

PAPERS AND ORIGINALS

British Regional Heart Study: geographic variations in cardiovascular mortality, and the role of water quality

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Summary and conclusions

In a study of regional variations in cardiovascular mortality in Great Britain during 1969-73 based on 253 towns the possible contributions of drinking water quality, climate, air pollution, blood groups, and socio-economic factors were evaluated. A twofold range in mortality from stroke and ischaemic heart disease was apparent, the highest mortality being in the west of Scotland and the lowest in south-east England. A multi-factorial approach identified five principal factors that substantially explained this geographic variation in cardiovascular mortality—namely, water hardness, rainfall, temperature, and two social factors (percentage of manual workers and car ownership). After adjustment for other factors cardiovascular mortality in areas with very soft water, around 0.25 mmol/l (calcium carbonate equivalent 25 mg/l), was estimated to be 10-15% higher than that in areas with medium-hard water, around 1.7 mmol/l (170 mg/l), while any further increase in hardness beyond 1.7 mmol/l did not additionally lower cardiovascular mortality.

Thus a negative relation existed between water hardness and cardiovascular mortality, although climate and socioeconomic conditions also appeared to be important influences. Cross-sectional and prospective surveys of 7500 middle-aged men from 24 towns are in progress and will permit further exploration of these geographic differences, especially with regard to personal risk factors such as blood pressure, blood lipid concentrations, and cigarette smoking.

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Introduction

Over the past 20 years there has been considerable research into the relation between hardness of drinking water and cardiovascular disease.^{1,2} Although most studies have shown a negative association between water hardness and cardiovascular mortality, uncertainty remains about the magnitude of the effect and the extent to which other confounding factors such as climate and socioeconomic conditions might account for it. No convincing evidence exists showing which water parameters are responsible for the association. Thus whether there is a beneficial effect from bulk minerals (for example, calcium and magnesium) or a harmful effect from other minerals or trace elements (for example, sodium, lead, and cadmium) is unknown. Furthermore, it is not known whether the water effect is mediated by hypertension or some other risk factor for cardiovascular disease. Because of this uncertainty it has not been possible to recommend specific remedial measures.

The Regional Heart Study was undertaken to explain the substantial regional variations in coronary heart disease and stroke in Great Britain. The intention is to assess the role of environmental, socioeconomic, and personal risk factors on cardiovascular mortality and morbidity, with particular reference to the possible effects of water quality. The study falls into three main phases, although this report presents only the results and conclusions from phase 1.

PHASE 1

Cardiovascular and other mortality over five years around the 1971 census (1969-73) in 253 towns in England, Wales, and Scotland was related to a wide range of environmental, socioeconomic, and other data. Previous British studies examining the relation between cardiovascular mortality and water hardness have concentrated on the county boroughs of England and Wales.³⁻⁷ The present study, besides bringing research more up to date, also considerably expanded on this earlier work, since (a) it covered a much wider range of urban areas including Scotland, where cardiovascular rates are generally higher; (b) the water data were more detailed and reliable than previously; and (c) more extensive information on socioeconomic factors, weather, air pollution, and blood groups was incorporated.

PHASE 2

From the broad data of phase 1, 24 towns were selected to represent the wide distribution of cardiovascular mortality and water hardness. In each town over 400 men aged 40-59 years, selected at random from a collaborating general practice, are invited to attend for screening. A questionnaire is administered to each man, who is examined for a wide range of physical, physiological, and biochemical measurements. The principal objectives are as follows. (1) To examine the variation between towns in the distribution of established and possible risk factors for cardiovascular disease and to relate these variations to cardiovascular mortality rates. (2) To examine the relations between risk factors and variables of water quality and to see whether water quality affects cardiovascular mortality via any of the risk factors. The role of trace metals in tap water in relation to risk factors is also being studied by using a 12% sample of the subjects in each town.

Fieldwork, undertaken by a mobile team of three nurses, was begun in January 1978 and will be completed in June 1980. By December 1979 over 6000 men from 19 towns had been surveyed, the average response rate being over 75%.

PHASE 3

We aim at following up the 7500 men examined in phase 2 to record the incidence of cardiovascular morbidity and mortality. We can then determine which of the many individual risk factors are most strongly related to cardiovascular events and their behaviour under differing environmental conditions—for example, water hardness. In addition to the "usual" risk factors we shall examine plasma high-density lipoprotein and fatty-acid patterns, blood lead and cadmium concentrations, alcohol consumption, and drinking water quality. The records of all men are tagged at the Office of Population Censuses and Surveys for mortality follow-up, and a system of morbidity reporting has been introduced into the practices by using (i) a standard report card in each man's case records, and (ii) an annual review system. All men will have been followed up for at least five years by spring 1985, by which time we estimate that there will have been about 200 deaths from coronary heart disease, 200 cases of non-fatal coronary heart disease, and a total of 300 deaths from all cardiovascular diseases.

Phase 1 data

Towns—A total of 253 urban areas, henceforth referred to as towns, were studied. In England and Wales these comprised 83 county boroughs, 32 London boroughs, and 113 municipal boroughs and urban districts of which 32 were aggregates of adjacent small towns combined to achieve areas with a population over 50 000. Twenty-five Scottish cities and large burghs were studied: 15 of these had populations of under 50 000, but we thought it important to include all such Scottish towns in view of their higher mortality rates.

Mortality—For each town we obtained from the Office of Population Censuses and Surveys and the Scottish Registrar General the numbers of deaths from 42 different causes in each year (1969-73) by sex and 10-year age group. In this report we concentrate on cardiovascular mortality (excluding rheumatic heart disease) as defined by codes B27-30 in the B listing of the International Classification of Diseases (8th revision). We subdivided this into stroke (B30) and ischaemic heart disease (B27-29), the latter including hypertensive and other forms of heart disease as recommended for national and international comparisons.⁸ The population of each town by age and sex was obtained from the 1971 census to enable mortality rates and standardised mortality ratios (SMRs) to be computed for any combination of age, sex, and cause.

Water quality—Data on water were collected by making a special request to the water authorities and companies in England and Wales and to the Scottish regional councils, and by visiting every relevant division. The objective was to estimate, for each town during 1969-73, the mean concentrations of some 40 water constituents. The information used consisted of analytical results on water passing from each

source into the distribution system. The means were weighted according to the population served. Historical data on the quality of tap water were not available. Thus no direct information on lead, copper, and zinc concentrations could be obtained. Information was, however, obtained on the chemicals used in treating water and on the materials used in the distribution and plumbing systems in each town. Information on water was available for all but 18 towns in which the complexity of supply made estimation unreliable or data were not available. Moreover, data on certain water parameters were not obtainable for some towns. Initially, work focused on the following 23 variables: aluminium, calcium, carbonate hardness, chloride, ratio of chloride to carbonate hardness, conductivity, iron, Langelier index, magnesium, manganese, nitrate, non-carbonate hardness, orthophosphate, permanganate value, pH, potassium, silica (molybdate reactive), sodium, sulphate, total chlorine, total fluoride, total hardness, and percentage of water from upland sources.

Climate—Each town was linked to an appropriate nearby meteorological station and data were obtained from the Meteorological Office, Bracknell. In all, 164 stations were used, in some cases linked to more than one town. For each station data available for each year included the mean daily maximum and minimum temperatures; total rainfall, days with more than 0.2 mm rain, and days with more than 1 mm rain; mean daily hours of sunshine; and mean minimum daily temperature for January and December. The altitude, hilliness, distance from the sea, latitude, and longitude of each town were also included as being geographic measurements related to climate. More detailed meteorological data on 46 stations, including such factors as wind speed, wind chill, relative humidity, and atmospheric pressure, were also available as background data.

Socioeconomic factors—The Small Area Statistics from the 1971 census were obtained from the Office of Population Censuses and Surveys for each town. Initially 62 socioeconomic indicators were computed for each town, including the 40 variables used in the Webber and Craig socioeconomic classification of local authority areas.⁹ After some preliminary analysis and discussion with Richard Webber this list was reduced to the following 15 major socioeconomic variables: percentage of manual heads of household; percentage of unskilled heads of household; percentage with degree or equivalent among economically active persons; percentage in manufacturing employment; percentage unemployment in economically active men; mean social class score obtained from a ranking of socioeconomic groups and their distribution among heads of household in each town; number of cars per household; percentage of households with no inside toilet; dwelling size (number of rooms per household); percentage of owner-occupied households; proportion of large families (percentage of married couples with five or more dependent children); percentage of married adults; percentage walking to work; percentage of married women economically active; and persons aged 45-64 as a percentage of persons aged 15-64.

Blood groups—National Blood Transfusion Service data on the ABO distribution by postal districts were converted to obtain the ABO distribution for each town. B-gene frequency varies little geographically, so that the main interest was the relative frequencies of A and O genes, O genes being more common in Scotland.

Air pollution—Data on air pollution were obtained from the annual reports for April 1968 to March 1974 of the National Survey of Smoke and Sulphur Dioxide (Warren Spring Laboratory). Six-year means of smoke and sulphur dioxide values were computed for each town by including all reporting sites that were not wholly industrial. This was done for 134 of the towns, there being insufficient data for the remainder.

Diet, tobacco, and alcohol—No town-based data were available on diet, tobacco, and alcohol, but information was obtained for the 11 regions covering England, Wales, and Scotland. Sources included national surveys on food¹⁰ and expenditure¹¹ and the *General Household Survey*.¹²

Results

INITIAL IMPRESSIONS

In this study we concentrated initially on the SMRs for all cardiovascular disease in 1969-73 for men and women combined aged 35-74. The standard population used was the total of all 253 towns in the study, so that a SMR of 100 for a town would indicate that its mortality was the same as that for urban Britain as a whole. In view of the high correlation ($r > 0.90$) between mortality rates among men and women it seemed reasonable to consider both sexes together initially, though later analyses will relate to the separate causes

(stroke and coronary heart disease), sexes, and age groups. The combined SMR had a twofold range from 69 in the London suburbs of Chigwell and Esher to 147 in the Glasgow suburbs of Hamilton and Dumbarton: this indicates that in these parts of Glasgow there was a 47% excess of cardiovascular deaths compared with the norm for urban Britain. Figure 1 shows the map of SMRs and indicates an appreciable geographic variation with generally high SMRs in Scotland, south Wales, and north-west England and low SMRs in south-east England. Figure 2 shows the map of total water hardness for towns in the study: soft water predominated in Scotland, Wales, and north-west and south-west England. The softest water supplies were in Glasgow and the aggregate Colwyn Bay, Conway, and Llandudno in North Wales, while the hardest were in Hartlepool and Ipswich.

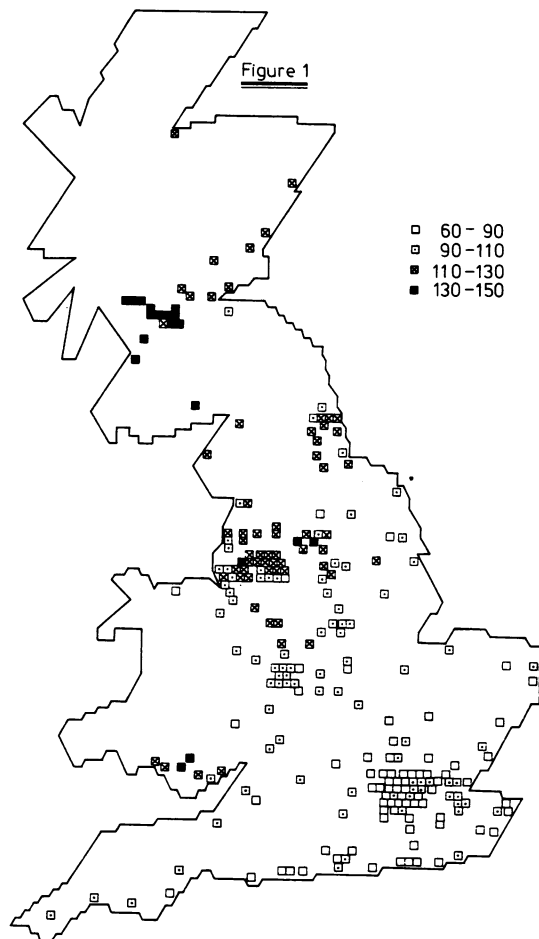


FIG 1—Standardised mortality ratios for cardiovascular disease in men and women aged 35-74. FIG 2—Total water hardness. Conversion: SI to traditional units—Water hardness: 1 mmol/l=calcium carbonate equivalent 100 mg/l.

Table I lists 24 factors studied here, each of which had a marked association with cardiovascular mortality. The influence of climate was especially relevant, since high rainfall and areas with soft water tended to coincide ($r = -0.70$ between total hardness and days with over 0.2 mm rain). Thus it would have been naive to conclude that the simple relation shown in figure 3 implied a causal effect of water hardness on cardiovascular mortality. Instead, such initial impressions merely substantiated the need to consider water hardness as one of many factors (environmental, socioeconomic, and personal) that might influence cardiovascular mortality. This multifactorial approach, which is crucial to any serious study of cardiovascular disease, was undertaken by constructing statistical models using multiple regression techniques. The results are presented below.

Total hardness was not the only water parameter associated with

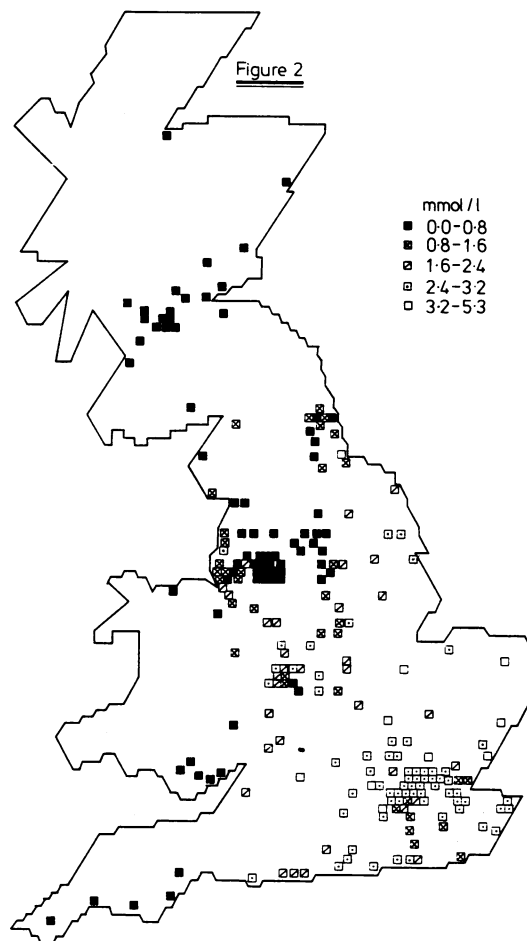


Figure 3 shows the association between the SMR and total hardness for 234 towns. Towns with soft water tended to have a higher cardiovascular mortality than towns with hard water, but there was a considerable scatter in SMRs at any given hardness. Exceptions existed: for instance, the North Wales aggregate with the softest water had a lower SMR (89) than Hartlepool (108), which had the hardest water. Nevertheless, all but one of the towns with SMRs over 120 had soft water (<1 mmol (100 mg)/l) and 95% of the towns whose water hardness was over 2 mmol (200 mg)/l had SMRs less than 100. Figure 3 shows clearly the problems inherent in studies comparing two towns. Pairs of towns might easily be selected that would show that towns with soft water have lower mortality rates than those with hard water, or that differing levels of water hardness are associated with the same SMR. For this reason replication of towns in terms of cardiovascular mortality and water hardness is an essential feature of phases 2 and 3 of the Regional Heart Study.

Although there is a statistically significant association between cardiovascular mortality and water hardness, the relation does not allow for the effects of other factors on cardiovascular mortality.

cardiovascular mortality. Each of the others, however, had a high correlation with total hardness, so that they did not necessarily give any extra insight into the specific nature of the effect of water. The correlation coefficients with total hardness were calcium +0.97, carbonate hardness +0.94, conductivity +0.93, % upland water -0.80, nitrate +0.77, silica +0.75, and Langelier index +0.73. In contrast, two water parameters (magnesium and sodium) that have previously been considered in relation to cardiovascular disease^{13 14} did not appear to have any obvious association with cardiovascular mortality in this study ($r = -0.13$ and -0.16 respectively). Nevertheless, these were only initial impressions, and the underlying relative importance of the various water parameters was assessed multifactorially.

THE MULTIFACTORIAL APPROACH

We considered the extent to which water quality, climate, socio-economic conditions, blood groups, and air pollution might

simultaneously explain the variation between towns in cardiovascular mortality rates. We used the logarithm of the SMR for all cardiovascular disease in 1969-73 for men and women aged 35-74 as the dependent variable in a multiple regression model. Thus the effects of the various factors on mortality were assumed to be multiplicative—that is, the proportional effect of one factor (for example, water hardness) was assumed to be the same for towns with high or low levels of another (for example, rainfall).

TABLE I—Factors associated with the standardised mortality ratio (SMR) for all cardiovascular diseases in men and women aged 35-74

Factor	Correlation coefficient with SMR	No of towns with data available
<i>Water quality</i>		
Total hardness	-0.67	234
Nitrate	-0.68	229
Calcium	-0.67	163
Langelier index	-0.65	159
Carbonate hardness	-0.65	232
Conductivity	-0.63	178
Silica	-0.58	146
% water from upland sources	+0.69	235
<i>Climate</i>		
Days with >0.2 mm rain	+0.75	253
Days with >1 mm rain	+0.73	
Total annual rainfall	+0.58	
Mean daily maximum temperature	-0.70	
Mean hours of sunshine	-0.53	
<i>Geographic</i>		
Latitude	+0.74	253
Longitude	+0.68	
<i>Socioeconomic</i>		
% manual workers	+0.64	253
% unskilled workers	+0.61	
Mean social class score	+0.63	
No of cars per household	-0.61	
% large families	+0.56	
unemployment	+0.53	
<i>Blood group</i>		
% A-gene frequency	-0.59	253
% O-gene frequency	+0.58	
<i>Air pollution</i>		
Mean annual smoke	+0.54	134

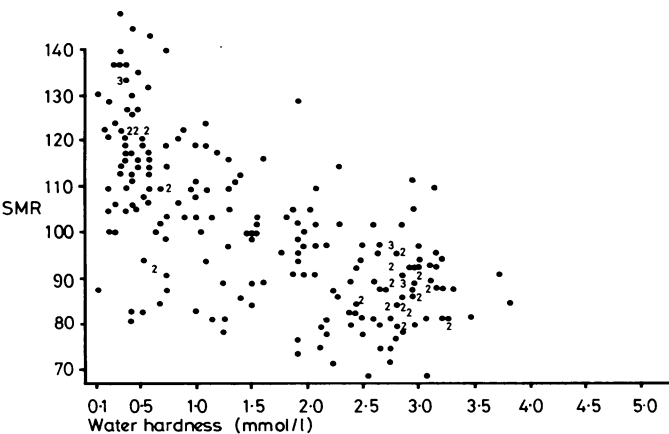


FIG 3—Water hardness plotted against SMR for all men and women aged 35-74 with cardiovascular disease for each town. (Water hardness: 1 mmol/l = calcium carbonate equivalent 100 mg/l.)

TABLE II—Details of five key factors related to geographic variations in cardiovascular mortality

	Mean	SD	Minimum	Maximum
Total water hardness (mmol)	1.70	1.09	0.10 (Colwyn Bay)	5.28 (Hartlepool)
% days with >0.2 mm rain	44.9	4.9	37 (Aylesbury)	58 (Greenock)
Mean daily maximum temperature (°C)	13.11	0.88	11.1 (Aberdeen)	14.6 (Southampton)
% of manual workers	60.5	11.8	30 (Epsom)	83 (Port Glasgow)
No of cars per 100 households	55.2	15.1	26 (Glasgow)	97 (Solihull)

Conversion: SI to traditional units—Water hardness: 1 mmol/l = calcium carbonate equivalent 100 mg/l.

We considered 23 water variables, six climatic variables, 15 socio-economic variables, two blood-group variables, and two air-pollution variables (all as defined earlier) as potential candidates in a multiple regression model. After testing many different regression models we concluded that there were five variables that collectively had a highly significant effect on the SMR—namely, water hardness, percentage of days with rain, mean daily maximum temperature, percentage of manual workers, and car ownership. The interpretation of these effects is discussed after a statistical description of the five-variable model. We also considered a few other variables that seemed to affect the SMR.

THE FIVE-VARIABLE MODEL

Table II shows some facts about each variable in the model. Multiple regression of log SMR on these five variables resulted in each having a highly significant regression coefficient (p < 0.001): rain and the percentage of manual workers had positive associations with cardiovascular mortality while water hardness, maximum temperature, and car ownership had negative associations. This means that each variable made a separate and important contribution to explaining regional variations in cardiovascular mortality, which could not be attributed to its association with other variables in the study. For example, the effect of water hardness could not be explained away by its correlation with rainfall.

Further investigation showed that the effect of water hardness was non-linear, being much greater in the range from very soft to medium-hard water than from medium to very hard water. Figure 4 shows the geometric mean SMR for cardiovascular disease for towns grouped according to water hardness both with and without adjustments for the effects of the four climatic and socioeconomic variables. (Analysis of covariance based on log SMR is the statistical method of adjustment, and geometric means arise as a consequence of this log transform, which eliminates skewness.) The adjusted SMR decreased steadily in moving from a hardness of 0.1 to 1.7 mmol (10 to 170 mg)/l but changed little in moving from 1.7 to 2.9 mmol (170 to 290 mg) or more/l. Importantly, adjusting for climatic and socioeconomic differences considerably reduced the apparent magnitude of the effect of water hardness.

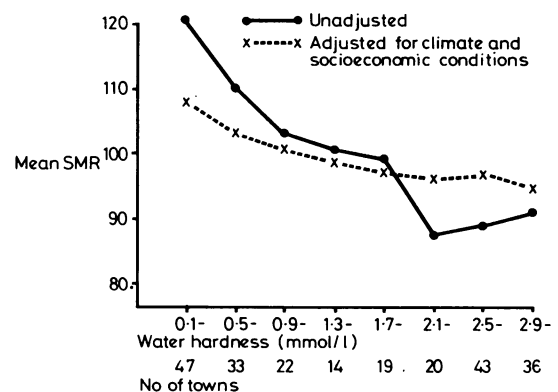


FIG 4—Geometric means of SMR (for all men and women aged 35-74 with cardiovascular diseases) for towns grouped according to hardness of water. (Water hardness: 1 mmol/l = calcium carbonate equivalent 100 mg/l.)

TABLE III—Regression of log (SMR for cardiovascular diseases in men and women aged 35-74) on five key variables, based on 234 towns

Variable	Standardised regression effect*
Water hardness:	
Up to 1.7 mmol/l	-7.8
Over 1.7 mmol/l	-0.8
Rain	+4.1
Maximum temperature	-3.0
% manual workers	+5.1
Car ownership	-2.9

*Defined as % change in SMR for a 1 SD increase in the variable, keeping all other variables constant.

Conversion: SI to traditional units—Water hardness: 1 mmol/l = calcium carbonate equivalent 100 mg/l.

Thus a better-fitting regression model was obtained by considering the effects of hardness on the SMR in two separate intervals, above and below 1.7 mmol (170 mg)/l, and the results are shown in table III. The standardised regression effects¹⁵ (defined as the per cent change in SMR for a 1 SD increase in each variable, keeping all other variables constant) give some idea of the relative importance of the variables. Thus the effects of all four climatic and socioeconomic variables were fairly similar but greatest for the percentage of manual workers and rainfall. Water hardness below 1.7 mmol/l had an even greater standardised regression effect, but for water hardness above this value the regression coefficient was not significantly different from zero.

INTERPRETATION OF THE MODEL

As regards water hardness, the model estimated that in the range below 1.7 mmol (170 mg)/l an increase in total hardness of 1 mmol (100 mg)/l—say from 0.5 to 1.5 mmol (50 to 150 mg)/l—while keeping the other variables constant should result in a 7.2% decrease in cardiovascular mortality (with 95% confidence interval 4.4% to 10.0%), whereas there was no evidence of an equivalent decrease beyond 1.7 mmol/l. Thus it might be argued that the maximal effect on cardiovascular mortality of water hardness lies principally between medium-hard and very soft waters and may be of the order of 10-15%.

The model accounted for 78% of the variance in SMRs, and figure 5 shows the actual SMR and the SMR predicted from the model for each town in the study. Some towns, especially in Scotland, had a

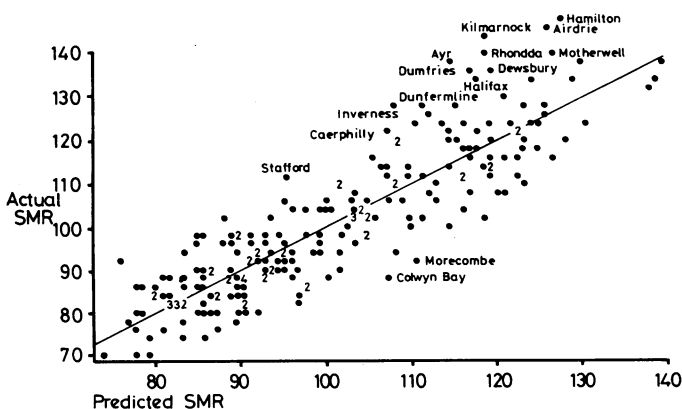


FIG 5—Actual SMR for cardiovascular diseases plotted against SMR predicted from five-variable model for 234 towns.

higher cardiovascular mortality than the model predicted. Furthermore, such towns tended to occur in geographic clusters, implying that there were some additional local factors that raised this mortality. More generally, adjacent towns tended to have similar death rates, and we intend to investigate further this geographic clustering in mortality and try accordingly to improve on our model.

In 163 towns data for water calcium and magnesium were available separately. Regression analysis indicated that magnesium did not correlate with cardiovascular mortality and that replacing total hardness by water calcium in the regression model only fractionally improved the prediction of SMR. This was hardly surprising, since calcium is by far the largest component of hardness, and in view of the missing data on calcium for some towns it seemed better to use total hardness in the model. Both carbonate and non-carbonate hardness seemed to have a separate, significant association with cardiovascular mortality, making their sum, total hardness, an appropriate measure.

After total hardness was included in the above five-variable regression model only one other water parameter showed any additional relevance to mortality—namely, the ratio of chloride to carbonate hardness. This is an indicator of water corrosiveness, especially with regard to zinc in brass fittings, and all five towns with the highest values (namely, Ayr, Dumfries, Kilmarnock, Halifax, and Dewsbury) had SMRs much greater than predicted (fig 5), while the five towns with the next highest values had SMRs slightly greater than predicted. Since chloride and sodium concentrations are related while

calcium and carbonate hardness are highly correlated, this relation might indicate that the relative balance of sodium and calcium in the water is relevant to cardiovascular diseases. Indeed, evidence exists¹⁶ that a combination of low calcium intake and high sodium intake might induce hypertension. Nevertheless, this finding should be interpreted cautiously and further study is needed.

There has been considerable speculation about why rain and temperature should be related to cardiovascular mortality.¹⁷ The cold weather might enhance the spread of viral infections or directly affect body temperature, either of which might precipitate cardiovascular events, and wet conditions might accentuate these effects. Furthermore, cold and wet weather predisposes to physical inactivity. In this respect, an American study¹⁸ showed that a "comfort index" combining temperature and humidity is strongly associated with cardiovascular mortality. Interestingly, the percentage of days with rain correlated better with the SMR than did total rainfall. The former has a high negative correlation with atmospheric pressure, a factor that has been negatively associated with cardiovascular mortality in Finland.¹⁹

The effect of socioeconomic factors—namely, percentage of manual workers and car ownership—was stronger than in studies conducted around 1951 and 1961. The higher cardiovascular mortality ratio in manual workers shown in 1971 occupation mortality data²⁰ is consistent with our finding that towns containing predominantly manual workers had higher SMRs. Car ownership is associated with income (for which we have no direct measure), skilled rather than unskilled workers, and outer rather than inner suburbs of conurbations; hence it is a composite measure of the relative prosperity and attractiveness of different urban areas. Thus a high proportion of manual workers and low car ownership in a town may reflect a generally unhealthy life style: since both are also strongly associated with non-cardiovascular mortality this seems plausible.

Differences in blood-group distribution between towns was the only other factor to show a possible association with cardiovascular mortality: the O-gene frequency expressed as a percentage had a significant partial correlation with the SMR for cardiovascular diseases after adjusting for the five variables in the regression model ($r = +0.21$, $p < 0.01$). Applying this result to individuals, however, would imply that blood group O has more than twice the cardiovascular mortality risk of blood group A, which is contradicted by studies of individuals with ischaemic heart disease.²¹ This doubtful blood-group effect arose because of the higher incidence of the O-gene in Scotland, and thus other features as yet not considered might help to explain further the high cardiovascular mortality rates in Scotland.²² For instance, data for 1969-73¹¹ indicate that expenditure on tobacco in Scotland was more than 20% higher than the British average, and since smoking is a well-established risk factor for cardiovascular diseases this might be an important difference.

Regional information on diet for 1969-73 was obtained from national food surveys.¹⁰ The average dietary intake of total fats in Scotland was slightly lower than that in south-east England and over 20% lower than that in Wales, giving no support to the suggestion that the high incidence of cardiovascular disease in Scotland is related to excess fat consumption.²³ This does not refute the role of high fat intakes in the development of ischaemic heart disease but indicates that they do not account for regional variations in cardiovascular diseases. The most noticeable difference in the Scottish diet was that consumption of fresh fruit and green vegetables was less than half that in south-east England, as reported elsewhere.²⁴ This finding might be related to the evidence that development of ischaemic heart disease may be associated with a deficiency of linoleic and linolenic acid,²⁵ both of which occur in high concentrations in fresh fruit and vegetables.²⁶

The simple association between cardiovascular mortality and air pollution, as measured by annual smoke levels (table I), was not sustained once other factors such as socioeconomic conditions were taken into account. The partial correlation between smoke and the SMR for cardiovascular mortality adjusting for the five variables in the model was not significant ($r = +0.02$).

SPECIFICITY OF RELATIONS

Whether the apparent effect of water hardness on mortality is specific to cardiovascular disease is important, since a more general mortality effect has sometimes been suggested.²⁷ Table IV shows that recomputing the five-variable regression on the SMR for non-cardiovascular mortality showed no effect for total hardness. The strength of effect on cardiovascular diseases, however, was sufficient to produce a significant relation between total hardness and total

TABLE IV—Regressions of mortality for stroke, ischaemic heart disease (IHD), and non-cardiovascular disease (non-CVD) on five key variables

Variable	Standardised regression effects*		
	Stroke	IHD	non-CVD
Water hardness:			
Up to 1.7 mmol/l	-6.8	-8.2	-0.1
Over 1.7 mmol/l	-3.0	+0.0	+0.0
Rain	+4.2	+4.3	+1.8
Maximum temperature	-7.5	-2.1	-0.4
% manual workers	+6.1	+5.0	+3.5
Car ownership	-2.2	-3.2	-6.5

*Defined as % change in SMR for a 1 SD increase in the variable, keeping all other variables constant.

Conversion: SI to traditional units—Water hardness: 1 mmol/l = calcium carbonate equivalent 100 mg/l.

mortality. Socioeconomic effects were of paramount importance in explaining geographic variations in non-cardiovascular mortality, whereas the effect of climate was much reduced.

Table IV shows that the effect of water hardness remained significant and of similar magnitude for both stroke and ischaemic heart disease. Water hardness above 1.7 mmol (170 mg)/l had a slight additional lowering effect on mortality from stroke, though the standardised regression effect (-3.0%) was not significantly different from zero ($0.1 < p < 0.2$). The climatic and socioeconomic effects also remained for these subdivisions of cardiovascular disease. The association between mortality and maximum temperature was greater for stroke than ischaemic heart disease. Further regression analysis showed that for men and women and for both age ranges 35-64 and 65-74 the effect of water hardness on geographic variations in cardiovascular mortality was of the same order of magnitude. The association between cardiovascular mortality and percentage of manual workers was greater in women than men, a finding compatible with a 1971 occupational mortality study.²⁰ Lastly, the negative association between cardiovascular mortality and car ownership was greater in the under 65s than the 65-74 age group, possibly implying that the extra risk of cardiovascular disease in less affluent areas is most evident in the younger age groups.

ARTIFICIALLY SOFTENED WATERS

Thirteen towns included in this study had over 90% of their water supply artificially softened. The softening process (either precipitation or ion exchange) had been operating for many years. Most of these towns were in south-east England, and although the water was softened, it was still harder than the upland waters in Scotland, Wales, and north-west England. The lowest levels of hardness of artificially softened water were 0.84 mmol (84 mg)/l in Dearne (Yorkshire) and 0.99 mmol (99 mg)/l in Leatherhead and Reigate (Surrey), while in six of these softened towns hardness was still above 1.7 mmol (170 mg)/l. We compared these 13 towns with adjacent towns with non-softened water matched for socioeconomic variables and found no increase in cardiovascular mortality. Indeed, Leatherhead, with softened water, had the third lowest mortality from cardiovascular diseases in the country. Given the relatively small estimated effect of soft water on cardiovascular mortality, which appeared to apply only below 1.7 mmol/l, it is not surprising that there was no effect of softening on cardiovascular mortality when only 13 towns were available for study.

Discussion

Our results show that after allowing for climatic and socioeconomic conditions a significant negative association remained between water hardness and cardiovascular mortality. This apparent effect of water hardness was present for stroke and ischaemic heart disease but not for non-cardiovascular disease. This study was more extensive and used more reliable data on water quality than previous studies of British regional variations in cardiovascular disease, and hence we were able to examine the form of the association between water hardness and cardiovascular mortality in greater detail. We concluded that the relation was non-linear; we estimated a 10-15% excess of cardiovascular deaths in areas with very soft water compared

with areas of medium hardness, say 1.7 mmol (170 mg)/l, while there was no evidence of any extra decrease in cardiovascular mortality at hardness beyond this value.

We do not claim to have identified the exact shape of the underlying curve for cardiovascular mortality plotted against hardness, but we believe that it may smoothly approach a horizontal line (that is, constant cardiovascular mortality) at some point around 1.5-2.0 mmol (150-200 mg)/l of hardness (fig 4). Rather than introduce more complex curvilinear regression methods, we thought that it was better to focus on 1.7 mmol/l, the mean level of hardness, as a convenient dividing point to show this non-linear effect.

One plausible explanation of this finding relates to the dietary intake of calcium. Thus, provided that total hardness was above 1.7 mmol/l, the intake of calcium and magnesium from water and food may have been sufficient to prevent any mineral deficiency related to cardiovascular risk. Indeed, at higher levels of hardness, as in Ipswich and Hartlepool, there may have been a considerable surplus intake of these minerals.

In this type of retrospective geographic study, no single water factor that is causing an increase in cardiovascular mortality can be isolated, since many of the water parameters are highly correlated with one another. Total hardness was the water factor that we used to show that the effect of water cannot be explained away by other environmental factors such as rainfall, though we could for example have shown this just as convincingly by using water calcium concentration or conductivity.

We expect that results from phases 2 and 3 of the Regional Heart Study will help to elucidate this relation further, particularly with regard to the role of trace elements in water (for example, lead and cadmium) and the possible effect of water factors on cardiovascular risk factors such as blood pressure.

Finally, the policy implications of this study should be considered. Given the following points, we do not consider that there is any immediate need for action regarding water supplies that are naturally soft, though the situation should be kept under review pending further research findings. (1) Clinical trials for the prevention of cardiovascular disease generally aim at a much greater—say 20% or more—reduction in mortality; (2) the potential risks from smoking, hypertension, hypercholesterolaemia, and physical inactivity are far greater than the apparent risk from drinking soft water; (3) there is at present no accepted physiological explanation for the relation; and (4) the nature of the "water factor" and duration of exposure necessary to produce an effect are both unknown. Our results have somewhat clarified the position on artificially softening water supplies, since we found no increase in cardiovascular mortality in 13 towns with softened water. Moreover, the evidence that there is no cardiovascular mortality gradient down to a water hardness of around 1.7 mmol/l gives additional support to the argument that softening to such medium hardness is acceptable. Whether it is acceptable to soften drinking water below this level, however, either at source or by domestic installations, remains uncertain.

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Humoral immune response in children with iron-deficiency anaemia

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Summary and conclusions

The humoral immune response (as shown by plasma immunoglobulin concentrations and antibody response to diphtheria and tetanus toxoids) was evaluated in 14 children with iron-deficiency anaemia and in 24 normal controls. Mean concentrations of haemoglobin and serum iron and mean transferrin saturation were significantly lower in children with iron-deficiency anaemia than in controls. Serum immunoglobulin concentrations were within the normal range in both groups. Two weeks after immunisation with diphtheria and tetanus toxoids the concentrations of IgG increased significantly in both groups. Antibody titres in iron-deficient children were similar to those of controls before and after immunisation. The mean T-lymphocyte count was significantly lower in iron-deficient children than that in controls, but the mean B-lymphocyte counts were similar in the two groups.

These observations suggest that humoral immunity in children is not affected by iron deficiency and that conventional immunisation programmes would be effective in children with iron-deficiency anaemia.

Introduction

Iron-deficiency anaemia is widely prevalent in many groups of the Indian population, particularly children and pregnant

women. There is increasing evidence that iron deficiency can affect host defence mechanisms.¹⁻³ Earlier studies from these laboratories have shown that the cell-mediated immune response and bactericidal activity of leucocytes were impaired in children with haemoglobin concentrations of under 10 g/dl. After iron supplementation, haemoglobin concentrations and immune functions were restored to normal.⁴⁻⁵ We report here on the humoral immune response in children with iron-deficiency anaemia.

Subjects and methods

We studied 14 children with iron-deficiency anaemia, and 24 apparently normal children served as control subjects. Their ages ranged from 2 to 10 years. Their weights were over 80% of the appropriate standard.⁶ Fasting samples of blood were collected for the estimation of haemoglobin concentration, packed cell volume, plasma iron concentration, and transferrin saturation. Informed consent was obtained from the parents of the control subjects before the samples were taken. Children were considered anaemic if their haemoglobin concentrations were 11.0 g/dl or less, as suggested by the World Health Organisation expert group.⁷ Plasma albumin concentrations were estimated to enable us to exclude the effects of associated protein and energy malnutrition. Haemoglobin concentrations were determined by a cyanmethaemoglobin technique,⁸ plasma iron concentrations and total iron binding capacities by the method suggested by the International Committee for Standardisation in Haematology,⁹ and plasma albumin concentrations by the dye method using Bromocresol green.¹⁰ Plasma vitamin B₁₂ and red blood cell folate concentrations were assayed microbiologically using *Euglena gracilis* (Z strain)¹¹ and *Lactobacillus casei*¹² respectively.

Humoral immune response was assessed by determining the following variables: plasma IgA, IgG, and IgM concentrations (determined by the radial immunodiffusion technique¹³); and rise in titres of antibody to diphtheria and tetanus toxoid two weeks after immunisation (determined by the indirect haemagglutination method¹⁴).

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