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Seasonal variations in fibrinogen concentrations among elderly people

ROBERT W. STOUT VIVIENNE CRAWFORD

Mortality and morbidity in elderly people are higher in winter than in summer months, with seasonal variations in rates of both fatal and non-fatal myocardial infarction and stroke. To identify factors that might contribute to the excess winter frequency of cardiovascular disease in the elderly, we studied 100 subjects aged 75 and over who lived in either their own homes or in sheltered or residential accommodation. Each person was visited each month for one year, body and environmental temperatures were noted, and cardiovascular risk factors were measured. 32 subjects withdrew from the study. Significant seasonal effects were found for fibrinogen, plasma viscosity, and HDL cholesterol ($p < 0{\cdot}003$, Bonferroni adjustment). Plasma fibrinogen concentrations showed the greatest seasonal change and were 23% higher in the coldest six months compared with summer months. Fibrinogen was significantly ($p < 0{\cdot}05$) and negatively related to core body temperature and all measures of environmental temperature. Those living in institutions had greater changes in plasma fibrinogen than those living in the community. The seasonal variation in plasma fibrinogen concentration is large enough to increase the risk of both myocardial infarction and stroke in winter.

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Introduction

Although hypothermia is an important and potentially preventable cause of death in elderly people during winter, the excess morbidity and mortality from other disease in the colder months of the year is more important in numerical terms.[1,2] The causes of this seasonal effect include not only infectious diseases such as respiratory tract infections, but also vascular disease, especially coronary heart disease and stroke,[1] and fractured femur.[3] Excess winter mortality is found in countries in both northern[2] and southern[4] hemispheres, but seasonal variation is lowest in those countries with very cold winters—eg, Scandinavia—which suggests that insulation and indoor heating may be preventive factors.[2] Furthermore, mortality correlates with the minimum average monthly temperatures, and the

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TABLE I—STUDY GROUP CHARACTERISTICS

—	Own home (n=43)	Residential or sheltered accomodation (n=35)
Age (yrs)	79·0 (77·8–80·2)	82·6 (80·5–84·7)
Body mass index (kg/cm²)	24·1 (23·0–25·2)	22·9 (21·1–24·7)
Waist/hip ratio	0·90 (0·88–0·93)	0·89 (0·84–0·93)
Subscapular/triceps ratio	1·24 (1·02–1·47)	0·88 (0·76–1·02)
Mental score	9·9 (9·7–10·0)	9·1 (8·6–9·6)

Mean (*95% CI*)

seasonal effect is greater in older than in younger people.[5] To identify factors that might contribute to the excess winter frequency of cardiovascular disease in elderly people, we studied a group of people aged 75 and over for one year, and measured their cardiovascular risk factors at monthly intervals. The findings were compared with the temperature of the individual, the home, and the outside environment.

Subjects and methods

100 people aged 75 and over were identified from the age/sex register of a local general practice. Half the subjects lived in their own homes and the other half lived in either sheltered dwellings or residential homes that had centrally heated environments. Informed written consent was obtained from all subjects and the study was approved by the Queen's University of Belfast Research Ethical Committee. An initial assessment was made of the type and age of the dwelling, heating, general health, mental, and functional status of the subjects, and their medication and anthropometric measurements, including height, weight, skinfold thickness at the subscapular and triceps areas, and waist and hip circumference.

The study took place during 1989, and was extended into the first three months of 1990 because the 1989 winter was exceptionally mild. Subjects were visited by a research nurse at monthly intervals. The nurse reminded subjects of the nature and purpose of the investigation and left two maximum/minimum thermometers, one in the living room and one in the bedroom. She also left a urine temperature measuring device[6] and gave instructions on its use; the temperature of urine voided on rising in the morning was taken as a measure of core body temperature. The following morning the

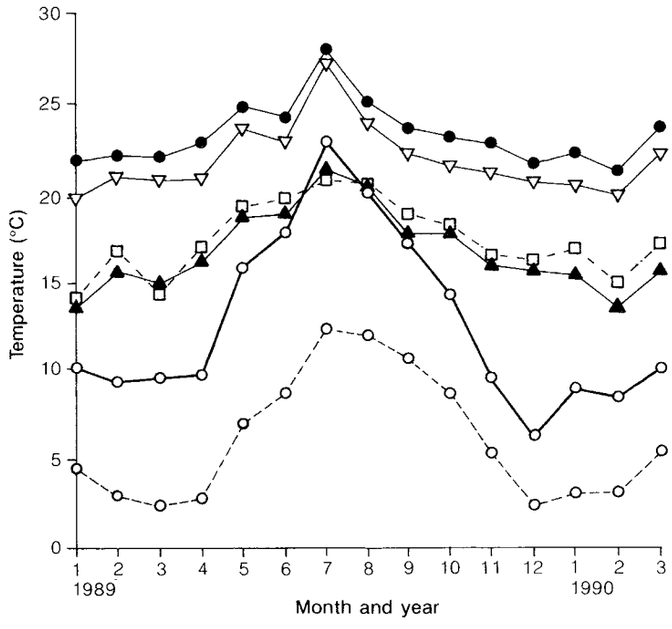

Fig 1—Mean monthly temperature inside and outside the home.

—▽—, Maximum bedroom temperature, —▲—, minimum bedroom temperature, —●—, maximum living room temperature; — —□—·—, minimum living room temperature, —○—, maximum ambient temperature; ---○---, minimum ambient temperature.

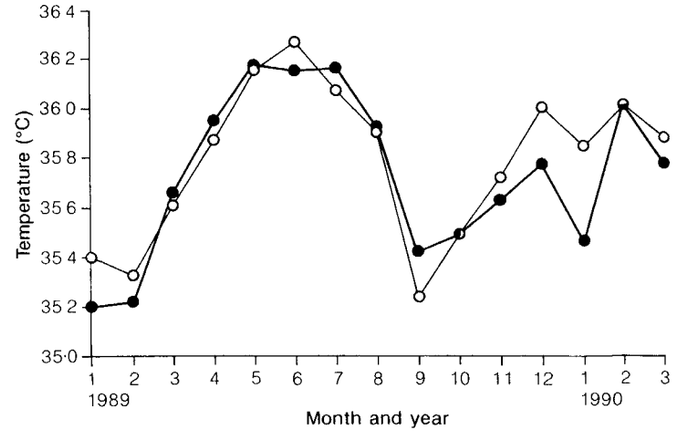

Fig 2—Core body temperatures.

—○—, Community; —●—, institution.

nurse visited again, retrieved the thermometers and the urine temperature measuring device, took a fasting blood sample, and measured blood pressure. For each individual for one day each month we obtained a series of readings of core body temperature, maximum and minimum temperatures in the home and in the environment (obtained from the Meteorological Office), blood pressure, and biochemical and haematological data from the blood sample.

Blood samples were analysed for C-reactive protein, plasma viscosity, haemoglobin, white cell count, platelet count, packed cell volume, plasma fibrinogen (by measuring clotting time of dilute plasma when thrombin is added[7]), blood glucose, cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein.[8] Blood pressure was measured by a Hawksley random zero sphygmomanometer and skinfold thickness by Harpenden's calipers.

32 subjects withdrew from the study either because they became ill or because they declined to have the study continued. Data from 68 subjects, on whom there were more than six sets of monthly results, were analysed. 85% of the study sample had ten or more readings of plasma fibrinogen, and 91% had 10 or more readings of plasma viscosity.

To test whether the season affected our results, data from the six coldest months of 1989 were compared with data from the remaining six months. The coldest six months identified from the mean monthly minimum temperatures supplied by the

TABLE II—RESULTS IN COLD AND WARM MONTHS

Variable	Cold 6 months	Warm 6 months	p
Seasonal effect			
Fibrinogen (g/l)	3·44 (3·35–3·53)	2·66 (2·60–2·72)	0·0005
Viscosity (cP)	1·73 (1·71–1·74)	1·69 (1·68–1·71)	0·002
HDL cholesterol (mmol/l)	1·23 (1·18–1·27)	1·14 (1·10–1·17)	0·001
No seasonal effect			
C-reactive protein (mg/l)	7·47 (6·28–8·65)	5·70 (4·83–6·57)	0·02
Cholesterol (mmol/l)	5·54 (5·41–5·68)	5·35 (5·23–5·47)	0·04
LDL cholesterol (mmol/l)	3·74 (3·61–3·86)	3·59 (3·48–3·69)	0·07
Haemoglobin (g/dl)	12·84 (12·70–12·99)	12·72 (12·58–12·86)	0·23
White cell count (×10⁹/l)	6·70 (6·48–6·91)	6·86 (6·55–7·17)	0·40
Packed cell volume	0·38 (0·379–0·387)	0·38 (0·377–0·385)	0·42
Platelet count (×10⁹/l)	268 (258–278)	271 (262–281)	0·63
Glucose (mmol/l)	5·49 (5·33–5·65)	5·69 (5·51–5·88)	0·11
HbA_1 (%)	6·80 (6·68–6·91)	6·79 (6·68–6·90)	0·94
Triglycerides (mmol/l)	1·33 (1·28–1·39)	1·34 (1·28–1·41)	0·86
Systolic BP (mmHg)	143·8 (142·1–145·5)	143·7 (141·7–145·7)	0·95
Diastolic BP (mmHg)	85·9 (84·6–87·3)	85·1 (83·9–86·2)	0·32

Mean (95% CI)

Meteorological Office were January, February, March, April, November, and December. An independent samples *t*-test was completed, and because of the multiple comparisons, a Bonferroni adjustment was made to the level of significance, which was set at $p < 0.003$.[9]

For each individual a regression between the monthly values of each variable measured against temperature was completed and the slope of the line calculated; this analysis incorporated data for the 15 months studied. The slope is a summary measure of an individual's responsiveness to temperature for each given variable. All slopes for each variable were plotted as a histogram, and a single sample *t*-test applied to determine whether the mean slope of the sample was significantly displaced from zero. Significance was set at $p < 0.05$. This is a simple and statistically valid method of analysing serial measurements.[10] To compare the effect of temperature on those living in their own homes with those in centrally heated conditions, mean slopes for subjects in each domestic environment were analysed by multiple regression analysis taking into account age, sex, and adiposity. Adiposity was calculated as the body mass index (BMI; weight/height^2), and fat distribution by both the ratio of waist to hip circumference and of subscapular to triceps skinfold thickness. Results for each measurement were divided into quartiles, and analysis of variance was applied to test for differences in the temperature slopes between the four groups. Data were analysed by the Superior Performance Software Systems Extended Version.

Results

Details of study groups are shown in table I. The maximum and minimum temperatures outdoors and indoors (fig 1) varied throughout the year with a maximum in July, 1989, and a minimum in March, 1989. Core body temperatures varied similarly throughout the year although the difference between summer and winter was less striking (fig 2). Mean core body temperature was significantly higher in the warmer six months than in the colder six months. There was a small but significant difference ($p < 0.0005$) between the internal temperatures of homes and institutions; temperatures in institutions were 2–4°C higher. There were no significant differences in urine temperatures between the groups (fig 2). Therefore, the two groups were analysed together.

Results for cold and warm half-yearly periods are shown in table II. Significant ($p < 0.003$) seasonal effects were found for fibrinogen (fig 3), plasma viscosity, and HDL cholesterol.

When the relation between temperature and each variable was calculated, the most consistent response and most significant displacement from zero in a negative direction was for fibrinogen ($p < 0.05$). Significant associations were found between fibrinogen and all measured temperatures: urine ($p < 0.05$), maximum ($p < 0.05$) and minimum

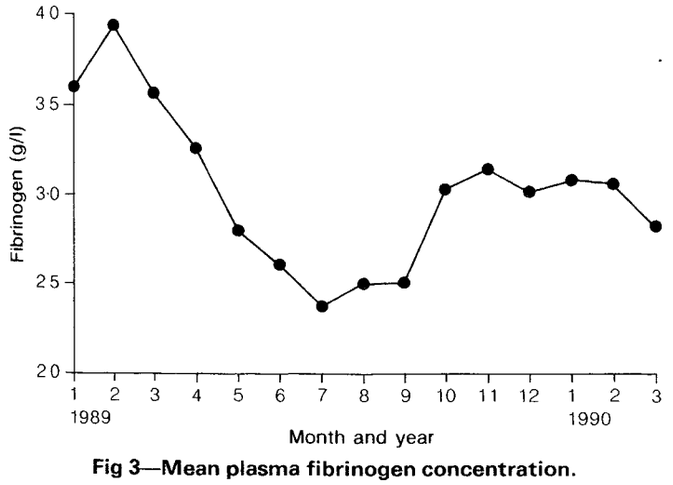

Fig 3—Mean plasma fibrinogen concentration.

TABLE III—INSTITUTIONAL VERSUS COMMUNITY ACCOMMODATION

—	Regression coefficient	p
Adjusted for	−0·019 (0·003 to −0·041)	0·064
Age	−0·029 (−0·007 to −0·051)	0·011
Sex	−0·021 (0·001 to −0·043)	0·058
BMI	−0·021 (0·001 to −0·043)	0·046
Age, sex, BMI	−0·032 (0·001 to −0·054)	0·006

($p < 0.05$) external ambient temperature, as well as maximum ($p < 0.05$) and minimum ($p < 0.05$) bedroom and living room temperatures (data not shown). Plasma viscosity and HDL cholesterol were also found to have seasonal variation according to temperature, but the changes were not as large as with fibrinogen and did not occur with all the temperatures that were measured. There was no significant displacement of mean slope from zero for blood pressure, glucose, haemoglobin, triglyceride, total cholesterol, LDL cholesterol, C-reactive protein, or white cell count, when compared with either environmental or personal temperature readings. The only variables that showed a significant displacement from zero with body-core temperature were fibrinogen, total cholesterol, HDL cholesterol, and C-reactive protein.

Effects of age, sex, and BMI on the relation of temperature to fibrinogen in community dwellers and those in residential homes and sheltered dwellings were examined by multiple regression analysis (table III). Those people who lived in institutions tended to be older with a greater proportion of women. When these differences were allowed for, those living in institutions had greater changes in plasma fibrinogen in relation to change in body temperature than those living in the community.

Our analysis also showed that the response of plasma fibrinogen to ambient minimum temperature seemed to decline with increasing age, and that this responsiveness increased with increasing BMI. Some of the effect of BMI on responsiveness was accounted for by age since older persons tended to be lighter, but accommodation had the greatest effect. A reduced responsiveness was noted in females compared with males, which could not be accounted for by either age or accommodation.

Discussion

The higher mortality rate in winter compared with summer, especially for myocardial and cerebral infarction,[11] has been known for some time. This effect is greater in older than younger age groups,[12] and there is an interval between change in temperature and death of 1−2 days for myocardial infarction and 3–4 days for stroke.[13]

The main finding in our study was a striking seasonal variation in fibrinogen concentrations that were 23% higher in the colder part of the year than in the summer months. There was a strong negative relation between both personal and environmental temperature and fibrinogen concentration. Plasma viscosity, to which fibrinogen is an important contributor, also varied with season and temperature, but the relation was not as strong as with fibrinogen. The small changes in cholesterol subfractions are unlikely to explain the greater frequency of cardiovascular disease in the winter. Seasonal changes in blood pressure were not found. No data have been reported for younger people. A cross-sectional study of people under 65 years of age found no seasonal effect on fibrinogen.[14] Older people often have impaired thermoregulation

compared with younger people,[15] and may be more prone to seasonal metabolic changes.

Fibrinogen is synthesised in the liver and is an acute phase protein.[16] Acute phase protein concentrations change in response to several stimuli, notably acute and chronic inflammation. Modest changes in temperature have not been described as initiators of an acute phase response. Minor infections, perhaps of the respiratory tract, are more frequent in colder months and may be related to both temperature and the acute phase response. However, a seasonal variation in white cell count was not found, which suggests that important infections were not more common in winter.

Prospective studies have shown that fibrinogen predicts the development of cardiovascular disease.[17,18] The risk in those with high fibrinogen concentrations is greater in younger than in older people,[18] although previously reported subjects were not as old as those in our study. The predictive effect of plasma fibrinogen on ischaemic heart disease and stroke was independent of other risk factors including serum cholesterol, blood pressure, and smoking. The differences in mean fibrinogen concentrations for those at low risk of cardiovascular disease and those at high risk in these studies are comparable with the differences in mean fibrinogen concentrations between winter and summer which we found in the present study.

There have not been any longitudinal studies of the effect of season and temperature on haematological and haemostatic factors, and no studies of any sort have been reported in older people. One report showed a positive correlation between air temperature and clotting factor VII, antithrombin III, and cholesterol, together with a negative correlation for fibrinolytic activity.[14] The correlations were all low and there was no association between temperature and fibrinogen. The subjects were all below 65 years of age. In a study of acute cooling in normal volunteers aged 18 to 25 years, six hours of mild surface cooling increased packed cell volume, platelet count, mean platelet volume, blood viscosity, arterial blood pressure, and both HDL and LDL cholesterol.[19] Large multicentre trials have reported seasonal variation in cardiovascular risk factors. The Lipid Research Clinics Coronary Primary Prevention Trial analysed seasonal variation in lipids and lipoproteins in 1446 hypercholesterolaemic 35–59 year old men who were members of the placebo group and who were followed for seven years.[20] Serum cholesterol concentration was significantly effected by the season and was 7·4 mg/dl higher in December than in June. Both LDL and HDL cholesterol showed similar seasonal effects, with mean seasonal changes of 6·4 mg/dl and 0·8 mg/dl, respectively. Triglyceride concentrations also showed a seasonal pattern but with slightly different periodicity compared with cholesterol subfractions. Cholesterol subfractions changed in a similar way in our study.

We did not find any seasonal variation in either blood pressure or glucose concentrations. This lack of association differs from previously published reports,[21,22] and could be accounted for by the different design of the study protocols although the exact reason remains unclear.

Low indoor temperatures seem to be an important factor in excess winter mortality.[5] Nevertheless, in the UK, elderly people living in centrally heated warden-controlled accommodation showed similar seasonal variation in mortality rates compared with those living in their own homes.[23] In this study, the temperatures of homes and subjects were not measured during the night. Keatinge suggested that the beneficial effects of heating were counteracted by subjects going outdoors on cold days. Furthermore, over a period of time when the proportion of households with central heating increased from 13% to 69%, excess winter mortality from respiratory disease declined by 69%, while excess winter mortality from coronary and cerebrovascular disease did not fall significantly.[24] Our study suggests that central heating may not greatly increase minimum indoor temperature or affect core body temperature at all. The greater change in plasma fibrinogen in relation to temperature for institutional rather than community residents may be because institutionalised individuals are frailer and less mobile.

The increase in fibrinogen concentrations in winter months may contribute to the higher frequency of cardiovascular disease reported in the winter. Further studies of the effects of age and temperature on the fibrinolytic system are needed to assess the full importance of the seasonal changes in fibrinogen. The role of thrombosis in the pathogenesis of acute myocardial infarction gives increased weight to our findings of changes in plasma fibrinogen concentrations. The contribution of thrombosis to stroke is not as well understood, but is likely to be similar to that of myocardial infarction.

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Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan

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The combination of measurements of regional cerebral blood flow (rCBF) and blood velocity in the middle cerebral arteries (MCA) by transcranial doppler sonography was used to investigate cerebrovascular involvement in migraine. Ten migraine patients with unilateral headache were studied during an attack and when they had been free of attacks for 5 days (non-attack). On both occasions they were given an intravenous infusion of sumatriptan (2 mg), a 5-HT_1-like receptor agonist, which relieved the symptoms within 30 min without affecting rCBF. The MCA velocity was normal on both sides on the non-attack day and on the unaffected side during the attack. However, during the attack the MCA velocity on the headache side was significantly lower than that on the non-headache side (45 *vs* 61 cm/s:mean difference 16·3 [95% confidence interval 10·3–22·3]; p = 0·02). The MCA velocity on the headache side returned to normal after treatment with sumatriptan and recovery. Since rCBF in the MCA supply territory was unaffected, the lower velocity can be explained only by dilatation of the MCA. The mean MCA diameter increase was estimated to be 20%. Thus, headache was associated with intracranial large arterial dilatation on the headache side. Sumatriptan predominantly had effects on the distended artery, which suggests that the 5-HT receptor system has a role in the pathogenesis of migraine.

Lancet 1991; **338**: 13–17.

Introduction

Attacks of migraine with aura are initiated by a focal reduction of regional cerebral blood flow, rCBF, which occurs most commonly in the posterior regions of one hemisphere.[1–6] The neurological symptoms of the aura can be related to areas of the brain with reduced tissue perfusion.[1–7] Although aura symptoms last for only 30–60 min, the focal hypoperfusion can continue for hours and is present during the succeeding headache phase.[5–8] Thus, headache is not causally related to increased rCBF. Migraine without aura is not associated with measurable changes in brain tissue perfusion.[5,6,9,10] However, a common feature of both types of migraine is the severe throbbing headache and associated symptoms such as photophobia, nausea, and vomiting. Methods of measuring rCBF actually measure tissue perfusion; this is regulated by the arterioles which account for more than 80% of the total cerebrovascular resistance. To explore further cerebrovascular involvement in migraine, we have combined rCBF recordings with simultaneous measurements of blood velocity in the middle cerebral arteries (MCA), by means of transcranial doppler.[11] The combination of these two methods allows semiquantitative estimation of changes in the diameter of the MCA. Treatment of the attack with the new rapidly acting antimigraine drug, sumatriptan (formerly GR43175)[12,13] allowed us to follow the cerebrovascular changes from the early phase of spontaneous migraine attacks and into complete remission.

Patients and methods

We examined ten migraineurs (eight women, two men; mean age 50 [range 36–73] years). Migraine was classified according to the Headache Classification Committee of the International Headache Society.[14] The patients were asked to telephone us immediately when the first symptoms of a migraine attack appeared. They were instructed to come to the hospital by taxi as quickly as possible. The rCBF equipment was therefore ready when the patient arrived. After the first series of measurements made during an attack, the patients returned for a series of "non-attack" measurements, at a time when they had been free from attacks for at least 5 days. The patients and control subjects consented to take part in the study after receiving full oral and written information. The study was approved by the Danish Health Authorities and the local ethical committee.

Two groups of healthy young volunteers served as controls: eight volunteers (two women, six men; mean age 23 [range 20–28] years) were examined three times on one occasion with the same regimen as the migraine patients, including sumatriptan infusion; rCBF was measured in all subjects, but transcranial doppler recordings of MCA velocity were done in only four. In the second group of ten volunteers (four women, six men; mean age 24 [range 20–29] years) rCBF and transcranial doppler of both MCAs were done twice with an interval of 160 min. These subjects were not given sumatriptan. They rested supine between measurements. They were studied to show the variability of the examined features in untreated healthy subjects.

At all examination points, transcranial doppler recordings were done straight after the rCBF measurements. During a migraine attack the first measurement was made as soon as possible after the

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