# **BMJ Open** Association between ambient temperature and cognitive function in a community-dwelling elderly population: a repeated measurement study

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#### ABSTRACT

**Objectives** Evidence on the associations between short-term and long-term air temperature exposure and cognitive function in older adults, particularly those in Asia, is limited. We explored the relationships of short-term and long-term air temperature exposure with cognitive function in Taiwanese older adults through a repeated measures survey.

**Design and setting** We used data the ongoing Taiwan Longitudinal Study on Aging, a multiple-wave nationwide survey.

Participants We identified 1956, 1700, 1248 and 876 older adults in 1996, 1999, 2003 and 2007, respectively. Primary and secondary outcome

measures Participants' cognitive function assessment was based on the Short Portable Mental Status Questionnaire. We calculated the temperature moving average (TMA) for temperature exposure windows between 1993 and 2007 using data from air quality monitoring stations, depending on the administrative zone of each participant's residence. Generalised linear mixed models were used to examine the effects of short-term and long-term temperature changes on cognitive function. Results Short-term and long-term temperature exposure was significantly and positively associated with moderateto-severe cognitive impairment, with the greatest increase in ORs found for 3-year TMAs (OR 1.247; 95% CI 1.107 to 1.404). The higher the quintiles of temperature exposure were, the higher were the ORs. The strongest association found was in long-term TMA exposure (OR 3.674; 95% CI 2.103 to 6.417) after covariates were controlled for. Conclusions The risk of mild cognitive impairment increased with ambient temperature in communitydwelling older adults in Taiwan.

#### INTRODUCTION

According to the Intergovernmental Panel on Climate Change, global surface temperature was 1.09°C (95% CI 0.95°C to 1.20°C) higher in 2011–2020 than 1850–1900.<sup>1</sup> Elevated temperature is a public heath threat and is expected to lead to an increase in deaths

## Strengths and limitations of this study

- The study is a representative cohort with a repeated measurement design.
- We assessed the different exposure windows of temperature.
- This study control possible covariates and perform the sensitivity analyses.
- This study results can provide evidence to the health department which can seek the climate change mitigation within rising older population.
- This study does not generalise to other population such as young adult.

and illness. Most studies conducted the heat waves and found the evidence of increased mortality from heat waves in various locations. In studies of heat waves and elevated temperature, cardiovascular diseases, respiratory diseases and cerebrovascular diseases were prominent causes of death.<sup>2 3</sup> Exposure to extreme heat conduction may cause health problems and increased the chance of death. Adults older than 65 years with cardiopulmonary and other chronic diseases, and very young children are vulnerable to effects of heat.<sup>4 5</sup>

Older adults with mild cognitive impairment (MCI) are at an increased risk of developing Alzheimer's disease (AD) or other forms of dementia.<sup>6</sup>

An estimated 40%–60% of individuals aged 58 years and over with MCI have an underlying AD pathology.<sup>7</sup> Thus, MCI is an intermediate stage in the trajectory from normal cognition to dementia.<sup>8 9</sup> Cognitive declines in older adults is associated with poor health outcomes (eg, falls, congestive heart failure and mortality) and higher utilisation rates of hospital and nursing homes.<sup>10–14</sup> The

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Correspondence to Dr Han-Bin Huang; toly2000@gmail.com world's population is ageing and Taiwan is no exception. We had reached aged society and the ageing population percentage will be the second highest in the world.<sup>15 16</sup>

In experimental studies, exposure to passive heat stress at a temperature of approximately 50°C and passive cold stress at temperatures below 10°C impaired cognitive function in younger or older adults.<sup>17–19</sup> However, several epidemiological studies have not indicated any temperature-related changes in cognitive function.<sup>19 20</sup> A previous study revealed a U-shaped association at lag 1 day between residential air temperature and poor cognitive function among older adults in the USA.<sup>21</sup> However, whether this pattern or association exists in Asian older adults is unclear, as is the association of cognitive function with temperature, particularly different exposure windows for temperature. Taiwan is a small island located in East Asia at the western edge of the Pacific Ocean and affect by urban heat island, the threat of extreme heatrelated mortality is clear, but the risks of ambient temperature in regarding to elderly MCI were lacking. To add this knowledge gap can integrate the interdisciplinary heat action plan for ageing society. Thus, we investigated the associations of short-term and long-term air temperature exposure with cognitive function in community-dwelling older adults in Taiwan.

## **METHODS**

#### Study participants

The Taiwan Longitudinal Study on Aging (TLSA), an ongoing prospective longitudinal study with a nationally representative sample of 4049 participants aged 60 years or over, was established in 1989 by the Health Promotion Administration of the Ministry of Health and Welfare. It has a three-stage equal probability sampling design, and the initial sample had a survey response rate of 92%.<sup>22</sup> Participants were administered questionnaires by trained interviewers at baseline as well as in follow-up surveys in 1996, 1999, 2003 and 2007, for which the response rates were 92%, 91%, 89%, 90% and 91%, respectively.<sup>22</sup> Participants provided verbal consent in all survey years before 2007, and the Health Promotion Administration obtained written consent in 2007. We used TLSA data between 1996 and 2007. The inclusion criteria were as follows: being aged 65 years or older, having completed a cognitive test, having no cognitive impairment, having no history of stroke and not moving house during the study period. A total of 285 participants were excluded at the baseline in 1996. Participant numbers in 1996, 1999, 2003 and 2007 were 1956, 1700, 1248 and 876, respectively.

## Patients and public involvement

Patients and the public were not involved in this study, including data collection, analysis and interpretation.

#### **Cognitive function assessment**

Participant cognitive function was assessed using the Short Portable Mental Status Questionnaire (SPMSQ), which was validated by a Chinese version of the Mini-Mental State Examination<sup>23</sup> and has been used elsewhere.<sup>24–26</sup> The Cronbach's alpha value of the SPMSQ was 0.63. Participants were asked five questions: (1) 'What is today's date (month, day and year)?' (2) 'What is the day of the week?' (3) 'What is your home address?' (4) 'Where are you)?' and (5) 'How old are you?' In addition, they were asked to subtract 3 from 20 over four consecutive repetitions. One point was given for each correct answer, and the total score ranged from 0 to 5. In consideration of the ceiling effect of the SPMSQ, we dichotomised the SPMSQ scores for the analysis of cognitive impairment risk. An SPMSQ score of <3 was used to identify individuals with moderate-to-severe cognitive impairment.<sup>24 27</sup>

## **Environmental assessment of air temperature**

Hourly temperature data (in °C) were obtained from 75 monitoring stations on Taiwan's main island, which were established by the Taiwan Environmental Protection Administration (TEPA) in or after 1993.<sup>28</sup> The data were subjected to rigorous quality assurance and control procedures through independent projects. The TEPA authorised an independent private sector organisation to perform annual performance audits and regular performance checks of monitoring instruments. The daily mean temperature obtained from each station was included for analysis. The daily mean temperatures from monitoring stations within the same city or county were assigned to participants living in the same city or county.<sup>29</sup> If a city or county had more than one monitoring station, the data were averaged. We calculated the temperature moving averages (TMAs) over periods of 7, 14, 21, 30, 60 and 90 days and 3 years prior to each participant's interview date.

## **Statistical analysis**

We summarised the participant characteristics by survey year and the ambient temperature distribution during the study period. In consideration of the ceiling effect of SPMSQ, we dichotomised the SPMSQ scores for the analysis of cognitive impairment risk. An SPMSQ score of <3 was used to identify individuals with moderate-tosevere cognitive impairment, as described previously.24 27 We applied generalised linear mixed models fitted using the PROC GLIMMIX procedure in SAS software (SAS Institute) to accomplish two goals: to explore the relationship between cognitive function and exposure to temperature, which was modelled as a binary outcome (on the basis of SPMSQ scores of <3 for moderate-tosevere cognitive impairment), and to account for random effects of repeated measures for participants. We examined temperature exposure windows between 7 days and 3 years prior to the participants' interview dates to assess the effect of short-term and long-term temperature exposure on cognitive function.

Furthermore, we adjusted for the following covariates measured at each visit: age, sex, educational level, marital status, (self-reported) current financial status, smoking, alcohol consumption, physical activity, scores

Table 1 Participants' demographic characteristics by survey year					
Variables	Year 1996 (n=1956)	Year 1999 (n=1700)	Year 2003 (n=1248)	Year 2007 (n=876)	
Male	1172 (59.9)	998 (58.7)	727 (58.3)	464 (53.0)	
Age, year, mean±SD	73.44±4.91	76.10±4.69	78.64±4.05	82.29±3.76	
Spouse, yes, n (%)	1233 (63.0)	1007 (59.2)	673 (53.9)	403 (46.0)	
Personal education, n (%)					
Illiterate	664 (33.9)	555 (32.6)	379 (30.4)	285 (32.5)	
Primary and secondary school	1047 (53.5)	928 (54.6)	689 (55.2)	461 (52.6)	
High school and above	245 (12.5)	217 (12.8)	180 (14.4)	130 (14.8)	
Self-reported financial status, n (%)					
Very satisfied	163 (8.30)	125 (7.40)	71 (5.70)	47 (5.40)	
Satisfied	655 (33.5)	562 (33.1)	515 (41.3)	365 (41.7)	
Fair	843 (43.1)	678 (39.9)	427 (34.2)	310 (35.4)	
Dissatisfied	243 (12.4)	250 (14.7)	180 (14.4)	117 (13.4)	
Very dissatisfied	52 (2.70)	85 (5.00)	55 (4.40)	37 (4.20)	
Physical activity, n (%)	1164 (59.5)	1099 (64.6)	844 (67.6)	591 (67.5)	
Smoking status, n (%)	542 (27.7)	401 (23.6)	231 (18.5)	107 (12.2)	
Alcohol consumption, n (%)	381 (19.5)	380 (22.4)	265 (21.2)	170 (19.4)	
Hypertension, n (%)	512 (26.2)	634 (37.3)	540 (43.3)	407 (46.5)	
Diabetes, n (%)	192 (9.80)	254 (14.9)	203 (16.3)	121 (13.8)	
SPMSQscore (0–5), mean±SD	4.50±0.87	4.47±0.90	4.23±1.02	3.75±1.33	
<3, n (%)	95 (4.90)	93 (5.50)	93 (7.50)	159 (18.2)	
≥3, n (%)	1861 (95.1)	1607 (94.5)	1155 (92.5)	717 (81.8)	
IADL score (0–18), mean±SD	1.81±3.49	2.27±3.91	3.10±4.42	4.13±5.04	

IADL, instrumental activities of daily living.

for instrumental activities of daily living (IADLs) and season (spring: March-May, summer: June-August, fall: September-October, winter: December-February). Covariate selection was based on the following criteria: (1) being associated with exposure and outcome and not being intermediate variables between exposure and outcome,<sup>30</sup> and (2) having a change-in-estimate criterion of  $\geq 10\%$ .<sup>31</sup> To examine non-linear associations between ambient temperature and cognitive function, we divided ambient temperature into quintiles. To adjust for additional variables, namely hypertension, diabetes, air conditioning, and air pollutant exposure (eg, PM<sub>10</sub> and O<sub>3</sub> levels), we conducted a sensitivity analysis. All analyses were performed using SAS software V.9.3 of the SAS System for Unix (SAS Institute), and the level of significance was set at p<0.05.

## RESULTS

## **Demographic characteristics**

Table 1 presents the demographic characteristics of the participants between 1996 and 2007. At baseline, participants had a mean age of 73 years, and 59.9% were men. Most of the participants were married. Only 12.5% had a high school degree, and approximately 40% considered their financial status to be fair. Higher rates of

regular physical activity, non-consumption of alcohol, nonsmoking status and absence of hypertension and diabetes were observed. In total, 4.9% of participants had SPMSQ scores of <3, and the mean IADL score was 1.81. In 2007, the demographic characteristics were similar, but participants were older (mean age 82.29 years). The rates of hypertension and diabetes were higher in 2007 than in 1996. In total, 18.2% of participants had SPMSQ scores of <3, and the mean IADL score was 4.13.

## Short-term and long-term TMAs

Significant increasing trends in short-term mean and median temperatures between 1996 and 2007 were observed (p<0.001). The 7-day TMAs in 2007 (mean 27.69°C; median 27.76°C) were higher than those in 1996 (mean 19.57°C; median 19.31°C). The 3-year TMAs in 2007 (mean 24.23°C; median 24.00°C) were higher than those in 1996 (22.38°C; median 22.16°C) (table 2).

## Relationship of short-term and long-term temperature exposure with cognitive function

Both the crude and adjusted models revealed significant and positive associations of short-term (7 days, 14 days, 21 days, 30 days, 60 days and 90 days) and long-term (3years) TMAs with moderate-to-severe cognitive impairment (table 3). A 1°C-increase in TMA was significantly

Table 2 Shor	t- and long-te.	Table 2 Short- and long-term temperature moving averages	g averages						
Temperature Year 1996 (n=1956)	Year 1996 (r	1=1956)	Year 1999 (n=1700)	1=1 700)	Year 2003 (n=1248)	=1248)	Year 2007 (n=876)	=876)	
moving average (°C)	Mean±SD	moving average (°C) Mean±SD Median (Q1, Q3)	Mean±SD	Mean±SD Median (Q1, Q3)	Mean±SD	Mean±SD Median (Q1, Q3)	Mean±SD	Mean±SD Median (Q1, Q3)	P for trend
7 days	$19.57 \pm 0.95$	19.31 (18.97, 20.49)	20.83±1.83	19.57±0.95 19.31 (18.97, 20.49) 20.83±1.83 20.63 (19.07, 22.11) 24.50±2.87 24.86 (22.92, 26.83) 27.69±2.20 27.76 (26.04, 29.25)	24.50±2.87	24.86 (22.92, 26.83)	27.69±2.20	27.76 (26.04, 29.25)	<0.001
14 days	20.55±1.39	19.98 (19.46, 22.16)	21.50±1.82	20.55±1.39 19.98 (19.46, 22.16) 21.50±1.82 21.28 (19.79, 22.67) 24.87±2.84 25.26 (23.32, 27.18) 27.41±2.12 27.74 (26.09, 28.82)	24.87±2.84	25.26 (23.32, 27.18)	27.41±2.12	27.74 (26.09, 28.82)	<0.001
21 days	20.23±1.67	20.23±1.67 19.67 (18.82, 22.06) 21.37±1	21.37±1.99	21.05 (19.40, 22.60)	25.21±2.81	25.61 (23.67, 27.52)	27.12±2.23	27.38 (25.81,28.55)	<0.001
30 days	19.67±1.84	19.00 (18.13, 21.58)	20.93±2.13	19.67±1.84 19.00 (18.13, 21.58) 20.93±2.13 20.53 (18.82, 22.27) 25.59±2.76 26.10 (23.98,27.88)	25.59±2.76	26.10 (23.98,27.88)	26.75±2.37	26.75±2.37 27.10 (25.19, 28.35)	<0.001
60 days	19.59±1.93	19.59±1.93 19.06 (17.82, 21.32)	19.96±1.79	19.96±1.79 19.69 (18.34, 20.96)	26.61±2.51	26.61±2.51 27.36 (25.65, 28.35)	25.45±2.58	25.66 (23.53, 27.39)	<0.001
90 days	18.39±1.89	17.88 (16.60, 19.82)	19.14±1.71	18.39±1.89 17.88 (16.60, 19.82) 19.14±1.71 18.77 (17.68, 19.95) 27.40±2.18 27.96 (26.63, 28.88)	27.40±2.18	27.96 (26.63, 28.88)	24.23±2.55	24.23±2.55 24.42 (22.25, 25.96)	<0.001
3 years	22.38±1.12	22.16 (21.33, 23.40)	23.04±1.14	22.38±1.12 22.16 (21.33, 23.40) 23.04±1.14 22.97 (21.95, 23.77) 23.75±0.84 23.53 (22.92, 24.67) 24.23±0.90 24.00 (23.58, 24.98)	23.75±0.84	23.53 (22.92, 24.67)	24.23±0.90	24.00 (23.58, 24.98)	<0.001

and positively associated with moderate-to-severe cognitive impairment after adjustment for covariates, with the greatest increase in odds found for 3-year exposure (AOR 1.247; 95% CI 1.107 to 1.404). To examine the nonlinear associations between air temperature and cognitive function, we grouped the quintiles of temperatures from different exposure windows. Compared with the that for quintile 1, the TMA for quintile 5 in the short term (over 7, 14, 21, 30, 60 and 90 days) was significantly positively associated with moderate-to-severe cognitive impairment. The strongest association observed was for long-term (3-year) exposure (AOR 3.674; 95% CI 2.103 to 6.417) after all potential covariates were controlled for (figure 1 and online supplemental table S1). In addition, we noted a monotonic trend of temperature over all but the 90-day exposure windows and cognitive function. In the sensitivity analysis, we further adjusted for hypertension, diabetes and air conditioning in 1996, and exposure to air pollutants from the same exposure window (eg, PM<sub>10</sub> and O<sub>3</sub>), and the same patterns were observed (online supplemental table S2).

## DISCUSSION

We observed significant and positive associations between short-term and long-term temperature exposure and moderate-to-severe cognitive impairment. In particular, long-term exposure to higher-quintile temperatures was significantly associated with higher risks of cognitive impairment among older adults. The results suggest that exposure to higher temperatures could affect cognitive function among community-dwelling, free-living older adults.

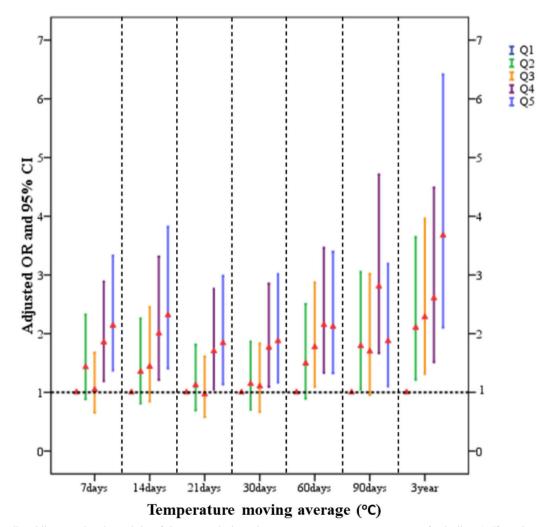
In a study by,<sup>17</sup> 16 middle-aged participants performed cognitive tests on attention and working memory in control, hot (room temperature of 50°C), or hot head cool (hot condition with application of cold packs to the head) conditions. Compared with those in the control condition, participants in the hot condition had a significant decline in working memory. Another study indicated that young adults in non-air-conditioned buildings experienced reduction in cognitive function on working memory and selective attention or processing speed.<sup>18</sup> Further, another study revealed that higher-temperature environments could negatively affect productivity in participants with a mean age of 23 years.<sup>32</sup> Even short-term exposure to hot temperatures impaired cognitive function in participants with a mean age of 31 years.<sup>33</sup> Most relevant research focuses on young people rather than on older adults. In a longitudinal cohort study of older men, short-term exposure to higher air temperatures was significantly associated with low scores on the Mini-Mental State Examination.<sup>21</sup> Similarly, Erkan's research was found that shortterm indoor ambient temperature changed people's cognitive perception.<sup>34</sup> Our finding of an association between short-term exposure to higher temperatures and moderate-to-severe cognitive impairment

Table 3 Crude and adjusted associated	ions between t	temperature exposure (each 1	°C) and cognitiv	e function (n=5780)
	SPMSQ <3		SPMSQ <3	
Temperature moving average (°C)	OR	(95% CI)	AOR	(95% CI)
7 days	1.321	(1.255 to 1.390)	1.079	(1.038 to 1.121)
14 days	1.352	(1.277 to 1.432)	1.082	(1.037 to 1.129)
21 days	1.335	(1.262 to 1.411)	1.072	(1.029 to 1.117)
30 days	1.315	(1.247 to 1.387)	1.063	(1.023 to 1.105)
60 days	1.277	(1.215 to 1.343)	1.048	(1.010 to 1.087)
90 days	1.228	(1.175 to 1.282)	1.033	(1.000 to 1.067)
3 years	2.708	(2.213 to 3.315)	1.247	(1.107 to 1.404)

AOR (for age, sex, educational level, marital status, current financial status, smoking, alcohol consumption, physical activity, scores for instrumental activities of daily living, and season).

AOR, adjusted OR; SPMSQ, Short Portable Mental Status Questionnaire.

in community-dwelling older adults was consistent with those of other studies. In addition, in this study, long-term exposure to higher temperatures affected participant cognitive function. It could be that longterm means are more stable (less fluctuation around the mean) than short-term ones and therefore stronger



**Figure 1** Generalised linear mixed models of the associations between temperature exposure (quintiles 1–5) and cognitive function (n=5780). Models were adjusted for age, sex, educational level, marital status, current financial status, smoking, alcohol consumption, physical activity, scores for instrumental activities of daily living and season.

predictors of cognition. Further large-scaled studies are required to confirm this finding.

Studies have demonstrated that short-term exposure to acute low temperature leads to a decline in cognitive function in young adults<sup>35–37</sup> as well as in older adults.<sup>21</sup> However, we did not observe this association. This may be because our study was conducted in Taiwan, where the climate is subtropical to tropical and acute low temperatures are rare.

Several possible mechanistic and observational theories may explain cognitive alterations induced by high air temperatures. In a study reported an association between warmer outdoor temperatures and worse cognitive status in patients with multiple sclerosis,<sup>38</sup> functional MRI revealed greater blood-oxygen-level-dependent activation within frontal/dorsolateral prefrontal and parietal regions of the brains of patients with multiple sclerosis, indicating reduced neurological function.<sup>39</sup> This was not found in healthy controls. Human body temperature also affects the function of the hippocampal gyrus, which plays an essential role in brain functions such as learning and memory. Warm temperatures activate transient receptor potential vanilloid 4, a temperature-sensitive channel. Increased physiological temperature activates and controls the activity of hippocampal neurons.<sup>40 41</sup> This channel parallels the behaviour of the corresponding afferent sensory fibres.<sup>42</sup> A plausible explanation for the negative association of heat stress with cognitive function is that it increases levels of plasma serotonin, which inhibits the production of dopamine, a neurotransmitter involved in complex task performance.<sup>19</sup> Previous studies in the general population reported that ambient temperatures could be associated with the circulating levels of markers of inflammation and oxidative stress,<sup>43–45</sup> which could be involved in the biological process of temperaturescognitive decline associations.

Although previous studies suggested that hypertension and diabetes could be associated with cognitive decline,<sup>46</sup> our results in this study did not find significant associations between them. Furthermore, having/using air conditioning in the household could affect the indoor temperature. However, we did not observe any significant associations between air conditioning and ambient temperature. Besides, our previous work reported that exposure to PM or O<sub>3</sub> could be positively associated with the risk of cognitive decline.<sup>27</sup> These air pollutants could be related to ambient temperature. Thus, these air pollutants could be confounding factors or mediator in these associations between ambient temperature and cognitive function. Based on these reasons, we also carried out additional analyses adjusting for hypertension, diabetes, air conditioning and air pollutant exposure to verify our main findings.

Reducing the adverse health effects of hot weather particular in elderly people is vital. There should be a integrated surveillance and early warning system. Communication and education the public about the cooling strategies like drinkable water or air conditioning. However, more sustainable and affordable cooling interventions are needed.<sup>47</sup> Strategies at the landscape and urban (eg, blue and green spaces) and building (eg, changing materials and natural ventilation) levels can greatly augment society's adaptive capacity to heat extremes and hot weather.<sup>48</sup> Moreover, ambient technology could be a possible solutions to assist elderly people to against indoor risks and increase their life quality.<sup>49</sup>

## Limitations and strengths

Our study had several limitations. First, the air temperatures in the study setting are much higher than those in relevant studies; therefore, observing whether lower air temperatures negatively affect cognitive function was challenging. Second, data on exact air temperatures from participants' specific locations could not be collected. The air temperatures we used were outdoor air temperatures recorded by monitoring stations that were matched to each participant's city or county. This could have caused misclassification in temperature exposure. However, this likely had a limited impact on our results because our estimations of individual exposures to air temperature from monitoring station data were equivalent to those from spatiotemporal modelling.<sup>50</sup> Third, the longitudinal studies involving older adults, the attrition effect should be noticed. Lost to follow-up participants or those who died most likely had poor physical health according to the previous studies.<sup>51</sup> Hence, the samples with cognitive impairment could be underestimated in this study and this could cause our results towards the null. Fourth, several exposure variables, such as noise, were not considered; this could also have influenced the results.

Fifth, the fact that the SPMSQ, rather than clinical diagnosis, was used for the cognitive function assessment could restrict our findings. Although is the SPMSQ a valid and reliable instrument for identifying cognitive impairment, it is unlikely to identify subtle deficits.<sup>52</sup> Nevertheless, the measures we used evaluated working memory and orientation, for which deficits may reflect cognitive loss.<sup>25 53 54</sup>

The principal strengths of our study were that the sample was nationally representative,<sup>55</sup> and that potential confounders were accounted for in assessing the association between short-term and long-term temperature exposure and cognitive function.

## Conclusions

In a nationally representative sample of Taiwanese older adults, short-term and long-term exposure to higher ambient temperatures were associated with risks of MCI. Moreover, a monotonic trend of air temperature exposure and cognitive function was observed. Thus, mitigating the effects of high temperature stress on the health of vulnerable populations such as older adults is advised. To reduce the health impacts on elderly people for ageing society, it is suggested to operate a national or local heat action plan which can be adopted effective by local communities. Sustainable and affordable cooling interventions and green/blue city designed need to be considered for ageing society.

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**Contributors** H-BH accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. H-BH and Y-TCL conceptualised and designed the Study. W-PS, Y-TCL, S-HM and H-BH analysed the data. Y-YJ provided administration support. S-HM and Y-TCL drafted the initial manuscript. H-BH provided critical revisions for important intellectual content. All authors contributed substantially to its revision. H-BH takes responsibility for the paper as a whole.

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