loss in follow-ups during three years, 249 households and 461 children were studied.

2.3.2. Obtaining consent and assigning of study Unique Identification Number (UID) to the recruited child

The children were recruited in the study after the written consent was obtained from either of the parents at the time of enrollment either in English or Hindi (S1). Information's in the consent form was read aloud and explained to the illiterate parents. The parents were informed that they had the right not to respond to questions that they did not want to and could stop at any point of time in the survey if they wanted. At the time of the recruitment procedure, each child was assigned a unique identification number (UID) of 3 digits that are given in order of the recruitment.

2.3.3. Survey duration and follow up

The data were collected using a face-to-face administrated pretested semi-structured questionnaire adapted from reviewed articles (S2). A pre-test was performed in few wards not included in the main survey, and the necessary modifications were made in the questionnaire before the data collection was undertaken. Parents (mostly mothers) were requested on recalling disease symptoms. A disease event was reported as the occurrence of one or more disease categories at the time of the home visit or in the preceding months (not considering multiple events within the same month).

The unannounced visits were done every 3–4 months. A total of 11 home visits has been done in 3 years. For each individual, there were a total of 36 observations from Jan 2017 to Dec 2019.

2.4. Variables

2.4.1. Dependent variable (Operational definitions)

(i) **Upper respiratory tract infections (URTI):** Mainly include problems related to common cold and flu, laryngitis, tonsillitis, sinusitis. Symptoms include headaches, aching muscles, a stuffed-up or runny nose, sneezing and a sore throat, difficulty in breathing.
(ii) **Lower respiratory tract infections (LRTI; Pneumonia)**: Mainly include pneumonia symptoms of cough and fast breathing.
(iii) **Gastrointestinal tract infection (GIT):** diarrhea, dysentery, gastroenteritis, enterocolitis. Symptoms include diarrhea or dysentery, nausea, vomiting, and abdominal cramping.
(iv) **Vector-borne diseases (VBD):** includes malaria and dengue.
(v) **Skin disease**: includes scabies, furuncle, impetigo, defined as vesiculopustular skin lesions which rupture with heaped up honey-colored crusts.
(vi) **Others**: includes diseases for which the presenting symptom can't be categorized into the above-mentioned causes.

Considering the complexity associated with the etiology of different diseases grouped in each infectious disease category, in the present study, all statistical analysis has been conducted on the most prevalent disease in each infectious disease category, viz. diarrhea (GIT), common cold and flu (URTI), pneumonia (LRTI), malaria and dengue (VBD), and skin Disease.

2.4.2. Independent variables

2.4.2.1. Climate variables. The observed daily minimum (Tmin, °C), and maximum (Tmax, °C) temperature; rainfall (RF, mm), relative humidity (RH, %), wind speed (WS, Kmph), solar radiation (SLR, $MJ/m^2/day$) and vapor pressure (in hPa) for the city of Varanasi from 2017 to 2019 was obtained from India Meteorological Department, New Delhi. The AH (g/m^3) was also used in the study as one of the climate parameters that was calculated using the gas law equation (REA, 2014). Daily observations of climate parameters was initially checked for data quality and outliers and further averaged for monthly values that were used in the study.

2.4.2.2. Socio-economic, Environmental, and Behavioral variables. At enrollment, the information was collected on education, and occupation of the head of the family, family income/month, house toilet, water filter, drinking water source, vaccination, open container, house type, hand washing practice, and street food consumption rate, health insurance, visit doctor/medical shop, mosquito intervention, and house cleaning.

2.4.2.3. Anthropometric variables. Information on age (date of birth), gender, weight, and height of the child was collected. The information on the weight and height of the child was reported at each time of the visit.

2.5. Categorization of socio-economic profile

The Socio-Economic Status (SES) of the selected households was calculated by scoring different indicators based on the scores given by revised SES scales of Kuppuswamy (Shaikh and Pathak, 2017). These indicators include education of household head, Ooccupation of house owner, and family income per month in Rupees. The indicators were given scores based on their sub-domains or presence or absence. The scores were summed for a total score for each household. Based on scores, the SES class was then categorized into three sub-categories: Lower class, middle class, and Upper class.

2.6. Weight and height measurement

At each visit, the child's weight and height were recorded to monitor the child's health by calculating body mass index (BMI) adopted from the WHO training module (WHO, 2006). To do so a digital weighing machine was used that can bear a maximum weight of up to 200Kgs and an inch of tape to measure the length or height of the child. The children who were elder than 2 years of age and who could stand independently were weighed standing straight on a weighing machine. Otherwise, if the child was younger than 2 years or is unable to stand, in that case, the mother was weighed alone; then the mother and the child were weighed together and the mother's weight was subtracted from the combined weight to obtain the child's weight. If the child was less than 2 years old and if his height was measured standing straight, in that case, a value of 0.7 cm was added to the height and the result was recorded as the length in the survey sheet.

2.7. Calculation of body mass index (BMI)

The child's BMI was calculated by dividing weight in kilograms by the square of height in meters, and the result was analyzed using the BMI-for-age percentile growth charts made available by the Centers for Disease Control and Prevention (CDC, 2020) for ages 2 to 16 years separately for boys and girls (Fig. S1 a&b). The BMI-for-age weight categories and the corresponding percentiles are given in table S3. Each child was categorized into a respective category based on their BMI percentiles. BMI helps in the screening of weight categories that may be a cause for serious health problems. A low and high BMI both can put children at risk for health issues.

2.8. The Anthro Survey Analyser

In the study, the weight and height were further used to assess child nutrition status for the most vulnerable age categories of the children under 5 years of age. For this, an online tool "Anthro Survey Analyser" developed by the Department of Nutrition for Health and Development, WHO was used (WHO, 2020). Anthro Survey Analyser allows performing a comprehensive analysis of anthropometric survey data. The tool provides analysis for four of the anthropometric indices: height-for-age, weight-for-age, weight-for-height, and BMI-for-age. The report provides prevalence estimates by different disaggregation factors for the five main indicators, namely stunting, wasting, and severe wasting, overweight and underweight (Table 2).

2.9. Data preparation

The climate, SES, and anthropometric parameters were a mixture of numerical (continuous), categorical (nominal), and ordinal variables. On that basis, the climate variables, anthropometric variables (age, weight, and height) were considered numerical variables. The diseases were included as a categorical variable and categorized as 0 when the disease was absent and 1 when the disease was present. Similarly, street food consumption and handwashing practices, presence of the open container, use of water filter, the presence of house toilet, vaccination and health coverage, use of mosquito net, and a visit to doctor/medicine use were categorized as 0 and 1. Gender was classified into 1 (Male) and 2 (Female). Education and occupation of house owner, family income/month, economic class, type of house, and type of water source were considered as ordinal data and numbered from low to high.

2.10. Statistical methods

2.10.1. Correlation coefficient

The point-biserial, rank biserial, and phi correlation were carried between the nominal-nomial, nomial-ordinal and nomial-continuous variables respectively, while spearman's and Pearson's correlation was calculated between ordinal-ordinal and ordinal-continuous variables to identify the direction and significance of association between them (Khamis, 2008). The result of the correlation matrix is presented in Fig. S2. The study further took into account only the significantly correlated climate variables, SES, and anthropometric parameters with disease outcomes for multivariate regression analysis. The multicollinearity, among the SES, anthropometric parameters, and the climate variables was assessed by correlation coefficient. Collinearity among the two variables was considered if the correlation coefficient value remains >0.7, in that case only one variable was considered for the model construction. The analysis was done using package "*PerformanceAnalytics*" and "*ltm*", "*sjstats*", "*rstatix*" in R. Further, the variables were checked for any autocorrelation in the residuals using Durbin-Watson statistics (D—W), that ranges from 0 to 4 (2 indicates no autocorrelation, below 2 indicates positive autocorrelation and above 2 indicates negative autocorrelation). Any autocorrelation, if exist was consequently removed. The package "*orcutt*" was used for D—W test.

The above statistical tests were two-tailed, and associations with *p*-Value < 0.05 were considered statistically significant.

2.10.2. Regression analysis

The use of generalized additive mixed modeling (gamm) over generalized linear modeling (glm) and generalized additive modeling (gam) allows dealing with within observation dependencies by using random intercept for each observation. In the fixed-effect model, we have single measurement data for each observation that deal with "between" observation dependencies. But when dealing with data that is divided into clusters, each participant/observation within a cluster creates a problem of "within" observation dependencies along with "between" observation dependencies. The fixed model cannot deal with it but the mixed model takes into account the "within" observation dependencies by using random intercept for each observation and therefore it is used for follow-up studies (Longitudinal study) (Wood, 2017). Generalized additive mixed models are frequently used for studies that deal with clustered, hierarchical and spatial designs to take into account overdispersion and correlated data, where the linear predictors are linearly dependent upon smooth functions of some other covariates (Lin and Zhang, 1999).

Thus in the present study, generalized additive mixed-effect modeling (gamm) was used with binomial regressions (log-link), and random effects for individual IDs to control for potential within-individual-correlation. Seasonality and time trend were adjusted, using penalized cubic smoothing spline (Peng et al., 2009). The model was also adjusted for potential confounders and effect modifiers (*socioeconomic, and anthropometric variables*).

The generalized additive mixed-effect core model is represented as follows:

$$\mathrm{Log}\{\mathrm{E}[(Morbidity)]\} = \alpha + (\beta_1(X_1)_{(t)} \cdots \beta_n(X_n)_{(t)}) + (\gamma_1(Y_1)_{(t)} \cdots \gamma_n(Y_n)_{(t)}) + f_1(Time_t) + b_i \tag{1}$$

Where, $\mathrm{E}[(Morbidity)] = \begin{cases} 1, & if\ disease\ on\ t^{th}\ month \\ 0, & otherwise \end{cases}$ represent the morbidity due to each class of infectious disease, viz. diarrhea (GIT), common cold and flu (URTI), pneumonia (LRTI), malaria and dengue (VBD), and skin Disease, β is the regression coefficients corresponding to the climate parameters "X" (monthly Tmax and Tmin, RF, SLR, WS, RH and AH) over time 't'; γ is the regression coefficients corresponding to the anthropometric/SES/other parameters "Y" over time 't', "n" is the number of parameters, f is the smoothed function (penalized cubic smoothing spline) of nonlinear confounding factors such as time, $b_i \sim N(0,\sigma_b^2)$ is a random-effects intercept for each individual i that accounts for child-specific variations. The models were fit using gamm() function from the "MASS" library in R.

For model construction, only the significantly correlated parameters were considered. The stepwise backward regression was used to include the significant parameters within the model. After running several iterations considering the correlation between covariates and the outcome, multicollinearity, autocorrelation, R^2, and significance level ($p < 0.05$), intuitively each model was constructed separately for each disease class. It is to be emphasized that a separate model was constructed for each disease class based on the significant association of explanatory climate variables, anthropometric and SES variables with disease outcomes. Thus the parameters in Eq. (1) vary from disease to disease. The final parameters that contributed to the model construction for each disease class can be viewed in Fig. 5.

2.10.3. Dose response relationship

The dose-response curves for different disease categories were created with the application of penalized cubic spline function on the climate parameters in a quasi-Poisson semi-parametric regression model after adjusting other covariates and confounding factors to observe the changes in monthly disease prevalence at a different exposure level of climate parameters. We refitted our core model (Eq. (1)) as follows:

$$\mathrm{Log}\{\mathrm{E}[(\mathrm{Prevalence})]\} = \alpha + (f_1(X_1)_{(t)} \cdots f_n(X_n)_{(t)}) + (\gamma_1(Y_1)_{(t)} \cdots \gamma_n(Y_n)_{(t)}) + f(Time_t) \tag{2}$$

Where f(X(t)) is the smooth function of the monthly average climate parameter over time t; rest remain unchanged.

The statistical analysis was performed in R software, version 3.5.1 (R Core Team, 2018), and "mgcv" package (version 1.8–18.) was used (Wood, 2017). The above statistical tests were two-tailed, and associations with p-Value < 0.05 were considered statistically significant.

2.10.4. Attributable fraction

In epidemiological research, an attributable fraction (AF) is a tool to quantify the proportion of cases that are attributable to risk factors that helps to prioritize prevention, better planning and evaluation of public health intervention strategies to reduce or eliminate the exposure to the most accountable risk factors (Gasparrini and Leone 2014; Bray and Soerjomataram, 2018).

Gasparrini and Leone (2014) have given a general formula to calculate the attributable fraction AFx for a given exposure x as:

$$\mathrm{AF_x} = 1 - \exp(-\beta_\mathrm{x}) \tag{3}$$

The term βx in Eq. (3) is the logarithm of the risk at a certain exposure level, usually measured as relative risk (RR), relative rate (RR), or odds ratio (OR). Mainly, βx refers to the association with an exposure level x in comparison to a reference value x0 (βx = (x-x0)*OR). In the specific case of climate variables where it is hard to define a condition for null exposure, a reasonable selection of points for variables that correspond to minimum risk was suggested that was derived from the exposure-response curve (Fig. 6) (Honda et al., 2014). This value of minimum risk is defined as the optimum value (OV) and is used as the reference point "x0" to compute attributable risk measures "βx" and attributable fraction "AFx". These are computed for each month of the series for each climate variable, and the AFx contributed by each respective month are obtained by separating the associations with "x-x0" higher or lower than "x0" to obtain average "AFx", shown in percentage (%). Risks (OR) associated with multiple exposures are obtained from multivariate regression models adjusting for potential confounders as shown in Eq. (1). In the next step the adjusted attributable fraction (AFx) due to risk associated with multiple exposures x1, …,xp are defined as:

$$\mathrm{AFx1}, \ldots, \mathrm{xp} = 1 - \exp\left(-\sum_{i=1}^{p} \beta \mathrm{xi}\right) \tag{4}$$

where p stands for number of exposures. In general AFx1,...,xp ≤ AFx1 + … + AFxp, which means the sum of all AFx due to individual exposures is generally higher than the sum of all AFx combined (Gasparrini and Leone, 2014).

3. Result

3.1. Socio-demographic and SES profile of the study subjects

Table 1 shows the summary of demographic, SES, and anthropometric characteristics of the study population at baseline measurement. From a 3 year follow-up (2017–2019) of 461 children from 249 households considering the loss in follow-ups (527 children and 288 households at initial) and death of two children, the total number of observations from the sample was 16,646. Of all recruited children, 51% were females, and a large proportion of the selected sample fall in the 5–16 years of age. In about 50% of the households, the parents of the recruited children were middle school passed. In about 46% of the sample household, either of the parents were an unskilled worker and about 33.7% were semi-skilled workers. In about 55.42% of households, family income was in the range of Rs. 2165–6430 per month. In all, around 73% of the population falls under the lower socioeconomic (SES) category. There was also a large percentage of children with high street food eating practices, and fewer had regular hand washing practices before the meal and after defecation making them more vulnerable to infections.

Table 1
Summary of demographic, SES, and water, sanitation, and hygiene characteristics of the study population at baseline measurement.

Study characteristics	N (%)	Diseases	N (%)
Observation	16,646	Total GIT cases	2229 (35.6)
Children (initial)	527	Diarrhea cases (GIT)	2151 (34.38)
Children (final)	461	Diarrhea-episode/child/year (0–5 year of age)	1.7
Households (initial)	288		
Households (final)	249		
No. of zones	5	Diarrhea-episode/child/year (above 5 year of age)	1.5
No. of sub-zones	10		
No. of wards	26		
Sex		Total URTI cases	2666 (42.6)
Female	233 (51)	Common cold and flu cases (URTI)	2375 (38)
Male	228 (49)		
Breastfeeding		Common cold and flu-episode/child/year (0–5 year of age)	1.7
Currently Breastfeeding	439 (2.6)		
Not currently breastfeeding	16,207 (97.4)		
Occupation		Common cold and flu-episode/child/year (above 5 year of age)	1.7
Unemployed	9 (3.61)		
Unskilled Worker	115 (46.18)		
Semi-Skilled Worker	84 (33.73)	Total LRTI/pneumonia cases	284 (4.5)
Skilled Worker	18 (7.23)	Pneumonia-episode/child/year (0–5 year of age)	0.4
Clerical, Shop Owner, Farmer	8 (3.21)		
Semi Professional	3 (1.20)	Pneumonia-episode/child/year (above 5 year of age)	0.1
Professional	12 (4.82)		
SES class			
Lower Class	182 (73.09)	Total VBD cases	84 (1.3)
Middle class	57 (22.89)	Malaria	38 (0.6)
Upper Class	10 (4.02)	Malaria episode/child/year (0–5 year of age)	0.0
Education			
Illiterate	68 (27.3)	Malaria-episode/child/year (above 5 year of age)	0.0
Primary school	32 (12.9)		
Middle school	31 (12.5)	Dengue	46 (0.7)
High school	57 (22.9)	Dengue-episode/child/year (0–5 year of age)	0.0
Intermediate	27 (10.8)		
Graduate or postgraduate	21 (8.4)	Dengue-episode/child/year (above 5 year of age)	0.0
Professional	13 (5.2)		
Family income		Skin disease cases	292 (4.7)
≤2164	8 (3.21)	Skin disease-episode/child/year (0–5 year of age)	0.3
2165-6430	138 (55.42)		
6431-10,718	47 (18.88)		
10,719–16,077	24 (9.64)	Skin disease-episode/child/year (above 5 year of age)	0.2
16,078–21,437	13 (5.22)		
21,438–42,875	7 (2.81)		
≥42,876	12 (4.82)	Others cases	701 (11.2)
Water source		Days of weather data	1095
Well	2 (0.80)	Age	
Hand pump	41 (16.47)	0–≤2 years	80 (17.3)
Tube well/bore-well/summer sable	45 (18.07)	>2–≤5 years	82 (17.8)
		>5–≤16 years	299 (64.9)
Municipal water supply	161 (64.66)	Street food	
Mosquito intervention		Irregular	189 (41)
Yes	128 (51.41)	Regular	223 (48.4)
No	121 (48.59)	Not applicable	49 (10.6)
Vaccine		Hand washing	
Yes	416 (90.2)	Irregular	254 (55. 1)
No	45 (9.8)	Regular	158 (34.3)
House type		Not applicable	49 (10.6)
Temporary House	39 (15.66)	Cleaning	
Semi Pacca (Cemented)	203 (81.53)	Satisfactory	149 (59.84)
Pacca (Well Furnished)	7 (2.81)	Unsatisfactory	100 (40.16)
Open container		Defecation	
Yes	241 (96.79)	Open field/community toilet	30 (12)
No	8 (3.21)		
Water filter		House toilet	219 (88)
Yes	74 (29.72)	Health insurance	
No	175 (70.28)	Yes	19 (4.1)
		No	442 (95.9)

3.2. Anthropometric analysis and BMI distribution by age and gender

The result from the anthropometric analysis indicates that for children under 5 years of age, *Z*-score distributions show that around 39.6% of children suffer from "stunting" that becomes more prominent in the age group of 1 to 3 years (Table 2 & Fig. 2a). Compared to males, females account for more observations falling under various categories of nutritional deficiencies (Fig. 2a). Around, 5.3% of children fall into "Severe wasting", 18.9% into "wasting", 3.8% in "overweight" and 37.3% in the underweight, and 45.7% in the healthy weight category. Further, the Z score distribution for "Height to age", weight to "age", "weight for length or height" and "BMI" for age show a negatively

Table 2
Most common anthropometric indicators to assess child nutrition status for children aged 0–5 years of age.

Indicators	Definitions	Observations (%)
Stunting	Height-for-age < -2SD	105 (39.6)
Severe wasting	Weight for height < -3SD	14 (5.3)
Wasting	Weight for height < -2SD	50 (18.9)
Underweight	Weight-for-age < -2SD	99 (37.3)
Overweight	Weight for height > +2SD	10 (3.8)

Note: SD represent Standard Deviation.

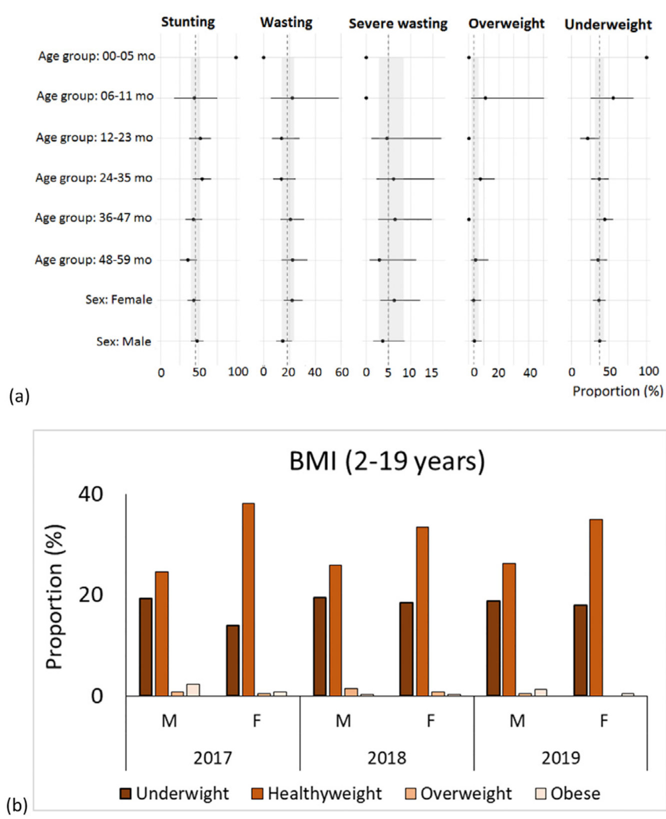

Fig. 2. Nutritional status by stratification variable for age (a) 0–5 Years, (b) 2–16 Years.

skewed distribution of both the sexes in comparison to WHO standards (Fig. 3). The "BMI for age" calculated for children between 2 and 16 years of age using percentile cut-offs (CDC chart) shows that there lies a good proportion of children that fall under the "underweight" category (36%) and a greater portion is accounted by males (Fig. 2b). However, the proportion of children falling under the category of overweight and obese was low. The year-wise distribution of the proportion of children (2–16) falling under each category categorized by sex is presented in Fig. 2b.

3.3. Disease prevalence and cases

Table 1 shows the summary of cases belonging to different disease categories and Fig. 4 shows the overall, annual, and seasonal distribution of cases and prevalence for each disease category. The highest number of cases belong to URTI (38.9%) and GIT (32.5%) disease categories broadly in which common cold and flu (URTI; 37.96%) and diarrhea (GIT; 34.38%) contributed to maximum cases. Table 1 also shows the number of episodes/child/year for each infectious disease category that was higher in children in the age group 0–5 years. The seasonal analysis showed a higher prevalence for GIT cases during pre-monsoon and URTI during winter and post-monsoon. For other disease categories, the prevalence remained less than 10%. However, based on the number of cases, the cases for URTI were higher in winter and monsoon. The prevalence and cases for diarrhea, and common cold and flu followed a similar pattern of seasonal distribution as shown by GIT and URTI cases respectively. Skin diseases showed high cases during monsoon but high prevalence during post-monsoon. Pneumonia (LRTI) shows a slightly higher number of cases and prevalence in pre-monsoon. Malaria and dengue (VBD) show high cases and prevalence in the post-monsoon season. No significant difference in cases was noted from one year to another may be due to only 3-year follow-up.

3.4. Association between disease outcomes and climatic factors

The results from generalized additive mixed effect modeling showed that the increase in cases of diarrhea was associated with Tmax, WS, and RF (Fig. 5). With every unit rise in Tmax and WS, diarrhea cases increased by 3.97% (95%CI: 2.92, 5.02%) and 14.16% (95%CI: 6.52, 21.80%) respectively. On the other hand, RF was marginally associated with an increase in diarrhea cases by only 0.12%(95% CI:-0.17,-0.08%). The cases of diarrhea decreased in females, with an increase in age and better SES, and with frequent hand washing practices and changes

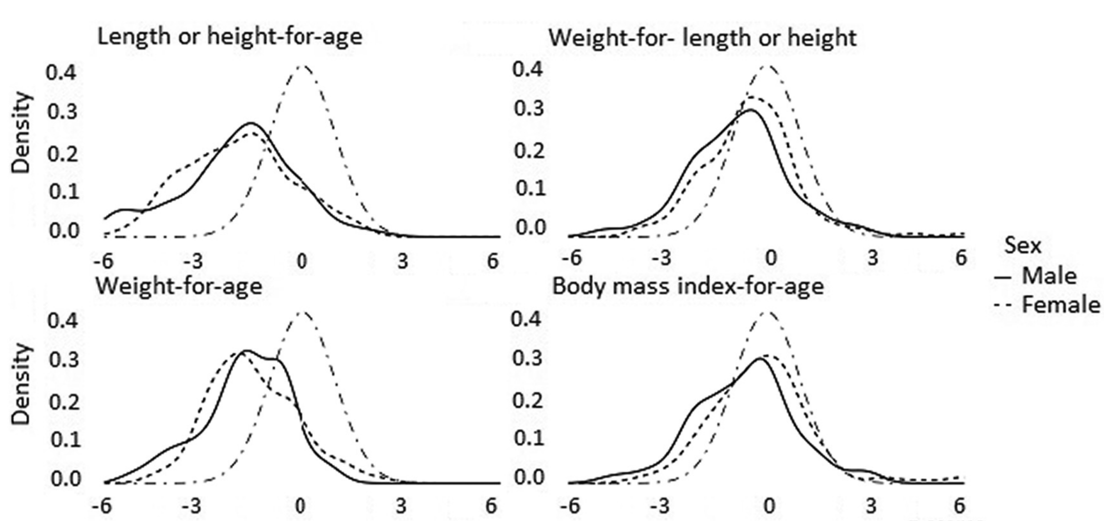

Fig. 3. *Z*-score distributions by sex for 0–5 years of age.

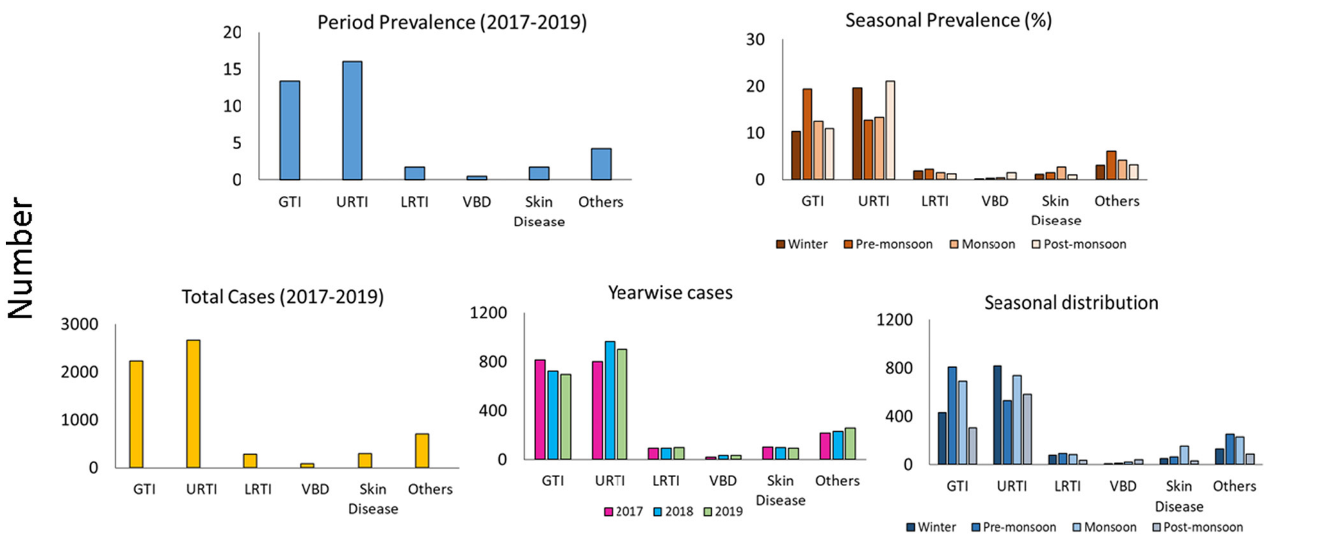

Fig. 4. No of cases and prevalence of different disease categories at total, annual and seasonal basis.

in drinking water source from piped municipal water to underground water. The common cold and flu cases showed a very distinct impact of climatic factors that was eventually less confounded by other SES conditions (Fig. 5). Common cold and flu showed a negative association with Tmax (3.87%; 95% CI: 2.97, 4.76) and positive with RH (0.73%; 95% CI: 0.38, 1.08) that decreased with increase in age. Pneumonia showed association only with AH, each unit decrease in AH observed an increase of 3.02% (95% CI: 0.75, 5.30) in pneumonia cases. The present study suggests that AH and WS are better predictors for modeling VBD than the other unique weather variables (Fig. 5). The per-unit increase in AH and decrease in WS were associated with an increase of 7.19% (95% CI: 1.51, 12.87) and 17.40% (95% CI: 12.32, 22.48) in malaria and dengue cases respectively. The malaria cases was found to be higher in aged children whereas dengue was associated with children having underground drinking water source. The cases of skin disease in children were significantly associated with Tmax and RF. For each unit increase in Tmax and RF, an increase of 3.94% (95% CI: 1.67, 6.22) and 0.18% (95% CI: 0.1, 0.27) in skin disease cases was observed. (Fig. 5). The susceptibility to skin disease decreases with an increase in age.

The AFx due to each climate variable for each infectious disease and the concurrent AFx due to combined risk of all-climate variables for each infectious disease is shown in Table. 3. Our findings showed that non-optimum temperature accounted for an AFx of 10.79% in common cold and flu cases, 7.46% in diarrhea cases, and 6.51% in skin diseases in Varanasi, India (Table 3). Humidity accounts for a 9.11% fraction in pneumonia (AH) while 5.43% in common cold and flu (RH). Rainfall on the other hand contributes to 11.47% in skin disease and 4.09% in diarrhea cases. WS accounts for 3.94% of diarrhea cases. The combined contribution of climate to the disease proportion remains within 14–18% for diarrhea, common cold and flu, and Skin diseases and 9% for pneumonia. However, the combined AFx due to all risk factors remained less than the individual AFx associated with each risk factor.

3.5. Exposure response curve

The exposure-response curves with a 95% CI for individual disease categories (with a dashed line marking the OV attributed to minimum prevalence) and climate parameters are included in Fig. 6. All disease categories displayed variation in the prevalence with variation in levels of exposure to climate parameters. The common cold and flu (URTI) showed an increase in cases with a decrease in monthly Tmax below 37 °C and with an increase in RH above 65%. Diarrhea (GIT) cases showed an increase with monthly Tmax above 30 °C and monthly WS above 1.5 kmph and with monthly RF below 60 mm. Skin diseases show a linear increase with monthly Tmax and RF above 33 °C and 40 mm respectively. Pneumonia (LRTI) showed association only with AH, with a decrease in AH below 200 g/m^3, pneumonia cases increased linearly.

4. Discussion

In the present cohort of children ≤16 years of age in different wards of Varanasi over 3 years (Jan 2017 to December 2019), the cases of diarrhea/GIT and common cold and flu/URTI outnumbered other disease-related morbidities. The finding was consistent with other studies that reported a high incidence rate (IR)/prevalence for respiratory tract diseases, and GIT (Mohapatra et al., 1989; Awasthi and Pande, 1997) followed by skin diseases and pneumonia with seasonal dominance of GIT and skin diseases in pre-monsoon (March–June) and monsoon (July to September), respectively (Awasthi and Pande, 1997). This suggests the need for season-specific health care strengthening to combat specific morbidities associated with children. Importantly, the episodes/child/year remains high in under 5 children though it has declined in the recent past (Sutariya et al., 2011).

Another important result from the present study shows a high percentage of children falling under poor nutritional categories. The girl child contributes to significant numbers falling under the stunting and undernutrition category in comparison to the world standards (based on WHO criteria). The finding is backed by similar observations over Haryana, India for children under 6–12 years of age that show about 22.5% of the recruited children felled under the thin/severe thin category. Similarly Awasthi and Pande (1997), found that among children of 1.5 to 3.5 years, about 67.6% ($n = 717$) were underweight, 62.8% ($n = 666$) stunted and 26.5% ($n = 281$) were wasted. A similar finding was reported by Damor et al., 2013. The evidence highlights the need for increased nutritional demand for the children over Varanasi in general.

The cases of diarrhea (GIT), common cold and flu (URTI), pneumonia (LRTI), malaria and dengue (VBD), and skin diseases were significantly associated with climate, and the strength and direction varied with each disease class. The association between child morbidities and climate in this population is consistent with past studies in similar settings (Awasthi and Pande, 1997). Studies by Xu et al. (2012) and Phung et al. (2017) have also identified the positive relationship between ambient temperature and paediatric gastrointestinal infections. The higher temperature in association with humidity and rainfall increases bacterial causes of infectious diarrhea/GIT and survival times of bacteria (Ghazani et al., 2018). In drought periods (pre-monsoon), an increase in temperature may cause a rise in the evaporation rate from turbid

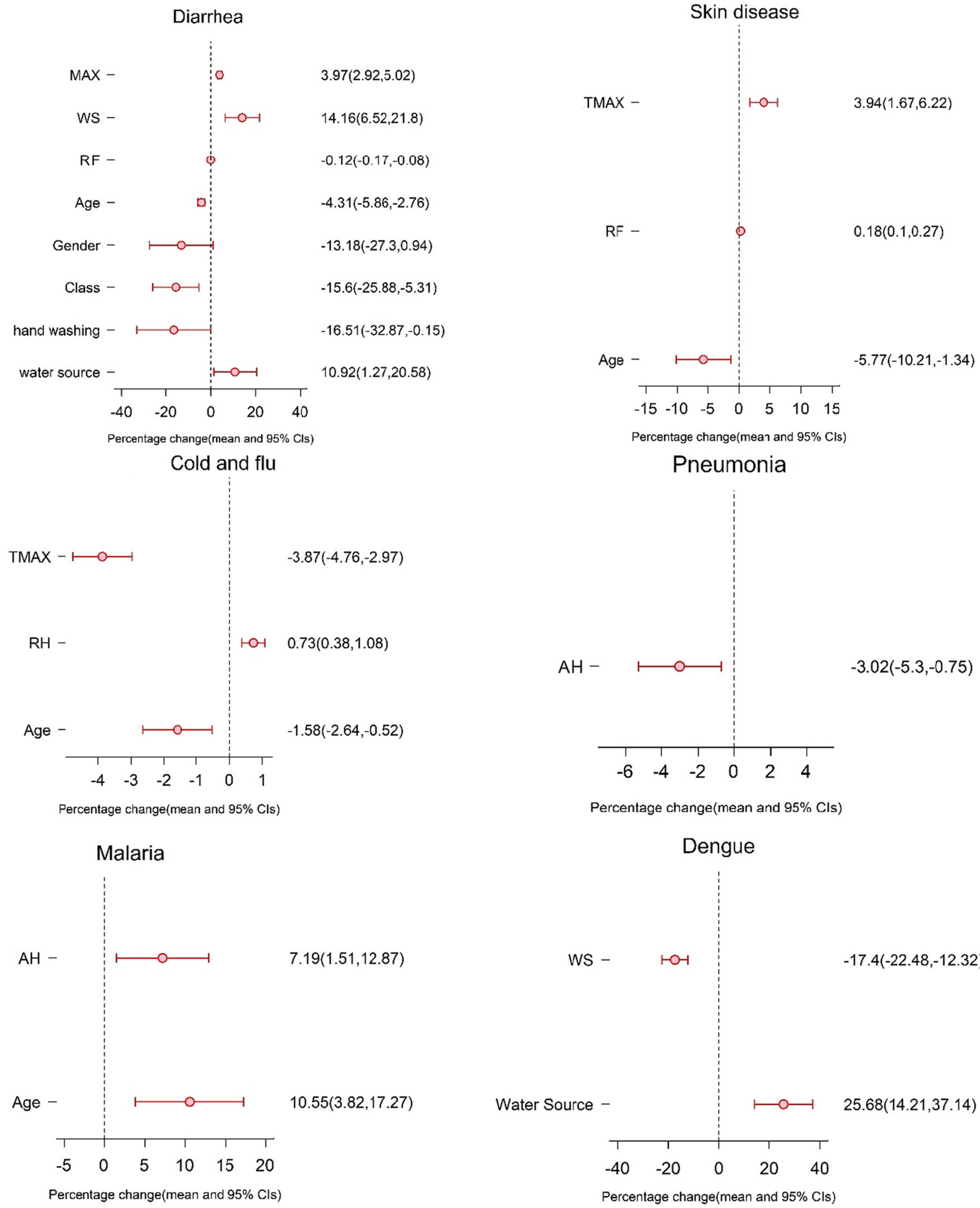

Fig. 5. Percent change in cases associated with different disease categories with 1 unit increase in climate parameters and with change in SES and anthropometric classes. All values are significant at $p < 0.05$.

and polluted water bodies that in turn may increase the concentration of fecal pathogens in the water bodies and subsequent consumption of the polluted water causes diarrhea/GIT infections in children (Jofre et al., 2009; Phung et al., 2017). WS, on the other hand, may help in the mixing of the water bodies and thus in the distribution or transport of the microorganisms (Hervás et al., 2014). However, few studies have reported no significant association of diarrhea infection to RH, or rainfall, or WS (Lama et al., 2004; Prasetyo et al., 2015). RF on the other hand show only marginal association with an increase in diarrhea cases. In conditions of heavy rainfall (monsoon), surface water flush feces that mix with municipal water sources and contaminate the same (Bunyavanich et al., 2003) thus causing increased diarrhea cases on the consumption of infected water or food. Improved SES conditions, better hygiene practices like frequent hand washing practices before a meal and after defecation, and protected water sources caused fewer children to fall sick due to diarrhea. Our results on climate-diarrhea (GIT) association are similar to those reported from Tamil Nadu, India (Mertens et al., 2019), Bangladesh (Hashizume et al., 2008), New York (Lin et al., 2016), and other tropical regions (Lama et al., 2004).

The association between climate parameters with common cold and flu (URTI) cases in the present study are similar to those reported from The Netherlands and Toronto, Ontario, Canada that shows a negative association of temperature with Influenza cases (URTI) (Caini et al., 2018; Peci et al., 2019). Inhibited response of the immune system in winter

Table 3
Total attributable fraction (%) due to climate risk factors to disease proportion for each infectious diseases.

Infectious Disease	Climate Risk factors	Direction of association	OR (LCL, UCL)	AFx (%) (LCL, UCL)	Concurrent AFx (%)
Common cold and flu (URTI)	Tmax (°C)	<OV	0.96 (0.95, 0.97)	10.79 (8.44, 13.05)	15.88
	RH (%)	>OV	1.007 (1.004, 1.011)	5.43 (2.85, 7.93)	
Diarrhea (GIT)	Tmax (°C)	>OV	1.04 (1.03, 1.05)	7.46 (5.55, 9.32)	14.66
	WS (Kmph)	>OV	1.15 (1.07, 1.24)	3.94 (1.84, 5.99)	
	RF (mm)	<OV	0.98 (0.97, 0.99)	4.09 (2.07, 6.07)	
Pneumonia (LRTI)	AH (g/m^3)	<OV	0.997 (0.995, 0.999)	9.11 (2.33, 15.36)	9.11
Skin Disease	Tmax (°C)	>OV	1.04 (1.02, 1.06)	6.51 (2.84, 9.96)	17.79
	RF (mm)	>OV	1.002 (1.001, 1.003)	11.47 (6.27, 16.18)	

Note: The AFx is calculated for variables above or below optimum value (OV). The less than sign (<) shows that the values less than OV were taken while greater than sign (>OV) shows that values greater than OV were taken into consideration.

due to the decreased levels of vitamin D production (Roussel et al., 2016) and decreased clearance ability of respiratory cilia on inhalation of cold air (Hajat et al., 2004) are the plausible reasons. Indoor crowding and close contact in winters may also facilitate virus transmission (Hirve et al., 2015). Besides temperature, high humidity during monsoon season in tropical/sub-tropical populations aids virus survival and transmission, thus low temperature and high RH (70–80%) is the driving factor for peaked Influenza activity in temperate, subtropical, and tropical regions (Tamerius et al., 2013). Importantly, the temperature shows a stronger effect compared to RH. In a nonlinear exposure-response relation, Tamerius et al. (2013) reported peaked influenza activity in winter as monthly average specific humidity or temperature decrease below 11–12 g/kg and 18–21°. Though, the evidence from most high latitude regions suggests that low temperature and low humidity (winter) increase influenza activity through increased respiratory virus survival and subsequent transmission (Peci et al., 2019). But because subtropical cities like Varanasi witness large cases of cold and flu (URTI) both during winter (low temperature but relatively

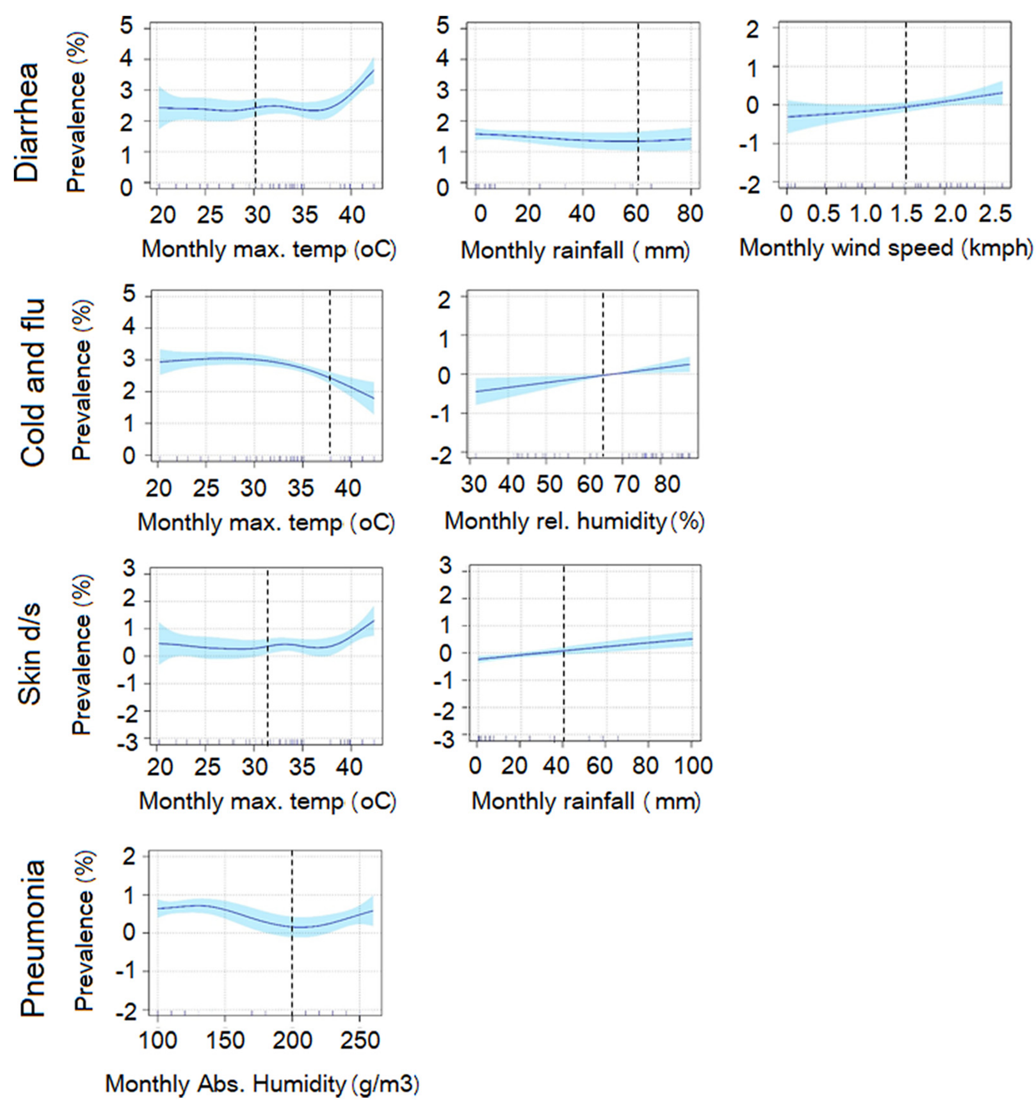

Fig. 6. Exposure-response curves between individual morbidity for each disease categories and climate parameters.
Note. The blue areas are the 95% CIs.

high RH) and monsoon (high RH), therefore the old conventional relation of low temperature and humidity didn't actualize. The decrease in common cold and flu (URTI) cases as the age advanced were apparent may be due to strengthened immune response with age.

We found evidence that lower monthly AH was associated with increased pneumonia (LRTI) cases. A study by Wiemken et al. (2017), from an International Cohort Study showed a similar negative association between hospitalization due to LRTI and AH (RR = 1.01, 95% CI; 0.85, 1.2). The role of low humidity in increasing viral stability and transmission associated with influenza virus and respiratory syncytial virus (RSV) responsible for causing LRTI was previously established (Wiemken et al., 2017). Though the LRTI (Pneumonia) occurs mostly in the colder months, climatic factors like temperature and rainfall drive regional differences in LRTI, with higher deaths between June and August in India's humid subtropical region (including UP and Bihar). For a humid subtropical climate, pneumonia deaths show a bimodal peak in a year (July and Jan) (Farrar et al., 2019). Several other studies from India have shown an association of LRTI with air temperature, atmospheric pressure, RF, and RH (Liu et al., 2016). Further, interhost factors such as changes in viral stability, airflow and respiratory droplet size, viral clearance, nutrition changes, ultraviolet light, and close indoor contact have been described as potential factors to increase the susceptibility (Pica and Bouvier, 2012; Wiemken et al., 2017).

It is important to note that different climatic factors (RF, temperature, and RH) play a vital role in determining the timing of mosquito activities through their interaction with the seasonal and circadian regulation of species' behaviors and other ecological constraints (Bates, 1949; Veronesi et al., 2012). However, in the present study, malaria and dengue (VBD) were found to show association only with AH and WS respectively. High humidity enhances mosquito activity and survival time (Lauderdale et al., 2014). Thus mosquito's more often prefer to feed at night time when the humidity is relatively high. Huang et al. (2011) showed that humidity (relative) ($55 \leq RH \leq 80$) play an important role in altering the life cycle of the mosquito and biting behavior that ultimately influence malaria transmission. A positive association between humidity and malaria cases was also reported from other parts of the country (Kumar et al., 2020). WS acts as one of the influential factors that favor mosquito dispersal at low WS but may reduce mosquito upwind flight activity and capability at higher WS (Bidlingmayer et al., 1995). The high WS may also affect the feeding habits and oviposition dynamics of the *Aedes* mosquito and the overall dengue transmission as was observed in a study by Santos et al., 2020 that showed higher WS was associated with a decrease in the average number of eggs of *Aedes aegypti* ($\beta = -125.2$; 95% CI: -198.8 to -51.6).

Skin disease among children is not considered an important public health issue at the individual level as the most common skin infections are not lethal. However, it may put an important health problem within the population. Being the most exposed part, skin diseases are inclined to be highly sensitive towards the climate. The present study shows that increased temperature and humidity aids in skin diseases among children in Varanasi. Higher temperature and humidity (55% and 78%) during the summer and rainy seasons aid the rapid proliferation of pyogenic bacteria that may lead to an increased rate of bacterial skin infections (Balato et al., 2014). Apart from climate, the other important factors accounting for the spread of skin diseases include SES status, malnutrition, overcrowding, and poor standards of hygiene practices (Mahé et al., 1995; Balato et al., 2014) that all seemed to favor skin diseases for children in Varanasi. Though no significant association could be established for these parameters. The association further shows decreased cases with an increase in age.

We also evaluated the disease burden attributable to non-optimum values of climate variables. Tmax, humidity (relative and absolute), RF, and WS were identified as the major climate contributors to disease classes. Importantly, the sum of the AFx due to individual climate variables remains less than their combined contributions. This is because of the overlapping contributions of the coexisting risk factors that combine to cause an adverse health effect (Gasparrini and Leone, 2014). It should be noted that the climate variables could only explain part of the accountability for the occurrence of infectious diseases. Thus, there might exist some other salient city-specific and individual-specific characteristics that impact the occurrence of these prevalent infectious diseases. Importantly, in this paper, we could not establish a larger role of SES on all diseases except diarrhea. Therefore, including other information such as city-specific attributes, population immunity, community health literacy, population behavior, vegetation coverage, urbanization, and public-health intervention might further explain the possible effect modification for the climate-disease relationship.

Comparative studies on AFx due to climate variables showed consistent results. Wang et al. (2021) reported the AFx due to high ambient temperatures (above the 95th percentile of temperature) on category C notifiable infectious diarrhea over mainland China was 4.5%. Whereas, Zhao et al. (2019) show AFx of 13.6% in hospital outpatient visits for respiratory illness attributable to ambient temperature exposure for age < 65 years. Thus solely depending upon the conventional methods of showing the association between climate and disease, incorporation of AFx, in combination with other relevant information's like RR, OR or prevalence rate (PR) or percent change (%), will together help in prioritizing a given exposure and steps to improve the population health.

5. Strength and limitations

The study has its strengths and weaknesses. The study presents evidence of an association between climate parameters and infectious diseases in children in Varanasi, India. Up to the knowledge of authors, no such study exists in this region of India that presents such evidence taking into account extensive parameters for confounding and effect modification. The health effects have been poorly investigated in this part of India and any evidence that provides the disease burden associated with climate parameters will help the policymakers and the government to avert the risk that may arise due to climate change. The study also presents the results in the form of attributable fraction due to risk associated with climate variables accountable to diseases proportion in children. The present study provides evidence about the optimum values for each climate variable for each disease category that have rarely been investigated over India. The study further presents the nutritional status of children based on various indexes proposed by WHO. That shows a substantial number of children fall under the undernourished condition as visible through their proportion in wasting, stunting, and underweight conditions. Nevertheless, this identified association may contribute to early preparedness and prevention of notified infectious diseases.

The weakness of the study lies in the fact that it didn't take into account the non-independence of observations for children from the same household that can have a bias associated with the results. The reported cases for infectious diseases were not confirmed for identification of causal pathogens in a laboratory and thus are subject to reporting bias. Further, the meteorological parameters collected from the IMD weather station at Banaras Hindu University was assumed to apply to all wards because Varanasi has a single weather station. This assumption could be more reasonable for parameters like temperature that are more homogeneous than for rainfall, which can be more heterogeneous at provincial scales. Thus, the uncertainty in the true exposure to weather at the individual level is a limitation of this study, and misclassification aroused due to lack of true exposure may have led to bias and reduced precision. Another important assumption made in the study was that the regression model was adjusted for all potential confounders. Remarkably, due to epidemiological data constraints, all statistical analyses were conducted using monthly aggregated data. Though evidence-based on long time scales may limit statistical or predictive power in establishing the influences that appear over daily or weekly periods, in absence of large scale evidence over the subject from the socioeconomically backward areas, the present evidence could prove important to highlight the present association of infectious diseases with climate and anticipated future risks under the climate change scenario in children with already very high under 5 mortality.

6. Conclusion

The key message derived from the present study that was carried out on a representative sample of children under 16 years of age in Varanasi city highlights that in spite of several important measures taken to reduce child morbidity and mortality pertaining to infectious diseases, the burden still remains high among children, prominent in under 5 age group and is significantly associated with climatic parameters. The association between infectious diseases and climatic parameters was modified and confounded by socioeconomic and child anthropometric factors. It is important to note that climate variables contributed only a small fraction of the disease proportion. Thus, there might exist some other important city and individual-specific characteristics that may account for further effect modification and confounding effect. The study further highlights the poor socioeconomic conditions of the families of the children that is evident through a large section of children falling under the undernourished condition (stunting, wasting, and underweight). On a broader trajectory, the findings for the study may spark interest in testing the association link between climatic parameters and infectious disease across a wide range of infectious diseases particularly in the predominating respiratory and enteric disease with apparent seasonality. Because, enhanced learning of the existing interaction between environmental, social, and demographic drivers and the marked seasonality in infectious disease may play an unprecedented role in the refinement of the disease transmission models and augmenting interventions.

Based on the results of the study, countries like India, that seek locally constructed disease burden estimates to advocate efforts and actions at the local/regional/and national level will be benefitted. The study may provide diverse opportunities for government, policymakers, and researchers to interpret the results based on their prime concerns. However, the major emphasis of the study was to provide an evidence-based estimate to the government and policymakers to highlight the present burden of morbidities among pediatrics, some of which need immediate attention to take preventive actions to combat the additional burden of climate change.

CRediT authorship contribution statement

NS: Conceptualization, methodology, survey & Investigation, formal analysis, interpretation, review, and writing of the original draft;

RKM: Conceptualization, Supervision & project administration, methodology, interpretation as well as review and editing of the draft; resources; funding acquisition

TB: Methodology, interpretation as well as review and editing of the draft

AG: Interpretation as well as review and editing of the draft.

Ethics approval and consent to participate

The authors have obtained the consent to participate from the parent or legal guardian of each child and the epidemiological information related to their children to be used in the research.

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Declaration of competing interest

The authors declare no conflict of interest relating to the material presented in this article. Its contents, including any opinions and/or conclusions expressed, are solely those of the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.148769.

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