

Preplanned Studies

Evaluating the Applicability and Health Benefits of the Graded Heat Health Risk Early Warning Model — Jinan City, Shandong Province, China, 2022

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Summary

What is already known about this topic?

The heat health early warning model serves as an effective strategy for reducing health risks related to heatwaves and improving population adaptability. Several high-income countries have taken the lead in conducting research and implementing measures aimed at safeguarding their populations.

What is added by this report?

The graded heat health risk early warning model (GHREWM) in Jinan City has demonstrated efficacy in safeguarding males, females, individuals aged above 75 years, and those with cardiopulmonary diseases. During the summer of 2022, the warning stage of GHREWM contributed to the prevention of 10.9 deaths per million individuals, concurrently averting health-related economic losses estimated at approximately 227 million Chinese Yuan (CNY).

What are the implications for public health practice?

The GHREWM has the potential to enhance cities' adaptability to climate change. It is crucial to incorporate additional adverse health endpoint data in the development of early warning models, as this will improve their applicability and protective efficacy.

In the summer of 2022, the world experienced unprecedented heatwaves, which broke previous records and led to severe droughts and wildfires. Due to global warming, heatwaves are expected to become more frequent and intense (1). Some high-income countries have implemented heat health early warning models to mitigate the impacts of heatwaves and have reported initial positive health outcomes (2). The World Health Organization (WHO) and the World Meteorological Organization (WMO) jointly endorsed heat health early warning models as proactive adaptation measures to reduce heat-related mortality and prevent the onset of heat-sensitive diseases during

summer months (3). However, research on heat health early warning models in China began relatively late, and a national model has yet to be established (2).

In 2021, Jinan City, Shandong Province implemented a graded heat health risk early warning model (GHREWM) focused on population-health-oriented management (4). Further investigations are necessary to assess the utility and effectiveness of this novel heat health early warning model in safeguarding the health of residents. In the current study, an episode-based approach was employed to evaluate the applicability of Jinan's GHREWM for heat-sensitive diseases and mortality across various populations. Additionally, this study aimed to quantify the health benefits associated with the reduction of mortality risks. These findings can serve as a critical foundation for the scientific establishment of a national GHREWM in China.

In order to evaluate GHREWM's capacity to identify health risks, daily mortality data from 8 urban areas in Jinan City, Shandong Province, China, during the warm seasons (May to October) between 2013 and 2018 were collected utilizing the Disease Surveillance Point System of the China CDC. Three categories of mortality causes were considered: non-accidental, circulatory diseases, and respiratory diseases, further stratified by age (<65 years, 65–74 years, and >74 years) and gender (female and male). Daily 24-hour average temperature, relative humidity, and ozone (O₃) concentrations were obtained from the National Climate Centre, the European Centre for Medium-range Weather Forecasts, and the National Urban Air Quality Real-time Release Platform, respectively.

In calculating health benefits, we gathered data from the GHREWM, including daily 24-hour average temperatures for the 2022 warm season, number of resident populations, and gross domestic product (GDP)-adjusted provincial value of a statistical life (VSL). The GHREWM, organized by heatwave mortality risks, encompasses surveillance, watch, and warning stages. The warning stage consists of warning

levels 1, 2, and 3 (Supplementary Figure S1, available in <https://weekly.chinacdc.cn>). The GHREWM's structure and warning grading thresholds for different climate-architecture regions are depicted in Supplementary Figure S1 and Supplementary Table S1 (available in <https://weekly.chinacdc.cn>). Additional information regarding the sources and contents of the data can be found in the Supplementary Materials (available in <https://weekly.chinacdc.cn>).

This study utilized an episode-based approach and a two-stage statistical model to examine associations between warning levels and daily mortality risks for three sensitive diseases and sub-populations, determining if mortality risks varied with increasing warning levels. In the first stage, a generalized linear model employing quasi-Poisson regression was applied to fit county-specific associations, adjusting for relative humidity, time trends, and days of the week. In the second stage, a random-effects meta-analysis was conducted to pool the associations. The settings for the primary model and sensitivity analysis can be found in Supplementary Materials. Associations were expressed as percentage increases in mortality associated with a one-rank increase in warning levels, using the surveillance stage as the reference level.

We calculated the number of deaths prevented per million individuals and the economic losses averted during the warm season of 2022, as a result of the warning stage, in order to assess the health benefits provided by GHREWM in Jinan (5–6).

$$\Delta Lives = \sum (\Delta Mortality \times days_i \times pop_i)$$

$$VSL_{total} = \sum (\Delta Mortality \times days_i \times pop_i \times VSL_i)$$

In this formula, $\Delta Lives$ and VSL_{total} represent the number of lives saved and the economic loss avoided by the warning stage, respectively. $\Delta Mortality$ [0.69 persons/(million people·day)] refers to the number of deaths prevented per million people per day and is derived from the estimated number of deaths per million population per day saved by the warning stage in Benmarhnia's study, as described in detail in Supplementary Materials and adjusted for population size (5). $days_i$ represents the number of days in the warning stage for area i ; pop_i denotes the local population for area i ; and VSL_i is the VSL at the provincial level for area i (6).

Assuming the nationwide implementation of the GHREWM model in 2022, health benefits were estimated for six climatic-architecture regions (covering 366 cities), utilizing the number of lives saved and adjusting for the local population in Jinan.

The R Statistical software (version 4.0.2; Kurt Hornik and the R Core Team, Vienna, Austria) was used to perform all analyses. Statistical significance was set at $P < 0.05$. ArcGIS (version 10.7; Esri Inc., Redlands, California, USA) was used to draw the map of China.

Between 2013 and 2018, during the warm seasons, a total of 104,346 non-accidental disease-related deaths were reported in Jinan. Of these, 55.8% were males, and 44.2% were females. The majority of the deceased were aged 75 years and older (Table 1).

As illustrated in Figure 1, the watch level demonstrated a substantial rise in the risk of non-accidental and circulatory disease-related deaths in comparison with the surveillance stage. This increase amounted to 8.20% [95% confidence interval (CI): 5.37%, 11.11%] and 9.34% (95% CI: 5.43%, 13.40%), respectively. During the warning stage, the augmentation in mortality risks associated with non-accidental, circulatory, and respiratory diseases in the general population correlated with an escalation in the warning level. The most significant increase was observed at warning level 3, with risks of 31.81% (95% CI: 17.41%, 47.97%), 39.94% (95% CI: 19.12%, 64.41%), and 49.24% (95% CI: 22.03%, 82.51%), respectively. These findings suggest that the GHREWM model possesses a robust capacity for identifying health risks based on their ranking.

There was a positive correlation between the increasing mortality risks and warning levels observed for both sexes and individuals aged over 75 years (Figure 1 and Supplementary Table S3 available in <https://weekly.chinacdc.cn>). However, this trend was not observed in the other two age groups.

Following the implementation of GHREWM in Jinan during the warm seasons of 2022, the warning stage resulted in a reduction of 10.9 deaths per million individuals and averted economic losses of approximately 227 million CNY. If applied on a nationwide scale, this strategy could have led to significant health benefits, with a potential savings of 15,115 deaths and a prevention of economic losses amounting to 62.0 billion CNY.

DISCUSSION

Jinan's GHREWM utilizes population mortality risk as a foundation for establishing warning ranks and adopts the three-stage risk management concept of risk surveillance, watch, and warning to address heat-related health risks during summer (4). Existing heat

TABLE 1. Overview of daily mortality causes, meteorological factors, and ozone (O₃) levels in Jinan City, Shandong Province during warm seasons (May–October) from 2013 to 2018.

Variable	Total	Mean±SD	P ₅₀ (P ₂₅ , P ₇₅)
Cause of Mortality			
Non-accidental disease	104,346	12±6	11 (7, 15)
Female	46,130	5±3	5 (3, 7)
Male	58,212	7±4	6 (4, 9)
Age <65 years	26,877	3±2	3 (1, 4)
Age 65–74 years	22,377	3±2	2 (1, 4)
Age >74 years	55,082	6±4	6 (4, 8)
Circulatory disease	54,809	6±4	6 (4, 8)
Respiratory disease	8,864	1±1	1 (0, 2)
Environmental Factors			
Temperature (°C)		22.7±5.1	23.6 (19.7, 26.5)
Relative humidity (%)		66.2±14.6	67.4 (55.7, 77.4)
O ₃ 8 h-average (µg/m ³)		133.5±58.8	135.9 (91.1, 175.8)

Note: Mean represents the daily average of a variable during the warm seasons from 2013 to 2018.

Abbreviation: SD=standard deviation; P₂₅=the 25th percentile; P₅₀=the 50th percentile; P₇₅=the 75th percentile.

health early warning models in high-income countries, such as the United Kingdom and France, primarily focus on identifying heatwaves associated with elevated health risks (2). In contrast, Jinan's GHREWMM refines the classification of early warning levels, which our findings suggest effectively represents the increasing tendency of heat health risks, particularly for individuals over 75 years of age and those with cardiopulmonary diseases.

This study demonstrates that early warning grading based on mortality risk is more sensitive to populations with death as the primary effect endpoint (e.g., adults over 65 years of age). However, it also indicates that constructing a health early warning model solely based on death data may not capture the full range of heat-related effects on all populations. For instance, children tend to spend more time outdoors, exposing themselves to higher temperatures for extended periods, and their limited self-protection abilities (7) increase their susceptibility to high-temperature-induced diseases, such as heat stroke. Consequently, future heat health warning research should consider incorporating various sensitive effect endpoints.

The United Nations Intergovernmental Panel on Climate Change's Sixth Assessment Report highlights the positive effects of 24 representative adaptation measures on human well-being, with the benefits of disaster early warning systems on human health being particularly notable (8). Successful implementations in high-income countries have shown significant health benefits from population-based risk approaches for

early disaster warnings. Benmarhnia et al. estimated that heat action plans in Montreal, Quebec, reduced mortality by 2.52 deaths per day during heatwaves (5). Additionally, the nationwide heatwave plan for England saved 1,189 lives over a 20-day heatwave in 2013 (9). Philadelphia's Hot Weather-Health Watch/Early Warning System resulted in 117 lives saved between 1995 and 1998, generating 468 million USD in revenue (10). Our study also illustrates the benefits of implementing Jinan's GHREWMM in the summer of 2022. As the negative effects of climate change are irreversible, effective adaptation measures (such as GHREWMM) provide a practical and timely means of preventing further losses.

Rapid urbanization has led to increased population density, which, when combined with the urban heat island effect and severe air pollution, negatively impacts urban living conditions. Addressing the growing health needs of the population and enhancing urban resilience and adaptability to climate change have become critical challenges. Our study indicates that implementing the Jinan's health warning model nationwide in 2022 could have yielded significant health benefits for residents. Consequently, we recommend the immediate establishment of a national heat health early warning system to better adapt to the escalating trend of extreme heat events, accompanied by the execution of a multi-sectoral heat health collaboration action plan.

This study was subject to several limitations. First, due to the inability to accurately measure personal

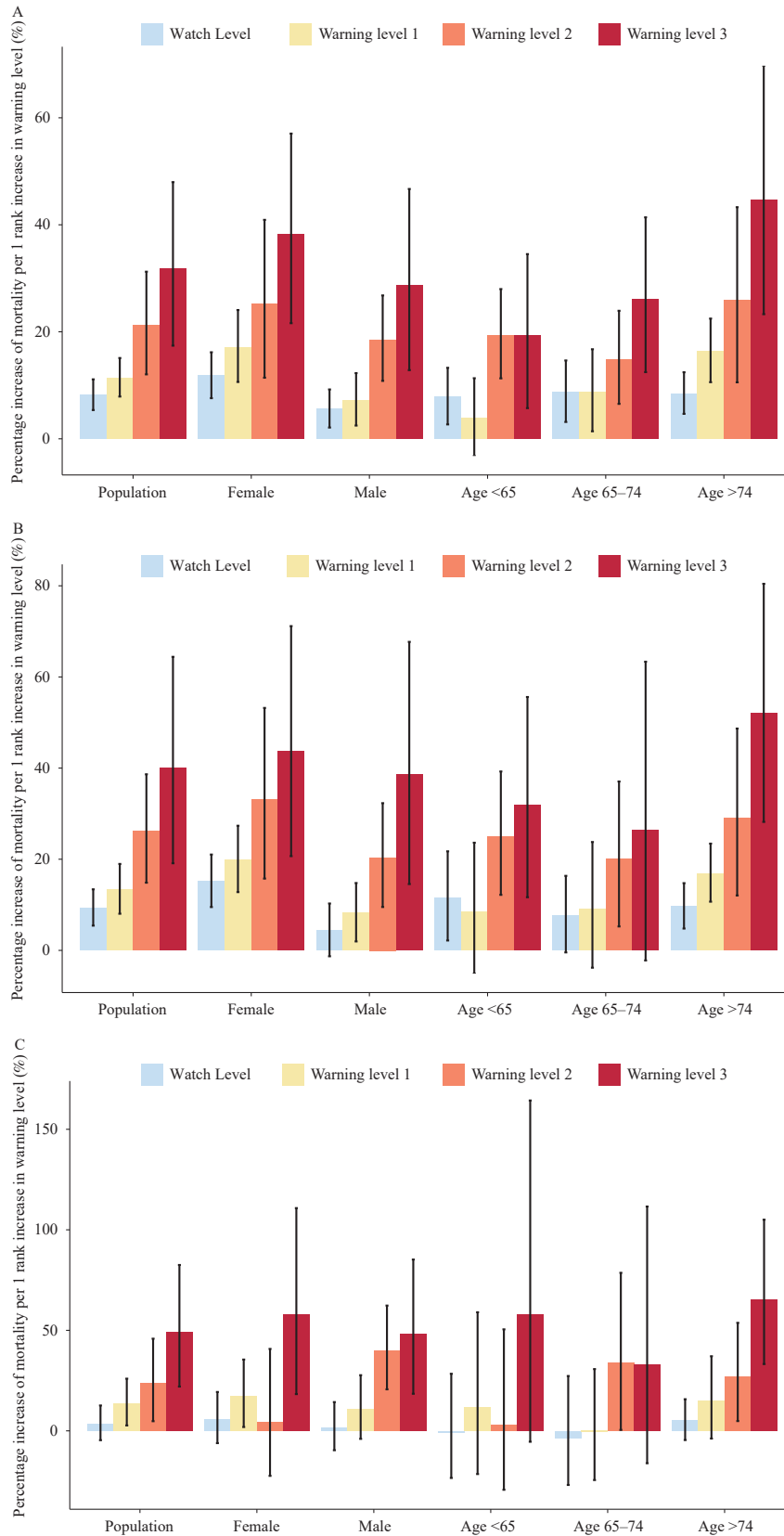


FIGURE 1. Percentage increase in non-accidental mortality (A), circulatory mortality (B), and respiratory mortality (C) per 1 rank increase in warning level during warm seasons in Jinan from 2013 to 2018, with population and sub-population estimates displayed.

temperature exposure, we utilized ambient temperature as a proxy for individual exposure, potentially introducing exposure uncertainty. Second, the assessment of national health benefits relied on scenario assumptions, serving as a reference for the nationwide value derived from the application of GHREWM. Furthermore, the establishment of GHREWM did not encompass certain western regions; hence, these areas were excluded from the estimation of nationwide health benefits.

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REFERENCES

1. IPCC. Summary for policymakers. In: Masson-Delmotte V, Zhai P, Pirani A, Connors SL, Péan C, Berger S, et al, editors. Climate change 2021: the physical science basis. Contribution of working group I to the sixth assessment report of the intergovernmental panel on climate change. Cambridge: Cambridge University Press. 2021; p. 3 – 32. https://www.ipcc.ch/report/ar6/wg1/downloads/report/IPCC_AR6_WGI_SPM.pdf.
2. Chen C, Liu J, Zhong Y, Li TT. A review on heat-wave early warning based on population health risk. *Chin J Prev Med* 2022;56(10):1461-6. <https://rs.yiigle.com/CN112150202210/1430211.htm>. (In Chinese).
3. World Meteorological Organization, World Health Organization. Heatwaves and health: guidance on warning-system development. Genève: World Meteorological Organization; 2015 Jul. Report No.: WMO-No. 1142. https://www.who.int/docs/default-source/climate-change/heat-waves-and-health---guidance-on-warning-system-development.pdf?sfvrsn=e4813084_2.
4. Li TT, Chen C, Cai WJ. The global need for smart heat-health warning systems. *Lancet* 2022;400(10362):1511 – 2. [http://dx.doi.org/10.1016/S0140-6736\(22\)01974-2](http://dx.doi.org/10.1016/S0140-6736(22)01974-2).
5. Benmarhnia T, Bailey Z, Kaiser D, Auger N, King N, Kaufman JS. A difference-in-differences approach to assess the effect of a heat action plan on heat-related mortality, and differences in effectiveness according to sex, age, and socioeconomic status (Montreal, Quebec). *Environ Health Perspect* 2016;124(11):1694 – 9. <http://dx.doi.org/10.1289/EHP203>.
6. Sun QH, Sun ZY, Chen C, Yan ML, Zhong Y, Huang ZH, et al. Health risks and economic losses from cold spells in China. *Sci Total Environ* 2022;821:153478. <http://dx.doi.org/10.1016/j.scitotenv.2022.153478>.
7. Smith CJ. Pediatric thermoregulation: considerations in the face of global climate change. *Nutrients* 2019;11(9):2010. <http://dx.doi.org/10.3390/nu11092010>.
8. IPCC. Climate change 2022: impacts, adaptation, and vulnerability. Contribution of working group II to the sixth assessment report of the intergovernmental panel on climate change. Cambridge: Cambridge University Press. 2022. https://www.ipcc.ch/report/ar6/wg2/downloads/report/IPCC_AR6_WGII_FrontMatter.pdf.
9. Green HK, Andrews N, Armstrong B, Bickler G, Pebody R. Mortality during the 2013 heatwave in England—how did it compare to previous heatwaves? A retrospective observational study. *Environ Res* 2016;147:343 – 9. <http://dx.doi.org/10.1016/j.envres.2016.02.028>.
10. Ebi KL, Teisberg TJ, Kalkstein LS, Robinson L, Weiher RF. Heat watch/warning systems save lives: estimated costs and benefits for Philadelphia 1995-98. *Bull Am Meteor Soc* 2004;85(8):1067 – 74. <http://dx.doi.org/10.1175/BAMS-85-8-1067>.

SUPPLEMENTARY MATERIAL

Methods

Data: To evaluate the capability of graded heat health risk early warning model (GHREWM) in identifying health risks, daily mortality data for eight urban areas in Jinan City, China, during the warm seasons (May to October) from 2013 to 2018 were collected from the Disease Surveillance Point System of China CDC. Three categories of death causes were classified based on the 10th Revision of the International Statistical Classification of Diseases, which included: non-accidental diseases (A00–R99), circulatory diseases (I00–I99), and respiratory diseases (J00–J99). These categories were further divided by age groups (<65, 65–74, and >74 years) and gender (female and male). Daily 24-hour average temperature, relative humidity, and O₃ concentrations data were acquired from the National Climate Centre (www.ncc-cma.net), the European Centre for Medium-range Weather Forecasts (<https://cds.climate.copernicus.eu/>), and the National Urban Air Quality Real-time Release Platform (<http://www.cnemc.cn>), respectively.

In the assessment of health benefits, the GHREWM information, the number of resident populations, and the GDP-adjusted provincial VSL were gathered from various sources. These included the Jinan CDC, the China Meteorological Administration (<https://weather.cma.cn>), the Seventh National Population Census of China in 2020, and Sun's study (1).

The structure of the GHREWM: The GHREWM was developed using historical mortality monitoring data to conduct a time-series study. This study aimed to quantify the characteristics of the mortality risk curve by constructing the exposure-response relationship between temperature and non-accidental death in various climate regions and subsequently categorizing the warning levels. The GHREWM comprises surveillance, watch, and warning stages, with the warning stage including levels 1, 2, and 3 (Supplementary Figure S1).

During the surveillance stage, heat health risks are consistently monitored throughout the summer season. At the watch stage, health risks are relatively low, indicating that authorities should prepare for potential heatwaves. As the warning stage commences, health risks increase, becoming more significant as the warning level escalates. In response to this heightened risk, authorities must provide health guidance and implement protective measures based on the current warning level.

The structure of the GHREWM and the warning thresholds for different climatic-architecture regions can be found in the Chinese Environmental Public Health Tracking project conducted by China CDC (Supplementary Figure S1 and Supplementary Table S1) (2). In accordance with the climate patterns in Jinan, the warning grading thresholds were determined using the 91st, 95th, 98th, and 99.5th percentiles of daily 24-hour average temperatures recorded from 2013 to 2018.

Early warning stages		Early warning signals	Heat health risk grading information	Heat health risk grading basis
Health risk surveillance		Green	heat health risks are lower	/
Health risk watch		Blue	there are certain heat health risks	The temperature threshold is the 91–92th percentile of historical daily mean temperature, and the daily mean temperature exceeds the threshold within 24-h.
Health risk early warning	Level 1	Yellow	heat health risks are high	The temperature threshold is the 95–97th percentile of historical daily mean temperature, and the daily mean temperature exceeds the threshold for two consecutive days.
	Level 2	Orange	heat health risks are higher	The temperature threshold is the 97–98th percentile of historical daily mean temperature, and the daily mean temperature exceeds the threshold within 24-h.
	Level 3	Red	heat health risks are extremely high	The temperature threshold is the 99.5th percentile of historical daily mean temperature, and the daily mean temperature exceeds the threshold within 24-h.

SUPPLEMENTARY FIGURE S1. Structure of the graded heat health risk early warning model (GHREWM).

Statistical Analyses

Main model: $\text{Log}[E(Y_t)] = \alpha + \beta \text{warning level}_t + \text{ns}(\text{time}, \text{df}) + \text{RH} + \text{dow}$

where $E(Y_t)$ is the expected number of mortality on day t ; β represents the associations between warning levels and mortality; warning level_t , a dummy variable of 0, 1, 2, 3 or 4, represents the warning level on day t ; $\text{warning level}_t = 0$ if day t is surveillance stage, 1 if day t is watch level, 2 if day t is warning level 1, 3 if day t is warning level 2, and 4 if day t is warning level 3; RH is relative humidity; and $\text{ns}(\text{time}, \text{df})$ is the natural spline functions of time trends with 2 degrees of freedom (df) per year. dow is a dummy variable for the day of the week.

Sensitivity analysis: We performed three sensitivity analyses for non-accidental mortality, as demonstrated by 1) the specification of df in the natural spline of the time trend ($\text{df}_{\text{time}}=3/\text{year}$) to investigate the effect of df adjustment changes on model estimates; 2) controlling relative humidity using a natural spline with 2 df to assess model stability; and 3) adjusting for ozone (O_3) in the analysis to evaluate the influence of air pollutants on model estimates. Results from the sensitivity analyses indicated that our findings were relatively robust (Supplementary Table S2).

Health benefits: $\Delta \text{Mortality} = \Delta \text{Deaths}/\text{pop} \times 1 \text{ million}$

SUPPLEMENTARY TABLE S1. Relative thresholds for each warning level in different climatic-architecture regions.

Region	Watch level	Warning level		
		Warning level 1	Warning level 2	Warning level 3
Severe cold region	91.0	95.0	98.0	99.5
Cold region	91.0	95.0	98.0	99.5
Hot summer & cold winter region	91.0	96.0	98.0	99.5
Temperate region	92.0	95.0	97.0	99.5
Hot summer & warm winter region	92.0	96.0	98.0	99.5
Severe cold & cold (northwestern) region	91.0	97.0	98.0	99.5

SUPPLEMENTARY TABLE S2. Percentage increase (95% CI) in non-accidental mortality associated with a per 1 level increase in warning level for sensitivity analysis via model setting adjustments.

Warning level	Main model		$\text{df}_{\text{time}}=3/\text{year}$		Controlling relative humidity by nature spline		Adjusting O_3	
	PI (95% CI)	QAIC	PI (95% CI)	QAIC	PI (95% CI)	QAIC	PI (95% CI)	QAIC
Watch level	8.20 (5.37, 11.11)	3.90	8.43 (5.52, 11.42)	5.28	8.19 (5.36, 11.10)	3.98	7.69 (4.70, 10.75)	4.17
Warning level 1	11.44 (7.90, 15.10)	6.28	11.45 (7.86, 15.17)	5.55	11.39 (7.85, 15.05)	6.38	11.71 (7.63, 15.95)	8.24
Warning level 2	21.26 (12.05, 31.24)	30.41	21.35 (12.67, 30.71)	27.08	21.04 (11.69, 31.16)	31.23	20.28 (12.15, 29.01)	21.83
Warning level 3	31.81 (17.41, 47.97)	26.97	31.17 (16.89, 47.20)	27.02	31.36 (16.86, 47.67)	27.59	31.82 (17.49, 47.90)	25.53

Note: df_{time} refers to the natural spline of the df for the time trend.

Abbreviation: PI=percentage increase; CI=confidence interval.

SUPPLEMENTARY TABLE S3. Percentage Increase (95% CI) in mortality associated with a per 1 level increase.

Cause of Mortality	Watch level	Warning level		
		Warning level 1	Warning level 2	Warning level 3
Non-accidental disease	8.20 (5.37, 11.11)	11.44 (7.90, 15.10)	21.26 (12.05, 31.24)	31.81 (17.41, 47.97)
Female	11.80 (7.59, 16.18)	17.16 (10.63, 24.07)	25.31 (11.42, 40.93)	38.20 (21.61, 57.05)
Male	5.61 (2.11, 9.23)	7.27 (2.48, 12.28)	18.55 (10.83, 26.80)	28.65 (12.83, 46.69)
Age <65 years	7.85 (2.69, 13.27)	3.85 (-3.12, 11.32)	19.35 (11.30, 27.98)	19.26 (5.73, 34.52)
Age 65–74 years	8.74 (3.15, 14.64)	8.80 (1.40, 16.74)	14.90 (6.53, 23.93)	26.10 (12.46, 41.39)
Age >74 years	8.48 (4.67, 12.44)	16.37 (10.58, 22.47)	25.86 (10.56, 43.29)	44.62 (23.29, 69.64)
Circulatory disease	9.34 (5.43, 13.40)	13.37 (8.04, 18.97)	26.19 (14.85, 38.64)	39.94 (19.12, 64.41)
Respiratory disease	3.63 (-4.64, 12.62)	13.73 (2.69, 25.95)	23.63 (4.80, 45.85)	49.24 (22.03, 82.51)

Where $\Delta Mortality$, 0.69 persons/(million people·day), is the cases saved per million people per day; $\Delta Deaths$ is the daily mortality reduced by the heat action plan in Montreal, 2.52 deaths (3); pop is the population in Montreal, 3.64 million, from 2006 Census of Canada.

REFERENCES

1. Sun Q, Sun Z, Chen C, Yan M, Zhong Y, Huang Z, et al. Health risks and economic losses from cold spells in China. *Sci Total Environ* 2022;821:153478. <https://doi.org/10.1016/j.scitotenv.2022.153478>.
2. Chinese Center For Disease Control And Prevention. National Disease Control and Prevention Agency issued guidelines for public health protection in high temperature and heat waves. 2023. https://www.chinacdc.cn/yrdgz/202306/t20230621_266977.html. [2023-6-21]. (In Chinese).
3. Benmarhnia T, Bailey Z, Kaiser D, Auger N, King N, Kaufman JS. A difference-in-differences approach to assess the effect of a heat action plan on heat-related mortality, and differences in effectiveness according to sex, age, and socioeconomic status (Montreal, Quebec). *Environ Health Perspect*. 2016;124(11):1694 – 9. <https://doi.org/10.1289/EHP203>.