Regional differences in coronary heart disease in Britain: do antioxidant nutrients provide the key?

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In Britain, there are large regional differences in mortality rates from coronary heart disease which can not be explained by established risk factors such as elevated levels of blood cholesterol or high blood pressure. These regional differences can to a large extent be explained by a cluster of inter-related factors: a poor diet lacking in fresh fruit and vegetables, cigarette smoking, and low socio-economic status. All of these factors are associated with a low dietary intake and hence a low blood concentration of antioxidant nutrients. Increased oxidative stress resulting from a low antioxidant status may therefore be the common mechanism by which these factors operate.

Introduction

Food technologists have long known about the involvement of free radicals in rancidity and 'off' flavours in food. More recently, there has been growing awareness among medical researchers of the importance of free radicals in normal human metabolism and disease processes. The mechanisms by which our immune system defends us against bacterial infection is mediated by free radicals as is the way our liver breaks down toxins. However, if production of free radicals, whether from normal 'house-keeping' systems or from environmental sources (eg smoking, radiation, dietary toxins) becomes so great that the body's antioxidant defence system can no longer cope, a state of 'oxidative stress' is said to exist. Oxidative stress has been implicated in more than 50 human diseases including coronary heart disease (CHD), cancer, diabetes, and rheumatoid arthritis[1]. The fact that the diet provides crucial ingredients of the body's antioxidant defence system (eg vitamins C and E, the carotenoids, and selenium) is leading to a renaissance of research into these micronutrients.

In Britain, the Ministry of Agriculture, Fisheries and Food (MAFF) have recognized that more information is needed about the biological significance of these nutrients and their optimal levels in the diet. The MAFF, as part of a Special Emphasis Programme, is funding a number of projects which are investigating diverse aspects of the antioxidant nutrients, many focusing on their relevance to CHD. It will be some years yet before the fruits of this research can be realized and published. This paper offers some background on why dietary antioxidant nutrients and oxidative stress might explain the high incidence of CHD in Britain.

Coronary heart disease in Britain

As in many industrialized countries, CHD is still the major cause of death in Britain. Particularly devastating in middle age, CHD accounts for more than a third of all deaths in men aged 45–64 and about a fifth of all deaths in women in the same age group[2]. Unlike other industrialized countries such as Australia and the USA, Britain has experienced a much slower and later decline in the coronary epidemic[3]. Considerable regional differences occur within Britain. Indeed, Scotland and Northern Ireland have among the highest CHD mortality rates in the world, and exhibit a 25% higher rate than England and Wales[2]. Even within Scotland, mortality rates vary two- to three-fold[4].

Why do such large regional variations occur? The answer is not only pertinent to Britain but should bring us closer to understanding the underlying causes of CHD. The Scottish Heart Health Study was designed in the early 1980s to try to explain these regional differences[4]. Data was collected from 10 359 men and women (aged 40–59) living in 22 Scottish districts. Established risk factors such as blood pressure and blood cholesterol levels did not account for the differences in CHD mortality[5], although they may still be important within a region[6]. We and other groups believe that the reason revolves around the antioxidant nutrients.

Fresh fruit and vegetables

If the classic Mediterranean diet with an emphasis on fruit, salad, and olive oil[7] is the ideal we should be striving towards, the antithesis is the traditional Scottish diet. Largely devoid of fresh fruit and green vegetables, the stereotypical Scottish diet is low in fibre, high in saturated fat and incorporates many fried foods. Habit,

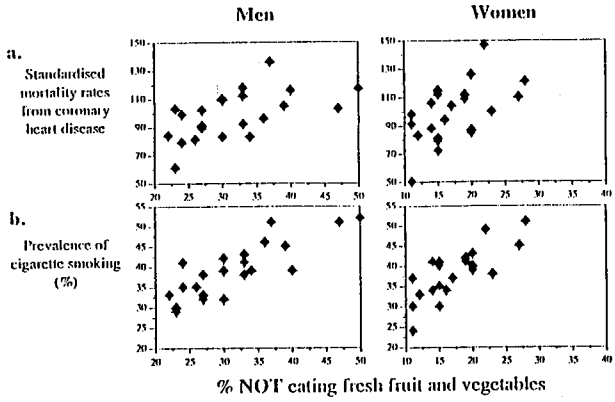

Fig. 1. Relationship between the proportion of people within a district who do not usually consume fresh fruit and vegetables and:

a. the district mean standardized mortality rate for coronary heart disease. Equations of lines of best fit: $y=1.24x+59.4$ (men: $r=0.56$, $p<0.01$); $y=2.39x+57.5$ (women: $r=;0.55$; $p<0.0$).

b. smoking prevalence in the district. Equations of lines of best fit: $y=0.738x + 15.9$ (men: $r=0.83, p<0.001$); $y=1.01gx+20.7$ (women $r=0.78$; $p<0.001$). Data for 22 districts were derived from the Scottish Heart Health Study[5]

expense, and lack of availability all contribute to the traditional Scots' low intake of fresh fruit and vegetables which are the best dietary sources of many of the antioxidant nutrients. Data derived from the Scottish Heart Health Study[5] show that standardized mortality rates from CHD for a given district are significantly correlated with the proportion of people who did not eat fresh fruit in the previous week or those who did not usually consume green vegetables (Figure 1a). Interestingly, lack of fresh fruit and vegetable consumption appeared to have a more pronounced influence on regional CHD mortality rates for women (slope=2.4) than men (slope=1.2).

The Scot's dietary lack of fresh fruit and vegetables is reflected in their low plasma levels of antioxidant nutrients. Compared to Italian men, beneficiaries of the Mediterranean diet, Scottish men on average had a 30% lower plasma vitamin E to cholesterol ratio[8]. Plasma vitamin E concentrations are generally expressed in relation to circulating cholesterol because they are transported in the same lipoprotein particles and are therefore strongly associated. Plasma concentrations of the principal water-soluble antioxidant, vitamin C, were also much lower in the Scottish men (mean=18.2μmol/l) compared to the Italians (mean=38.0μmol/l)[8]. Indeed, a third of the Scottish men displayed plasma vitamin C levels below 11 μmol/l indicating biochemical depletion and 15% were on the threshold of scurvy (<6μmol/l)[9]. Occasional cases of scurvy are still reported in Britain. The elderly, particularly men who live alone and eat a poor diet, are the most commonly affected[10]. Even in 'developed' countries, vitamin deficiencies have not yet been eradicated.

Dietary fat composition

Further data from the Scottish Heart Health Study on 20 of the 22 districts suggest that dietary fatty acid composition may also be important in explaining the regional variation in CHD mortality rates[11]. Regional CHD mortality rates were inversely correlated with the proportions of linoleic acid in adipose tissue (men $r=-0.62$, $p<0.01$; women $r=-0.64$, $p<0.01$). Co-ordinates from two districts, one with the highest CHD mortality rate and the other with the lowest, gave considerable weight to the correlation and when these were removed from the analysis, the significant association disappeared (men: $r=-0.25$, NS; women: $r=-0.26$, NS). Previous reports of the inverse relationship between adipose tissue linoleate and CHD risk[12,13] have been more convincing. Adipose tissue linoleate reflects long-term dietary intake of linoleic acid[14], the principal polyunsaturated fatty acid in the diet. However, because diets rich in polyunsaturated fatty acids also tend to contain large amounts of vitamin E[15], adipose tissue linoleate may merely be a proxy measure of long term vitamin E intake.

Dietary fibre

In the Scottish Heart Health Study, risk from CHD was significantly lower at higher intakes of fibre, β-carotene, and vitamins A, C, and E for men, but only lower for fibre in women[16]. CHD risk in this study was based on subjects who had been identified by the WHO Chest Pain Questionnaire and therefore were unlikely to have changed their lifestyle (diet, smoking habits, physical activity) at the time of interview as a result of medical advice. Diet was assessed by a food frequency questionnaire which was designed to target fibre intake[17,18] rather than consumption of antioxidant nutrients. Food intake methodology is notoriously fraught with difficulties[19] and dietary fibre is not a homogenous entity[20]. Moreover, fibre is thought to exert its protective influence on CHD principally by lowering blood cholesterol levels. However, the reduced risk of CHD with higher fibre intake observed in the Scottish Heart Health Study was independent of serum cholesterol concentrations[16]. Fibre itself may be an indicator of overall antioxidant nutrient intake, since the main sources of these nutrients (fruit and vegetables) contributed to about a half of total fibre intake[21]. Indeed, when the antioxidant nutrients (β-carotene, vitamins A, C, and E) were considered together, a significant improvement in CHD risk was seen in both men and women at higher intakes[16].

Cigarette smoking

Smoking, a classical risk factor, was strongly associated with CHD mortality rates in the Scottish Heart Health Study (men: $r=0.66$, $p<0.001$; women: $r=0.88$, $p<0.001$). Cigarette smokers have lower concentrations of antioxidant nutrients in their blood when compared to non-smokers. Plasma carotenoids such as α- and β-carotene, and β-cryptoxanthin are all lower in smokers than non-smokers as is the plasma vitamin E to cholesterol ratio[22]. Smokers also have a drastically reduced level of plasma vitamin C[21] and a higher ratio of oxidized to reduced vitamin C (dehydroascorbate: ascorbate)[23]. The lower levels of antioxidant nutrients seen in the blood of smokers results from a combination of two factors. Firstly, smokers tend to have a poorer diet than non-smokers as evidenced by the highly significant relationship between smoking prevalence and the lack of fresh fruit and vegetables in the diet (Figure 1b). Secondly,

smoking itself exerts many deleterious effects: each puff on a cigarette has been estimated to contain of the order of a million billion free radicals[24].

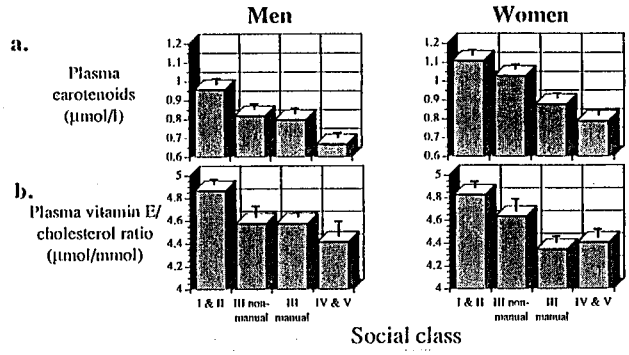

Fig. 2. Plasma concentrations of antioxidant nutrients by social class. Social class is based on the occupation of the head of household ranging from social class I (professional) to social class V (unskilled manual). Each column represents data (mean+SEM) collected from at least 120 subjects. Data were derived from the British Adult Survey[22]
a. Plasma carotenoids comprising β-carotene, α-carotene, lycopene, and β cryptoxanthin.
b. Plasma vitamin E to cholesterol molar ratio.

Socio-economic factors

Socio-economic factors also play a part in explaining regional differences in CHD mortality. In Britain, death from a wide range of diseases including CHD is unequally distributed between the social classes[25]. In the Scottish Heart Health Study, social factors like male unemployment and low social class explained most (73%) of the regional variation in CHD mortality[26]. Other studies have been fortunate if they could explain 50% of CHD mortality using a battery of classical risk factors[27]. Although social variables may tell us who is at greatest risk, they have limited value in revealing the aetiology of the disease. For that, more biochemical measures are required.

Results from the British Adult Survey[22] show that there was a downwards gradation in blood concentrations of antioxidant nutrients from professional (class I and II) to unskilled manual workers (class IV and V) (Figure 2). Furthermore, the unemployed had substantially lower concentrations of antioxidant nutrients in their blood than workers. On average, unemployed men had a 25% lower concentration of plasma carotenoids and a 14% lower vitamin E to cholesterol ratio. These differences again reflect a combination of lower intakes of antioxidant nutrients[22] and the destructive effects of smoking since smoking is more common among lower socio-economic groups[21,22].

The measure of social class based on the head of the household's occupation has been the focus of much criticism in recent years. Census data such as not having a car, overcrowding, and unemployment are better indicators of deprivation than social class, and offer a promising basis for explaining health differences[28].

Concluding remarks

CHD is a multi-factorial disease which has kept researchers guessing for more than a century. It is very doubtful that a single factor will every fully explain CHD, but antioxidant nutrients may come closer than the more established risk factors. Blood cholesterol levels and blood pressure do not account for the regional differences in CHD mortality observed in Britain. These regional differences can to a large extent be explained by a cluster of inter-related factors: poor diet, smoking, and low socio-economic status. Increased oxidative stress resulting from a low antioxidant status may be the common mechanism by which these factors operate.

This paper has focused on CHD in Britain but the conclusions may be equally applicable to other diseases and other countries (including Australia) where large variations in risk exist[25,29].

Many correlations have featured in this paper. Correlations are merely sign-posts pointing to possible research directions. More basic research is required to understand how the antioxidants function in health and disease on a molecular and cellular level. Novel approaches are required to reliably measure antioxidant status and oxidative stress. If these can distinguish between high- and low-risk groups (eg smokers versus non-smokers) they can serve as clinical end-points to test the efficacy of preventative and therapeutic regimens and may also be useful as diagnostic tools to assess disease risk in individuals[30]. Ways of screening foods and food additives for anti- and pro-oxidant activity also need to be developed. Research programmes like that initiated by the MAFF which bring together researchers, industry, and government, will build a solid foundation of science on which to base future dietary recommendations.

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英國冠心病的地區差异

摘　要

英國冠心病的死亡率有很大的地區差异，這不能用已建立的危險因素如血膽固醇升高或高血壓來解釋。這些地區差异在很大範圍內可用一群內部相關的因素來解釋：如缺乏新鮮水果和蔬菜的粗劣膳食，吸烟和低經濟收入等，所有這些因素是與低劣膳食，并引起血液抗氧化劑濃度降低相聯系。由于低抗氧化劑狀態而增加了人體的氧化壓力，這也許是冠心病地區差异的一般機理。