Effect of heatwaves on mortality of Alzheimer's disease and other dementias among elderly aged 60 years and above in China, 2013–2020: a population-based study

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Summary

Background China has the largest number of dementia patients in the world, posing a significant health and economic burden. Alzheimer's disease (AD) and other dementia patients face a higher risk of mortality during heatwaves, but relevant studies on this topic have been limited so far.

Methods The study extracted data from the China Cause of Death Reporting System (CDRS) on deaths of AD and other dementia patients aged 60 years and above between 2013 and 2020. Using an individual-level, time-stratified, and case-crossover study design, the effects of heatwaves across nine scenarios on dementia mortality were quantified by conditional logistic regression combined with distributed lag non-linear model (DLNM). Additionally, the attributable fractions (AFs) of deaths due to heatwaves were calculated.

Findings A total of 399,036 death cases were reported caused by AD and other dementias during the study period. It was found that heatwaves significantly increased the risk of death among people with AD and other dementias. As the intensities and durations of the heatwaves increased, the lag0-7 cumulative odds ratios (CORs) of mortality increased progressively from 1.140 (95% CI: 1.118, 1.163) under the mildest heatwave to 1.459 (95% CI: 1.403, 1.518) under the most severe one, across nine heatwave scenarios examined. Additionally, under specific heatwave scenarios, sex and regions modified the mortality risk, but no significant age differences were observed. The AFs of AD and other dementia mortality due to milder heatwaves were lower compared to more severe heatwaves, ranging from 12.281% (95% CI: 10.555%, 14.015%) to 31.460% (95% CI: 28.724%, 34.124%).

Interpretation The study provided critical insights into the substantial increase in heatwave-related mortality among AD and other dementia patients during and after heatwave events. The results from our quantitative analyses will provide needed scientific evidence for policymakers and practitioners to develop relevant policies and guidelines to protect the health and well-beings of vulnerable populations in future in the context of both seasonal changes and long-term climate change.

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Keywords: Alzheimer's disease (AD) and other dementias; Mortality; Heatwave; Climate change; Attributable fraction

Research in context

Evidence before this study
Prior to this study, it was known that environmental factors, including high temperatures and heatwaves were associated with increased all-cause mortality. Studies conducted in some countries had also found the effect of heatwaves on dementia-related health outcomes. However, the specific relationship between heatwave exposure and mortality among elderly with Alzheimer's disease (AD) and other dementias in China, as well as the modifying effects of demographic and regional factors, has not been thoroughly explored.

Added value of this study
This study provides important new insights into the impact of heatwaves on AD and other dementia mortality. It quantified the exposure-response relationships, lag-response relationships, and attributable fractions (AFs), while also exploring the modifying effects of demographic and regional factors.

Implications of all the available evidence
These findings can inform the development of targeted interventions and public health policies to effectively reduce heatwave-related mortality in the elderly dementia populations in China. This research also has significant implications for other countries with comparable climatic and geographic features.

Introduction
China has the largest number of dementia patients in the world, accounting for about one-fourth of dementia patients globally, bringing a heavy health and economic burden.[1,2] A cross-sectional study conducted in 2020 estimated that there were 15.07 million dementia patients aged 60 years and above in China, of which 9.83 million had Alzheimer's disease (AD), 3.92 million had vascular dementia, and 1.32 million had other dementias.[3] Despite extensive scientific inquiry, neurodegenerative diseases including AD and other dementias, remain uncurable, posing a growing challenge to public health systems and caregiving networks worldwide as populations continue to age.[4]

Climate change increases the frequency, intensity, and unpredictability of extreme weather events such as heatwaves, cold spells, droughts, and floods. These events are becoming escalating and multifaceted threats to human health. Many studies have confirmed that high temperatures can increase the risk of all-cause mortality.[5,6] A few studies have explored the relationship between heatwaves and AD-related health outcomes. For instance, a study conducted in Spain found that heatwaves increased the hospital emergency admissions for AD.[7] A population-based cohort study from Australia reported that heatwaves heightened the risk of hospitalization and post-discharge mortality among Alzheimer's patients.[8] These findings indicate that due to impaired cognitive and functional capacities, individuals with dementias may have difficulty regulating their body temperatures and coping with heat stress, thereby increasing the risk of death due to heatwaves.[9–11] Furthermore, physiological stress caused by heat exposure can exacerbate health conditions in people with dementias, leading to an elevated risk of death.[12]

The effects of heatwaves on the mortality of AD and other dementias among the elderly in China remains unclear. Only few studies have investigated the effects of ambient temperatures on AD and other dementia mortality.[13,14] At the same time, AD and other dementia patients face a higher risk of death due to heatwave exposure, but relevant studies on this topic have been limited so far. To fill this research gap, the present study aimed to investigate the effects of heatwaves on the elderly AD and other dementia population in China. Such efforts are critical for informing the development of effective mitigation and adaptation strategies to protect this vulnerable population from the escalating threats posed by heatwave events.

Methods
Death records and meteorological data
A total of 399,036 de-identified individual death records were obtained from the China Cause of Death Reporting System (CDRS) for AD and other dementia patients aged 60 years and above in China from January 1, 2013 to December 31, 2020. The causes of death were categorized according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10), where codes F01 (vascular dementia), F03 (unspecified dementia), G30 (Alzheimer's disease), and G31 (other degenerative diseases of nervous system, not elsewhere classified) were defined as deaths caused by AD and other dementias. The collected individual death records encompass detailed information for each

decedent, including cause of death, date of death, sex, age, and address of residence. The accuracy of cause of death reporting is maintained through regular training, supervision at all administrative levels, and monthly verification by higher-level CDC staff, all within a framework of strict protocols and quality control measures.

Meteorological data were obtained from the Resource and Environmental Science Data Platform. The dataset consists of daily monitoring data from December 1, 2012 (December 2012 was included for investigating the lagged effects in January 2013) to December 31, 2020 (a total of 2953 days) from 2417 national-level surface meteorological observation stations across China. The data include five variables including longitude, latitude, daily mean temperature, daily mean relative humidity, and daily mean pressure. In order to match heatwave exposure and individual cases, four steps were conducted, including 1) the inverse distance weighting (IDW) method was applied to interpolate 2953 days' discrete site data into continuous raster data. The interpolation process had a spatial resolution of 15 km by 15 km to ensure a reliable representation for the spatial distribution of meteorological variables; 2) a total of 30,532 different coordinate points were identified based on the longitude and latitude of decedents' address of residence; 3) heatwave events and heatwave days were calculated and identified based on the daily mean temperatures between December 1, 2012 and December 31, 2020, at these 30,532 coordinates across nine heatwave scenarios; 4) for each individual case, whether heatwave events occurred on the day of death, on the control day, and on their lag days were identified.

Definitions of heatwave events

There has been no universal heatwave definition globally due to different climatic characteristics in various geographic locations.[15] Our research focused on individual-level exposure. Given the climatic diversity and varying adaptive capacities of residents in China, using an absolute threshold may underestimate the impact of heatwaves on different individuals.[16] Therefore, defining heatwaves based on the percentiles of daily mean temperatures at each decedent's address of residence (relative threshold) is more appropriate for individual-level studies, as it better captures local climate characteristics and residents' actual experiences.[17] Previous studies had found that heatwaves with different intensities and durations correspond to different health impacts.[8,17,18] Consequently, in this study, two indicators, intensity and duration were used to define heatwaves. At each decedent's address of residence, a heatwave event was defined as the daily mean temperatures for 2, 3 or 4 consecutive days of that location were equal to or greater than 90th, 95th or 97.5th percentile of the daily mean temperature of the entire study period. This resulted in nine heatwave scenarios defined as: P90 & 2-day, P90 & 3-day, P90 & 4-day, P95 & 2-day, P95 & 3-day, P95 & 4-day, P97.5 & 2-day, P97.5 & 3-day, and P97.5 & 4-day, where P90 & 2-day and P97.5 & 4-day had been defined as the mildest and the most severe heatwave scenarios. This multidimensional approach allows for a comprehensive analysis on how heatwaves of different intensities and durations may impact dementia mortality.

Study design

An individual-level time-stratified case-crossover study design was adopted to understand the impact of heatwaves on AD and other dementia mortality. First, by directly assessing exposure and characteristic data at individual level, rather than using regional level averages, the association between the exposure and health outcomes could be more accurately estimated.[19] Second, by applying time-stratified design, the long-term trends, seasonal patterns, and day-of-the-week (DOW) were automatically controlled for, when matching within the same year, month, and DOW.[18] Furthermore, the case-crossover design compares each decedent to his or her self, effectively eliminating confounding factors from inherent individual characteristics (such as sex, age, lifestyle, and comorbidities), thereby improving the internal validity of the study.[20] In summary, this study design could provide more precise and reliable evidence on the effects of heatwave exposure on dementia mortality.

Statistical analysis

In this study, a conditional logistic regression model was used to compare the mortality risk of AD and other dementia patients during heatwave days versus non-heatwave days at individual level. As the impact of heatwaves on health, usually persist for seven days,[8,18] which is in line with the result of lag-response analysis (Fig. 1), a distributed lag non-linear model (DLNM) was incorporated into the conditional logistic regression model to capture the lag0-7 lagged effects. Furthermore, the daily mean relative humidity, daily mean pressure, sex, age, cities, and holidays were controlled as potential confounding factors. The model is as follow:

$$\begin{aligned} E(Y) = \alpha + cb(HW, lag = 7) + stratum \\ + ns(RHmean, df = 3) + ns(Pmean, df = 3) \\ + \text{sex} + \text{age} + \text{cities} + \text{holidays} \end{aligned} \quad (1)$$

where $E(Y)$ refers to the expected mortality of AD and other dementias. α is the intercept term. $cb(HW, lag = 7)$ is the cross-basis function for heatwaves of lag0-7. *stratum* is categorical variable representing the time-stratification, defined as the same year, month, and DOW. $ns(RHmean,\ df = 3)$ is a natural spline function with degrees of freedom (df) = 3 for the

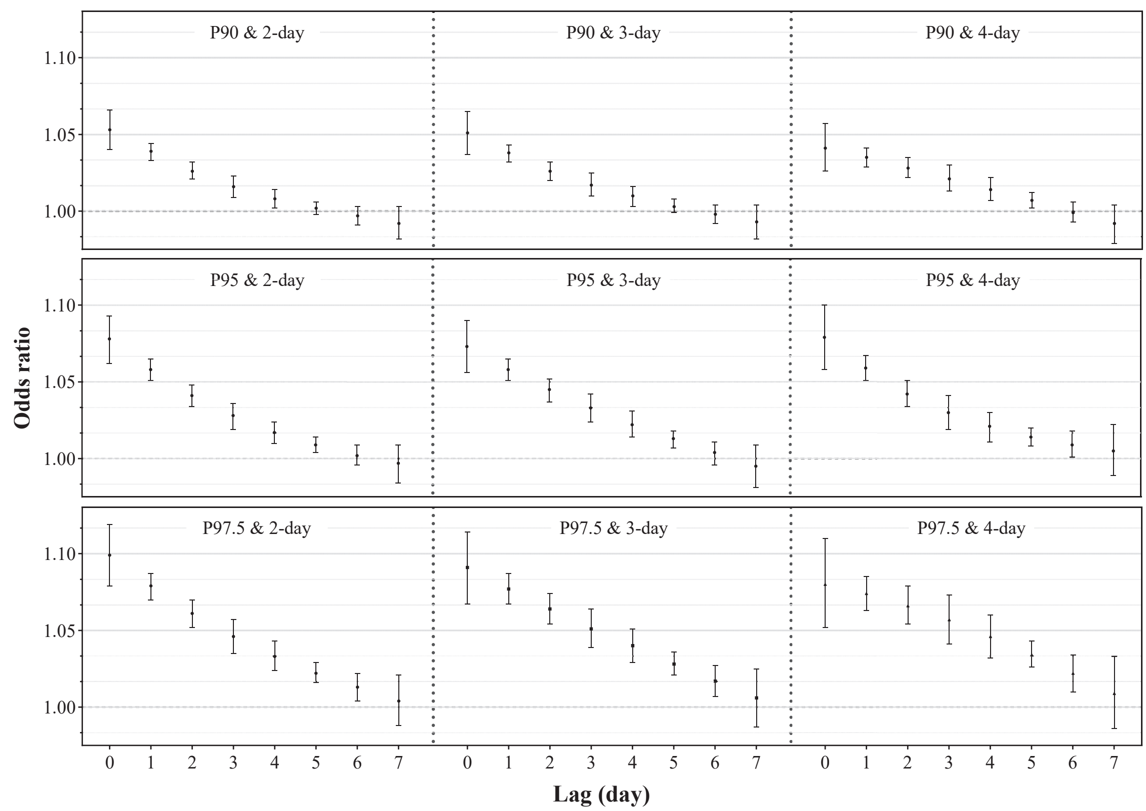

Fig. 1: Lag-response curves of mortality from Alzheimer's disease and other dementias among elderly aged 60 years and above across nine heatwave scenarios, China, 2013–2020.

daily mean relative humidity. *ns(Pmean, df = 3)* is a natural spline function with df = 3 for the daily mean pressure.[13,18,21] Sex, cities, and holidays are categorical variables and age is a continuous variable.

Based on the results of the cumulative odds ratios (CORs) from conditional logistic regression, the attributable fraction (AF) is calculated as follow:

$$AF = \frac{(COR\text{–}1)}{COR} \times 100\% \quad (2)$$

where AF is the attributable fraction of AD and other dementia mortality due to heatwaves, and COR is the cumulative odds ratio.[18]

To analyze the effects of different subgroups, stratified analyses were also conducted by sex (male and female), age (60–74 years and ≥75 years), geographic regions (northern China and southern China), and administrative regions (North China, North–east China, East China, Central–south China, South-west China, and North-west China). The statistical significance of differences between subgroups are performed as follow:

$$(\hat{Q}_1 - \hat{Q}_2) \pm 1{\cdot}96\sqrt{\widehat{SE}_1^{\,2} + \widehat{SE}_2^{\,2}} \quad (3)$$

where $\hat{Q}_1$ and $\hat{Q}_2$ are the estimates for the two categories, and $\widehat{SE}_1$ and $\widehat{SE}_2$ are standard error.[22]

Sensitivity analysis

The df of the relative humidity and pressure were set at 3 and not adjusting the temperature throughout the study. To test the robustness of the model, we tried following three adjustments: 1) adjusted the relative humidity's df = 4, others remain unchanged; 2) took out the pressure factor from the model, others remain unchanged; 3) controlled the temperature as a confounding factor using *ns(Tmean,2df)*, others remain unchanged.

All data analyses were performed by R software, version 4.1.2 (R Project for Statistical Computing, Vienna, Austria, http://www.-project.org).

Statistical significance was defined as $p < 0.05$ for all statistical tests.

Ethics approval

The ethical approval was granted by the Ethics Committee of the National Institute of Environmental Health, Chinese Center for Disease Control and Prevention with the approval number 201606. Individual patient consent was not required for our analysis of de-identified data collected from CDRS. Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Role of the funding sources

The funders had no role in the study design, data collection, data analysis, interpretation, or writing of the manuscript.

Results

Descriptive statistics

Table 1 shows that a total of 399,036 deaths were included in the study. Among them, 55.85% were female and 85.54% were aged 75 years and above. The number of deaths occurring on heatwave days (HWDs) and non-heatwave days (non-HWDs) varies under nine different heatwave scenarios. There are 37,542 deaths during HWDs under the P90 & 2-day scenario, and only 5522 under the P97.5 & 4-day scenario. This demonstrates how the specific scenario used to define a heatwave event can have a substantial impact on identifying the number of heatwave days, and consequently influence the number of deaths occurring during these heatwave days.

Associations between heatwaves and AD and other dementia mortality

Fig. 1 displays the lag-response curves across nine heatwave scenarios, exploring the lagged effects of heatwave exposure on AD and other dementia mortality. Under all heatwave scenarios, the mortality risk on the exposure day (lag0) is the largest. Subsequently, the risk gradually decreases and becomes non-significant before lag7. Based on this result, lag0-7 was chosen to conduct the subsequent exposure-response analyses. Furthermore, Fig. 1 also shows that as the intensity and duration of heatwaves increase, the impact exhibited an increased trend.

Fig. 2 demonstrates the exposure-response relationship between heatwaves and AD and other dementia mortality by the lag0-7 CORs under nine different heatwave scenarios. It can be observed that as the intensity and duration of heatwaves increase, the CORs gradually increases, from 1.140 (95% CI: 1.118, 1.163) under the P90 & 2-day scenario to 1.459 (95% CI: 1.403, 1.518) under the P97.5 & 4-day scenario. The stratified analysis by gender revealed that there is an increased mortality risk of females compared to that of males under the P95 & 2-day and P97.5 & 2-day scenarios. Stratification analysis of geographical regions revealed significant higher mortality risk in the northern China than it in the southern China under the P90 & 3-day and P95 & 2-day scenarios. For administrative regions, the mortality risks displayed an increasing trend from west to east and from south to north across regions in China. No significant differences were found in the stratification by age.

	P90 & 2-day		P90 & 3-day		P90 & 4-day		P95 & 2-day		P95 & 3-day		P95 & 4-day		P97.5 & 2-day		P97.5 & 3-day		P97.5 & 4-day	
	HWDs	non-HWDs	HWDs	non-HWDs	HWDs	non-HWDs	HWDs	non-HWDs	HWDs	non-HWDs	HWDs	non-HWDs	HWDs	non-HWDs	HWDs	non-HWDs	HWDs	non-HWDs
Overall	37,542	361,494	32,831	366,205	28,668	370,368	18,892	380,144	15,434	383,602	12,830	386,206	9320	389,716	7170	391,866	5522	393,514
Sex																		
Male	16,415	159,774	14,306	161,883	12,411	163,778	8134	168,055	6631	169,558	5516	170,673	3955	172,234	3023	173,166	2310	173,879
Female	21,127	201,720	18,525	204,322	16,257	206,590	10,758	212,089	8803	214,044	7314	215,533	5365	217,482	4147	218,700	3212	219,635
Age group (years)																		
60~74	5824	51,905	5088	52,641	4475	53,254	2918	54,811	2373	55,356	1975	55,754	1426	56,303	1107	56,622	841	56,888
≥75	31,718	309,589	27,743	313,564	24,193	317,114	15,974	325,333	13,061	328,246	10,855	330,452	7894	333,413	6063	335,244	4681	336,626

Abbreviation: HWDs refers to heatwave days. Non-HWDs refers to non-heatwave days.

Table 1: Number of deaths from Alzheimer's disease and other dementias on heatwave days and non-heatwave days under nine different heatwave scenarios, 2013–2020, China.

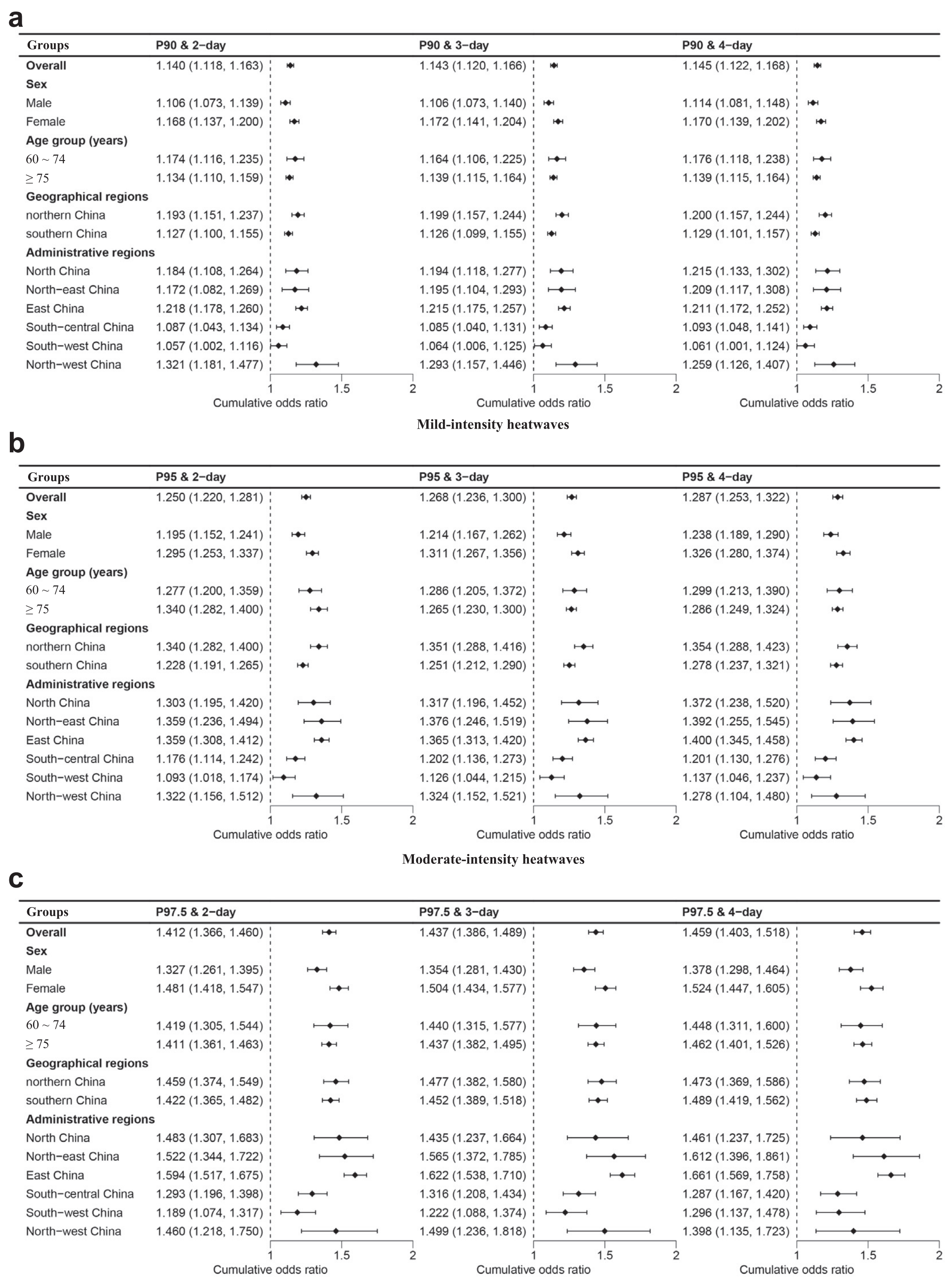

Fig. 2: Cumulative odds ratios of mortality from Alzheimer's disease and other dementias among elderly aged 60 years and above across nine heatwave scenarios, China, 2013–2020.

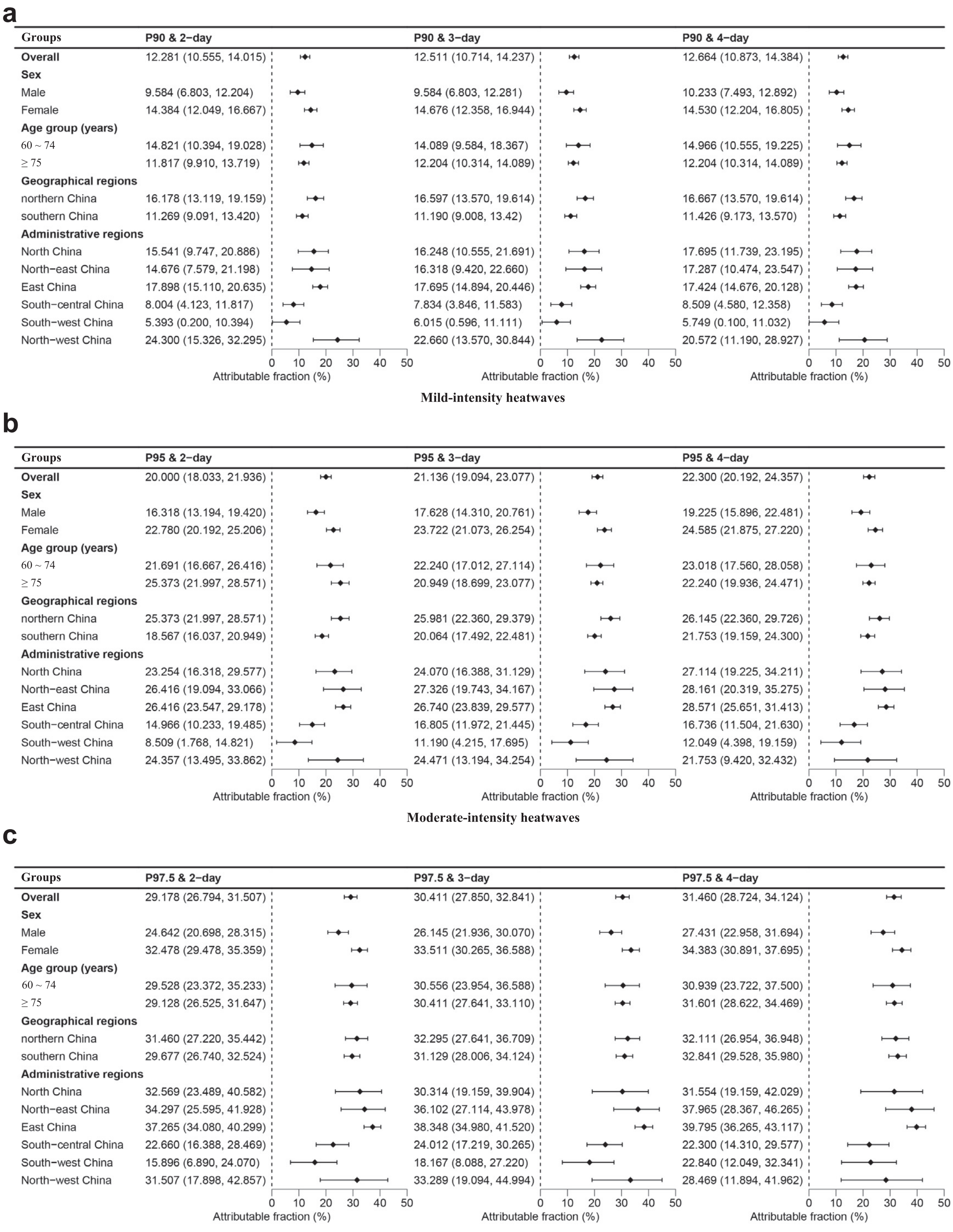

Fig. 3: Attributable fractions of mortality from Alzheimer's disease and other dementias among elderly aged 60 years and above due to heatwaves across nine heatwave scenarios, China, 2013–2020.

The AFs of AD and other dementia mortality due to heatwaves

The trends in AFs of AD and other dementia mortality due to heatwaves were consistent with the trends in CORs. Specifically, Fig. 3 shows that the AFs due to milder heatwaves were lower than that due to more severe ones. Overall, the AF increased from 12.281% (95% CI: 10.555%, 14.015%) under the P90 & 2-day scenario to 31.460% (95% CI: 28.724%, 34.124%) under the P97.5 & 4-day scenario.

Sensitivity analysis

The sensitivity analysis results (Table S1) showed that the CORs remained almost unchanged, which indicated that the models were stable.

Discussion

We used a nationwide dataset to examine the relationship between heatwave exposure and AD and other dementia mortality among the Chinese population aged 60 and above, under nine different heatwave scenarios. The study found that heatwaves were significantly associated with an increased risk of AD and other dementia mortality among the elderly, with the lagged effect observed. Additionally, under specific heatwave scenarios, sex and regions modified the effects, but no significant age differences were observed. Notably, more severe heatwaves brought greater attributable disease burden compared to those under milder heatwaves. To our knowledge, this is the first study in China to date that has explored the association between heatwaves and mortality of AD and other dementias among the elderly. These findings have important implications for developing targeted public health policies and intervention measures to protect the vulnerable elderly from the adverse effects of heatwaves.

The study found that heatwaves significantly increase the risk of elderly mortality caused by AD and other dementias. An Australian study also found that heatwaves increase the risk of hospitalization and post-discharge mortality for AD patients.[8] There are three potential reasons for this result. Firstly, due to cognitive impairment, dementia patients have difficulty perceiving their surrounding environment and are unable to proactively take effective coping measures. This makes them more susceptible to heat-related complications such as dehydration and heatstroke, which can exacerbate their condition and increase the risk of death.[8] Secondly, high temperatures may worsen the symptoms of neurological diseases through mechanisms such as activating immune responses, disrupting neurological homeostasis, and rising oxidative stress, ultimately increasing the risk of death.[14,23] Thirdly, medications for AD and other dementia patients could impact the body's thermoregulation. For example, cholinesterase inhibitors can reduce sweating, impairing the body's ability to dissipate heat. Neurotransmitter-modulating drugs may interfere with the normal functioning of the hypothalamus by impacting neurotransmitters such as dopamine and serotonin.[24–26] Under severe heatwave events, the effects would be amplified and even lead to death. Therefore, when heatwaves occur, targeted preventive measures need to be taken, such as providing better cooling facilities and strengthening health monitoring, to mitigate the harm on this vulnerable population. At the same time, medical institutions need to strengthen monitoring at dementia patients to reduce the occurrence of complications and the risk of death.

Another interesting founding is that heatwaves have both acute and lagged effects on the mortality of AD and other dementia patients. The acute effect is that the physiological stress response caused by the heatwave can quickly affect the condition of patients, such as raised body temperature, dehydration, and increased cardiovascular load.[8,14] This physiological imbalance can directly lead to the deterioration of AD and other dementias' conditions, triggering serious complications, and even causing death. The lagged effect indicates that the heatwaves may continue to affect the physical and mental state of patients for several days afterward. Lagged effect stems from a combination of factors as organ damage, immune impairment, temperature dysregulation, and psychological stress.[7,8] In summary, heatwaves pose both acute and lagged threats to dementia patients, increasing their risk of death. It requires the close collaboration and comprehensive support of the healthcare system, community resources, and family caregivers, not only providing timely assistance during the heatwave events but also continuing to monitor and to care for patients in the following days.

The research found that under specific heatwave scenarios, heatwaves had a greater impact on the mortality risk of females than that of males. This result is consistent with a previous study, in which women not only have a higher risk of developing AD, but also show significantly faster rates of cognition decline compared to age-matched men.[27] The exact causes of gender differences are still unclear. Potential factors may involve biological mechanisms, such as female-specific neuroendocrine mechanisms,[27] as well as sociocultural factors, such as caregiving burden.[28,29] Further in-depth exploration of the mechanisms driving by sex differences is crucial for better understanding the impact of heatwaves on dementia mortally.

The exposure-response relationship exhibited regional differences, where the risk tended to increase from south to north and west to east across China. This is consistent with the findings from other studies.[14] The regional heterogeneity could be due to the variations in climate, geography, socioeconomic conditions, and adaptation abilities across different regions.[13,30] For example, the southern regions of China generally have a hotter climate compared to the northern regions, but the southern population may be more adapted to heatwaves and have a higher tolerance.[13,31–33] Furthermore, the architectural design tailored to the local climate in southern China, along with differences in materials and construction methods, is likely a key factor contributing to better heat insulation and dissipation performance of residences in that region compared to the north.[34] Additionally, for more economically developed eastern coastal regions, it could experience stronger urban heat island effects that could increase the intensity and duration of heatwaves, which is leading to a greater harm to vulnerable groups.[32,35] These factors collectively contribute to the regional differences in the impact of heatwaves on the risk of dementia mortality.

The AFs of AD and other dementia mortality due to more severe heatwaves were significantly higher than those due to milder heatwaves. With the intensification of global warming, high-intensity and long-duration heatwaves may occur more frequent worldwide in the future. It is projected that heat-related mortality will increase further, resulting in numerous excess deaths. This will undoubtedly increase the mortality risk and disease burden for dementia patients.[12,30] Therefore, authorities must pay closer attention to heatwaves and take targeted preventive measures to provide more comprehensive and effective protection for this vulnerable population.

Several limitations should be acknowledged. First, the study used data from the CDRS, which may have reporting biases and omissions. Second, the study did not obtain detailed individual-level information on demographics, clinical characteristics, lifestyles, and other potential interactive factors, thereby limiting the possibility to conduct in-depth analyses of how these factors may influence the relationship between heatwaves and mortality of AD and other dementias.

Conclusions

This nationwide study provided important insights into understanding the impact of heatwaves on mortality among elderly people with AD and other dementias in China. The study found that, during and after heatwave events, AD and other dementia-related mortality increased notably with significant differences across sex and regions. This underscores the urgent need for regional targeted public health interventions to this vulnerable population. In fact, a great number of heat-related deaths could be reduced through the implementations of appropriate heatwave response policies. The findings could provide valuable information for developing policies to enhance society's capacity when facing heatwaves, especially in the context of both seasonal changes and long-term climate change.

Contributors

RZ and LS: Writing—original draft, Software, Methodology, Formal analysis. SWW and QG: Writing—review & editing, Resources, Funding acquisition. YW: Software, Methodology, Formal analysis. AJ, CW and HZ: Writing—original draft, Visualization. SYW: review & editing. XS: review & editing, Conceptualization. PB: review & editing. YL: review & editing, Conceptualization, Funding acquisition. JW: review & editing, Conceptualization. All authors approve the final version of the manuscript. The author JW and RZ verified the data and had full access to all the raw data in the study. JW had final responsibility for the decision to submit for publication.

Data sharing statement

The mortality data can only be applied from National Population and Health Science Data Sharing Platform (http://www.phsciencedata.cn/Share/en/index.jsp).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101217.

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