Heat and Cold-related Hospitalization Risk in North-East of Iran: A Time-stratified Case Crossover Design

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Research Article

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Posted Date: May 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-513713/v1

Version of Record: A version of this preprint was published at Environmental Science and Pollution Research on August 10th, 2021. See the published version at https://doi.org/10.1007/s11356-021-15677-6.

Heat and Cold-related Hospitalization Risk in North-East of Iran: A Time-stratified Case Crossover Design

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Abstract

Background: This study aimed to estimate hospitalization risk/number attributed to air extreme temperatures using time-stratified case crossover study and distributed lag non-linear model in a region of Iran during 2015-2019.

Methods: A time-stratified case crossover design based on aggregated exposure data was used in this study. In order to have no overlap bias in the estimations, a fixed and disjointed window by using one-month strata was used in the design. A conditional Poisson regression model allowing for over dispersion (Quasi-Poisson) was applied into Distributed Lag Non-linear Model (DLNM). Different approaches were applied to estimate Optimum Temperature (OT). In the model, the interaction effect between temperature and humidity was assessed to see if the impact of heat or cold on Hospital Admissions (HAs) are different between different levels of humidity.

Results: The cumulative effect of heat during 21 days was not significant and it was the cold that had significant cumulative adverse effect on all groups. While the number of HAs attributed to any ranges of heat, including medium, high, extreme and even all values were negligible, but a large number was attributable to cold values; about 10000 HAs were attributable to all values of cold temperature, of which about 9000 were attributed to medium range and about 1000 and less than 500 were attributed to high and extreme values of cold, respectively.

Conclusion: This study highlights the need for interventions in cold seasons by policymakers. The results inform researchers as well as policy makers to address both men and women and elderly when any plan or preventive program is developed in the area under study.

Keywords: Hospital Admissions, Cold, Heat, Attributable risk, Case crossover, Iran

1 Introduction

The exposure to weather parameters such as air temperature and humidity have been increasingly paid attention due to many extreme events which have several health outcomes. The impact of heat and cold on human health has been documented by several studies. For example, more recently, a study conducted by multicountry data showed that heat waves had significant cumulative risk of mortality in all countries involved in the study(Guo et al. 2017) . More importantly, climate change is projected to increase weather extreme events such as heat and cold waves as well as extreme temperature values that might highly endanger human health (Son et al. 2014). Hence, it is important to have elaborately clear evidence of how cold, heat and their extreme values affect human health by which researchers can design a preventive intervention to protect vulnerable people in future.

Previous researches illustrated that both high and low temperature values can increase Hospital Admissions (HAs) due to some diseases (Chang et al. 2004; Luo et al. 2018; Wichmann et al. 2012). A possible mechanism may be explained by increased sympathetic nervous symptoms, high blood pressure, heart rate, late clinical symptoms of heart failure and myocardial oxygen consumption, as well as decreased ischemia threshold, the change of hemodynamics changes (Aboubakri et al. 2019; Danet et al. 1999; Liu et al. 2018; Spencer et al. 1998). Accordingly, direct or indirect human health outcomes including mortality and disability as results of extreme values of temperature are essential to be addressed by health policy makers.

The climate or weather change seems to be more serious problem in the Middle East countries, especially in Iran. Iran is expected to experience an increase of 2.6 °C in mean temperatures and a decrease of 35% in precipitation by the next decades(Mansouri Daneshvar et al. 2019). Thus, the heat and cold continue to be big health problems in Iran. In this study, we aimed to assess the association between air extreme temperatures and HAs using time-stratified case crossover study and distributed lag non-linear model in a region located to the North-East of Iran. In addition, Attributable Risk/Number were estimated in the study which can be useful for policymakers to make decision about the problem.

2 Material and methods

2.1 Data

The Hospital Admissions (HAs) were obtained from a referral hospital in North Khorasan. The HAs due to all causes during 2015-2019 were included in analysis. They were also categorized based on sex and age group in order to determine high risk groups. The weather and pollutants data were collected by national weather organization and department of environment. In this study, daily mean temperature was used as the predictor of HAs because many study showed that it is better predictor than minimum and maximum temperature for mortality or disability (Aboubakri et al. 2020a; Aboubakri et al. 2020b; Xu et al. 2018; Xu and Tong 2017). Number of missing data for HAs, mean temperature and humidity was negligible (lower than 5 percent). However, there

were a higher number of missing data for air pollutants, but they were still low number (<20%), thereby allowing us to impute the data by multiple imputation method.

2.2 Design

A time-stratified case crossover design was used in this study. In order to have no overlap bias in the estimations, a fixed and disjointed window was used in the design(Janes et al. 2005). In this design, a given exposure for a case occurring on Monday, 8 July, for example, would be compared to the exposure occurring on all other Mondays in July (i.e. 1 July, 15 July, 22 July, and 29 July). Indeed, we developed one-month strata in which for a case that falls in a stratum the every seven days before or after the case day in the same stratum were chosen as reference, thereby allowing the reference period to be randomly selected over the months so that days of week and months were controlled. The strata therefore deserve a conditional model which has been illustrated in the section 2.4. It should be mentioned that the inference is still based on aggregated exposure data(Armstrong et al. 2014). Therefore it is different from individual case-crossover design and the estimations are interpreted as if they are estimated from ecological studies where the exposure is not distinct for each participant.

2.3 Optimum Temperature(OT), Heat and Cold

To determine the OT, we did sensitivity analysis and used two different approaches. In first approach, a nonlinear function (loess spline) was fitted on the association between temperature and ARIMA models' residuals. Indeed, arima (1, 1, 1), was fitted on HAs, and then the residuals of the model were extracted. The residual mean value would be near to zero if the ARIMA model fitted to the daily HAs series was suitable (i.e., if its variability were entirely explained by the model). Therefore, the further away the residual of temperatures from the mean value(reference) and its standard error, the more this variation will be attributed to the influence of those temperatures (Miron et al. 2012), thereby being not considered as OT. The results of the analysis has been provided in supplementary file for total HAs (Fig S2). As seen, there was uncertainty in OT based on CI 95% provided in the figure. In the second approach, the temperature with minimum relative risk come from the model in equation 1 was used as OT. In the approach a natural cubic B-spline function was used in the relationship between daily mean temperature and total HAs. The details of the approach has been illustrated in the study by Tobías et al (Tobías et al. 2017). The function was separately fitted for two models with and without confounders (figure S1 in supplementary file). However, there was still a big uncertainty in the optimum temperature by this approach (i.e. the 95% empirical confidence interval were wide). Eventually, the OT was considered as 25°C for total HAs risk based on the model with all confounders.

Median temperature has also been considered as OT in some studies(Guo et al. 2011) , though, it had higher risk than the temperature in our study. In addition, the CI95% (in in figure S1, b) does not included the median (14.9°C), showing unsuitable as OT in our study.

Cold and heat were the temperatures below and above the OT, respectively. Also, percentiles 5th, 1th , 95th and 99th were defined as cold, extreme cold, heat and extreme heat values. The ranges between the values were, therefore, defined as different levels of cold and heat (i.e. the values from the OT to percentile 5th , the percentile 5th to percentile 1th, percentile 1th to minimum value were defined as medium, high and extreme values of cold, respectively).

2.4 Model

A conditional Poisson regression model allowing for over dispersion (Quasi-Poisson) was applied into Distributed Lag Non-linear Model (DLNM). Conditional Poisson regression does not necessarily estimate each stratum parameter by conditioning on number of HAs in each stratum, and it provides identical estimations to unconditional Poisson in time-stratified case crossover design(Armstrong et al. 2014).

The DLNM have been explained elsewhere in literatures(Gasparrini et al. 2010; Schwartz 2000). Totally, the model provides a framework in which linear or non-linear associations can be simultaneously defined in two dimensions, entitled exposure-response and lag-response associations. Therefore our model used in the time-stratified case crossover design was as bellow:

Equation 1

$$\log(Y_t) = \alpha + Cb(temperature_{tl}) + NS\,(humidity, 3) + NS\,(SO_2\,, 3) + +NS\,(NO_2, 3) + NS\,(PM_{10}, 3) + Holiday + \varepsilon_t$$

Where Y_t is the number of HAs in day t, α is intercept, cb is crossbasis function obtained by DLNM. In the two dimensional function, natural cubic B-spline was used for both exposure-response and lag-response associations. To facilitate comparisons between countries, similar approach to other studies was used in order to place knots, in the spline function. In addation, several sensitivity analysis were done in order to choose the best function and the knots location. Therefore, three internal knots were placed at the 10th, 75th, and 90th percentile as used in a multicountry study for the natural cubic B-spline (Gasparrini et al. 2015). Also three internal knots were placed at equally spaced values in the log scale for lag-response dimension.

In the model, NS represents natural spline function. The df=3 was chosen for the confounders (humidity,SO_2, NO_2 and PM_{10}) based on literatures(Stafoggia et al. 2008; Yang et al. 2015) and sensitivity analysis by using Akaikes's Information Criterion for over dispersed count data(Q-AICc). Holiday is an indicator variable which represent public holidays in Iran including any national festival or mourning. In the model, there are not parameters for strata because, as mentioned, they are conditioned out in the conditional model.
Maximum lag was set to 21 in order to capture both harvesting effect of heat and delayed effect of cold. Also, to calculate cumulative and non-cumulative relative risk in each lag, the OT was used as reference value.

2.5 Interaction effect

In our study, we assessed the interaction effect between temperature and humidity to see if the effect of heat or cold on HAs are different between different levels of humidity(dry and moist). To assess the interaction effect, humidity was categorized to three levels of dry, optimum and moist based on 33.3th and 66.6th percentile. The optimum level (values between 33.3th and 66.6th percentile) was considered as reference category (optimum). Therefore the coefficients of main exposures (heat and cold) in the levels of dry and moist were graphically compared to the optimum.

2.6 Attributable Risk/Number

Attributable risk was calculated in DLNMs. The methodology of the AF has been explained by Gasparrini et al (Gasparrini and Leone 2014). Basically, it comes from Relative Risk (e^{β} in exponential form) and prevalence of exposure. The overall formula for AF is:

Equation 2

$$AF_{x,t} = 1 - e^{-\beta} = 1 - e^{-\sum_{\ell=\ell 0}^{L} \beta_{x_{t-\ell},\ell}}$$

In which, AF indicate the attributable fraction at time t associated to risk factor x in the past time t-0… 21. Therefore, the AF in DLNM comes from cumulative relative risk. In this models, Attributable Number (AN) in a specific day as to previous risk factor x can also be calculated by multiplying the AF to number of events (HAs) in the same day (n_t in equation 3). The latter is more likely to be easily interpreted by policy makers. So, we calculated both AF and AN.

Equation 3

$$AN_{x,t} = AF_{x,t}.n_t$$

In equation 3 it is evident that we can estimate AN/AF for several days by limitation n_t to any arbitrary range. The AN/AF were therefore estimated for medium, high, extreme and all values of cold and heat in this study.

3 Results

About 79000 hospitalizations were accrued during the period of our study, of which about 54000 and 25000 were as to young and elderlies, respectively. Men and women were almost equally admitted to the hospital. Table 1 represents descriptive statistics of daily number of hospital admissions by sex and age groups. It also illustrates daily mean temperature, relative humidity and air pollutants.

Figures 1 and 2 show relative risk of HAs by different sex and age groups in each single lag(lag-response associations) due to heat and cold (extreme values), respectively. Seen together, while, heat tended to have no significant adverse effect in any days but cold showed the significant adverse effect on total HAs in later days. Meanwhile, male and elder people seem to be more vulnerable to heat in early days (the plots b and e in figure 1); the relative risks were insignificantly higher in lags 1 and 2 for both groups. Cold, in the other hand, had significant relative risk on elderlies and males in later lags; men were significantly vulnerable to cold in lags 15 and 16 and elderlies were significantly vulnerable to cold not only in those lags but also earlier (e.g. lags 2 and 11).

Additionally, the interaction effect of humidity was not significant. The lag-response associations of both heat and cold were not significant in either dry or moist days relative to days with optimum humidity (figure3 and figure4 in supplementary file). Indeed, the heat and cold effects were not significant when the weather was dry or moist compared to optimum (RR was not significant in any lags in figures S3 and S4).

While the cumulative effect of heat during 21 days was not significant for any subgroups, cold had significant cumulative adverse effect on all groups (table 2). As seen in the table, although, the CRRs were significant for both men and women or young and elderlies, but female and elderlies were slightly more vulnerable to cold (CRR for females= 1.83; 95% CI= 1.06, 3.15 and CRR for elderlies= 1.52; 95% CI= 1.15, 2.01) and extreme cold values (CRR for females= 2.02; 95% CI= 1.15, 3.58 and CRR for elderlies= 1.59; 95% CI= 1.11, 2.28), compared to men and young people.

In figure3, the total number of HAs attributed to different ranges of cold and heat temperatures have been showed. While the numbers were negligible for any ranges of heat, including medium, high, extreme and even all values, but a huge number were attributable to cold values; about 10000 HAs were attributable to all values of cold temperature, of which about 9000 were attributed to medium range and about 1000 and less than 500 were attributed to high and extreme values of cold, respectively. Although the number for high and extreme values were lower than medium, they were statistically significant based on empirical confidence interval for attributable fraction presented in table 3. The respective attributable fraction of all ranges of temperature for all groups have also been presented in table 3. No AN was significant for heat values. In the table, it is evident that elderly were in higher risk of hospitalizations than young for all values of cold (16.6 percent of all hospitalized elderlies were attributable to all values of cold, of which 15, 1.1 and 0.5 percent were significantly attributable to medium, high and extreme values, respectively). Also the significant ANs of high and extreme values were more for women than men.

4 Discussion

The results of lag-response associations showed that heat had neither immediate nor later effect on HAs. The results of AF revealed that the fraction attributed to heat was not significant and a low number of HAs were attributable to heat values as well. Cold values, in the other hand, had not

only significant cumulative effect, but considerable attributable risk of HAs. Therefore, cold had higher contribution to AF/AN than heat in the area of under study. Similarly, several studies have shown that cold has higher AF than heat. For example, Hang Fu et al (Fu et al. 2018) found that cold temperatures contributed to higher AF of mortality than heat temperatures in India. In addition, a multicountry study showed that more temperature-attributable fraction was caused by cold (7·29%, 7·02–7·49) than by heat values (0·42%, 0·39–0·44)(Gasparrini et al. 2015). The cold effect might be explained by some mechanisms leading to cardiovascular and respiratory diseases. For example, the HAs might be because of more quick spread of infectious diseases, decreased response mechanisms of upper respiratory system, immune system suppression, chronic respiratory or coronary diseases, and increase of fibrinogen concentration as to the respiratory diseases(Zhou et al. 2014). In addition, it is important to say that the effect of heat and cold on HAs tended not to be significant when the humidity was either dry or moist compared to optimum (figure S3), showing no potential interaction effect between temperature and humidity. Therefore, the findings about impact of heat and cold can be interpreted with high confidence and no worry about humidity in our study.

We also demonstrated that medium values of cold shares larger proportion of AF than high and extreme values. This finding is also accordance to other studies' results as well. The study conducted by Gasparrini et al(Gasparrini et al. 2015) revealed that in all countries entered into analysis in the study, most of AF was due to medium cold values, and extreme values (either cold or heat) shared a small AF. The reason for the finding in our study can be found in figure S5. The number of days with medium values is apparently more than the others two, resulting in higher AF based on the function presented in equation 3. Also, that the low AF/AN for the high and extreme values of cold were statistically significant can be explained by the significant relative risk presented in the figure S5.

In our study, elderlies tended to be at higher risk for cold compared to heat values and young people. The higher risk of elderly to cold may be due to chronic diseases and the weakened blood circulation (Cui et al. 2019). We also showed that both men and women were high risk for cold values. However, women were slightly more vulnerable to cold compared to men. This result is similar to several previous evidences. For example, a study conducted in Korea found that women were in higher risk of cold-related hospitalization(Son et al. 2014). Also Barnett et al(Barnett et al. 2005) showed that the odds for women to have a coronary diseases in cold periods were 1.07 higher than the odds for men. A reasonable explanation for the different between men and women might be different casual wear in Bojnourd, high resistance of men to several diseases due to exercise, different physiological structure and job. The later one points to outdoor working women in Iran. However, in our view, the interaction effect of job need to be assessed in next studies in Iran. Meanwhile there are some studies that have shown no different relationship between air temperature and HAs in men and women. An example of this is the study conducted by Basu and Ostro(Basu and Ostro 2008) using a similar design to our study(time-stratified case crossover design). They found no different in temperature effect on mortality between men and women. Although there might be no agreement between results of different studies but different

methodology, models, or even more importantly the different climate should be taken account when their results are compared. OT, reflecting different climate, has a key role in studies assessing heat or cold temperatures on human health. Some studies might estimate the OT imprecisely(Tobías et al. 2017), and the results should therefore be thoroughly interpreted .For example in a study conducted by Wang et al(Wang et al. 2015) in china mean temperature was used in order to estimate the impact of heat and cold values. They also compared percentile 1th to percentile 10th and percentile 99th to 90th in order to estimate the relative risks of the cold and hot temperature. In our opinion, to compare two temperature values that are approximately the same is not suitable to calculate relative risk. Because the denominator of RR is supposed to be the number of events in unexposed group (a temperature value that has the lowest risk). In addition to the methodological or statistical different, type of morbidity outcome, or other factors such as population characteristics and socioeconomic status might be the reason for the heterogeneity between studies. Meanwhile, our finding about the susceptibility of both men and women and elderly to cold temperature reminds policy makers to make interventions based on this group in Bojnourd.

5 Conclusion

In summary, the study showed that cold temperatures had adverse impact on Hospitalization in Bojnourd and a high number of hospitalizations were attributable to cold values. It therefore highlights and support the hypothesis of need for interventions in cold seasons by policymakers in the region. Both men and women and elderly were high risk groups for the cold values in the region. This evidence, consequently, informs researchers as well as policy makers to address these groups when any plan or preventive program is developed in the area under study.

Declarations

Acknowledgements

This study was financially supported by North Khorasan University of Medical Sciences The authors thank the Deputy of Health of North Khorasan University of Medical Sciences for providing the data.

Funding:

This work was supported by the Deputy of research and technology, North Khorasan University of Medical Sciences [Grant No. 990175].

Competing interests

The authors declare that they have no conflict of interest.

Availability of data and materials

The dataset analysed during the current study are not publicly available due to ethical concerns but are available from the corresponding author on reasonable request.

Code availability

The R codes are available under request from corresponding author

Author contributions

Hamid Reza Shoraka: Project administration, Conceptualization; Data curation; Funding acquisition, Roles/Writing - original draft; Writing - review & editing.

Omid Aboubakri: Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Roles/Writing - original draft; Writing - review & editing.

Joan Ballester: Methodology; Validation; Writing - review &editing.

Rahim Sharafkhani: Writing - review &editing, Investigation

Ethics approval

The proposal for this study was approved by the Ethics Committee of North Khorasan University of Medical Sciences. Ethics code is IR.NKUMS.REC.1400.032

Consent to participate

The data from hospital was collected with no personal identification.

Consent for publication

Not applicable

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Figures

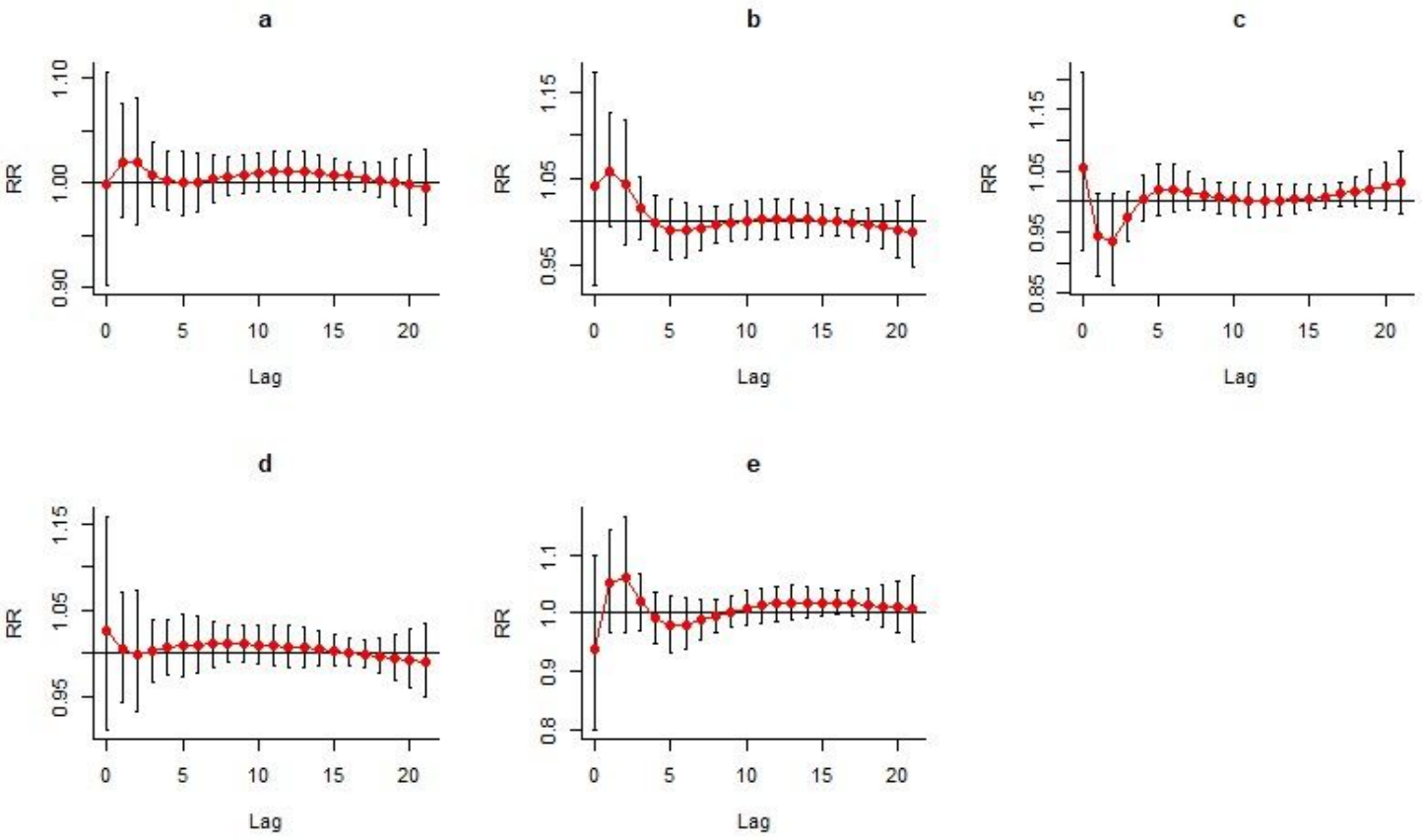

Figure 1

Relative risk (RR) of hospital admissions due to extreme temperature in different lags by different sex and age groups; Percentile 99th was compared to reference value (OT). The plots a, b, c, d, e, f provides the RR for total, male, females, young and elderlies HAs, respectively.

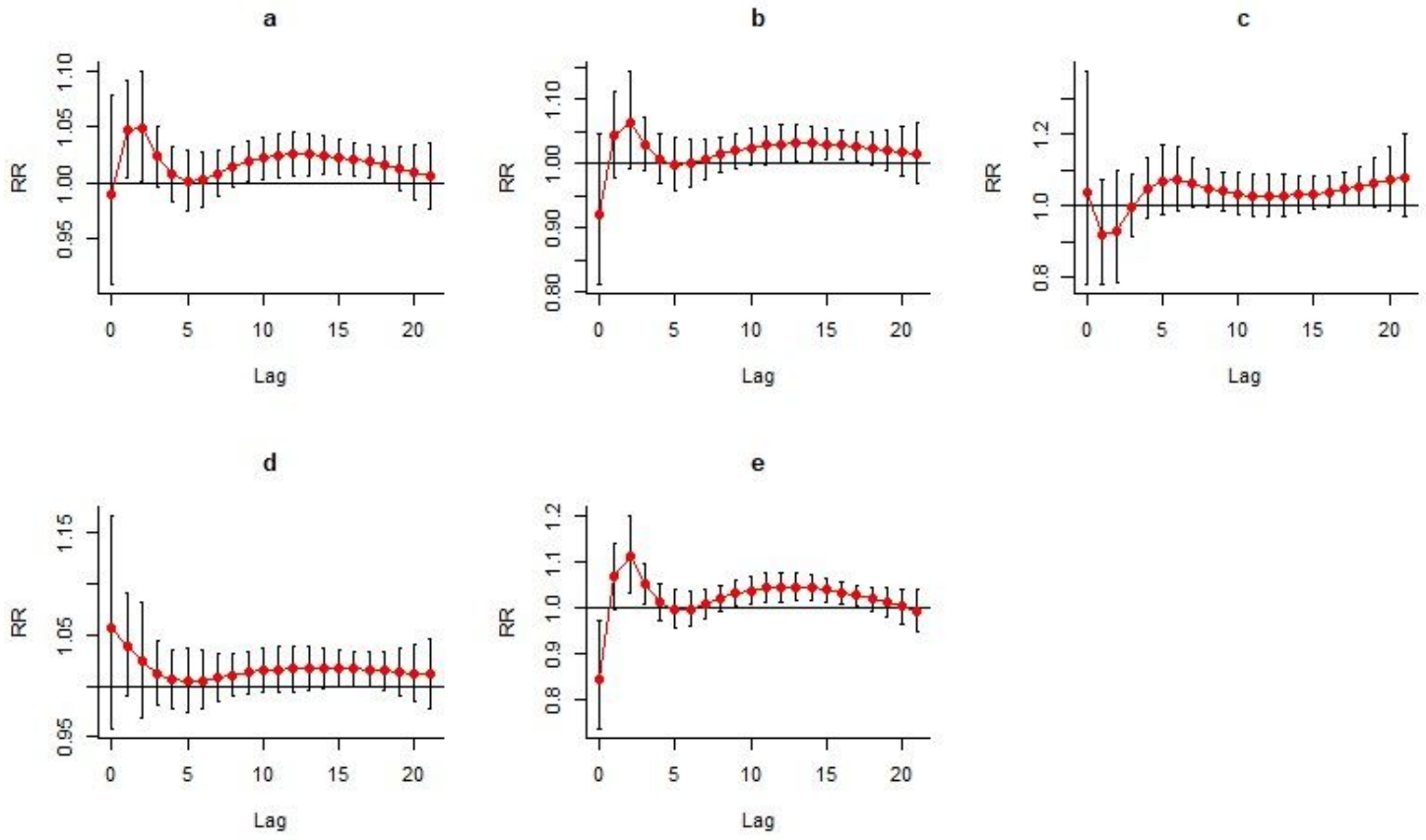

Figure 2

Relative risk (RR) of hospital admissions due to extreme temperature in different lags by different sex and age groups; Percentile 1th was compared to reference value(OT). The plots a, b, c, d, e, f provides the RR for total, male, females, young and elderlies HAs, respectively.

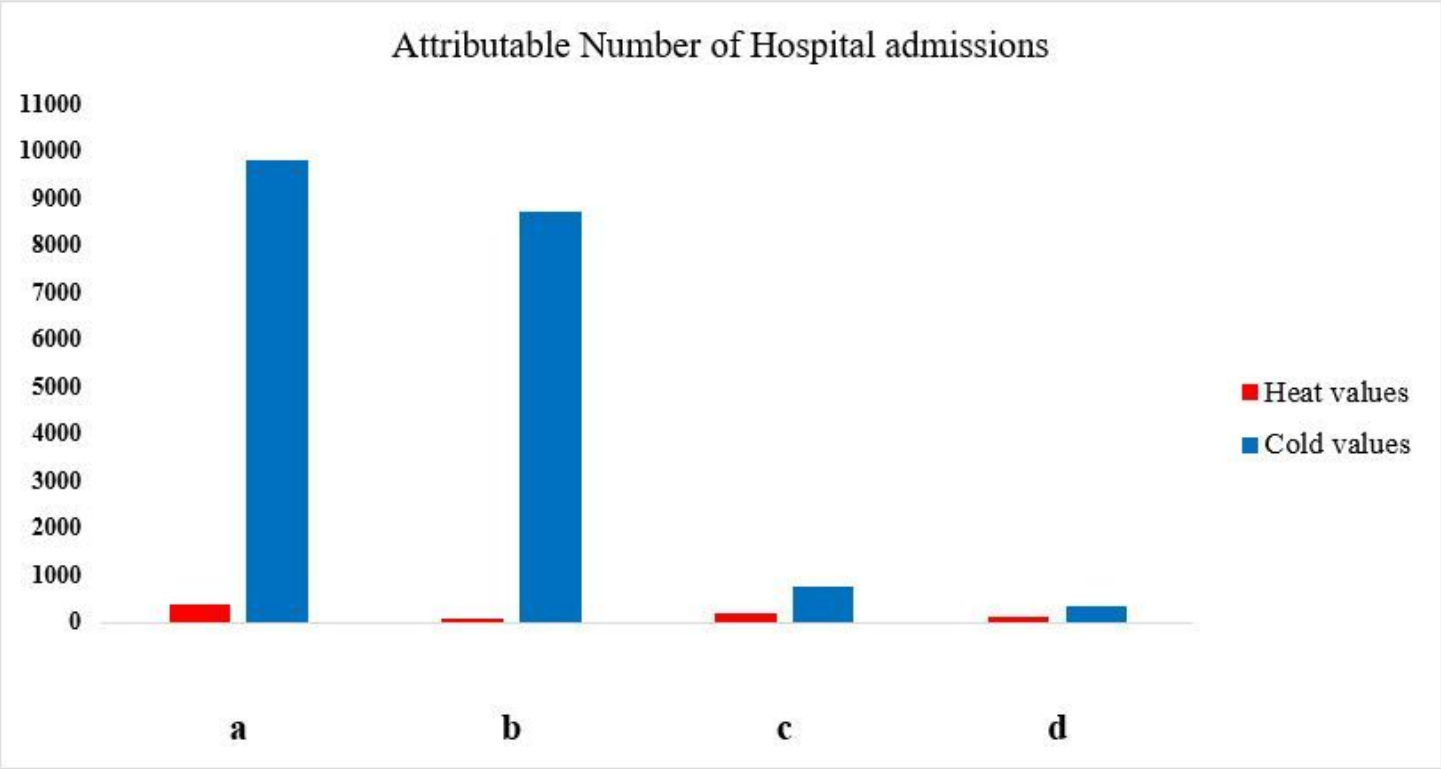

Figure 3

Number of HAs attributed to different levels of heat and cold; a represent the number attributed to all values of heat and cold. b, c, and d represent the number attributed to medium, high and extreme values of the events.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx