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Extreme temperature events and dementia mortality in Chinese adults: a population-based, case-crossover study

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Abstract

Background: The effect of exposure to extreme temperature events (ETEs) on dementia mortality remains largely unknown. We aimed to quantify the association of ETE exposure with dementia mortality.

Methods: We conducted a population-based, case-crossover study among 57 791 dementia deaths in Jiangsu province, China, during 2015–20. Daily mean temperatures were extracted from a validated grid dataset at each subject's residential address, and grid-specific exposures to heat wave and cold spell were assessed with a combination of their intensity and duration. We applied conditional logistic regression models to investigate cumulative and lag effects for ETE exposures.

Results: Exposure to ETE with each of all 24 definitions was associated with an increased odds of dementia mortality, which was higher when exposed to heat wave. Exposure to heat wave (daily mean temperature ≥95th percentile, duration ≥3 days (d); P95_3d) and cold spell (≤5th percentile, duration ≥3 d; P5_3d) was associated with a 75% (95% CI: 61%, 90%) and 30% (19%, 43%) increase in odds of dementia mortality, respectively. Definitions with higher intensity were generally associated with a higher odds of dementia mortality. We estimated that 6.14% of dementia deaths were attributable to exposure to heat wave (P90_2d) and cold spell (P10_2d). No effect modifications were observed by sex or age, except that the association for heat wave was stronger among women.

Conclusions: Exposure to both heat wave and cold spell was associated with an increased odds of dementia mortality. Our findings highlight that reducing individual ETE exposures may be helpful in preventing deaths from dementia, especially among women in summer.

Keywords: Extreme temperature events, dementia, mortality, case-crossover study.

Key Messages

- We comprehensively investigated the association of extreme temperature event (ETE) exposure with dementia mortality, based on the grid-specific ETE exposure.
- Exposure to both heat wave and cold spell was associated with an increased odds of dementia mortality, which was higher when exposed to heat wave.
- During 2015–20, 3551 deaths were attributable to ETE exposures, accounting for 6.14% of all dementia deaths in Jiangsu province, China.
- Our findings suggest that reducing individual exposure to ETEs can be helpful in preventing dementia deaths, especially among women in summer.

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Introduction

Under the scenario of global climate change, extreme temperature events (ETEs) including heat waves and cold spells were projected to be more frequent, intense and with a longer duration in the next decade.[1] Accumulating evidence has suggested that ETE exposure is associated with increased risks of mortality from a variety of causes,[2,3] notably with vulnerable populations of older adults[4,5] and patients with nervous system diseases.[6] In the context of population ageing, age-related neurodegenerative disease like dementia shows a persistent increase in incidence, prevalence and mortality globally. The population with dementia continues to increase and is expected to triple to more than 152 million by 2050.[7] According to the top 10 causes of death,[8] dementia has ranked as the 7th leading cause of death globally and was responsible for 1.6 million deaths in 2019.[9] Given the increasing occurrence of ETEs, the growing number of vulnerable dementia populations and the substantial mortality burden, the adverse effects of ETEs on dementia mortality have drawn much concern worldwide. Patients suffering from dementia are characterized by impaired environment judgment ability and altered thermoregulation ability.[10,11] Compared with the general population, dementia patients may have a higher risk of dehydration or hypothermia during ETEs, which can accelerate the disease progression, worsen the disease status and increase the susceptibility to ETE-related mortality.[12,13] Therefore, it is necessary to systematically investigate the effects of ETEs on dementia mortality, which can provide useful clues for formulating target intervention strategies and establishing early warning systems for ETEs to prevent dementia deaths.

Existing studies have found adverse effects of ETEs on mental health[14] and have linked ETE exposures to the clinical aggravation of dementia, using hospital admissions as the outcome.[15] However, the health impacts of ETEs on dementia mortality remains less clear. To date, only two single-city studies in Australia intended to explore the association between heat wave and dementia mortality. A time-series analysis of 1953 dementia deaths in Adelaide, Australia, during 1993–2006 reported that heat wave was associated with an increased risk of dementia mortality.[15] The other case-crossover study in Brisbane, Australia, during 2005–13 also reported a positive association between heat wave and post-discharge mortality risk in 307 patients with a previous hospitalization for Alzheimer's disease.[16] Overall, these results are limited due to a small sample size and city-level exposure assessment. In contrast, the effect of cold spells on dementia mortality is yet to be investigated. A time-series study in China concluded that extreme cold temperatures exposure was associated with an increased risk of dementia mortality, suggesting possible adverse effects of sustained extreme cold days on dementia mortality.[17]

For better understanding potential adverse effects of ETEs on dementia mortality, we conducted a population-based, case-crossover study to systematically investigate the association between ETE exposure and dementia mortality among adult dementia deaths in Jiangsu province, China, during 2015–20. Corresponding excess mortality was assessed to quantify the mortality burden.

Methods

Study area

The study area covered all 13 prefectural cities in Jiangsu province, China, which includes 55 districts, 21 county-level cities and 19 counties. Jiangsu (116°21'-121°56' E, 30°45'-35°08' N) is a densely populated province on the east-central coast of China, with a population of 84.8 million and an average population density of 1264.2 per km^2 in 2020. Jiangsu province has four distinct seasons with a wide range of temperatures, with the daily mean temperature ranging from -10.9 to 36.4 °C during 2015–20.

Study population

Dementia mortality data were obtained from the Jiangsu provincial mortality surveillance system in 2015–20.[18] During the study period, we identified 57 791 individuals who were 18 years or older and died from dementia as the underlying cause defined by professional staff, based on the information of chain of events on the death certificates.[18,19] Demographic information on sex, marital status, residential address, date of birth and date of death was collected for each subject.

Study design

We applied a time-stratified case-crossover design to investigate the association between ETE exposure and dementia mortality. In this design, each subject served as his or her own reference. For each death, the exposure on date of death (case day) was compared with the exposure on its corresponding control days, which were defined as days sharing the same year, month and day of week as the case day.[20,21] In total, 196 302 control days were matched for 57 791 case days. According to this approach, potential confounding effects by time-invariant variables, day of week, long-term trend and season can be adequately controlled.[22]

Exposure assessment

Grid meteorological data (spatial resolution: 0.0625° × 0.0625°) on daily 24-h average temperature and relative humidity in Jiangsu province during 2015–20 were obtained from the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0).[23–25] As there are no standard definitions, we defined 24 ETEs as a daily temperature higher or lower than a certain threshold for a few consecutive days, as proposed in previous studies (Supplementary Table S1, available as Supplementary data at *IJE* online).[3]

We took two steps to assess ETE exposures. First, we identified ETEs using each of the 24 definitions for each CLDAS grid based on temperature distribution within the grid, and generated a new grid data on ETEs for each definition. For each grid, heat wave and cold spell days were assigned 1 and 2, respectively, and the remaining days were assigned 0. Second, we assessed the exposure to ETEs by extracting values at each subject's residential address from the ETE grid data. To flexibly account for potential acute or longer-lasting lag effects of ETEs, lags up to 10 days for heat waves and 14 days for cold spells were used.[2,3]

Covariates

For each subject, we extracted 24-h average temperature and relative humidity at his or her residential address with up to 10 or 14 days lag. According to the results of our previous study,[26] exposure to ambient air pollution on the date of death and 4 days prior was estimated by extracting 24-h average fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) at each subject's residential address from the

ChinaHighAirPollutants (CHAP) dataset (spatial resolution: 10 km × 10 km).[27,28]

Outcomes

International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) was used to code the underlying cause for each death. The outcome of interest was mortality from dementia (ICD-10 codes: F01, F03, G30 and G31).

Statistical analysis

We investigated the cumulative association between ETE exposure and dementia mortality using a conditional logistic regression model combined with a distributed lag non-linear model (DLNM).[5,29,30] To capture potential lag effects and mortality displacement, we specified a lag structure of up to 10 and 14 days for exposure to heat wave and cold spell, respectively.[31] Specifically, we first built a cross-basis function for ETE exposure, in which a 'strata' function with two internal cut-off points placed at 1 and 2 for the exposure-response dimension was used to create dummy variables for ETE exposure, where 1 denoted heat wave days, 2 denoted cold spell days and 0 denoted the remaining days. Based on minimized Akaike information criterion (AIC),[30] we constructed the lag-response dimension as a natural cubic spline function with two equally spaced internal knots in the log scale and selected a maximum lag up to 10 and 14 days for heat wave and cold spell, respectively. Second, we included the cross-basis function for ETE exposure in the model and controlled for the daily mean relative humidity (lag 0-day) using a natural cubic spline function with three degrees of freedom (*df*). The cumulative association between ETE exposure and dementia mortality was quantified using odds ratio (OR) and its 95% confidence interval (CI). We also examined whether the prolonged period of extreme hot/cold temperature had added effects above the effects of daily temperature on dementia mortality, by further including daily mean temperature as a cross-basis function in the model (see Supplementary Methods, available as Supplementary data at *IJE* online).

We quantified the excess dementia mortality attributable to ETE exposure by calculating the excess fraction of mortality from dementia, based on the estimated cumulative association.[32–34] The empirical confidence interval (eCI) of excess mortality was calculated by Monte Carlo simulations.[34] We multiplied the total dementia deaths by excess fractions to estimate the number of dementia death attributable to ETE exposures.

Stratified analyses by sex (male, female), and age (<85, ≥85) were conducted to identify vulnerable populations, and two-sample z tests were performed to examine the difference across stratifications.[35] Sensitivity analyses were performed to test the robustness of our results (see Supplementary Methods, available as Supplementary data at *IJE* online). R version 4.1.2 was used for the data analyses.[36] All statistical analyses were two-sided, and *P*-values were reported.

Results

As shown in the Supplementary Figure S1 (available as Supplementary data at *IJE* online), we identified 57 791 dementia deaths (including 19 695 Alzheimer's disease deaths) in Jiangsu province, China, during 2015–20. Among these dementia deaths, 38.6% were male, 46.5% died before 85 years, and 51.2% died in cool season (Table 1). The spatial distributions of ETEs during 2015–20 are provided in Figure 1 (daily mean temperature ≥95th percentile, duration ≥3 consecutive days, P95_3d; ≤5th percentile, duration ≥3 consecutive days, P5_3d), and Supplementary Figures S2–S4 (available as Supplementary data at *IJE* online). The temperature distribution of grid-specific ETEs under a series of temperature thresholds is presented in Supplementary Table S2 (available as Supplementary data at *IJE* online).

Table 1. Characteristics of study population in Jiangsu province, China, 2015–20

Characteristic	Dementia	Alzheimer's disease
No. of deaths (case days)	57 791	19 695
No. of control days	196 306	66 947
Sex		
Male	22 332 (38.6%)	7194 (36.5%)
Female	35 459 (61.4%)	12 501 (63.5%)
Age in years, mean (SD)	84.2 (9.2)	84.5 (7.5)
<85 years	26 849 (46.5%)	9329 (47.4%)
≥85 years	30 942 (53.5%)	10 366 (52.6%)
Race		
Han	57 710 (99.9%)	19 665 (99.8%)
Other	81 (0.1%)	30 (0.2%)
Marital status		
Unmarried	1030 (1.8%)	323 (1.6%)
Married	24 594 (42.6%)	7859 (39.9%)
Divorced	410 (0.7%)	149 (0.8%)
Widowed	31 594 (54.7%)	11 314 (57.4%)
Unknown	163 (0.3%)	50 (0.3%)
Season at death		
Cool (November–March)	29 583 (51.2%)	10 105 (51.3%)
Warm (April–October)	28 208 (48.8%)	9590 (48.7%)
Year of death		
2015	9076 (15.7%)	2280 (11.6%)
2016	9423 (16.3%)	2707 (13.7%)
2017	9217 (15.9%)	2770 (14.1%)
2018	9538 (16.5%)	3145 (16.0%)
2019	9854 (17.1%)	4040 (20.5%)
2020	10 683 (18.5%)	4753 (24.1%)

SD, standard deviation.

The overall lag structures demonstrate that the odds of dementia mortality associated with heat wave exposure was the strongest on the first day, decreased in 1–5 days, and levelled off or slightly increased in the next days. In comparison, the odds of cold spell exposure peaked on the first 2 days and attenuated but remain stable or followed by a mortality displacement on the subsequent days (Figure 2).

Table 2 illustrates the cumulative association of ETE exposure with dementia mortality over lag 0–10 and 0–14 days for heat wave and cold spell, respectively. A consistent association of ETE exposure with dementia mortality was identified for all definitions, in which exposure to heat wave was generally associated with higher odds of dementia mortality than that for cold spell, with the OR ranging from 1.49 to 2.33 and 1.24 to 1.36, respectively. Specifically, exposure to heat wave in the definition of P95_3d and exposure to cold spell in the definition of P5_3d was associated with a 75% and a 30% increase in odds of mortality from dementia, respectively. In addition, exposure to ETEs with a higher temperature threshold was generally associated with higher odds of dementia mortality. For ETEs defined using the same threshold, the effects of heat wave on dementia mortality increased with prolonged durations, especially for definitions with

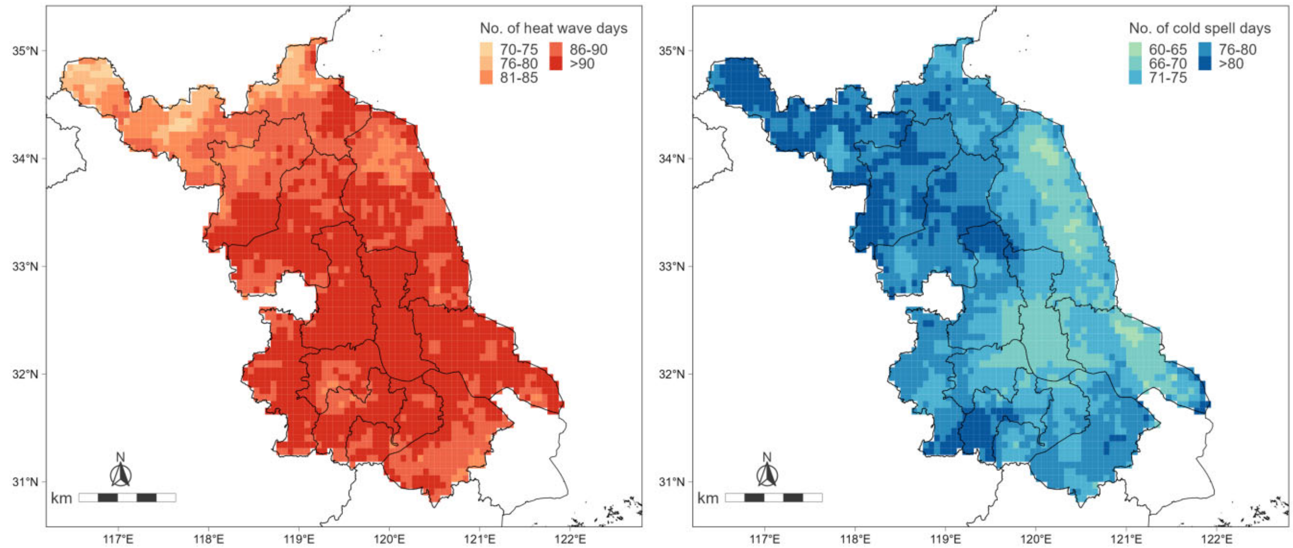

Figure 1. Spatial distribution of extreme temperature events in the definitions of P95_3d and P5_3d in Jiangsu province, China, during 2015–20. The grids with different colours in the left and right panel denote the number of heat wave and cold spell days in the definitions of P95_3d and P5_3d at a 0.0625° × 0.0625° spatial resolution, respectively. P95_3d, daily mean temperature ≥95th percentile of temperature distribution with ≥3 consecutive days; P5_3d, daily mean temperature ≤5th percentile of temperature distribution with ≥3 consecutive days

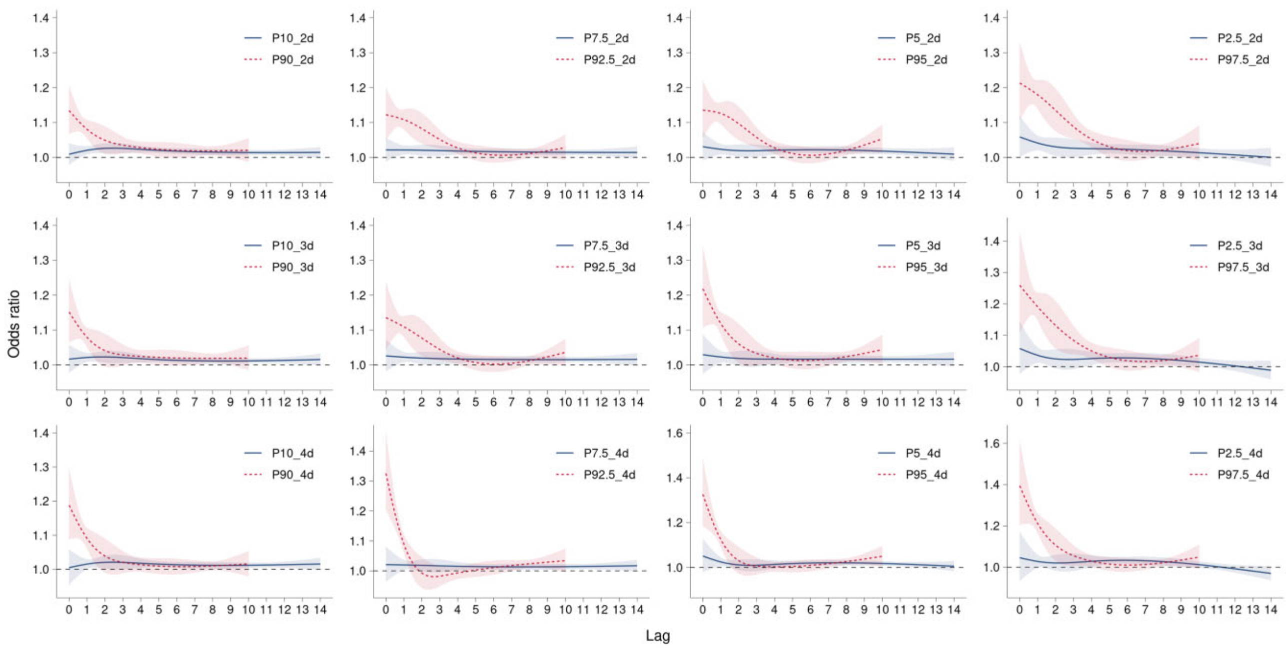

Figure 2. Overall lag structure for the association of extreme temperature event exposure with dementia mortality in Jiangsu province, China, during 2015–20. The definitions of extreme temperature events are given in Supplementary Table S1 (available as Supplementary data at *IJE* online). The horizontal dotted line in each panel indicates an odds ratio of 1. The red and blue solid lines indicate the odds ratio of dementia mortality associated with exposure to heat wave and cold spell, respectively, with shaded regions representing their corresponding 95% CIs. CI, confidence interval

higher intensities (e.g. P95, P97.5). In contrast, the estimated effects for cold spells were similar across durations. With further adjustment for daily mean temperature in the main analyses, the associations of ETE exposure with dementia mortality decreased but remained for nine heat wave definitions, and definitions with longer duration and higher intensity generally associated with higher added effects. However, associations of cold spell exposure with dementia mortality were not observed after the adjustment (Table 2).

Table 3 presents the excess fraction and corresponding number of dementia deaths attributable to ETE exposures. Heat wave in the P95_3d definition contributed to 1.91% of dementia mortality, corresponding to 1104 dementia deaths. Exposure to cold spell in the definition of P5_3d accounted for 1.21% of dementia mortality, which was translated to 699 dementia deaths. Overall, restricting analyses to Alzheimer's disease deaths yielded very similar results, except that the odds of mortality and ETE-related mortality burden was slightly higher.

In stratified analyses, no effect modification was identified by sex or age (Table 4; all P for effect modification >0.05), except for exposure to heat wave in the definition of

Table 2. Cumulative associations and added effects of exposure to ETEs with dementia mortality in Jiangsu province, China, 2015–20

ETE[a]	Dementia		Alzheimer's disease	
	Cumulative OR (95% CI)	Added[b] OR (95% CI)	Cumulative OR (95% CI)	Added[b] OR (95% CI)
Heat wave				
P90_2d	1.54 (1.43–1.66)	1.02 (0.89–1.16)	1.56 (1.38–1.78)	1.05 (0.84–1.32)
P90_3d	1.53 (1.42–1.65)	1.05 (0.92–1.18)	1.59 (1.41–1.81)	1.16 (0.94–1.44)
P90_4d	1.49 (1.39–1.60)	1.02 (0.91–1.14)	1.56 (1.38–1.76)	1.14 (0.94–1.39)
P92.5_2d	1.58 (1.46–1.70)	1.15 (1.01–1.31)	1.67 (1.47–1.90)	1.33 (1.07–1.66)
P92.5_3d	1.57 (1.46–1.69)	1.14 (1.01–1.29)	1.71 (1.51–1.95)	1.39 (1.13–1.71)
P92.5_4d	1.57 (1.46–1.69)	1.13 (1.01–1.27)	1.70 (1.49–1.93)	1.37 (1.13–1.67)
P95_2d	1.74 (1.60–1.88)	1.34 (1.18–1.53)	2.06 (1.78–2.37)	1.89 (1.51–2.37)
P95_3d	1.75 (1.61–1.90)	1.35 (1.19–1.54)	2.13 (1.84–2.46)	1.95 (1.57–2.43)
P95_4d	1.79 (1.64–1.94)	1.36 (1.21–1.54)	2.05 (1.77–2.39)	1.77 (1.43–2.19)
P97.5_2d	2.17 (1.95–2.40)	1.76 (1.52–2.04)	2.58 (2.16–3.09)	2.39 (1.86–3.08)
P97.5_3d	2.23 (2.00–2.49)	1.79 (1.55–2.08)	2.58 (2.14–3.11)	2.22 (1.72–2.85)
P97.5_4d	2.33 (2.08–2.62)	1.83 (1.58–2.12)	2.83 (2.31–3.47)	2.37 (1.84–3.06)
Cold spell				
P10_2d	1.29 (1.19–1.39)	1.03 (0.89–1.20)	1.55 (1.36–1.78)	1.16 (0.89–1.52)
P10_3d	1.25 (1.16–1.35)	1.06 (0.93–1.21)	1.47 (1.29–1.67)	1.12 (0.90–1.41)
P10_4d	1.24 (1.15–1.33)	1.10 (0.97–1.24)	1.45 (1.28–1.64)	1.17 (0.95–1.44)
P7.5_2d	1.28 (1.18–1.39)	0.98 (0.83–1.16)	1.53 (1.32–1.77)	1.00 (0.75–1.34)
P7.5_3d	1.29 (1.19–1.40)	1.11 (0.96–1.29)	1.50 (1.31–1.73)	1.10 (0.85–1.42)
P7.5_4d	1.26 (1.16–1.37)	1.09 (0.95–1.26)	1.46 (1.26–1.69)	1.05 (0.83–1.34)
P5_2d	1.32 (1.21–1.45)	1.06 (0.89–1.27)	1.55 (1.32–1.82)	0.92 (0.68–1.26)
P5_3d	1.30 (1.19–1.43)	1.07 (0.92–1.26)	1.50 (1.28–1.76)	0.96 (0.73–1.26)
P5_4d	1.30 (1.18–1.44)	1.10 (0.94–1.29)	1.46 (1.23–1.73)	0.95 (0.73–1.25)
P2.5_2d	1.36 (1.21–1.53)	1.03 (0.85–1.24)	1.58 (1.29–1.94)	0.87 (0.63–1.21)
P2.5_3d	1.34 (1.18–1.53)	1.04 (0.87–1.25)	1.54 (1.24–1.91)	0.93 (0.68–1.27)
P2.5_4d	1.27 (1.10–1.47)	0.97 (0.80–1.17)	1.57 (1.23–2.01)	0.98 (0.71–1.34)

CI, confidence interval; ETE, extreme temperature event; OR, odds ratio.
[a] ETEs were defined using the combination of intensity and duration; for example, P95_3d denotes heat waves with daily mean temperature ≥95th percentile of temperature distribution and with ≥3 consecutive days. The definitions of ETEs are given in Supplementary Table S1 (available as Supplementary data at *IJE* online).
[b] Added effects of dementia mortality associated with ETE exposure were estimated by further adjusting daily mean temperature in the model.

P97.5_4d, in which the odds of dementia mortality was higher in women than in men ($P = 0.048$). Sensitivity analyses generally yielded similar results (Supplementary Tables S3–S11, Supplementary Figures S5 and S6, available as Supplementary data at *IJE* online).

Discussion

In this large population-based case-crossover study, we found that ETE exposure was associated with an increased odds of mortality from dementia, in which the odds were higher for heat wave exposure. Definitions for ETEs with a higher threshold and heat wave with longer durations generally yielded higher odds of dementia mortality. Added effects were observed for heat wave exposure with further adjustment for temperature. During 2015–20, ETE exposure was responsible for up to 6.14% of dementia deaths in Jiangsu province, China. The association between heat wave and dementia mortality was stronger among women.

The observed association between heat wave and dementia mortality was generally consistent with the previous studies. Our estimated effects of extreme heat exposure on dementia mortality were higher than those on all-cause mortality in a recent time-series study in the same study area,[37] indicating a possible vulnerability of dementia patients during ETEs. The time-series study in Adelaide, Australia, estimated that the risk of dementia mortality during the heat waves increased by 405.8%, which was higher than mortality from other mental and behavioural disorders.[15] The other case-crossover study in Brisbane, Australia, found that exposure to moderate intensive heat wave (lag 0-day) was associated with a 269% increase in odds of dementia mortality.[16] Estimates of the two Australian studies were much higher than our results (74%). Note that the sample size of these two studies (1953 and 307, respectively) was much smaller, which may add uncertainties to the estimates. Besides, the city-level exposure assessment used in the two studies, the study population and the exposure metrics used in the case-crossover study were not equivalent to our study, which may also contribute to the different estimates. To date, the adverse effect of cold spells on dementia mortality has not been studied. Our study provides novel evidence that cold spell exposure was also associated with an increased odds of dementia mortality, which can be partly supported by results of a time-series study conducted in China.[17]

The underlying mechanisms of ETE exposures on dementia mortality remain largely unknown, but several mechanisms are plausible. The majority of dementia patients were older adults and were vulnerable to ETE exposures.[4,5] When exposed to ETEs, older patients were unable to keep heat balance by adjusting circulatory stress, changing the skin blood flow and regulating eccrine sweat glands and cardiac outputs[38,39] due to the diminished thermoregulatory ability,[40,41] which may increase ETE-related mortality risk. In addition to age, the nature of dementia is another essential risk factor. Dementia causes irreversible cognition decline and impairment of environmental judgment capacity with time,[10] and hinders the ability of patients to take adaptive behaviours

Table 3. Excess fraction and number of excess deaths from dementia associated with ETE exposure

ETE[a]	Dementia		Alzheimer's disease	
	Excess fraction, % (95% eCI)	Excess deaths (95% eCI)	Excess fraction, % (95% eCI)	Excess deaths (95% eCI)
Heat wave				
P90_2d	3.08 (2.59–3.53)	1782 (1511–2025)	3.11 (2.24–3.84)	612 (451–755)
P90_3d	2.76 (2.31–3.18)	1596 (1348–1847)	2.87 (2.14–3.53)	565 (425–686)
P90_4d	2.33 (1.94–2.69)	1345 (1105–1575)	2.53 (1.87–3.11)	499 (372–621)
P92.5_2d	2.57 (2.19–2.91)	1483 (1256–1685)	2.79 (2.15–3.35)	549 (433–660)
P92.5_3d	2.34 (2.00–2.68)	1354 (1164–1536)	2.65 (2.07–3.13)	522 (405–616)
P92.5_4d	1.93 (1.60–2.24)	1113 (917–1281)	2.40 (1.87–2.87)	473 (366–565)
P95_2d	2.15 (1.86–2.38)	1240 (1093–1395)	2.57 (2.13–2.97)	506 (419–585)
P95_3d	1.91 (1.66–2.14)	1104 (953–1236)	2.30 (1.87–2.70)	453 (368–531)
P95_4d	1.65 (1.42–1.87)	954 (815–1074)	1.96 (1.61–2.30)	387 (312–451)
P97.5_2d	1.59 (1.43–1.76)	921 (811–1013)	1.81 (1.54–2.06)	357 (299–403)
P97.5_3d	1.39 (1.24–1.53)	804 (711–887)	1.48 (1.22–1.73)	292 (241–336)
P97.5_4d	1.22 (1.08–1.35)	705 (614–780)	1.33 (1.10–1.52)	261 (214–302)
Cold spell				
P10_2d	3.06 (2.16–3.93)	1769 (1256–2237)	4.92 (3.49–6.21)	970 (696–1232)
P10_3d	2.26 (1.58–2.91)	1308 (898–1684)	3.43 (2.21–4.48)	676 (451–880)
P10_4d	1.73 (1.20–2.27)	1000 (680–1317)	2.68 (1.85–3.51)	527 (356–673)
P7.5_2d	2.19 (1.49–2.83)	1266 (857–1670)	3.46 (2.31–4.46)	682 (470–890)
P7.5_3d	1.78 (1.20–2.27)	1028 (704–1328)	2.55 (1.61–3.32)	503 (321–654)
P7.5_4d	1.32 (0.89–1.76)	764 (514–997)	1.92 (1.18–2.61)	379 (238–500)
P5_2d	1.66 (1.12–2.18)	960 (684–1242)	2.38 (1.52–3.13)	468 (282–627)
P5_3d	1.21 (0.80–1.57)	699 (454–925)	1.73 (1.10–2.38)	342 (213–459)
P5_4d	0.97 (0.63–1.30)	562 (356–754)	1.32 (0.73–1.87)	261 (150–358)
P2.5_2d	0.87 (0.55–1.18)	504 (314–685)	1.25 (0.70–1.72)	247 (138–338)
P2.5_3d	0.64 (0.37–0.92)	373 (224–523)	0.93 (0.44–1.31)	184 (95–264)
P2.5_4d	0.39 (0.17–0.59)	224 (94–347)	0.68 (0.30–1.00)	134 (61–198)

eCI, empirical confidence interval; ETE, extreme temperature event.
[a] ETEs were defined using the combination of intensity and duration; for example, P95_3d denotes heat waves with daily mean temperature ≥95th percentile of temperature distribution and with ≥3 consecutive days. The definitions of ETEs are given in Supplementary Table S1 (available as Supplementary data at *IJE* online).

including drinking enough fluid, being appropriately dressed and clearly expressing their needs to caregivers during ETEs. These limited response capacities can increase the risk of dehydration or hypothermia during ETEs,[12,13] which may aggravate the disease status or even lead to death. Besides, medications used in dementia treatment can cause side effects on thermoregulation,[42,43] and increase patients' vulnerability to heat and further increase the mortality risk. In addition, limited availability of medical services during ETEs may also increase the risk of death.[5] Our results suggest that in comparison with men, women are more susceptible to heat wave exposures, which may be explained by the physiological differences between sexes. Women have poor thermoregulation ability and a lower sweating capacity than men,[44–46] which can decrease heat dissipation, aggravate the burden on the human body and increase mortality risk during heat waves.

Our study provides novel evidence that ETE exposure may be an enviable risk factor for dementia mortality, especially among women in summer. In the scenarios of climate change and population ageing, there has been much concern on how to achieve target primary preventions for dementia in facing ETEs. Therefore, getting timely ETE warning services, and taking effective cause-specific preventive measures during ETEs can be of great public health importance. The results of adverse health impacts of ETEs on dementia mortality in our study provide useful clues for policy makers to develop effective intervention strategies and provide informative evidence for governments to establish ETE early warning systems based on an optimal definition. In clinical practice, our findings suggest that clinical physicians and caregivers need to strengthen the awareness of implementing ETE preventive measures during dementia treatments.

This study has several strengths. First, dementia deaths in this study were derived from a base population of 84.8 million over 6 years, which can provide sufficient statistical power. Second, the wide range of temperatures in Jiangsu province allowed us to simultaneously investigate the association of exposure to heat wave and cold spell with dementia mortality in a single study and to directly compare the difference in health effects. Third, taking advantage of case-crossover study design, we assessed ETE exposure for each subject from a high-resolution temperature dataset. Unlike previous studies relying on temperature data from fixed monitoring stations, the grid-specific ETE exposure used in this study enabled us to reduce potential bias caused by spatial heterogeneity of temperature and the heat/cold adaption for subjects living in different climate regions.

Several limitations should also be noted. First, meteorological and air pollutant exposures were extracted from grid datasets based on residential address, which were not individual direct measurements. In addition, we were unable to account for personal factors including outdoor activities, which could introduce inevitable exposure misclassifications. However, this exposure misclassification tended to be random and non-differential, which was unlikely to bias the results.[47] Second, although we have used case-crossover study design to control time-invariant covariates and time-varying meteorological conditions in the model, some potential unmeasured and residual confounders may still exist. Third, this study was conducted in a single province in China, although the sample size was large. Given the difference in climate characteristics across climate zones, generalization of our results to other regions should be cautious.

Table 4. Cumulative associations of ETE exposure with dementia mortality, stratified by sex and age, in Jiangsu province, China, 2015–20

ETE[a]	Sex			Age		
	Male OR (95% CI)	Female OR (95% CI)	*P* for effect modification	<85 years OR (95% CI)	≥85 years OR (95% CI)	*P* for effect modification
Heat wave						
P90_2d	1.41 (1.26–1.59)	1.62 (1.48–1.78)	0.07	1.56 (1.41–1.74)	1.52 (1.37–1.68)	0.67
P90_3d	1.40 (1.25–1.58)	1.61 (1.47–1.77)	0.07	1.55 (1.40–1.72)	1.51 (1.37–1.67)	0.73
P90_4d	1.39 (1.24–1.55)	1.55 (1.42–1.70)	0.13	1.48 (1.34–1.64)	1.49 (1.35–1.65)	0.94
P92.5_2d	1.46 (1.29–1.64)	1.66 (1.51–1.82)	0.10	1.58 (1.42–1.75)	1.58 (1.42–1.75)	0.99
P92.5_3d	1.45 (1.29–1.64)	1.65 (1.50–1.81)	0.11	1.58 (1.42–1.75)	1.57 (1.41–1.74)	0.92
P92.5_4d	1.44 (1.28–1.62)	1.65 (1.51–1.82)	0.08	1.55 (1.39–1.72)	1.59 (1.44–1.77)	0.68
P95_2d	1.64 (1.43–1.87)	1.80 (1.62–1.99)	0.28	1.70 (1.52–1.91)	1.77 (1.58–1.99)	0.64
P95_3d	1.67 (1.46–1.91)	1.80 (1.62–2.00)	0.39	1.73 (1.54–1.95)	1.77 (1.58–1.99)	0.77
P95_4d	1.74 (1.52–2.00)	1.81 (1.62–2.02)	0.66	1.74 (1.54–1.97)	1.83 (1.63–2.07)	0.56
P97.5_2d	1.93 (1.64–2.28)	2.32 (2.03–2.65)	0.09	2.16 (1.87–2.50)	2.17 (1.88–2.52)	0.95
P97.5_3d	1.99 (1.67–2.37)	2.39 (2.08–2.75)	0.11	2.17 (1.86–2.53)	2.29 (1.96–2.67)	0.64
P97.5_4d	2.00 (1.66–2.42)	2.55 (2.20–2.96)	0.048	2.20 (1.86–2.59)	2.49 (2.11–2.94)	0.29
Cold spell						
P10_2d	1.24 (1.09–1.40)	1.32 (1.20–1.46)	0.43	1.30 (1.16–1.46)	1.28 (1.15–1.42)	0.81
P10_3d	1.22 (1.08–1.37)	1.28 (1.16–1.40)	0.58	1.27 (1.14–1.42)	1.24 (1.12–1.37)	0.73
P10_4d	1.27 (1.13–1.43)	1.22 (1.11–1.33)	0.57	1.27 (1.14–1.42)	1.21 (1.09–1.33)	0.49
P7.5_2d	1.28 (1.12–1.46)	1.28 (1.15–1.42)	0.97	1.31 (1.16–1.49)	1.25 (1.11–1.40)	0.57
P7.5_3d	1.29 (1.13–1.46)	1.29 (1.17–1.43)	0.96	1.34 (1.19–1.51)	1.25 (1.12–1.39)	0.41
P7.5_4d	1.32 (1.16–1.51)	1.23 (1.10–1.36)	0.39	1.30 (1.15–1.47)	1.23 (1.10–1.38)	0.52
P5_2d	1.31 (1.13–1.52)	1.34 (1.19–1.50)	0.82	1.36 (1.19–1.56)	1.29 (1.14–1.47)	0.62
P5_3d	1.30 (1.12–1.51)	1.31 (1.16–1.47)	0.97	1.39 (1.21–1.59)	1.23 (1.09–1.40)	0.22
P5_4d	1.34 (1.15–1.57)	1.28 (1.13–1.45)	0.64	1.36 (1.18–1.57)	1.26 (1.10–1.43)	0.43
P2.5_2d	1.43 (1.18–1.73)	1.32 (1.14–1.54)	0.54	1.43 (1.20–1.70)	1.31 (1.12–1.54)	0.48
P2.5_3d	1.44 (1.17–1.76)	1.29 (1.10–1.52)	0.43	1.42 (1.18–1.71)	1.28 (1.08–1.53)	0.45
P2.5_4d	1.29 (1.02–1.64)	1.26 (1.05–1.52)	0.87	1.25 (1.01–1.55)	1.29 (1.06–1.58)	0.83

CI, confidence interval; ETE, extreme temperature event; OR, odds ratio.
[a] ETEs were defined using the combination of intensity and duration; for example, P95_3d denotes heat waves with daily mean temperature ≥95th percentile of temperature distribution and with ≥3 consecutive days. The definitions of ETEs are given in Supplementary Table S1 (available as Supplementary data at *IJE* online).

Conclusion

In conclusion, we found that exposure to both heat wave and cold spell was associated with an increased odds of dementia mortality, with stronger associations for heat wave exposure and for women in summer. The results suggest that exposure to ETEs with a higher intensity generally yielded stronger associations. Our findings provide an important scientific basis for governments and policy makers to formulate ETE intervention strategies, and highlight the importance of establishing early warning systems for ETEs to prevent dementia deaths especially among women in summer.

Ethics approval

This study was approved by the Ethics Committee of School of Public Health, Sun Yat-sen University, with a waiver of informed consent.

Data availability

The air pollution data (CHAP dataset) are available at [https://weijing-rs.github.io/product.html]. The data on meteorological condition and dementia mortality used in this study are not publicly available.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

Y.Liu and H.S. participated in the formulation of research idea and study design. Y.Liu, H.S., J.W. and C.S. participated in the data collection and curation. T.L., R.X., Y.Li, L.L., Z.Z. and Y.Z. participated in the retrieval of literature and references. T.L. participated in the data analysis and prepared the draft manuscript. Y.Liu, H.S., T.L, and C.S. participated in the interpretation of results. Y.Liu, H.S., T.L. and R.X. participated in the verification of the data. All authors participated in the concept and revision of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Conflict of interest

None declared.

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