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Season-specific cold spells and sudden cardiac death: a case-crossover study

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Season-specific cold spells and sudden cardiac death:

a case-crossover study

Niilo RI Ryti, Elina MS Mäkikyrö, Harri Antikainen, Eeva Hookana, M Juhani Junttila, Tiina M Ikäheimo, Marja-Leena Kortelainen, Heikki V Huikuri, Jouni JK Jaakkola

Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Niilo RI Ryti doctoral student and Elina MS Mäkikyrö doctoral student Department of Geography, University of Oulu, FI-90014, Finland Harri Antikainen post-doctoral researcher Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, FI-90029, Finland Eeva Hookana post-doctoral researcher and M Juhani Junttila adjunct professor of cardiology Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Tiina M Ikäheimo adjunct professor of environmental health Department of Forensic Medicine, University of Oulu, FI-90014, Finland Marja-Leena Kortelainen professor of forensic medicine Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, FI-90029, Finland Heikki V Huikuri professor of cardiology Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Jouni JK Jaakkola professor of public health

Correspondence to: Professor Jouni JK Jaakkola Jouni.jaakkola@oulu.fi Tel: (358) 50 3613276

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Abstract

Objective To test *a priori* hypothesis of an association between season-specific cold spells and sudden cardiac death (SCD).

Methods We conducted a case-crossover study of 3614 autopsy-verified cases of SCD in the Province of Oulu, Finland (1998-2011). Cold spell was statistically defined by applying an individual frequency distribution of daily temperatures at the home address during the hazard period (7 days preceding death) and 50 reference periods (same calendar days of other years) for each case using the home coordinates. Conditional logistic regression was applied to estimate odds ratios for the association between the occurrence of cold spells and the risk of SCD after controlling for temporal trends.

Results The risk of SCD was associated with a preceding cold spell (OR 1.33; 95%CI: 1.00, 1.78). A greater number of cold days preceding death increased the risk of SCD approximately 19% per day (OR 1.19; 95%CI 1.07-1.32). The association was strongest during autumn (OR 2.51; 95%CI 1.27-4.96) and winter (OR 1.70; 95%CI 1.13-2.55) and lowest during summer (OR 0.42; 95%CI 0.15-1.18) and spring (OR 0.89; 95%CI 0.45-1.79). The association was stronger for ischaemic (OR 1.55; 95%CI 1.12-2.13) than for non-ischaemic SCD (OR 0.68; 95%CI 0.32-1.45) verified by medico-legal autopsy.

Conclusions Our results indicate that there is an association between cold spells and SCD, that this association is strongest during autumn, when the weather event is prolonged, and with cases suffering ischaemic SCD. These findings are subsumed with potential prevention via weather forecasting, medical advice, and protective behavior.

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Article summary

Strengths and limitations of this study

- 3614 cases of the worlds' largest autopsy-verified dataset of sudden cardiac death were linked with 51 years of season-specific weather data at their home coordinates.
- Cold spell was statistically defined for each individual as a period of unusually cold weather pertinent to the season and location.
- In a case-crossover setting, it was analysed whether cold spells occurred more commonly preceding death than during the same calendar dates of 51 other years.
- Stratified analyses were conducted to estimate the role of season, age, sex, and ischaemic versus non-ischaemic aetiology of the sudden cardiac death verified my medico-legal autopsy.
- The study did not elaborate the relative roles of temperature and air pollution during the weather phenomenon. The overall effect of the entire weather phenomenon was estimated rather than focusing on individual physical parameters related to it.

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INTRODUCTION

Sudden cardiac death (SCD) is the leading cause of death, currently estimated to represent 60% of all cardiovascular deaths.[1, 2] In contrast to acute myocardial infarction, or most chronic cardiovascular diseases, SCD affects individuals who have been considered at zero-to-low risk of cardiovascular death.[3, 4] In over half of the cases, SCD is the first manifestation of the underlying cardiac disease.[3] It commonly occurs in the prime of life,[1] affecting approximately one in every five people in the western society.[4] Substantial global research efforts have yielded specific risk markers of SCD, such as certain abnormalities in ECG.[4] However, predicting SCD on both an individual level and in the general population remains challenging.[4]

Weather, on the other hand, can be predicted and preventive measures taken. There is substantial evidence that cardiovascular mortality is associated with the temperature of the day or the preceding days.[5, 6] According to our recent systematic review and meta-analysis, cold spells are associated with 11% increase in cardiovascular mortality rates around the world.[6] Whether or not and how much SCD might contribute to these associations is unknown. There are only a handful of studies on the association between cold weather and SCD,[7-10] and one study on the association between cold spells and ischemic SCD.[11] We recently showed an association between cold spells and ischaemic SCD, with effect modification by cardioprotective medications.[11] There is also considerable evidence on the association between cold ambient temperature and acute myocardial infarction,[12-14] with pathophysiological basis previously described.[15] Whether or not and how much SCD might contribute to these associations is also unknown, since SCD entails a broader range of pathologies and has many distinctive features from acute myocardial infarction or out-of-hospital coronary death.[4, 16-18]

Based on the international shift from broad to specific approaches on SCD risk assessment,[4, 18] our general objective was to estimate the association between cold weather and SCD applying measures that maximise the accuracy of both the exposure and the outcome. Our specific objectives were to test the *a priori* hypotheses that cold spells are associated with the risk of SCD; that the effect is stronger according to an increasing number of unusually cold days preceding the death; and to assess potential seasonal

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modification of the effect; to identify susceptible groups in terms of age and sex; to investigate if the association is stronger for ischaemic than for non-ischaemic SCD.

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METHODS

This study is based on *a priori* protocol accessible at www.oulu.fi/cerh/node/31850. STROBE guidelines were applied to ensure transparency of the reporting of results.

Study design and population

We conducted a case-crossover study to assess the relation between cold spells and SCD. Case-crossover design is well suited for studying the effects of transient short-term exposures on the risk of acute events.[19] We assigned to each case a hazard period (HP) of seven days preceding the day of death and 50 reference periods (RP) comprising of the same calendar days of the other years of the study period 1961-2011.

The study population included 3707 cases from The Finnish Study of Genotype and Phenotype Characteristics of Sudden Cardiac Death (FinGesture) in the province of Oulu, Northern Finland,[16] who died between 1998 and 2011. 93 cases were excluded because their home coordinates for the time of death were unavailable. This resulted in 3614 cases. All cases underwent post mortem examinations at the Department of Forensic Medicine of the University of Oulu. Case validation was conducted by a forensic specialist through medico-legal autopsy, detailed histological sampling, full medical history, and police reports. Those with any other cause than SCD, including intoxications during an acute coronary event, were excluded. All witnessed SCDs occurred within 6 hours of the onset of the forewarning symptoms. All unwitnessed victims of SCD were seen alive and in a normal state of health within 24 hours preceding the death. Post mortem studies of unexpected death are mandatory in Finland, and the selection bias in victims with unexpected SCD is minimal.[16] Hence, this provides unique opportunity to cover the entire breadth of SCD cases in the general population.

Exposure assessment

The home coordinates (EUREF ETRS-TM35FIN) of the cases at the time of death were retrieved from the Population Register Centre. Geographical Information System (GIS) was used to allocate daily temperatures at the home coordinates of each case for the days in hazard and reference periods over the study years 1961-2011. For this purpose, a dataset containing minimum, mean, and maximum daily temperatures in the study period was obtained from the Finnish Meteorological Institute. In this dataset, point measurements have been

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interpolated onto a 10×10 km grid covering the whole of Finland, using a Kriging method.[20] We organised the temperature dataset into a GIS database, and GIS based functions were then used to extract temperature values from the database according to location and date.

Individual frequency distributions of daily temperatures during the hazard and reference periods for the home coordinates of each case were formed. Cold spell was defined as a period of ≥3 consecutive days with daily minimum temperature below the 5th percentile of the individual frequency distribution. Conceptually this approach identifies events that are unusually cold in the respective place and time of the year. We used the same frequency distributions and thresholds to identify singular cold days and any combination of singular cold days in different cold spell definitions used in this study (e.g. 2 consecutive days). Individual exposure assessment was conducted for the hazard period. In contrast to this, the occurrence of cold spells during the reference periods represent the usual exposure at the individual's place of residence. Thus, we estimated the occurrence of the weather phenomenon during the two period types and analysed whether the possible differences in the occurrence could be explained by random variation.

Calendar time was used to define the 4 seasons (autumn Sept-Nov, winter Dec-Feb, spring Mar-May, summer, Jun-Aug).

Statistical methods

Conditional logistic regression was applied to estimate the odds ratios (OR) and 95% confidence intervals (CI) representing the proportion of cold spells occurring during hazard and reference periods. Conditional logistic regression was performed using PROC PHREG in SAS (SAS, version 9.4, SAS Institute, Cary, NC) using the discrete logistic model and forming a stratum for each ID. An indicator variable consisting of 5-year intervals over the study period was formed to control for long time trends in the occurrence of cold spells. Season, month, day of the week, weekends, and holidays were controlled by design.[19] We conducted *a priori* stratified analyses according to gender, age, season, and ischaemic versus non-ischaemic aetiology of the death confirmed by the autopsy finding. The difference between odds ratios in each subgroup was estimated using Q-statistics for heterogeneity, by applying the DerSimonian-Laird-method

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using a SAS-macro provided by Herzmark and Spiegelman.[21,22] Cases aged under 35 were excluded from the subgroup analyses *a priori* because of the few numbers (n=48) and expected heterogeneity.

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RESULTS

The characteristics of the study population are shown in Table 1.

Table 1. The characteristics of the study population.

Characteristic	Men, n (%)	Women, n (%)	Total, n (%)
All	2878 (79.63)	736 (20.37)	3614 (100.0)
Age			
0-64	1615 (87.11)	239 (12.89)	1854 (51.30)
≥65	1263 (71.76)	497 (28.24)	1760 (48.70)
Autopsy finding			
Ischaemic	2214 (80.25)	545 (19.75)	2759 (76.34)
Non-ischaemic	664 (77.66)	191 (22.34)	855 (23.66)
Season of death			
Autumn	688 (77.65)	198 (22.35)	886 (24.52)
Winter	688 (79.81)	174 (20.19)	862 (23.85)
Spring	802 (81.01)	188 (18.99)	990 (27.39)
Summer	700 (79.91)	176 (20.09)	876 (24.24)

A total of 3974 location specific cold spells were entified for the analyses. The distributions of temperature and exposure parameters are shown in Table 2.

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Table 2. The distributions of temperature (T) and exposure parameters by season.

Variable	Autumn	Winter	Spring	Summer	Total
Mean T (SD), °C	+0.29 (6.78)	-13.54 (9.28)	-5.04 (7.92)	+9.16 (3.96)	-2.31 (10.88)
T range, °C	53.4	51.8	56.0	28.2	67.7
Lowest T, °C	-35.70	-45.80	-40.10	-6.30	-45.80
Highest T, °C	+17.70	+6.00	+15.90	+21.90	+21.90
T quartiles, Q1, Q2, Q3, °C	-3.10, +0.90, +5.00	-20.60, -12.40, -5.90	-9.30, -3.00, +0.30	+6.60, +9.40, +12.00	-8.70, -0.70, +6.00
Threshold T, mean (SD), °C	-8.64 (7.09)	-29.00 (3.07)	-15.38 (8.79)	+3.36 (2.41)	-
Individual cold days, n (%)	14711 (24.5)	14436 (24.0)	16496 (27.5)	14415 (24.0)	60058 (100.0)
2 consecutive cold days, n (%)	1466 (25.5)	1582 (27.5)	1600 (27.8)	1104 (19.2)	5752 (100.0)
3 consecutive cold days, n (%)	421 (21.5)	753 (38.4)	498 (25.4)	287 (14.7)	1959 (100.0)
4 consecutive cold days, n (%)	129 (17.0)	317 (41.7)	213 (28.0)	101 (13.3)	760 (100.0)
Cold spells, n (%)	810 (20.4)	1563 (39.3)	1046 (26.3)	555 (14.0)	3974 (100.0)

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Cold spells were associated with an increased risk of SCD (OR 1.33; 95%CI 1.00-1.78). The effect estimate for a singular cold day was below unity (OR 0.84; 95%CI 0.72-0.97), and increasing the number of cold days occurring during the hazard period increased the risk of SCD approximately 19% per day (OR 1.19; 95%CI 1.07-1.32). Figure 1 shows the risk for 1, 2, 3, and ≥ 4 consecutive days below the threshold temperature.

In the stratified analyses, distinct seasonal differences in the association between cold spells and SCD were observed. The effect estimates were highest during autumn and winter, and lowest during summer and spring (Table 3), while the underlying seasonal variation in the incidence of SCD was negligible (Table 1).

Table 3. The relation between the occurrence of cold spells and the risk of SCD by season.

Season	Odds ratio (95% CI)
Autumn	2.51 (1.27-4.96)
Winter	1.70 (1.13-2.55)
Spring	0.89 (0.45-1.79)
Summer	0.42 (0.15-1.18)

We conducted several stratified analyses for the purpose of elaborating effect modification of the relation between cold spells and SCD. There were no distinct differences in sensitivity to cold spells between subjects aged over 65 years (OR 1.36; 95%CI 0.91-2.04) and those aged under 65 years (OR 1.28; 95%CI 0.84-1.97) (Heterogeneity Q-statistic 0.03, p-value 0.8436). Likewise, gender did not significantly modify the effect (OR 1.30; 95%CI 0.94-1.81 males versus OR 1.41; 95%CI 0.74-2.67 females) (Heterogeneity Q-statistic 0.04, p-value 0.83).

In the stratified analysis according to the aetiology of underlying structural heart disease at autopsy, the effect estimate for ischaemic SCD (OR 1.55; 95%CI 1.12-2.13) was greater than for non-ischaemic SCD (OR 0.68; 95%CI 0.32-1.45) (Heterogeneity Q-statistic 3.85, p-value 0.05).

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DISCUSSION

We conducted a case-crossover study using world's largest autopsy-verified study on SCD and 51 years of weather data in individual home addresses of the cases. Cold spells were associated with an increased risk of SCD. Additional number of cold days during the one-week period preceding death increased the risk of SCD by approximately 19% per cold day. The association between cold spells and SCD was strongest during autumn and winter, and nonexistent during spring and summer. Cold spells increased the risk of SCD caused by ischaemic heart disease, whereas there was no association with non-ischaemic aetiology.

The incidence of SCD was similar during different seasons (Table 1), but the associations between seasonally defined cold spells and the risk of SCD varied significantly depending on the season (Table 3). The highest effect estimate during autumn promotes the concept of relative, instead of absolute, temperature playing an important role in the association.[6] The first few cold temperatures of autumn might involve an increased risk due to lack of cold habituation and the associated aggravated physiological responses,[23] or due to a delay in behavioral adaptation such as appropriate clothing and sufficient indoor heating.[24] The contrast in effect estimates between autumn and spring, both of which have similar average temperature, similar temperature range, and similar threshold temperature (Table 2), is noteworthy. A gradual change towards colder temperatures or the rapidly doubling temperature range might modify the association with cold spells. The contrast in the effect estimates between winter and summer suggest that absolute temperature level, complementary to the relative or changing temperature, plays a role in the association. None of these interpretations are in conflict with previous evidence, and the results suggest that physicians should start advising cardiologic patients on the risks associated with cold weather before winter.

Additional number of cold days during the one-week period preceding death increased the risk of SCD. This could indicate sustained cold-related physiological strain and/or increasing probability of exposure. On the other hand, the protective effect of a single cold day might be explained by protective behavior such as first staying indoors but then having to return to normal behavior. Both speculations presume that the most harmful exposure during cold spells occurs outdoors, which has not been confirmed.[6]

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Cold spells increased the risk of sudden cardiac death caused by ischaemic heart disease, whereas there was no association with non-ischaemic aetiology. This finding, if repeated in other settings, might provide further insight into the cold-induced pathological pathways of SCD. We have recently summarised some of the hypothesised pathways between cold spells and SCD.[11] Briefly, evidence from experimental studies show that exposure to cold ambient temperature induces changes in blood composition, loss of plasma fluid, haemoconcentration, redistribution of thrombogenic factors;[25, 26] induces peripheral vasoconstriction and a sudden increase in systemic vascular resistance, systolic and diastolic and central aortic blood pressure, pre-load, cardiac output, and oxygen demand of the heart;[15, 27] and under experimental conditions induces coronary spasm in susceptible individuals.[28] All these factors increase specifically the susceptibility to SCD caused by acute ischaemic event, which was evident in our findings. Cooling of the face or body also results in simultaneous coactivation of sympathetic and parasympathetic nervous systems, which may be pro arrhythmic given suitable myocardial substrates.[29] This pathway might be less significant during cold weather, since cold spells were not associated with an increased risk of SCD in subjects with non-ischaemic heart disease. However, no definite conclusions should be made on the pathways or their relevance before extensive studies into the topic. Insight might offer direct targets for intervention with pharmacologic agents, as recently shown.[11]

Improvements were introduced to the definition of cold spell based on the findings of our recent systematic review and meta-analysis.[6] In the reviewed studies, cold spell threshold was commonly defined as the 1-5th percentile of the frequency distribution of the daily temperatures over the entire study period. Conceptually this tends to place all cold spells in cold winter months and disregards unusually cold events occurring during warmer months. Because the adverse effects of cold temperatures have been shown to be more pronounced in warmer climates,[5, 24] or because lack of cold habituation during warmer months could elicit aggravated cardiovascular responses to a suddenly decreasing temperature,[23] it is reasonable to ask whether exceptionally cold weather during months other than those of winter could also have adverse effects on health. Our approach identifies events that are unusually cold in the respective place and time of the year. It is telling that we would not have been able to observe the highest risk during autumn without this approach. Generally speaking, frequency distribution-based exposure assessment is beneficial for the

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generalizability of results, making it easier to compare estimates obtained from different geographical regions.[6]

Limitations

The present study assessed the association between cold spells and occurrence of SCD without elaborating the relative roles of temperature and air pollution. In other words, we estimated the overall effect of the entire weather phenomenon rather than focusing on individual physical parameters related to this phenomenon. Ours is the primary question from clinical and public health practice, although additional information on the contribution on air pollution in general and specific compounds would be interesting. If part of the effects of cold spells were mediated by increased air pollution levels, adjustment for air pollution would lead to underestimation of the overall effects of cold spells.

Conclusions

Our results suggest that there is an association between cold spells and SCD, that this association is strongest during autumn, when the weather event is prolonged, and with cases suffering ischaemic SCD. These findings are subsumed with potential prevention via weather forecasting, medical advice, and protective behavior. We believe more studies on these associations should be commenced to identify the most potential targets for intervention, be it pharmacological modification, diagnosis and treatment of underlying cardiovascular diseases, or behavioral patterns during cold weather.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none of the authors have support from any company for the submitted work; (2) none of the authors have relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have non-financial interests that may be relevant to the submitted work.

Contributorship statement

NR and JJ designed the study. MLK contributed significantly to the performing of the medico-legal autopsies over 1998-2011. EH complemented the autopsy data to constitute the FinGesture database under the supervision of MJJ and HH. HA collected the weather data from Finnish Meteorological Institution, designed and applied the GIS-model to produce the case specific exposure data. EM designed the SAS-program for the main analyses and executed the analyses together with NR. TI contributed expertise in cold-related physiology and substantial scientific input in interpretation of the results. HH contributed expertise in cardiology and substantial scientific input in the interpretation of the results. JJ contributed expertise in epidemiology and public health and substantial scientific input in interpretation of results. NR and JJ drafted the manuscript and all authors have accepted the final version. JJ and HH have equal senior authorship, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval

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This study complies with the Declaration of Helsinki and has been approved by the Ethics Committee of the Oulu University Hospital (ID of the approval EETTMK:18/2014). National Supervisory Authority for Welfare and Health (Valvira) has approved the review of post mortem data by the investigators.

Transparency declaration

The senior authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

Data sharing: no additional data available.

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References

1 Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. Nat Rev Cardiol 2010;7:216–225.

2 Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis 2008;51:213–228.

3 Myerburg RJ, Junttila J. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043–1052.

4 Wellens HJJ, Scwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J 2014;35:1642–1651.

5 Analitis A, Katsouyanni K, Biggeri A, et al. Effects of cold weather on mortality: results from 15 European cities within the PHEWE project. Am J Epidemiol 2008;168:1397–408.

6 Ryti NRI, Guo Y, Jaakkola JJK. Global association of cold spells and adverse health effects: a systematic review and meta-analysis. Environ Health Perspect 2016;124:12–22; doi:10.1289/ehp.1408104.

7 Törő K, Batholy J, Pongrácz R, Kis Z, Keller É, Dunay G. Evaluation of meteorological factors on sudden cardiovascular death. J Forensic Leg Med 2010;17:236–242.

8 Gerber Y, Jacobsen S, Killian J, Weston S, Roger V. Seasonality and daily weather conditions in relation to myocardial infarction and sudden cardiac death in Olmsted County, Minnesota, 1979-2002. J Am Coll Cardiol 2006;48:287–292.

9 Arntz H-R, Müller-Nordhorn, Willich S. Cold Monday mornings prove dangerous: epidemiology of sudden cardiac death. Curr Opin Crit Care 2001;7:139–144.

10 Katz A, Biron A, Ovsyshcher E, Porath A. Seasonal variation in sudden death in the Negev desert region of Israel. Isr Med Assoc J 2000;2:17–21.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11 Ryti NRI, Mäkikyrö EMS, Antikainen H, et al. Cold spells and ischaemic sudden cardiac death: effect modification by prior diagnosis of ischaemic heart disease and cardioprotective medication. Sci. Rep. 2017;7,41060; doi: 10.1038/srep41060.

12 Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of ambient temperature on the incidence of myocardial infarction. Heart 2009;95:1760–1769.

13 Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Short term effects of temperature on risk of myocardial infarction in England and Wales: time-series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry. BMJ 2010;341:c3823.

14 Chen R, Li T, Cai J, Yan M, Zhao Z, Kan H. Extreme temperatures and out-of-hospital coronary deaths in six large Chinese cities. J Epidemiol Community Health 2014;68:1119–1124.

15 Manou-Stathopoulou V, Goodwin CD, Patterson T, Redwood SR, Marber MS, Williams RP. The effects of cold and exercise on the cardiovascular system. Heart. 2015;101:808–820.

16 Hookana E, Junttila J, Puurunen V-P, et al. Causes of nonischemic sudden cardiac death in the current era. Heart Rhythm 2011;8:1570–1575.

17 Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to arrhythmias. N Engl J Med 2001;345:1473–1482.

18 Chugh SS, Jui J, Gunson K, et al. Current Burden of Sudden Cardiac Death: Multiple Source Surveillance Versus Retrospective Death Certificate-Based Review in a Large U.S. Community. J Am Coll Cardiol 2004;44:1268–1275.

19 Maclure M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. Am J Epidemiol 1991;133:144–152.

20 Venäläinen A, Heikinheimo M. Meteorological data for agricultural applications. Phys Chem Earth 2002;27:1045–1050.

21 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.

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22 Hertzmark E, Spiegelman D. The SAS METAANAL Macro. Written for the Channing Laboratory, 24 May 2012. Available at http://www.hsph.harvard.edu/donna-spiegelman/software/metaanal/ Accessed 24.6.2015.

23 Mäkinen TM. Different types of cold adaptation in humans. Front Biosci 2010;S2:1047–1067.

24 The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 1997;349:1341–1346.

25 Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. 1984. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. Br Med J 1984;289:405–1408.

26 Neild PJ, Syndercombe-Court D, Keatinge WR, Donaldson GC, Mattock M, Caunce M. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X. Clin Sci 1994;86:43–48.

27 Hintsala H, Kandelberg A, Herzig KH. et al. Central aortic blood pressure of hypertensive men during short-term cold exposure. Am J Hypertens 2014;27:656–664.

28 Raizner A, Chahine RA, Ishimori T, et al. Provocation of coronary artery spasm by the cold pressor test. Circulation 2980;62:925–932.

29 Shattock MJ, Tipton MJ. 'Autonomic conflict': a different way to die during cold water immersion? J Physiol 2012;590:3219–30.

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Figure legends

Figure 1. The relation between sudden cardiac death and consecutive days below threshold temperature. X-axis presents the odds ratios (OR) and 95% confidence intervals (95% CI) on a logarithmic scale; y-axis presents the number of consecutive days used in the cold spell definition for each analysis, an integer being the exact number of consecutive days, and "≥" indicating the minimum number of consecutive days (e.g. at least n consecutive days).

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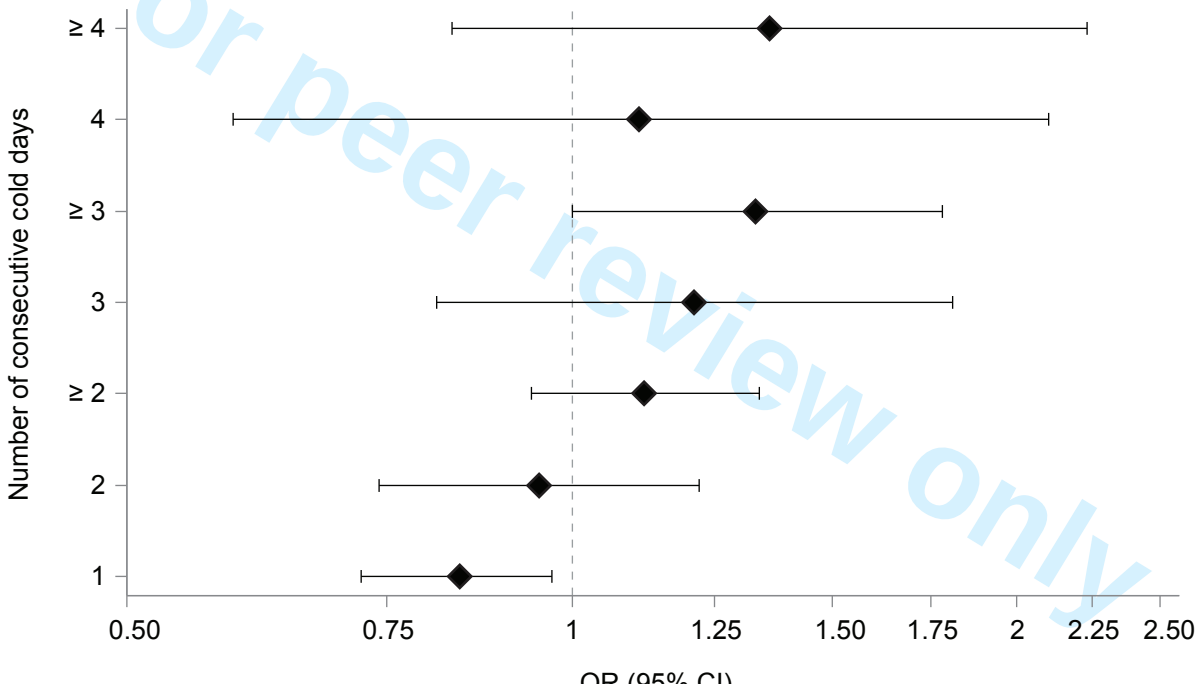

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Title of the manuscript: Season-specific cold spells and sudden cardiac death: a case-crossover study applying individual exposure assessment

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Author's note (status)	Author's note (page number)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ok	p1,p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Ok	p2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Ok	p4
Objectives	3	State specific objectives, including any prespecified hypotheses	Ok	p4,p5
Methods				
Study design	4	Present key elements of study design early in the paper	Ok	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Ok	p6,p7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Ok	p6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Ok/NA	p6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Ok	p6,p7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Ok	p6, p7, p8

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Bias	9	Describe any efforts to address potential sources of bias	Ok	p7, p8
Study size	10	Explain how the study size was arrived at	Ok	p6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Ok	p7, p8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Ok	p7, p8
		(*b*) Describe any methods used to examine subgroups and interactions	Ok	p7, p8
		(*c*) Explain how missing data were addressed	Ok	p6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Ok	p6
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Ok	p9 (see p6)
		(b) Give reasons for non-participation at each stage	Ok	p6
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Ok	p9, p10
		(b) Indicate number of participants with missing data for each variable of interest	Ok	(see p6)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Ok	p11
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of	NA	NA

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		relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Ok	p11
Discussion				
Key results	18	Summarise key results with reference to study objectives	Ok	p12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Ok	p14 (see p7, p8)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Ok	p12,p13,p14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Ok	p13, p14
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Ok	p15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The risk of sudden cardiac death in relation to season-specific cold spells: a case-crossover study in Finland

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Complete List of Authors:	Ryti, Niilo; University of Oulu, Center for Environmental and Respiratory Health Research Mäkikyrö, Elina; University of Oulu, Center for Environmental and Respiratory Health Research Antikainen, Harri; University of Oulu Hookana, Eeva; Oulun Yliopisto Laaketieteellisen tiedekunta, Research Unit of Internal Medicine Junttila, Juhani Ikäheimo, Tiina; University of Oulu, Center for Environmental and Respiratory Health Research Kortelainen, Marja-Leena; Institute of Diagnostics, Department of Forensic Medicine, Oulu University Hospital Huikuri, Heikki; University of Oulu, Dept. of Internal Medicine Jaakkola, Jouni; University of Oulu, Center for Environmental and Respiratory Health Research
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The risk of sudden cardiac death in relation to season-specific cold spells: a case-crossover study in Finland

Niilo RI Ryti, Elina MS Mäkikyrö, Harri Antikainen, Eeva Hookana, M Juhani Junttila, Tiina M Ikäheimo, Marja-Leena Kortelainen, Heikki V Huikuri, Jouni JK Jaakkola

Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Niilo RI Ryti doctoral student and Elina MS Mäkikyrö doctoral student Department of Geography, University of Oulu, FI-90014, Finland Harri Antikainen post-doctoral researcher Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, FI-90029, Finland Eeva Hookana post-doctoral researcher and M Juhani Junttila adjunct professor of cardiology Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Tiina M Ikäheimo adjunct professor of environmental health Department of Forensic Medicine, University of Oulu, FI-90014, Finland Marja-Leena Kortelainen professor of forensic medicine Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, FI-90029, Finland Heikki V Huikuri professor of cardiology Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Jouni JK Jaakkola professor of public health

Correspondence to: Professor Jouni JK Jaakkola Jouni.jaakkola@oulu.fi Tel: (358) 50 3613276

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NOTE: JJ and HH have equal senior authorship.

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Abstract

Objective To test *a priori* hypothesis of an association between season-specific cold spells and sudden cardiac death (SCD).

Methods We conducted a case-crossover study of 3614 autopsy-verified cases of SCD in the Province of Oulu, Finland (1998-2011). Cold spell was statistically defined by applying an individual frequency distribution of daily temperatures at the home address during the hazard period (7 days preceding death) and 50 reference periods (same calendar days of other years) for each case using the home coordinates. Conditional logistic regression was applied to estimate odds ratios for the association between the occurrence of cold spells and the risk of SCD after controlling for temporal trends.

Results The risk of SCD was associated with a preceding cold spell (OR 1.33; 95%CI: 1.00, 1.78). A greater number of cold days preceding death increased the risk of SCD approximately 19% per day (OR 1.19; 95%CI 1.07-1.32). The association was strongest during autumn (OR 2.51; 95%CI 1.27-4.96) and winter (OR 1.70; 95%CI 1.13-2.55) and lowest during summer (OR 0.42; 95%CI 0.15-1.18) and spring (OR 0.89; 95%CI 0.45-1.79). The association was stronger for ischaemic (OR 1.55; 95%CI 1.12-2.13) than for non-ischaemic SCD (OR 0.68; 95%CI 0.32-1.45) verified by medico-legal autopsy.

Conclusions Our results indicate that there is an association between cold spells and SCD, that this association is strongest during autumn, when the weather event is prolonged, and with cases suffering ischaemic SCD. These findings are subsumed with potential prevention via weather forecasting, medical advice, and protective behavior.

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and ischaemic versus non-ischaemic aetiology of the death confirmed by the autopsy finding as BY-variables in conditional logistic regression. Cases aged under 35 were excluded from the subgroup analyses *a priori* because of the few numbers (n=40) and expected heterogeneity. The difference between odds ratios in each subgroup was estimated using Q-statistics for heterogeneity, by applying the DerSimonian-Laird-method using a SAS-macro provided by Herzmark and Spiegelman.[21,22]

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RESULTS

The characteristics of the study population are shown in Table 1.

Table 1. The characteristics of the study population.

Characteristic	Men, n (%)	Women, n (%)	Total, n (%)
All	2878	736	3614
Age			
0-34	32 (1.1)	8 (1.1)	40 (1.1)
35-64	1583 (55.0)	231 (31.4)	1814 (50.2)
≥65	1263 (43.9)	497 (67.5)	1760 (48.7)
Autopsy finding			
Ischaemic	2214 (76.9)	545 (74.0)	2759 (76.3)
Non-ischaemic	664 (23.1)	191 (26.0)	855 (23.7)
Season of death			
Autumn	688 (23.9)	198 (26.9)	886 (24.5)
Winter	688 (23.9)	174 (23.6)	862 (23.9)
Spring	802 (27.9)	188 (25.5)	990 (27.4)
Summer	700 (24.3)	176 (23.9)	876 (24.2)

A total of 3974 location specific cold spells were identified for the analyses. The distribution parameters of daily temperatures in the province of Oulu 1961-2011 are shown in Table 2.

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Table 2. The distribution parameters of daily temperatures (T) in the province of Oulu, Finland, over the study period 1961-2011.

Variable	Autumn	Winter	Spring	Summer	Total
Mean average T (SD), °C	+1.7 (6.7)	-10.5 (7.9)	+0.4 (7.2)	+13.8 (3.7)	+1.4 (10.8)
T range, °C	58.6	49.7	61.9	35.7	74.3
Lowest minimum T, °C	-34.4	-41.3	-34.2	-2.7	-41.3
Highest maximum T, °C	+24.2	+8.4	+27.7	+33.0	+33.0
T quartiles, Q1, Q2, Q3, °C	-2.1, +2.1, +6.4	-16.0, -9.2, -4.1	-3.9, +0.8, +5.0	+11.3, +13.7, +16.2	-5.5, +1.6, +10.3

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Cold spells were associated with an increased risk of SCD (OR 1.33; 95%CI 1.00-1.78). The effect estimate for a singular cold day was below unity (OR 0.84; 95%CI 0.72-0.97), and increasing the number of cold days occurring during the hazard period increased the risk of SCD approximately 19% per day (OR 1.19; 95%CI 1.07-1.32). Figure 1 shows the relation between the occurrence of different combinations of consecutive days below the threshold temperature and the risk of SCD.

In the analyses stratified by season, distinct seasonal differences in the association between cold spells and SCD were observed. The effect estimates were highest during autumn and winter, and lowest during summer and spring (Table 3), while the underlying seasonal variation in the incidence of SCD was negligible (Table 1).

Table 3. The relation between the occurrence of cold spells and the risk of SCD based on stratified analyses by season.

Season	Odds ratio (95% CI)
Autumn	2.51 (1.27-4.96)
Winter	1.70 (1.13-2.55)
Spring	0.89 (0.45-1.79)
Summer	0.42 (0.15-1.18)

We conducted several subgroup analyses for the purpose of elaborating effect modification of the relation between cold spells and SCD (Table 4). There were no distinct differences in sensitivity to cold spells between subjects aged over 65 years and those aged 35-64 years. Likewise, gender did not significantly modify the effect.

Table 4. The relation between the occurrence of cold spells and the risk of SCD by various subgroups of cases over 34 years of age.

Subgroup	Odds ratio (95% CI)	Q-statistics (p)
Age		
35-64	1.28 (0.84-1.97)	0.03 (0.84)
≥65	1.36 (0.91-2.04)	
Sex		
Men	1.30 (0.94-1.81)	0.04 (0.83)
Women	1.41 (0.74-2.67)	
Autopsy finding		
Ischaemic	1.55 (1.12-2.13)	3.85 (0.05)
Non-ischaemic	0.68 (0.32-1.45)	

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In the subgroup analysis according to the aetiology of underlying structural heart disease at autopsy, the effect estimate for ischaemic SCD was greater than for non-ischaemic SCD, confirmed by Q-statistic 3.85, p 0.05 (Table 4).

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DISCUSSION

Cold spells were associated with an increased risk of SCD. Additional number of cold days during the one-week period preceding death increased the risk of SCD by approximately 19% per cold day. The association between cold spells and SCD was strongest during autumn and winter, and nonexistent during spring and summer. Cold spells increased the risk of SCD caused by ischaemic heart disease, whereas there was no association with non-ischaemic aetiology.

The incidence of SCD was similar during different seasons (Table 1), but the associations between seasonally defined cold spells and the risk of SCD varied significantly depending on the season (Table 3). The highest effect estimate during autumn promotes the concept of relative, instead of absolute, temperature playing an important role in the association.[6] The first few cold temperatures of autumn might involve an increased risk due to lack of cold habituation and the associated aggravated physiological responses,[23] or due to a delay in behavioral adaptation such as appropriate clothing and sufficient indoor heating.[24] The contrast in effect estimates between autumn and spring, both of which have similar temperature indices (Table 2), and similar incidence of SCD (Table 1), is noteworthy. A gradual change towards colder temperatures or the rapidly increasing temperature range after summer might modify the association with cold spells. The contrast in the effect estimates between winter and summer suggest that absolute temperature level, complementary to the relative or changing temperature, plays a role in the association. None of these interpretations are in conflict with previous evidence, and the results suggest that physicians should start advising cardiologic patients on the risks associated with cold weather before winter.

Additional number of cold days during the one-week period preceding death increased the risk of SCD. This could indicate sustained cold-related physiological strain and/or increasing probability of exposure. On the other hand, the protective effect of a single cold day might be explained by protective behavior such as first staying indoors but then having to return to normal behavior. Both speculations presume that the most harmful exposure during cold spells occurs outdoors, which has not been confirmed.[6]

Cold spells increased the risk of sudden cardiac death caused by ischaemic heart disease, whereas there was no association with non-ischaemic aetiology. This finding, if repeated in other settings, might provide further

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insight into the cold-induced pathological pathways of SCD. We have recently summarised some of the hypothesised pathways between cold spells and SCD.[11] Briefly, evidence from experimental studies show that exposure to cold ambient temperature induces changes in blood composition, loss of plasma fluid, haemoconcentration, redistribution of thrombogenic factors;[25, 26] induces peripheral vasoconstriction and a sudden increase in systemic vascular resistance, systolic and diastolic and central aortic blood pressure, pre-load, cardiac output, and oxygen demand of the heart;[15, 27] and under experimental conditions induces coronary spasm in susceptible individuals.[28] All these factors increase specifically the susceptibility to SCD caused by acute ischaemic event, which was evident in our findings. Cooling of the face or body also results in simultaneous coactivation of sympathetic and parasympathetic nervous systems, which may be pro arrhythmic given suitable myocardial substrates.[29] This pathway might be less significant during cold weather, since cold spells were not associated with an increased risk of SCD in subjects with non-ischaemic heart disease. However, no definite conclusions should be made on the pathways or their relevance before extensive studies into the topic. Insight might offer direct targets for intervention with pharmacologic agents, as recently shown.[11]

Strengths and limitations

Improvements were introduced to the definition of cold spell based on the findings of our recent systematic review and meta-analysis.[6] In the reviewed studies, cold spell threshold was commonly defined as the 1-5th percentile of the frequency distribution of the daily temperatures over the entire study period. Conceptually this tends to place all cold spells in cold winter months and disregards unusually cold events occurring during warmer months. Because the adverse effects of cold temperatures have been shown to be more pronounced in warmer climates,[5, 24] or because lack of cold habituation during warmer months could elicit aggravated cardiovascular responses to a suddenly decreasing temperature,[23] it is reasonable to ask whether exceptionally cold weather during months other than those of winter could also have adverse effects on health. Our approach identifies events that are unusually cold in the respective place and time of the year. It is telling that we would not have been able to observe the highest risk during autumn without this approach. Generally speaking, frequency distribution-based exposure assessment is beneficial in terms of being able to generalise results, making it easier to compare estimates obtained from different geographical

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regions.[6] It would be interesting to see whether comparable results obtained with these methods would produce different effect estimates in different climates.[30]

There is evidence on the benefits of confirming the diagnosis and mode of sudden death by medico-legal autopsy in order to provide unbiased information on the incidence of SCD.[2, 3, 18] It is difficult to distinguish between cardiac and non-cardiac cause of sudden death without an autopsy, since many conditions that evolve rapidly, such as aortic dissection, massive pulmonary embolism, or stroke, can lead to sudden collapse and death. We conducted our analyses using the world's largest autopsy-verified dataset of SCD. We took advantage of the individual-level nature of the data by forming and assessing individual frequency distributions of temperatures at each home coordinate to define cold weather for the cases.

The present study assessed the association between cold spells and occurrence of SCD without elaborating the relative roles of temperature and air pollution. In other words, we estimated the overall effect of the entire weather phenomenon rather than focusing on individual physical parameters related to this phenomenon. Ours is the primary question from clinical and public health practice, although additional information on the contribution on air pollution in general and specific compounds would be interesting. If part of the effects of cold spells were mediated by increased air pollution levels, adjustment for air pollution would lead to underestimation of the overall effects of cold spells.

Although we estimated the outdoor temperatures for each home coordinate for the week preceding the death of the resident, the behavioral activity patterns for the week preceding death were not available. Therefore, it was not possible to estimate how much time the cases spent outdoors, and what kind of thermal patterns they were exposed to. This is a common limitation in studies without personal measuring devices and activity pattern diaries. It also remains an important question how changes in weather manifest as changes in different indoor environments, and whether some of these changes mediate the harmful effects of weather. Variations between individuals in their attitudes toward cold weather, use of protective clothing, physical activity, comorbidity, substance abuse, and use of medications are likely to exist in our data and in the general population. Combinations of these and other individual factors might influence personal risk profiles in ways that are difficult to predict from an epidemiological stance, and although our results can be

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generalized over a population, they can't be directly translated to individual risk. It is reasonable to assume that the association between cold spells and risk of SCD is modified by a variety of factors still unknown.

Conclusions

Our results suggest that there is an association between cold spells and SCD, that this association is strongest during autumn, when the weather event is prolonged, and with cases suffering ischaemic SCD. These findings are subsumed with potential prevention via weather forecasting, medical advice, and protective behavior. We believe more studies on the associations between cold weather and SCD should identify potential targets for intervention, be it pharmacological modification, diagnosis and treatment of underlying cardiovascular diseases, or behavioral patterns during cold weather.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none of the authors have support from any company for the submitted work; (2) none of the authors have relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have non-financial interests that may be relevant to the submitted work.

Contributorship statement

NR and JJ designed the study. MLK contributed significantly to the performing of the medico-legal autopsies over 1998-2011. EH complemented the autopsy data to constitute the FinGesture database under the supervision of MJJ and HH. HA collected the weather data from Finnish Meteorological Institution, designed and applied the GIS-model to produce the case specific exposure data. EM designed the SAS-program for the main analyses and executed the analyses together with NR. TI contributed expertise in cold-related physiology and substantial scientific input in interpretation of the results. HH contributed expertise in cardiology and substantial scientific input in the interpretation of the results. JJ contributed expertise in epidemiology and public health and substantial scientific input in interpretation of results. NR and JJ drafted the manuscript and all authors have accepted the final version. JJ and HH have equal senior authorship, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval

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This study complies with the Declaration of Helsinki and has been approved by the Ethics Committee of the Oulu University Hospital (ID of the approval EETTMK:18/2014). National Supervisory Authority for Welfare and Health (Valvira) has approved the review of post mortem data by the investigators.

Transparency declaration

The senior authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

Data sharing: no additional data available.

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References

1 Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. Nat Rev Cardiol 2010;7:216–225.

2 Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis 2008;51:213–228.

3 Myerburg RJ, Junttila J. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043–1052.

4 Wellens HJJ, Scwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J 2014;35:1642–1651.

5 Analitis A, Katsouyanni K, Biggeri A, et al. Effects of cold weather on mortality: results from 15 European cities within the PHEWE project. Am J Epidemiol 2008;168:1397–408.

6 Ryti NRI, Guo Y, Jaakkola JJK. Global association of cold spells and adverse health effects: a systematic review and meta-analysis. Environ Health Perspect 2016;124:12–22; doi:10.1289/ehp.1408104.

7 Törő K, Batholy J, Pongrácz R, Kis Z, Keller É, Dunay G. Evaluation of meteorological factors on sudden cardiovascular death. J Forensic Leg Med 2010;17:236–242.

8 Gerber Y, Jacobsen S, Killian J, Weston S, Roger V. Seasonality and daily weather conditions in relation to myocardial infarction and sudden cardiac death in Olmsted County, Minnesota, 1979-2002. J Am Coll Cardiol 2006;48:287–292.

9 Arntz H-R, Müller-Nordhorn, Willich S. Cold Monday mornings prove dangerous: epidemiology of sudden cardiac death. Curr Opin Crit Care 2001;7:139–144.

10 Katz A, Biron A, Ovsyshcher E, Porath A. Seasonal variation in sudden death in the Negev desert region of Israel. Isr Med Assoc J 2000;2:17–21.

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11 Ryti NRI, Mäkikyrö EMS, Antikainen H, et al. Cold spells and ischaemic sudden cardiac death: effect modification by prior diagnosis of ischaemic heart disease and cardioprotective medication. Sci. Rep. 2017;7,41060; doi: 10.1038/srep41060.

12 Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of ambient temperature on the incidence of myocardial infarction. Heart 2009;95:1760–1769.

13 Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Short term effects of temperature on risk of myocardial infarction in England and Wales: time-series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry. BMJ 2010;341:c3823.

14 Chen R, Li T, Cai J, Yan M, Zhao Z, Kan H. Extreme temperatures and out-of-hospital coronary deaths in six large Chinese cities. J Epidemiol Community Health 2014;68:1119–1124.

15 Manou-Stathopoulou V, Goodwin CD, Patterson T, Redwood SR, Marber MS, Williams RP. The effects of cold and exercise on the cardiovascular system. Heart. 2015;101:808–820.

16 Hookana E, Junttila J, Puurunen V-P, et al. Causes of nonischemic sudden cardiac death in the current era. Heart Rhythm 2011;8:1570–1575.

17 Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to arrhythmias. N Engl J Med 2001;345:1473–1482.

18 Chugh SS, Jui J, Gunson K, et al. Current Burden of Sudden Cardiac Death: Multiple Source Surveillance Versus Retrospective Death Certificate-Based Review in a Large U.S. Community. J Am Coll Cardiol 2004;44:1268–1275.

19 Maclure M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. Am J Epidemiol 1991;133:144–152.

20 Venäläinen A, Heikinheimo M. Meteorological data for agricultural applications. Phys Chem Earth 2002;27:1045–1050.

21 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.

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22 Hertzmark E, Spiegelman D. The SAS METAANAL Macro. Written for the Channing Laboratory, 24 May 2012. Available at http://www.hsph.harvard.edu/donna-spiegelman/software/metaanal/ Accessed 24.6.2015.

23 Mäkinen TM. Different types of cold adaptation in humans. Front Biosci 2010;S2:1047–1067.

24 The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 1997;349:1341–1346.

25 Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. 1984. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. Br Med J 1984;289:405–1408.

26 Neild PJ, Syndercombe-Court D, Keatinge WR, Donaldson GC, Mattock M, Caunce M. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X. Clin Sci 1994;86:43–48.

27 Hintsala H, Kandelberg A, Herzig KH. et al. Central aortic blood pressure of hypertensive men during short-term cold exposure. Am J Hypertens 2014;27:656–664.

28 Raizner A, Chahine RA, Ishimori T, et al. Provocation of coronary artery spasm by the cold pressor test. Circulation 1980;62:925–932.

29 Shattock MJ, Tipton MJ. 'Autonomic conflict': a different way to die during cold water immersion? J Physiol 2012;590:3219–30.

30 Stewart S, Keates AK, Redfern A, McMurray JJV. Seasonal variations in cardiovascular disease. Nat Rev Cardiol 2017: doi: 10.1038/nrcardio.2017.76.

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Figure legends

Figure 1. The relation between sudden cardiac death and consecutive days below threshold temperature. X-axis presents the odds ratios (OR) and 95% confidence intervals (95% CI) on a logarithmic scale; y-axis presents the number of consecutive days with daily minimum temperature below threshold occurring during the week preceding death. Each effect estimate is derived by a stratified analysis according to the number of days, an integer being the exact number of consecutive days, and "≥" indicating the minimum number of consecutive days (e.g. at least n consecutive days).

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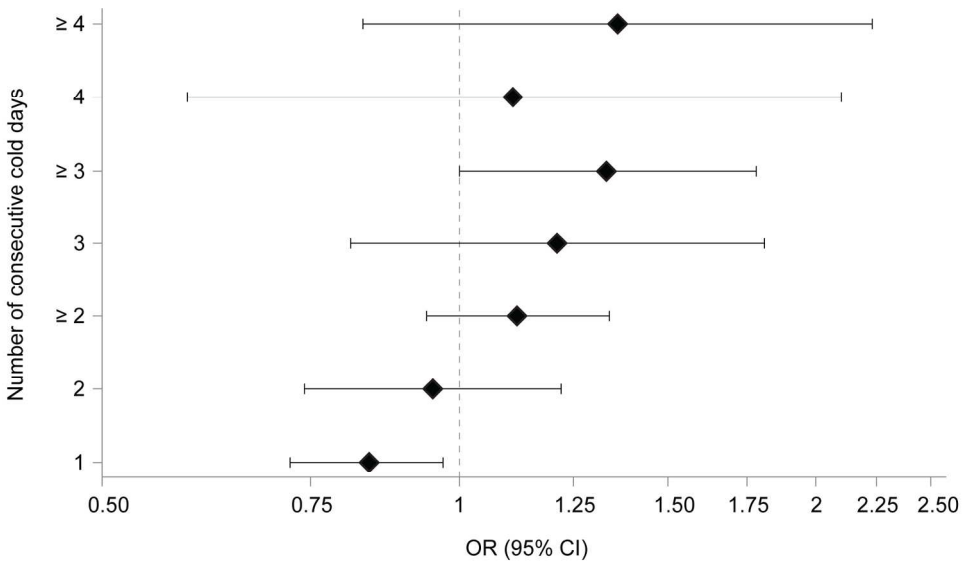

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Title of the manuscript: **The risk of sudden cardiac death in relation to season-specific cold spells: a case-crossover study in Finland**

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Author's note (status)	Author's note (page number)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ok	p1,p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Ok	p2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Ok	p4
Objectives	3	State specific objectives, including any prespecified hypotheses	Ok	p4,p5
Methods				
Study design	4	Present key elements of study design early in the paper	Ok	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Ok	p6,p7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Ok	p6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Ok/NA	p6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Ok	p6,p7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Ok	p6, p7, p8

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Bias	9	Describe any efforts to address potential sources of bias	Ok	p7, p8
Study size	10	Explain how the study size was arrived at	Ok	p6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Ok	p7, p8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Ok	p7, p8
		(*b*) Describe any methods used to examine subgroups and interactions	Ok	p7, p8
		(*c*) Explain how missing data were addressed	Ok	p6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Ok	p6
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Ok	p9 (see p6)
		(b) Give reasons for non-participation at each stage	Ok	p6
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Ok	p9, p10
		(b) Indicate number of participants with missing data for each variable of interest	Ok	(see p6)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Ok	p11
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of	NA	NA

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		relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Ok	p11, p12
Discussion				
Key results	18	Summarise key results with reference to study objectives	Ok	p13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Ok	p15, p16 (see p7, p8)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Ok	p13,p14,p15, p16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Ok	p14, p15, p16
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Ok	p17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Complete List of Authors:	Ryti, Niilo; University of Oulu, Center for Environmental and Respiratory Health Research Mäkikyrö, Elina; University of Oulu, Center for Environmental and Respiratory Health Research Antikainen, Harri; University of Oulu Hookana, Eeva; Oulun Yliopisto Laaketieteellisen tiedekunta, Research Unit of Internal Medicine Junttila, Juhani Ikäheimo, Tiina; University of Oulu, Center for Environmental and Respiratory Health Research Kortelainen, Marja-Leena; Institute of Diagnostics, Department of Forensic Medicine, Oulu University Hospital Huikuri, Heikki; University of Oulu, Dept. of Internal Medicine Jaakkola, Jouni; University of Oulu, Center for Environmental and Respiratory Health Research
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The risk of sudden cardiac death in relation to season-specific cold spells: a case-crossover study in Finland

Niilo RI Ryti, Elina MS Mäkikyrö, Harri Antikainen, Eeva Hookana, M Juhani Junttila, Tiina M Ikäheimo, Marja-Leena Kortelainen, Heikki V Huikuri, Jouni JK Jaakkola

Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Niilo RI Ryti doctoral student and Elina MS Mäkikyrö doctoral student Department of Geography, University of Oulu, FI-90014, Finland Harri Antikainen post-doctoral researcher Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, FI-90029, Finland Eeva Hookana post-doctoral researcher and M Juhani Junttila adjunct professor of cardiology Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Tiina M Ikäheimo adjunct professor of environmental health Department of Forensic Medicine, University of Oulu, FI-90014, Finland Marja-Leena Kortelainen professor of forensic medicine Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, FI-90029, Finland Heikki V Huikuri professor of cardiology Center for Environmental and Respiratory Health Research (CERH), University of Oulu, FI-90014, Finland Jouni JK Jaakkola professor of public health

Correspondence to: Professor Jouni JK Jaakkola Jouni.jaakkola@oulu.fi Tel: (358) 50 3613276

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Abstract

Objective To test *a priori* hypothesis of an association between season-specific cold spells and sudden cardiac death (SCD).

Methods We conducted a case-crossover study of 3614 autopsy-verified cases of SCD in the Province of Oulu, Finland (1998-2011). Cold spell was statistically defined by applying an individual frequency distribution of daily temperatures at the home address during the hazard period (7 days preceding death) and 50 reference periods (same calendar days of other years) for each case using the home coordinates. Conditional logistic regression was applied to estimate odds ratios for the association between the occurrence of cold spells and the risk of SCD after controlling for temporal trends.

Results The risk of SCD was associated with a preceding cold spell (OR 1.33; 95%CI: 1.00, 1.78). A greater number of cold days preceding death increased the risk of SCD approximately 19% per day (OR 1.19; 95%CI 1.07-1.32). The association was strongest during autumn (OR 2.51; 95%CI 1.27-4.96) and winter (OR 1.70; 95%CI 1.13-2.55) and lowest during summer (OR 0.42; 95%CI 0.15-1.18) and spring (OR 0.89; 95%CI 0.45-1.79). The association was stronger for ischaemic (OR 1.55; 95%CI 1.12-2.13) than for non-ischaemic SCD (OR 0.68; 95%CI 0.32-1.45) verified by medico-legal autopsy.

Conclusions Our results indicate that there is an association between cold spells and SCD, that this association is strongest during autumn, when the weather event is prolonged, and with cases suffering ischaemic SCD. These findings are subsumed with potential prevention via weather forecasting, medical advice, and protective behavior.

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Article summary

Strengths and limitations of this study

- Cases from the worlds' largest autopsy-verified dataset of sudden cardiac death were linked with 51 years of coordinate-specific weather data at their home coordinates.
- Individual frequency distributions of daily temperatures at each home coordinate were used to define unusually cold weather pertinent to the location and time of death.
- Stratified analyses between ischaemic and non-ischaemic sudden cardiac death in relation to unusually cold weather were performed based on medico-legal autopsy findings.
- The study did not elaborate the relative roles of temperature and air pollution during the weather phenomenon.
- Behavioral activity patterns of the cases for the week preceding death were not available.

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INTRODUCTION

Sudden cardiac death (SCD) is the leading cause of death, currently estimated to represent 60% of all cardiovascular deaths.[1, 2] In contrast to acute myocardial infarction, or most chronic cardiovascular diseases, SCD affects individuals who have been considered at zero-to-low risk of cardiovascular death.[3, 4] In over half of the cases, SCD is the first manifestation of the underlying cardiac disease.[3] It commonly occurs in the prime of life,[1] affecting approximately one in every five people in the western society.[4] Substantial global research efforts have yielded specific risk markers of SCD, such as certain abnormalities in ECG.[4] However, predicting SCD on both an individual level and in the general population remains challenging.[4]

Weather, on the other hand, can be predicted and preventive measures taken. There is substantial evidence that cardiovascular mortality is associated with the temperature of the day or the preceding days.[5, 6] According to our recent systematic review and meta-analysis, cold spells are associated with 11% increase in cardiovascular mortality rates around the world.[6] Whether or not and how much SCD might contribute to these associations is unknown. There are only a handful of studies on the association between cold weather and SCD,[7-10] and one study on the association between cold spells and ischemic SCD.[11] We recently showed an association between cold spells and ischaemic SCD, with effect modification by cardioprotective medications.[11] There is also considerable evidence on the association between cold ambient temperature and acute myocardial infarction,[12-14] with pathophysiological basis previously described.[15] Whether or not and how much SCD might contribute to these associations is also unknown, since SCD entails a broader range of pathologies and has many distinctive features from acute myocardial infarction or out-of-hospital coronary death.[4, 16-18]

Based on the international shift from broad to specific approaches on SCD risk assessment,[4, 18] our general objective was to estimate the association between cold weather and SCD applying measures that maximise the accuracy of both the exposure and the outcome. Our specific objectives were to test the *a priori* hypotheses that cold spells are associated with the risk of SCD; that the effect is stronger according to an increasing number of unusually cold days preceding the death; and to assess potential seasonal

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modification of the effect; to identify susceptible groups in terms of age and sex; to investigate if the association is stronger for ischaemic than for non-ischaemic SCD.

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METHODS

This study is based on *a priori* protocol accessible at www.oulu.fi/cerh/node/31850. STROBE guidelines were applied to ensure transparency of the reporting of results.

Study design and population

We conducted a case-crossover study to assess the relation between cold spells and SCD. Case-crossover design is well suited for studying the effects of transient short-term exposures on the risk of acute events.[19] We assigned to each case a hazard period (HP) of seven days preceding the day of death and 50 reference periods (RP) comprising of the same calendar days of the other years of the study period 1961-2011.

The study population included 3707 cases from The Finnish Study of Genotype and Phenotype Characteristics of Sudden Cardiac Death (FinGesture) in the province of Oulu, Northern Finland,[16] who died between 1998 and 2011. 93 cases were excluded because their home coordinates for the time of death were unavailable. This resulted in 3614 cases. All cases underwent post mortem examinations at the Department of Forensic Medicine of the University of Oulu. Case validation was conducted by a forensic specialist through medico-legal autopsy, detailed histological sampling, full medical history, and police reports. Those with any other cause than SCD, including intoxications during an acute coronary event, were excluded. All witnessed SCDs occurred within 6 hours of the onset of the forewarning symptoms. All unwitnessed victims of SCD were seen alive and in a normal state of health within 24 hours preceding the death. Post mortem studies of unexpected death are mandatory in Finland, and the selection bias in victims with unexpected SCD is minimal.[16] Hence, this provides unique opportunity to cover the entire breadth of SCD cases in the general population.

Exposure assessment

The home coordinates (EUREF ETRS-TM35FIN) of the cases at the time of death were retrieved from the Population Register Centre. Geographical Information System (GIS) was used to allocate daily temperatures at the home coordinates of each case for the days in hazard and reference periods over the study years 1961-2011. For this purpose, a dataset containing minimum, mean, and maximum daily temperatures in the study period was obtained from the Finnish Meteorological Institute. In this dataset, point measurements have been

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interpolated onto a 10×10 km grid covering the whole of Finland, using a Kriging method.[20] We organised the temperature dataset into a GIS database, and GIS based functions were then used to extract temperature values from the database according to location and date.

Individual frequency distributions of daily temperatures during the hazard and reference periods for the home coordinates of each case were formed. Cold spell was defined as a period of ≥3 consecutive days with daily minimum temperature below the 5th percentile of the individual frequency distribution. Conceptually this approach identifies events that are unusually cold in the respective place and time of the year. We used the same frequency distributions and thresholds to identify single cold days and any combination of single cold days in different definitions of unusually cold weather used in this study (e.g. 2 consecutive days). Individual exposure assessment was conducted for the hazard period. In contrast to this, the occurrence of cold spells during the reference periods represent the usual exposure at the individual's place of residence. Thus, we estimated the occurrence of the weather phenomenon during the two period types and analysed whether the possible differences in the occurrence could be explained by random variation.

To describe the general weather during the study, we formed a time series of minimum, mean, and maximum daily temperatures at the central coordinate 27.39E/64.79N of the province of Oulu, Finland, over the study period 1961-2011, using the same databases, programs, and methods as described above.

Statistical methods

Conditional logistic regression was applied to estimate the odds ratios (OR) and 95% confidence intervals (CI) representing the proportion of cold spells occurring during hazard and reference periods. Conditional logistic regression was performed using PROC PHREG in SAS (SAS, version 9.4, SAS Institute, Cary, NC) using the discrete logistic model and forming a stratum for each ID. An indicator variable consisting of 5-year intervals over the study period was formed to control for long time trends in the occurrence of cold spells. Season, month, day of the week, weekends, and holidays were controlled by design.[19] We conducted *a priori* stratified analyses according to an increasing number of cold days preceding death and according to the season of death. Calendar time was used to define the 4 seasons (autumn Sept-Nov, winter Dec-Feb, spring Mar-May, summer, Jun-Aug). We conducted *a priori* subgroup analyses using gender, age,

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and ischaemic versus non-ischaemic aetiology of the death confirmed by the autopsy finding as BY-variables in conditional logistic regression. Cases aged under 35 were excluded from the subgroup analyses *a priori* because of the few numbers (n=40) and expected heterogeneity. The difference between odds ratios in each subgroup was estimated using Q-statistics for heterogeneity, by applying the DerSimonian-Laird-method using a SAS-macro provided by Herzmark and Spiegelman.[21,22]

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RESULTS

The characteristics of the study population are shown in Table 1. Table S1 elaborates the underlying cardiac disease of the victims of non-ischaemic SCD, with diagnostic criteria previously reported.[16]

Table 1. The characteristics of the study population.

Characteristic	Men, n (%)	Women, n (%)	Total, n (%)
All	2878	736	3614
Age			
0-34	32 (1.1)	8 (1.1)	40 (1.1)
35-64	1583 (55.0)	231 (31.4)	1814 (50.2)
≥65	1263 (43.9)	497 (67.5)	1760 (48.7)
Autopsy finding			
Ischaemic	2214 (76.9)	545 (74.0)	2759 (76.3)
Non-ischaemic	664 (23.1)	191 (26.0)	855 (23.7)
Season of death			
Autumn	688 (23.9)	198 (26.9)	886 (24.5)
Winter	688 (23.9)	174 (23.6)	862 (23.9)
Spring	802 (27.9)	188 (25.5)	990 (27.4)
Summer	700 (24.3)	176 (23.9)	876 (24.2)

A total of 3974 location specific cold spells were identified for the analyses. The distribution parameters of daily temperatures in the province of Oulu 1961-2011 are shown in Table 2.

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Table 2. The distribution parameters of daily temperatures (T) in the province of Oulu, Finland, over the study period 1961-2011.

Variable	Autumn	Winter	Spring	Summer	Total
Mean average T (SD), °C	+1.7 (6.7)	-10.5 (7.9)	+0.4 (7.2)	+13.8 (3.7)	+1.4 (10.8)
T range, °C	58.6	49.7	61.9	35.7	74.3
Lowest minimum T, °C	-34.4	-41.3	-34.2	-2.7	-41.3
Highest maximum T, °C	+24.2	+8.4	+27.7	+33.0	+33.0
T quartiles, Q1, Q2, Q3, °C	-2.1, +2.1, +6.4	-16.0, -9.2, -4.1	-3.9, +0.8, +5.0	+11.3, +13.7, +16.2	-5.5, +1.6, +10.3

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Cold spells were associated with an increased risk of SCD (OR 1.33; 95%CI 1.00-1.78). The effect estimate for a singular cold day was below unity (OR 0.84; 95%CI 0.72-0.97), and increasing the number of cold days occurring during the hazard period increased the risk of SCD approximately 19% per day (OR 1.19; 95%CI 1.07-1.32). Figure 1 shows the relation between the occurrence of different combinations of consecutive days below the threshold temperature and the risk of SCD.

In the analyses stratified by season, distinct seasonal differences in the association between cold spells and SCD were observed. The effect estimates were highest during autumn and winter, and lowest during summer and spring (Table 3), while the underlying seasonal variation in the incidence of SCD was negligible (Table 1).

Table 3. The relation between the occurrence of cold spells and the risk of SCD based on stratified analyses by season.

Season	Odds ratio (95% CI)
Autumn	2.51 (1.27-4.96)
Winter	1.70 (1.13-2.55)
Spring	0.89 (0.45-1.79)
Summer	0.42 (0.15-1.18)

We conducted several subgroup analyses for the purpose of elaborating effect modification of the relation between cold spells and SCD (Table 4). There were no distinct differences in sensitivity to cold spells between subjects aged over 65 years and those aged 35-64 years. Likewise, gender did not significantly modify the effect.

Table 4. The relation between the occurrence of cold spells and the risk of SCD by various subgroups of cases over 34 years of age.

Subgroup	Odds ratio (95% CI)	Q-statistics (p)
Age		
35-64	1.28 (0.84-1.97)	0.03 (0.84)
≥65	1.36 (0.91-2.04)	
Sex		
Men	1.30 (0.94-1.81)	0.04 (0.83)
Women	1.41 (0.74-2.67)	
Autopsy finding		
Ischaemic	1.55 (1.12-2.13)	3.85 (0.05)
Non-ischaemic	0.68 (0.32-1.45)	

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In the subgroup analysis according to the aetiology of underlying structural heart disease at autopsy, the effect estimate for ischaemic SCD was greater than for non-ischaemic SCD, confirmed by Q-statistic 3.85, p 0.05 (Table 4).

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DISCUSSION

Cold spells were associated with an increased risk of SCD. Additional number of cold days during the one-week period preceding death increased the risk of SCD by approximately 19% per cold day. The association between cold spells and SCD was strongest during autumn and winter, and nonexistent during spring and summer. Cold spells increased the risk of SCD caused by ischaemic heart disease, whereas there was no association with non-ischaemic aetiology.

The incidence of SCD was similar during different seasons (Table 1), but the associations between seasonally defined cold spells and the risk of SCD varied significantly depending on the season (Table 3). The highest effect estimate during autumn promotes the concept of relative, instead of absolute, temperature playing an important role in the association.[6] The first few cold temperatures of autumn might involve an increased risk due to lack of cold habituation and the associated aggravated physiological responses,[23] or due to a delay in behavioral adaptation such as appropriate clothing and sufficient indoor heating.[24] The contrast in effect estimates between autumn and spring, both of which have similar temperature indices (Table 2), and similar incidence of SCD (Table 1), is noteworthy. A gradual change towards colder temperatures or the rapidly increasing temperature range after summer might modify the association with cold spells. The contrast in the effect estimates between winter and summer suggest that absolute temperature level, complementary to the relative or changing temperature, plays a role in the association. None of these interpretations are in conflict with previous evidence, and the results suggest that physicians should start advising cardiologic patients on the risks associated with cold weather before winter.

Additional number of cold days during the one-week period preceding death increased the risk of SCD. This could indicate sustained cold-related physiological strain and/or increasing probability of exposure. On the other hand, the protective effect of a single cold day might be explained by protective behavior such as first staying indoors but then having to return to normal behavior. Both speculations presume that the most harmful exposure during cold spells occurs outdoors, which has not been confirmed.[6]

Cold spells increased the risk of sudden cardiac death caused by ischaemic heart disease, whereas there was no association with non-ischaemic aetiology. This finding, if repeated in other settings, might provide further

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insight into the cold-induced pathological pathways of SCD. We have recently summarised some of the hypothesised pathways between cold spells and SCD.[11] Briefly, evidence from experimental studies show that exposure to cold ambient temperature induces changes in blood composition, loss of plasma fluid, haemoconcentration, redistribution of thrombogenic factors;[25, 26] induces peripheral vasoconstriction and a sudden increase in systemic vascular resistance, systolic and diastolic and central aortic blood pressure, pre-load, cardiac output, and oxygen demand of the heart;[15, 27] and under experimental conditions induces coronary spasm in susceptible individuals.[28] All these factors increase specifically the susceptibility to SCD caused by acute ischaemic event, which was evident in our findings. Cooling of the face or body also results in simultaneous coactivation of sympathetic and parasympathetic nervous systems, which may be pro arrhythmic given suitable myocardial substrates.[29] This pathway might be less significant during cold weather, since cold spells were not associated with an increased risk of SCD in subjects with non-ischaemic heart disease. However, no definite conclusions should be made on the pathways or their relevance before extensive studies into the topic. Insight might offer direct targets for intervention with pharmacologic agents, as recently shown.[11]

Strengths and limitations

Improvements were introduced to the definition of cold spell based on the findings of our recent systematic review and meta-analysis.[6] In the reviewed studies, cold spell threshold was commonly defined as the 1-5th percentile of the frequency distribution of the daily temperatures over the entire study period. Conceptually this tends to place all cold spells in cold winter months and disregards unusually cold events occurring during warmer months. Because the adverse effects of cold temperatures have been shown to be more pronounced in warmer climates,[5, 24] or because lack of cold habituation during warmer months could elicit aggravated cardiovascular responses to a suddenly decreasing temperature,[23] it is reasonable to ask whether exceptionally cold weather during months other than those of winter could also have adverse effects on health. Our approach identifies events that are unusually cold in the respective place and time of the year. It is telling that we would not have been able to observe the highest risk during autumn without this approach. Generally speaking, frequency distribution-based exposure assessment is beneficial in terms of being able to generalise results, making it easier to compare estimates obtained from different geographical

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regions.[6] It would be interesting to see whether comparable results obtained with these methods would produce different effect estimates in different climates.[30]

There is evidence on the benefits of confirming the diagnosis and mode of sudden death by medico-legal autopsy in order to provide unbiased information on the incidence of SCD.[2, 3, 18] It is difficult to distinguish between cardiac and non-cardiac cause of sudden death without an autopsy, since many conditions that evolve rapidly, such as aortic dissection, massive pulmonary embolism, or stroke, can lead to sudden collapse and death. We conducted our analyses using the world's largest autopsy-verified dataset of SCD. We took advantage of the individual-level nature of the data by forming and assessing individual frequency distributions of temperatures at each home coordinate to define cold weather for the cases.

The present study assessed the association between cold spells and occurrence of SCD without elaborating the relative roles of temperature and air pollution. In other words, we estimated the overall effect of the entire weather phenomenon rather than focusing on individual physical parameters related to this phenomenon. Ours is the primary question from clinical and public health practice, although additional information on the contribution on air pollution in general and specific compounds would be interesting. If part of the effects of cold spells were mediated by increased air pollution levels, adjustment for air pollution would lead to underestimation of the overall effects of cold spells.

Although we estimated the outdoor temperatures for each home coordinate for the week preceding the death of the resident, the behavioral activity patterns for the week preceding death were not available. Therefore, it was not possible to estimate how much time the cases spent outdoors, and what kind of thermal patterns they were exposed to. This is a common limitation in studies without personal measuring devices and activity pattern diaries. It also remains an important question how changes in weather manifest as changes in different indoor environments, and whether some of these changes mediate the harmful effects of weather. Variations between individuals in their attitudes toward cold weather, use of protective clothing, physical activity, comorbidity, substance abuse, and use of medications are likely to exist in our data and in the general population. Combinations of these and other individual factors might influence personal risk profiles in ways that are difficult to predict from an epidemiological stance, and although our results can be

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generalized over a population, they can't be directly translated to individual risk. It is reasonable to assume that the association between cold spells and risk of SCD is modified by a variety of factors still unknown.

Conclusions

Our results suggest that there is an association between cold spells and SCD, that this association is strongest during autumn, when the weather event is prolonged, and with cases suffering ischaemic SCD. These findings are subsumed with potential prevention via weather forecasting, medical advice, and protective behavior. We believe more studies on the associations between cold weather and SCD should identify potential targets for intervention, be it pharmacological modification, diagnosis and treatment of underlying cardiovascular diseases, or behavioral patterns during cold weather.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none of the authors have support from any company for the submitted work; (2) none of the authors have relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have non-financial interests that may be relevant to the submitted work.

Contributorship statement

NR and JJ designed the study. MLK contributed significantly to the performing of the medico-legal autopsies over 1998-2011. EH complemented the autopsy data to constitute the FinGesture database under the supervision of MJJ and HH. HA collected the weather data from Finnish Meteorological Institution, designed and applied the GIS-model to produce the case specific exposure data. EM designed the SAS-program for the main analyses and executed the analyses together with NR. TI contributed expertise in cold-related physiology and substantial scientific input in interpretation of the results. HH contributed expertise in cardiology and substantial scientific input in the interpretation of the results. JJ contributed expertise in epidemiology and public health and substantial scientific input in interpretation of results. NR and JJ drafted the manuscript and all authors have accepted the final version. JJ and HH have equal senior authorship, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval

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This study complies with the Declaration of Helsinki and has been approved by the Ethics Committee of the Oulu University Hospital (ID of the approval EETTMK:18/2014). National Supervisory Authority for Welfare and Health (Valvira) has approved the review of post mortem data by the investigators.

Transparency declaration

The senior authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

Data sharing: no additional data available.

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References

1 Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. Nat Rev Cardiol 2010;7:216–225.

2 Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis 2008;51:213–228.

3 Myerburg RJ, Junttila J. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043–1052.

4 Wellens HJJ, Scwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J 2014;35:1642–1651.

5 Analitis A, Katsouyanni K, Biggeri A, et al. Effects of cold weather on mortality: results from 15 European cities within the PHEWE project. Am J Epidemiol 2008;168:1397–408.

6 Ryti NRI, Guo Y, Jaakkola JJK. Global association of cold spells and adverse health effects: a systematic review and meta-analysis. Environ Health Perspect 2016;124:12–22; doi:10.1289/ehp.1408104.

7 Törő K, Batholy J, Pongrácz R, Kis Z, Keller É, Dunay G. Evaluation of meteorological factors on sudden cardiovascular death. J Forensic Leg Med 2010;17:236–242.

8 Gerber Y, Jacobsen S, Killian J, Weston S, Roger V. Seasonality and daily weather conditions in relation to myocardial infarction and sudden cardiac death in Olmsted County, Minnesota, 1979-2002. J Am Coll Cardiol 2006;48:287–292.

9 Arntz H-R, Müller-Nordhorn, Willich S. Cold Monday mornings prove dangerous: epidemiology of sudden cardiac death. Curr Opin Crit Care 2001;7:139–144.

10 Katz A, Biron A, Ovsyshcher E, Porath A. Seasonal variation in sudden death in the Negev desert region of Israel. Isr Med Assoc J 2000;2:17–21.

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11 Ryti NRI, Mäkikyrö EMS, Antikainen H, et al. Cold spells and ischaemic sudden cardiac death: effect modification by prior diagnosis of ischaemic heart disease and cardioprotective medication. Sci. Rep. 2017;7,41060; doi: 10.1038/srep41060.

12 Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of ambient temperature on the incidence of myocardial infarction. Heart 2009;95:1760–1769.

13 Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Short term effects of temperature on risk of myocardial infarction in England and Wales: time-series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry. BMJ 2010;341:c3823.

14 Chen R, Li T, Cai J, Yan M, Zhao Z, Kan H. Extreme temperatures and out-of-hospital coronary deaths in six large Chinese cities. J Epidemiol Community Health 2014;68:1119–1124.

15 Manou-Stathopoulou V, Goodwin CD, Patterson T, Redwood SR, Marber MS, Williams RP. The effects of cold and exercise on the cardiovascular system. Heart. 2015;101:808–820.

16 Hookana E, Junttila J, Puurunen V-P, et al. Causes of nonischemic sudden cardiac death in the current era. Heart Rhythm 2011;8:1570–1575.

17 Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to arrhythmias. N Engl J Med 2001;345:1473–1482.

18 Chugh SS, Jui J, Gunson K, et al. Current Burden of Sudden Cardiac Death: Multiple Source Surveillance Versus Retrospective Death Certificate-Based Review in a Large U.S. Community. J Am Coll Cardiol 2004;44:1268–1275.

19 Maclure M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. Am J Epidemiol 1991;133:144–152.

20 Venäläinen A, Heikinheimo M. Meteorological data for agricultural applications. Phys Chem Earth 2002;27:1045–1050.

21 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.

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22 Hertzmark E, Spiegelman D. The SAS METAANAL Macro. Written for the Channing Laboratory, 24 May 2012. Available at http://www.hsph.harvard.edu/donna-spiegelman/software/metaanal/ Accessed 24.6.2015.

23 Mäkinen TM. Different types of cold adaptation in humans. Front Biosci 2010;S2:1047–1067.

24 The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 1997;349:1341–1346.

25 Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. 1984. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. Br Med J 1984;289:405–1408.

26 Neild PJ, Syndercombe-Court D, Keatinge WR, Donaldson GC, Mattock M, Caunce M. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X. Clin Sci 1994;86:43–48.

27 Hintsala H, Kandelberg A, Herzig KH. et al. Central aortic blood pressure of hypertensive men during short-term cold exposure. Am J Hypertens 2014;27:656–664.

28 Raizner A, Chahine RA, Ishimori T, et al. Provocation of coronary artery spasm by the cold pressor test. Circulation 1980;62:925–932.

29 Shattock MJ, Tipton MJ. 'Autonomic conflict': a different way to die during cold water immersion? J Physiol 2012;590:3219–30.

30 Stewart S, Keates AK, Redfern A, McMurray JJV. Seasonal variations in cardiovascular disease. Nat Rev Cardiol 2017: doi: 10.1038/nrcardio.2017.76.

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Figure legends

Figure 1. The relation between sudden cardiac death and consecutive days below threshold temperature. X-axis presents the odds ratios (OR) and 95% confidence intervals (95% CI) on a logarithmic scale; y-axis presents the number of consecutive days with daily minimum temperature below threshold occurring during the week preceding death. Each effect estimate is derived by a stratified analysis according to the number of days, an integer being the exact number of consecutive days, and "≥" indicating the minimum number of consecutive days (e.g. at least n consecutive days).

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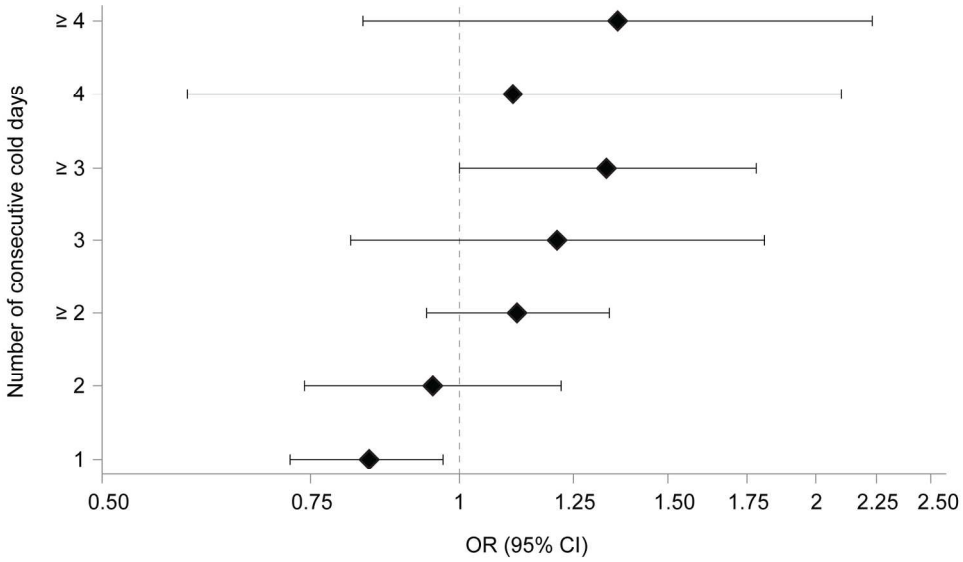

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Table S1. Underlying cardiac disease of victims of non-ischaemic SCD based on autopsy finding.

Underlying cardiac disease	n (%)
Hypertensive cardiomyopathy	163 (19.1)
Valvular heart disease	44 (5.1)
Inflammatory heart disease	34 (4.0)
Dilated cardiomyopathy	26 (3.0)
Alcoholic cardiomyopathy	170 (19.9)
Hypertrophic obstructive cardiomyopathy	3 (0.4)
Hypertrophic cardiomyopathy	12 (1.4)
Cardiomyopathy related to obesity	237 (27.7)
Arrhythmogenic right ventricular dysplasia	6 (0.7)
Fibrotic cardiomyopathy	128 (15.0)
Primary arrhythmia	10 (1.2)
Anomalous coronary arteries	3 (0.4)
Not classified	19 (2.2)

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Title of the manuscript: **The risk of sudden cardiac death in relation to season-specific cold spells: a case-crossover study in Finland**

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Author's note (status)	Author's note (page number)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ok	p1,p2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Ok	p2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Ok	p4
Objectives	3	State specific objectives, including any prespecified hypotheses	Ok	p4,p5
Methods				
Study design	4	Present key elements of study design early in the paper	Ok	p6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Ok	p6,p7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Ok	p6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Ok/NA	p6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Ok	p6,p7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Ok	p6, p7, p8

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Bias	9	Describe any efforts to address potential sources of bias	Ok	p7, p8
Study size	10	Explain how the study size was arrived at	Ok	p6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Ok	p7, p8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Ok	p7, p8
		(*b*) Describe any methods used to examine subgroups and interactions	Ok	p7, p8
		(*c*) Explain how missing data were addressed	Ok	p6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Ok	p6
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Ok	p9 (see p6)
		(b) Give reasons for non-participation at each stage	Ok	p6
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Ok	p9, p10
		(b) Indicate number of participants with missing data for each variable of interest	Ok	(see p6)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Ok	p11
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of	NA	NA

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		relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Ok	p11, p12
Discussion				
Key results	18	Summarise key results with reference to study objectives	Ok	p13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Ok	p15, p16 (see p7, p8)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Ok	p13,p14,p15, p16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Ok	p14, p15, p16
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Ok	p17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title of the manuscript: Season-specific cold spells and sudden cardiac death: a case-crossover study applying individual exposure assessment

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		(*e*) Describe any sensitivity analyses	NA	NA
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Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA	NA
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		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Ok	p11
Discussion				
Key results	18	Summarise key results with reference to study objectives	Ok	p12
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Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Ok	p12,p13,p14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Ok	p13, p14
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Ok	p15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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