

A systematic review of analytical observational studies investigating the association between cardiovascular disease and drinking water hardness

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ABSTRACT

The aim of this study is to systematically review and critically assess analytical observational epidemiology studies investigating the association between levels of drinking water hardness and cardiovascular disease. We searched electronic databases and used standardised forms to extract data and assess study quality. Of 2,906 papers identified, 14 met the inclusion criteria (nine case control and five cohort studies). Of the nine case control studies, seven examined both drinking water magnesium and calcium and risk of death from cardiovascular disease. A pooled odds ratio showed a statistically significant inverse association between magnesium and cardiovascular mortality (OR 0.75 (95%CI 0.68, 0.82), $p < 0.001$). Only two studies reported a statistically significant effect for calcium. Substantial heterogeneity between studies made calculation of a summary estimate for drinking water calcium inappropriate. Of three cohort studies reviewed, two were of good quality. A weak suggestion that soft water was harmful in females and possibly associated with a slightly greater risk of sudden death was reported, but there was no association between water hardness and mortality from stroke or cardiovascular disease. This study found significant evidence of an inverse association between magnesium levels in drinking water and cardiovascular mortality following a meta-analysis of case control studies. Evidence for calcium remains unclear.

Key words | calcium, cardiovascular disease, drinking water, magnesium, systematic review, water hardness

INTRODUCTION

It is now almost 50 years since the publication of the first papers suggesting an inverse association between drinking water hardness and cardiovascular mortality in Japan (Kobayashi 1957) and the US (Schroeder 1960). Thereafter, a considerable number of studies have been published investigating this general association in many different nations. Furthermore, recent studies have begun to examine more diverse health outcomes including cancer (Yang & Hung 1998; Yang *et al.* 1999, 2000, 2002). The hardness of drinking water is directly determined by the concentration of dissolved minerals, predominantly calcium and magnesium, mainly in combination with bicarbonate,

sulphate and chloride. The possible role of drinking water hardness, calcium or magnesium in the pathogenesis of cardiovascular disease remains unclear.

A new dimension in the continued interest in what has become known as 'the water story' is presented by the increased use of alternative sources for the provision of drinking water in regions where resources are becoming increasingly strained due to population growth. Two such important practices are water desalination and wastewater reuse. Both technologies generate demineralised water which must then be reblended to increase the concentrations of nutrients including calcium and magnesium.

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The identification of any population health effect that may be associated with the chemical quality of drinking water may therefore be of paramount importance before such demineralised then reblended water may be utilised on a large scale (WHO 1979).

A number of reviews of predominantly ecological studies have been undertaken (e.g. Marx & Neutra 1997; Sauvant & Pepin 2002; Monarca *et al.* 2006); however, these previous publications used a narrative style. We conducted a comprehensive and systematic review of studies examining the apparent effects of soft water on cardiovascular disease and cancer commissioned by the UK Drinking Water Inspectorate (Catling *et al.* 2005). Our systematic review incorporated a defined qualitative assessment of all studies and concluded that further investigation was required.

To date, the body of literature on this topic is dominated by studies of an ecological design (75%, $n = 60$ Catling *et al.* 2005), which generally favour an inverse association between drinking water hardness and cardiovascular mortality. Whilst such studies are beneficial for hypothesis generation and preliminary investigation, the ecological study design has a number of inherent limitations and is unable to address causality. This study concentrates on analytical epidemiological studies examining drinking water hardness, calcium or magnesium and cardiovascular disease, and reports a focused assessment of methodologically superior studies (case control and cohort) including meta-analysis where appropriate.

METHODS

Search strategy

A standardised search strategy was devised including the following major search terms as both medical subject headings (MeSH) and text words where appropriate: water, calcium or calcium compounds, magnesium or magnesium compounds, hardness or hardness tests, soft, softened, water supply, water softening, hydrotimetry, cardiovascular disease, coronary disease, coronary arteriosclerosis, heart disease, cerebrovascular disease, hypertension, blood pressure. Electronic databases including MEDLINE (1985–2006), EMBASE (1985–2006), BIOSIS (1985–2006), Web of Science

(1985–2006), CINAHL (1985–2006), Toxline, SIGLE, the UK National Research Database and the Cochrane database were searched. This search strategy was designed to be broad and inclusive to increase sensitivity.

Data extraction

The titles and abstracts of the papers were screened by two reviewers (LC and IA). Papers were retained if they presented primary data of human studies, were related directly to the research question, involved a comparison of populations or individuals at different levels of exposure using a case control or cohort design, and were in the English language. Disagreements were settled by consensus.

Separate forms were designed to abstract data on results and study quality for case control and cohort studies. Papers were independently reviewed by two individuals to extract data including patient or population characteristics, location of the study, outcome measures examined (types of illness/health effects considered) and exposure characteristics (levels of drinking water hardness or specific constituents). The age and gender adjusted effect estimates (odds ratios and relative risk where appropriate) and corresponding measures of precision were extracted for the highest level of exposure compared with the referent category.

The methodological quality of studies was assessed using components of the Newcastle-Ottawa criteria (Wells *et al.* 2001). The information extracted for the different study types variously examined exposure characterisation (use of a proxy or average measure of exposure, role of bias, timing of measurement), population characteristics (selection of cases and controls, adequacy of response rate/follow up, adequacy of length of follow up) and statistical analysis (confounding, collinearity, adequacy of reporting, method of analysis).

Statistical analysis

Where appropriate data were available, studies were then summarised according to type of exposure (total water hardness, magnesium and/or calcium) and meta-analysis was used to pool odds ratios. Heterogeneity was assessed using the Cochran's Q test statistic and quantified using the

I^2 statistic (Higgins *et al.* 2003). Where heterogeneity was not significant, fixed effects models were used, otherwise random-effects models were generated. The possibility of publication bias was examined by funnel plot and Egger's test. All analyses were conducted using the software Stata (version 9, StataCorp, USA).

RESULTS

Figure 1 illustrates the process of study selection. The initial search identified 2,906 studies. Following exclusions, a total of 14 papers presenting analytical results of epidemiological studies were included in this review. Characteristics of these studies are detailed in Tables 1 and 2. A total of nine case control studies were identified, all of which were defined as good quality using the criteria previously described. Of the case control studies, only two considered cardiovascular morbidity as the outcome of interest. There was no significant association between acute myocardial infarction (AMI) and drinking magnesium or calcium (Luoma *et al.* 1983; Rosenlund *et al.* 2005) or water hardness (Rosenlund *et al.* 2005).

The majority of case control studies considered cardiovascular mortality as the outcome of interest. From a total of

nine studies, only one considered drinking water hardness as the exposure variable and examined its association with deaths from atherosclerotic cardiovascular disease (Comstock 1971). That study reported no significant association. The case definition used by Luoma *et al.* (1983) included individuals both alive and deceased following first acute myocardial infarction (AMI), therefore differential effects on morbidity or mortality could not be examined. The remaining seven case control studies assessed concentrations of specific drinking water constituents, namely magnesium and calcium, and cardiovascular disease mortality. Of these, five studies reported no evidence of a statistically significant association between calcium concentrations and cardiovascular mortality with no consistent direction of association (Rubenowitz *et al.* 1996, 2000; Yang 1998; Yang & Chiu 1999; Rosenlund *et al.* 2005). Two studies reported a protective effect of drinking water calcium on mortality from AMI for females (Rubenowitz *et al.* 1999) and males and females combined (Yang *et al.* 2006). Contrastingly, five of the seven studies showed a statistically significant protective effect of drinking water magnesium against mortality from AMI (Rubenowitz *et al.* 1996, 1999, 2000), hypertensive disease (Yang & Chiu 1999) and stroke (Yang 1998) for males and females.

Three cohort studies reported in five publications were identified. There were two high quality studies

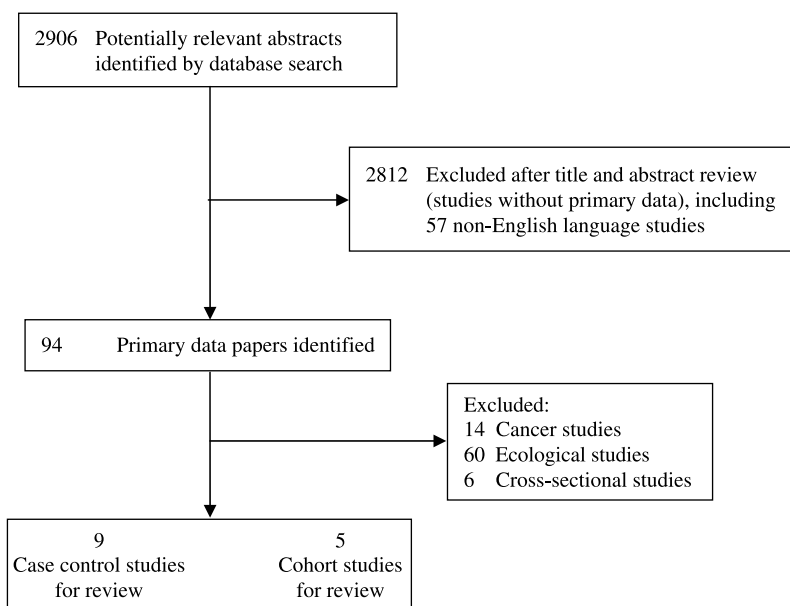


Figure 1 | Illustration of selection process for studies examining cardiovascular disease and drinking water hardness, calcium or magnesium concentrations.

Table 1 | Characteristics of case control studies examining the association between drinking water hardness, calcium or magnesium and cardiovascular disease

Author	Country, population characteristics, period	Cases and controls	Drinking water parameters
Yang <i>et al.</i> (2006)	Taiwan, 252 municipalities, males and females, 50–69 years, 1994–2003	10,094 cases AMI deaths 10,094 controls	Cases vs. controls: mean \pm SD (mg l ⁻¹) Calcium (33.6 \pm 19.5 vs. 36.3 \pm 19.1) Magnesium (11.3 \pm 7.6 vs. 11.8 \pm 7.7)
Rosenlund <i>et al.</i> (2005)	Sweden, males and females, 45–70 years, 1992–1994	497 cases AMI (alive or dead) 677 controls 58 cases AMI deaths 171 controls	Water hardness median 4.5dH° Calcium median 25.1 mg l ⁻¹ Magnesium median 4.4 mg l ⁻¹ [Calcium intake mg day ⁻¹] [Magnesium intake mg day ⁻¹]
Rubenowitz <i>et al.</i> (2000)	Sweden, 18 municipalities, males and females, 50–74 years, 1994–1996	263 cases AMI deaths 258 controls	Calcium range 0–235 mg l ⁻¹ Magnesium range 0–44 mg l ⁻¹
Rubenowitz <i>et al.</i> (1999)	Sweden, 16 municipalities, females, 50–69 years, 1982–1993	378 cases AMI deaths 1368 controls	Calcium range 8–230 mg l ⁻¹ Magnesium range 1.3–21.5 mg l ⁻¹
Yang & Chiu (1999)	Taiwan, 252 municipalities, males and females, 50–69 years, 1990–1994	2,336 cases hypertension deaths 2,336 controls	Cases vs. controls: mean \pm SD (mg l ⁻¹) Calcium (32.9 \pm 20.3 vs. 34.8 \pm 19.5) Magnesium (10.9 \pm 7.6 vs. 11.2 \pm 7.5)
Yang (1998)	Taiwan, 252 municipalities, males and females, 50–69 years, 1989–1993	17,133 cases cerebro-vascular deaths 17,133 controls	Cases vs. controls: mean \pm SD (mg l ⁻¹) Calcium (34.5 \pm 19.5 vs. 34.8 \pm 19.5) Magnesium (11.3 \pm 7.5 vs. 11.4 \pm 7.5)
Rubenowitz <i>et al.</i> (1996)	Sweden, 17 municipalities, males, 50–69 years, 1982–1989	854 cases AMI deaths 989 controls	Calcium range 22–225 mg l ⁻¹ Magnesium range 1.3–20.0 mg l ⁻¹
Luoma <i>et al.</i> (1983)	Finland, males 30–64 years, 1974–1975	50 case-control pairs cases first AMI (alive or dead) 113 hospital controls 127 population controls	Cases vs. PC: mean \pm SD (mg l ⁻¹) Calcium (20.7 \pm 11.7 vs. 18.8 \pm 8.2) Magnesium (3.93 \pm 7.98 vs. 2.85 \pm 2.50)
Comstock (1971)	USA, white males 45–65 years	189 cases arteriosclerotic heart disease deaths 2 controls per case	Water hardness (range 0–450 ppm CaCO ₃)

SD = standard deviation, dH° = German hardness degree, AMI = acute myocardial infarction, PC = population controls.

examining drinking water hardness as the predictor variable: Comstock (1979) Comstock *et al.* (1980) and the British Regional Heart Study (Morris *et al.* 2001). There was also one poor quality study by Punsar *et al.* (1975) and Punsar & Karvonen (1979).

Comstock *et al.* reported mortality from stroke (Comstock 1979) and arteriosclerotic heart disease (Comstock *et al.* 1980) in a large cohort of males and females in the US. There was no significant association between water hardness and stroke mortality, and only a weak suggestion that soft water was harmful in females and possibly associated with a slightly greater risk of sudden death. Punsar *et al.* examined coronary heart disease (CHD) incidence and mortality in Finnish males.

Neither drinking water calcium or magnesium concentrations were associated with individual level risk factors for CHD (Punsar *et al.* 1975). A lower, but non-significant, drinking water magnesium concentration was described for males dying from CHD during a follow up period of 10 years (Punsar *et al.* 1975) and 15 years (Punsar & Karvonen 1979). The cohort study by Morris *et al.* (2001) presented findings of a 15 year follow up of the British Regional Heart Study. During this study, 7,735 males were followed within 24 towns. The occurrence of both fatal and non-fatal CHD was examined at the town level by multilevel modelling of individual level risk factors of males within towns, and town level environmental variables, including drinking water hardness. There was an

Table 2 | Characteristics of cohort studies examining the association between drinking water hardness, calcium or magnesium content and cardiovascular disease

Author	Country, population characteristics, period	Outcome measures	Drinking water parameters
Morris <i>et al.</i> (2001)	UK, 15 year follow up of 7,735 males in 24 towns, aged 40–59 years at baseline, 1978–1996	Major fatal and non-fatal coronary heart disease	Drinking water hardness
Comstock (1979)	USA, enumeration districts, 12 year follow up of 36,860 males and females adults >25 years, 1963–1975	Stroke mortality	Categories of drinking water hardness (range 0–389 ppm CaCO ₃)
Comstock <i>et al.</i> (1980)	USA, enumeration districts, 12 year follow up of 30,942 white adults >25 years, 1963–1975	Arteriosclerotic heart disease mortality	Categories of drinking water hardness (range 0–389 ppm CaCO ₃)
Punsar <i>et al.</i> (1975)	Finland, 10 year follow up of 2 rural male cohorts (east, n = 622 and west, n = 504), 1970	Coronary heart disease mortality, survivors classified by heart health status, also examined individual blood pressure, serum cholesterol and ECGs	west v east (mean ± SD) mg l ⁻¹ Calcium (22.7 ± 3.7 vs. 11.9 ± 4.5) Magnesium (13.6 ± 6.6 vs. 3.5 ± 1.5)
Punsar & Karvonen (1979)	Finland, 15 year follow up of 2 rural cohorts: 888 males (west) and 888 males (east), 1959–1974	CHD mortality and sudden death (unexpected and within 1 hour)	Magnesium

SD = standard deviation. ppm = parts per million.

inverse but non-statistically significant association between water hardness and CHD incidence after controlling for age alone (OR 0.91 (95%CI 0.83, 1.00)), or all individual level risk factors (OR 0.96 (0.88, 1.05)).

The studies conducted by Punsar *et al.* (1975) and Punsar & Karvonen (1979) were of poorer quality comparing two areas only with no adjustment for individual level risk factors. All cohort studies applied an average measure of areal drinking water quality to the individual. However greater efforts were made by Comstock (1979) and Comstock *et al.* (1980) to increase the likelihood of homogeneity of drinking water exposure by area by aggregating repeated samples at the individual level, compared with the application of town level water parameters by the other cohort studies (Punsar *et al.* 1975; Punsar & Karvonen 1979; Morris *et al.* 2001).

Figure 2(a) and (b) presents the odds ratios as described by the case control studies for cardiovascular mortality and drinking water magnesium and calcium concentrations, respectively. Figure 2(a) illustrates a more consistent trend of decreased odds ratios at higher magnesium concentrations. It was not possible to summarise relative risks from the cohort studies using meta-analysis because of differences in the

outcome measures used. The results given in the seven case control studies examining cardiovascular mortality and drinking water magnesium or calcium were then considered for meta-analysis. Two papers were excluded from analysis. Rosenlund *et al.* (2005) did not present the exposure data in a manner comparable to the other studies (exposure expressed as intake mg day⁻¹ compared with concentration mg l⁻¹), and Rubenowitz *et al.* (2000) did not present data for the drinking water calcium concentrations examined.

Figure 3(a) illustrates the result of the meta-analysis for drinking water magnesium. Drinking water magnesium concentrations in the highest exposure category (range 8.3 to 19.4 mg l⁻¹) were significantly associated with a decreased likelihood of cardiovascular mortality (OR 0.75 (95% CI 0.68, 0.82), $p < 0.001$), compared with the baseline (range 2.5 to 8.2 mg l⁻¹). Inclusion of the data from Rosenlund *et al.* (2005) did not affect the pooled estimate. Heterogeneity between studies was found to be moderate ($Q = 9.80$, $p = 0.081$, $I^2 = 49\%$). Subgroup analysis showed that the pooled estimate was not sensitive to the cardiovascular outcome considered (AMI only, 0.73 (0.62, 0.86), $p < 0.001$) or differences between the centres conducting the studies (Sweden 0.65 (0.54, 0.78) $p < 0.001$, Taiwan 0.77 (0.70, 0.86) $p < 0.001$).

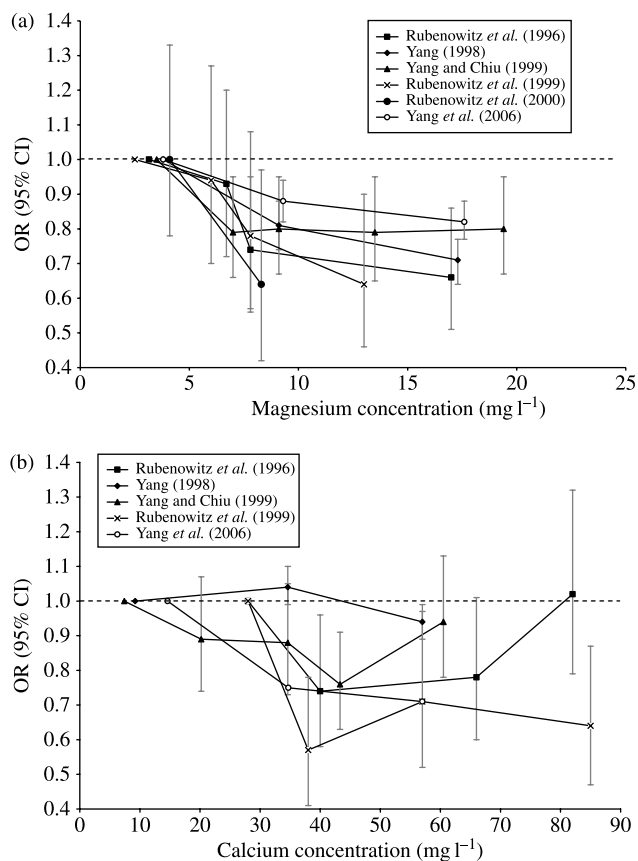


Figure 2 | Plot of odds ratios (and 95% confidence intervals) of risk of cardiovascular mortality in relation to (a) drinking water magnesium concentration (mg l⁻¹) by study, (b) drinking water calcium concentration (mg l⁻¹) by study.

Meta-analysis of observations for drinking water calcium showed a high degree of heterogeneity between studies ($Q = 45.04$ $p < 0.001$, $I^2 = 91.1\%$). This signifies substantial inconsistency between studies therefore it was not appropriate to derive a single summary estimate for calcium and cardiovascular mortality. A funnel plot illustrating the variation in study results according to study size is presented in Figure 4. There was no statistical evidence of publication bias (Egger's test $p = 0.49$). However, only a small number of studies were considered in this meta-analysis therefore it is possible that smaller studies showing odds ratios closer to unity with higher standard errors may be missing. This may be indicative of publication bias against smaller studies finding a non-significant association. The individual study observations for the highest level of drinking water calcium against the referent category are illustrated in Figure 3(b).

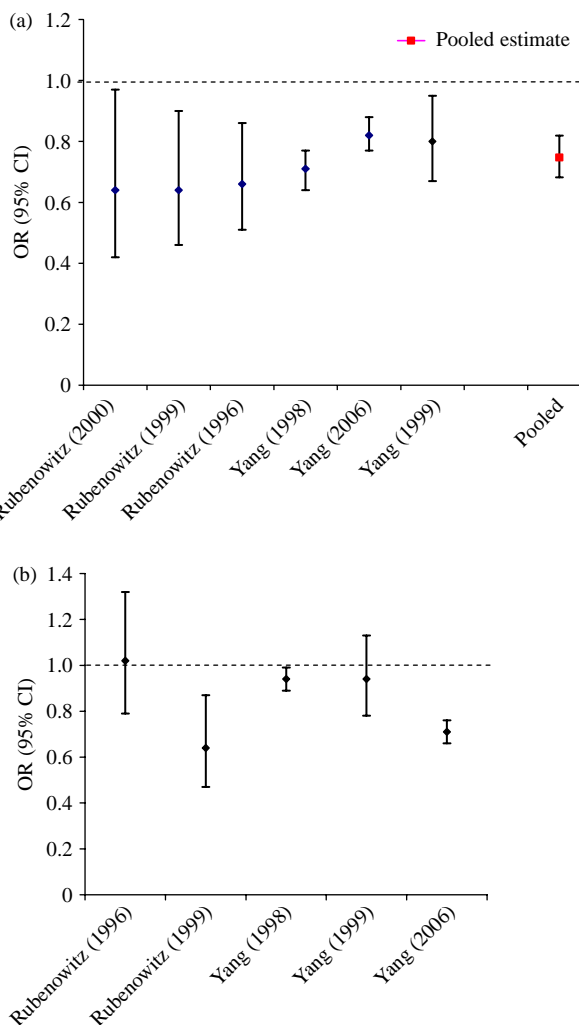


Figure 3 | Forest plot showing individual study odds ratios and 95% confidence intervals for cardiovascular mortality for (a) the highest level of exposure (by first author) and the estimate - drinking water magnesium, (b) the highest level of exposure (by first author) - drinking water calcium.

DISCUSSION

This systematic review found evidence to support an inverse association between cardiovascular mortality and drinking water magnesium levels from a meta-analysis of case control studies. There was limited evidence to support an association between cardiovascular mortality and calcium levels. There was insufficient evidence to examine drinking water hardness, calcium or magnesium and cardiovascular morbidity.

Prospective cohort studies are the methodological ideal for the examination of a causal association between an

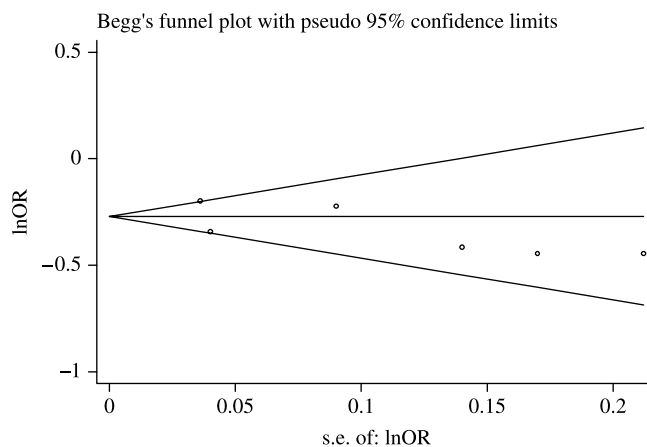


Figure 4 | Funnel plot showing the natural logarithms of the odds ratios (lnOR) for cardiovascular mortality at the highest level of magnesium exposure against the corresponding standard errors of the lnOR for the six case control studies considered in meta-analysis.

exposure and an outcome. However the exposure variable was poorly presented in two cohort studies making comparisons difficult (Punsar *et al.* 1975; Punsar & Karvonen 1979; Comstock 1979; Comstock *et al.* 1980). The third cohort study (Morris *et al.* 2001), and perhaps the best designed, has a notable limitation due to the inadequacy of exposure characterisation. An ecological measure of water hardness was utilised at the town level. Consequently the large potential for measurement error of the drinking water variable, together with the small sample size of 24 towns, may reduce the ability of this study to detect an association.

The aetiology of cardiovascular disease is multifactorial and complex. Many factors can contribute to its development and progression including atherosclerosis, blood coagulability and electrical factors. Both calcium and magnesium have been the subjects of a number of extensive studies with regard to cardiovascular disease (Durlach *et al.* 1985; Rylander 1996; Marx & Neutra 1997). An increased calcium intake from dietary intervention and supplementation studies has been associated with a general decrease in blood pressure, a major established risk factor for cardiovascular disease (McCarron & Reusser 1999). Furthermore, the greatest blood pressure decreases have been observed in individuals with the lowest calcium intakes (Dwyer *et al.* 1998; McCarron & Reusser 1999) and hypertension (Appel *et al.* 1997).

A similar beneficial role has been suggested for increased magnesium intake (Chakraborti *et al.* 2002). Animal studies have demonstrated magnesium deficiency to be associated with cardiac arrhythmias, which predispose to fatal myocardial infarction (Anderson *et al.* 1975). Moreover, animal studies have also shown that supplemental magnesium delivered via drinking water significantly improved the lipid profile and inhibited atherosclerosis (Sherer *et al.* 1999; Sherer *et al.* 2000; Cohen *et al.* 2002). There is also evidence that magnesium deficiency may contribute to insulin resistance, a risk factor for cardiovascular disease (Ma *et al.* 1995). Further evidence supporting an association comes from a prospective population based cohort study showing that serum magnesium concentrations were significantly and inversely associated with future risk of cardiovascular mortality (Ford 1999). However, the evidence to date is too weak and inconsistent to allow any firm conclusions to be drawn regarding the possible biological mechanism linking drinking water quality and cardiovascular disease.

An important question is whether the amount of calcium and magnesium obtained through drinking water can realistically and critically contribute to body status to an extent that could be reflected in cardiovascular health. Dietary surveys have shown an insufficient calcium and magnesium intake within both the general population (Galan *et al.* 2002) and the elderly (Aptel *et al.* 1999). A nationally representative dietary survey of British adults (aged 19–64 years) found dietary sources to be barely adequate for calcium and inadequate for magnesium provision in the general population (Ruston *et al.* 2004). The calcium bioavailability of calcium rich waters has been shown to be similar to that of both milk and supplements (Galan *et al.* 2002). Similarly, hydrated magnesium ions sourced from drinking water may be more rapidly and efficiently absorbed than the complexed magnesium ions present in food (Durlach *et al.* 1985).

Drinking water concentrations at levels detailed by the epidemiological studies reviewed here have been demonstrated to significantly contribute both to the total daily intake and overall body status of calcium and magnesium. This was shown by a well controlled large observational study (Galan *et al.* 2002) and high quality intervention studies in both healthy elderly (Rubenowitz *et al.* 1998) and

young (Guillemant *et al.* 2000) subjects. Additionally, the potential importance of drinking water as a source of calcium and magnesium is supported by the greater absorption efficiency seen with a frequent intake of smaller doses, as would be the case with regular consumption of drinking water throughout the day (Guillemant *et al.* 2000). Furthermore, two intervention studies demonstrated significant improvements in cardiovascular risk factors following consumption of highly mineralised drinking water, with significant blood pressure reductions (Rylander & Arnaud 2004) and beneficial changes in the lipid profile (Schoppen *et al.* 2004). It is therefore not infeasible that calcium and magnesium in drinking water may significantly contribute to daily intake and mineral status, and cardiovascular health.

An important consideration is that this meta-analysis is dependent upon the quality of the studies included in this review. A key limitation of all the studies examined within this review was the characterisation of the exposure variable, drinking water hardness, calcium and/or magnesium. The vast majority of individual level studies, including the cohort studies, applied an ecological measure of drinking water quality to the individual level data in the analysis of exposure and outcome. This introduces an ecological bias as the exposure value assigned to the individual does not necessarily reflect that individual's true exposure. Furthermore, in these studies of cardiovascular mortality the individual's level of consumption was not quantified. A recent study examined magnesium and calcium intake from water (mg day^{-1}) (Rosenlund *et al.* 2005). However, the narrow range of water concentrations considered means it is doubtful that a sufficient number of individuals would have been living in areas of high drinking water magnesium to detect an effect if one existed. Another important limitation is the lack of consideration of all possible confounding factors by the studies examined. If individual level cardiovascular risk factors vary with exposure, residual confounding may have resulted in our finding of a significant protective effect of magnesium. Conversely, if the biological mechanism operates by moderating an individual level risk factor, for example blood pressure, controlling for that factor will reduce the ability of the study to detect an association. In addition, this meta-analysis was not carried out using individual level

data; therefore, the variables adjusted for in the included studies were different.

Figure 1 showed that 57 non-English language studies were excluded. Of the seven with abstracts, all were identified as ecological studies and would not have contributed to this study. Our full search identified studies with negative, neutral and positive results suggesting that the effect of publication bias may not be a major issue. Whilst there was no statistical evidence of publication bias, only a small number of studies contributed to the meta-analysis.

CONCLUSION

The evidence from this review supports an association between cardiovascular mortality and magnesium levels in water; however, the studies had important limitations. This finding may explain the associations reported between total water hardness and cardiovascular mortality in earlier studies. Despite the weak evidence from the limited cohort studies, the statistically significant inverse association observed in the meta-analysis of case control studies requires further investigation.

Cardiovascular disease is the leading cause of death in industrialised nations. Consumption of mains drinking water in England and Wales was reported to be greater in the population groups and areas at highest risk for cardiovascular disease (MEL Research 1996). If the association between drinking water characteristics and cardiovascular disease is causal, this represents a great potential for possible health benefits through drinking water hardness modification. Furthermore the accessibility of any intervention at the population level may bring widespread benefit when compared with resistance at attempts to modify behavioural risk factors such as smoking and obesity.

The comparatively small reduction in cardiovascular risk seen with increasing magnesium concentrations in drinking water may translate to a substantial public health benefit at the population level. Despite there being a large volume of literature examining this topic, there are few high quality analytical observational studies, most of which are based in two centres (Sweden and Taiwan). This highlights the need for more well designed epidemiological investigations of health outcomes in a wider variety of settings

to address the deficiencies of the studies to date, and facilitate a more appropriate assessment of a possible causal association between drinking water quality and cardiovascular disease. A major challenge for future studies is the accurate measurement of individual consumption of minerals in drinking water and diet (both qualitative and quantitative), the mineral nutritional status of the study population and the determination of the biologically relevant dose. Such essential individual level studies are costly and as such face a number of challenges. Studies specifically based on natural experiments where changes in water hardness have taken place provide an alternative means for assessing this hypothesis and contributing to the current state of knowledge.

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