

# Ambient temperature and activation of implantable cardioverter defibrillators

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**Abstract** The degree to which weather influences the occurrence of serious cardiac arrhythmias is not fully understood. To investigate, we studied the timing of activation of implanted cardiac defibrillators (ICDs) in relation to daily outdoor temperatures using a fixed stratum case-crossover approach. All patients attending ICD clinics in London between 1995 and 2003 were recruited onto the study. Temperature exposure for each ICD patient was determined by linking each patient's postcode of residence to their nearest temperature monitoring station in London and the South of England. There were 5,038 activations during the study period. Graphical inspection of ICD activation against temperature suggested increased risk at lower but not higher temperatures. For every 1 °C decrease in ambient temperature, risk of ventricular arrhythmias up to 7 days later increased by 1.2 % (95 % CI -0.6 %, 2.9 %). In threshold models, risk of ventricular arrhythmias increased by 11.2 % (0.5 %, 23.1 %) for every 1° decrease in temperature

below 2 °C. Patients over the age of 65 exhibited the highest risk. This large study suggests an inverse relationship between ambient outdoor temperature and risk of ventricular arrhythmias. The highest risk was found for patients over the age of 65. This provides evidence about a mechanism for some cases of low-temperature cardiac death, and suggests a possible strategy for reducing risk among selected cardiac patients by encouraging behaviour modification to minimise cold exposure.

**Keywords** Arrhythmia · Environment · Epidemiology · Risk factor · Weather

## Introduction

There is evidence that sudden cardiac death occurs more frequently in the winter (Eurowinter Group 1997; Kloner et al. 1999; Peckova et al. 1999; Arntz et al. 2000; Barnett et al. 2005). Low temperature has been identified as a factor in risk of myocardial infarction (Danet et al. 1999; Chang et al. 2004; Dilaveris et al. 2006; Medina-Ramón and Schwartz 2007; Bhaskaran et al. 2010) and heart failure, (Milo-Cotter et al. 2006) but the question of whether cold weather increases the risk of potentially fatal ventricular tachyarrhythmias has yet to be clarified.

Implanted cardioverter defibrillators (ICD) are devices implanted in people who have experienced, or are at high risk of experiencing, life-threatening arrhythmias. They monitor the heart rate and store detailed information on the timing and nature of arrhythmia events (mainly ventricular tachycardias and episodes of ventricular fibrillation), thus providing the potential to analyze the timing of events in relation to environment conditions. One study of ICD activations observed a winter peak in arrhythmias (Muller et al. 2003), and three other studies linked events to cold weather conditions (Fries et al. 1997; Anand et al. 2007; Gluszek et al. 2008). However, these studies were limited by small numbers of patients and events.

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A large study was set up in the UK to assess effects of outdoor air pollution exposure on ICD activation in all patients attending nine National Health Service (NHS) clinics in London (Anderson et al. 2010). Using data from the same cohort, we examined the relationship between days of activation and daily outdoor temperature. The study benefits from the availability of data from the extensive network of weather and air pollution monitoring stations in the UK, which enables exposure to be characterised at fine spatial resolutions.

## Materials and methods

### Health data

All London NHS hospitals implanting ICDs from 1995 to 2003 participated in the current study. These were: King's College Hospital, St Bartholomew's Hospital, The Royal Brompton Hospital, Hammersmith Hospital, Harefields Hospital, The Heart Hospital, St George's Hospital, St Mary's Hospital, and St Thomas' Hospital. Hospital records were used to identify those patients registered at any time during the study period, 1 January 1995–31 December 2003. Local ethical approval was obtained from the South Thames Multiple Research Ethics Committee, committees from each of the participating hospitals, and the London School of Hygiene and Tropical Medicine. Data were extracted by research assistants with medical and nursing backgrounds.

Information recorded for each patient included underlying cardiac diagnosis. General data were collected on patient age, sex, and coordinates of home address (indicated by an easting and northing). The therapy delivered by the ICD was mainly anti-tachycardia pacing (73 %) or shock (25 %). Activation of an ICD is followed frequently by subsequent activations over the next few hours which are unlikely to be related to environmental factors. Therefore, *days* of activation were chosen as the unit of analysis rather than each individual ICD activation. On activation days, the date of the event, time of day, and type of cardiac-related drug taken were recorded. Number of storm days, defined as  $\geq 3$  events in a 24-h period, were recorded additionally for each patient.

Of all ICD activations, 99 % were recorded as a ventricular arrhythmia based on the clinic review. In the 60 % of activations where the electrocardiogram (ECG) was examined by a trained cardiologist, 87 % of ventricular diagnosis was confirmed as such by cardiologist assessment. Verification criteria are documented elsewhere (Anderson et al. 2010).

### Environmental data

Daily minimum and maximum temperature data from all monitoring stations in Southern England were obtained from the British Atmospheric Data Centre (BADC) website ([http://](http://badc.nerc.ac.uk/home/)

[badc.nerc.ac.uk/home/](http://badc.nerc.ac.uk/home/)). Daily mean ambient temperature was generated by taking the average of the daily minimum and maximum temperature, and was used as the main exposure of interest. Exposure for each day of each patient-event period (see statistical approach below) was determined by assigning data from the nearest monitoring station to each patient's home address, but with the condition that exposure was recorded on all activation days and on at least 90 % of days within each patient-event period. If no such station existed within 50 km from the respective patient, then that patient-event period was discarded from analysis.

Data on daily mean levels of particulate matter with aerodynamic diameter less than 10  $\mu\text{m}$  ( $\text{PM}_{10}$ ) were obtained from all monitors measuring concentrations in the study area, excluding roadside and kerbside sites. Again, exposure assignment was conducted using the same linkage algorithm as above, except the maximum distance was set to 20 km. Also, based on previous findings (Anderson et al. 2010), possible confounding by one regional measure of particle sulfate ( $\text{SO}_4$ ) was also assessed.

### Statistical approach

The analysis used a fixed-stratum case-crossover design to assess short-term associations between temperature and ICD activation. This approach compares temperatures on activation days with temperatures on surrounding days only, and so eliminates possible confounding from long-term seasonal patterns or trends (Lumley and Levy 2000). Risk sets (patient-event periods) were constructed around each patient-activation day as the 28-day period (person-lunar month) including the activation day. Lunar months, phased to begin on 1 January 1995, were preferred to calendar months because of their equal duration. The case day in the current study was the day or days of ICD activation. The referent days were all non-event days in the 28-day risk set. Conditional logistic regression was used to assess the association of activation days with ambient temperature within person-lunar months. Indicator variables for day of the week were included in the model as potential confounders, and all models included two autoregressive terms to allow for serial correlation between events on days and subsequent days (Brumback et al. 2000). Day-of-week effects were controlled for explicitly (rather than using a design whereby cases and controls are matched to the same day of week) as this confers greater power to detect statistical significance. Humidity was not associated with activations in this cohort (Anderson et al. 2010), thus it was not included in the final model. Also, there was no evidence of any strong seasonal patterns remaining within each lunar month.

To assess activation relationships with temperature, natural cubic splines (with four knots) were used to plot the association as a smoothed function of temperature at various lags. This graphical inspection suggested a broadly linear

relationship between activation risk and decreasing temperature. Therefore, the effect of mean temperature was quantified by means of a linear term in the final model. A linear-threshold model was also examined, with the threshold being chosen based on statistical model fit, i.e. the threshold was set at the temperature value which maximized likelihood over an integer grid of candidate values.

Elevated CVD mortality associated with high ambient temperature is usually seen within 48 h of exposure, whereas cold associations may be delayed from a few days up to several weeks later (Braga et al. 2002). Thus, in order to distinguish possible heat and cold effects, both immediate and longer lags (to 28 days) were examined. In the event, however, no associations were observed beyond 7 days following initial exposure. The final estimation model therefore included eight separate terms for each lag of the temperature measure, ranging from lag 0 to lag 7—an unconstrained distributed lag model—and the cumulative effect of temperature on ICD activation was estimated by summing the separate effects of the individual lags.

The temperature-activation association was examined for interactions with sex, age, underlying cardiac diagnosis, drug use at activation, and event number per patient. Because some characteristics of patients could potentially be different between those residing inside London and those residing outside, a sensitivity analysis was performed by comparing the temperature-activation relationship for patients living within Greater London to those living in the surrounding regions. Further sensitivity analyses were conducted by assessing the confounding effects of air pollution (PM<sub>10</sub> or SO<sub>4</sub>—distributed lag over 5 days) in the model. In addition, activation rates specifically during the heat-wave episodes of summer 1995 and 2003 were assessed graphically. All results are presented as odds ratios (OR) and 95 % confidence intervals (CI). All quantitative analyses were performed using STATA version 10.0 (College Station, TX).

## Results

### Patient and exposure characteristics

There were 2,188 registered patients from nine ICD clinics in London. Of these patients, 726 had data relating to an activation day. Seventy-eight of these patients had missing coordinates for their home address, so their data could not be analyzed in relation to ambient temperature. Analysis was based on the remaining 648 patients who experienced a total of 5,038 activation days. Figure 1 shows the patient locations. For the 9-year study period, approximately 23 % of patients experienced only one ICD activation, while the same percentage of patients experienced ten or more activations (Table 1).

Patients were aged 10–99 years, with a median age of 66 (IQR 57–73). The majority of the patients were male and had an underlying cardiac diagnosis of IHD. Forty-eight percent of patients lived within Greater London. The main implant device models used were Medtronic, Guidant and Ventritex (not shown).

A total of 281 temperature monitoring stations across London and the South of England were available for linkage. Applying the linkage protocol, the three stations used most commonly to represent exposure were: the London Weather Centre (for 61 activation events), Hampstead (59) and Greenwich Observatory (58). All events were linked successfully, with the median distance between activations and temperature monitors being 7.6 km (range 0.4, 46.1). Distances were shorter for activations among patients resident in Greater London: median distance 6.3 km (range 0.4, 20.1). For all other patients, the median distance was 9.2 km (range 0.7, 46.1).

### Association of season and other covariates with activations

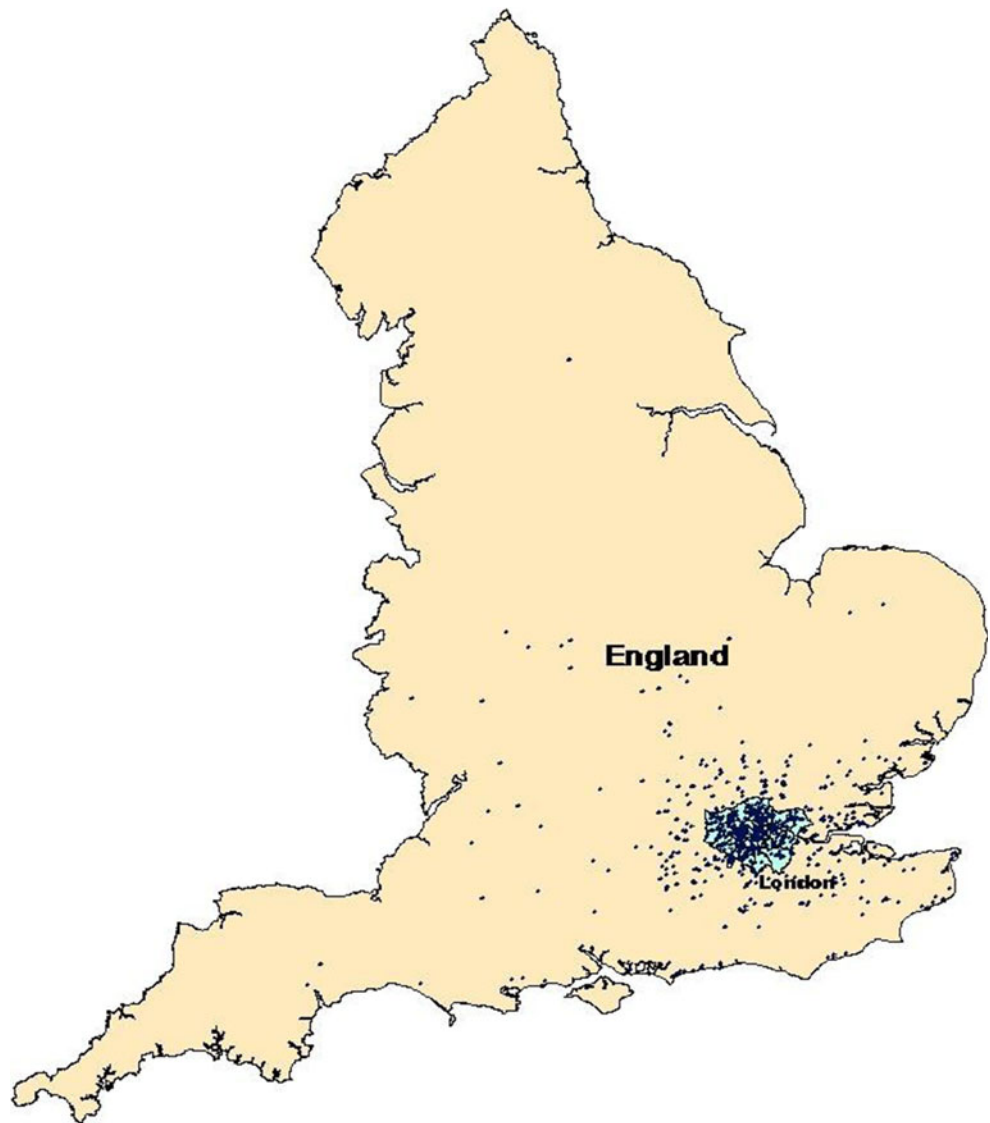
There was seasonal variation in the frequency of ICD activation, with the highest frequency in winter. ICD activation was most frequent in January (9.90 %), followed by December (9.63 %) and November (9.07 %) (Figure 2). A similar distribution was observed for rate of activation as a function of person-years studied.

### Association of temperature with activations

During the period of analysis, the daily mean temperature (averaged across lags 0–7 days) had a median value of 10.5 °C (IQR 7.0 to 15.1), a minimum value of –1.9 °C and a maximum of 26.3 °C. Figure 3 shows the adjusted relationship between risk of ICD activation and this daily mean temperature measure, i.e. averaged across lags 0–7 days. It shows some evidence of increased risk of activation at cooler temperatures. Similar relationships were observed when single day temperature measures were considered instead, with a zero day lag exhibiting the strongest relationship among the eight single day measures. All subsequent effect estimates are based on the summation of individual lag terms from 0 to 7 days. There was little significant evidence of non-linearity, although there was some suggestion that the slope was steepest at lowest temperatures. Fitting a non-threshold linear model indicated a 1.2 % (95 % CI –0.6, 2.9 %) increase in risk of ICD activation per 1 °C decrease in mean temperature across the whole range of the temperature distribution.

Although model fit was best for the linear model, when modelling the relationship using a linear-threshold model, the best fitting threshold was estimated at a temperature value of 2 °C based on maximum likelihood estimation; 105 activations (2.1 %) occurred on days on which the averaged lag 0–7

**Fig. 1** Map displaying distribution of ventricular arrhythmia patients with implanted cardioverter defibrillators (ICD) activations



temperature measure was below 2 °C. Below this threshold, the risk of ICD activation increased by 11.2 % (95 % CI 0.5 %, 23.1 %) for each degree Celsius fall in temperature. There was no evidence of increased risk of arrhythmias with high temperatures, and specifically none during the heat-wave episodes in the summers of 1995 and 2003 (results not shown).

#### Effect modification by patient characteristics

Interaction models by sex, age, event per person, number of storm days, cardiac diagnosis, use of beta blockers, and London residence are presented in Table 2. Each interaction was assessed in separate models. There was an increased risk of temperature-related activation in patients 65 years or over, which was statistically significant ( $P=0.02$ ) in the non-threshold model. London residency was associated with a greater risk of activation, especially at temperatures below 2 °C.

#### Sensitivity analysis

Temperature effects were not changed significantly when air pollution was added to the models. In the subset of patients (63.1 %) for whom exposure to PM<sub>10</sub> could be assigned, the temperature effect estimated from the non-threshold linear model was 1.021 (0.995, 1.043) per 1 °C decrease in temperature without control for PM<sub>10</sub>, and 1.018 (0.995, 1.041) with PM<sub>10</sub> control.

## Discussion

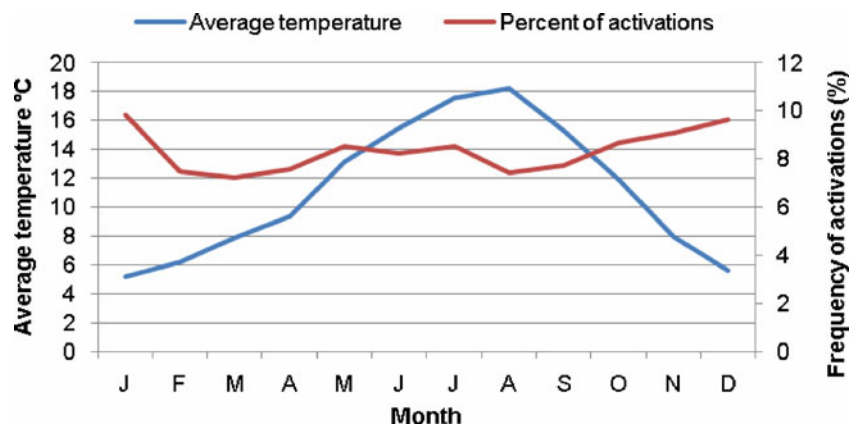
#### Summary of findings

This study is one of the largest published to date of patients with implanted cardiac defibrillators. It provides evidence that individuals with life-threatening cardiac arrhythmias,

**Table 1** Characteristics of ventricular arrhythmia patients. *IHD* Ischemic heart disease

Characteristic	No.	%
Male	555	85.6
Age (years) at first activation ( <i>n</i> =591)		
<55	137	23.2
55–64	140	23.6
65–74	223	37.7
>75	91	15.4
No. events per patient ( <i>n</i> =648)		
1	147	22.7
2	102	15.7
3	64	9.9
4–9	186	28.7
≥10	149	23.0
Cardiac diagnosis ( <i>n</i> =648)		
Myocardial infarction	270	41.7
Other IHD	111	17.1
Cardiomyopathy	126	19.4
Other	141	21.8
Drugs recorded as implantation (multiple drugs taken in some cases)		
Beta blockers	186	28.7
Anti-arrhythmics	302	46.6
Digoxin	36	5.6
Diuretic	189	29.2
ACE inhibitors	217	33.5
Anticoagulant	74	11.4
London residency	312	48.1

especially older patients over 65 years of age, may be at a greater risk of an event during periods of low outdoor temperature. This association appears independent of exposure to outdoor air pollution and is strongest for same day temperature than for other lags (not shown), although effects persisted for up to 7 days following exposure. High temperatures were not associated with an increased risk of activation.

**Fig. 2** Monthly average ambient temperature (°C) modelled against monthly frequency of activations

We also noted some evidence of stronger associations among London residents though a possible explanation of this is the shorter distances between London patients and temperature monitors, so that their exposure to outdoor temperatures may have been better represented.

#### Previous studies

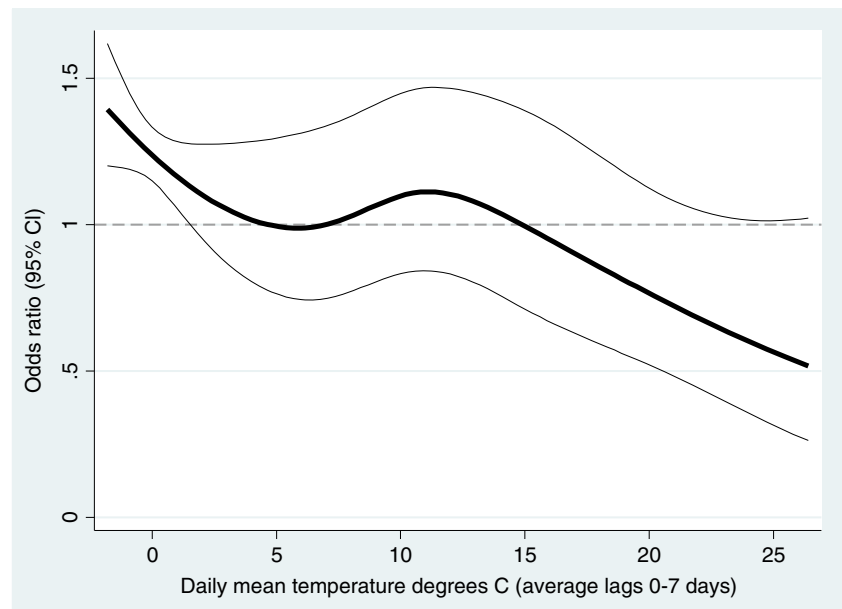
To date, few studies have examined the specific role of temperature on activations of ICDs (Fries et al. 1997; Anand et al. 2007). A German study found some evidence that very cold and very hot conditions may be associated with an increased frequency of ventricular tachyarrhythmia (VT) (Fries et al. 1997), a Croatian study observed a positive relationship between VT episodes and temperature in women and the elderly (Culic et al. 2004), whilst a US study reported evidence of higher risk on cooler days in both IHD and non-IHD patients (Anand et al. 2007). A Brazilian study that used 24-h Holter monitors to detect VT found evidence of increased risk of tachyarrhythmias at *higher* ambient temperature (Pimentel et al. 2006). The average maximum temperature in Brazil is around 27 °C, whereas the average maximum temperature in the UK is around 13 °C. Thus, the results are not comparable with the current study, where extremely elevated temperatures are rare. There were, however, two marked heat-waves in the summers of 1995 and 2003 in Southern England, yet no associations were found between these episodes and an increased risk of ICD activation.

We found that patients over the age of 65 were at increased risk of arrhythmia associated with low temperatures compared to younger patients, which is consistent with research that has shown that elderly mortality rises most during periods of low outdoor temperatures (Hajat et al. 2007).

#### Potential mechanisms

There are many plausible behavioural and physiological mechanisms behind temperature exposure and exacerbation of cardiac disease. Exposure to low temperatures leads to

**Fig. 3** Adjusted relationship between temperature and risk of ICD activation



decreased body temperature, which may lead to reflex mechanisms or increased catecholamine responses (Cheng 2005a; Raven et al. 1970). Small-scale studies have reported

cardiovascular responses from cold exposure such as increased arterial pressure, plasma cholesterol, and altered fibrinogen concentrations (Raven et al. 1970; Cheng

**Table 2** Odds ratio of implanted cardioverter defibrillator (ICD) activation per decrease (in °C) in mean temperature, by potential modifier

Potential modifier	No. activations	Linear model		Threshold model – at 2 °C	
		Odds ratio (95 % CI)	Interaction <i>P</i> -value	Odds ratio (95 % CI)	Interaction <i>P</i> -value
[All events]	5,038	1.012 (0.994, 1.029)	-	1.112 (1.005, 1.231)	-
Gender					
Male	4,406	1.012 (0.993–1.030)		1.098 (0.932, 1.293)	
Female	623	0.998 (0.946–1.047)	0.62	1.176 (0.777, 1.779)	0.76
Age					
<65	1,746	0.990 (0.964–1.015)		1.080 (0.867, 1.347)	
≥65	2,635	1.031 (1.006–1.055)	0.02	1.100 (0.886, 1.364)	0.49
Events per patient					
<10	1,625	1.014 (0.983–1.043)		1.038 (0.816, 1.322)	
≥10	3,413	1.008 (0.986–1.030)	0.76	1.155 (0.912, 1.454)	0.50
Number of storm days <sup>a</sup>					
0	1,542	1.021 (0.999, 1.042)		0.960 (0.746, 1.234)	
1 or more	3,483	0.988 (0.956, 1.018)	0.09	1.209 (0.996, 1.466)	0.15
Cardiac diagnosis					
IHD	2,947	1.012 (0.985–1.039)		1.156 (0.912, 1.454)	
Other	2,091	1.008 (0.984–1.031)	0.81	1.060 (0.865, 1.299)	0.60
Use of beta blockers <sup>b</sup>					
No	3,973	1.009 (0.990–1.028)		1.039 (0.880, 1.228)	
Yes	1,065	1.015 (0.961–1.066)	0.84	1.471 (0.977, 2.215)	0.12
Live in London					
No	2,491	1.000 (0.969–1.021)		0.913 (0.754, 1.106)	
Yes	2,547	1.023 (0.998–1.047)	0.13	1.602 (1.231, 2.085)	0.001

<sup>a</sup> Defined as 3 or more events in a single day

<sup>b</sup> At time of ICD activation

2005b; Mercer et al. 1999; Keatinge et al. 1984). Additionally, increases in red blood cell count, platelets, blood viscosity, and markers of thrombotic risk have been reported during the winter months (Woodhouse et al. 1993; Madsen and Nafstad 2006; Hampel et al. 2010). Cold exposure is associated with higher systolic and diastolic blood pressure, which may be brought about by stimulation of the sympathetic nervous system (Rintamaki 2007). However, it is unclear which, if any, of these responses explain the association between low temperature and specifically arrhythmia.

#### Strengths and limitations of the study

This study has some limitations. First, exposure was based on outdoor measures, which may not reflect personal exposure, especially in subjects who may spend the majority of their time indoors, leading to some inevitable exposure misclassification. We also used place of residence to classify exposure as there was no data from which to capture excursions outside the home. We were not able to take account of other time-varying factors, such as levels of physical activity, which may have some association with outdoor temperature as well as ICD activation.

Based on clinic review, a very high proportion (99 %) of our ICD activations were recorded as a ventricular diagnosis. It is likely that some of these may have been supra-ventricular arrhythmias (SVAs) which may have a different relationship with temperature. Indeed, in the subset of cases where a cardiologist assessment was available, the incidence of SVAs was 7 %; however, we chose not to restrict analysis to just those events where ECGs were available for assessment as this would have reduced the power of the study considerably.

The study has a number of strengths. It has the largest sample size of any related study to date. The use of a case cross-over approach allowed assignment of temperature exposure of each individual to much nearer monitoring stations than would have been possible using traditional ecological time series methods. And possible confounding from air pollution exposure was examined, again using monitored data linked to patient's home address in the case of PM<sub>10</sub> to minimise exposure misclassification.

#### Public health implications

This study provides evidence to suggest a mechanism by which *some* people may be at risk of cardiac death during cold weather, and also a potential strategy for reducing risk by encouraging selected patients to modify behaviour to minimise exposure to cold, especially at temperatures below 2 °C. The UK Meteorological Office has already set up an early warning system for chronic obstructive pulmonary disease patients, by phoning them when temperatures reach a certain reduced level. This study suggests that in principle

a similar warning system might be beneficial for both ICD patients and perhaps for cardiovascular disease patients in general, although the operation and cost-benefit of such a strategy is clearly a complex question. Low temperature is, of course, only one of a large number of potential triggers for life-threatening cardiac events.

#### Conclusions

Our results suggest an inverse association between low outdoor temperature and risk of life-threatening cardiac arrhythmias as reflected by the frequency of activation of implanted cardiac defibrillators. The importance of this for clinical advice and management is unclear, but it adds weight to the view to advise caution about cold exposure in patients who may be at particular risk of serious arrhythmic events.

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**Competing Interests** None.

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