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Effect of cold spells and their modifiers on cardiovascular disease events: Evidence from two prospective studies

Claudio Sartini [a,*], Sarah J.E. Barry [b], S. Goya Wannamethee [a], Peter H. Whincup [c], Lucy Lennon [a], Ian Ford [b], Richard W. Morris [d]

[a] Department of Primary Care & Population Health, University College London, Rowland Hill Street, NW3 2PF London. UK
[b] Institute of Health and Wellbeing, College of Medical, Veterinary and Life Sciences, Robertson Centre for Biostatistics, Boyd Orr Building, Level 11 University of Glasgow, Glasgow G12 8QQ, UK
[c] Population Health Research Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK
[d] School of Social & Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Rd, Bristol BS8 2PS, UK

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ABSTRACT

Objective: To investigate effects of cold weather spells on incidence of cardiovascular disease (CVD), and potential effect modification of socio-demographic, clinical, behavioural and environmental exposures.
Methods: Data from two prospective studies were analysed: the British Regional Heart Study (BRHS), a population-based study of British men aged 60–79 years, followed for CVD incidence from 1998–2000 to 2012; and the PROSPER study of men and women aged 70–82 recruited to a trial of pravastatin vs placebo from 1997 to 9 (followed until 2009). Cold spells were defined as at least three consecutive days when daily mean temperature fell below the monthly 10th percentile specific to the closest local weather station. A time-stratified case-crossover approach was used to estimate associations between cold spells and CVD events.
Results: 921 of 4252 men from BRHS and 760 of 2519 participants from PROSPER suffered a first CVD event during follow-up. More CVD events were registered in winter in both studies. The risk ratio (RR) associated with cold spells was statistically significant in BRHS (RR = 1.86, 95% CI 1.30–2.65, $p < 0.001$), and independent of temperature level: results were similar whether events were fatal or non-fatal. Increased risk was particularly marked in BRHS for ever-smokers (RR of 2.44 vs 0.99 for never-smokers), in moderate/heavy drinkers (RR 2.59 vs 1.41), and during winter months (RR 3.28 vs 1.25). No increased risk was found in PROSPER.
Conclusions: Although CVD risks were higher in winter in both BRHS and PROSPER prospective studies, cold spells increased risk of CVD events, independently of cold temperature, in the BRHS only.

1. Background

Cardiovascular disease (CVD) is the most common cause of death globally, remaining a considerable burden both in terms of health and costs [1]. As in many countries, CVD mortality in the UK exhibits a marked seasonal variation; more people die during the winter months (December–March) than in other periods of the year and the majority of deaths occur among those aged 75 and over [2,3]. This seasonal variation in death rates has been mainly attributed to cold weather and fall in temperature, which can alter vulnerability to specific diseases, in particular myocardial infarction, stroke and respiratory infection (especially influenza) [4–7]. However, uncertainty still exists about the range in temperature which produces an increased risk of CVD and other health outcomes, [8,9] since effects of both extremely cold days [10,11] and moderately cold days [8] on mortality have been demonstrated. To date, there is neither an established definition of a cold day nor a precise definition of the period for which a cold spell (e.g. two or more consecutive cold days) should last for detrimental health effects [9]. Less frequently, cold spells in the UK can also occur during the non-winter months (May–November) [12], with lowest minimum and maximum temperatures in England of −2 °C and 9 °C in August [13].

A much debated question is which people are more susceptible to cold temperature or cold spells, and the relative importance of individual characteristics such as age, previous chronic conditions, low income and cold homes [7,14–17]. The elderly have been long considered more susceptible to cold weather [5], but the evidence is not consistent [17], For example, the odds of death in the elderly may be significant only if associated with cold spells, but not a linear decrease in temperature [15]. In other studies the statistical power to examine evidence for effect modification was low and evidence for differences in effect of cold temperature on cardiovascular mortality according to obesity, smoking habit, alcohol intake, and hypertension was not found [16].

Therefore, the aims of this study are threefold: (i) to investigate the effect of cold spells on cardiovascular events during 1997–2012

* Corresponding author.
E-mail address: c.sartini@ucl.ac.uk (C. Sartini).

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(subdivided into fatal and non-fatal, and coronary and stroke) using data from two large prospective studies of older adults; (ii) to explore whether the effect of cold spells is modified by established cardiovascular risk factors (e.g. age and smoking) and previously unexplored individual characteristics (e.g. physical activity score, central heating and double glazing in the house); (iii) to explore whether the effect of cold spell is independent from average temperature over periods up to 6 days previously.

We carried out a primary analysis on men from an established UK population-based study, the British Regional Heart Study (BRHS) [18], and secondarily on participants of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) [19,20] recruited from Glasgow (UK), Cork (Republic of Ireland), Leiden (The Netherlands) and the surrounding areas.

2. Methods

2.1. Methods and participants

Participants from BRHS and PROSPER provided informed written consent, which was performed in accordance with the principles of the Declaration of Helsinki. The designs of both BRHS [21] and PROSPER [19,20], which are both prospective studies of several thousand participants with cardiovascular disease as their key endpoints, have been previously described in detail and included in this work as supplementary material (Supplementary File 1 – BRHS and PROSPER methods and participants).

2.2. Case ascertainment and follow-up

The BRHS cohort was followed-up from Jan. 1998–March 2000 until the end of 2012, while the PROSPER participants were followed-up from December 1997–May 1999 until the end of June 2009. The events considered during the corresponding study periods for the two studies were fatal or nonfatal stroke and CHD death or non-fatal myocardial infarction (MI). The definitions of non-fatal/fatal stroke and CHD death/non-fatal MI are reported in supplementary material (Supplementary File 1 — Definition of fatal and non-fatal CVD events).

2.3. Climatic data and definition of cold spell

Mean temperature of the day for the study towns was provided by the national meteorological offices (Supplementary File 1 — Climatic data). The definition of cold spell used in this study was derived from daily mean temperatures and related to spells which were, for at least 3 or 4 consecutive days, below the 10th percentile for that geographical location for the specific month of the year (for details see Supplementary File 1 — Definition of cold spell).

2.4. Statistical methods

Firstly, baseline characteristics of BRHS and PROSPER participants were compared between those who did or did not experience the CVD events (non-fatal or fatal) during follow-up.

Then, monthly descriptive statistics of number of events were calculated. Average mean temperatures, and number of cold spells of at least 3 and 4 consecutive days were calculated by month, for both BRHS and PROSPER separately, and during event days and control days (defined below).

Only participants who suffered an event were included in subsequent analysis, and short-term associations between cold spell and CVD events were assessed using a time-stratified case-crossover approach, widely used in environmental epidemiology [22]. A case-crossover study can be seen as a self-matched case–control study: for each individual, exposure data are collected for the “case” day (that is, the day of the cardiovascular event) and a set of “control” days that were not associated with the event of interest. The “control” days were selected by using the same days of the week of the same month and year [23]. For each “case” and “control” day we determined whether the specific day and days preceding were cold days.

We then compared cases with their set of controls using conditional logistic regression. The outcome was a binary variable (case or control) as was the exposure variable (day of event being part of a cold spell or not). Therefore, the odds ratios from the conditional-logistic-regression model can be interpreted as risk ratios (RRs). By design, the analyses are adjusted for long-term changes in environmental exposures, for day of the week, and for all participant characteristics that are expected to remain stable over a 1-month period (e.g., smoking status).

We reported results for 7 different outcomes: (1) all causes of death; (2) fatal events (fatal stroke or CHD death); (3) CHD death; (4) fatal stroke; (5) earliest of fatal/non-fatal stroke or CHD death/non-fatal MI; (6) MI events (earliest nonfatal MI or CHD death); (7) stroke events (earliest non-fatal or fatal) stroke. For each outcome type, only the first event of the relevant type was included. Results are presented separately for the two studies but we also carried out a fixed effects meta-analysis to pool results.

We made use of the wide range of individual risk factors in BRHS to examine interaction effect between cold spells and these risk factors.

3. Results

3.1. Participants' characteristics

In the BRHS, 4252 men out of 5875 men (72.4%) were alive at 01/01/1998 and participated at the 20 year follow-up examination and survey. 3977 men (67.7%) did not change town of residence during the study period 1998–2012. Participants were followed for a median of 12.7 years (inter-quartile range 8.7, 13.5). The BRHS participants' characteristics are shown in Table 1a, according to whether or not they later experienced CVD events (921 participants: 23.2%, and 521 (13.1%) fatal events (fatal stroke or CHD death). The baseline characteristics of the study participants for PROSPER are reported in Table 1b. In the PROSPER study non-fatal events were available for the Glasgow Centre only: 760 out of 2520 participants (30.2%) had development of CVD (earliest of fatal or non-fatal stroke or non-fatal MI or CHD death). Considering all PROSPER cohorts (Glasgow plus Cork and Leiden), the number of CVD deaths (fatal stroke or CHD death) registered during the follow up period (median = 10.3 years (IQR 6.9 to 10.7) was 810 out of 5804 (14%).

PROSPER participants in comparison with BRHS participants (see Table 1a vs Table 1b) were about 5 years older, with a higher CVD prevalence, but also less likely to have diabetes, to be smokers, or to drink alcohol. PROSPER participants were also more likely to live alone and use aspirin, beta-blockers, ACE-inhibitors, diuretics, calcium channel blockers and nitrates. Owing to the nature of the PROSPER study, 50% were initially assigned to statins, while less than 10% of BRHS participants took statins at baseline.

3.2. Monthly distribution of events, temperatures and cold spells

During the study period, mortality from all causes and from CVD (fatal stroke or CHD death) was highest during the winter months (December–March) in both BRHS (Table 2a) and PROSPER (Table 2b) cohorts, see also eFigure 1 (Supplementary material). The excess winter mortality (EWM) from all causes of death was 18% in both studies, but the EWM from CVD was higher (36% in BRHS and 23% in PROSPER).

Mean temperatures on event or control days (where ‘events' were first events of any type; ie. outcome 5 as defined in the Methods section) were lowest from December to March in both BRHS (Table 2a) and PROSPER (Table 2b).