

The influence of extreme cold ambient temperature on out of hospital cardiac arrest: A systemic review and meta-analysis

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Abstract

Objective: Many researches have demonstrated the effects of the extreme cold ambient temperature on the risk of out-of-hospital cardiac arrest (OHCA); yet, the results have been inconsistent. We performed a meta-analysis to evaluate whether extreme cold ambient temperature is related to OHCA. **Methods:** We searched for time-series studies reporting associations between extreme cold ambient temperature and OHCA in PubMed, web of science and Cochrane database. **Results:** Six studies involving 2 337 403 cases of OHCA were qualified for our meta-analysis. The odds ratio (OR) of OHCA was significantly increased in extreme cold weather (defined as the 1st or 5th centile temperature year-round) compared to reference temperature (as the 25th centile temperatures or daily mean temperature with minimum risk of OHCA) (OR=1.49, 95% CI 1.18-1.88). The subgroup analysis for the elderly and the female failed to detect the influence of extreme cold weather on OHCA, the ORs are 1.25 (95% CI 0.89-1.75) and 1.19 (95% CI 0.87-1.64), respectively. **Conclusion:** The risk of OHCA is significantly higher in extreme cold ambient temperatures than in reference temperature, according to a relative temperature scale with percentiles of the region-specific temperature distribution.

Keywords

extreme cold weather; cardiac arrest; meta-analysis

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1 Introduction

Out-of-hospital cardiac arrest (OHCA) remains a global health problem with a survival rate ranging from 2% to 22% even in patients who received cardiopulmonary resuscitation (CPR) across different countries^[1], and only 0.6% in Beijing, China from 2012 to 2015. OHCA represents a leading cause of premature death from cardiovascular disease, contributing to approximately half of the cardiovascular mortality in the world and over 55 million of deaths in China each year^[2]. In spite of the education program of “bystander CPR” and increasing distribution of automated external defibrillator (AED) in public area, the success rate of resuscitation is still not optimistic. Therefore, identifying the risk factor and trigger of OHCA and implementing appropriate prevention measures are crucial for reducing the incidence of OHCA.

Extreme cold ambient temperature has long been recognized

as a significant provocative factor of major cardiovascular event and winter peaks of myocardial infarction incidence, and cardiovascular mortality has been associated with latitude zones of climate^[3]. Cold pressor test has been routinely performed for decades to provoke coronary artery spasm in patients suspected of coronary artery disease, especially variant angina pectoris. It is commonly believed that the cold pressor stimulates α 1-adrenergic receptors to cause peripheral and coronary vasoconstriction, thereby resulting in myocardial ischemia or infarction, blood pressure elevation, and cardiac load and myocardial oxygen consumption increases. These alterations could be further enhanced with age via unopposed vasoconstriction secondary to endothelial dysfunction. Cold pressor test is also clinically utilized to predict cardiovascular events in patients with coronary or peripheral artery disease^[4].

With rapid industrialization, worsening environmental pollution and increasing emission of greenhouse gases, as well as

drastically fluctuating global climate have caused extreme weather and disaster frequently. Therefore, it is necessary to clarify the influence of extreme cold environmental temperature on OHCA and to minimize its incidence and the global health burden. While many researches have demonstrated the effects of the extreme cold ambient temperature on the risk of OHCA, the results have been inconsistent. It is still in debate as to whether the effect of absolute cold temperature or the substantial change of ambient temperature plays a role in the cold weather-associated OHCA. It is essential to carry out a systematic review and meta-analysis to ascertain the relationship between extreme cold ambient temperature and OHCA by collecting and scrutinizing the evidence from relevant epidemiological observations.

2 Materials and methods

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement^[5].

2.1 Literature search

We performed a comprehensive literature search of all published articles without time and language limitations through January 2022, using the major electronic databases including PubMed, Cochrane Library, and Web of Science. Search terms included any possible combination of the keywords of “heart arrest” and “extreme cold weather”, which are medical subject headings (MeSH) and were also substituted by some synonyms in searching process. “Cardiac arrest” or “cardiopulmonary arrest” or “asystole” were used to replace “heart arrest”; and “extreme cold” or “cold spell” or “cold surge” to replace “extreme cold weather”.

2.2 Study selection

Studies were included in our analysis only when they met all of the following criteria: (1) population-based time-series study, (2) the definition of “extreme cold weather” and the reference temperature were clearly described and the meteorological data were collected from governmental meteorological department and cover a long period of time, (3) reported data of the risk ratio of OHCD on exposure to extreme cold weather were compared to reference ambient temperature, and the original data were obtained from authorized official institution. Letters, comments, reviews and meeting abstract without full-text access were excluded from this review.

Two independent reviewers (YXL and HRZ) were engaged in

the search for potentially eligible studies and in the inclusion process. In case of disagreement, a consensus was made under the supervision of the corresponding author (WT).

2.3 Data abstraction and quality assessment

One reviewer (YXL) assessed the study quality and extracted the relative data independently, then another reviewer (HRZ) confirmed the information. In case of discrepancies, a consultation was made by referral to the corresponding author (WT). The extracted data included author, year of publication, time range of research, study sites or regions, sample size, exposure factors, outcomes, risk ratio and confidential interval. The quality of the studies was assessed according to the AHRQ scale for cross-sectional/prevalence study quality, which was scored by the source of information, inclusion and exclusion criteria for exposed and unexposed subjects, time period used for identifying patients, evaluators of subjective components masked by other aspects of the participants, assessments undertaken for quality assurance purposes, confounding assessment, missing data handling, patient response rates and follow-up information.

2.4 Statistical analysis

Data were analyzed by Review Manager version 5.4.1 (The Cochrane Collaboration). The exposure effect is presented as pooled odds ratios (ORs), and studies with no OHCA or cardiac death were waived. I^2 test was utilized to test the heterogeneity among the studies, and a value of $I^2 > 50\%$ manifested significant heterogeneity among the studies. The fixed-effects (FE) model (Mantel–Haenszel method) was applied only if $I^2 \leq 50\%$. In case significant heterogeneity ($I^2 > 50\%$) existed among the studies, further explorations including sensitivity analysis and subgroup analysis were conducted. If heterogeneity remained, a random effects (RE) model was adopted. The publication bias of enrolled studies was assessed using funnel plots. The difference was regarded as statistically significant when a P value was less than 0.05.

3 Results

3.1 Selected studies and baseline characteristics

Sixty-six records were initially collected according to our literature search strategy, of which 25 duplicate records were waived and 41 studies were kept. After screening the title and abstract, another 27 records were removed as letters, comments, meeting abstract or articles not relevant to our theme. After full-text reading, 4 studies were discarded due to the population overlapping with the final enrolled studies; and

another 4 studies were abandoned because they did not provide odd ratio or risk ratio of cardiac arrest or *P* values. Finally, a total of 6 studies were included in our meta-analysis, which involved a total of 2 337 403 deaths. The definitions of exposure factors and outcome were rechecked. The extreme cold temperature was defined as the 1st or 5th centile temperature year-round and the reference as the 25th centile temperatures or daily mean temperature with minimum risk of OHCA. The flow of the literature selection process is depicted in Fig. 1, and the Meta-

data of the included studies are provided in Table 1^[6-11].

3.2 Quality assessment

An assessment of the quality of the enrolled studies was conducted. Most of the enrolled studies reported the most items listed in the AHRQ scale, and the quality scores ranged from 8 to 10, indicating that all of the enrolled studies were highly qualified for this meta-analysis. The assessment of studies with

Table 1 Characteristics of enrolled studies

Study cohort	Study range	Study region	Study type	Sample	Definition of extreme cold & Temperature	Reference	Outcome	OR or RR (95% CI)
Borghei, <i>et al.</i> 2020 ^[6]	3 years (unspecified)	Rasht in Iran	single center time-series study	392	the 5th centile temperature, 5°C	the 25th centile temperatures	OHCA	1.31 (1.01-1.52)
Chen, <i>et al.</i> 2014 ^[7]	2009-2011	6 cities in China	multi-center time-series study	126 925	the 1st centile temperatures, -24.2°C-7.9°C	the 25th centile temperatures	OHCA	1.33 (1.20-1.47)
Medina-Ramón, <i>et al.</i> 2006 ^[8]	1989-2000	50 cities in US	multi-center time-series study	1 542 351	the 1st centile temperatures -17.2°C-10°C	the 25th centile temperatures	OHCA	1.14 (1.05-1.23)
Niu, <i>et al.</i> 2016 ^[9]	2008-2012	Guangzhou, China	multi-center time-series study	4 369	the 1st centile temperatures, 6.8°C	28°C [daily mean temperature with minimum risk]	OHCA	2.85 (1.44-5.63)
Onozuka, <i>et al.</i> 2017 ^[10]	2005-2014	47 prefectures in Japan	multi-center time-series study	659 752	the 1st centile temperatures, -	the 84th centile temperatures [minimum risk]	OHCA	2.10 (1.84-2.40)
Ryti, <i>et al.</i> 2017 ^[11]	1961-2011	Oulu in Finland	multi-center time-series study	3 614	the 5th centile temperature, -9.2°C	reference periods of the same calendar days of other years	Sudden cardiac death	1.33 (1.00-1.78)

OHCA, out-of-hospital cardiac arrest.

Table 2 Assessment of methodological quality of included studies

Item	Medina-Ramón, <i>et al.</i> 2006 ^[8]	Chen, <i>et al.</i> 2014 ^[7]	Niu, <i>et al.</i> 2016 ^[9]	Onozuka, <i>et al.</i> 2017 ^[10]	Ryti, <i>et al.</i> 2017 ^[11]	Borghei, <i>et al.</i> 2020 ^[6]
1 Define the source of information (survey, record review)	Yes	Yes	Yes	Yes	Yes	Yes
2 List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Yes	Yes	Yes	Yes	Unclear	Yes
3 Indicate time period used for identifying patients	Yes	Yes	Yes	Yes	Yes	Yes
4 Indicate whether or not subjects were consecutive if not population-based	Yes	Yes	Yes	Yes	Yes	Yes
5 Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Yes	Yes	Yes	Yes	Yes	Yes
6 Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	Yes	No	Yes	Yes	Yes	No
7 Explain any patient exclusions from analysis	Yes	Yes	No	No	Yes	Yes
8 Describe how confounding was assessed and/or controlled	Yes	Yes	Yes	Yes	No	Yes
9 If applicable, explain how missing data were handled in the analysis	No	Yes	No	No	No	No
10 Summarize patient response rates and completeness of data collection	Yes	Yes	Yes	Yes	Yes	Yes
11 Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Yes	Yes	Yes	Yes	Yes	Yes
Total score	10	10	9	9	8	9

Score 0-3 represents for literature with low quality, 4-7 for moderate quality and 8-11 for high quality.

AHRQ scale is summarized in Table 2.

3.3 Primary meta-analysis

We analyzed the publication bias using a funnel plot, and no publication bias was found (Fig. 2). Six time-series studies reported the *OR* of OHCA in those exposed to extreme cold weather^[6-11], with significant heterogeneity being found across these studies ($I^2 = 92\%$, $P < 0.0001$). We then performed a sensitivity analysis and found that the heterogeneities remained even after having discarded the suspected studies. Finally, random effect model was used to perform the meta-analysis. The summary *OR* of OHCA exposed to extreme cold weather was 1.49 (95% *CI* 1.18-1.88) compared to reference temperature periods, indicating a significant provocative effect of extreme cold weather on OHCA (Fig. 3).

3.4 Subgroup analysis

Considering higher incidence of OHCA and associated cardiovascular disease in the elderly and relatively lower incidence of sudden death in women, we conducted sub-analysis for the elderly and the female. The information of OHCA in the elderly who were 65 years of age and older and women was only reported in 3 studies. However, the concerning data in male and adults were not provided, and thus there was no ground for comparisons of *ORs* of OHCA between elderly and adults and between male and female exposed to extreme cold weather. In addition, the detailed information of the patients, such as the number or proportion of the elder or female patients, the average age, history of disease, etc., was not provided in the original articles either as they focused on environmental exposures and health rather than clinical medicine. Because of the substantial heterogeneity among the studies ($I^2 = 92\%$ for the elderly and $= 60\%$ for female), random effect model was used to conduct sub-analysis. The stratified analysis showed that the summary *ORs* for OHCA was slightly (not statistically significant) higher in the elderly (*OR* = 1.25, 95% *CI* 0.89-1.75, Fig. 3A) and the female (*OR* = 1.19, 95% *CI* 0.87-1.64, Fig. 4B) exposed to extreme cold environment.

4 Discussion

Based on multi-regional (105 regions in 4 countries) time-series studies and the large sample size, this meta-analysis demonstrated adverse influence of extreme cold ambient temperatures on OHCA. Theoretically, advanced age increases susceptibility to extreme cold temperature relative to adults. Several studies revealed evidences of the effects of extreme cold temperature on OHCA^[7,12] and mortality^[13-14]. However, the increased risk of OHCA was not prominent in the population older than 65 years old, probably due to the large heterogeneity

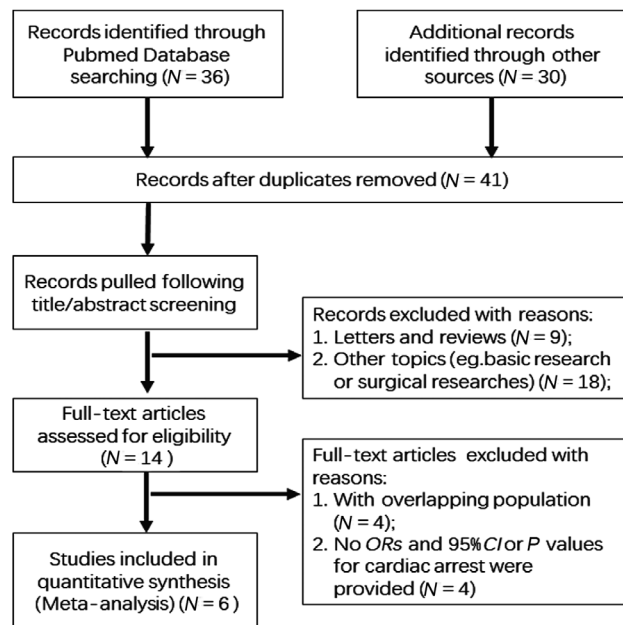


Fig. 1 Flow chart of literature selection process

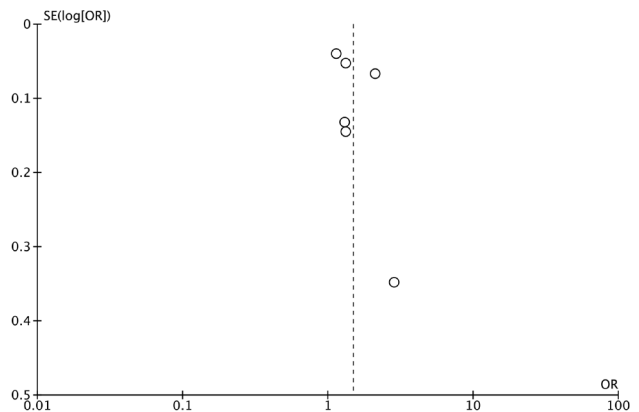


Fig. 2 Funnel plot on the events of OHCA. OHCA, out-of-hospital cardiac arrest

of only 3 studies and small number of studies enrolled in the meta-analysis. Sudden cardiac death or OHCA has been reported to be more common in males than in females^[15], and consistently, the subgroup analysis for the female in the present meta-analysis did not reveal a significant influence of extreme cold weather on OHCA either.

A negative correlation between daily average temperature and cardiovascular mortality has been established for long time. Cagle *et al.*^[16] demonstrated that every 5°C increment in temperature was associated with a significantly reduced mortality (*RR* = 0.971, 95% *CI* 0.961-0.982). OHCA is more

prevalent in frigid region than warm region, however, cold temperature remains an important triggering factor of cardiac events even in regions with relatively mild winters.

It is widely recognized that overall effects of extreme cold weather depend more on temperature percentiles than on absolute temperature scales, due to the adaptation to climate change among populations. All of the enrolled time series studies in this meta-analysis defined the extreme cold temperature as the 1st or 5th centile temperature year-round and denoted the reference as the 25th centile temperatures or daily mean temperature with minimum risk of OHCA, reflecting the effects of climate change rather than cold temperature per se on OHCA. Moreover, this study collected data from 105 regions in 4 countries distributed across different climate zones. The extreme cold ambient temperatures defined in studies ranged from -24.2°C in Harbin to 7.9°C in Guangzhou^[7] and from -17.2°C in Minneapolis to 10°C in San Francisco^[8]. The summary effect of extreme cold weather on OHCA was

consistent, indicating that a relative temperature scale with percentiles of the region-specific temperature distribution may be a more appropriate model for alarming of health issues of susceptible population, especially OHCA. This finding is especially important in the era of climate change and population aging. Incidence of OHCA may be reduced through implementing preventive measures prior to the coming of extreme cold weather.

It should be noted that the mechanisms of out-of-hospital cardiac arrest associated with the extreme cold weather remain yet to be fully clarified. Only 1 out of the 6 enrolled studies presented the information on the causes of cardiac death with proofs from autopsy findings: 76.3% of the death was ischemic and the rest of 23.7% was non-ischemic^[11]. This finding indicates that the extreme cold weather could trigger coronary artery spasm or induce blood clotting, the common mechanisms underlying fatal myocardial infarction. Although no direct evidence was provided that cold weather can cause coronary artery spasm,

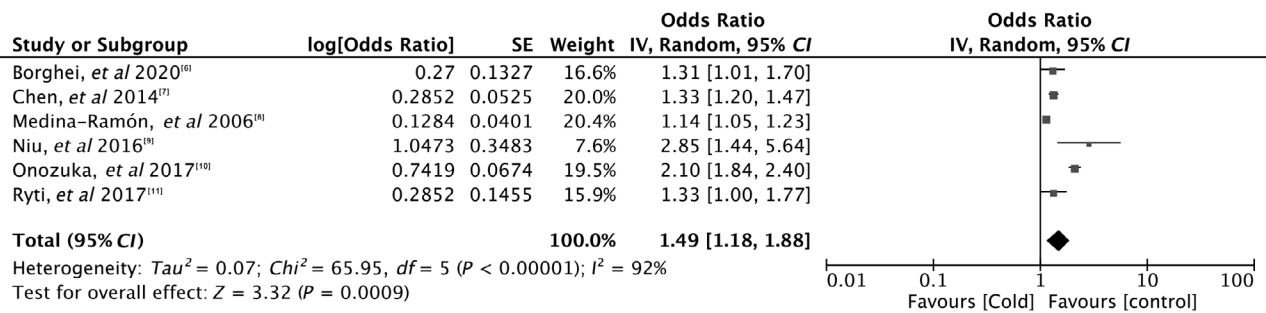


Fig. 3 Forrest plot on the OHCA in extreme cold ambient temperature and reference temperature

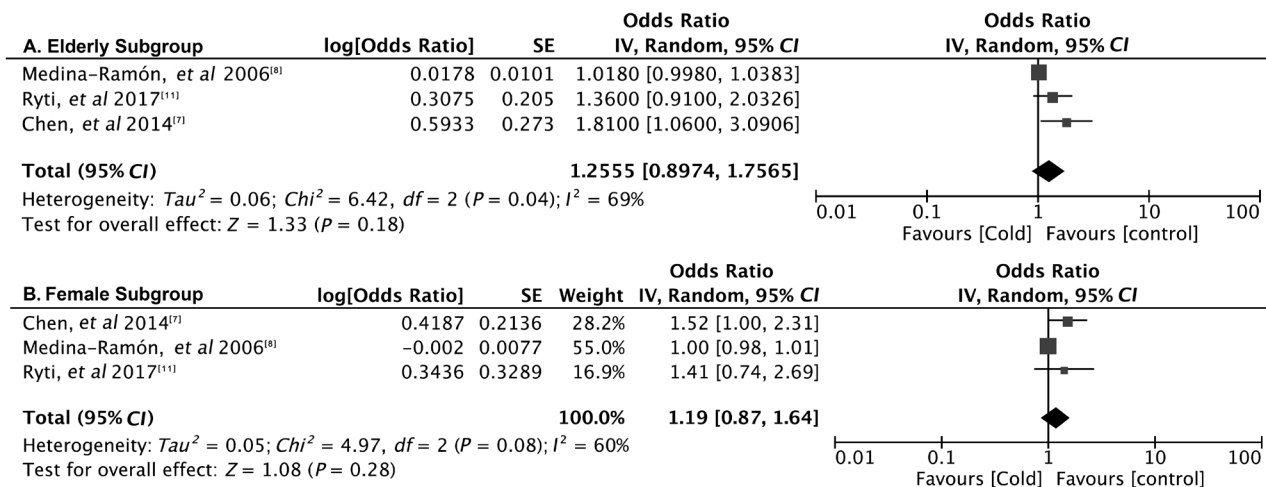


Fig. 4 Subgroup analysis on the elderly(A) and the female(B)

the cold pressor test has long been established as a standard method for coronary spasm provocation in routine clinical practice^[17]. Furthermore, some studies demonstrated that cold ambient temperature was significantly associated with deep vein thrombosis and pulmonary embolism compared with high temperature^[18-19], suggesting the prothrombotic feature of cold. In addition, cold may be the most important environmental factor associated with heart failure hospitalization with an inverted correlation, and heart failure admissions peaked in winter^[20]. It was depicted that the sympathetic nerve system can be activated secondary to cutaneous thermoreceptor stimulation followed by increasing circulating level of catecholamines^[21], leading to peripheral vasoconstriction, blood pressure elevation, tachycardia, and pressure and volume overload. All these factors are common incentives of onset or deterioration of heart failure.

5 Limitations

There are some limitations in the present meta-analysis. First, the prominent heterogeneity and the relatively small number of the enrolled study may likely influence the accuracy of the overall analysis, especially the subgroup analysis. Second, the definitions of the exposure factor and reference are not exactly consistent, and the lag days after the designated extreme cold day vary from 3 to 21 days, which limits the results qualitative rather quantitative. Third, we did not analyze the confounding factors influencing the effect of cold weather on OHCA, e.g.,

humidity, air pollution and economic status, etc.

6 Conclusion

In conclusion, this meta-analysis demonstrated that the risk of OHCA is significantly higher in extreme cold ambient temperatures than in reference temperature, according to a relative temperature scale with percentiles of the region-specific temperature distribution.

Author contributions

Yanxia Lin and Wen Tian designed the study and analyzed data. Yanxia Lin and Shijie Zhao wrote the draft of the manuscript. All authors contributed to the interpretation of data, critical revision of the manuscript, and provided final approval of the submitted and published version.

Conflicts of interests

Yanxia Lin, Huanrui Zhang, Shijie Zhao and Wen Tian declare that they have no conflicts of interests.

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