lactate content of blood in the coronary sinus the effects of fast atrial pacing have been studied in control patients (group 1). The change in the coronary-sinus lactate in 1 patient (7) was at the extreme for the group ($P<0.03$). It is therefore possible that he has significant obstructive coronary arterial disease to account for his atypical symptoms, and his clinical progress is being followed with interest.

In each of the patients in group 2, angina was precipitated repeatedly by a rising heart-rate caused by physical exertion. In the absence of other known pathological lesions it can be assumed that symptoms of myocardial hypoxia in group 2 were due to the presence of obstructive atheromatous coronary arterial disease. In 3 patients (20, 22, and 35) this had been confirmed by coronary arteriography. In 17 patients in group 2, angina was precipitated by fast atrial pacing, but in all the end-point of the pacing stress was paralleled by the development of abnormal myocardial lactate metabolism ($P<0.005$ in 3 patients; $P<0.0001$ in 15 patients). 6 of the patients who had an abnormal resting standard twelve-lead E.C.G. did not develop changes attributable to myocardial ischæmia on the exercise-test bipolar chest lead despite the evidence of abnormal lactate production.

In group 3, no patient had an abnormal standard twelve-lead E.C.G. at rest and none had changes in the bipolar chest lead during the exercise test. 15 patients (37, 38, 40, 41, 42, 43, 46–54) had a history of severe angina produced by physical exertion. As a result of fast atrial pacing each of these patients developed angina which was paralleled by abnormal myocardial lactate metabolism ($P<0.005$ in 12 patients). The apparent failure of the coronary-sinus-lactate studies to confirm the clinical diagnosis of I.H.D. in the remaining 3 patients (39, 44, and 45) was at first not understood until it was realised that their severe symptoms of typical angina occurred predominantly at rest in association with bradycardia. We think that angina in these patients resulted from tissue hypoperfusion due to severe bradycardia.[29]

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Requests for reprints should be addressed to S. O.

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ISCHÆMIC-HEART-DISEASE MORTALITY AND DIETARY INTAKE OF CALCIUM

E. G. KNOX

Health Services Research Centre, Department of Social Medicine, University of Birmingham, Birmingham B15 2TJ

Summary Correlation analysis was carried out between the standardised mortality ratios (S.M.R.S) for ischæmic heart-disease in different regions of England and Wales in different years and dietary intakes of a number of nutrients. Calcium intakes showed a strong negative correlation, consistent with variations between mortalities in hard and soft water areas. Fat and vitamin-D intakes both showed positive associations with residual variation of the mortality-rates after the effects of calcium had been excluded. Good pathophysiological explanations are available. However, examination of the correlations between different nutrients and S.M.R.S related to deaths from a range of other diseases showed a consistent pattern which was not at all specific for ischæmic heart-disease. The regional nutrient associations of ischæmic heart-disease are probably best explained as indirect effects.

Introduction

DEATH-RATES from ischæmic heart-disease in different parts of Great Britain vary according to the hardness of local water supplies, high mortalities being associated with soft water.[1] Soft water is also associated with high serum-cholesterol levels and high blood-pressures.[2–5] Attention to indirect social and demographic associations has so far failed to explain the correlations.[1]

Although the calcium content is the most obvious difference between hard and soft waters, there are several other actual or potential differences. Metal ions, including lead, may be present in higher concentrations in soft water than in hard, and there may be differences in organic content. Nevertheless, it seemed worth while first to examine the hypothesis of a direct effect of the calcium itself and to do this through

DR LIVESLEY, DR ORAM: REFERENCES—*continued*

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examining mortalities from ischæmic heart-disease in relation to regional variations in dietary calcium intake other than through drinking-water. This is the purpose of the present study.

Water hardness is usually expressed as parts per million (p.p.m.) of calcium, and different water-supplies in Great Britain range from very low values up to about 130 p.p.m. Parts per million is equivalent to mg. per litre, so that persons drinking 1·5 litres of water per day may obtain up to 200 mg. of calcium daily from this source, a substantial fraction of the total daily calcium intake from all sources. The mean calcium intake from food in England and Wales is about 1000 mg. per day and the mean calcium intake through water-supplies in Great Britain is about 50 mg. per day—about 5% of the total dietary intake. If the effect of calcium in drinking-water were simple and direct, we would expect quite small variations in dietary calcium to produce detectable effects upon mortality.

Materials and Methods

The National Food Survey of the Ministry of Agriculture, Fisheries and Food, on the basis of sample surveys, provides annual statements of mean daily intakes of a number of nutrients, for each of the standard regions of England and Wales.[6] These nutrients include total calories: grammes of protein, animal protein, fat, and carbohydrates; and amounts of calcium, iron, vitamin A, thiamine, riboflavine, nicotinic acid, vitamin C, and vitamin D. The Registrar General of England and Wales provides standardised mortality-ratios (S.M.R.s), by standard region, for a list of important diseases.[7] This includes "coronary thrombosis and ischæmic heart disease".

The boundaries and names of the standard regions of England and Wales have been changed from time to time; the usage of terms has not always coincided in the two sets of data; and there were also changes in methods of estimating nutrient intakes. It was necessary to choose a period during which the various changes were not too disturbing, and the years chosen were 1964–69 inclusive.

During this time several regions remained constant in the Registrar General's reports—namely, North, North West, South West, Wales I, and Wales II. Midlands changed its name in 1955 to West Midlands, and North Midlands to East Midlands. East lost part of its territory and became East Anglia. East and West Ridings gained some territory and became Yorkshire and Humberside. London and South East combined with South and were renamed South East. Unfortunately, the National Food Survey did not adopt these changes until later, and throughout the period it combined the two Welsh Regions into a single group, and East Anglia and South East into another, so that, so far as the nutrient intakes were concerned, there were only eight regions of England and Wales.

These difficulties were met by using the S.M.R.s most nearly appropriate to the food-survey regions and by combining subdivisions of regions, weighted according to relative population sizes. The inaccuracies of this procedure were small and resulted in an assembly of data for eight regions, over six years and each sex, to give a total of 96 ischæmic-heart-disease S.M.R.s, for entry to the analysis. For control purposes the analysis was later repeated using S.M.R.s for "all causes", and for five other diseases, each of which supplied another 96 S.M.R. values.

There were changes also in the presentation of the nutrient intakes, although several remained constant throughout, including total protein, animal protein, fat, carbohydrate, calcium, and iron. Vitamin-A values changed from international units (I.U.) to μg. retinol equivalents, and vitamin D also from I.U. to μg. (both in 1968); but it was possible in each case to calculate equivalents in terms of the earlier units. More fundamental changes were made in the method of estimating nicotinic acid, so that estimates of this nutrient were limited to the years 1964–67. In 1969 changes were made in the method of estimating thiamine, riboflavine, vitamin C, and vitamin D to allow for absorption fractions, and this necessitated their exclusion from the last year of the study.

Simple product-moment correlations and regression equations were computed between the S.M.R.s and each of the available nutrient estimates. For the ischæmic-heart-disease analysis particular nutrients were excluded in turn by standardisation; at each step the mortality was reduced to the excess (±) over the expected rates computed on the basis of the excluded nutrient, and the excess re-examined in relation to the other nutrients. This amounts to a crude step-by-step multiple regression exploration.

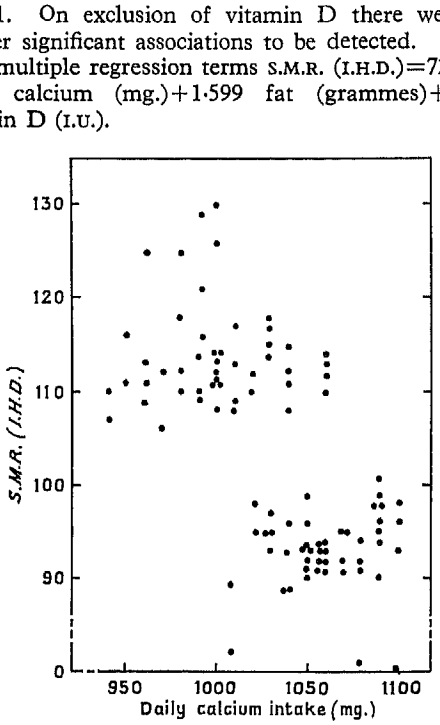
Results

Ischæmic Heart-disease

On the first correlation analysis several of the nutrients showed significant associations. The strongest was with calcium, which had a negative coefficient of −0·67. The accompanying figure illustrates the association between the calcium intakes and the ischæmic-heart-disease S.M.R.s.

The effect of calcium was then excluded through the process described above and the analysis repeated, again with several significant results. The strongest residual association was with fat intake, with a positive correlation coefficient of +0·56. The effect of fat was excluded in turn and the residual variation was found to be associated most strongly with the intake of vitamin D. The correlation coefficient was +0·31. On exclusion of vitamin D there were no further significant associations to be detected.

In multiple regression terms S.M.R. (I.H.D.)=72·01−0·176 calcium (mg.)+1·599 fat (grammes)+0·212 vitamin D (I.U.).



S.M.R.s for ischæmic heart-disease.

MATRIX OF CORRELATIONS BETWEEN S.M.R.s AND NUTRIENT INTAKES

Nutrients	Causes of death						
	All causes	Ischæmic heart-disease	Cancer of stomach	Diabetes	Cerebro-vascular disease	Hypertension	Bronchitis
K.cal.	+0·54	+0·44	+0·57	+0·27	+0·53	+0·63	+0·34
Protein	+0·29	+0·28	+0·29	+0·17	+0·29	+0·31	+0·16
Animal protein	−0·40	−0·33	−0·45	−0·34	−0·45	−0·29	−0·31
Fat	+0·25	+0·33	+0·28	+0·04	+0·23	+0·38	+0·06
Carbohydrate	+0·56	+0·38	+0·58	+0·33	+0·55	+0·61	+0·40
Calcium	−0·61	−0·67	−0·56	−0·24	−0·59	−0·02	−0·52
Iron	+0·37	+0·49	+0·37	+0·19	+0·39	+0·12	+0·17
Vitamin A	−0·04	+0·04	+0·09	−0·30	−0·16	+0·04	−0·08
Thiamine	+0·09	+0·07	+0·17	+0·17	+0·13	+0·35	+0·04
Riboflavine	−0·04	−0·04	−0·47	−0·33	−0·47	−0·19	−0·38
Nicotinic acid	+0·22	+0·28	+0·20	+0·01	+0·16	+0·09	+0·16
Vitamin C	−0·63	−0·49	−0·45	−0·19	−0·68	−0·13	−0·52
Vitamin D	+0·57	+0·58	+0·43	+0·12	+0·49	−0·16	+0·56

Other Diseases

The S.M.R.s selected for control purposes included "all causes", cancer of stomach, diabetes, cerebrovascular disease, hypertension, and bronchitis. The first-order correlations of each of these (together with that of ischæmic heart-disease), against each of the thirteen nutrients, is given in the accompanying table.

Discussion

Correlation analysis by large region is a crude technique which would scarcely have been justified in the absence of a strong prior hypothesis that calcium intake was related to ischæmic-heart-disease mortality, but the result of the initial analysis appeared to confirm the findings of the water-supply studies. Calcium showed the strongest of the 13 nutrient correlations with ischæmic heart-disease, and ischæmic heart-disease showed the strongest of the disease associations (among the controls chosen) with calcium intake. The correlation coefficient between ischæmic-heart-disease mortality and calcium intake was the second strongest encountered in the overall analysis. (The strongest was a negative association between cerebrovascular disease and vitamin-C intake.)

Progression to search for a second determining variable for ischæmic heart-disease was a highly tentative step, yet the finding of a strong positive association with fat intake made good pathophysiological sense. Indeed, it was only this fact which led to the search for a third associated variable. The association with vitamin-D intake was entirely unexpected, but again is capable of tentative pathophysiological explanations. Vitamin D is known to enhance the absorption of lead,[8] and, if lead absorption were postulated as a factor determining ischæmic-heart-disease mortality, one could readily see how vitamin D could enhance mortality, while both hard-water supplies and non-water dietary calcium could protect. If the multiple regression relationship were interpreted in direct biological terms such as this, it would imply the possibility of achieving very substantial alterations of ischæmic-heart-disease mortality through relatively simple dietary manipulations.

The chief reservations about conclusions such as these arise from the overall pattern displayed in the table. This table shows a broad consistency of nutrient correlations covering all the disease groups examined rather than a pattern specific to ischæmic heart-disease. Deaths from all causes and from each of the six specific disease groups are consistently, positively, and strongly associated with total calorie intakes, and with protein, fat, and carbohydrate intakes. The intakes of animal protein are correlated in a consistently negative manner. All the correlations with calcium and with vitamin C were negative; all those with iron and thiamine and all but one of those with vitamin D were positive. With respect to its calcium and fat intake correlations, ischæmic-heart-disease deaths did not differ substantially from deaths from "all causes"; nor indeed with respect to any nutrient.

The pattern suggests an overriding set of determinants, not specific for any individual disease but influencing all forms of mortality. It probably represents a long-established regional gradient of life style and social circumstance, associated only in a secondary manner with a variety of causes of death. For ischæmic heart-disease almost all the high S.M.R.s and almost all the low calcium intakes are located northwest of a frontier passing through the Roman legionary fortresses of York, Chester, and Caerleon-on-Usk.

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"The problem of the overdeveloped technostructure must . . . be a subject of profound public concern. We must recognize that we get weapons, automobiles, highways, space travel, in their present abundance not because we want or need them but because the planning system has the power to obtain them. . . . The Problem of the modern legislature is to allocate resources in accordance with the public need as opposed to the power of the planning system. If legislatures respond to the planning system, they will (as now) reinforce the positions of abundance in the economy. Only if they resist technocratic need and respond to the differing public need will they effectively enhance economic and public well-being."—J. K. GALBRAITH, *Proc. R. Soc. Med.* 1973, **66**, 559.