An analysis of arterial disease mortality and BUPA health screening data in men, in relation to outdoor temperature

G. C. DONALDSON, D. ROBINSON* and S. L. ALLAWAY*
Department of Physiology, Queen Mary and Westfield College, London, U.K., and *BUPA Research and Clinic Audit, Battle Bridge House, London, U.K.

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1. Laboratory studies have shown that cold exposure causes an increase in blood pressure, cholesterol and erythrocyte count. However, whether the mild cold exposures received during everyday life are sufficient to cause such changes is unclear.

2. To test this, outdoor temperatures in central London between 1986 and 1992 were related to both haematological and blood pressure data on 50–69-year-old men attending BUPA health screening examinations in London, and to mortality in South-East England. Since any association with temperature may be an artifact due to common, temperature-independent, annual rhythms in the parameters, these data were also analysed after removal of these circannual components by digital filtering.

3. It was found that short-term falls in temperature produced significant increases in Hb, erythrocyte count, packed cell volume, mean corpuscular Hb concentration, serum albumin, systolic and diastolic blood pressure, and significant decreases in mean corpuscular volume and erythrocyte sedimentation rate. Mean corpuscular Hb, leucocyte count, platelet count and serum cholesterol concentrations were unchanged. Time-series analysis showed that these changes occurred almost immediately in response to a fall in temperature, but persisted for longer intervals of up to 1–2 days.

4. Mortalities from ischaemic heart disease and cerebrovascular disease were also significantly increased by short-term falls in temperature.

5. These findings indicate that in the general population the cold exposures of normal life are sufficient to induce significant and prolonged haemoconcentration and hypertension, which may explain why deaths from arterial disease are more prevalent in the winter.

INTRODUCTION

There is considerable epidemiological evidence for an association between deaths in England and Wales from ischaemic heart and cerebrovascular diseases and outdoor air temperature [1, 2]. The underlying pathological processes have been studied experimentally by exposing lightly clad young and old adults in the morning to cold conditions sufficient to depress core temperature slightly [3–5]. Increases were seen in erythrocyte and platelet counts, whole-blood viscosity, plasma cholesterol, fibrinogen and blood pressure, but not in Factor X or Protein C. Cross-sectional time-series analyses have also found significant relationships between fibrinogen, plasma viscosity and high-density lipoprotein cholesterol and temperature [6]. The mechanism producing these changes was thought to be a haemoconcentration, due to loss of plasma fluid through cold-induced diuresis and filtration into interstitial tissues in the lungs and liver, associated with the raised intravascular pressures caused by peripheral vasoconstriction. Upper respiratory tract infections could also contribute to cardiovascular mortality, as bacterial infections may initiate an acute-phase response that causes a rise in fibrinogen levels [7–9], although there is some evidence to the contrary [10–12]. Both mechanisms may contribute to the excess cardiovascular and cerebrovascular mortality in winter, as they both increase the risk of thrombus formation. A reverse trend occurs with increases in mortality and blood constituents when a heatwave occurs and minimum outdoor temperatures rise above 20°C [13].

However, little work has been published relating outdoor temperature to haematological and cardiovascular data from individuals receiving cold exposures during the course of their daily activities. Information on this is important as not only might it differ from the experimental studies, but it will be more germane to any explanation of excess winter arterial disease mortality in the general population.

In the current study, weighted linear regression analyses were performed both on data collected during routine health screening examinations at the British United Provident Association (BUPA) Health Screening Centre, London, and also on mortality data for various causes of death in men...
aged 50–69 years from the South-East of England, in relation to outdoor temperatures in Central London. However, a number of previous authors have suggested that any relationship with temperature could be merely an artifact due to the coincidence of circannual trends [8, 14, 15], and other studies using spectral analysis and periodic regression have shown annual cycles in haematological and cardiovascular parameters [16–18]. The data were accordingly filtered to remove any long-term seasonal trends, and then reanalysed by relating short-term changes in the mortality and health screening parameters to those in temperature. Time-series analyses were also performed by lagging these parameters with respect to temperature, to determine the time course of changes after a fall in temperature.

The screening data were not obtained at the same time of day or under any standardized thermal conditions, nor were the subjects’ means of transport to the screening centre regulated — thus increasing the variation of the measurements and reducing the likelihood of any correlation with outdoor temperature. Although unwell individuals were encouraged not to take part in the screening process, it is conceivable that among the large number of people investigated, a few had some chronic or covert illness. Exclusion of these either before or after examination would have been impractical, and so the data presented are on individuals self-selected as healthy. Moreover, as it was uncertain whether the people attending screening lived and worked exclusively within Greater London or any other definable area, mortality statistics from the South-East of England (which would encompass all but the very long-distance London commuters) were used.

DATA AND METHODS

Haematological and cardiovascular data

Haematological and cardiovascular data were obtained from the BUPA Research and Clinical Audit Unit, on men aged 50–69 years attending the London Health Screening Centre. The data were collected between 2 January 1986 and 24 December 1992 and consisted of 38,780 individual measurements of erythrocyte count, Hb, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular Hb concentration, mean corpuscular Hb and leucocyte count; 38,812 measurements of serum cholesterol and albumin; 35,302 measurements of systolic and diastolic blood pressures; 20,842 measurements of erythrocyte sedimentation rate (ESR) up to 17 December 1991 and 11,191 measurements of platelet count from 2 July 1990 onwards. Subjects were bled after approximately 15 min of supine rest, between 09.00 hours and 17.00 hours on weekdays, using a Becton-Dickinson Vacutainer® system, and specimens were dispatched twice daily to JS Pathology Services in London. Blood for biochemical analysis was taken into tubes containing a plastic plug and clot enhancer, and centrifuged within 1 h to separate the serum above the plug. Haematology specimens were collected in tubes containing EDTA. Biochemical samples were analysed on a Technicon SMAC and haematology specimens on a Coulter S+4 analyser. Serum albumin was assayed with Bromocresol Green [19] and serum cholesterol with cholesterol esterase [20]. Calibration procedures followed manufacturers’ guidelines. The laboratory practised strict external and internal quality assurance techniques. Daily mean values for patients were also monitored by BUPA research staff to detect errors due to changes in procedures or personnel. In addition, data on alcohol and tobacco consumption were collected, and heights and weights were measured to determine body mass index.

Temperature data

The Meteorological Office provided temperature data, recorded initially on the roof of the London Weather Centre in High Holborn, and after April 1992 at the Ministry of Defence, Whitehall. Three-hourly readings were averaged to give daily values. There were no missing data.

Mortality data

Death registration data for England and Wales collated by the Office of National Statistics for the years 1986 to 1992 were obtained with their agreement from the Department of Public Health Sciences, St George’s Hospital Medical School. The number of daily deaths of 50–69-year-old men in South-East England from ischaemic heart disease (IHD) and cerebrovascular disease (CVD) was extracted according to the ninth International Classification of Diseases coding — IHD: 410.0–414.9, CVD: 430.0–438.9. These were then divided by daily estimates of population, obtained by linear regression of mid-year population estimates based on the 1981 and 1991 censuses (Office of Population Censuses and Surveys, Mortality statistics, Series DH1, Table 2) against date, to give mortality as deaths day⁻¹ 10⁻⁶ people. Populations were 1638 × 10³ in 1986 and 1644 × 10³ in 1992.

Statistical analysis

Weighted linear regression (statistical package Stata; Stata Corp., TX, U.S.A.) was used to relate outdoor temperature on each day to haematological and cardiovascular parameters measured on the same day, and to daily mortality recorded on the same day in the case of IHD and 2 days later for CVD. This 2-day lag was used in the latter instance
because the delay between temperature change and peak mortality from CVD is thought to be longer than that for IHD [21], although the reason is unknown. The weights used with the health screening data corresponded to the number of individual measurements made on a given day, on average 23.9 (range 1–71) for the haematological and clinical chemistry assays, 23.7 (range 1–72) for blood pressures, 17.8 (range 2–69) for platelet counts and 22.3 (range 1–70) for ESR. Weights for the mortality data were set to 1. The analysis was confined to those days on which the temperature fell within the range 0–20°C, in order to avoid the confounding effects of extreme hot weather, which can concentrate blood constituents through fluid loss via sweating [13], and problems with heteroscedasticity in the data at the extremes of the temperature range due to the small number of days at these temperatures. The initial and final 256 days’ data were excluded so that the data analysed matched those after filtering (see below). The F-test was used to test the significance of the regression lines from zero [22]. Scattergrams of each variable were made by sorting the data, into 1°C temperature bins, averaging, and plotting against mid-interval temperature. Similar plots were made using the filtered data.

**Time series**

Time series were constructed from the daily mortality and daily mean haematological and cardiovascular data. In the latter, missing values occurred at weekends, public holidays and between 1 January 1990 and 30 June 1990. Data for missing days were replaced with the mean of the two preceding days to generate an unbroken time-series for subsequent filtering, but were not used in later analyses.

**Removal of long-term seasonal trends, and subsequent analysis.**

Long-term periodic variations in the mortality, health screening and temperature time-series were removed by the subtraction of low-pass filtered data obtained using a Dolph-Chebyshev 5 cycles/year filter [23]. This procedure gave high-pass filtered data from which cycles of less than 4.0 per year had been completely removed, and those between 4.0 and 6.0 per year partially removed, with those greater than 6 per year (equivalent to a cycle length of 61 days) remaining unaltered. The filtering technique meant the loss of 256 data points from both the beginning and the end of the time series. Weighted linear regressions were then computed using filtered data for the same days, i.e. those on which temperature (unfiltered) fell within a 0 to 20°C range, and with the same weights as described above. Extrapolated values used to replace missing data for the purpose of filtering were excluded from this analysis. To allow comparison between parameters, the slopes of these regression lines were expressed as a percentage of a ‘reference’ value estimated at 10°C from the analysis of the unfiltered data. Quadratic and cubic functions were also fitted to test the adequacy of the linear model.

**Analysis of time courses with respect to a fall in temperature**

This analysis was performed using the same filtered time-series as described above, with the same weights and days, but with the haematological and cardiovascular data successively lagged from −15 days to +15 days, with respect to the temperature on a single day (day 0). A negative lag refers to the days before day 0 and a positive lag to days after. The analysis was also made for lagged temperature with respect to temperature on day 0. The regression coefficients were plotted against lag. Parameters which increase when the temperature falls will have negative regression coefficients, and those which decrease will have positive coefficients. Thus, points below the x-axis (zero) refer to an increase in the parameter with falling temperature and those above the x-axis to a decrease.

**RESULTS**

Approximately 11% of the subjects smoked and 7% drank more than 50 g of alcohol per day. There was no variation in these parameters or in the age of those attending the screening centre with season. Mean body mass index increased significantly in winter and was on average 25.9 kg/m² in January (maximum) and 25.7 kg/m² in August (minimum) (P = 0.008).

Figure 1 shows scattergrams of the haematological, cardiovascular and mortality parameters against temperature. Above 0°C and below 20°C, the majority of these parameters appeared linearly related to temperature, but outside this range there was a tendency for the curve to show an upturn – although the data were more scattered. Fitting quadratic and cubic functions produced only a minor improvement in some parameters (<2.4% reduction in deviations from the model in the worst case), and so the linear model was retained for purposes of simplicity and consistency. The results of the regression analyses on unfiltered data at temperatures between 0 and 20°C are given in Table 1. Scattergrams of the parameters against temperature (both filtered) are presented in Fig. 2. The results of the regression analyses after filtering are summarized in Table 2. The final column gives the estimated change associated with a 1°C change in temperature, expressed as a percentage of the
Fig. 1. Scattergrams of haematological, cardiovascular and mortality parameters against temperature (unfiltered data). Abbreviations: MCH, mean corpuscular Hb; MCHC, mean corpuscular Hb concentration.

Table 1. Relationship of daily haematological, cardiovascular and mortality parameters to outdoor temperature (unfiltered data). NS, not significant (P<0.05).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression coefficient on temperature (units/°C)</th>
<th>P-value</th>
<th>Estimated value at 10 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>-0.0061</td>
<td>&lt;0.01</td>
<td>14.8 g/dl</td>
</tr>
<tr>
<td>Erythrocyte count</td>
<td>-0.0010</td>
<td>NS</td>
<td>4.77 x 10^{12} cells/l</td>
</tr>
<tr>
<td>PCV</td>
<td>-0.0009</td>
<td>NS</td>
<td>43.14%</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>0.0177</td>
<td>&gt;0.05</td>
<td>90.72 fl</td>
</tr>
<tr>
<td>Mean corpuscular Hb concentration</td>
<td>-0.0141</td>
<td>&lt;0.001</td>
<td>34.3 g/dl</td>
</tr>
<tr>
<td>Mean corpuscular Hb</td>
<td>-0.0064</td>
<td>NS</td>
<td>31.1 pg</td>
</tr>
<tr>
<td>Leucocyte count</td>
<td>-0.0114</td>
<td>&lt;0.001</td>
<td>6.75 x 10^{9} cells/l</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-0.0101</td>
<td>&lt;0.001</td>
<td>6.38 mmol/l</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.0069</td>
<td>NS</td>
<td>44.8 g/l</td>
</tr>
<tr>
<td>ESR</td>
<td>0.1104</td>
<td>&lt;0.001</td>
<td>4.94 mm/h</td>
</tr>
<tr>
<td>Platelet count</td>
<td>1.0282</td>
<td>&lt;0.001</td>
<td>232 x 10^{9}/l</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.1795</td>
<td>&lt;0.001</td>
<td>129.5 mmHg</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.1366</td>
<td>&lt;0.001</td>
<td>82.2 mmHg</td>
</tr>
<tr>
<td>IHD mortality</td>
<td>-0.2505</td>
<td>&lt;0.001</td>
<td>17.56 deaths day^{-1} x 10^{-4} people</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>-0.0564</td>
<td>&lt;0.001</td>
<td>2.89 deaths day^{-1} x 10^{-4} people</td>
</tr>
</tbody>
</table>
Haematology and outdoor temperature

Fig. 2. Scattergrams of haematological, cardiovascular and mortality parameters against temperature (filtered data). Abbreviations: MCH, mean corpuscular Hb; MCHC, mean corpuscular Hb concentration.

Table 2. Relationship of daily haematological, cardiovascular and mortality parameters to outdoor temperature (filtered data). NS, not significant (P < 0.05).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression coefficient on temperature (units/°C)</th>
<th>P-value</th>
<th>% of value at 10 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>-0.0188</td>
<td>&lt;0.001</td>
<td>0.127</td>
</tr>
<tr>
<td>Erythrocyte count</td>
<td>-0.0057</td>
<td>&lt;0.001</td>
<td>0.119</td>
</tr>
<tr>
<td>PCV</td>
<td>-0.0333</td>
<td>&lt;0.001</td>
<td>0.077</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>0.0366</td>
<td></td>
<td>0.040</td>
</tr>
<tr>
<td>Mean corpuscular Hb concen.</td>
<td>-0.0168</td>
<td>&lt;0.01</td>
<td>0.049</td>
</tr>
<tr>
<td>Mean corpuscular Hb</td>
<td>-0.0023</td>
<td>NS</td>
<td>0.007</td>
</tr>
<tr>
<td>Leucocyte count</td>
<td>-0.0069</td>
<td>NS</td>
<td>0.102</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-0.0039</td>
<td>NS</td>
<td>0.051</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.0232</td>
<td>&lt;0.01</td>
<td>0.61</td>
</tr>
<tr>
<td>ESR</td>
<td>0.0827</td>
<td>&lt;0.01</td>
<td>1.674</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.0489</td>
<td>NS</td>
<td>0.021</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.2989</td>
<td>&lt;0.001</td>
<td>0.231</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.1950</td>
<td>&lt;0.001</td>
<td>0.237</td>
</tr>
<tr>
<td>IHD mortality</td>
<td>-0.1114</td>
<td>&lt;0.01</td>
<td>0.634</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>-0.0469</td>
<td>&lt;0.01</td>
<td>1.623</td>
</tr>
</tbody>
</table>
estimated value of the parameter at 10°C, as given in Table 1.

Figure 3 shows the regression coefficients for temperature, systolic and diastolic blood pressures, erythrocyte count, PCV, ESR, serum albumin, and IHD and CVD mortalities at lags of -15 days to +15 days with respect to temperature on a single day (day 0). These results are most easily interpreted by considering the effect of a unit (1°C) fall in temperature on day 0, so that the y-axis scale would then have, for diastolic blood pressure, units of mmHg rather than mmHg°C, and, for temperature, °C rather than °C°C. Thus, a day on which temperature fell will have been preceded by five increasingly cold days, and followed by five increasingly less cold days (see top left graph in Fig. 3). The response to such a cold interval was an almost simultaneous increase in all the parameters depicted (except ESR, which showed the opposite and decreased). The peak changes were generally seen on day 0, with the exception of erythrocyte count and PCV which were maximal on day +1, IHD mortality which peaked on day -1 and CVD mortality which reached maximum at day +3. Although the changes in temperature on either side of day 0 appeared almost symmetrical, the cold-induced responses of the haematological and cardiovascular parameters appeared to be characterized by a faster rise to peak than return.

DISCUSSION

We have approached the question as to whether everyday cold exposures experienced by 50–69-year-old men affect their blood pressure and haematology, by relating health screening data collected over a 7-year interval to outdoor temperature. An association would strengthen the argument that excess winter arterial disease mortality is due in part to cold-induced haemoconcentration, as the only other evidence for this is based on experimental cold exposures which are not typical of everyday life. Other confounding factors such as barometric pressure and sunlight have not been included in our analysis as it is not clear how, or indeed whether, these have any direct, independent effect on the cardiovascular system.

We are aware of only one similar study, involving just 2036 men living in South Wales [24], in which health screening data have been related to outdoor temperature. This study found similar increases in blood pressure to ours, but dissimilar and non-significant changes in cholesterol and leucocyte count, and a significant rise in platelet count, with falls in temperature. We cannot explain these differences, but our data are from approximately 19 times as many men and cover 6 more years.

We did not find any seasonal differences in the age, smoking or drinking habits of those attending screening, and only a small, albeit significant (P < 0.01), increase in body mass index in the winter. This, together with the rigorous scrutiny to which the results were subject, make it unlikely that any major seasonal bias was unwittingly introduced into the data. We reanalysed the data after applying a filter which completely removed seasonal cycles of less than 4 per year, and partially removed those between 4 and 6 per year. This was necessary because otherwise any association between the mortality, haematological and cardiovascular parameters and temperature could simply be attributed to seasonal rhythms they had in common. By removing the seasonal fluctuations it was hoped to show that short-term changes in these parameters would remain related to short-term changes in temperature. This would provide evidence that the much larger overall temperature changes occurring during the year also affect the parameters.

We chose not to use a sine-wave model to eliminate the circannual fluctuations [8, 11, 15] as we could not be certain that asymmetries did not exist – e.g. between spring, when temperature rises, and autumn, when it falls – and because there were non-linear changes in the annual means which could not simply be removed by subtraction of a single sine-wave. Although we have no evidence, these year-on-year changes may have been due to health
education campaigns in the last few years which have encouraged the population to eat less fat to lower cholesterol concentrations, and reduce salt intake to lower blood pressure.

After removal of seasonal trends, IHD mortality with zero lag, and CVD mortality with 2 days' lag, were still significantly related to temperature, a 1°C fall being associated with increases of 0.11 and 0.04 deaths day⁻¹ 10⁻⁶ people respectively. These values may appear small, but it should be remembered that they ignore the grosser swings in temperature between summer and winter.

After eliminating long-term trends, Hb, erythrocyte count, PCV, mean corpuscular Hb concentration, systolic and diastolic blood pressures still increased significantly with falls in temperature on the same day. One notable finding, contrary to laboratory-based studies [4, 5], was that MCV decreased significantly with a fall in temperature. The mechanism causing this might be a cold-induced increase in urinary sodium excretion [4], which, while plasma sodium concentrations are maintained by the renin–angiotensin–aldosterone system, causes a decrease in cellular sodium and a consequential decrease in erythrocyte volume as water is lost by osmosis. Another new finding was that mean corpuscular Hb was unrelated to temperature. This was to be expected, as only about 1/120 of erythrocytes in the blood are destroyed and replaced per day, so that if any cold-related change in erythrocyte turnover took place, it would have a negligible effect within 24 h. Changes in serum cholesterol were not significantly related to temperature once seasonal trends had been removed, which confirms suggestions that fluctuations in cholesterol concentrations are circannual [25, 26], although their explanation is difficult as they appear unrelated to diet and lifestyle [27, 28]. Erythrocytes increased by 0.119% per 1°C drop in temperature, whereas albumin, a small protein (69 kDa molecular mass), increased by only 0.052% per 1°C drop. This supports the hypothesis that large plasma constituents remain in the blood during cold exposure and become more concentrated, while smaller factors can leave the plasma through capillary pores and therefore their serum concentrations rise less [5]. Increases in erythrocyte and leucocyte counts per 1°C fall in temperature were almost identical (0.119% and 0.102% of the 10°C 'reference' value, respectively). However, with seasonal trends included, changes in erythrocyte count were much less than those of leucocyte count (increases of 0.021% and 0.169% per °C drop in temperature, respectively). This suggests that fluctuations in leucocyte count are predominantly circannual in nature, possibly due to increased respiratory infections in the winter [8, 29]. In the absence of seasonal fluctuations, ESR fell dramatically by 1.67% per °C drop in temperature. This was the largest percentage change in any of the parameters, and has not we believe been reported before. It was a surprising finding as the concentration of fibrinogen normally increases in the cold [5] or in winter [6, 8, 30] and this would be expected to increase ESR since it favours aggregation of erythrocytes into rouleaux, which precipitate quickly. One possible explanation might be that the loss of plasma fluid increases whole-blood viscosity, which in turn slows erythrocyte sedimentation.

One possible explanation for why erythrocyte count, PCV and albumin were not significantly related to temperature before removal of seasonal trends, but were afterwards, might be the influence of circannual rhythms that decrease these in winter, thus masking the effect of temperature. The converse situation where leucocyte count, cholesterol and platelet count were significantly related to temperature before filtering, but were not afterwards, suggests that temperature is not a major influence in their circannual variations.

Time-series analysis of the time course of the haematological and cardiovascular reactions to cold indicated an almost immediate response, which generally peaked on the coldest day, but which took longer to return to reference than to reach peak. This suggests that the consequences of cold exposure will persist for up to 1–2 days after the exposure ends, rather than for only several hours as reported previously [5]. Indirect evidence for this comes from the fact that the haematological and cardiovascular parameters were still related to temperature when measured after an interval in the warm conditions of the health screening clinic. This persistence is a new and major finding, as it may explain how the relatively small haematological changes can lead to increased mortality from arterial disease.

We have shown that short-term changes in temperature encountered during everyday activities can produce small but significant changes in haematological and cardiovascular parameters that persist for several days. That these relationships are independent of seasonal trends, together with the fact that in general risk factors for arterial disease act synergistically [31], suggests that the brief cold exposures of everyday life are sufficient to cause the large observed increase in arterial disease mortality during winter.

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REFERENCES