The association between apparent temperature and cardiovascular mortality in Puducherry, India: an exploratory study between 2010 and 2020

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Abstract

Background and aim

Climate change has far reaching consequences on all aspects of life, including health. Cardiovascular diseases (CVDs), the global leading cause of death, have also been found to be climate sensitive, mainly to temperature. However, the associations between CVDs and temperature are region-specific with relatively few studies focusing on low and middle-income countries. This study explores this association in Puducherry, a coastal district in the Eastern part India.

Methods

We analyzed the association between apparent temperature (T_{app}) and in-hospital CVD mortalities in Puducherry between 2010 and 2020 using a binomial regression model. We used a distributed lag non-linear model to capture the delayed and non-linear trends and identify the optimal temperature range for Puducherry. The results are expressed as the fraction of CVD mortalities attributable to non-optimal temperatures. We also performed stratified analysis to explore the associations between T_{app} and age and sex combined and different types of CVDs.

Results

We found that the optimal temperature range for Puducherry is between 33°C and 35°C with respect to CVDs. Temperatures both above and below the optimal temperature range were associated with an increased risk of overall in-hospital CVD mortalities, resulting in a U-shaped association curve. Up to 20% of the CVD deaths could be attributable to non-optimal temperatures, with a slightly higher burden attributable to cold (11.2%) than heat (9.1%). We also found that males above 60 years of age were more vulnerable to colder temperatures, while females above 60 years were more vulnerable to heat. Mortality with cerebrovascular accidents was associated more with heat compared to cold, while ischemic heart diseases did not seem to be affected by temperature.

Conclusions

We found the optimal temperature range for Puducherry to be higher than that previously reported for India as a whole, with a relatively high burden attributable to ‘cold’ temperatures, despite being an inherently hot region. Our study also identified the age and gender differences in temperature attributable CVD mortalities, which can be socio-cultural. Further studies from India could identify the regional associations and enhance the development of region and context specific climate-health action plans.

Background

Anthropogenic activity contributes to the accelerating pace of natural climate change leading to an increase in the frequency, intensity and impact of extreme weather events and a global rise in temperatures [1, 2]. The last decade has seen the highest temperatures recorded with 2016 and 2020 emerging as the hottest years on record [3].

Climate change has emerged as a threat to human health and a major public health challenge over the past few decades [4]. Indeed, the recent Global Burden of Disease Study showed that non-optimal temperatures are now among the top-10 leading causes of death globally [5]. Climate change and health research has recently expanded to include direct and indirect effects of temperature, mainly heat, on non-communicable diseases (NCDs) such as cardiovascular diseases (CVDs) [6–8].

CVDs is an umbrella term for a multifactorial group of diseases affecting the structure and function of the heart. They are the leading cause of death globally, claiming an estimated 17.9 million lives each year, accounting for 32% of global deaths [9]. Most CVDs are linked to lifestyle and environmental exposures such as smoking, alcohol and substance abuse, obesity, physical inactivity, stress, unhealthy diets, air pollution and noise. In addition, ethnicity, biological sex and age are also important factors driving the risk for the development of CVDs [9, 10].

CVDs are also climate-sensitive, with the risk of mortality or severe illness exacerbating with very high and low ambient temperatures [7, 11–14]. There are several mechanisms postulated to explain the increased risk of temperature-CVD mortality. The cardioregulatory response to heat stress involves an increase in peripheral circulation to allow for thermoregulation along with an increase in core body temperature. When the cardiac output cannot compensate for this, it results in heat intolerance leading to a CV event [10, 13]. Meanwhile, the cardiac workload increases as a response to cold, along with a sustained increase in systemic blood pressure, leading to CV dysregulation, primarily through vasoconstriction, which reduces both blood flow and oxygen supply to the heart [15].

The effects of temperature on CVDs are global, although the exact relationship varies by region, climate and population [7, 16]. A systematic review found that out of 34 studies on temperature-CVD associations, two-thirds (64%) were conducted in high-income countries with little research from low- and-middle income countries (LMICs), most of it being from The People's Republic of China [7]. With a lower adaptive capacity and relative lack of resources to face the challenge, understanding the regional temperature-CVD association in LMICs is a priority research area, especially as the burden of both extreme temperatures and CVDs is projected to increase in the future [17, 18].

India has already seen an increase in the burden of CVDs over the past decade with CVDs now being the leading cause of mortality and a major public health problem. Ischemic heart disease (IHD) has seen a 40% rise in the number of deaths reported between 2009 and 2019. Related CVDs like strokes or co-morbidities like diabetes have also become more prevalent over this period [19, 20]. It is therefore important to consider the role temperature might play as a CVD risk factor. The air surface temperature might rise by as much as 4.4°C by the end of the 21st century, based on the RCP 8.5 scenario, thereby posing a serious threat to many aspects of life, including human health [21].

The climate and socio-cultural diversity is one of the bigger challenges faced when studying climate-health relationships for India. There are six major Köppen-Geiger climate classification zones in India with temperatures ranging from > 0°C to < 40°C [22]. The socio-cultural differences between regions and communities is also an important factor determining health and vulnerability [23, 24]. For instance, coastal regions and densely populated urban areas are particularly vulnerable [25]. It is thus essential to study the regional temperature-CVD associations in India.

We conducted an exploratory study analysing the effects of apparent temperature (T_{app}) on CVD mortality in Puducherry, India. To our knowledge, there were no previous region specific studies done on the association between apparent temperature and CVD mortality in this region.

Methods

We analysed the fraction of in-hospital CVD-related mortalities attributable to T_{app}, the so-called 'fatal admissions' using a case-crossover design with a distributed lag non-linear model (dlnm).

Study area

Puducherry is a unique Union Territory (UT) in India, comprising of four erstwhile French colonies (i.e Puducherry District, Karaikal, Mahe and Yanam region). Puducherry and Karaikal lie on the eastern coast, within the state of Tamil Nadu, while Yanam, also on the east coast, is surrounded by the state of Andra Pradesh. Mahe lies on the western coast within the state of Kerala. The total area of the UT is 492 km^2 as seen in Fig. 1A.

Figure 1: Map showing the four districts of the Union Territory of Puducherry. A.) shows the location of the four districts that make up the Union Territory of Puducherry, namely Puducherry, Karaikal, Mahe and Yanam, spread out on either side of the coast of India. B.) Focuses on Puducherry district which is nestled within the state of Tamil Nadu with Andra Pradesh to the north (inlaid map). The shaded area in panel C.) highlights the non-continuous geographical area of Puducherry district.

This study focuses on Puducherry, which itself covers an area of 294 km^2 spread out over 4 non-continuous sub-districts or 'Taluks' as shown in Figure 1C. As per the Government of India census of 2011, the population of Puducherry is 950,289 with an almost equal distribution of males and females [26, 27].

Puducherry falls within the equatorial savannah with a dry winter climate type as per the Köppen-Geiger classification. The region has a tropical climate with a generally high relative humidity, which is around 80% during October to April and around 70% in June and July. The mean annual temperature is around 30^o C.

There are only two state government run tertiary care hospitals in Puducherry, out of which only the Indira Gandhi Government General Hospital and Post Graduate Institute (IGGGH) is a large, multispecialty general hospital with a cardiology department. Our project was limited to this main state government hospital serving the entire Puducherry district.

The unique characteristics of Puducherry added to our interest in focusing on it. First, there are no studies on this topic from this region. Second, as a small area with one main state-government multi-speciality hospital; the quality of the individual level patient data we were allowed access to was suitable for the exploratory study; and finally, as a coastal and one of the most urbanized cities of India, it is more vulnerable to the effects of climate change [27].

Health data

Daily hospital mortality records were obtained from the IGGGH for the four year period 2011–2020 (n = 7,190). Data included information on age, sex, date of admission, date of death, hours spent in hospital before death and cause of death.

For the period 2011–2015, mortality records were only available from the cardiology department (n = 633) in a non-digital format with several missing months due to fire damaged files, while records for 2016–2020 were in a digital format and included data from all hospital departments (n = 6,552). For this latter period, cases from all other departments that had a CVD involvement were identified and included in the analysis (n = 3,327). As cases were not classified by ICD codes, we went through all cases manually with a cardiologist consultant and classified them into categories. We adopted the categories of the ICD-10 codes as our classification to have 3 broad categories; namely (i) IHD; (ii) cerebrovascular accidents (CVA); and (iii) other. Other is comprised of cardiopulmonary diseases, hypertensive disorders, peripheral vascular disease, rheumatic heart disease, congenital heart disease, aortopathies and all other CVDs. A total of 3,960 mortality cases over the 10 year period with CVD involvement were included in the study. The codebook is presented in the supplementary material table 1.

Our main analysis was based on the aforementioned individual CVD mortality data. We also obtained the monthly hospital records for the entire hospital and cardiology department showing the total monthly admissions and deaths and presented it graphically to highlight the overall trends in hospital mortalities and admissions (Supplement Fig. 5). Missing records were assumed to be missing-at-random, since missingness was likely only related to time. As time was accounted for in our model, a complete case analysis should give unbiased estimates.

Meteorological data

Daily weather records from two weather stations serving Puducherry (i.e, Puducherry city and Cuddalore) covering the period 2010–2020, were obtained from the Indian Meteorological Department (IMD). The variables included maximum temperature (T_{max}), minimum temperature (T_{min}), average wind speed (AW), dry bulb temperature (DBT), relative humidity (RH) and vapour pressure (VP).

We chose to use T_{app} as the main exposure variable of interest as it also accounts for the effect of RH and VP along with temperature, thereby better capturing the physiologically 'felt' exposure. An average T_{app} for Puducherry was calculated by combining individual station data with the Steadman's equation [28], as follows:

$$T_{APP} = Ta + 0.33 \times hPa - 0.7 \times WS - 4$$

$$hPa = \frac{RH}{100} \times 6.105 \times e^{\left(\frac{17.27 \times Ta}{237.7 + Ta}\right)}$$

where Ta is the dry bulb temperature (^{o}C), hPa is the VP, RH is the relative humidity (%) and WS is the wind speed (m/s).

Statistical model

Our model consisted of the self-matched case-crossover design using dlnm, as described in [29] to capture the non-linearity and delayed association between T_{app} exposure and risk of in-hospital CVD mortality (hereon referred to only as CVD mortality). As our dataset consisted only of patients who died in hospital, we chose to use the day of admission as our main 'event' since there was no way to determine environmental exposure (presence or absence of air conditioning), medical treatments administered prior to death or other prognostic factors that might have differed between out-of-hospital and in-hospital days. Our study therefore focussed on the association between T_{app} and the risk of 'fatal CVD admission' following hospitalisation.

We used a time-stratified approach in which each case of mortality served as its own control, with the comparable control days being matched by the same day of the week within the same month to generate a sample size of 17,352 cases and controls used in the final model. We chose to model the T_{app}-CVD mortality risk over 21 days as done in other similar studies [22]. We constructed the crossbasis by creating a lag matrix over 21 days using the whole T_{app} series, which was matched with the cases and bi-directionally sampled controls. For modelling the lagged effects, we used a natural cubic spline with 3 internal knots placed equally on the log scale to model the lag-response and capture long term lags as well as any short term harvesting. This was to allow for consistency and comparability with similar studies done previously [22]. The exposure-response association was similarly modelled with a natural cubic spline with 2 knots placed at the 25th and 75th percentile of the local temperature using a binomial likelihood within the dlnm package. A time-stratified design was adopted to regulate potential timeinvariant confounders (e.g., age and sex) using self-control and limit bias from temporal confounders (e.g. secular trend, seasonality, day of the week effects, etc.) and exclude long-term impact of air pollutants.

Our study is explorative in nature. We expressed risks in relation to the minimum mortality temperature (MMT). The MMT was derived from the point on the cumulative exposure-response curve with the lowest associated risk of mortality. This value was also used to centre the overall cumulative exposure-response and also considered to be the optimal temperature. We have reported our findings as the fraction of CVD mortalities which can be attributed to temperature, or the attributable fraction (AF). The total number of deaths attributable to non-optimal temperatures, both hot and cold was calculated using the MMT as a reference with a backward perspective. The ratio of the number of deaths during MMT to the total number of deaths gives us the AF [30]. We feel this measure is better suited to show the general trend for how temperature affects CVD mortalities in Puducherry. Additionally, to limit spurious values at the extremes we have restricted plots and analyses to the central 95th percentile of the T_{app} distribution.

Subgroup analysis

Age and sex

We performed subgroup analyses with stratifications for age and sex combined. The age categories used were above and below 60 years of age to account for post-menopausal women.

CVD class specific

We stratified the analyses by type of CVD using 3 main classes: (i) IHD; (ii) CVA; and (iii) all other CVDs. Many cases presented with multiple classes of CVDs and since the dataset did not contain ICD-10 codes, there was no way to know the primary cause of death. Such cases were considered in all the CVD classes they presented with and therefore, this cause-specification is patients who died with the particular CVD as opposed to from.

Sensitivity analysis

Sensitivity analyses were performed to explore the impact of different numbers and placement of knots, changing the regression to quasi-Poisson, excluding patients who stayed in hospital for longer than 10 days and also using only 5 years of data (2016–2020). The results are presented in Supplement Figs. 1–4.

All data were analysed using a combination of Microsoft Excel 2016 and the R software (version 4.0.3, The R Foundation for Statistical Computing Platform 2020). The main packages used were '*dlnm*' to fit the dlnm model and '*attrdl*' for the attributable fraction [29]. R scripts for the analyses will be available on GitHub.

Results

Descriptive statistics

Out of the 3,960 cases of in-hospital mortality with a CVD involvement between 2011 and 2020 that were included in this study, the average patient spent 4 days in hospital. There is no data on whether these were emergency visits or planned visits. More than half (54%) of patients died within 48 hours of being admitted to the hospital.

Table 1: Table of descriptive statistics showing the distribution of the climate data and patient data. NA denotes missing information.

Climate variables		
	Mean (Min,Max)	**SD**
Average Temperature (°C)	29 (19.6,35.78)	2.6
Humidity (%)	76.6 (43, 100)	3.4
Apparent Temperature (°C)	33.4 (23.3,40.6)	8.6
Patient data		
	Count	**% of total**
Gender		
Male	2,366	59.70%
Female	1,591	40.20%
NA	3	0.10%
Age category (years)		
<60	2,581	65.20%
≥60	1,376	34.70%
NA	3	0.10%
State		
Puducherry	3,064	77.40%
Tamil Nadu	879	22.20%
Andra Pradesh	7	0.20%
Other/NA	10	0.30%
Time in hospital		
<48h	2,121	53.60%
>48h	1,839	46.40%
Mean days (min, max, SD)	4 (1, 82, 4.9)	
Comorbidities		
Yes	2,176	54.90%
No	1,784	45%

As seen in Table 1, the mean dry bulb temperature and humidity for Puducherry was around 29°C and 76%, respectively. The mean T_{app}, which takes both of these into account along with VP and WS was slightly higher in Puducherry between 2010 and 2020, around 33°C. Two thirds of the patients were older than 60 years (65.2%). More males than female patients died of a CVD related mortality. Over 50% of patients in this study also had at least one co-morbidity associated with CVDs, namely hypertension, diabetes or alcoholism.

Overall cumulative exposure-response and AF

Figure 2 shows the relative risk (RR) estimates for the association between T_{app} and CVD mortality, cumulatively across the 21-day lag period, and the temperature distribution with the MMT and heatwave threshold as defined by the Indian Meteorological Department (IMD) [31]. The association shows a distinct U-shaped curve cumulatively across the entire 21-day lag period days with temperatures below and above the MMT showing an increased RR of in-hospital CVD mortality. The MMT itself is 34.2°C. The temperature distribution shows that the MMT is close to both the median and mean T_{app} (34°C and 33.4°C, respectively).

The optimal temperature corresponds to the MMT and can be thought of as the temperature with the least associated risk of in-hospital CVD related mortality. Here, all temperatures below and above 34°C will be considered 'cold' and 'hot', respectively.

Table 2: The overall AF attributable to non-optimal temperatures in Puducherry, to cold Tapps and hot Tapps with the 95% CI.

	Attributable fraction (%)	95% CI (%)
Non-optimal T_{app}	20.2	7.0 - 29.7
Cold T_{app}	11.2	-2.2- 20.2
Hot T_{app}	9.1	0.9- 15.2

Overall, 20.2% (95% CI 7.0-29.7%) of the in-hospital CVD related deaths can be attributed to non-optimal temperatures within the study period (Table 2). Out of these, colder temperatures have a higher burden with 11.2% of deaths (95% CI -2.2-20.1%) attributable to cold as compared to 9.1% (95% CI intervals 0.9-15.2%) of deaths being attributable to heat.

Exposure-lag-response association

Figure 3 represents the lagged response association for the 5th (27.3°C) and 95th (38.0°C) percentile of the T_{app} distribution over a 21-day period.

Colder temperature has an almost immediate response or increase in RR, while hot temperatures show a delayed association. The cold effect peaks at day 1 before gradually decreasing to a protective risk at lag day 5 (with no statistical significance). The cold-CVD mortality association risk then increases slightly again from around day 7 to day 16 where it peaks around day 11 as seen in Figure 3a. Hot temperature related risk of CVD-mortality is only seen after a 5-day lag period, with an initial protective effect, and persists for 16 days, although the confidence intervals are quite wide as shown in Figure 3b. This risk is relatively lesser compared to the cold-CVD mortality risk.

Age and sex

In order to better understand this association in different groups, we performed age-and-sex stratified analyses. Sex and age group both seem to be a contributing factor to the risk temperature related CVD mortality, as seen in Figure 4.

Males both above and below 60 years of age seem to be unaffected by heat (Figure 4a and b). Females below 60 years of age are affected by both heat and cold, although the heat effect is predominant (Figure 4c). Females over 60 years are unaffected by cold with the RR driven entirely by heat.

We found that males of all ages are at a relatively similar risk for temperature attributable CVD mortality (Table 3). Females below 60 years have a higher AF to non-optimal temperatures compared to older females, primarily since they are also sensitive to cold. Females over 60 years are unaffected by cold and their AFs are mainly heat related.

Table 3: The AF for CVD mortality attributable to overall non-optimal temperatures, cold and hot non-optimal temperatures for males and females above and below the age of 60 years.

Sex and age (years)	AF% (95% CI)	Cold AF% (95% CI)	Hot AF% (95% CI)
Males below 60	11.81 (-14.88- 27.2)	15.32 (-7.31- 28.6)	-3.54 (-23.15- 10.02)
Males over 60	12.85 (-8.62- 26.93)	16.91 (-3.39- 28.6)	-4.16 (-19.68- 6.82)
Females below 60	23.21 (-32.86- 41.93)	3.15 (-56.42- 27.52)	20.01 (3.47- 29.38)
Females over 60	8.63 (-22.44- 27.47)	-6.62 (-46.69- 14.22%)	15.2 (5.56- 22.29)

CVD class specific

Stratified analyses for the type of CVD revealed that IHDs do not seem to be particularly affected by heat and minimally affected by cold, as shown in Figure 5a. For CVAs, cold temperatures affect the risk of mortality less than heat while all other CVDs combined are affected by both heat and cold. All other forms of CVDs seem to display the same U-shaped association seen in the cumulative association (Figure 5c). As such, the results shown here are of patients who died with that particular
CVD as opposed to from that particular CVD.

Discussion

Through this study, we found and characterised a general trend for a lagged, non-linear association between T_{app} and in-hospital CVD mortalities in Puducherry, India. We found that the MMT temperature over the study period for Puducherry was approximately 34°C, with respect to CVDs, corresponding to an optimal temperature range between 33°C and 35°C. The MMT occurred at around the 60th percentile of the T_{app}.

The overall temperature-mortality association follows a U-shaped curve as described previously with both cold and hot T_{app} contributing to increasing the risk of CVD related mortality attributable to non-optimal temperatures with respect to the MMT [32-34]. While the overall AF for temperature was 20.2%, majority of it was attributable to cold non-optimal temperature (11.2%) and only 9.1% could be attributed to hot non-optimal temperature. This seems to be in line with similar studies from around the world as seen in a study spanning 750 locations across 43 countries found that out of 9.4% of all-cause excess deaths attributable to non-optimal temperatures, 8.5% were cold related while 0.9% were heat related [35]. Thus, it is important to consider cold exposure as an important contributor to mortality, even in inherently hot regions like Puducherry.

We found that cold exposure had a bi-level response with a sharp, immediate increase in mortality risk followed by a brief protective effect that then culminated in a second peak of increased risk in CVD mortality, most likely due to the long-term effects of cold. On the other hand, heat exposure showed a 4-to-5 day lag before contributing to the CVD response. This differs from other studies, which found an immediate effect due to heat and a more lagged cold response [22, 32, 36, 37]. The harvesting effect or mortality displacement, when the most vulnerable people are affected earlier than the healthier members of the population, thereby bringing mortality forward in time, could explain the immediate increase in cold related mortalities followed by the slightly reduced risk till about lag day 7 [38, 39]. Since the average T_{app} in Puducherry is 34°C, the population is likely more adapted to temperatures above 30°C. Repeated exposures to temperatures above 30°C, considered as hot in many places around the world, could induce a form of thermal pre-conditioning. This sub-lethal, frequent heat exposure could help to build tolerance and confer protection against further lethal thermal stress brought on by extremely high temperatures [13]. The thermal pre-conditioning effect has been found to set in within hours of exposure and can last up to 5 days, possibly explaining the 5-day lag seen for hot temperatures in Puducherry [40].

Additionally, there is a greater proportion of 'cold' days compared to 'hot' days or 'extremely hot' days. The Indian Meteorological Department as several definitions of heatwaves. For the coastal regions, a heatwave is declared when the maximum temperature rises above 37°C and is a departure of 4.5°C or more from the normal temperature [31]. There are few days with temperatures this high in Puducherry. In addition, there are relatively few consecutive 'extremely hot' days, while there is often a cold spell lasting for several days, especially during the winter months, causing people to suffer more, especially if they are unaccustomed to it. Indoor heating systems are also uncommon in the southern part of India where temperatures rarely drop below 20°C. However, the IMD definition of a cold wave in coastal areas is when the minimum temperature is <15°C or a departure of 4-5°C from minimum temperature, meaning that there has been no cold wave recorded in Puducherry for several years [41, 42]. Thus, our results also highlight the importance of regionally defining cold and heat from a health perspective using the MMT. Puducherry is one of the most urbanized territories in India with 68.3% of the population considered as urban according to the 2011 Census [27]. Typical urban characteristics that modify the temperature effect on health, such as tightly packed spaces and living quarters, population density, air pollution and green spaces, might contribute to the overall relatively high heat AF we found [43].

One of the advantages of using the case-crossover method was that we were able to identify the differences in the temperature-CVD mortality association between sexes and age simultaneously, which to our knowledge has not been identified in the Indian context before. Our results demonstrate that age and sex together act as effect modifiers. All males were more susceptible to cold compared to heat. Males aged above 60 years were more vulnerable to cold non-optimal temperatures than females in the same age bracket, who were more susceptible to hot non-optimal temperatures and seem to withstand cold better. Meanwhile, females below 60 years were affected by both hot and cold non-optimal temperatures. We postulated several possible explanations for this phenomenon. Overall, age is a common risk factor for CVD mortality with older people, especially women, being more susceptible [13, 44-47]. Most women over the age of 50 years have undergone menopausal transition, which has long been associated with decreased cardio-protection and an increase in the risk of developing CVDs and vulnerability to heat [48]. Sex differences in thermoregulation could also be a factor for these findings. For example, the temperature threshold, above which sweating is induced, is higher in women than in men while their overall sweat output is lesser, resulting in reduced heat tolerance [49, 50]. On the other hand, men have found to have a greater decrease in core body temperatures when exposed to cold compared to women, leading to a higher cold intolerance or sensitivity [51, 52]. A study by Achebak *et al.* in Spain reported a similar relationship between older females and males being more susceptible to CVD mortality from heat and cold respectively [53]. The context of Puducherry might also play a role. Many of the men could be engaged in manual outdoor labour including agriculture and construction, helping them build tolerance to higher temperature. Traditionally, females, especially older females, are more likely to spend a larger part of the day indoors where the urban island effect, inadequate air conditioning and physiological factors could make them more vulnerable to heat [54]. There is need for further studies to be done on this topic in Puducherry to identify the extent to which age and sex together act as effect modifiers for the association between temperature and CVD mortality.

The findings from our cause-specific analysis compare to a recent study by Schulte *et al.* in Switzerland which found limited risks of temperature attributable risk of myocardial infarction (part of IHD in our study), with a protective heat effect [46]. They also found the risk of mortality from strokes (CVA in our study) increases with heat. The findings are also similar to the Fu *et al.* study from India, which found a protective effect for IHD with heat and smaller cold-attributable risk in addition to a U-shaped curve for CVAs as seen in Figure 5 of our study [22].

Many studies look at the temperature-mortality association, but few look at CVDs in particular. The MMTs for all-cause mortality are derived as a function of disease-specific MMT [16]. In fact, temperature-CVD mortality associations have been found to be U or J-shaped while various patterns including the inverse U or reverse-J shape have been associated with infectious diseases [32, 33, 55, 56].The association between temperature-CVDs also varies by region and latitude, with different regions within a country reporting different relationships [16, 32, 57, 58]. For example, a study from Tianjin found a 1^{o}C increase in temperatures above the MMT of 25.1^{o}C associated with a 2.8% increase in CVD deaths while in Brisbane, Australia, a 1^{o}C rise above the MMT of 24^{o}C lead to an increase in CVD mortality by 3.5% [36, 59]. While most studies have found an increase in CVD events due to heat exposure, a study done across China found that the bigger burden of CVD mortality can be attributed to cold temperatures [32]. Therefore, a one-measure-fits-all approach cannot be used to describe the temperature-CVD mortality or all-cause mortality relationship [58].

As of 2016, 28.1% of all deaths in India were due to CVDs as compared to 15.2% in 1990 and this burden is projected to increase along with the level of epidemiological transition (ETL) [60]. Puducherry falls in the higher-middle ETL bracket with 53.1% of deaths below 70 and 46.9% of total deaths above 70 years due to CVDs [60], making it a severe public health issue.

We found few studies that looked at the temperature-mortality association in India; however, none of them were from Puducherry. In addition, only one paper by Fu *et al.* considered CVDs separately but this focused on the Köppen-Geiger climate regions pan-India and therefore could not represent the microclimatic associations and capture the aforementioned regional trends [22]. The association they found between temperature and all-cause mortality is consistent with the U-shaped association we found considering the same temperature range, with cold-related deaths having a higher AF than heat. Their model predicted a MMT of 30^{o}C for the entire country with a mean temperature range of 0.4^{o}C to ~40^{o}C, which when compared with our model MMT of around 34^{o}C and a smaller temperature range, highlights the microclimatic, socio-cultural and demographic effects on acclimatization and mortality [22].

While there are relatively fewer “heat wave” days in Puducherry, if the warming trend continues as projected, the temperatures for Puducherry could increase or lead to erratic extreme temperatures. It could lead to either a potential right-shift of the optimal temperatures, if this occurs gradually or a significant increase in the AF for CVD mortality due to hot temperatures if there are more erratic extreme days. For example, a study from Hyderabad, a city with higher mean temperatures than Puducherry, found an increase in all-cause mortality by 16% and 17% for maximum temperatures above 40^{o}C and heat index > 54^{o}C respectively [61]. The pattern of anthropogenic climate change over India is a complex one. Mean temperatures in the South Asian region have been decreasing in the past decades and India has not seen an increase in the maximum temperature trends since the 1970s [35, 62]. From a health perspective, T_{app}, which accounts for humidity, is better at measuring the health effects. The increase in humidity in India has led to T_{apps} increasing in India and thereby the severity and occurrence of heat has increased [62]. In the future, pollution control measures and a slower pace of irrigation expansion will likely counter the present cooling effects being seen and as humidity is projected to increase, the net effect will be a gradual rise in hot temperatures, especially during heat waves [62]. It is difficult to assess whether the rise in temperatures might be accompanied by a decrease in the AF for cold-related mortalities or whether only the severity and frequency of heat waves will increase. The absolute number of CVD mortalities attributable to non-optimal temperatures are likely to increase, however, since more people will be at risk or have CVDs in the future.

A recent multi-country, multi-community study found that most excess deaths occur in eastern/southern Asia, especially in coastal cities, highlighting the difficulties to protect, react and reduce adverse temperature effects in these regions, partially due to the large and dense population [35]. As there are several large cities both within this region and along the extensive coastline of India, it is imperative that further research is done on how temperature affects the health of the local population. There is also a need to develop a tailored temperature-health impact management and adaptation plan to reduce the burden of CVD mortalities due to non-optimal temperatures that accounts for regional demographics. These preliminary estimates can be used as a basis to support further detailed research on this topic in Puducherry or elsewhere.

Strengths

Our study has several strengths. First, it demonstrates how both relatively cold and hot temperatures affect CVD mortality in the tropical region of Puducherry. The high quality of patient level data allowed for examining the effects of age-and-sex grouped together, which has not been explored in the Indian context. It highlights the added vulnerability of older women to extreme heat. Second, the case-crossover approach adjusted for stable within subject and residual individual confounders, particularly from variables that may not have been recorded, by design and allowed us to preserve individual characteristics. We could thus conduct individual-level and inter-individual analysis through subgrouping. Third, ss this is the first study of its kind in this region, we were able to show how regional and demographic variations play an important role in determining the fraction of CVD mortalities attributable to non-optimal temperatures over a relatively long time period. Additionally, the small size of Puducherry coupled with a single multi-speciality state government hospital and robust health system means that we were able to capture the general trends from the main state government hospital which caters to majority of the population within Puducherry. Finally, we were able to demonstrate that cold temperatures have a larger AF to CVD mortalities compared to heat, consistent with other Indian studies as shown. Overall, our study is comparable to global studies from different climate zones and areas, implying a greater contribution of population, genetics and acclimatization to the temperature-CVD mortality relationship. The results from our sensitivity analyses using only 5 year data from the whole hospital, or changing the knot placement were all insensitive to the changes in the model, supporting the robustness of our findings about the association in Puducherry.

Limitations

The study has several limitations that we offer for consideration. The small sample size that we managed to obtain greatly reduces the certainty with which we can draw inferences, particularly regarding subgroups. Since the data comes from a state-run government hospital, we cannot account for patients of a higher socio-economic stratum or those who might have chosen to seek treatment in a private hospital or travelled to neighbouring states. We also did not include air pollution in our study, although temperature has been shown to have a relationship that is independent from the effects of air pollution. This study assumes that the effects of temperature on CVD mortality are through an acute exposure (the effect on CVD is assumed to only happen over the 21 day-lag that was modelled) as opposed to the chronic nature of temperature exposure. Finally, as there is no way to separate the temperature effects on the CV system from the medical interventions or hospital conditions that might counter the actual effects and work to prolong life, used the outcome of ‘fatal admission’ as opposed to simply mortality, as is commonly used.

This allowed us to assume that exposure lasted only until hospital admission, following which treatments and climate control in the hospital could be expected to modify the exposure-mortality association, especially since patients who were admitted for more than 48 hours spent an average of 7 days in hospital before dying. We have performed sensitivity analysis including only those who spent a maximum of 10 days in hospital (Supplement Figure 7). While we tried to assess the cause-specific risk of morality, there were some limitations, for example as most of the patients presented with multiple CVDs, the overall risk from individual CVDs cannot be confidently assessed and there is likely a mixed effect.

Conclusion And Recommendations

Our exploratory study highlighted the burden of CVD mortality within hospitals attributable to non-optimal temperatures. We found the MMT for Puducherry differs from the MMT reported at the national level, pointing towards a need to follow up with larger, regional studies. For Puducherry, the MMT is around 34^{o}C and more deaths can be attributed to colder temperatures than heat. Females over 60 are more vulnerable to heat while men are more affected by cold. If the warming trend over India continues, heat will likely become a bigger challenge for public health and increase the increase vulnerability of females. As such, public health interventions need to be contextually and gender tailored for the local population and need to address the cold-impacts as well as the heat-impacts, even in tropical regions. In addition, optimal temperatures should be the measure used against which ‘cold’ and ‘hot’ are refined for a region.

Finally, we feel that there needs to be an increased awareness about the health impacts of climate change. Research is one of the main ways to raise awareness and ensure measures such as healthcare system preparedness, early warning systems, climate resilient infrastructural developments and urban planning are taken. It can also contribute to the development or enhancement of climate informed health policies. . There is also an urgent need to have central, individual level, health registers which can be accessed for research. Overall, we hope this study will lead to bigger regional studies that can confirm the exploratory associations we have identified here.

Abbreviations

1. AF- Attributable fraction
2. AW- Average wind-speed
3. CV- Cardiovascular
4. CVA- Cerebrovascular accidents (also commonly referred to as cerebrovascular disease)
5. CVD- Cardiovascular diseases
6. DBT- Dry bulb temperature
7. Dlnm- distributed lag non-linear model
8. hPA- vapour pressure (in the context of the Steadman’s equation)
9. ICD-10- International classification of diseases
10. IGGGH- Indira Gandhi Government General Hospital
11. IHD- Ischemic heart disease
12. IMD- Indian Meteorological Institute
13. LMIC- Low and middle income countries
14. MMT- Minimum mortality temperature

15. NCDs- Non-communicable diseases
16. RCP- Regional concentration pathway
17. RH- Relative humidity
18. Ta- Dry bulb temperature (in the context of the Steadman's equation)
19. T_{app}- Apparent temperature
20. T_{max}- Maximum temperature
21. T_{min}- Minimum temperature
22. UT- Union Territory
23. VP- Vapour pressure
24. WS- wind speed (in the context of the Steadman's equation)

Declarations

Author contribution statement

S.S, M.R, M.A.D, J.U and G.C conceptualized and planned the study. S.S and R.L acquired and provided access to the data. S.S, H.P and A.G designed and carried out the modelling and statistical analysis. S.S wrote the main manuscript with inputs from H.P. The manuscript was revised by all authors.

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Competing interests

The authors declare that they have no competing interests

Availability of data and materials

The health data that support the findings of this study are available from the Puducherry Department of Health but restrictions apply to the availability of these data which is not publicly available. Data are however available from the authors upon reasonable request and with permission of the Puducherry Department of Health with ethical permissions from an Indian ethics review committee.

The meteorological data used in this study is available from the Indian Meteorological Department, upon request, from their Climate Data Service Portal (https://cdsp.imdpune.gov.in/)

Ethical approval

This study was approved by the Institute Ethics Committee (Human Studies) of the Indira Gandhi Medical College and Research Institute (A Govt. of Puducherry Institution); No. 318/IEC-31/IGM&RI/PP/2021 and by the Ethics Committee Northwest and Central Switzerland (EKNZ); Statement ID- AO_2020_00034

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Figures

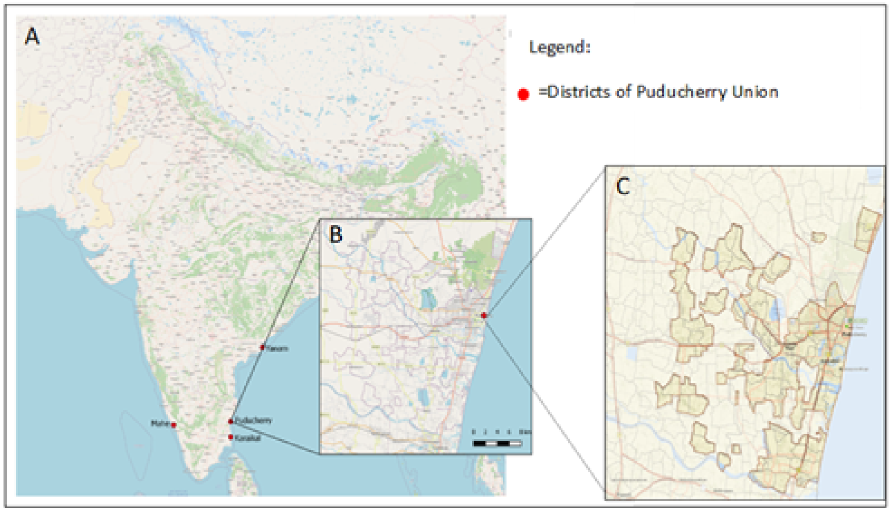

Figure 1

Map showing the four districts of the Union Territory of Puducherry. A.) shows the location of the four districts that make up the Union Territory of Puducherry, namely Puducherry, Karaikal, Mahe and Yanam, spread out on either side of the coast of India. B.) Focuses on Puducherry district which is nestled within the state of Tamil Nadu with Andra Pradesh to the north (inlaid map). The shaded area in panel C.) highlights the non-continuous geographical area of Puducherry district.

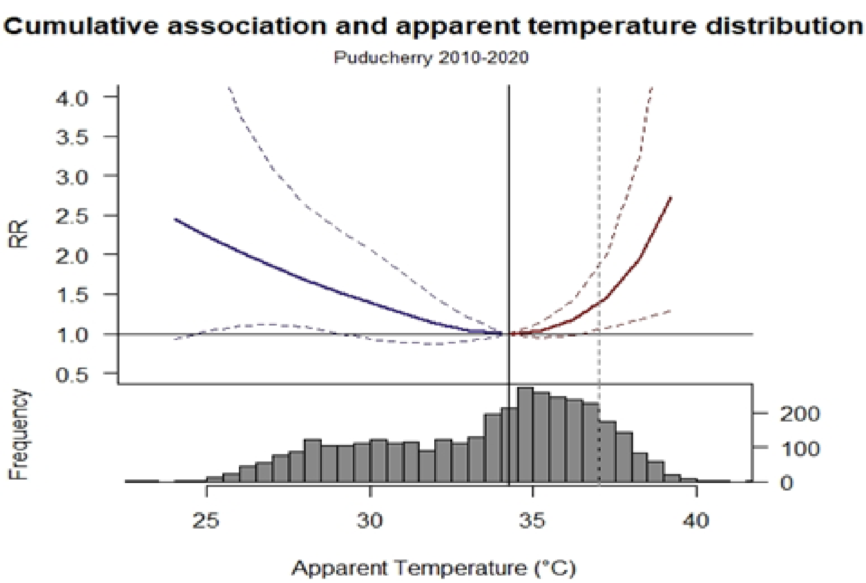

Figure 2

Cumulative T_{app}-CVD mortality RR with a 21-day lag (dotted lines show the 95% CI) with a histogram of the T_{app} distribution for Puducherry between 2010 and 2020. The black solid vertical line represents the minimum mortality temperature (MMT), while the dotted grey line represents the heat wave threshold at 37^{o}C. The blue line and red line represent the exposure-response curve for cold and hot temperature relative to the MMT respectively.

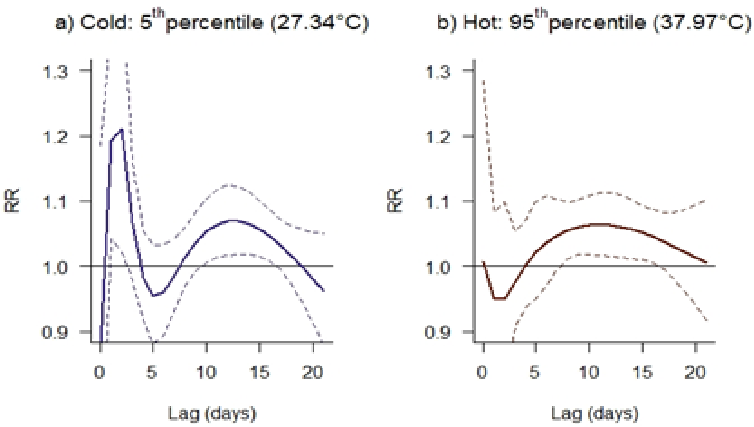

Figure 3

The RR for the lagged T_{app}-CVD mortality association at the 5th and 95th percentiles of the T_{app} range. a.) The blue line represents the cold temperature at 27.3°C and b.) The red line represents the hot temperature at 38.0°C. The dotted lines represent the 95% CI. Graphs are restricted to the central 95% of temperature due to wide CIs at the extreme ends.

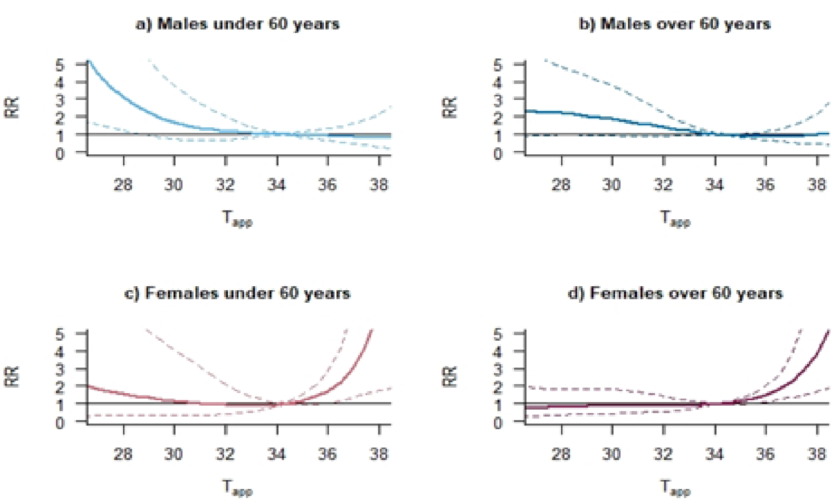

Figure 4

The RR of Tapp attributable CVD mortality among a) males under 60 years, b) males over 60 years, c) females under 60 years and d) females over 60 years. Graphs are restricted to the central 95% of temperature due to wide CIs at the extreme ends.

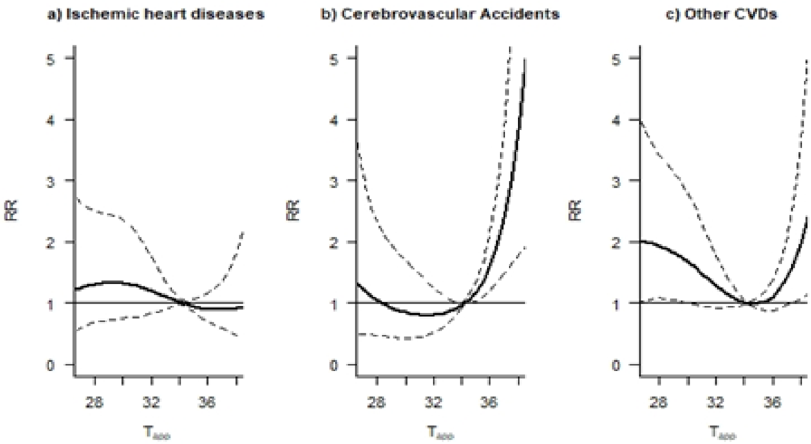

Figure 5

Cause-specific Tapp-mortality association for patients who died with a.) Ischemic heart diseases, b.) Cerebrovascular accidents and c.) All other types of CVDs. The graphs have been restricted to the central 95th percentile of the Tapp range.

Supplementary Files

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- 250422Supplementarymaterial.docx