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EPIDEMIOLOGICAL STUDIES OF HEALTH EFFECTS OF WATER FROM DIFFERENT SOURCES

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WATER HARDNESS AND CARDIOVASCULAR DISEASES

Cardiovascular Mortality and Hardness of Drinking Water

The multicausal nature of cardiovascular diseases (CVD) is well established and clinical factors such as hypertension and hyperlipidemia, as well as behavioral factors like overnutrition, smoking, physical inactivity, and stressful living, play a predominant role in their etiology and pathogenesis. Nevertheless, attempts were made to correlate the geographic distribution of CVD with the characteristics of the geological and geochemical environments, particularly the chemical composition of the water.

The first evidence of a direct connection between human health and water composition was presented by Kobayashi (41) in Japan, where death rates from cerebral hemorrhage were found to be directly correlated with the SO_4/CO_3 content of the river waters in the various districts of that country. After Kobayashi, a number of investigators in several countries have reported relationships between the quality of drinking water and mortality, particularly from CVD. The abundant literature in this field has been reviewed by several authors (15, 16, 50, 58, 60, 78, 80).

Many studies (4, 20, 21, 46, 50, 62, 70, 72, 75, 83) have reported a negative association between water hardness and mortality rates from arteriosclerotic or coronary heart disease (CHD), from hypertensive heart disease, or sudden deaths attributable to CHD. That is, areas served by relatively hard waters experienced lower deaths rates from these diseases.

A WHO study of 15 European cities (50) showed a negative association between water hardness and incidence of heart attacks, in both males and females (Figure 1).

Preliminary results from an ongoing survey by the US Environmental Protection Agency to measure the association between mortality rates and mean inorganic chemical constituents of drinking water in 35 geographic areas in the US show that "hardness and calcium appear to follow the normal trend of negative associations with mortality rates for most groups of cardiovascular disease . . . " (29).

The negative association is more evident in the studies that covered very wide geographical areas and involved large numbers of people. On the other hand, smaller studies comparing, for instance, districts within the same town, or counties within the same state or province, or comparing a few cities among themselves, often produced contrasting results (7, 8, 40, 43, 51, 53, 54). Some revealed a negative association whereas others revealed no association at all.

Studies in such small areas are indeed likely to be influenced by the small population size and by such factors as the use of water softeners in the home. Some of these small-scale studies, which initially failed to show any consistent association, were later expanded or revised by the same or other authors and negative associations did result (39, 55, 90).

Although all the studies mentioned above dealt with treated municipal water supplies, the influence of broader geochemical environmental factors as expressed by data on raw river waters was also investigated.

Following Kobayashi (41), who found a parallel between the geographic distribution of apoplexy and the acidity of river water in Japan, Masironi (46) examined the cardiovascular mortality rates in populations living along four rivers in the US, the Ohio, Missouri, Colorado, and Columbia rivers, which contrast in water hardness. Mortality rates from hypertensive heart disease and, less markedly, from arteriosclerotic heart disease were significantly lower in the populations living along the hard-water Colorado river than in the populations living along the soft-water Columbia and Ohio rivers. The non-cardiovascular mortality rates did not differ in the four areas.

The choice of primitive communities living in a relatively isolated area with very little exposure to industrialization is likely to ensure a closer relationship between the population and the geochemical environment. One such community was found in New Guinea, and blood pressure was measured in villagers living along the banks of the Wogupmeri river. These villagers subsist on a non-cash economy and drink the river water. The mean content of the water decreases downstream from about 8 to about 3 ppm as the river flows away from the limestone mountains where it originates. Contrary to this trend of decreasing Ca content in water, the mean of the blood pressure measurements taken in inhabitants of the 11 villages was found to increase from 97 to 110 mm of Hg (48).

Water Components and Their Significance to Human Health

Although calcium and magnesium will usually account for essentially all of what is known as "water hardness," some waters can contain appreciable amounts of other metals that can contribute significantly to hardness. Monovalent metallic ions such as sodium, potassium, and lithium, however, do not contribute to water hardness (30).

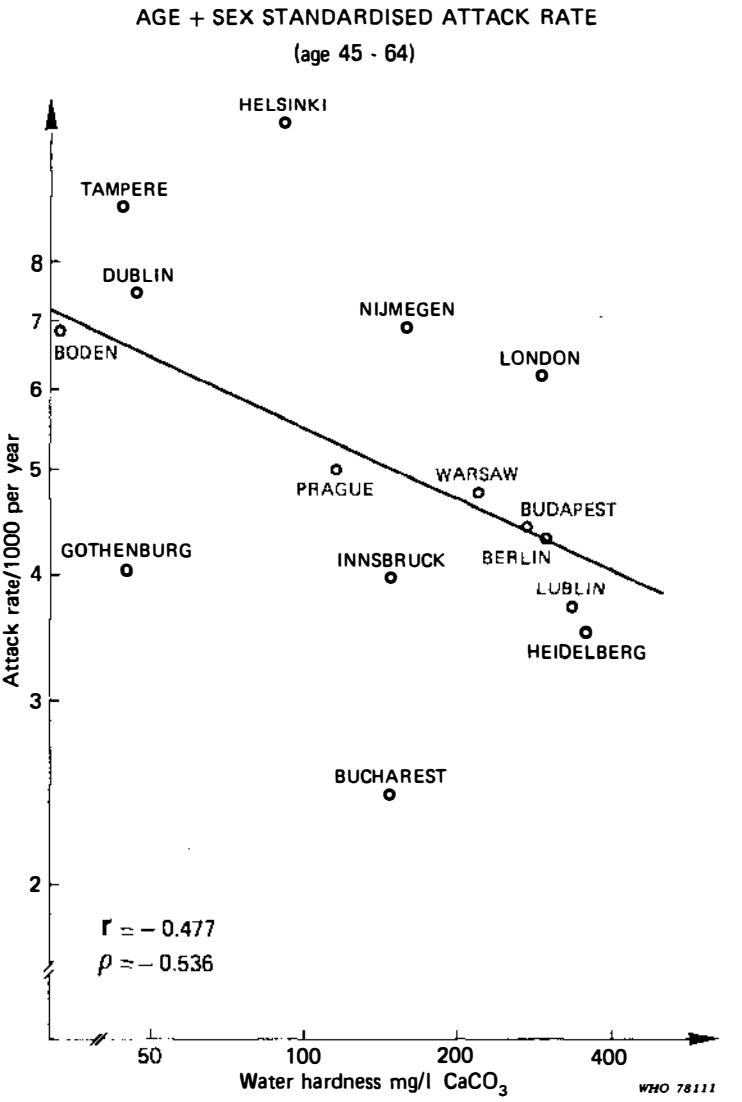

Figure 1 Age and sex standardized myocardial infarction attack rates in relation to drinking water hardness in European cities.

There is general agreement that a water with total hardness of less than 75 mg/liter (expressed as $CaCO_3$) can be classified as soft, whereas waters with more than 100 mg/liter can be regarded as hard. A total hardness above 200 is usually regarded as very hard (45). Water hardness measurements, however, do not necessarily provide useful information about respective concentrations of calcium, magnesium, and other metals that

contribute to hardness. Thus, it is not surprising that waters can have a similar total hardness, yet can have very dissimilar concentrations of calcium and magnesium.

Soft waters are easier to use as they require less soap, cause less scaling of pipes, leave fewer stains, etc, but they are corrosive, i.e. dissolve metals from distribution pipes.

In a survey of Canadian domestic waters, Neri et al (61) have shown that soft tap waters tend to leach cooper, zinc, and cadmium from piping systems, whereas this does not occur to a significant degree in hard waters.

Water hardness may simply be an indicator of other environmental conditions (e.g. climate, degree of urbanization, etc), and some authors have suggested that it may be these that have a direct effect on heart disease. Nevertheless, postulating a direct relationship between water hardness and CVD, several mechanisms of action are possible. Soft waters could be carrying trace levels of toxic elements from pipes or soil into supply; hard waters could be protective due to their content in Ca and Mg or in beneficial trace elements.

Schroeder (74) speculated that cadmium, dissolved from galvanized pipes, could be causing hypertension and might be the harmful water factor. Other authors (34, 65, 87) considered that hard waters might be protective due to their higher content in lithium, iodine, or chromium. It seems unlikely that any one element could explain the various findings in different areas and much more data on trace elements in drinking water are needed to see if any pattern emerges.

The possibility that the hard waters may be protective due to their bulk mineral content must be considered. Calcium, magnesium, and sodium are the main cations in drinking water, and of these, lack of calcium in the water is the most closely associated with mortality in some studies, particularly those carried out in the UK, whereas lack of magnesium was found to correlate better in studies done in the US and Canada.

The health significance of chemical elements in drinking water depends not only on adverse effects due to their presence or excess, but also on possible adverse effects due to their decreased concentration.

Evidence is accumulating that the chemical composition of the drinking water in terms of naturally occurring inorganic elements may be of nutritional interest. So far, the belief was widely held that water could not be a significant source of minerals since the human organism gets all of its mineral requirements from food that contains much higher concentrations than does water, but this attitude is now being challenged.

Drinking water is not only the water people actually drink, it is also the water used for cooking and for preparing food. The chemical composition of the water used for cooking influences the chemical composition of the food eaten. If water is poor in minerals, as is the case when it is naturally

or artifically softened, the food cooked in it would lose minerals, and vice versa, food would gain minerals when cooked in hard water.

The human body takes in a substantial amount of water, about 2 liters, and more in hot climates. Among European countries, tap water consumption is very high in Italy, i.e. 420 liters per capita per year, whereas in the other European countries consumption is only 70 liters (94). Water is not the only form in which the human body makes up its liquid balance. However, tap water makes up a substantial amount of it, about 60%. Therefore, even if the concentration of chemical elements in water is very low, the total amount ingested through water is not irrelevant, and this amount may make the difference between optimal and suboptimal intake of desirable substances and may lead to excessive intake of undesirable ones. Interactions between the elements themselves, as well as interactions with food components, may reduce or enhance their biological availability and their health effects.

Some minerals may be absorbed more easily by the gastrointestinal tract when administered through drinking water rather than through food. For instance, some organic substances in food bind certain minerals. Such binding may, in turn, interfere with the absorption of the minerals in the gastrointestinal tract (93).

Because of the amount taken in, as well as of the free, ionic easily absorbable form in which the chemical elements are present, water is a source of trace and major elements in human nutrition that cannot be disregarded. This is particularly true as far as Li, F, Ca, Cu, Mg, Fe, and Zn are concerned. According to some authors (94), more than 10% of the human daily need for these elements may be supplied by tap water.

This amount would not be very important in situations of abundant mineral intake from foods, but in the case of marginal mineral deficiencies, a 10% additional intake may make all the difference between life-long suboptimal and optimal status of health.

CALCIUM Crawford & Crawford (17, 19) postulated a protective effect of calcium against lead absorption in soft-water areas as well as a more complex mechanism involving the ratio of magnesium plus calcium to sodium. Joosens (38) and Langford et al (42) considered sodium as the noxious element, whereas calcium exerted a protective action.

According to Crawford (17), water calcium could be important in two ways. First, it might act by inhibiting the absorption of toxic elements from pipes and soil. Hard water is not as corrosive as soft water and therefore there is much less leaching of potentially harmful metals from water pipes, such as lead, copper, and cadmium. Calcium in the water plays a predominant role in this protective effect. Schroeder (71) has shown that the absorp-

tion of trace elements such as lead, cadmium, zinc, chromium, etc, is inversely related to the concentration of calcium in the medium. In drinking water, therefore, it may be more meaningful to look at the concentrations of trace elements relative to that of calcium rather than to absolute values. Moreover, calcium might decrease the absorption and the transfer of toxic ions from the intestine to the blood (42a, 71). Second, it might constitute an effective addition to dietary calcium. There is controversy concerning the contribution that water calcium makes to total calcium intake. Although the calcium intake is overwhelmingly from food, certain population groups living on calcium-poor diets may obtain a substantial amount of calcium from drinking water. According to Crawford (17), in the UK the difference in calcium intake between hard- and soft-water areas could amount to 2 g per day, and this amount would be meaningful. It is estimated that less than 30% of the calcium ingested through food is absorbed, and if factors that affect absorption are taken into account, the importance of water as a source of calcium may be greater than has been realized.

At low levels of calcium intake magnesium metabolism is altered, and Raab (67) speculates that derangement of intramyocardial electrolyte exchange plays a crucial role in the pathogenesis of the many syndromes involved in degenerative heart disease. The proportion of dietary calcium supplied by drinking water depends on its concentration in the water. Assuming an intake of 2 liters per day, the proportion of dietary calcium provided by the water of 21 major European cities was found to be 17%, with a range of 2–28% (94).

MAGNESIUM Magnesium provides an interesting contrast to calcium. Epidemiological evidence for an association of calcium deficiency with CVD is strong, but the possibility that the association is causal is not supported by animal and laboratory experiments. In the case of magnesium, supporting epidemiological evidence is still rather weak, but the magnesium hypothesis has an important feature, which the calcium one does not possess, namely, a strong biological plausibility that is well substantiated by animal and laboratory experiments (93). The hypothesis that magnesium deficiency might be critical for hearts already damaged or malfunctioning, as in cases of coronary disease or arrhythmias, is a reasonable one (44a).

Emphasis is currently being placed on evidence relating to the magnesium content of heart and other muscles. Lower levels have been found in male residents of soft-water areas who die from accidents compared with their counterparts from hard-water areas (5, 11, 12). Anderson et al (5) found the myocardial magnesium level at autopsy to be 7% lower in subjects from areas low in water magnesium than in matched subjects from areas high in water magnesium. However, the statistical significance of this

difference is small. They also found that the magnesium concentration in the myocardium of subjects dying of ischaemic heart disease was found to be 24% lower than that of subjects dying from accidents (5). High coronary heart disease rates in Ohio were found in areas with less than 15 mg of magnesium per liter in the drinking water, whereas low CHD rates were found in areas with 36 mg/liter. Similar findings were reported by other investigators. A comprehensive review was done by Marier et al (45).

It is difficult to judge whether the apparently lower magnesium content of a damaged heart is a result or a cause of that damage. Unlike calcium, magnesium does not seem to be contained in modern food in an amount sufficient to cover the daily requirements of all persons, although clear-cut magnesium deficiencies are not usually observed in humans. The daily magnesium requirements are estimated to range from 350-500 mg per day, but it has been calculated that the average daily intake often is below that amount. Under these circumstances, it is obvious that magnesium in the water may contribute a little, but useful, amount.

In Canada, Neri & Johansen (60) found that drinking water from water areas with a high magnesium concentration may contribute up to 20% of the total daily intake, compared with about 1% in water areas with a low magnesium concentration. These researchers calculated that residents in Canada where the hardness of the drinking water is greater than 150 mg/liter as $CaCO_3$ receive an average of 50 mg of magnesium more than people on a similar diet who live in soft-water areas. This amount may be important under circumstances where requirements might be raised by stressful situations (45).

Zoetman & Brinkmann (94) found that the average concentration of magnesium in European drinking water supplies is relatively low (about 12 mg/liter) and constitutes some 10% of the daily intake. The same authors report that bottled mineral water, which is quite widely used in some European countries, might contribute an average of 40% of the total daily intake of magnesium.

SODIUM Common methods of artificial softening of drinking water are ion exchange or soda/lime process, which substitute sodium for calcium ions. Therefore, the process of removing calcium, magnesium, and other ions with these methods may result in the addition of sodium to drinking water which because of its alleged hypertensive effects may be detrimental to health (92). A WHO working group (93) proposed that water softened by ion exchange methods should not be used for drinking and for the preparation of food, because the use of home deionized water not only adds sodium but also alters the proportion of sodium to potassium, to calcium, and to magnesium. Such alterations may be important in the pathogenesis

of hypertension. The group also recommended that if the sodium content of the water supply exceeds 20 mg/liter, the health authorities should be informed of the actual concentration, and that the sodium content of all drinking-water should be monitored.

For most people, the sodium ion concentration in drinking water does not pose a health hazard, but attention should always be paid to the existence of large, high-risk groups, such as those subjects with hypertension or heart diseases on restricted sodium diets, and people who live in hot climates whose water intake may be high.

CHROMIUM Trivalent chromium is an essential element (91). It reportedly plays a vital role in glucose metabolism through its influence on glucose tolerance. In water, chromium can be present in both the hexavalent and trivalent forms. Hexavalent chromium is easily reduced by the body to the trivalent state with consequent loss of toxicity and gain in nutritional importance. The use of waters rich in hexavalent chromium may supply a sufficient amount of trivalent chromium to man's daily requirements.

Trivalent chromium is the active ingredient of the glucose tolerance factor (52a). Studies from some countries have reported an association between low chromium intake and impaired glucose tolerance, which has been improved following the administration of chromium salts. In the United States, reports of abnormal glucose tolerance tests in middle age and the association of repeated pregnancies and diabetes with decreased tissue chromium levels have been interpreted to suggest that the population may be in a state of marginal chromium deficiency (52). A similar situation may exist in other parts of the world. Chromium was found to be protective against atherosclerotic lesions in experimental animals (76).

In Finland, an inverse association between CVD and the chromium content of drinking water has been reported (65). However, the beneficial elements Si, F, Mg, and Ca are also in higher concentrations in waters of areas in Finland with low cardiovascular mortality.

Because of reports associating low chromium levels in water with human pathology, the nutritional status of the population with respect to chromium should be considered in situations where water treatment could result in a significant decrease in the chromium content of drinking water. The possible significance of drinking water as a nutritional source of chromium deserves further investigation.

LITHIUM Higher rates of cardiovascular mortality, of hospital admissions for mental disorders, as well as a higher frequency of violent behaviour such as homicides and suicides, were found in areas which were otherwise very similar from all points of view (25), except that in the high disease rate

areas the water contained much less lithium than the low rate areas. Similarly, the low prevalence of coronary heart disease, and of gastroduodenal ulcers among the Pima Indians of Arizona, was thought to be related to the high Li content of their water supplies (100 μg/l), as compared to the U.S. average of only about 2 μg/1 (82). Voors (88) found a negative correlation between lithium levels in drinking water and cardiovascular death rates in the U.S. As lithium is a well known pharmacological agent for the treatment of certain behavioural disorders and it is a mood stabilizer, it is apparently reasonable to associate the presence of lithium in sufficient amounts in water with less aggressive and less competitive behaviour among the populations using the water, thus explaining a lower incidence of mental disorders, of violence, and also of heart attacks.

IODINE Water may contribute significantly to the daily requirement of iodine, perhaps up to 20%. The iodine content in water is negatively correlated to CVD rates in Finland (34). The susceptibility of the Finnish population to CVD apparently increases when there is less than 2–3 μg of iodine per liter of drinking water.

FLUORINE Calcification of the aorta was found to be less prevalent in areas where the water supplies were rich in fluorine (6). In Finland and the US, low death rates from CHD were reported in areas where the water supplies were richer in fluorine and magnesium (44, 86). The relationship of water fluorine to dental caries is discussed in detail in the article by Schamschula & Barmes (pp. 427–35 of this volume).

SILICON Silicon is widely distributed in rocks, as well as in water and food, and it is under investigation as being essential to animals and possibly to man. Lower death rates from coronary heart disease were reported in areas of the US that had hard water with 15 mg of Si per liter versus 8 mg per liter in high CHD areas (73). Similarly, Eastern Finland, which has high CHD rates, has lower silicon concentration in the water than in the west (77).

CADMIUM Contrary to the beneficial elements mentioned above, the deficiency of which is thought to be harmful to cardiovascular function, cadmium leached out of water pipes by soft water is thought to be harmful through its alleged hypertensive effect.

Schroeder's theory (74) of cadmium-induced hypertension as the harmful factor in the water story was based on four considerations: cadmium induction of hypertension in rats; the findings of higher cadmium concentration in human subjects who died of hypertension; the leaching of cadmium from pipes through corrosive action of soft water; and the relationship between soft water and cardiovascular mortality. This attractive theory is supported

by experimental and clinical evidence. However, epidemiologic support is not very strong.

Inconsistent with the cadmium theory is the fact that cadmium workers have never been shown to suffer excess hypertension (31, 36), and contrasting results were reported on the association between water cadmium and cardiovascular death rates (5, 7, 46, 59). Informative reviews on trace elements in water in relation to CVD were published by Sharrett (79) and Voors (89).

Other Variables

Other variables might also account for the apparent relationship between the hardness of water and cardiovascular mortality.

CLIMATE It has been suggested that the regional variation in CVD mortality rates may be accounted for in terms of climatic conditions. For instance, there is a well-known seasonal fluctuation in CVD mortality in England, with higher rates in mid-winter than in summer. Temperature is lower in the north than in the south and rainfall is higher in the west than in the east. In a very comprehensive search for confounding factors in England and Wales, over 80 indices of local social, economic, industrial, and other environmental conditions were correlated with water hardness and calcium (22, 28). There was no evidence that water hardness was merely reflecting other factors and rainfall was the only variable closely associated with these water components. Multiple regression analysis showed that after allowing for other environmental and social factors, both water calcium and rainfall made significant separate contributions to the variation of cardiovascular death rates between the towns studied. Soft waters are thought to be more widely present in areas of high rainfall.

Water hardness is related to both temperature and rainfall, and both the rainfall and temperature are related to CVD death rates, but neither variable alone shows as strong a relationship with CVD mortality, as does water calcium. This suggests that rainfall and temperature really add little if anything to the prediction of CVD mortality rates. Further analysis of climate and cardiovascular mortality was carried out by the British Regional Heart Study (see below).

Masironi et al (50) failed to show that temperature and other weather variables are connected in a clear-cut way with the occurrence of myocardial infarction. Elwood et al (27) also found practically no association between ischaemic heart disease and temperature in the UK, although they did find an association with water hardness. Dudley et al (26), instead, reported that in the US the association between water hardness and cardiovascular mortality is influenced by temperature.

LATITUDE AND TEMPERATURE Masironi et al (50) found a strong relationship between the frequency of myocardial infarction and latitude. The rates both of attack and of incidence were higher and water was softer at more northerly latitudes.

Figure 2 shows the relationship between attack rate and latitude; the fitted regression relationship was consistent with the attack rate doubling for each 15° of latitude. The associations with latitude and with hardness were practically the same.

The relationship between water hardness and latitude arises from the geological trends across the continent. The geographical distribution of CVD in Europe as a function of latitude, geochemical environment, and water hardness was studied by Masironi et al (47, 49). Northern countries with a higher cardiovascular death rate are underlain by very old geological substrata; these are poor sources of minerals essential to life and the waters are soft. In Europe, this pattern occurs in a north-south direction, but a similar association of higher cardiovascular mortality with lower levels of trace elements in soils and water is present in the US in an east-west direction. Latitude, therefore, does not seem to play the same role in cardiovascular mortality in Northern Europe and North America, whereas water hardness always shows the same type of relationship with cardiovascular mortality in both continents.

Epidemiological Plausibility of the Water Story

It results from the many studies so far carried out that no common relationship exists between water hardness and any one particular form of CVD. Whatever mechanism is involved it must be common to death from CHD, cerebrovascular disease (stroke), hypertensive heart disease, and those conditions labeled degenerative heart disease. Any one of the major processes in CVD could be involved—hypertension, myocardial function, intravascular thrombosis, or atherosclerosis.

According to Marier et al (45), many of the negative epidemiological findings could be attributed to an inadequate experimental design, e.g. small numbers of population were intercompared, the range of water hardness was too small, adequate control populations were lacking, and mortality rates were not standardized. Several authors simply used crude death rates, failing to make even such elementary adjustments as those for sex and age in the populations under study.

Intercomparison within a restricted geographical area poses problems of population mobility; conversely, the larger the area, the more broadly representative its population will be, and the more stable its death rates, but the sources of water supply may be more heterogeneous.

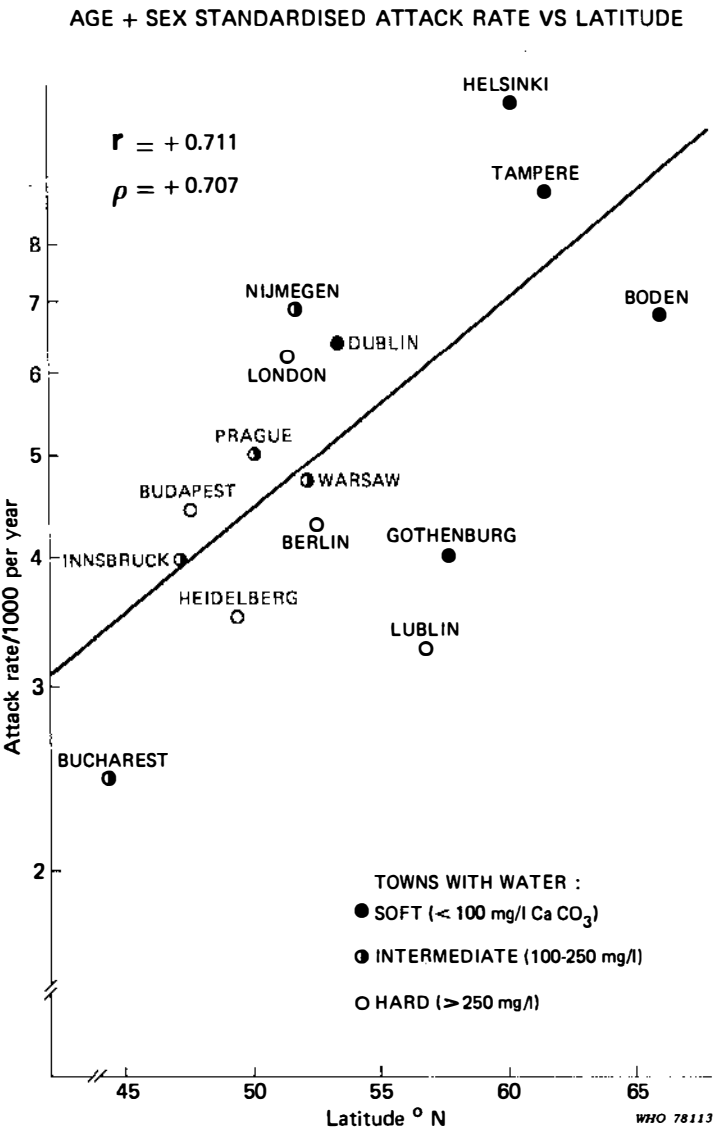

Figure 2 Age and sex standardized myocardial infarction attack rates in relation to latitude in European cities.

An additional problem arises if a considerable proportion of the residences is equipped with water-softening devices (2, 14). Thus far, this factor has not been examined with due regard, and yet in hard water areas of the US it is estimated that 60–70% of residences use water softeners (64).

Another source of potential misclassification is the insufficient knowledge

about the proportion of daily water intake that comes from the tap. Allwright et al (2) estimated that about one sixth of the population in Southern California drank bottled water, whereas Hankin et al (33) found that half of the people in a hard-water area drank softened or bottled water at home. Bottled water is drunk quite extensively in Europe.

The specificity of the reported water/CVD association is not very high either. Numerous other causes of death have been found in various studies to be associated with water hardness, many of them as strongly and negatively correlated as the CVD. This was the situation for water hardness and cancer deaths, liver cirrhosis, peptic ulcer, and bronchitis, whereas the correlation for gastritis and pulmonary disease were found to be positively associated. An association between infant mortality and hardness of drinking water was also reported (23, 68), but here again the association is not consistent. However, all these associations between water hardness and different diseases were found in isolated studies and did not have the degree of repeatability and of time and geographic consistency that the large-scale water hardness/cardiovascular studies have shown.

Another disease often reported to be negatively associated with water hardness is urolithiasis, or urinary stone formation. Incidence of urinary calculi was found to be higher in soft-water areas (3, 13, 81). The role of low calcium and magnesium levels in soft water (24, 63, 69), and the role of sodium replacing calcium and magnesium in artificially softened waters, has not yet been fully evaluated. The evidence for a role of trace elements in urolithiasis is too limited for any conclusion to be drawn, and more research is needed on the effects of lithium, potassium, zinc, silicon (10, 85), magnesium (13), fluorine (35, 84), and genetic factors (13a) on stone formation.

Conclusions

According to a WHO expert group (93), evidence from many properly designed epidemiological studies undertaken by independent investigators shows that hardness of drinking water (and particularly the calcium content) in Canada, the UK, and the US is inversely associated with cardiovascular mortality, and with adult mortality in general. The fact that some researchers have failed to find this association cannot negate the weight of evidence. Although it has not yet been possible to establish any relationship between cause and effect, the existence of an association with mortality cannot be dismissed. This was also the conclusion of an international group of experts who met in 1975 under the auspices of the Commission of the European Communities (15).

Unfortunately, there are not many animal experiments to provide an insight on the mechanism of action of the observed association. Neal & Neal

(57) found that rabbits supplied with distilled water developed more atherosclerosis than those on hard water, but studies on pigs raised in soft-water or hard-water areas showed little or no difference in aortic atherosclerosis (9, 37, 66).

Points that emerge from the water hardness/mortality studies are that all the main components of cardiovascular mortality may be involved, and this is so in the larger national studies. Ischaemic heart disease, although the largest fraction of all cardiovascular mortality, is neither the most closely nor the most consistently associated.

Soft waters are usually acidic due to carbon dioxide and are corrosive. Cadmium, lead, and other harmful elements are dissolved from piping by acidic waters and may have adverse effects on cardiovascular conditions. At present, the only biologically plausible mechanisms for linking water factors to CVD is the possibility that soft waters may contain a toxic substance (e.g. lead, cadmium), or more likely, that some hard waters supply a significant amount of some beneficial element like magnesium.

Water hardness is a geographical variable and it varies according to broad geographical patterns. However, other factors also vary in a similar manner and this prevents an understanding of the association.

Several authors have been critical of the water hardness theory and, rightly, have warned against reaching hasty conclusions, e.g. as to the alleged desirability of hardening soft-water supplies, or of adding specific elements to water, which are supposed to be beneficial. Some among such critical reviews, however, tend to be more nihilistic than would be useful (32), thus causing a disservice to the advancement of knowledge in this field. The Regional Heart Study discussed elsewhere in this paper makes this kind of negative approach appear out of place.

Critics of the water/CVD findings rely heavily in their criticism on the inconsistent results obtained from small-scale studies and do not take into consideration the various confounding factors that can play a role. For instance, if the association is not linear (see below) or is present only within a certain hardness range, this fact alone can account for many discordant results. The use of water softeners at home, population mobility, and the lack of appropriate standardization of mortality rates are other examples of confounding factors that attain far greater weight when small, contiguous population groups are studied. The data from some such small-scale studies, when recalculated by other, or even the same, authors produced different results. No investigator has ever proposed a causal relationship between water hardness and cardiovascular mortality simply on the basis of the evidence so far accumulated. Certain critics emotionally purporting to demonstrate that a causal relationship does not exist (32) storm therefore through open doors.

The research currently being carried out by the Environmental Protection Agency (29) and by the British Regional Heart Study (see below), as well as the opinions expressed in documents issued by the World Health Organization (93), the National Academy of Sciences of the US (56), and the Commission of European Communities (15), emphasize the need for further research. This is particularly justified when considering for example that in Ontario up to 10% of the variability in CHD can be associated with differences in the hardness and Ca and Mg content of water (1), and that in the soft-water areas of the US cardiovascular mortality may be elevated 15% over the hard-water areas (56, 80).

By way of conclusion it would be useful to quote from a report of the National Academy of Sciences of the US (56),

> It is evident from the review of the literature that there is considerable disagreement concerning the magnitude or even the existence of a "water factor" risk, the identity of the specific causal factor(s), the mode of action, and the specific pathologic effects. The wide spectrum of alleged associated effects, the lack of consistency in theorized or reported etiologic factors, the very small quantities of suspect elements in water relative to other sources, and the discrepancies between studies, raise serious questions as to whether drinking water really serves as a vehicle of causal agents, is an indicator of something broader within the environment, or represents some unexplained spurious associations. Despite these uncertainties the body of evidence is sufficiently compelling to treat the "water story" as plausible, particularly when the number of potentially preventable deaths from cardiovascular diseases is considered. In the United States, cardiovascular diseases account for more than one-half of the approximate 2 million deaths occurring each year. On the assumption that water factor(s) are causally implicated, it is estimated that optimal conditioning of drinking water could reduce this annual cardiovascular disease mortality rate by as much as 15% in the United States. In view of this potential health significance, it is essential to ascertain whether water factors are causally linked to the induction of cardiovascular or other diseases and, if so, to identify the specific factors that are involved. Much more definitive information is needed in order to identify what remedial water treatment actions, if any, can be considered.

BRITISH REGIONAL HEART STUDY: GEOGRAPHIC VARIATIONS IN CARDIOVASCULAR MORTALITY, AND THE ROLE OF WATER QUALITY

Introduction

The Regional Heart Study was undertaken to explain the substantial geographic variations in CHD and stroke in Great Britain (63a, 78a). In this it differed in primary objectives from previous British studies, which were basically concerned with investigating whether or not water quality (especially water hardness) played a role in cardiovascular mortality (18, 20, 83). The Regional Heart Study set out to assess the role of environmental,

socioeconomic, and individual 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 review is concerned mainly with the results and conclusions from phase 1.

In phase 1, cardiovascular and other mortality over 5 years around the 1971 census (1969–1973) in 253 towns in England, Wales, and Scotland was related to a wide range of environmental, socioeconomic, and other data.

From the broad data base 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 were selected at random. A questionnaire was administered to each man who was then examined for a whole range of physical, physiological, and biochemical measurements. The principle objectives of phase 2 studies are to relate the variations in the distribution of risk factors to cardiovascular mortality rates; to see whether or not water quality affects cardiovascular mortality by way of any of such risk factors; and to examine the interrelationship between risk factors in individuals and such variables as blood pressure. The role of trace metals in tap water in relation to risk factors is also being studied.

The aim of phase 3 is to follow the 8240 men examined in phase 2 and to record the incidence of cardiovascular morbidity and mortality.

Phase 1 Data

TOWNS A total of 253 urban areas (towns) mostly with populations over 50,000 at the 1971 census were studied.

MORTALITY Cardiovascular mortality rates for 1969–1973 by sex and 10-year age groups were calculated. The data were subdivided into stroke and ischaemic heart disease, the latter including hypertension and other forms of heart disease. Standardized mortality ratios (SMRs) were computed for various combinations of ages, sex, and cause.

WATER QUALITY For each town, the mean concentration of some 40 water constituents was estimated, and initial analyses have focused on some 23 variables. The means were weighted according to the population served. Information on water was available for all but 18 towns in which the complexity of supply made estimation unreliable or in which data were not available. In addition, data on certain water parameters were not obtainable for some towns.

CLIMATE The available data related to temperature, rainfall, hours of sunshine, altitude, hilliness, distance from the sea, latitude and longitude, wind speed, wind chill, relative humidity, and atmospheric pressure.

SOCIOECONOMIC FACTORS Data from the 1971 census were used and 15 major socioeconomic variables were computed, including for example percentage of heads of household in manual work, percentage unemployment in economically active men, number of cars per household, percentage of owner-occupied households, etc.

AIR POLLUTION Six-year means (1968–1974) of smoke and sulfur dioxide were computed for each town by including all reporting sites not wholly industrial. No town-based data were available on diet, tobacco, and alcohol, but information was obtained for the 11 regions covering England, Wales, and Scotland. Blood group data were also determined.

Results

THE UNIVARIATE APPROACH 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 at any given water hardness there was a considerable spread of SMRs. Nevertheless, all but one of the towns with SMRs over 120 had soft water less than 1 mmol (100 mg) per liter and 95% of the towns whose water hardness was over 2 mmol/liter had SMRs less than 100. This figure shows clearly the problems inherent in studies comparing two towns or less. 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 they might show that markedly different levels of water hardness are associated with

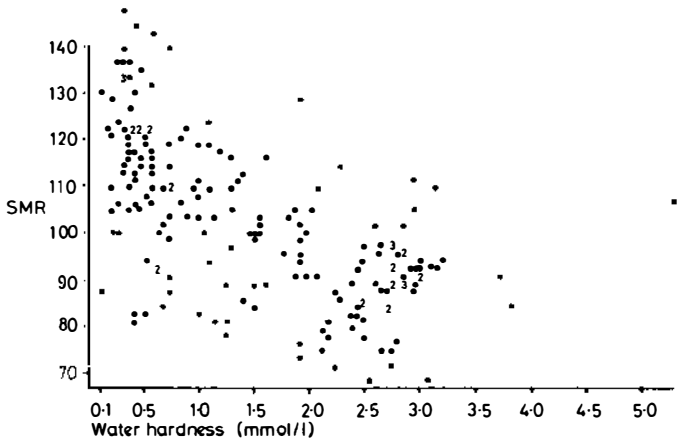

Figure 3 Water hardness plotted against SMR for all men and women aged 35–74 with cardiovascular diseases for each town. (Water hardness: 1 mmol/liter = calcium carbonate equivalent of 100 mg/liter.)

the same SMR. For this reason replication of towns in terms of cardiovascular mortality and water hardness is an essential feature.

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

Table 1 lists 24 factors, each of which had a marked association with cardiovascular mortality, i.e. correlation coefficient with SMR more than 0.50. The influence of climate is of particular importance since high rainfall and areas with soft water tend to coincide ($r = -0.70$ between total hardness and number of days with more than 0.2 mm of rain). In view of the large numbers of factors with a marked association with cardiovascular mortality, it would be simplistic to conclude that the relationship shown in Figure 3 implied a causal effect of water hardness on cardiovascular mortality. Indeed, the multiplicity of factors (environmental, socioeconomic, and personal) with strong univariate relationship with cardiovascular mortality emphasize the need to consider water hardness as only one of the several factors that might influence cardiovascular mortality. A multifactorial approach, therefore, was undertaken by constructing statistical models by using multiple regression techniques.

Table 1 Factors associated with the standardized 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
Water quality		
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
Climate		
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	
Geographic		
Latitude	+0·74	253
Longitude	+0·68	
Socioeconomic		
% 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	
Blood group		
% A-gene frequency	−0·59	253
% O-gene frequency	+0·58	
Air pollution		
Mean annual smoke	+0·54	134

OTHER WATER COMPONENTS ASSOCIATED WITH CARDIOVASCULAR MORTALITY It is important to appreciate that total hardness is not the only water parameter associated with cardiovascular mortality. The following components also had strong correlation coefficients with cardiovascular mortality: calcium (–0.67), carbonate hardness (–0.65), conductivity (–0.63), nitrate (–0.68), silica (–0.58), and Langelier index (an index of corrosiveness used in the water industry) (–0.65). Because each of these correlates highly with water hardness (0.73–0.97), they do not necessarily give any extra insight into the specific nature of the effect of water. Magnesium and sodium do not appear to have any obvious association with cardiovascular mortality (magnesium, $r = -0.13$; sodium, $r = -0.16$).

THE MULTIFACTORIAL APPROACH In the multifactorial approach, the extent to which water quality, climate, socioeconomic factors, blood groups, and air pollution might simultaneously explain the variation between towns in cardiovascular mortality rates has been examined. The logarithm of the SMR for all CVD in 1969–1973 for men and women aged 35–74 years was used as the dependent variable in a multiple regression model. After testing many different regression models, it was considered that there were five variables that collectively had a highly significant effect on the SMR—water hardness, percentage of days with rain, mean daily maximum temperature, percentage of manual workers, and car ownership.

Table 2 shows the mean, standard deviation, and range of the five variables used 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, whereas water hardness, maximum temperature, and car ownership had negative associations. This means that each variable made a separate and important contribution to

Table 2 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	5·28
% days with >0·2 mm rain	44·9	4·9	37	58
Mean daily maximum temperature (°C) ..	13·11	0·88	11·1	14·6
% of manual workers	60·5	11·8	30	83
No of cars per 100 households	55·2	15·1	26	97

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

Table 3 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.

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.

Figure 4 shows the geometric mean SMR for CVD for towns grouped according to water hardness both with and without adjustments for the effects of the other four variables (two climatic and two socioeconomic). The effect of water hardness is nonlinear, being greater in the range from very soft to medium-hard water than from medium to very hard water. Adjusting for climatic and socioeconomic factors considerably reduces the magnitude of the water hardness effect.

Because of the nonlinear effect of water hardness on cardiovascular mortality, the effects of hardness on SMR were considered at two separate intervals, above and below 1.7 mmol/liter. The results are shown in Table 3 in terms of the standardized regression effect (SRE), defined as the percentage change in SMR associated with a one standard deviation increase in each variable, keeping all other variables constant (83a).

The effects of the four climatic and socioeconomic variables were fairly similar, but they were greatest for the percentage of manual workers and rainfall. Water hardness below 1.7 mmol/liter had a greater SRE than any of these four variables, but water hardness above this level had very little effect.

The model estimates that in the range below 1.7 mmol/liter, an increase in total hardness of 1 mmol/liter (say from 0.5 to 1.5 mmol/liter) while keeping the other variables constant should result in a 7.2% decrease in cardiovascular mortality (with 95% confidence interval 4.4–10.0%). There is no evidence of an equivalent decrease beyond 1.7 mmol/liter. Thus it could be argued that the maximal effect on cardiovascular mortality of water hardness lies principally between medium-hard and very soft water and may be of the order of 10–15%.

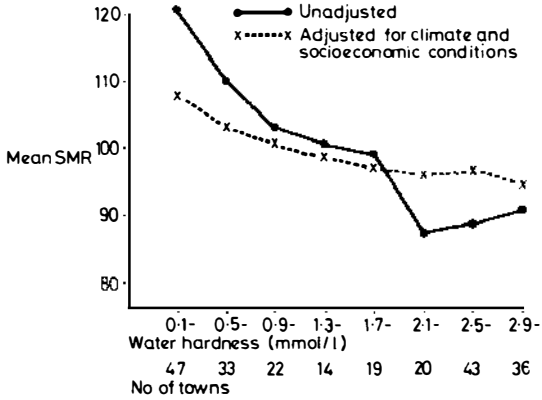

Figure 4 Geometric means of SMR (for all men and women aged 35–74 with cardiovascular diseases) for towns grouped according to hardness of water. (Water hardness: 1 mmol/liter = calcium carbonate equivalent of 100 mg/liter.)

SPECIFIC CARDIOVASCULAR DISEASES AND WATER HARDNESS It has been suggested that the effect of water hardness is on overall mortality and not specifically on CVD. Table 4 shows that computing the five-variable regression on the SMR for non-cardiovascular mortality shows no effect for total hardness, whereas the effect of water hardness remains significant and of similar magnitude for both stroke and ischaemic heart disease.

Conclusions

The results of phase 1 of the Regional Heart Study show that after allowing for climatic and socioeconomic conditions, a significant negative association remains between water hardness and cardiovascular mortality. The relationship between water hardness and cardiovascular mortality is nonlinear, and there appears to be a 10–15% excess of cardiovascular deaths in areas

Table 4 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.

with very soft water compared with areas of medium hardness. Since many water parameters are highly correlated with one another, no single water factor can be isolated as the causal factor in cardiovascular mortality.

The results from phases 2 and 3 of the Regional Heart Study are expected to help elucidate this relation further, particularly with regard to the role of trace elements in water (e.g. lead, cadmium) and with regard to the possible effects of water factors on CVD risk factors such as raised blood pressure.

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