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A New Method to Estimate Heat Exposure Days and Its Impacts in China

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Abstract: Understanding the spatiotemporal trends of temperature in the context of global warming is significant for public health. Although many studies have examined changes in temperature and the impacts on human health over the past few decades in many regions, they have often been carried out in data-rich regions and have rarely considered acclimatization explicitly. The most frequent temperature (MFT) indicator provides us with the ability to solve this problem. MFT is defined as the longest period of temperature throughout the year to which a human is exposed and therefore acclimates. In this study, we propose a new method to estimate the number of heat exposure days from the perspective of temperature distribution and MFT, based on the daily mean temperature readings of 2142 weather stations in eight major climate zones in China over the past 20 years. This method can be used to calculate the number of heat exposure days in terms of heat-related mortality risk without the need for mortality data. We estimated the distribution and changes of annual mean temperature (AMT), minimum mortality temperature (MMT), and the number of heat exposure days in different climate zones in China. The AMT, MMT, and number of heat exposure days vary considerably across China. They all tend to decrease gradually from low to high latitudes. Heat exposure days are closely related to the risk of heat-related mortality. In addition, we utilized multiple linear regression (MLR) to analyze the association between the risk of heat-related mortality and the city and its climatic characteristics. Results showed that the number of heat exposure days, GDP per capita, urban population ratio, proportion of elderly population, and climate zone were found to modify the estimate on heat effect, with an R^2 of 0.71. These findings will be helpful for the creation of public policies protecting against high-temperature-induced mortalities.

Keywords: heat exposure days; most frequency temperature; climate change; temperature distribution; climate zone

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1. Introduction

Global climate change not only causes ambient temperature to increase, but also changes the intensity, frequency, and duration of extreme weather events, such as heat waves, and temperature distribution [1–3]. The IPCC (2018) reported that, if the current greenhouse gas emission rate continues, by 2040, global mean temperatures may increase as much as 1.5 °C higher than mean temperatures before the industrial revolution [4]. Importantly, changes in temperature vary considerably across regions. In recent years, temperature change in China as a result of climate change has attracted a great deal of attention. Many studies revealed changes in temperature and extreme weather events over the past few decades [5–8]. Their choice of heat threshold has generally followed two approaches: (1) exceedance of fixed absolute values (e.g., 35 °C) or (2) deviation from normal. These approaches have a limitation in that they are based on statistical associations without explicit physical meaning. A population's adaptation to temperature is rarely explicitly considered.

Ambient temperature and human health are closely related. Many studies have revealed that the associations between temperature and human mortality account for non-external causes. They exhibit U-shaped, V-shaped, or J-shaped curves [9–11], with the minimum mortality temperature (MMT) reflecting the most optimum temperature. Outside the MMT, a higher or lower temperature may lead to higher morbidity and mortality rates. Although many studies have investigated the effects of climate change on health based on the relationship between temperature and mortality, these studies have usually been based on case studies in very few data-rich regions [12–16]. Likely due to the validity of the data, there is limited evidence regarding the distribution of heat exposure on a national or global scale in terms of heat-related mortality risk under climate change.

The most frequent temperature (MFT) indicator provides us with the ability to solve these problems. Temperature distribution over a full year in any region is characterized by moderate temperatures occurring more frequently than extreme temperatures (such as heat waves or cold waves). Specifically, the temperature distribution histogram shows a peak or two peaks at a certain moderate temperature; MFT is the temperature of this peak. By analyzing the MMTs in 420 locations covering six continents (excluding Antarctica) around the world, our previous study found that although the MMT varies considerably across regions, it is very close to the local MFT in the same period [17]. The association between MFT and MMT did not change when we adjusted for GDP/capita, latitude, and study year. Darwin's theory of evolution states that "species have evolved principally via natural selection, and living forms evolved to improve themselves to better fit with the environment". Human biological evolution is a process of pursuing self-advantage [18]. MFT is defined as the longest period of temperature to which a human is exposed and therefore acclimates. Adapting to MFT can be considered pursuant to self-advantage maximization in terms of temperature.

Therefore, in this study, we proposed a new method based on MFT from the perspective of temperature distribution throughout the year to estimate the number of heat exposure days. This method allowed us to calculate heat exposure days in terms of heat-related mortality risk without the need for mortality data. In addition, we estimated its impact on the risk of heat-related mortality. Our research has important implications for the development of more comprehensive and more accurate policies on heat warning.

2. Materials and Methods

2.1. Meteorological Data

The daily mean temperatures in 2142 locations in China from 2000–2019 were obtained from the National Meteorological Science Data Center [19,20]. These stations fall into three categories: baseline, basic, and general stations. From 2000 to 2019, all these stations adopted automatic observation 24 times a day on the hour. For more detailed observation stations information, please refer to the Surface Meteorological Observation Criterion [21]. All 2142 surface weather stations used the same thermometer type: Celsius. The accuracy is 0.1 °C. The daily mean temperature was calculated by averaging the hourly temperature readings that occurred throughout the day. The 2142 monitoring points cover 8 major climate types, as well as urban and rural areas.

The climatic regionalization of China released by the China Meteorological Administration was provided by the National Earth System Science Data Center [22]. In our research, according to their temperature value, temperature distribution (Figure S1), and humidity, the original 12 subgroups were reclassified into 8 groups [23]: frigid temperate zone, middle temperate zone, warm temperate zone, Tibetan Plateau area, north subtropical zone, middle subtropical zone, south subtropical zone, and marginal tropical zone. Within the same climatic zone, the temperature distribution is effectively the same.

2.2. Statistical Methods

First, we drew a histogram with a 1 °C bin based on the time series of daily mean temperature for each location. The MFT is the temperature with the most bin in the 54th–92nd range of the daily mean temperature during a given year, which is the 95% confidence interval of the minimum mortality percentile (MMP) [17]. Based on the association between MMT and MFT, MMT is approximately equal to MFT [17].

Second, the number of heat exposure days was obtained by calculating the number of days in a year when the daily mean temperature exceeded MMT.

Third, from prior publications [9,24], we obtained the percentage increase in mortality effect of heat (RR) per 1 °C increment in daily mean temperature in 24 typical cities covering all six major climate zones in China (Figure 1).

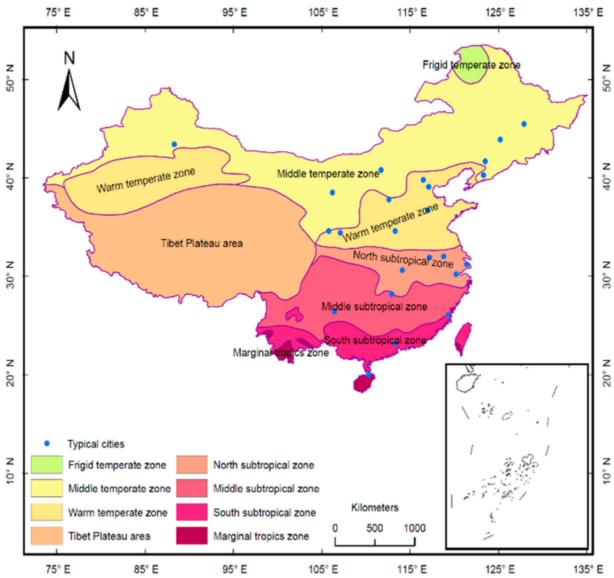

Figure 1. Locations of 24 Chinese cities in different climate zones.

Lastly, we utilised multiple linear regression (MLR) to explore the city heterogeneity. We chose 24 typical cites to investigate the associations between the percentage increase in mortality effect of heat (RR) per 1 °C increment in daily mean temperature and seven independent variables of city and climatic characteristics in Table 1. These variables represent potential effect modifiers.

Table 1. Independent variables considered in the statistical analysis.

Variable	Description
x_1	The number of heat exposure days
x_2	GDP per capita
x_3	Proportion of elderly population (≥65 years of age)
x_4	Urban population ratio
x_5	Latitude
x_6	Climate zone
x_7	Study year

The model is defined below (Equation (1)):

$$y = \alpha + \sum_{i=1}^{7} \beta_i x_i \tag{1}$$

where y is the percentage increase, α is the intercept, $x_1, \ldots x_7$ are the independent variables in Table 1, and $\beta_1, \ldots \beta_7$ are the regression coefficients.

The 20-year changes in AMT, MFT, and the number of heat exposure days were obtained based on a linear trend analysis. Using R software, we performed a linear regression to fit the trend of AMT, MFT, and heat exposure days for each station and then calculated the average of all stations.

The 24 locations in the present study covered six of the eight major climatic zones, including middle temperate zone, warm temperate zone, north subtropical zone, middle subtropical zone, south subtropical, and marginal tropical zone, excluding frigid temperate zone and the Tibetan Plateau area.

3. Results

3.1. Temperature Distribution in China

Figure 2 and Table 2 show the mean values of annual mean temperature (AMT), minimum mortality temperature (MMT), and heat exposure days of 2142 Chinese stations in the eight major climatic zones, respectively, during 2000–2019. Figure S1 shows the histogram of the daily mean temperature distributions and MFTs in the eight climate zones throughout the year. The abscissa is the daily mean temperature, and the ordinate is the percentage of the number of days that the temperature occurs in a year. In the same climatic zones, the temperature distribution is effectively the same. Among the 2142 stations, the AMT ranged from −5 °C to 26.5 °C (Figure 2a), the MMT ranged from 11 °C to 33 °C (Figure 2b), and the number of heat exposure days ranged from 40 to 120 days (Figure 2c). The maximum number of heat exposure days occurred in areas with high temperature, such as the marginal tropical zone and south subtropical zone, with the largest values at 120 days (Figure 2c). Meanwhile, the minimum days occurred in areas with low temperature, such as the frigid temperate zone and the middle temperature zone, with the lowest value at 40 days.

Table 2. The AMT, MMT, and heat exposure days ranges (95% CI) in eight major climatic zones in China during 2000–2019.

Climate Zone	Number of Stations	AMT (°C)	MMT (°C)	Heat Exposure Days (Days)
Frigid temperate zone	4	−3.5 (−3.8, −3.2)	15.9 (15.1, 16.9)	54 (52, 55)
Middle temperate zone	439	6.2 (1.1, 10.2)	20.6 (16.5, 23.8)	65 (55, 80)
Warm temperate zone	620	13.3 (9.7, 15.6)	24.6 (20.9, 26.7)	69 (55, 84)
North subtropical zone	258	16.7(14.9,18)	25.6 (22.8, 27.3)	78 (62, 95)
Middle subtropical zone	497	17.5 (14.2, 20.2)	25.1 (19.7, 28.5)	78 (63, 99)
South subtropical zone	195	21.2 (16.8,23.5)	26.6 (21, 28.9)	85 (66, 102)
Marginal tropical zone	26	23 (18.2,25.4)	26.3 (21.4, 29.1)	97 (81, 113)
Tibetan Plateau area	103	6.9 (−0.8, 15.8)	14.5 (8.2,22.1)	77 (58, 95)

3.2. Multiple Linear Regression Analysis

Table 3 shows the descriptive data on annual mean temperature at the 24 typical cities included in the analysis. The annual mean temperature ranged from 5.1 °C in Harbin to 24.2 °C in Haikou.

The heterogeneity across cities suggested that there would be some modifiers for heat-related mortality. Spearman correlations between the percentage increase in heat-related mortality and seven independent variables were calculated (Table 4). In Table 4, we can see that among the following seven independent variables, the number of heat exposure days, GDP per capita, urban population ratio, proportion of elderly population, and study year had stronger correlations with the percentage increase in heat-related mortality. The correlation coefficients between them are 0.37, 0.55, 0.55, 0.45, and −0.43, respectively.

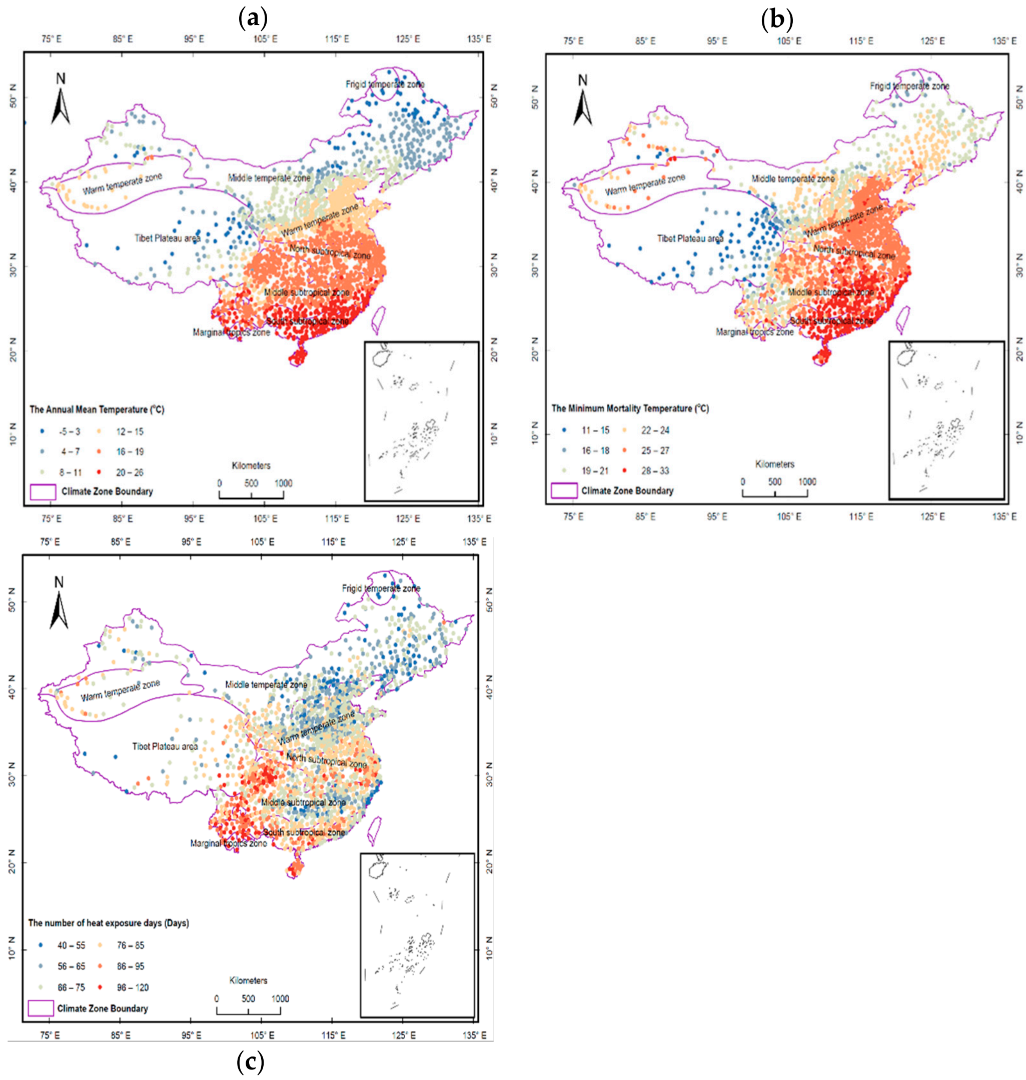

Figure 2. The mean values of AMT (**a**), MMT (**b**), and heat exposure days (**c**) of 2142 meteorological observation stations in China during 2000–2019.

Table 3. The descriptive data on annual mean temperature at the 24 typical cities in China.

Locations (Province)	(Longitude, Latitude)	Study Period	AMT (°C)	Climate Zone
Harbin (Heilongjiang)	(127.9°, 45.6°)	2008–2013	5.1	1
Changchun (Jilin)	(125.2°, 43.9°)	2008–2013	5.9	1
Urumqi (Xinjiang)	(88.3°, 43.4°)	2006–2007	8.5	1
Shenyang (Liaoning)	(123.5°, 41.7°)	2005–2008	6.4	1
Hohhot (Inner Mongolia)	(111.7°, 40.8°)	2008–2013	7.6	1
Anshan (Liaoning)	(123.3°, 40.3°)	2004–2006	10.7	1
Beijing (Beijing)	(116.5°, 39.8°)	2007–2008	10.5	2
Tianjin (Tianjin)	(117.1°, 39.1°)	2005–2008	11.8	2
Yinchuan (Ningxia)	(106.2°, 38.5°)	2008–2013	10.3	1
Taiyuan (Shanxi)	(112.6°, 37.8°)	2004–2008	10.1	2
Jinan (Shandong)	(117°, 36.7°)	2008–2013	14.5	2
Lanzhou (Gansu)	(105.8°, 34.6°)	2004–2008	10.4	1
Zhengzhou(Henan)	(113.3°, 34.6°)	2008–2013	15.6	2
Xi'an (Shaanxi)	(107.1°, 34.4°)	2004–2008	11.3	2
Nanjing (Jiangsu)	(118.8°, 32°)	2008–2013	16.3	3
Hefei (Anhui)	(117.2°, 31.9°)	2008–2013	16.6	3
Shanghai (Shanghai)	(121.4°, 31.2°)	2008–2012	17.4	3
Wuhan (Hubei)	(114.1°, 30.6°)	2003–2005	16.4	3

Table 3. *Cont.*

Locations (Province)	(Longitude, Latitude)	Study Period	AMT (°C)	Climate Zone
Hangzhou (Zhejiang)	(120.2°, 30.2°)	2002–2004	18.5	3
Changsha (Hunan)	(112.9°, 28.2°)	2008–2013	18.3	4
Guiyang (Guizhou)	(106.4°, 26.4°)	2008–2013	14.4	4
Fuzhou (Fujian)	(119.3°, 26.1°)	2004–2006	19.8	4
Guangzhou (Guangdong)	(113.3°, 23.2°)	2007–2008	21.2	5
Haikou (Hainan)	(110.3°, 19.7°)	2008–2013	24.2	6

Climate zones: 1: Middle temperate zone; 2: Warm temperate zone; 3: North subtropical zone; 4: Middle subtropical zone; 5: South subtropical zone; 6: Marginal tropical zone.

Table 4. Spearman correlations between increased RR and socioeconomic factors.

	Percentage Increase	*p*-Value
x_1 (The number of heat exposure days)	0.37	0.08
x_2 (GDP per capita)	0.55	0.005
x_3 (Urban population ratio)	0.55	0.005
x_4 (Proportion of elderly population) (≥65 years of age)	0.45	0.03
x_5 (Study year)	−0.43	0.03
x_6 (Latitude)	−0.21	0.33
x_7 (Climate zone)	/	/

Dependent variable is the percentage increase in heat-related mortality. Study year: the mean year of the study period.

We introduced city and climatic characteristics in the MLR analysis. The results of the optimal model are shown in Table 5, with an R^2 of 0.71. Results showed that the number of heat exposure days, GDP per capita, urban population ratio, proportion of elderly population, and climate zone were found to modify the estimate on heat effect. For example, the RR increased 0.11% for a one-day increment in the number of heat exposure days.

Table 5. Coefficients for multiple linear regression model.

Parameters	Estimate	Std. Error	*p*-Value
Intercept	−28.1	7.48	0.002 **
x_1 (The number of heat exposure days)	0.11	0.04	0.01 **
x_2 (GDP per capita)	7.25×10^{-5}	3.96×10^{-5}	0.09 ·
x_3 (Urban population ratio)	0.16	0.062	0.02 *
x_4 (Proportion of elderly population) (≥65 years of age)	1.18	0.59	0.06 ·
x_7 (Climate zone)	Dummy variable *		

** p-Value < 0.01; * p-Value < 0.05; · p-Value < 0.1.

3.3. Changes in Temperature over the Past 20 Years

Based on the time series of daily mean temperature at 2142 observation stations in China and using a linear trend analysis method, we calculated the changes of AMT, MFT, and heat exposure days at all observation stations and eight major climatic zones from 2000 to 2019. Table 6 shows the changes of AMT, MFT, and heat exposure days in different climatic zones.

As is demonstrated in Table 6, we found that in the past 20 years, AMT has increased in most parts (95%) of China, with the values increasing by 0.98 °C (95% CI: 0, 1.9) across the country. The highest increase in AMT mainly occurred in areas with low temperatures, such as the frigid and middle temperate zones, with the highest values reaching 1.43 °C and 1.12 °C. Conversely, the lowest increase in AMT mainly occurred in areas with high temperature (marginal tropical zone) and the Tibetan Plateau area, with the lowest value reaching 0.84°C and 0.76°C. In contrast to AMT, the increase in MMT mainly occurred in the south of China (the marginal subtropical zone) and the Tibetan Plateau area, with the largest value reaching 0.8 °C and 1 °C, and the decrease in MMT mainly occurred in the north of China (the frigid and middle temperate zones), with the lowest values reaching as low as –1.3 °C and –0.9 °C. The change has no significant impact on the number of heat exposure days. That is, in the same climate zone, stations with increased or decreased heat exposure days exist simultaneously. Figure 3 shows the distribution histogram of AMT and MMT changes at 2142 observation points.

Table 6. The AMT, MFT, and heat exposure days changes (95% CI) in eight major climatic zones from 2000 to 2019.

Climate Zone	AMT		MMT		Heat Exposure Days	
	Changes/20a (°C)	Increased Proportion *	Changes/20a (°C)	Increased Proportion *	Changes/20a (Days)	Increased Proportion *
Frigid temperate zone	1.43 (1.2, 1.6)	100%	−1.3 (−2.4, −0.1)	0%	3 (−24, 30)	75%
Middle temperate zone	1.12 (−0.1, 2.2)	93%	−0.9 (−3.6, 2.5)	33%	−12 (−49, 26)	31%
Warm temperate zone	1.1 (0, 2.0)	95%	−0.4 (−2.4, 1.6)	34%	−9 (−56, 36)	38%
North subtropical zone	0.96 (0.2, 1.9)	96%	−0.5 (−3.4, 3.2)	39%	−10 (−63, 36)	38%
Middle subtropical zone	0.9 (0, 1.6)	95%	0.8 (−1.5, 3.6)	69%	0 (−47, 50)	50%
South subtropical zone	0.89 (−0.1, 1.6)	93%	0.6 (−0.8, 2.2)	67%	−8 (−51, 35)	36%
Marginal tropical zone	0.84 (0.2, 1.4)	96%	0.8 (−0.5, 1.5)	81%	−1 (−32, 34)	50%
Tibetan Plateau area	0.76 (−0.2, 1.6)	88%	1 (−0.7, 3.2)	74%	1 (−40, 40)	55%
Overall	0.98 (0, 1.9)	95%	0.1 (−4.1, 4)	54%	−7 (−53, 37)	40%

* is the percentage of stations with rising temperature in all stations.

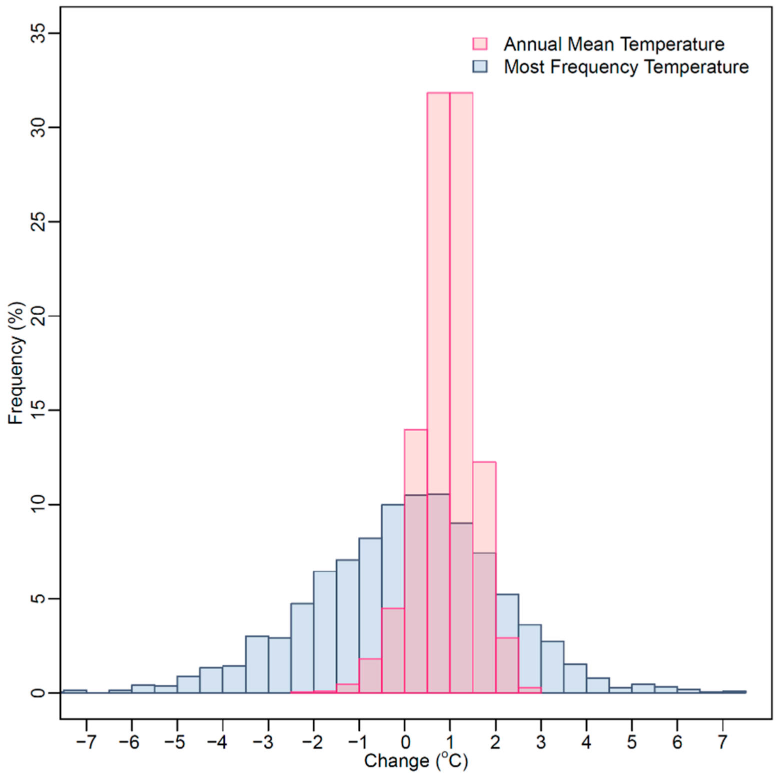

Figure 3. The histogram of changes in AMT and MFT at 2142 observation points.

4. Discussion

Although many studies have analyzed changes in temperature due to global warming in many different regions [8,25–27], they are based on statistical associations without explicit physical meaning and do not consider the physiological adaptations of humans to the local temperature. The most frequent temperature (MFT) indicator provides us with the ability to solve this problem [17]. On the one hand, MFT is the longest period of temperature to which a human is exposed and therefore acclimates. As such, it can reflect human adaptation to temperature. On the other hand, different temperature distributions reflect different climatic and exposure characteristics. These exposure characteristics are closely related to the risk of heat-related mortality. However, previous studies investigating heat exposure were usually based on case studies in very few data-rich regions [12–16]. Therefore, in this study, we proposed a new method from the perspective of temperature distribution (Figure S1) to estimate the number of heat exposure days in terms of heat-related mortality risk, without the need for mortality data, and then estimated its impact on the risk of heat-related mortality.

Humans adapt to ambient temperature in several ways, including physiologically, behaviorally, and technologically [18,28,29]. Our previous study found that the MFT is the temperature to which humans are most exposed and, therefore, physiologically acclimatized [17]. Accordingly, the MFT is a good indicator for fitting the MMT or most optimum temperature [17]. Based on this theory and the association between MFT and MMT, we proposed a new method from the perspective of temperature distribution throughout the year to estimate heat exposure days in terms of heat-related mortality risk. We estimated the distribution of the MMT and heat exposure days at 2412 stations in China. The MMT and heat exposure days vary considerably across the country; they both tend to decrease gradually from low latitudes to high latitudes. To the best of our knowledge, this is the first study to estimate the distribution of MMT and heat exposure days in terms of heat-related mortality risk on a national scale.

The number of heat exposure days is associated with the risk of heat-related mortality [30,31]. In the present study, we found the risk of heat-related mortality varied greatly across the 24 China cities studied. The percentage increase in heat-related mortality (RR) per 1 °C increment in daily mean temperature can be impacted by city-level characteristics and climatic characteristics, such as the number of heat exposure days, proportion of elderly population, urban population ratio, GDP per capita, and climate zone. The greater the number of days of heat exposure, the higher the RR. Additionally, older people may be more vulnerable to heat exposure. A similar pattern was observed in the previous study occurring on a global scale [31]. During hot weather, the elderly may become dehydrated, hypernatraemic, and experience renal failure, with resultant complications of the cardiovascular system. In addition, older people may be more vulnerable because they are more likely to live alone and have limited mobility. A previous study of 50 U.S. cities found that heat effects were associated with population density [32]. This pattern is consistent with our findings. Higher urban population ratio may reflect greater thermal storage capacity [33–35]; this process is termed the urban heat island effect. It may also cause greater thermal stress by increasing night temperature [36]. In our study, we found that higher GDP per capita was associated with higher heat risk. This result is inconsistent with some previous studies [32]. In part, GDP per capita may reflect technological protection measures, such as access to home air-conditioning. However, higher GDP per capita is also accompanied by higher population density.

With global warming, the change in temperature varies considerably across regions [37–39]. Our results show that the distribution of AMT and MFT have changed over the past 20 years. Although the mean value of their increases is similar, the distribution (Table 6) and the range of their changes (Figure 3) are significantly different. The biggest rise in AMT occurred in areas with low temperatures, and the lowest rise mainly occurred in areas with high temperatures. In contrast to AMT, the highest increase in MFT mainly occurred in areas with high temperatures and the Tibetan Plateau area, and the decrease mainly occurred in areas with low temperatures (such as frigid temperate zone and middle temperature zone). This result is consistent with those of certain extant studies [39–44]. The IPCC (2007) pointed out that warming was more obvious at high latitudes in the northern hemisphere due to global warming [39]. Guan (2015) found that the warming rate increased with an increase in latitude [40]. Qiao (2015) found that over the past 50 years, the surface temperature increased significantly in most areas of China, especially in Northern China, where the temperature increased at a rate of (0.2 °C–0.6 °C)/10a [43]. This change may be due to the combined effects of climate change and recent urbanization. On the one hand, from 2005 to 2016, air pollution in China showed an upward trend in the north, and a downward trend in the south [44]. Increased air pollution in northern China accelerates climate warming. On the other hand, from 1992–2015, the urbanization of southern China was faster than that of northern China [45]. Reducing vegetation cover and increasing anthropogenic heat emissions caused by rapid urbanization exacerbated climate warming. Climate change can be affected by many factors. The complicated geography of China has caused complex climate change within its borders. Temperature change shows that significant zonal differences in China may be related to the comprehensive influences of atmospheric circulation, humidity concentrations, solar irradiance, and topography [46].

In addition, in this study, we estimated the change in number of heat exposure days at 2412 stations in China for the first time. As expected, there were more heat exposure days in the south than in the north. However, unexpectedly, we did not find significant geographic patterns in the change of the number of heat exposure days (Table 6) in the past 20 years.

Based on these findings, this study promotes a more comprehensive understanding of temperature changes in the context of climate change. The heterogeneous characteristics of change across China indicate the need for location-specific and longer-term prevention strategies to help promote the sustainable development of cities. Northern areas of China with cold temperatures should be given more attention regarding heat-related mortality risk in the future. Those with sensitive diseases, including cardiovascular disease, CHD, and stroke, as well as the elderly, are identified as susceptible subpopulations. This study will be helpful in informing public policies to protect against high temperature-induced mortalities.

There are some limitations present in this study. Firstly, the time span is short, and could not have the optimal climatological representativeness of at least 30 years. Therefore, the statistical trends may be sensitive to the selected years. Secondly, some socio-economic and individual behavior factors require further consideration. For example, the use of air conditioning [47], which is a strong protective factor against extreme heat events, was not considered in this study.

5. Conclusions

Health effects attributed to heat exposure in China are a significant issue requiring more attention and allocation of existing resources. Based on MFT and temperature distribution throughout the year, this study proposed a new method to estimate the number of heat exposure days in terms of heat-related mortality risk without the need for mortality data, and then analyzed its spatiotemporal variation and impacts on heat-related mortality. The number of heat exposure days tends to decrease gradually from low latitudes to high latitudes. Heat exposure days, GDP per capita, urban population ratio, proportion of elderly population, and climate zone were found to modify the estimate on heat effect. The percentage of heat-related mortality increased 0.11% for each one-day increment in the number of heat exposure days. Our study will be beneficial in understanding the potential health effects of future climate change in different climate zones.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/atmos12101294/s1, Figure S1. The histograms of the daily mean temperature distribution and MFTs throughout the year in the eight climate zones (a–h).

Author Contributions: G.G. and Q.Y. conceived of and designed the study. Q.Y., Z.R., D.W. and Y.G. carried out the calculations and wrote the manuscript. All the authors contributed to the final version of this paper. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The authors declare that all data supporting the findings were obtained from open data. Data sources are available within the paper and its Supplementary Information Files.

Conflicts of Interest: The authors declare no conflict of interest.

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