Cardiovascular diseases and hard drinking waters: implications from a systematic review with meta-analysis of case-control studies

Vincenza Gianfredi, Nicola Luigi Bragazzi, Daniele Nucci, Milena Villarini and Massimo Moretti

ABSTRACT

This systematic review with meta-analysis, performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, aims at evaluating the potential correlation between magnesium and calcium concentration in drinking waters and the risk of cardiovascular diseases (CVD), which impose a considerable burden in high-income countries. Included studies were of the case-control studies type. From an initial list of 643 potentially eligible articles, seven studies were finally retained in the quantitative analysis. Since each one of them assessed different ion concentrations, subjects exposed to the highest concentration *versus* those exposed to the lowest concentration were compared. By including an overall figure of 44,000 subjects, the result suggests a protective effect of the ions on CVD prevention, with an effect-size (ES) of 0.82 (95% confidence interval CI = [0.70–0.95], *p*-value = 0.008) for calcium, and ES = 0.75 (95% CI = [0.66–0.86], *p*-value = 0.000) for magnesium. Hard water consumption seems to be protective against CVD. However, the high heterogeneity ($I^2 = 75.24$, *p*-value = 0.001 for calcium; $I^2 = 72.96$, *p*-value = 0.0024 for magnesium) and the existence of publication bias limits the robustness and generalizability of these findings. Further high-quality studies are needed to reproduce and confirm these results.

Key words | cardiovascular diseases, hard waters, meta-analysis, prevention, systematic review

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INTRODUCTION

Cardiovascular diseases (CVD) are characterized by a relevant mortality in high-income countries. CVD are influenced by lifestyle and the risk factors include obesity, dyslipidemia, type II diabetes mellitus, cigarette smoke, and physical inactivity, among others. During the last decade, many epidemiological studies have shown an association between high concentrations of calcium (Ca^{++}) and magnesium (Mg^{++}) in drinking water and the low risk for CVD (Anne 2011). On the other hand, some randomized controlled trials have concluded that the increased intake of Mg^{++} or Ca^{++} through diet or supplements is ineffective to reduce blood pressure in hypertensive and normotensive people (Grossman *et al.* 1997).

The 'Dietary approaches to stop hypertension' study has shown that diets rich in fruits, vegetables, as well as low-fat dairy foods and those with reduced saturated and total fat, can substantially lower blood pressure. This diet offers an extra Mg^{++} intake, which may be useful to prevent and treat hypertension (Hyp) (Appel *et al.* 1997; Conlin *et al.* 2000). Consuming hard water, rich in Ca^{++} and Mg^{++}, can reduce mortality, as shown by a number of case-control studies (Rubenowitz *et al.* 1996, 1999,

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2000; Yang & Chiu 1998, 1999; Rosenlund *et al.* 2005; Yang *et al.* 2006).

All in all, most studies suggest a moderate protective role between hard water and CVD. Scholars speculate that this can be due to three mechanisms (Hopps & Feder 1986; Atkinson *et al.* 2009): (1) soft water is more corrosive than hard water and promotes the dissolution of cadmium, lead, and other toxic substances from the plumbing system into the drinking water; (2) a protective effect from magnesium in water; and (3) other unknown reasons.

According to the World Health Organization (WHO) (2011), water hardness can be defined as the measure of the water capacity to react with soap and to produce a noticeable deposit of precipitate (e.g. insoluble metals or salts). Hardness is most commonly expressed as milligrams of calcium carbonate equivalent per liter (mg/L $CaCO_3$), where 10 mg/L $CaCO_3$ corresponds to 1 French degree. Although cations cause hardness, it may also be discussed in terms of carbonate (temporary) and non-carbonate (permanent) hardness (Nardi *et al.* 2003).

Hardness is not caused by a single substance but by a variety of dissolved polyvalent metallic ions, predominantly Ca^{++} and Mg^{++} cations, although other cations (e.g. aluminium, barium, iron, manganese, strontium and zinc) may also contribute.

Calcium and magnesium are essential minerals and are beneficial for human health. Ca^{++} is essential for blood clotting, nerve impulse transmission and muscle contraction; Mg^{++} is involved in energy transfer and release and plays a major role in heart physiology. The total body stores of calcium are in the order of 1,200 g, with about 99% in bones and teeth, whereas the total body scores of Mg^{++} are about 20–28 g.

Milk and dairy products contribute to more than 65% of total calcium intake (540 mg/day). The remaining amount is distributed as following: 12% from plants (97 mg/day); 8.5% from cereals (70 mg/day), 6.5% from meat and fish (53 mg/day).

Magnesium intake by food (excluding drinks) is 254 mg, with a very limited geographic variability: from 246 to 262 mg depending on the area (Turrini *et al.* 1991). The main source of magnesium are plant products: 30% from greens, 29% from cereals and derived products, 15% from fruits; 14% from eggs, meat and fish and 12% from milk and dairy products. Recommended daily intake is 800–1,000 mg for Ca^{++} and 170 mg for Mg^{++}. These values have been defined considering that body needs vary according to physiological conditions, age and gender (the intestinal absorption of Ca^{++} decreases with increasing age and this is even more true in female individuals) (SINU 2014).

Natural and treated waters have a wide range of mineral content from low levels to moderate and high levels (1–400 mg/L per Ca^{++}, 1–50 mg/L per Mg^{++}). Calcium and magnesium are present in water as ions, therefore being more bioavailable than mineral constituents of food and milk. Drinking water may largely contribute to total Ca^{++} and Mg^{++} intake in the population.

The aim of this investigation was to study the potential preventive role of hard water in CVD. The current meta-analysis reviews the scientific literature and attempts to explore the health effects of hard water in relation to the quality of water and mineral concentration.

METHODS

Database

We performed a structured computer search on PubMed in order to identify epidemiological studies reporting results of primary researches with cross-sectional evaluation of CVD in people exposed to different electrolyte concentrations. We used a string including the following search terms, with the appropriate combinations of Boolean connectors: hardness, calcium, magnesium, drinking water, cardiovascular disease, stroke, ischemia, ischemic heart disease, hypertension, myocardial infarction, cerebrovascular disorder. Two independent researchers performed these searches, which were broadened by extensive cross-checking of the reference lists of all retrieved articles.

Criteria of inclusion and exclusion

This meta-analysis includes only the studies with all the following characteristics:

- written in English;
- carried out on humans (studies using animal or in vitro models were excluded);

- focusing on CVD;
- case-control studies reporting adjusted odds ratio (OR) values.

Abstracts, case reports, letters, comments, reviews without original data, studies with lack of control groups or appropriate data for extraction have been excluded.

Data evaluation

Data extracted from each eligible study included: surname of the first author, years of publication, country and districts, years of study, study design, number of patients (including age, sex, etc.), journal of publication, duration of enrollment, definitions of cases (heart failure, HF; cerebrovascular disease, CeVD; Hyp) degree of exposition, number of controls, total number of cases and controls analyzed.

This meta-analysis has been realized with the commercial software ProMeta, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati *et al.* 2009). Heterogeneity among studies was evaluated using the I^2 statistics.

The effect size (ES) was estimated by OR reported with its 95% confidence interval (CI). Either a fixed effects model or

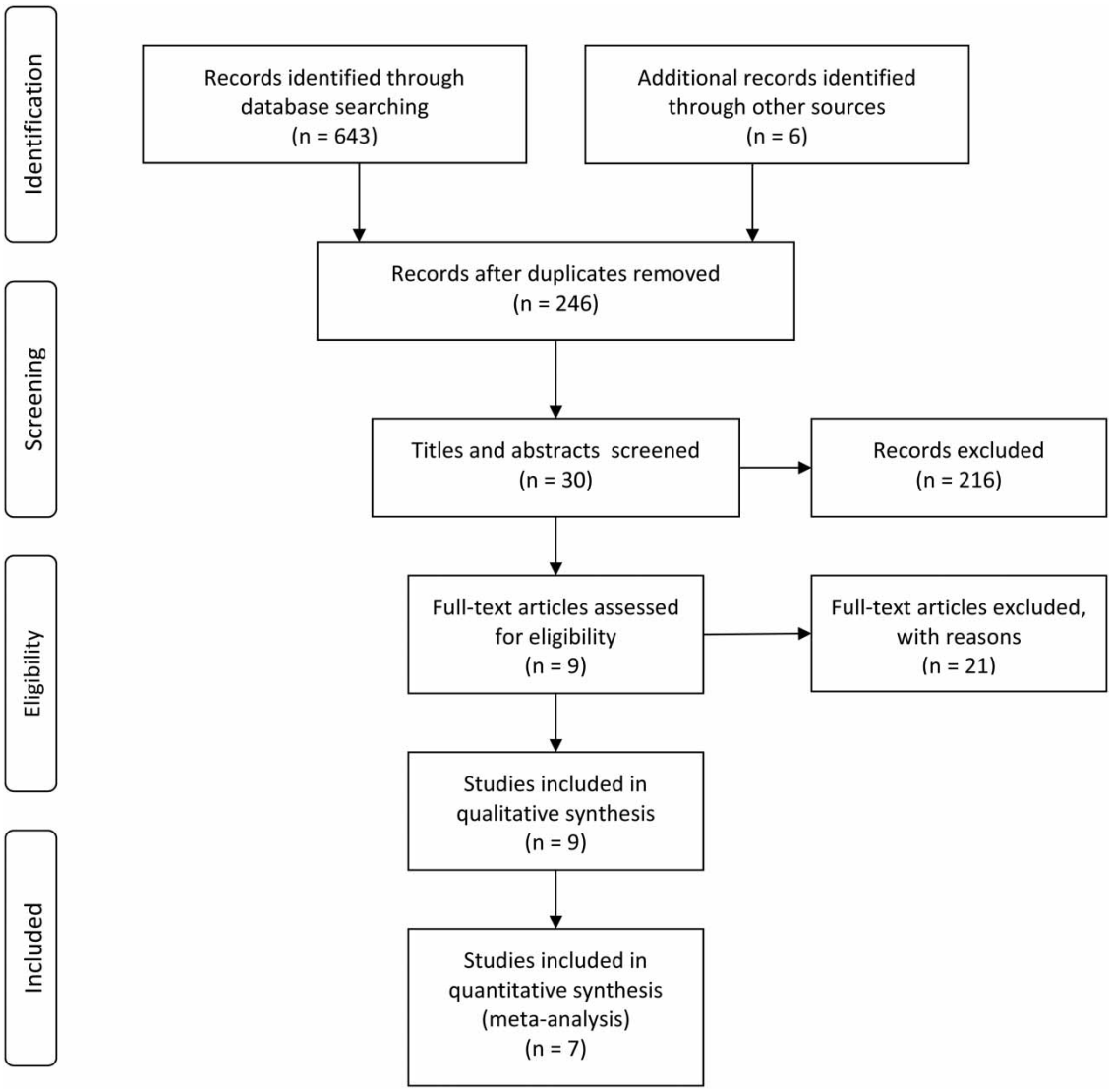

Figure 1 | Selection of studies flowchart (PRISMA flow diagram).

random effects model was applied to calculate the pooled effect based on the found heterogeneity (Mantel-Haenszel statistics).

Potential publication bias was assessed by visually inspecting funnel plots.

Since studies expressed Ca^{++} and Mg^{++} concentration in terms of range, subjects exposed to the highest level of Ca^{++} and Mg^{++} *versus* those exposed to the lowest level were compared.

RESULTS

Eligible studies

Two authors (VG and DN) independently screened titles and abstracts of each paper to exclude studies that did not meet with the inclusion criteria. These searches were broadened by extensive cross-checking of the reference lists of all retrieved articles. Full texts of eligible studies were obtained for further review and evaluated (NLB, VG and DN). The data were tabulated on a standardized data extraction form. Discrepancies and missing data were resolved by group discussion. If discrepancies still existed, we sought the opinions of another two researchers for further discussion (MM and MV).

Our initial search strategies produced 643 potential articles. Seven studies were finally retained and included in the meta-analysis. One study (Rubenowitz *et al.* 2000) evaluated only the effect of Mg^{++}, while the other six evaluated both Ca^{++} and Mg^{++} effect. The results of the literature search are shown in Figure 1. The detailed exclusion motivations of potentially eligible studies are shown in Table 1.

Calcium in drinking water and CVD

Table 2 shows the main characteristics of the six case-control studies included. Four trials were conducted in the

Table 1 | Detailed exclusion motivations

Author, Year of publication	Motivation
Fodor *et al.* (1973)	Observational study
Dawson *et al.* (1978)	Correlation between drinking water mineral intakes and urinary excretion
Masironi *et al.* (1979)	Electrolytes concentration not showed
Punsar & Karvonen (1979)	No individual data available
Comstock *et al.* (1980)	Cohort study
Luoma *et al.* (1983)	Total number of cases and controls not available
Lacey & Shaper (1984)	Ecological study
Leoni *et al.* (1985)	Observational study
Rylander *et al.* (1991)	No individual data available
Bernardi *et al.* (1995)	Electrolytes concentration not showed
Maheswaran *et al.* (1999)	Groups size not available
Sauvant & Pepin (2000)	Electrolytes concentration not showed
Marque *et al.* (2003)	No population data available
Nerbrand *et al.* (2003)	Evaluation of different endpoints
Rylander & Arnaud (2004)	Observational study
Ferrandiz *et al.* (2004)	Ecological study
Morris *et al.* (2008)	Electrolytes concentration not showed
Lake *et al.* (2010)	Ecological study
Leurs *et al.* (2010)	No individual data available
Aslanabadi *et al.* (2014)	Correlation between cholesterol levels and water hardness
Momeni *et al.* 2014	Descriptive study

Table 2 | Main characteristics of the six case-control studies included into the meta-analysis, related to the role of calcium and CVD prevention

Author, year of publication, journal, country	[Ca^{++}] (mg/L)	Case	Control	OR (IC)	Disease	Evaluation time	Characteristics of population
Rubenowitz *et al.* (1996) *Am. J. Epidemiol.* Sweden	≤33	258	263	1.0	Stroke	1982–1989	Male. Age (years): 50–69
	34–45	200	274	0.74 (0.57–0.95)			
	46–81	184	240	0.78 (0.60–1.01)			
	≥82	212	212	1.01 (0.78–1.31)			
Yang & Chiu (1998) *Aha Journals* Taiwan	≤24	5,474	5,442	1.0	Cerebrovascular diseases	1989–1993	Male and female. Age (years): 61.9 ± 5.3
	24.4–42.3	6,081	5,795	0.81 (0.74–0.88)			
	42.4–81.0	5,578	5,896	0.71 (0.64–0.77)			
Yang & Chiu (1999) *AJH* Taiwan	4–11.3	498	443	1.00	Hypertension	1990–1994	Male and female. Age (years): 62.9 ± 5.0
	11.4–30.0	473	473	1.23 (0.94–1.62)			
	30.1–37.3	453	459	1.32 (0.98–1.78)			
	37.4–53.4	423	498	1.12 (0.83–1.51)			
	53.5–81.0	489	463	1.26 (0.92–2.02)			
Rubenowitz *et al.* (1999) *Epidemiology* Sweden	≤31	129	339	1.0	Stroke	1982–1993	Female. Age (years): 50–69
	32–45	79	366	0.57 (0.41–0.78)			
	46–69	88	325	0.71 (0.52–0.97)			
	≥70	82	338	0.64 (0.47–0.87)			
Rosenlund *et al.* (2005) *Epidemiology* Sweden	<24	123	184	1.00	Stroke	1992–19944	Male and female. Age (years): 45–70
	24.0–25.1	182	272	1.05 (0.76–1.46)			
	25.1–28.5	69	110	1.04 (0.69–1.58)			
	≥28.5–610	78	100	1.21 (0.78–1.87)			
Yang *et al.* (2006) *Env. Res.* Taiwan	≤24.4	4,003	3,250	1.0	Stroke	1994–2003	Male and female. Age (years): 62.5 ± 5.3
	25.1–42.4	2,989	3,278	0.75 (0.70–0.80)			
	42.6–81.0	3,102	3,566	0.71 (0.66–0.76)			

1990s, and two in the first decade of 2000. The selection ranged from 1,118 to 34,246 participants. Several studies analyzed general adult population (Yang & Chiu 1998, 1999; Rosenlund *et al.* 2005; Yang *et al.* 2006) while Rubenowitz in 1999 analyzed only the female population (Rubenowitz *et al.* 1999) and in 1996 just the male population (Rubenowitz *et al.* 1996). Three studies were conducted in Sweden and three in Taiwan. The values of OR reported by the authors indicate a moderate CVD protective effect of water rich in calcium (Rubenowitz *et al.* 1996, 1999; Yang & Chiu 1998, 1999; Yang *et al.* 2006) in four cases, while in two studies no association was observed (Yang & Chiu 1999; Rosenlund *et al.* 2005). The poled ES was 0.82 (95% CI = [0.70–0.95], *p*-value = 0.008) (Figure 2(a)). However, a high statistical heterogeneity ($I^2 = 75.24$, *p*-value thinsp;= 0.001) was found. The asymmetrical Funnel plot (Figure 2(b)) shows a potential publication bias.

Magnesium in drinking water and CVD

Seven studies focused on the Mg^{++} effect (Table 3). Four trials were conducted in the 1990s, and three in the first decade of 2000. The recruitment ranged from 1,098 to 22,468 participants. Several studies analyzed general population (Yang & Chiu 1998, 1999; Rosenlund *et al.* 2005; Yang *et al.* 2006), whereas one study analyzed just the female population (Rubenowitz *et al.* 1999) and two the male population (Rubenowitz *et al.* 1996; 2000). Four were conducted in Sweden and three in Taiwan. The OR values reported by the authors generally indicate a protective

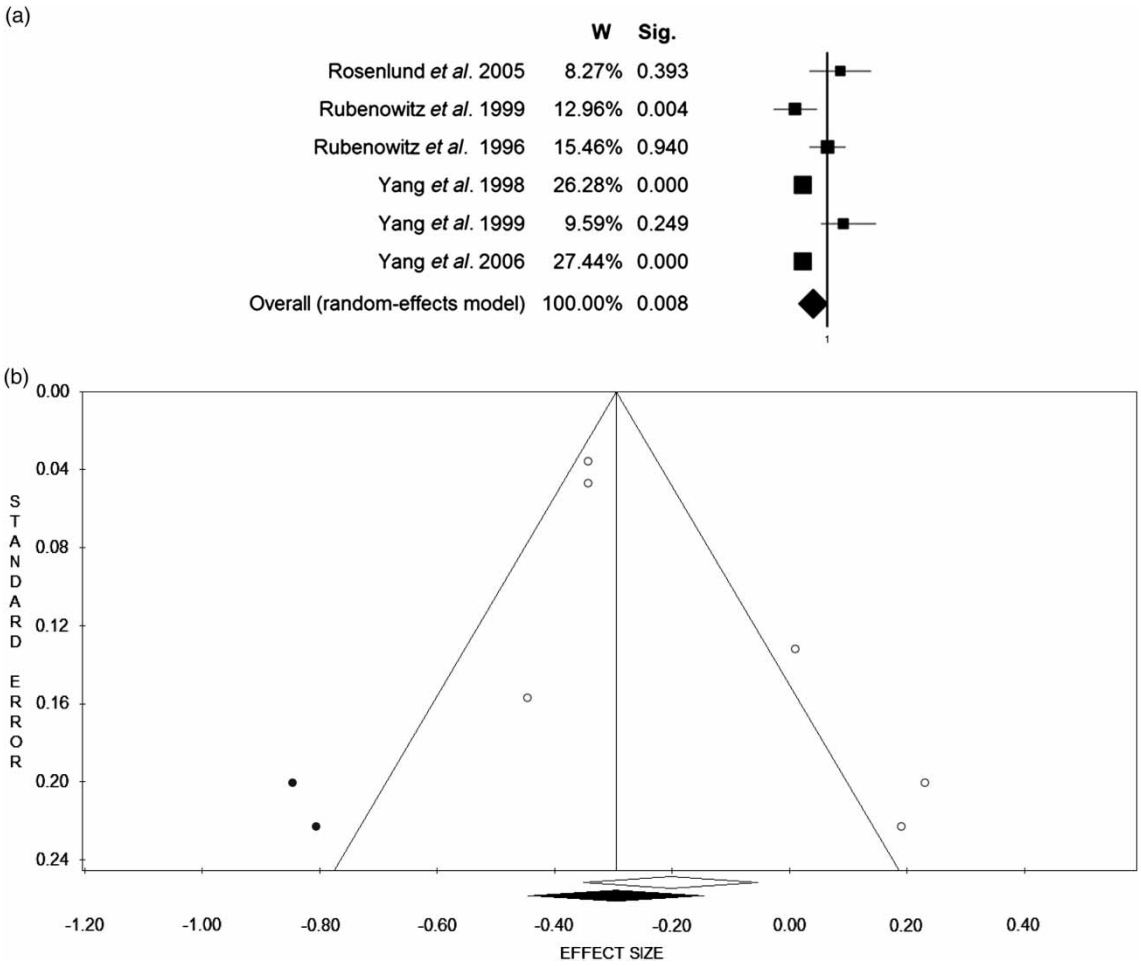

Figure 2 | Forest plot (a) and Funnel plot (b) of the meta-analysis comparing waters enriched in calcium (hard water; highest concentration) *versus* waters poor in calcium (soft water; lowest concentration) in the prevention of CVD (six case-control studies). Funnel plot statistics: ES = 0.82 [0.70–0.95], $p = 0.008$; Q = 20.20; sig. = 0.001; $I^2 = 75.24$; $T^2 = 0.02$; T = 0.14.

effect of the ions in four studies (Rubenowitz *et al.* 1996, 1999; Yang & Chiu 1998, 1999; Rosenlund *et al.* 2005; Yang *et al.* 2006). The pooled sample was constituted by 41,091 people and the ES was 0.75 (95% CI = [0.66–0.86], *p*-value = 0.000 (Figure 3(a)). However, a high statistical heterogeneity was found ($I^2 = 72.96$, *p*-value = 0.0024). The symmetrical Funnel plot (Figure 3(b)) shows no potential publication bias.

DISCUSSION

CVD is the leading cause of mortality in developed countries. Preventive interventions can be helpful in reducing CVD-generated burden. A proper diet can be an adequate measure. On the other hand, it is difficult to study the effect of risk factors on CVD incidence (Rylander 2014) and therefore correlating CVD and water hardness.

The first epidemiological study based on the relationship between health and minerals in drinking water was published by Kobayashi in Japan in 1957 (Kobayashi 1957). The author noticed a high incidence of CVD in areas with higher quantity of acid drinking water. Following this, ca. 30 epidemiological studies evaluated the relation between hard water and CVD. Several of them were ecological studies. For example, the studies carried out in Finland demonstrated that the area with soft water had a high incidence of CVD (Fodor *et al.* 1973; Dawson

Table 3 | Main characteristics of the seven case-control studies included into the meta-analysis, related to the role of magnesium and CVD prevention

Author, year of publication, journal, country	[Mg^{++}] (mg/L)	Case	Control	OR (IC)	Disease	Evaluation time	Characteristics of population
Rubenowitz *et al.* (1996) *Am. J. Epidemiol.* Sweden	≤3.5	243	243	1.0	Stroke	1982–1989	Male. Age (years): 50–69
	3.6–6.8	223	228	0.93 (0.72–1.20)			
	6.9–9.7	202	262	0.74 (0.57–0.95)			
	≥9.8	186	266	0.66 (0.51–0.86)			
Yang & Chiu (1998) *Aha Journals* Taiwan	≤7.3	6,406	5,335	1.0	Cerebrovascular disease	1989–1993	Male and female. Age (years): 61.9 ± 5.3
	7.4–13.4	5,430	5,581	0.81 (0.74.0.88)			
	13.5–41.3	5,297	6,197	0.71 (0.64–0.77)			
Rubenowitz *et al.* (1999) *Epidemiology* Sweden	≤3.4	113	346	1.0	Stroke	1982–1993	Female. Age (years): 50–69
	3.5–6.7	115	374	0.94 (0.70–1.27)			
	6.8–9.8	79	310	0.78 (0.56–1.08)			
	≥9.9	71	338	0.64 (0.46–0.90)			
Yang & Chiu (1999) *AJH* Taiwan	1.5–3.8	570	476	1.00	Hypertension	1990–1994	Male and female. Age (years): 62.9 ± 5.0
	3.9–8.2	435	458	0.73 (0.57–0.93)			
	8.3–11.1	438	461	0.66 (0.50–0.87)			
	11.2–16.3	388	413	0.67 (0.50–0.89)			
	16.4–41.3	505	528	0.63 (0.47–0.84)			
Rubenowitz *et al.* (2000) *Epidemiology* Sweden	≤3.6	273	211	1.00 (0.82–1.22)	Stroke	1994–1996	Male. Age (years): 50–74
	3.7–6	277	201	nd			
	6.1–8.2	266	288	nd			
	≥8.3	270	278	nd			
Rosenlund *et al.* (2005) *Epidemiology* Sweden	<4.3	138	216	1	Stroke	1992–1994	Male and female. Age (years): 45–70
	≥4.3– < 4.4	141	209	1.06 (0.76–1.48)			
	≥4.4– < 4.7	94	148	1.15 (0.78–1.68)			
	≥4.7–23	79	93	1.36 (0.91–2.02)			
Yang *et al.* (2006) *Env. Res.* Taiwan	≤7.7	3,566	3,203	1.0	Stroke	1994–2003	Male and female. Age (years): 62.5 ± 5.3
	7.8–13.5	3,419	3,483	0.88 (0.82–0.94)			
	14.1–41.3	3,109	3,408	0.82 (0.77–0.88)			

et al. 1978; Masironi *et al.* 1979; Punsar & Karvonen 1979; Luoma *et al.* 1983; Lacey & Shaper 1984; Leoni *et al.* 1985; Bernardi *et al.* 1995; Maheswaran *et al.* 1999; Sauvant & Pepin 2000; Nerbrand *et al.* 2003; Ferrandiz *et al.* 2004; Momeni *et al.* 2014). In particular Yang & Chiu (1998, 1999) and Yang *et al.* (2006) showed an inverse relationship between Ca^{++} concentration and CVD; Rubenowitz *et al.* (1996, 1999) strongly suggested a potential protective effect of high level of Mg^{++} in hard water and Marque *et al.* (2003) recommended a protective effect relation between CeVD and Mg^{++}. Similar results were obtained by both Rylander & Arnaud (2004) and Yang & Chiu (1999). They described an inverse relationship between the amounts of Ca^{++} and Mg^{++} in drinking water and the risk of hypertension. Rylander *et al.* (1991) basically demonstrated the relation of hard water with the risk of CVD in both genders and risk of HF due to Mg^{++}. On the other hand, several studies have not found a relation between hardness and CVD (Maheswaran *et al.* 1999; Morris *et al.* 2008; Lake *et al.* 2010; Leurs *et al.* 2010). The recent study carried out by Aslanabadi *et al.* (2014) showed that mean cholesterol and low density lipoprotein were significantly decreased in groups who drank mineral water rich in calcium, magnesium, and bicarbonate.

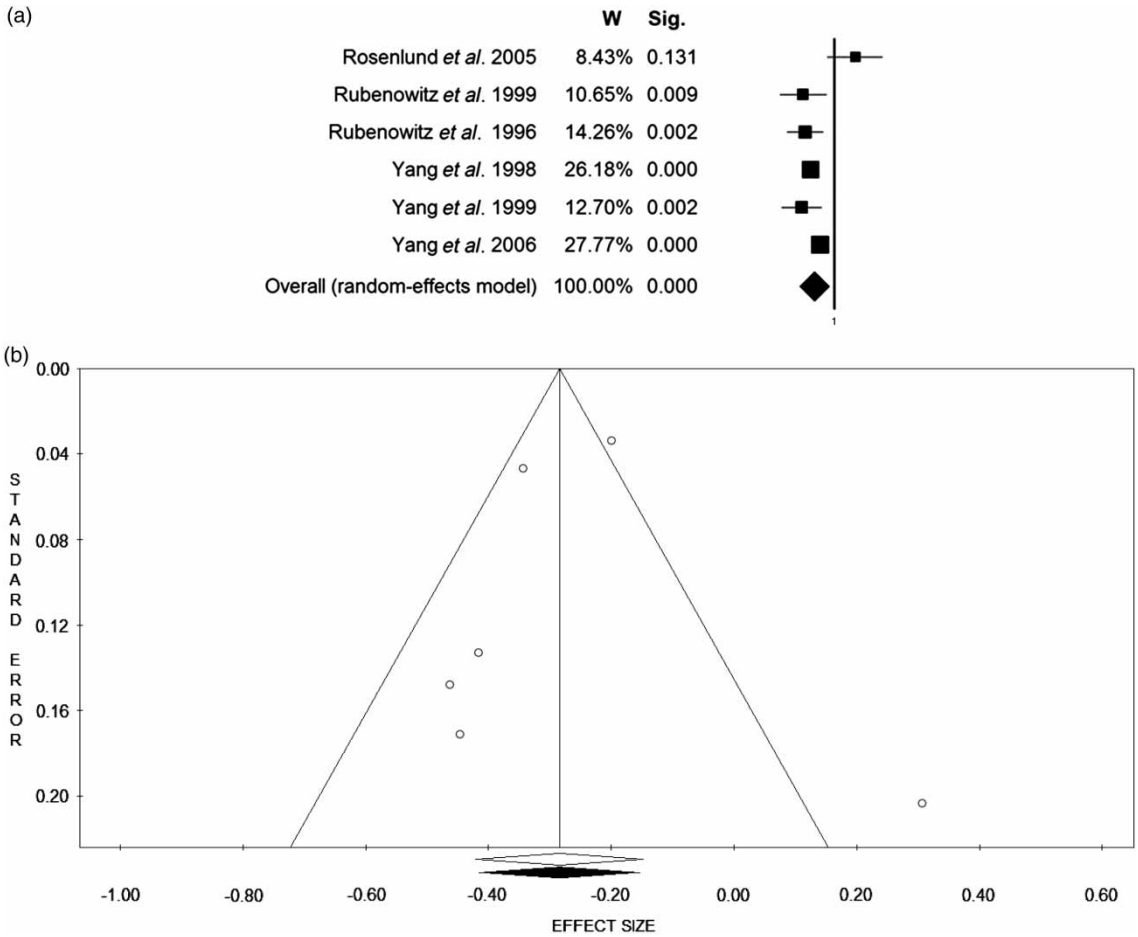

Figure 3 | Forest plot (a) and Funnel plot (b) of the meta-analysis comparing waters enriched in magnesium (hard water; highest concentration) *versus* waters poor in magnesium (soft water; lowest concentration) in the prevention of CVD (six case-control studies). Funnel plot statistics: ES = 0.75 [0.66–0.86], Q = 18.49; sig.= 0.0024; I^2=72.96; $T^2 = 0.02$; T = 0.13.

Many but not all epidemiological studies found a protective association between CVD mortality and water hardness; however, these results are not consistent (Monarca *et al.* 2006). Actually, few studies have geographic limitation, so it is relevant to check the results gingerly. The main reasons are as follows:

- Most studies are of an ecological nature implying that there might be other risk factors which could influence the results.
- Studies which usually referred to large areas produce an inverse relation between hard water and CVD. It becomes not true if the studies analyse smaller areas. It is not clear if the obtained relation is directly linked to drinking water or if it depends on other related factors.
- Interaction between micro/macroelements could lead to several consequences on humans, and it is hardly measurable through epidemiological studies. Autopsy examinations have shown quite concordant results only for magnesium. The authors observed low magnesium levels in tissues (heart, diaphragm, pectoral muscles) of heart attacks deaths. These data suggested that $Mg^{++} \geq 20$ mg/L is the most responsible factor of CVD decrease, while $49 \leq Ca^{++} \leq 80$ mg/L gives only extra protection (Chipperfield & Chipperfield 1979).

CONCLUSIONS

This systematic review and meta-analysis evaluated the impact of hard water consumption on CVD risk.

The strengths of our meta-analysis are: analysis of all included studies are case-control; testing of consumption's effect of Ca^{++} on 17,000 subjects and Mg^{++} on 19,000 subjects.

High heterogeneity was found, probably depending on the different recruited sample size, outcomes' evaluation, and population's characteristics. Another weakness is given by the finding of a potential publication bias.

Our results underline the beneficial effects of hard water and its role in curbing the incidence of CVD. Further high-quality studies are needed, in particular with exposure to Ca^{++} and/or Mg^{++} assessed by food frequency questionnaires or food diaries instead of on the basis of geographical data, to reproduce and confirm these results.

DISCLOSURE

All authors declare no potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. All authors have approved the final article.

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