Review

Seasonal variations in coronary heart disease

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Summary

Coronary heart disease exhibits a winter peak and summer trough in incidence and mortality, in countries both north and south of the equator. In England and Wales, the winter peak accounts for an additional 20,000 deaths per annum. It is likely that this reflects seasonal variations in risk factors. Seasonal variations have been demonstrated in a number of lifestyle risk factors such as physical activity and diet. However, a number of studies have also suggested a direct effect of environmental temperature on physiological and rheological factors. We review the available evidence on seasonal variations in coronary heart disease and possible explanations for them.

Introduction

Seasonal variations have been observed in coronary heart disease (CHD), cerebrovascular disease and respiratory disease.¹ These are all characterized by a winter peak and summer trough. In England and Wales, the winter peak in coronary and cerebrovascular disease accounts for an additional 20,000 deaths per annum.² Higher winter rates of cardiac events have been demonstrated in both the northern and southern hemispheres.³⁻¹⁰

Consensus is lacking on whether seasonal variations in CHD mortality reflect variations in incidence or survival. Variations in admission rates and trial recruitment of patients suffering from myocardial infarction (MI) have been cited as evidence of a seasonal variation in incidence.¹¹⁻¹³ However, seasonal variations in death are greater than those in admission,¹ suggesting that survival also varies throughout the year. Although Enquselassie et al. demonstrated winter peaks in both CHD deaths and non-fatal MIs, CHD events were more likely to be fatal when the temperature was low.¹⁴ In the study by Enquselassie et al., temperature did not influence whether those deaths which did occur were sudden or occurred more than one day following the onset of symptoms.¹⁴ By contrast, Douglas et al.¹ demonstrated greater seasonal variations in out-of-hospital mortality than in-hospital mortality.

The seasonal variation in CHD incidence and mortality is likely to reflect seasonal variations in one or more risk factors. The risk factors proposed by investigators have included: (i) environmental factors such as temperature and ultraviolet (UV) radiation; (ii) lifestyle risk factors such as diet, obesity, exercise and smoking; (iii) other risk factors such as blood pressure, serum cholesterol level, coagulation factors and glucose tolerance; and (iv) acute and chronic infections.

Environmental risk factors

Temperature

The geographical variation observed in CHD mortality cannot be fully explained by differences in the prevalence of known risk factors.¹⁵,¹⁶ Therefore, it has been postulated that the residual variation may

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be due to differences in environmental temperature. This is supported by a positive association between CHD mortality and distance from the equator.\textsuperscript{15,17,18} Rose demonstrated that temperature changes could account for practically all of the seasonal variation observed in CHD deaths.\textsuperscript{13} Furthermore, there was no evidence of a threshold effect. Fyfe \textit{et al.} also demonstrated a strong negative correlation between mean monthly temperature and CHD mortality.\textsuperscript{19}

In some patients, angina is known to be precipitated by exposure to cold weather. Lower environmental temperature may exert a direct effect on the heart\textsuperscript{13,20–22} or have an indirect effect via changes in blood pressure.\textsuperscript{23}

Generalized cooling of the body surface of unclothed subjects has been shown to cause peripheral vasoconstriction and to increase cardiac output, blood pressure and circulating noradrenaline.\textsuperscript{24} In some subjects who suffer from angina, localized cooling of the face whilst wearing protective clothing can also cause peripheral vasoconstriction, bradycardia, an increase in forearm vascular resistance and a reduction in maximum exercise capacity.\textsuperscript{25,26} This response does not occur in normal subjects,\textsuperscript{27} nor after cooling of the abdominal skin of subjects with angina.\textsuperscript{25} The effect is thought to be mediated via the vagus nerve through a mechanism akin to the ‘diving reflex’ found in babies and some mammals.\textsuperscript{25}

Cold is associated with both a higher systolic and diastolic blood pressure.\textsuperscript{28–30} This causes an increase in oxygen consumption by the heart. In patients whose coronary circulation is already compromised this extra demand may produce myocardial ischaemia and, therefore, angina pectoris or MI. In Britain, winter blood pressures exceed summer blood pressures by around 5 mmHg.\textsuperscript{31} Sustained blood pressure differences of this order have been associated with a 21\% increase in CHD events.\textsuperscript{32}

A number of studies suggest that CHD mortality is more strongly associated with the amount by which temperature deviates from average rather than its absolute value.\textsuperscript{8,33,34} Also, pertinent are the speed at which temperature falls\textsuperscript{35,36} and the duration of cold weather.\textsuperscript{6,20,22,37} In addition to cold temperatures being implicated as a contributor to CHD mortality, an association with extreme high temperatures has also been demonstrated in a number of studies.\textsuperscript{33,34,38–45}

It has been suggested that temperature has a dual impact on CHD mortality. Extreme cold or hot temperatures at variance with seasonal norms result in an early increase in CHD mortality which peaks between 1 and 4 days after the temperature change occurs, while the sustained low temperatures normally associated with winter result in a general increase in CHD mortality over this period.\textsuperscript{6,8,20}

If the association between temperature and CHD is causal, temperature insulation should exert a protective effect. Seasonal variations in CHD mortality differ in magnitude across Europe. Variations are least in countries such as those of Scandinavia, which have strict building regulations, and Iceland, which has ready access to plentiful natural energy resources.\textsuperscript{36,47} In a study comparing six regions in Europe, CHD mortality was independently associated with low living-room temperatures, limited bedroom heating, a low proportion of people wearing hats, gloves and anoraks, and inactivity.\textsuperscript{48}

Despite the above evidence, a number of observations cast doubt on a causal association between seasonal variations in temperature and seasonal variations in CHD. Living at higher altitude is associated with both exposure to lower temperature and a reduced incidence of CHD.\textsuperscript{49–51} Also, the seasonal variations in CHD demonstrated in northern and southern hemisphere countries are also observed in equatorial countries where the temperature range is much lower.\textsuperscript{52} As a result, a number of investigators have suggested varying exposure to UV radiation as an alternative hypothesis.

### Ultraviolet radiation

Most of our vitamin D is synthesized by the skin following exposure to UV radiation. Several studies have demonstrated lower levels of vitamin D metabolites in subjects with CHD.\textsuperscript{10,53,54} Higher exposure to UV radiation in summer may, therefore, protect against CHD events.

CHD patients have been shown to have significantly lower levels of 25-hydroxycholecalciferol (25-HCC) in both the summer\textsuperscript{53} and winter.\textsuperscript{10} However, Lund \textit{et al.} demonstrated that the seasonal variations in 25-HCC present in normal subjects were less pronounced in those with CHD.\textsuperscript{53} Scragg observed some evidence of a threshold effect, with CHD risk decreasing from the bottom to second quartile of 25-hydroxyvitamin D3 level but plateauing thereafter.\textsuperscript{10} The association between vitamin D levels and CHD has been shown to be independent of smoking, body mass index, treatment for hypertension, vigorous leisure activity, total serum cholesterol and a previous history of angina or MI.\textsuperscript{10}

### Lifestyle risk factors

#### Diet and obesity

Body weight varies by season, with obesity being more common in winter months.\textsuperscript{55–57} This may in part reflect a higher fat intake in winter,
although some investigators have demonstrated no seasonal variations in dietary fat.\textsuperscript{59} Even in those studies which have demonstrated greater fat intake in winter, this has been insufficient to account entirely for seasonal variations in weight.\textsuperscript{55,56} suggesting that lower levels of activity may also be a factor. Vitamin C intake and levels are also lower in winter than in summer.\textsuperscript{60,61}

**Exercise**

Regular physical activity is associated with a reduced risk of CHD, but the benefits reduce within a few weeks of cessation.\textsuperscript{62–64} Many physical activities are only undertaken at certain times of the year and may, therefore contribute to the seasonal variation in CHD risk. In both sexes, overall levels of physical activity are significantly higher in summer than in winter.\textsuperscript{55}

Magnus \textit{et al.} demonstrated that physical activities such as walking, cycling and gardening only protect against acute coronary events if undertaken throughout the year. Activities undertaken on a seasonal basis conferred no significant benefit.\textsuperscript{66}

Whilst regular exercise is beneficial, unaccustomed exertion may produce a deleterious effect. In Toronto, coronary deaths in men under 65 years increased by 85\% following a snowfall.\textsuperscript{67} This was attributed to people unaccustomed to exercise being required to shovel snow. A number of studies have shown that more deaths have been associated with shovelling snow than would be expected from the time spent on this activity.\textsuperscript{68–72} Sudden deaths are more often associated with high levels of physical activity in cold temperatures than they are in warm temperatures.\textsuperscript{72}

**Smoking**

Entrican demonstrated seasonal variations in cigarette sales, with a large increase in winter.\textsuperscript{57} However, sales may or may not be indicative of consumption.

**Other risk factors**

**Serum cholesterol level**

It has been suggested that vitamin D may simply be a confounding factor in the association between cholesterol and CHD risk. High blood cholesterol levels confer an increased risk of CHD.\textsuperscript{73–75} Furthermore, the fact that CHD risk is reduced by lowering cholesterol levels suggests that this association is causal.\textsuperscript{76,77}

Cholesterol and vitamin D are structurally similar and have a common precursor: squalene.\textsuperscript{78} It has been postulated that the relative amounts of cholesterol and vitamin D produced may be influenced by exposure to sunlight, resulting in higher cholesterol levels in populations exposed to less sunlight.\textsuperscript{59} This is corroborated by the findings of a correlational study involving ten towns which demonstrated a strong positive association between latitude and mean blood cholesterol, and a strong negative association between hours of sunshine and CHD mortality.\textsuperscript{59} Further evidence is provided by the fact that a number of investigators have shown cholesterol levels are higher in winter and lower in summer.\textsuperscript{19,55,56,59,68–82} Keatinge \textit{et al.} demonstrated that mild body surface cooling produces significant increases in both low-density lipoprotein (LDL) and total cholesterol levels.\textsuperscript{23}

The theory linking sunlight exposure and CHD risk appears to be refuted by the finding that CHD mortality rates vary within relatively small geographical areas where climates are similar.\textsuperscript{83,84} Within these areas, mortality tends to be inversely associated with social class. It is usually assumed that this reflects differences in lifestyle risk factors such as cigarette smoking. However, CHD mortality is associated with social class gradient in Sweden, where cigarette consumption varies little by social class.\textsuperscript{55} Therefore, Grimes \textit{et al.} proposed an alternative hypothesis that the variations in CHD mortality were, in part, due to social class differences in sunlight exposure due to differences in garden ownership, affordability of holidays and participation in outdoor recreational activities.\textsuperscript{59} Seretakis \textit{et al.} suggested the complementary hypothesis that social class differences in CHD mortality reflect the inability of poorer people to control the temperature of their microclimates to the same extent.\textsuperscript{86}

**Coagulation factors**

A number of haematological parameters vary throughout the year, including haemoglobin level, erythrocyte sedimentation rate (ESR), haematocrit, fibrinolytic activity and the percentage of adhesive platelets.\textsuperscript{87–89}

\textit{In vitro} and \textit{in vivo} experiments suggest that a reduction in temperature results in increases in platelets, red cells, and viscosity and a reduction in plasma volume.\textsuperscript{90–93} The winter rise in fibrinogen concentrations is likely to be due to both lower temperatures and an increase in the prevalence of respiratory infections.\textsuperscript{90,93} The magnitude of rise in fibrinogen which occurs in winter is around half that attributed to smoking.\textsuperscript{90}

A possible link between coagulation factors and seasonal variations in CHD is supported by the fact that seasonal variations are also evident in cerebrovascular disease and venous thromboembolic disease.\textsuperscript{46,55}
Bull et al. suggested that the early increase in CHD mortality occurring within days of a fall in temperature may be mediated through thrombotic effects, while Keatinge et al. suggested that the sustained increases in blood pressure which occur in winter months may be attributed to increases in blood viscosity.

**Glucose tolerance**

Fasting blood glucose and insulin levels are lower in normal subjects in summer than winter.

**Acute and chronic infections**

**Acute respiratory infections**

Both CHD and respiratory infections demonstrate a winter peak. Cold temperatures increase the risk of respiratory infection through the suppression of immune responses and a direct effect on the respiratory tree.

Respiratory infections have been implicated as a contributor to seasonal variations in CHD mortality through two mechanisms. Firstly, respiratory infections may increase the risk of developing or dying from CHD. Secondly, patients with CHD may be more vulnerable to developing or dying from respiratory infections, and these deaths may then be attributed to CHD.

A number of studies have demonstrated an association between acute respiratory infections, such as influenza, and CHD. It has been suggested that respiratory infections increase the risk of arterial thrombosis through an increase in plasma fibrinogen and endotoxin inhibition of fibrinolysis.

Marshall demonstrated that the association between CHD and respiratory deaths was only significant in very elderly patients in whom coding of the cause of death was unlikely to be accurate. In many countries, CHD mortality and morbidity are between 30% and 50% higher in winter than in summer. This is of a similar magnitude to the decline in CHD mortality observed in these countries. Deaths due to respiratory disease have also declined but the decline has lagged behind that in CHD. Therefore, Cooper et al. concluded that the decline in respiratory disease was unlikely to have caused the decline in CHD mortality but may, in fact, have resulted from it, due to a decreasing number of susceptible individuals.

**Chronic infections**

Studies have suggested links between CHD and a number of specific microbial agents. CHD is associated with the presence of antibodies to both *Helicobacter pylori* and *Chlamydia pneumoniae*, and both bacteria have been detected in atherosclerotic plaques. The evidence for an association with cytomegalovirus or Coxsackie virus is weaker. Microbial agents may exert a direct effect on the endothelium or smooth muscle of the arterial wall, or have an indirect effect on plaque progression or rupture through changes in cross-reactive antibodies, lipid levels, or coagulation factors.

The evidence that any of these agents play a role in the seasonal variations observed in CHD is weak. *Helicobacter pylori* is associated with the development of peptic ulceration which, as with CHD, exhibits a winter peak. Moshkowitz et al. demonstrated a winter peak in levels of *Helicobacter pylori* and proposed a causal link. However, this is refuted by some other investigators.

**Susceptibility rhythms**

As previously mentioned, seasonal variations occur in places with very different climates. Smolensky et al. suggested that this could be explained if they resulted from susceptibility rhythms rather than environmental changes. He used as evidence the well-recognized hormonal and physiological changes which occur over 24-h and 28-day cycles. Some supporting evidence comes from the presence of circannual rhythms in a number of hormones including corticosteroids, catecholamines, thyroid hormones, and testosterone.

**Age and sex**

Seasonal variations are not consistent across age and sex groups. Winter peaks in CHD mortality increase with age. This is likely to reflect a combination of factors including poorer autonomic control, lower levels of physical activity, less use of protective clothing, greater time spent at home, and poorer household heating and insulation. Younger age-groups exhibit a spring peak in addition to the winter peaks seen in other sub-groups. This is particularly prominent in younger men.

**Time-trends**

Seretakis et al. demonstrated a time-trend in the seasonality of disease in the USA. Between 1938 and 1991, the winter-summer total death ratio declined by about 2% per annum. The decline was less in the more southern states where winters were milder. Seretakis et al. suggested that this is likely to reflect improvements in indoor and vehicular
heating and air-conditioning, and suggested that it may have contributed to the overall decline in CHD mortality.86

Conclusions
It is unclear whether the excess deaths which occur in winter reflect avoidable deaths or merely slightly premature deaths which would have occurred anyway within a short period of time. Identifying and rectifying those factors associated with seasonal variations will only impact on overall mortality if the former is true.

Clearly, emigration is not an option for most of those who have or are at risk of developing CHD. However, the evidence suggests that a number of simple precautions to reduce the risk of dying from CHD in winter could be taken. These include adequate indoor heating, wearing protective clothing, especially outdoor protection of the face, and of temperature with deaths from myocardial and cerebral infarction. Age Ageing 1975; 4:19–31.

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