10.
WATER HARDNESS AND CARDIOVASCULAR DISEASE: A REVIEW OF THE EPIDEMIOLOGICAL STUDIES, 1957-78

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I. INTRODUCTION

Since publication of articles by Kobayashi (1) in 1957 and Schroeder in 1960 (2, 3) and 1969 (4), numerous epidemiologists throughout the world have studied the inverse (protective) association between drinking water hardness and cardiovascular disease mortality. Most investigators conducted ecological studies that considered population exposures to hard water and mortality statistics. Several community-intervention studies evaluated changes in mortality when drinking water hardness was increased or decreased. In more recent years, epidemiologists conducted analytical studies in which individual exposures and risk factors were considered.

Summarized in this chapter is the epidemiological literature published before 1979 and conclusions of scientific working groups convened by the National Academy of Sciences (NAS) and World Health Organization (WHO) during the 1970s.

II. SCIENTIFIC REVIEWS BY EXPERT GROUPS

1. National Academy of Sciences

In 1968, 1973, and 1974, the NAS-National Research Council (NRC) Subcommittee on the Geochemical Environment in Relation to Health and Disease held workshops to examine ways in which the geochemical environment might influence the processes of human health and disease. In the first two workshops, participants considered trace elements from natural sources and their essentiality. In the third workshop, participants evaluated the geographical distribution of diseases, their possible association with environmental trace elements, and sources of exposure. The diseases considered were esophageal, stomach, and colorectal cancer; cardiovascular disease including hypertension and stroke; and urolithiasis, particularly kidney stones. The report of the third workshop (5) acknowledged that "an enormous number of concise data that have been gathered together and correlated … show distribution patterns … of the geochemical environment that may affect health and disease …." However, the report also noted that more specific exposure data were needed, especially for water constituents and that there are problems relating the health and geochemical data.

The NAS-NRC Panel on Geochemistry of Water in Relation to Cardiovascular Disease (6) also reviewed the epidemiological studies of water hardness and cardiovascular disease reaching the following conclusions:

- In general, when studies encompass large geographical areas, hard water was correlated with low cardiovascular disease mortality rates. This association was not always observed when smaller areas were considered or when the study populations were grouped by altitude or the proximity of a seacoast. Some non-cardiovascular diseases were also associated occasionally with soft water, raising the possibility that water hardness may merely be a surrogate for another risk factor(s).

- Although most studies reported correlation coefficients and not risk estimates as a function of exposure, a few studies estimated risk. Upper estimates of the risk ratios for soft compared to hard water averaged approximately 1.25 for all cardiovascular diseases and 1.2 for stroke and arteriosclerotic and hypertensive diseases.

- Autopsy studies in Canada and the United Kingdom reported low magnesium levels in various tissues (heart, diaphragm, and pectoral muscle) of persons who died from myocardial infarction compared to persons who died from accidental causes. Although the data were not consistent, similar magnesium deficits were reported in persons from soft compared to hard water areas.

- There may be a water factor associated with cardiovascular disease risk, but this is far from certain. The factor is unlikely to be water hardness or softness as such, and its effect may be weak in comparison with other known risk factors. One possible mechanism is that enough magnesium is present in some hard waters to prevent borderline magnesium deficiencies in some persons, thereby reducing their liability to sudden cardiac death as a result of arrhythmia following an infarct.

- Another review of the evidence for an association between water hardness and cardiovascular disease was conducted as part of the congressional mandate of the Safe Drinking Water Act. In 1980, the NAS-NRC Safe Drinking Water Committee (7) concluded:

- "Given the current status of knowledge regarding water hardness and the incidence of cardiovascular disease, it is not appropriate at this time to recommend a national policy to modify the hardness or softness of public water supplies. The data do not indicate clearly which (if any) additions to soft water would benefit human health."

2. World Health Organization

The WHO Working Group on Health Significance of Chemicals Occurring Naturally in Drinking Water met in 1978 to consider the relationship between mineral content and cardiovascular disease with special reference to demineralized and desalinated water (8). This group was one of several convened by WHO to provide information for the possible revision of the drinking water guidelines. The Working Group was of the opinion that sufficient epidemiological evidence was available to support a protective association between the hardness of drinking water (particularly for calcium) and cardiovascular disease mortality but emphasized that the association was not consistently reported. Although some investigators failed to find a protective association, the Working Group felt that the inconsistent study results did not negate the weight of evidence to the contrary. Some scientists thought that the presence or absence of a certain substance or substances in drinking water might be directly associated with the differences in cardiovascular mortality. Others thought that the association was indirect. That is, the "existing epidemiological evidence suggests that the full picture may have an indirect explanation and have nothing at all to do with drinking water." Water quality may only be an indicator of other environmental conditions that have a direct effect on heart disease.

The Working Group concluded:

- "A better understanding is required of the true nature of the association between cardiovascular mortality and the concentration of calcium and magnesium ions (and other components of hardness) in drinking water … Should the relationship eventually prove to be a causal one, the benefits that could be derived from modifying the mineral content of drinking water would be so considerable that no opportunity should be missed to establish such studies as soon as possible … water could be an important source of certain essential substances, especially magnesium and calcium. This applies particularly in circumstances where the mineral intake from diet alone may be deficient."

The Working Group also made several recommendations for demineralized and desalinated water including the following:

- "The use of demineralized and/or desalinated water in a given area should be approached cautiously … only after careful study has been made of the total mineral intake of the local inhabitants."
- "The effects of water demineralization on health should be measured."
- "Increased corrosion of pipes should be taken into account when proposals for the use of demineralized drinking water are examined."

III.   SUMMARY OF THE EPIDEMIOLOGICAL STUDIES

From 1957 through 1978, more than 60 epidemiological studies of water hardness and cardiovascular disease mortality were conducted throughout the world. All were ecological studies where mortality statistics and drinking water quality measures were obtained from readily available information about the population groups being studied. A number of investigators including Punsar (9), Neri *et al*. (10, 11), Sharrett and Feinleib (12), Sharrett (13) and Comstock (14, 15) reviewed these studies and evaluated their findings. A summary of the study results is presented here, and readers who wish to obtain a more detailed description of the studies are encouraged to read not only the review articles but also the original articles.

1.   Study areas

Comstock (14, 15) tabulated the studies primarily by the size of geographical area considered. Country-wide studies of water hardness and mortality were conducted in the United States, Canada, United Kingdom, Ireland, Sweden, Netherlands, Finland, Italy, Rumania, and the Czech Republic. Studies in the United States considered mortality statistics for the periods 1949-1951 and 1951-1961 in standard metropolitan statistical areas and large municipalities or counties (14, 15). Masironi (16) studied mortality after 1961 in 42 of the states. In England and Wales, studies considered county boroughs and mortality statistics for the periods 1948-1954, 1958-1964, 1950-1965, and 1958-1967 (14, 15). In Canada, mortality during 1960-62 was evaluated in 516 municipalities and nine provinces (10, 11). Studies were also conducted in 33 large Swedish towns for 1951-60; 23 cities in the Netherlands for 1958-1962; 21 cities in Finland for 1967; 68 towns in Italy for 1955-1964; 10 localities in Rumania, and 53 districts of Bohemia and Moravia (14, 15). Studies in smaller regions (e.g., counties within a state, a province, or selected cities and localities) were also conducted in the United States, Wales, Scotland, Canada, Germany, Japan, Australia, Hungary, the Czechoslovakia, and Italy. International comparisons were conducted among populations in three Latin American cities, five European and 14 other cities (14, 15).

2.   Consistency of Study Results

An inverse or protective association of water hardness with cardiovascular mortality was reported in most, but not all, studies. In studies involving very large geographical areas, there was a strong tendency to observe lower cardiovascular mortality with increasing hardness of drinking water sources. Inverse associations were frequently not found in studies of small regions or when companion communities or counties were compared. For example, in Canada when the country was looked at as a whole, an inverse association was found for cardiovascular mortality and municipal water hardness levels, but when the same data were analyzed for individual provinces, inverse associations were found only in Quebec and Ontario Provinces (10, 11, 14, 15). Correlations found in the remaining three provinces suggested increased rather than decreased mortality associated with increased hardness. Associations were usually found for both men and women but were often statistically significant for only one gender. Few studies considered different ethnic groups. When nonwhites were studied in the United States, investigators did not find significant inverse associations.

Sharrett (13) felt that the observed associations were suspect because they often contradicted each other and cautioned that "Specious correlations should be expected in geographic studies because the assumption of statistical independence is not met. Cities are not independent sampling units. They are clustered into geographic units with similar characteristics and mortality rates." Comstock (14, 15) noted that the lack of consistency in observing an inverse association might be due to inadequate analysis, the limited range of water hardness values, and random or systematic error. However, he believed that these deficiencies did not account for all the failures to observe the inverse association. Instead, he felt that the causality of the association might be indirect rather than direct or direct only under certain conditions.

3.   Possible Random and Systematic Error

Since the studies are ecological, it is important to evaluate chance, confounding, and misclassification bias. This evaluation will affect how the association should be interpreted. In addition, water quality was determined for various time periods, and water exposures were reported in various ways. Many studies assessed water exposure in terms of hardness units rather than as concentrations of individual elements. Although calcium and magnesium ions are the two major contributors, all polyvalent cations contribute to what is known as water hardness. A further complication is that the water hardness units are defined differently in several countries.

4.   Random error

Too many studies reported statistically significant correlations to make chance a likely explanation for the observed associations. However, the studies conducted before 1980 might be due to systematic error. Limited information is available to adequately interpret the results in this regard.

5.   Ecological bias

Health, exposure, and demographic statistics in ecological studies characterize population groups, and the observed associations may not reflect a casual relationship (i.e., the ecological fallacy). The study of group attributes may lead to the observation of a relationship that is merely coincidental, and the magnitude and direction of an association at the group level may be quite different than the association observed when individuals are studied. The geographical area selected for study can also be a source of misclassification bias. When the group is not homogeneous with respect to the exposure, the average group exposures will not likely reflect individual exposures. The same caution applies for the outcome measures that are studied. However, if information is available to adequately characterize population exposures and health

outcomes, the ecological study, because of its statistical power, is valuable for assessing the health effects that may be associated with environmental exposures such as water hardness or other water quality parameters.

The success of cardiovascular disease studies in avoiding the ecological fallacy depends largely upon selecting areas that are relatively homogeneous in terms of population exposures to water hardness, calcium, or magnesium levels. The larger the geographical area, the more broadly representative its population and the more stable its death rates, but water supply sources may be more heterogeneous (13). Trace element exposure from water can vary considerably among individuals within a locality, the exposure assessment may be subject to sampling error (e.g., few samples collected for the relevant time period), and laboratory analyses may imprecise. All of these factors may contribute to exposure misclassification that can reduce the chance of detecting associations or increase the error in the assessment of their importance (13). Few investigators addressed the issue of heterogeneity for water exposures, and almost all of the studies classified areas by the hardness of finished water at the treatment plant rather than at the tap, and little regard was given to the use of home softeners in hard water areas. Not considering the use of home softeners might cause misclassification of exposure, since it was estimated in 1970 that the market saturation in the United States was 60-70 percent (14, 15). Another potential source of misclassification bias is the lack of consideration about water intake. Average daily water consumption may vary from area to area, and individuals may consume water not only from the home tap but also from other sources including bottled water.

6.   Confounding factors

Many human characteristics (e.g., demographic, socio-economic, and cultural) vary with geography, and the hardness of water also varies with geography. Thus, the correlation of hardness with cardiovascular disease might represent the correlation of some other geographically-related characteristic with cardiovascular disease. Water hardness and cardiovascular disease each might be associated with another variable or variables that may confound the observed association. Few studies considered potential confounders, and it is difficult to determine whether the observed associations are due to minerals that make up water hardness, other water quality parameters associated with hardness, or other exposures, risk factors, and characteristics that are associated with hardness.

For example, climatic factors are related to geography. Two studies considered temperature in their analysis (14, 15). In the United Kingdom, temperature was found to be more closely related to cardiovascular mortality than hardness. In the United States, the most important correlate, after adjustment for age and indicators of socioeconomic status, was the comfort index, which is based on relative humidity and air temperature; water factors were second in importance. In the United Kingdom, two studies found that rainfall was closely related to cardiovascular mortality, more so than water hardness. In Canada, a study in Ontario found that latitude and mean temperature were more important than water hardness, but a study in Nova Scotia found latitude and temperature to be less important.

Some studies failed to make adjustments for age, race, and gender; others used broad age groups (14, 15). In failing to adjust for age or using broad age groups, the investigator assumes there are no important differences within the age range studied, and this assumption may not be valid. Few studies considered the possibility that smoking patterns or serum cholesterol may differ in hard and soft water areas (14, 15). Smoking patterns did not differ in a study in the United States but did in a study in the United Kingdom. In one study, higher serum cholesterol levels were found in the soft water area, and in another study, mean cholesterol levels were slightly lower in two soft water cities. In a third study, no differences were found among populations in hard and soft water areas.

Confounding factors cannot be ruled out as a cause of the associations. Relatively few studies considered confounding, and those that did, provided inadequate information to evaluate possible confounding. Major confounders can be controlled or assessed in analytical studies, and better information about confounding effects should be available from more recently conducted studies.

7.   Water constituents associated with hardness or mortality

If the observed water hardness-cardiovascular associations are not confounded and not due to systematic bias, the question remains as to the water constituent that may be responsible. Constituents closely associated with hardness could be the explanation, or other water constituents may have their own direct correlation with the mortality rates. Sharrett (13) evaluated the composition of hard and soft water in terms of several biologically important elements, including calcium, magnesium, chromium, copper, zinc, cadmium, and lead. Voors (17) evaluated cadmium and lead as possibly increasing cardiovascular risks and selenium, zinc, and silicon as possibly being protective. Both investigators found that the available data were inconsistent and evidence inconclusive in regard to identifying any of these water constituents that might be associated with either hard water or independently associated with cardiovascular disease.

In the United States the hardness of water is just as closely associated with magnesium as with calcium levels, and the high correlation of both elements with each other and with hardness makes it difficult to attribute the association between hardness and mortality to either calcium or magnesium (13). In England and Wales, calcium was highly correlated with hardness but magnesium was not. These findings emphasize the importance of measuring specific constituents rather than water hardness.

IV.   STRENGTH OF ASSOCIATION

The majority of studies considered a correlation coefficient (r) rather than a regression coefficient to measure the association. The correlation coefficient is affected much more by chance and provides no indication of the magnitude of effect; the regression coefficient is primarily affected by variation in the independent variable (10, 14, 15). It is possible to obtain a good correlation (i.e., high r value) between cardiovascular mortality and water hardness even though the dependent variable (e.g., mortality rate) may change little with change in the independent variable (e.g., water hardness).

For studies that provided sufficient data, Comstock (14, 15) calculated the relative risk (RR) for cardiovascular disease mortality associated with soft water (Table 1). Using information from studies in the United States (18), England and Wales (19), Canada (10) and Colorado (20), Comstock reported the RR associated with soft water (defined as 0 mg/l hardness) compared to hard water (defined as 200 mg/l hardness). The RRs ranged from 1.07 to 1.42 depending upon the geographic location. In Colorado, the RRs differed when the geographic areas were grouped by altitude or river basin; the larger RR is reported in Table 1. Anderson *et al*. (21) and Comstock (14, 15, 22) reported RRs for studies in Ontario and Maryland. The RRs reported in Table 1 suggest a weak association (23).

Morris *et al*. (24) found that the mortality rate for all cardiovascular disease in 83 county boroughs of England and Wales was 1.20 higher in boroughs where the total hardness of drinking water was less than 100 mg/l compared to boroughs where the hardness was 200 mg/l or greater. In 53 county boroughs where calcium levels were also reported, increased cardiovascular disease mortality (RR=1.30) was found in boroughs where water contained less than 10 mg/l calcium compared to boroughs with 100 mg/l or greater calcium (19). Anderson *et al*. (21) reported an

increased mortality risk (RR=1.14) for ischemic heart disease in areas of Ontario with water hardness of less than 100 mg/l (expressed in terms of calcium carbonate) compared to areas where the hardness was greater than 200 mg/l (Table 1). When these hardness values are expressed in terms of calcium levels, the increased risk (RR=1.14) is associated with water calcium levels of 40 mg/l compared to greater than 80 mg/l. When cities of more than 100,000 people were excluded from the analysis, the mortality associated with soft water increased (RR=1.17). In Washington County, Maryland, Comstock (14, 15, 22) found that risks differed for men and women. In white men, no increased risk of arteriosclerotic heart disease was associated with drinking water less than 150 mg/l, but in white women, an increased relative risk was associated with water hardness of less than 100 mg/l (Table 1).

V.   EXPOSURE-RESPONSE RELATIONSHIP

Comstock (14, 15) concluded that the studies provided no information about either the exposure-response relationship or a threshold effect. Since the correlations tended to suggest a weak association, an exposure-response effect for water hardness might be difficult to detect in the studies.

VI.   SPECIFICITY OF THE ASSOCIATION

Most studies reported inverse associations for mortality from arteriosclerotic and degenerative heart disease, hypertensive disease, and strokes. However, the results were inconsistent as to the disease that was most strongly associated with water hardness. Other causes of death, including all causes, were found to be inversely associated with water hardness and about as strongly as cardiovascular causes. The other causes of death included cancer, cirrhosis, peptic ulcer, infant mortality, and congenital malformations (14, 15). A lack of specificity suggests that the association might not be causal, and this concern was best described by Winton and McCabe (25): "Dissolved solids [in drinking water] may be important to man but one would not expect them to be this important."

VII. REVERSIBILITY

If the association is causal, the modification or elimination of the suspected cause should affect the frequency of the disease in question, and community-intervention studies should be able to demonstrate this change. Several studies in the United States and United Kingdom evaluated changes in mortality following changes made in water hardness either due to softening or replacing a soft surface water source with hard groundwater source (Comstock 1979a, b; Crawford *et al*. 1971). Comstock (1979a, b) found data analysis errors in several studies that had reported favourable changes in mortality rates associated with increased water hardness. When the errors were corrected, the mortality either remained high or did not decrease among populations when the soft water source was replaced with a hard water source. In the United Kingdom, Crawford *et al*. (26) studied mortality in towns where the water became softer (6 towns), harder (5 towns), or did not change (72 towns). After standardizing for socioeconomic status, death rate changes consistent with the hypothesis that hard water is beneficial were observed in 9 of the 11 towns with water hardness changes. There was a large variability in the mortality rates with considerable overlap between the towns where water became softer, harder, or did not change. Except for women aged 65-74, the cardiovascular mortality increased least or decreased most in the towns where water hardness increased.

VIII. BIOLOGICAL PLAUSIBILITY

If the association between water hardness and cardiovascular disease were causal, what constituent in hard water might be beneficial or what constituent in soft water might be harmful? Scientists who reviewed the studies thought the presumed benefit might be due to the presence of supplemental quantities of an important nutritional component or presence of a harmful water constituent in soft water. Soft waters are corrosive and may contain toxic metals, such as cadmium and lead leached from plumbing materials. In addition, some artificially softened water may contain high levels of sodium. These were considered as possible harmful constituents.

Although in some studies calcium was found to be associated with cardiovascular disease, the WHO Working group (8) concluded that this association lacked biological plausibility. However, some scientists felt that certain types of cardiac disease might be aggravated by the lack of calcium because calcium is required for muscle contractions and had been shown to decrease serum lipid levels (7). Little evidence for a protective effect of calcium was available from animal and laboratory experiments.

The supporting epidemiological evidence available in 1980 for magnesium was weak (7), but the role of magnesium was considered biologically plausible and was substantiated by animal and laboratory experiments (8). A plausible explanation might focus on a magnesium deficiency. Enough magnesium could be present in some hard waters to prevent borderline magnesium deficiencies in some persons, thereby reducing their liability to sudden cardiac death.

IX. CONCLUSIONS

The primary value of the studies reported during 1957-1979 was to call attention to the possible public health benefits of water hardness and need for additional research. Many, but not all, of the epidemiological studies published during 1957 to 1979 reported an inverse association between cardiovascular mortality and water hardness. Lower cardiovascular death rates were found in populations where the water supply contained relatively high levels of water hardness or calcium and magnesium compared to populations in areas with low levels. This protective effect was found for populations throughout the world, especially when country-wide studies were conducted. Limited information was available about the magnitude of the association or causality. Several reviewers estimated that populations who live in soft water areas may have, at best, a 25% percent excess cardiovascular disease mortality risk than populations in hard water areas.

In 1979 and 1980, scientists generally agreed that the strength of the association was relatively weak, the existence of a specific water factor was far from certain, and sufficient evidence was lacking to support a causal association. It was also agreed that because the absolute effect of hard water or a constituent of hard water in reducing mortality could be substantial, studies should be conducted to provide better information about the exposure-response relationship, biological plausibility, and causality.

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Table 1. Relative risks of dying from specified causes associated with soft water compared to hard water (adapted from Comstock 1979 b)

Study area	Cause of death	Race, gender	Age	Hardness (mg/l CaCO^3)	Relative risk (RR)
USA	All CVD	WM	45-64	0 vs. 200**	1.25
England, Wales	All CVD	WM	45-64	0 vs. 200**	1.19
Canada	Stroke	M	35-64	0 vs. 200**	1.15
	Arteriosclerotic heart disease	M	35-64	0 vs. 200**	1.07
	Other circulatory	M	35-64	0 vs. 200**	1.10
Colorado (data grouped by river basin)	Hypertensive disease	M	*	0 vs. 200**	1.30
	Arteriosclerotic heart disease	M	*	0 vs. 200**	1.19
	Stroke	M	*	0 vs. 200**	1.11
	Other circulatory	M	*	0 vs. 200**	1.42
Ontario, Canada	Ischemic heart disease	MF	35-74	<100 vs. >200	1.14
Washington County, MD	Arteriosclerotic heart disease	WF	45-64	<100 vs. >150	1.47
	Arteriosclerotic heart disease	WM	45-64	<150 vs. >150	0.75

CVD= cardiovascular disease; M=male; F=female; W=white

*age-adjusted

**hardness units as reported by Comstock (1979 b) in his calculation of RR