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Epidemiological studies and the association of cardiovascular disease risks with water hardness

R. Calderon and P. Hunter

10.1 THE HARD WATER–CARDIOVASCULAR DISEASE HYPOTHESIS

Since the mid-1950s, there has been a steady source of epidemiological studies evaluating the relationship of water hardness to cardiovascular disease. The first paper to call attention to the marked geographic variation in death rates from heart disease appeared in 1956. Analysing death rates for the United States from 1949 to 1951, Enterline and Stewart (1956) noted that place of residence might be an important risk factor for cardiovascular disease.

The World Health Organization held an expert meeting in Rome, Italy, in November 2003 to address a number of questions relating to the nutrient composition of drinking-water and the possibility that drinking-water could in some circumstances contribute to total dietary nutrition (WHO 2005). Calderon and Craun (2005) reviewed the epidemiological studies of water hardness and cardiovascular disease published before 1980, and Monarca *et al.* (2005) reviewed the studies of water hardness and cardiovascular and other diseases published from 1980 to 2002. Because different kinds of epidemiological studies have been conducted during the past 35 years, close attention should be paid to the problem of interpreting their results.

The first part of this chapter describes important aspects of epidemiological studies to help readers better understand what each study design can contribute to our understanding of the possible benefits that may be attributed to hard water. The second part of the chapter reviews those epidemiological studies that have examined the association of cardiovascular disease risks with water hardness.

10.2 OVERVIEW OF EPIDEMIOLOGICAL METHODS, STRENGTHS AND WEAKNESSES

10.2.1 Types of epidemiological studies

Observational epidemiological studies are either descriptive or analytical (Table 10.1). Descriptive epidemiology is important for summarizing disease information (e.g. cardiovascular disease mortality) to help assess demographic and geographical patterns of disease and develop hypotheses about disease etiologies. Analytical epidemiology is used to test specific hypotheses. Ecological (also called geographical, correlational or aggregate) studies explore possible associations between health statistics, demographic measures and risk factors or exposures (e.g. environmental or water quality measures). The ecological study is relatively inexpensive and easy to conduct, but the associations that are observed must be cautiously interpreted (Greenland and Robins 1994a,b; Piantadosi 1994; Poole 1994). It must be remembered that the health, exposure and demographic statistics characterize population groups rather than the individuals within the groups. The group may not be the appropriate unit of study, and serious errors can result when it is assumed that inferences from an ecological analysis pertain to the individuals within the group. Neither theoretical nor empirical analyses have offered consistent guidelines for the interpretation of results from ecological studies. Although correlation coefficients can be obtained from ecological studies, a reliable quantitative estimate of risk cannot.

Table 10.1. Types of observational epidemiological studies (adapted from Monson 1990)

Descriptive studies	Analytical studies
Disease surveillance/surveys	Cross-sectional
Ecological	Longitudinal
	• Cohort or follow-up
	• Case–control

Analytical epidemiological studies are able to provide information about possible causal associations and the magnitude of the risk (Monson 1990). In contrast to ecological studies, individuals within a population group or geographic area are studied. For each study participant, information is obtained about his or her disease, his or her exposure to possible risk factors and other important individual behaviours or characteristics. Analytical studies can be either longitudinal or cross-sectional. In a longitudinal study, a time sequence can be inferred between exposure and disease; that is, it can be determined whether the exposure precedes the disease. In a cross-sectional study, the data on exposure and disease relate to the same time period, and this may present a problem when studying diseases with a long latency period. Longitudinal studies are of two distinct, opposite approaches. The cohort study (also called a follow-up study) begins with an exposure or characteristic of interest and seeks to determine disease consequences of the exposure or characteristic. The case–control (also called case–referent or case–comparison) study begins with a disease or health condition of interest and seeks information about exposures and risk factors.

In a case–control study, individuals enter the study solely on the basis of disease status without knowledge of their exposure status. A single disease or health outcome (e.g. cardiovascular mortality, blood lipid levels) is studied. Persons with the disease or outcome are selected within a defined geographical area or from selected hospital(s), clinic(s) or a specified cohort. A comparison group of individuals in which the condition or disease is absent (the controls or referents) is also selected, preferably randomly, from the same population from which the cases arise. Existing or past attributes and exposures thought to be relevant in the development of the disease are determined for all cases and controls. Because previous exposures are studied, a case–control study is sometimes called a retrospective study. The frequency of exposure is compared for individuals with and without the disease to determine possible associations with the disease being studied. This study design is usually more efficient than the cohort study, requires fewer study participants for adequate statistical power and is often considered as the first option when studying risk factors. Information about relevant individual exposures or behaviour (e.g. smoking, use of hard or soft water and, where water is consumed, calcium and magnesium exposures) is obtained by interview and/or measurement. Often, information must be obtained by questioning a surviving spouse. It may be difficult to accurately assess exposures that may have occurred many years ago and to ensure that the quality and accuracy of information about exposures are similar for cases and controls.

Individuals are selected for the cohort solely on the basis of the presence or absence of certain characteristics, a specific event or their exposure status (e.g. water hardness; high, moderate or low levels of calcium or magnesium in water). A fundamental requirement is that the investigator should not know the disease status of any individual when the cohort is assembled. Morbidity or mortality incidence is then determined for the diseases of interest, and rates are compared for the exposed and unexposed groups in the cohort. An advantage of this study is that more than one health-related outcome or disease can be studied. A cohort can be based on currently defined exposures and followed forward in time or based on historical exposures, if available. For diseases with a long latency period, it may be possible to assemble a historical cohort based on known exposures at some previous point in time. For example, if a cohort could be established based on known drinking-water exposures (e.g. to water hardness) in 1970, over 30 years of exposure would have already occurred, and the follow-up period could be relatively short.

A special kind of cohort study, the community intervention study can be conducted when a community changes water treatment or sources to improve its water quality. Both individual-level and group-level disease and water exposure information can be collected in this type of study. Community intervention studies helped demonstrate the effectiveness of water fluoridation in preventing dental caries. Advantages of this type of study include the following: a time-series analysis can be conducted; water quality is changed at all places where persons may consume water (e.g. home, school, work, restaurants), minimizing exposure misclassification; and a large number of routinely collected community health surveillance data can be evaluated. A major difficulty and limitation of cardiovascular disease studies is that the latency period to effect a detectable change in disease risk may require many years of follow-up, and the population demographics and behaviours may change significantly over time. Since the studies must be conducted in areas considering changes, the areas may not be optimal in terms of water quality or population characteristics.

10.2.2 Random and systematic error

The association observed in each study type should be evaluated to assess possible random and systematic error (Table 10.2). The likelihood that a positive association is due to random error can be assessed by calculating the level of statistical significance ("*p*" value) or the confidence interval. In epidemiology, the confidence interval is the preferred measure of random error because it provides a range of possible values for the risk estimate. It should be remembered, however, that random error or chance can never be completely ruled out as the explanation for an observed result and that statistical significance does not imply causality, biological significance or lack of systematic error.

Table 10.2. Interpreting epidemiological associations

Lack of random error (precision)	Lack of systematic error (validity)
Study size and statistical power	Selection bias
	Misclassification bias
	Observation bias
	Confounding bias

Systematic error or bias affects the validity of an observed association. Systematic error can occur in the design and conduct of the study, leading to a false or spurious association or a measure of risk that departs systematically from the true value. Systematic error should be avoided or controlled; in some instances, its effect may be assessed.

Error can be introduced by observation, selection, misclassification and confounding biases. Selection bias occurs when criteria used to enrol persons into the study are not comparable for exposed and unexposed individuals or cases and controls. Observation bias occurs when disease or exposure information is collected differently from the groups being studied (e.g. cases and controls). Selective or differential recall of cases or controls about their exposure will also result in a biased estimate of risk.

An erroneous diagnosis of disease or erroneous classification of a study participant's exposure will result in misclassification bias. The probability of misclassification can vary in either a differential or non-differential manner among the groups being studied. Non-differential misclassification will almost always bias a study towards not observing an association when one may actually be present or underestimating the magnitude of the association. Differential misclassification bias can result in associations that either under- or overestimate the magnitude of risk. In environmental epidemiological studies where the magnitude of the association is often small, accurate assessment of exposure is critical, as the impact of misclassification can be severe. The imprecise nature of the water hardness estimate presents a potential for exposure misclassification bias in cardiovascular studies.

Confounding bias may convey the appearance of an association; that is, a confounding characteristic rather than the suspected cause or exposure may be responsible for all or much of the observed association. A confounder is a characteristic that can cause or prevent the disease and is associated with the exposure being evaluated. Cigarette smoking is a potential confounder that should be assessed in studies of drinking-water and cardiovascular disease risks. Confounding bias does not necessarily result from any error of the investigator. It is potentially present in all epidemiological studies and must always be considered as a possible explanation for any observed association. If a risk factor or characteristic has no association with exposure or disease, that factor or characteristic cannot confound the association between exposure and disease. To avoid confounding, investigators may employ a technique known as matching. For example, controls may be selected to have similar characteristics as cases (e.g. age, smoking status). Not to be confused with a confounding bias, effect modification refers to a change in the magnitude of the effect of a putative cause (Monson 1990). The possible interactive effects of smoking and a drinking-water factor are an example of effect modification that should be assessed for cardiovascular disease risks.

10.2.3 Strength of association

The magnitude of the risk ratio or relative risk can help investigators assess the spurious nature of an observed association. Based on epidemiological experience (Monson 1990), it is difficult to interpret weak associations, or a relative risk of less than 1.5 (Table 10.3). One or more confounding characteristics can lead to a weak association between exposure and disease, and it is usually not possible to identify and adequately measure or control weak confounding bias. In contrast, a large relative risk is unlikely to be completely explained by an unidentified or uncontrolled confounding factor. The magnitude of a relative risk, however, has no bearing on the possibility that an association is due to observation, selection or misclassification bias. Any of these biases can lead to a total misrepresentation of an observed association. If a relative risk of less than 1.5 is observed in an environmental epidemiological study, a thorough assessment should be made to identify possible uncontrolled confounding.

Table 10.3. Assessing the strength of an epidemiological association (adapted from Monson 1990)

Relative risk	Strength of association
1.0	None
>1.0 – <1.5	Weak
1.5–3.0	Moderate
3.1–10.0	Strong
>10.0	Infinite

10.2.4 Causality of an association

The interpretation of epidemiological data should be made with caution and in the context of all relevant scientific information about the disease and its etiology. No single epidemiological study, even one with little systematic error, can provide a definitive answer about the exposure–disease association. Results from several studies of different design and different population groups allow a more definitive conclusion, and it may be necessary to consider studies in both the general and special populations. Judging causality in epidemiology is based on guidelines (Hill 1965; Rothman 1986; Beaglehole *et al*. 1993), which include:

- *Temporal association*: Exposure must precede the disease, and in most epidemiological studies this can be inferred. When exposure and disease are measured simultaneously, it is possible that exposure has been modified by the presence of disease.
- *Strength of association*: The larger the relative risk or odds ratio, the less likely the association is to be spurious or due to confounding bias. However, a causal association should not be ruled out simply because a weak association is observed.
- *Consistency*: Repeated observation of an association under different study conditions supports an inference of causality; however, its absence does not rule it out.
- *Specificity*: A putative cause or exposure leads to a specific effect. The presence of specificity argues for causality, but its absence does not rule it out.
- *Biological plausibility*: When the association is supported by evidence from clinical research or basic sciences (e.g. toxicology, microbiology) about biological behaviour or mechanisms, an inference of causality is strengthened.
- *Dose–response relationship*: A causal interpretation is more plausible when an epidemiological gradient is found (e.g. higher risk is associated with larger exposures).
- *Reversibility*: An observed association leads to some preventive action, and removal or reduction of the exposure leads to a reduction of disease or risk of disease.

Epidemiologists have debated how scientific evidence should be evaluated in an attempt to better understand causal inferences. Even when repetitions of an association are observed, questions may remain as to whether these associations really constitute an “empirical demonstration that serves as a valid platform for (causal) inference” or whether “the process is still steeped in uncertainty”

(Rothman 1986). Thus, when environmental policy-makers and regulators are confronted with epidemiological associations that suggest the need for action, they must be aware of the uncertainties about causality. Scientific evidence is often conflicting, and the type of evidence or studies that are considered in the evaluation must be given due weight based on the issues mentioned previously (i.e. study design, study precision and study validity).

10.2.5 Web of causation

Many diseases have multiple exposures or risk factors that cause the disease or increase the disease risk, and the disease process is often a complex one. This complexity is evident in the example conceptual model that might be used to describe the relationship between water exposures and other risk factors for cardiovascular disease (Figure 10.1). This model is often referred to as the web of causation (Rockett 1994). It places less emphasis on the role of the agent or water contaminant in favour of other factors that may be important in the onset of disease. Epidemiologists have found lower cardiovascular disease mortality in areas where water hardness (e.g. levels of calcium and magnesium) is high, and some studies have associated water constituents with decreased blood pressure. The use of a dotted line for water exposures in Figure 10.1 suggests that additional evidence may be warranted.

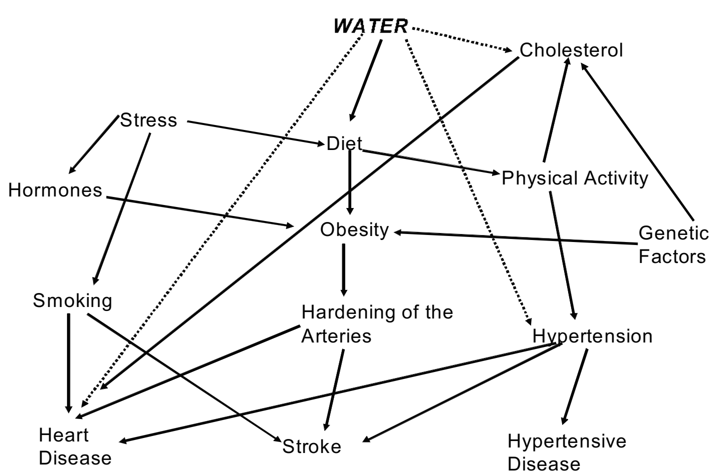

Figure 10.1. Web of causation applied to cardiovascular disease (adapted from Rockett 1994).

10.2.6 Conclusions

Results of ecological studies are useful to identify emerging problems, to develop specific hypotheses for study by analytical studies and, in some instances, to evaluate health conditions and control programmes. Results from analytical studies can provide evidence of a causal association between exposure and disease and estimates of the magnitude of risk, but the studies must be carefully designed and conducted. Because small risks have usually been observed in environmental epidemiological studies, it is extremely important to consider the effects of misclassification bias and confounding on the interpretation of the associations reported for water hardness and cardiovascular disease.

When considering epidemiological evidence for the hard water–cardiovascular disease hypothesis, it is important to critically evaluate each study to determine the quality and amount of information it can contribute to the evaluation of an association's causality and magnitude of risk. At present, sufficient information should be available to assess the causality of the observed association and estimate the benefits that may be attributed to hard water or a specific constituent found in hard water.

10.3 THE ASSOCIATION OF CARDIOVASCULAR DISEASE RISKS WITH WATER HARDNESS

We have summarized information published in recent reviews of the epidemiological studies of cardiovascular disease and drinking-water hardness and calcium and magnesium levels (Catling *et al*. 2005; Monarca *et al*. 2006). The results of these studies are briefly described below.

10.3.1 Epidemiological studies published from 1957 to 1978

More than 50 ecological (geographical correlation) studies were published from 1957 to 1978. Studies were conducted in the United States, the United Kingdom, Ireland, Canada, Sweden, the Netherlands, Finland, Italy, Romania, Czech Republic, Germany, Japan, Australia and Hungary. Populations in 21 cities around the world were also studied. Comstock (1979a,b) reviewed these studies based on size of geographical areas (national or international; province or state; county, borough or city).

10.3.2 Epidemiological studies published after 1978: ecological studies

Twenty ecological studies (Masironi *et al.* 1979; Scassellati Sforzolini *et al.* 1979; Pocock *et al.* 1980; Zielhuis and Haring 1981; Leary *et al.* 1983; Lacey and Shaper 1984; Leoni *et al.* 1985; Smith and Crombie 1987; Grillo *et al.* 1989; Flaten and Bolviken 1991; Gyllerup *et al*. 1991; Rylander *et al*. 1991; Nerbrand *et al*. 1992, 2003; Yang *et al*. 1996; Maheswaran *et al*. 1999; Sauvant and Pepin 2000; Marque *et al*. 2003; Miyake and Iki 2003; Kousa *et al*. 2004) were reviewed (Table 10.4). Some studies took into account potential confounders such as socioeconomic status, income or climate (Pocock *et al*. 1980; Gyllerup *et al.* 1991; Yang *et al*. 1996; Maheswaran *et al*. 1999; Nerbrand *et al.* 1992, 2003; Miyake and Iki 2003).

Ten studies reported a statistically significant inverse (i.e. protective) association between drinking-water hardness and cardiovascular disease mortality (Masironi *et al*. 1979; Pocock *et al.* 1980; Leary *et al*. 1983; Lacey and Shaper 1984; Leoni *et al*. 1985; Rylander *et al*. 1991; Yang *et al*. 1996; Sauvant and Pepin 2000; Marque *et al*. 2003; Kousa *et al*. 2004). When calcium and magnesium were evaluated separately, similar associations with cardiovascular disease mortality were frequently found for each. Four of these studies estimated the effect of drinking-water hardness. A 7.5% reduction of cardiovascular disease mortality in men for 100 mg/l increased water hardness was reported in England and Wales (Lacey and Shaper 1984). In Finland (Kousa *et al*. 2004), the risk of acute myocardial infarction decreased 0.56% for each 10 mg/l increase in water hardness. A 10% increase in the risk of ischaemic heart disease mortality was reported in municipalities in Taiwan, China (Yang *et al*. 1996), with <75 mg/l water hardness compared with those with >150 mg/l hardness. In France (Marque *et al*. 2003), a 10% reduction of the relative risk for cardiovascular disease and ischaemic heart disease mortality and a 14% reduction of the relative risk for stroke mortality were found for the highest compared with the lowest concentrations.

Six of the remaining 10 studies found either a very small inverse association or no association (Scassellati Sforzolini *et al.* 1979; Zielhuis and Haring 1981; Smith and Crombie 1987; Gyllerup *et al*. 1991; Maheswaran *et al*. 1999; Kousa *et al*. 2004). In Norway (Flaten and Bolviken 1991), ischaemic heart disease and stroke mortality rates increased with increased drinking-water magnesium, but these findings are questionable, since virtually all municipalities in the study had soft water.

Table 10.4. Ecological (geographic correlation) studies on the relationship between cardiovascular diseases or stroke and hardness and/or calcium/magnesium concentration of drinking-water

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results
Masironi *et al*. (1979)	Europe, 17 towns, 45–64 years	1974	Total hardness[a] 32–354 mg/l	AMI incidence	M & F: $r = -0.46$
Scassellati Sforzolini *et al*. (1979)	Italy, Umbria Region, 12 municipalities	1967–1976	Total hardness	Mortality for:	
				IHD	M & F: $r = +0.28$
				Stroke	M & F: $r = -0.07$
			Calcium concentration	Mortality for:	
				IHD	M & F: $r = +0.37$
				Stroke	M & F: $r = -0.05$
			Magnesium concentration	Mortality for:	
				IHD	M & F: $r = -0.26$
				Stroke	M & F: $r = -0.28$
Pocock *et al*. (1980)	Great Britain, 253 municipalities, 35–74 years	1969–1973	Total hardness[a] 10–528 mg/l	Mortality for CVD	M & F: $r = -0.67$

Table 10.4 *(continued)*

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results
Zielhuis and Haring (1981)	The Netherlands, 30 communities, ≥30 years	1977	Calcium concentration	Mortality for:	
			16–117 mg/l	IHD	M: $r = -0.01$ F: $r = -0.11$
				Stroke	M: $r = -0.14$ F: $r = -0.12$
			Magnesium concentration	Mortality for:	
				IHD	M: $r = -0.19$ F: $r = -0.10$
			1–15 mg/l	Stroke	M: $r = -0.02$ F: $r = -0.07$
Leary *et al.* (1983)	South Africa, 12 districts, all ages	1978–1982	Magnesium concentration 1–45 mg/l	Mortality for IHD	White M: $r = -0.68$*
Lacey and Shaper (1984)	England and Wales, 14 areas, 45–74 years	1968–1972	Total hardness[a] 19–409 mg/l	Mortality for CVD	M: 7.5% reduction of mortality for 100 mg/l increase of hardness*
Leoni *et al.* (1985)	Italy, Abruzzo Region, 11 water supplies in four provinces, 45–64 years	1969–1978	Total hardness[a]	Mortality for:	
			105.6–443.5 mg/l	CVD	M & F: $r = -0.55$*
				IHD	M & F: $r = -0.59$*
				Stroke	M & F: $r = -0.24$

Table 10.4 *(continued)*

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results	
Smith and Crombie (1987)	Scotland, 56 districts, 35–64 years	1979–1983	Total hardness[a] 0–180 mg/l	Mortality for IHD	M: $r = -0.17$	
Grillo *et al.* (1989)	Italy, Sicily Region, 12 municipalities	1980–1982	Total hardness	Mortality for:		
			NR	CVD	M & F: $r = -0.55$	
				IHD	M & F: $r = +0.50$	
				Stroke	M & F: $r = -0.60$	
Flaten and Bolviken (1991)	Norway, 97 municipalities, all ages	1974–1983	Calcium concentration	Mortality for:		
			0.44–21.7 mg/l	IHD	NR	NR
				Stroke	NR	NR
			Magnesium concentration	Mortality for:		
				IHD	M: $r = +0.33$***	F: $r = +0.23$*
			0.08–2.64 mg/l	Stroke	M: $r = +0.22$**	F: $r = +0.35$**
Gyllerup *et al.* (1991)	Sweden, 259 municipalities (males only), 40–64 years	1975–1984	Total hardness[a] 54.3–92.5 mg/l	Mortality for AMI	Inverse association, with lower relevance after adjusting for cold climate	
			Magnesium concentration NR	Mortality for AMI	Inverse association, with lower relevance after adjusting for cold climate	

Table 10.4 *(continued)*

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results	
Rylander *et al.* (1991)	Sweden, 27 municipalities, 45–64 years	1969–1978	Total hardness[a]	Mortality for:		
			14.32–370.53 mg/l	IHD	M: $r = -0.60$***	F: $r = -0.45$**
				Stroke	M: $r = -0.48$*	F: $r = -0.37$*
			Calcium concentration	Mortality for:		
			3.4–131 mg/l	IHD	M: $r = -0.47$**	F: $r = -0.41$*
				Stroke	M: r = −0.52*	F: $r = -0.32$
			Magnesium concentration	Mortality for:		
				IHD	M: $r = -0.62$**	F: $r = -0.45$**
			0.57–15.0 mg/l	Stroke	M: $r = -0.16$	F: $r = -0.49$
Nerbrand *et al.* (1992)	Sweden, 76 municipalities, 45–74 years	1969–1983	Total hardness[b]	Mortality for:		
			1–216 mg/l	IHD	M***	F*
				Stroke	M***	F***
			Calcium concentration	Mortality for:		
			NR	IHD	M**	F***
				Stroke	M	F***

Table 10.4 *(continued)*

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results	
			Magnesium concentration	Mortality for:		
				IHD	M	F
			NR	Stroke	M	F
Nerbrand *et al.* (1992) *(contd)*			Total hardness[b]	Prevalence of:		
			36.3–315.0 mg/l	IHD	M: not significant association after adjusting for major risk factors	
			Calcium concentration NR	Prevalence of:		
				IHD	M: not significant association after adjusting for major risk factors	
Yang *et al.* (1996)	Taiwan, 227 municipalities, all ages	1981–1990	Total hardness[a]	Mortality for: IHD	RR (95% CI) adjusted for age and urbanization:	
			<75 mg/l		1.096 (1.084–1.108)*	
			75–150 mg/l		1.045 (1.032–1.058)*	
			>150 mg/l		Reference	

Table 10.4 *(continued)*

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results
Maheswaran *et al.* (1999)	England, 305 areas, >45 years	1990–1992	Calcium concentration	Mortality for AMI	RR (95% CI) for 4-fold increase in calcium and magnesium concentration in drinking-water, adjusted for age and SES:
			5–215 mg/l		
			Magnesium concentration		Ca: 0.99 (0.94–1.05)
			2–111 mg/l		Mg: 1.01 (0.96–1.06)
Sauvant and Pepin (2000)	France, Puy de Dôme Department, 52 districts, all ages	1988–1992	Total hardness	Mortality for:	
			NR	IHD	M: $r = -0.33$* F: $r = -0.18$
				Stroke	M: $r = -0.32$* F: $r = -0.34$**
				CVD	M: $r = -0.34$** F: $r = -0.37$**
Marque *et al.* (2003)	France south-west, 69 areas, >65 years	1990–1996	Calcium concentration	Mortality for:	M & F: RR (95% CI) for highest vs lowest tertile adjusted for age:
			94–146 mg/l		
				CVD	0.90 (0.84–0.96)**
				IHD	0.90 (0.84–0.97)**
				Stroke	0.86 (0.77–0.96)*
			Magnesium concentration	Mortality for:	M & F: RR (95% CI) for highest vs lowest tertile adjusted for age:

Table 10.4 *(continued)*

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results
Marque *et al.* (2003) *(contd)*			11–34 mg/l	CVD	0.93 (0.86–1.01)
				IHD	0.96 (0.87–1.05)
				Stroke	0.92 (0.80–1.06)
Miyake and Iki (2003)	Japan, 44 municipalities, all ages	1995	Total hardness[a]	Mortality for stroke	RR (95% CI) adjusted for age, sex, SES, health care status:
			<46.5 mg/l		Reference
			46.5–51.9 mg/l		0.97 (0.91–1.03)
			>51.9 mg/l		0.93 (0.84–1.02)
Nerbrand *et al.* (2003)	Sweden, 2 municipalities in the west and east, 40–59 years	1989–1998	West	Mortality for:[c]	Mortality rates:
			Ca: 8.8 mg/l	IHD	M: 21/1000 F: 5/1000
			Mg: 0.74 mg/l	CVD	M: 31/1000 F: 11/1000
			East	Mortality for:[c]	
			Ca: 66 mg/l	IHD	M: 10/1000 F: 2/1000
			Mg: 4.1 mg/l	CVD	M: 20/1000 F: 6/1000
					RR (West/East) adjusted for age:
					IHD = M: 2.03**** F: 2.56****
					CVD = M: 1.56**** F: 1.71****

Table 10.4 *(continued)*

Reference	Country, area and population age	Period	Drinking-water parameters	CVD or stroke mortality	Results
Kousa *et al*. (2004)	Finland, whole country (males only), 35–74 years	1983, 1988 and 1993	Total hardness[a] (mg/l):	Incidence of AMI per year	Age standardized incidence per 100 000
			<30.6		562.1*
			30.6–93.08		469.5*
			>93.08		437.6*
					Overall effect: 1% reduction of mortality for an increase of 20 mg/l of total hardness

AMI, acute myocardial infarction; Ca, calcium; CI, confidence interval; CVD, cardiovascular diseases; F, females; IHD, ischaemic heart diseases; M, males; Mg, magnesium; NR, not reported; r, correlation coefficient; RR, relative risk; SES, socioeconomic status

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.000\,01$; otherwise, $P > 0.05$; $P < 0.10$ for Masironi *et al*. (1979)

[a] Total hardness in mg/l of calcium carbonate ($CaCO_3$).

[b] Total hardness expressed as mg/l of calcium carbonate ($CaCO_3$) estimated by authors.

[c] Study of 207 inhabitants found positive association for calcium and systolic blood pressure; inverse association for calcium in drinking-water and low-density lipoprotein and total cholesterol; no association for magnesium and major cardiovascular disease risk factors.

10.3.3 Epidemiological studies published after 1978: case–control studies

Associations between cardiovascular disease mortality and calcium or magnesium in drinking-water were investigated in Finland, Taiwan, China, and Sweden (Table 10.5) (Luoma *et al*. 1983; Rubenowitz *et al*. 1996, 1999, 2000; Yang 1998; Yang and Chiu 1999; Rosenlund *et al*. 2005). Five of the seven studies (Luoma *et al*. 1983; Rubenowitz *et al*. 1996, 2000; Yang 1998; Yang and Chiu 1999) found a statistically significant inverse association between magnesium levels in drinking-water and mortality risks for acute myocardial infarction, stroke or hypertension; one study found a significant inverse association between acute myocardial infarction and both calcium and magnesium levels (Rubenowitz *et al*. 1999). Investigators considered major cardiovascular disease risk factors in two studies (Rubenowitz *et al*. 2000; Rosenlund *et al*. 2005); these were the only studies that found no significant association with either mineral.

10.3.4 Epidemiological studies published after 1978: cohort studies

Neither of the two cohort studies (Punsar and Karvonen 1979; Comstock *et al*. 1980) considered major cardiovascular disease risk factors (Table 10.6). Punsar and Karvonen (1979) conducted a 15-year follow-up of 1711 men resident in two rural areas of Finland; all used private well water. Mortality due to coronary heart disease was almost twice (14.7% vs 8.7%) as high in the area with lower drinking-water magnesium. Among 1126 men who submitted a household water sample for analysis, those who died of coronary heart disease had significantly lower mean levels of drinking-water magnesium compared with those alive at the end of the study.

In Washington County, Maryland, USA, Comstock *et al*. (1980) found no consistent association between water hardness and cardiovascular disease mortality. Water samples from 1569 households were analysed for total hardness. An analysis that accounted for socioeconomic characteristics and cigarette smokers showed no significant trend of cardiovascular disease mortality with water hardness. A reduced risk of mortality for arteriosclerotic heart disease was found in men but not women.

Table 10.5. Case–control studies on the relationship between cardiovascular diseases and hardness and/or calcium/magnesium concentrations of drinking-water

Reference	Country, area, year	Population	Age (years)	Drinking-water parameters (years of analysis)	Odds ratio (95% CI)	
Luoma *et al.* (1983)	Finland; south-eastern region; 1974–1975	58 males with AMI, alive or dead (cases)	37–64	Ca concentration	OR unadjusted:	OR unadjusted:
		58 males (hospital controls)		(1974–1975)	Hospital controls	Population controls
		50 males (population controls)		<16 mg/l	0.73 (0.22–1.99)	0.56 (0.25–1.28)
				16–18 mg/l	0.77 (0.30–1.91)	1.07 (0.48–2.42)
				19–20 mg/l	0.91 (0.35–2.36)	1.64 (0.73–3.85)
				>20 mg/l	Reference	Reference
				Mg concentration	OR unadjusted:	OR unadjusted:
				(1974–1975)	Hospital controls	Population controls
				<1.2 mg/l	2.00 (0.69–6.52)	4.67 (1.30–25.32)*
				1.2–1.5 mg/l	1.11 (0.41–3.10)	2.29 (0.88–6.58)
				1.6–3.0 mg/l	1.00 (0.36–3.08)	1.63 (0.62–4.52)
				>3.0 mg/l	Reference	Reference

Table 10.5 *(continued)*

Reference	Country, area, year	Population	Age (years)	Drinking-water parameters (years of analysis)	Odds ratio (95% CI)
Rubenowitz *et al.* (1996)	Southern Sweden, 17 municipalities; 1982–1989	854 males dead for AMI (cases) 989 males dead for cancer (controls)	50–69	Ca concentration (1982–1989)	OR age-adjusted:
				<34 mg/l	Reference
				34–45 mg/l	0.88 (0.65–1.19)
				46–81 mg/l	0.84 (0.64–1.10)
				≥82 mg/l	1.06 (0.82–1.38)
				Mg concentration (1982–1989)	OR age-adjusted:
				<3.6 mg/l	Reference
				3.6–6.8 mg/l	0.88 (0.66–1.16)
				6.9–9.7 mg/l	0.70 (0.53–0.93)*
				≥9.8 mg/l	0.65 (0.50–0.84)*

Table 10.5 *(continued)*

Reference	Country, area, year	Population	Age (years)	Drinking-water parameters (years of analysis)	Odds ratio (95% CI)
Yang (1998)	Taiwan, China, 252 municipalities with single water source; 1989–1993	17 133 males and females dead from stroke (cases) 17 133 males and females dead from other causes, excluding CVD (controls)	50–69	Ca concentration (1990)	OR adjusted for age and sex:
				<24.4 mg/l	Reference
				24.4–42.3 mg/l	1.5 (0.99–1.11)
				42.4–81.0 mg/l	0.95 (0.88–1.01)
				Mg concentration (1990)	OR adjusted for age and sex:
				<7.3 mg/l	Reference
				7.4–13.4 mg/l	0.75 (0.65–0.85)*
				13.5–41.3 mg/l	0.60 (0.52–0.70)*
Rubenowitz *et al.* (1999)	Southern Sweden, 16 municipalities; 1982–1983	378 females dead from AMI (cases) 1368 females dead from cancer (controls)	50–69	Ca concentration (1982–1983)	OR adjusted for age and Mg:
				≤31 mg/l	Reference
				32–45 mg/l	0.61 (0.39–0.94)*
				46–69 mg/l	0.71 (0.49–1.02)
				≥70 mg/l	0.66 (0.47–0.94)*

Table 10.5 *(continued)*

Reference	Country, area, year	Population	Age (years)	Drinking-water parameters (years of analysis)	Odds ratio (95% CI)
Rubenowitz *et al.* (1999) *(contd)*				Mg concentration (1982–1983)	OR adjusted for age and Ca:
				≤3.4 mg/l	Reference
				3.5–6.7 mg/l	1.08 (0.78–1.49)
				6.8–9.8 mg/l	0.93 (0.64–1.34)
				≥9.9 mg/l	0.70 (0.50–0.99)*
Yang and Chiu (1999)	Taiwan, China, 252 municipalities with single water source; 1990–1994	2336 males and females dead from hypertension (cases) 2336 males and females dead from other causes, excluding CVD	50–69	Ca concentration (1990)	OR adjusted for age, sex, urbanization and Mg:
				4.0–11.3 mg/l	Reference
				11.4–30.0 mg/l	1.23 (0.94–1.62)
				30.1–37.7 mg/l	1.32 (0.98–1.78)
				37.8–53.4 mg/l	1.12 (0.83–1.51)
				53.5–81.0 mg/l	1.26 (0.92–2.02)

Table 10.5 *(continued)*

Reference	Country, area, year	Population	Age (years)	Drinking-water parameters (years of analysis)	Odds ratio (95% CI)
Yang and Chiu (1999) *(contd)*		(controls)		Mg concentration (1990)	OR adjusted for age, sex, urbanization and Ca:
				1.5–3.8 mg/l	Reference
				3.9–8.2 mg/l	0.73 (0.57–0.93)***
				8.3–11.1 mg/l	0.66 (0.50–0.87)***
				11.2–16.3 mg/l	0.67 (0.50–0.89)***
				16.4–41.3 mg/l	0.63 (0.47–0.84)***
Rubenowitz *et al.* (2000)	Southern Sweden, 18 municipalities; 1994–1996	263 males and females dead from AMI (cases)	50–74	Ca concentration (1996)	OR adjusted for age and Mg (highest vs lowest quartiles)
				0–235 mg/l	M & F: 0.89 (0.59–1.33)
		258 males and females dead from other causes (controls)		Mg concentration (1996)	OR adjusted for age and Ca (highest vs lowest quartiles)
				0–44 mg/l	M & F: 0.64 (0.42–0.97)*

Table 10.5 *(continued)*

Reference	Country, area, year	Population	Age (years)	Drinking-water parameters (years of analysis)	Odds ratio (95% CI)
Rubenowitz *et al.* (2000) *(contd)*		823 males and females surviving after an AMI (cases)	50–74	Ca concentration (1996)	OR adjusted for age and Mg (highest vs lowest quartiles)
				0–235 mg/l	M & F: 0.97 (0.78–1.21)
		853 males and females without AMI (controls)		Mg concentration (1996)	OR adjusted for age and Ca (highest vs lowest quartiles)
				0–44 mg/l	M & F: 1.16 (0.93–1.45)
Rosenlund *et al.* (2005)	Sweden; 1992–1994	497 males and females with AMI (cases)	45–70	Ca intake from tap water:	OR adjusted for age, gender, smoking, hypertension, DM, SES, physical activity, BMI, job stress (95% CI):
		677 males and females without AMI (controls)		<42.4 mg/day	1.00
				>42.3 mg/day	1.07 (0.62–1.85)
				Mg intake from tap water:	
				<6.9 mg/day	1.00
				>6.9 mg/day	1.07 (0.63–1.82)

Table 10.5 *(continued)*

AMI, acute myocardial infarction; BMI, body mass index; Ca, calcium; CI, confidence interval; CVD, cardiovascular diseases; DM, diabetes mellitus; F, females; M, males; Mg, magnesium; OR, odds ratio; SES, socioeconomic status

* $P < 0.05$; *** $P < 0.001$; all others not statistically significant

Table 10.6. Cohort studies of the relationship between cardiovascular diseases and drinking-water hardness and calcium and magnesium levels

Authors, year of publication	Country and area	Population	Age (years) at recruitment	Period	Cause of death	Drinking-water parameters (years of analysis)	Outcome measure
Punsar and Karvonen (1979)	Finland, two rural regions (West Finland and East Finland)	504 in the west, 622 in the east area with drinking-water Mg data (M)	49–59	1959–1974 (15 years of follow-up)	CHD, others	Mg concentration[a] (1970)	West Finland:
						12.7 mg/l	Died of CHD (*n* = 49/504; 9.7%)
						14.2 mg/l	Died of other causes (*n* = 89/504; 17.7%)
						13.6 mg/l	Survivors (*n* = 366/504 = 72.6%)
							East Finland:
						3.3 mg/l	Died of CHD (*n* = 95/622; 15.3%)
						3.2 mg/l	Died of other causes (*n* = 100/622; 16.1%)

Table 10.6 *(continued)*

Authors, year of publication	Country and area	Population	Age (years) at recruitment	Period	Cause of death	Drinking-water parameters (years of analysis)	Outcome measure	
Punsar and Karvonen (1979) *(contd)*						3.6 mg/l	Survivors ($n = 427/622 =$ 68.6%) RR for east vs west: CHD death = 15.3%/9.7%; 1.6*	
Comstock *et al.* (1980)	Washington County, Maryland, USA	30, 534 (M & F)	>25	1963–1975 (12 years of follow-up)	AHD	Water hardness: 0 vs 200 mg/l of $CaCO_3$ (1971)		RR:
							M: 7+ years[b]	0.69
							M: <7 years[b]	0.86
							F: 7+ years[b]	1.06
							F: <7 years[b]	1.73

AHD = arteriosclerotic heart disease; Ca, calcium; CHD, coronary heart disease; F = females; M = males; Mg, magnesium; RR = relative risk

* $P < 0.01$ (computed by the authors); otherwise, $P > 0.05$

[a] Mean concentrations of magnesium in the drinking-water of men who died in the study period or were still alive in 1974.

[b] Duration of residence prior to the 1963 census (beginning of the study).

10.3.5 A meta-analysis of epidemiological studies

In a systematic review of epidemiological studies, Catling *et al*. (2005) undertook a meta-analysis of case–control studies. They identified only one case–control study linking water hardness and deaths from arteriosclerotic cardiovascular disease, which found no significant association. In contrast, there were six case–control studies linking water magnesium and/or calcium with such deaths. Only one study reported a protective effect of drinking-water calcium on female mortality from acute myocardial infarction (Rubenowitz *et al.* 1996). In contrast, four studies showed a significant protective effect of drinking-water magnesium against mortality from acute myocardial infarction (Rubenowitz *et al.* 1996, 2000), hypertensive disease (Yang and Chiu 1999) and stroke (Yang 1998) for males and females. More recently, another study found no protective effect from water hardness, magnesium or calcium (Rosenlund *et al*. 2005). However, this last study seems to have been conducted in an area with generally low magnesium in the water, and it is doubtful that there would have been sufficient people living in high-magnesium drinking-water areas to see an effect, even if one existed.

The authors of this systematic review distinguished those case–control study papers where the outcome was morbidity from those where the outcome was mortality. It can be seen from Figure 10.2 that the single study of drinking-water calcium and morbidity does not indicate an association; indeed, this was not significant in the original study. The four studies that tested the relationship between drinking-water calcium and mortality from cardiovascular disease also do not support an association (Figure 10.3). From Figure 10.4, there were two case–control studies of drinking-water magnesium and cardiovascular morbidity. Taken together, these studies do not support an effect, and both were non-significant. From Figure 10.5, five case–control studies investigated water magnesium and cardiovascular mortality. Not all of these studies were statistically significant in themselves, and for some there are issues around inadequate control for confounding, but all five showed the same inverse trend, especially at magnesium levels of greater than about 5 mg/l.

The authors of this review concluded that the identified case–control studies do not support an association between water hardness or calcium and cardiovascular disease morbidity or mortality. In contrast, they concluded that water magnesium appears to be inversely associated with cardiovascular mortality but not morbidity (Catling *et al*. 2005).

In the light of this observation, the lack of a significant result for the three cohort studies would not be surprising, given that all three investigated the association with water hardness only.

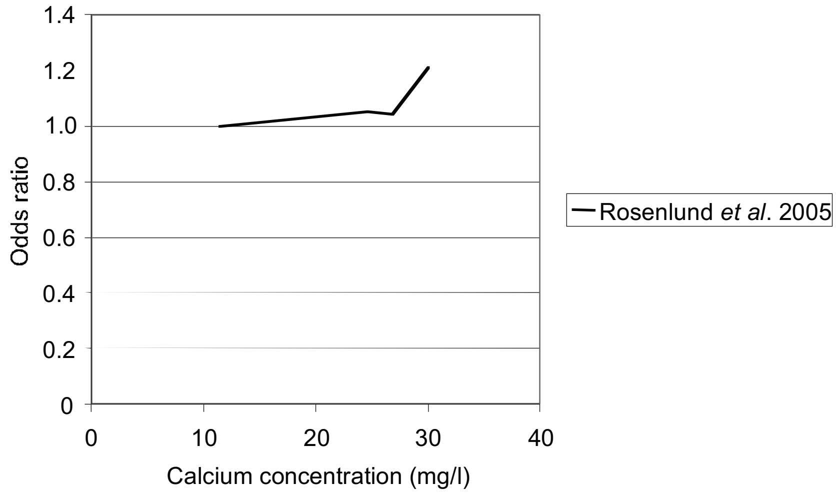

Figure 10.2. Odds ratios of risk of cardiovascular disease in relation to drinking-water calcium (data from Rosenlund *et al*. 2005).

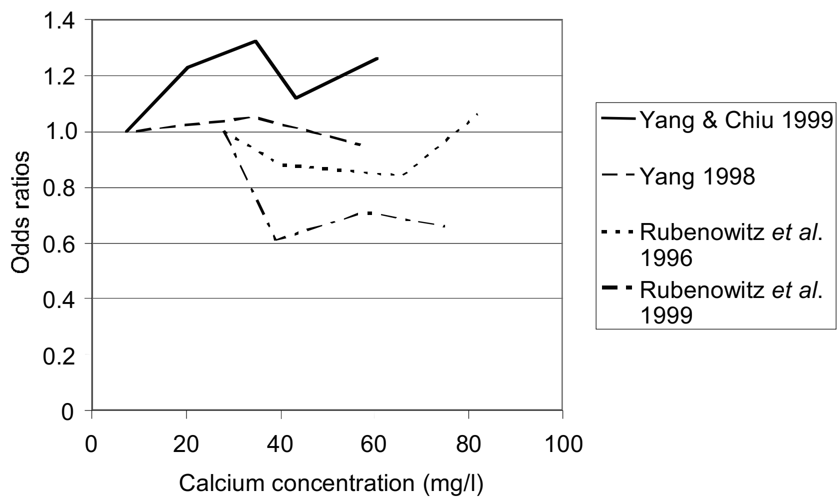

Figure 10.3. Odds ratios of risk of cardiovascular mortality in relation to drinking-water calcium (data from Rubenowitz *et al.* 1996, 1999; Yang 1998; Yang and Chiu 1999).

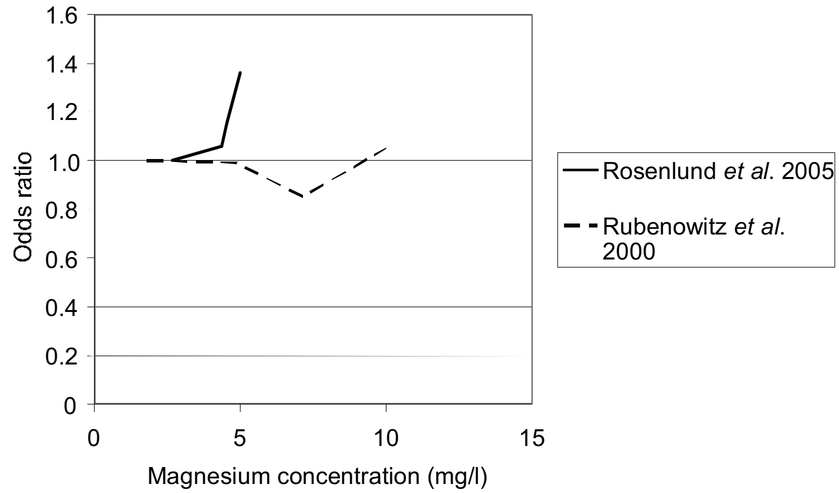

Figure 10.4. Odds ratios of risk of cardiovascular disease in relation to drinking-water magnesium (data from Rubenowitz *et al*. 2000; Rosenlund *et al*. 2005).

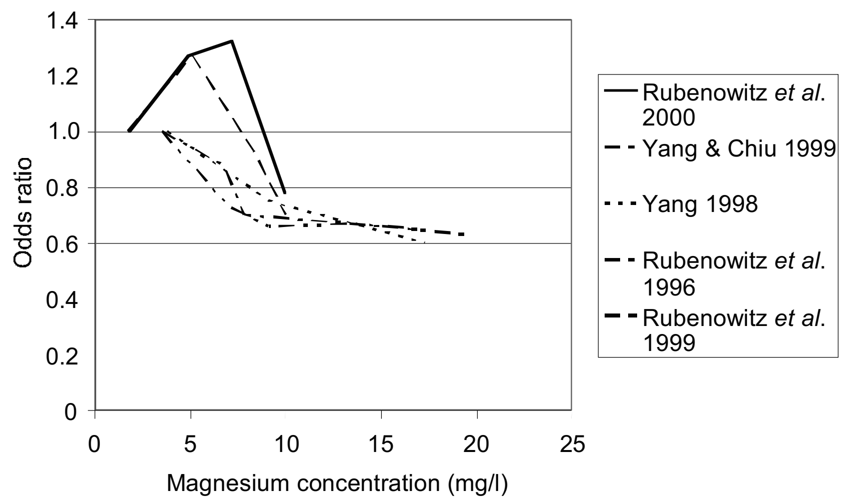

Figure 10.5. Odds ratios of risk of cardiovascular mortality in relation to drinking-water magnesium (data from Rubenowitz *et al*. 1996, 1999, 2000; Yang 1998; Yang and Chiu 1999).

10.3.6 Conclusions

Many ecological studies report an inverse (i.e. protective) association between cardiovascular disease mortality and water hardness, calcium or magnesium levels; however, results are not consistent. Various analytical studies report a reduction in cardiovascular disease mortality risk with increasing magnesium levels in drinking-water, but there is little evidence for an association with water hardness or calcium levels.

In conclusion, the epidemiological evidence for the water hardness–cardiovascular disease hypothesis is still not proven. However, at present, the balance of epidemiological evidence supports the link between magnesium and cardiovascular mortality. Such an association is consistent with evidence of the cardiovascular effects of magnesium deprivation and of inadequate magnesium in the diets of people from developing countries, as discussed elsewhere in this book.

Information from toxicological, dietary and epidemiological studies supports the hypothesis that a low intake of magnesium may increase the risk of dying from, and possibly developing, cardiovascular disease or stroke. Thus, not removing magnesium from drinking-water, or in certain situations increasing the magnesium intake from water, may be beneficial, especially for populations with an insufficient dietary intake of the mineral.

This raises a significant policy issue. How strong does the epidemiological and other evidence need to be before society acts to reduce a potential public health threat rather than await further evidence that such a threat is real? Such a decision is a political rather than a purely public health issue. There is a growing consensus among epidemiologists that the epidemiological evidence, along with clinical and nutritional evidence, is already strong enough to suggest that new guidance should be issued.

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