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Original Article

Association between the levels of calcium in drinking water and coronary heart disease mortality risk: evidence from a meta-analysis

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Abstract: Quantification of the association between the levels of calcium in drinking water with the risk of coronary heart disease (CHD) mortality is still conflicting. We therefore conducted a comprehensive meta-analysis to assess them. Pertinent studies were identified by a search of PubMed and Web of Knowledge to April 2015. The random effect model was used. Sensitivity analysis and publication bias were conducted. Finally, 8 articles with 9 studies (2 prospective studies and 7 case-control studies) involving 77623 CHD cases were used in this meta-analysis. Pooled results suggested that highest level of calcium in drinking water versus lowest level was significantly associated with reduced the risk of CHD mortality [summary relative risk (RR) = 0.88, 95% CI = 0.79-0.97, I^2 = 84.0%]. Eight of the 9 studies came from Europe, and the association was significant between the level of calcium in drinking water and the risk of CHD mortality [summary RR = 0.91, 95% CI = 0.82-0.99]. No publication bias was found. Our analysis suggested that the higher levels of calcium in drinking water could reduce the risk of CHD mortality, especially in Europe population.

Keywords: Calcium, drinking water, coronary heart disease, mortality, meta-analysis

Introduction

Coronary heart disease (CHD) is the leading cause of death in adults throughout their lifetime, affecting millions of people in both developed and developing countries [1]. Furthermore, it causes substantial mortality and morbidity [2]. And it is expected to be the leading cause of disease burden worldwide by 2020 [3]. Thus, primary prevention of CHD is an important matter in the current society. Some present studies had reported that CHD is related with some genetic gene [4, 5]. Also, some environment factors may influence the risk of CHD [6, 7]. Drinking water plays an important role in our daily life and human health. The role of water hardness has been widely investigated and evaluated for many years in several studies to assess the association for the risk of CHD. The hardness of drinking water is largely determined by its content of calcium and magnesium. Up to now, many studies had conducted to investigate the association between the levels of calcium in drinking water and CHD mortality risk. Only two studies reported an inverse association between them [8, 9], while other studies did not find any significant association between the levels of calcium in drinking water and CHD mortality risk [10-15]. Concerning the results are not consistent, we conducted a comprehensive meta-analysis to evaluate the evidence from observational studies on the levels of calcium in drinking water with the risk of CHD mortality.

Methods

Literature search strategies

Studies were identified by a literature search of PubMed and Web of Knowledge through April 2015. The following search strategy was carried out: [coronary heart disease (CHD) OR myocardial infarction (MI) OR ischemic heart disease (IHD)] and [calcium OR drinking water] and [mortality] and restricting studies conducted in humans. There were no restrictions regarding language. Furthermore, we reviewed citations

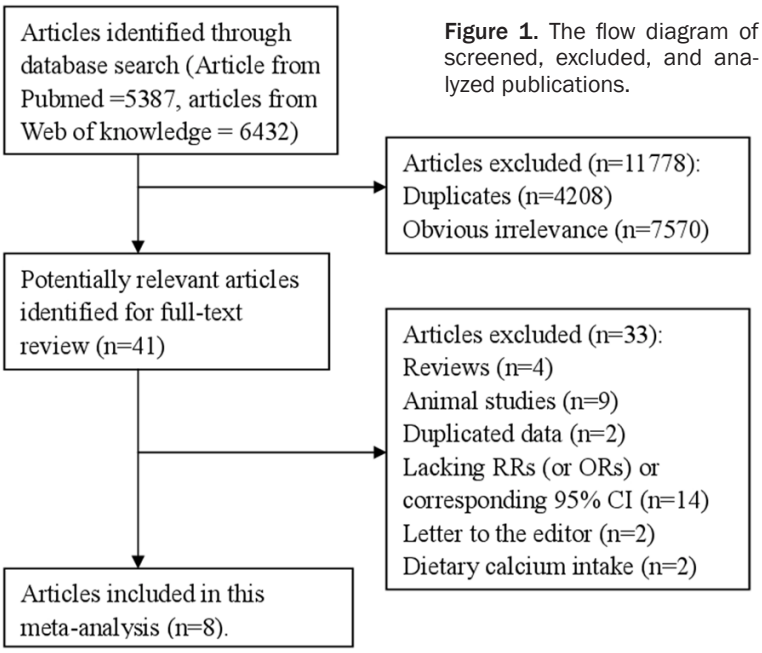

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

from the retrieved articles and relevant reviews to identify additional studies.

Inclusion criteria

The articles included in our meta-analysis should fulfill the following inclusion criteria: (1) The studies were prospective or case-control design; (2) The outcome measure was the incidence of the mortality of CHD; (3) The exposure of interest was the levels of calcium in drinking water; (4) All included studies provided the relative risk (RR) or hazard ratio (HR) or odds ratio (OR) and the corresponding 95% confidence intervals (CI), or provided enough data to calculate them. We only included the most complete or most recent paper when several papers from the same study had been published.

Exclusion criteria

The exclusion criteria for this meta-analysis were as follows: (1) Reviews; (2) The above-mentioned outcomes of interest were not reported; (3) Experiments on animals.

Data extraction

The following information was extracted from each study: the last name of first author, year of publication, study design, sex, geographic locations, number of cases and participants, the results of CHD mortality outcome. The RR estimates and 95% CI for the levels of calcium in drinking water and CHD mortality risk were also extracted, and confounding factors adjusted for in the analysis. For studies that reported results from various covariate analyses, we abstracted the estimates based on the model that included the most potential confounders. Otherwise, we abstracted the crude RR estimates. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

Statistical analysis

Pooled measure was calculated using the inverse variance-weighted mean of the logarithm of RR with 95% CI, to assess the strength of association between the levels of calcium in drinking water and the risk of CHD mortality. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [16]. The I^2 was used to assess heterogeneity, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity [17], respectively. Meta-regression analysis and subgroup analysis were performed to assess the potentially important covariate exerting substantial impact on between-study heterogeneity [18]. Publication bias was estimated using Egger's regression asymmetry test [19]. Sensitivity analysis [20] was conducted to describe how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis. All the statistical analyses were performed with STATA version 10.0. Two-tailed $P<0.05$ was accepted as statistically significant.

Results

Search results and study characteristics

The search strategy identified 5387 articles from PubMed and 6432 from the Web of

Table 1. Characteristics of studies on the levels of calcium in drinking water and CHD mortality risk

Study, year	Country	Study design	Participants (cases)	Age (years)	CHD out-come	RR (95% CI) for highest versus lowest category	Adjustment for covariates
Leurs et al. 2010	Netherlands	Prospective study	33258 (1642)	55-69	IHD	Male 0.91 (0.60-1.38) Female 1.11 (0.59-2.07)	Adjusted for Age, current smoking, number of cigarettes smoked, years of active smoking, diabetes, hypertension, BMI, dietary calcium, dietary magnesium, saturated fat, monounsaturated fat, polyunsaturated fat, fruit and vegetable consumption, alcohol consumption, total energy intake (kilocalories), physical activity, educational level, volume of water consumption, magnesium or calcium concentration in tap water (depending on the exposure variable), use of diuretics, and use of multivitamins with minerals or calcium supplementation.
Luoma et al. 1983	Finland	Case-control study	100 (50)	30-64	MI	0.50 (0.22-1.07)	Adjusted for age and municipality with the cases.
Maheswaran et al. 1999	England	Case-control study	2496659 (64226)	≥45	IHD	0.98 (0.94-1.04)	Adjusted for Age, sex, Carstairs deprivation quintile and geographical gradients.
Rosenlund et al. 2005	Sweden	Case-control study	458 (116)	45-70	IHD	1.21 (0.78-1.87)	Adjusted for Age, sex, catchment area, smoking, hypertension, socio-economy, job strain, diabetes mellitus, body mass index, and physical inactivity.
Rubenowitz et al. 1996	Sweden	Case-control study	1843 (854)	50-69	IHD	1.06 (0.82-1.38)	Adjusted for Age and magnesium and calcium, respectively.
Rubenowitz et al. 1999	Sweden	Case-control study	1746 (378)	50-69	IHD	0.66 (0.47- 0.94)	Adjusted for Age and magnesium and calcium, respectively.
Rubenowitz et al. 2000	Sweden	Case-control study	521 (263)	50-74	IHD	0.89 (0.59-1.33)	Adjusted for Age and magnesium and calcium, respectively.
Yang et al. 2006	China	Case-control study	20188 (10094)	50-69	IHD	0.71 (0.65-0.77)	Adjusted for Age, sex, urbanization level of residence, and magnesium and calcium levels in drinking water respectively.

Abbreviations: CHD = coronary heart disease; IHD = ischemic heart disease; MI = myocardial infarction; BMI = body mass index; CI = confidence interval; RR = relative risk.

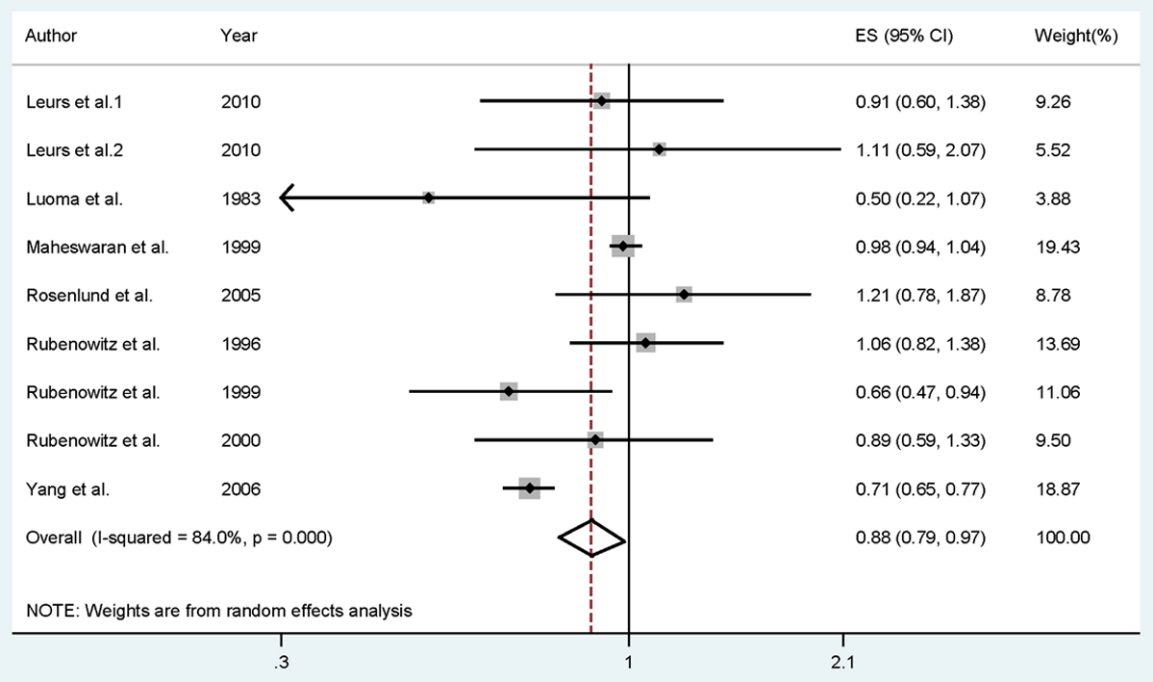

Figure 2. The forest plot between the levels of calcium in drinking water and CHD mortality risk. White diamond denotes the pooled RR. Black squares indicate the RR in each study, with square sizes inversely proportional to the standard error of the RR. Horizontal lines represent 95% CI.

Table 2. Summary risk estimates of the levels of calcium in drinking water and CHD mortality risk

Subgroups	No. (cases)	No. studies	RR (95% CI)	Heterogeneity test I^2 (%)	Heterogeneity test *P*-value
All studies	77623	9	0.88 (0.79-0.97)	84.0	0.000
Study design					
Cohort	1642	2	0.97 (0.68-1.37)	0.0	0.605
Case-control	75981	7	0.85 (0.72-0.98)	87.9	0.000
Geographic locations					
Europe	67529	8	0.91 (0.82-0.99)	25.9	0.223
Asia	10094	1	-	-	-
CHD outcome					
IHD	65868	3	0.98 (0.93-1.03)	0.0	0.872
MI	11755	6	0.83 (0.67-0.98)	67.1	0.010

Abbreviations: CHD = coronary heart disease; IHD = ischemic heart disease; MI = myocardial infarction; CI = confidence interval; RR = relative risk.

Knowledge, and 41 articles were reviewed in full after excluding the duplicates and reviewing the title/abstract. Thirty-three of these 41 articles were subsequently excluded from the meta-analysis for various reasons. One study [10] reported the association between the levels of calcium in drinking water and the risk of CHD mortality for males and females, respectively. Therefore, we put them as two separate studies. Finally, 8 articles [8-15] with 9 studies (2 prospective studies and 7 case-control studies) involving 77623 CHD cases were used in this study. The detailed steps of our literature search are shown in **Figure 1**. The characteristics of the included studies are presented in **Table 1**. Four studies come from Sweden, 2 from Netherlands, 1 from Finland, 1 from England and 1 from China.

High versus low analyses and subgroup analysis

Two of the included studies reported that the highest levels of calcium in drinking water could reduce the risk of CHD mortality, while no significant association was reported in 7 studies. Pooled results suggested that highest level of calcium in drinking water versus lowest level was significantly associated with reduced the risk of CHD mortality [summary RR = 0.88, 95% CI = 0.79-0.97, I^2 = 84.0%] (**Figure 2**).

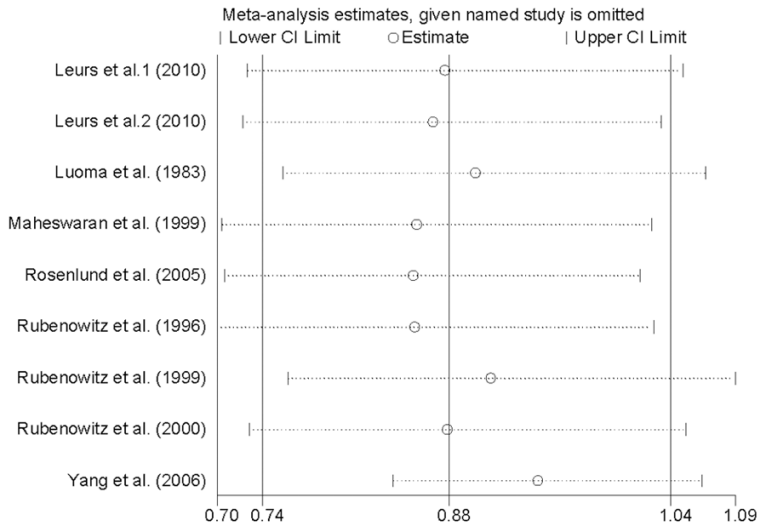

Figure 3. Analysis of influence of individual study on the association between the levels of calcium in drinking water and CHD mortality risk. Open circle, the pooled RR, given named study is omitted. Horizontal lines represent the 95% CIs.

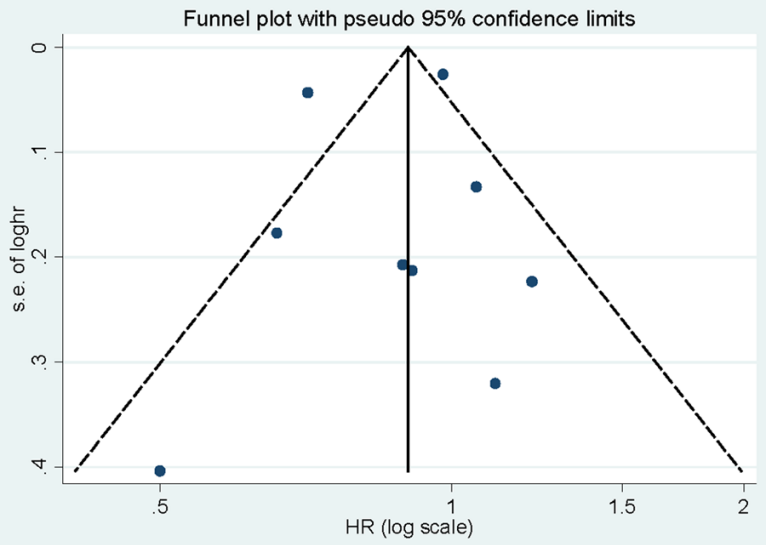

Figure 4. Funnel plot for the analysis of publication bias between the levels of calcium in drinking water and CHD mortality risk.

When we conducted the subgroup analysis by study design, the association was also found in the case-control studies [summary RR = 0.85, 95% CI = 0.72-0.98] but not in the cohort studies [summary RR = 0.97, 95% CI = 0.68-1.37]. In subgroup analyses for geographic locations, highest levels of calcium in drinking water versus lowest level was significantly associated with reduced the risk of CHD mortality in Europe [summary RR = 0.91, 95% CI = 0.82-0.99]. The limited data was not supported the association for other population while only one study come from China. Furthermore, in stratified analysis by CHD mortality outcomes, the association was significant in MI group, but not in the IHD group. The details results are summarized in **Table 2**.

Sources of heterogeneity and meta-regression

In our pooled results, evidence of high heterogeneity (I^2 = 84.0%, $P_{heterogeneity}$ = 0.000) was found. In order to explore the moderate to high between-study heterogeneity founded in several analysis, univariate meta-regression with the covariates of publication year, location where the study was conducted, study design (case-control or cohort), CHD mortality outcome, number of cases and source of controls were performed. We found that geographic location was significantly contributed to the high between-study heterogeneity. When we conducted the subgroup analysis by geographic location, the between-study heterogeneity was low (I^2 = 25.9%) in the Europe population.

Sensitivity analysis

Sensitivity analysis showed that no individual study had excessive influence on the levels of calcium in drinking water and CHD mortality risk (**Figure 3**).

Publication bias

Egger's test (P = 0.696) and funnel plot (**Figure 4**) showed no significant publication bias was found between the association of the levels of calcium in drinking water and CHD mortality risk.

Discussion

Findings from this meta-analysis suggested that the highest levels of calcium in drinking water could reduce the risk of CHD mortality. The associations were also found in case-control studies and Europe population. However, in the pooled analysis, we found evidence of high between-study heterogeneity.

Previous study [21] had reported that between-study heterogeneity is common in the meta-analysis, and exploring the potential sources of between-study heterogeneity is the essential component of meta-analysis. In order to explain the high heterogeneity, we used meta-regression to analyze. The between-study heterogeneity might arise from publication year, location where the study was conducted, study design (case-control or cohort), CHD mortality outcome, number of cases and source of controls. Thus, meta-regression with the covariates was to explore the causes of heterogeneity. In the above mentioned covariates, only geographic location was significantly contributed to the high between-study heterogeneity. Therefore, we conducted the subgroup analysis by geographic location, the between-study heterogeneity was low (I^2 = 25.9%) in the Europe population. However, CHD is a complex etiology and pathophysiology disease generated by the combined effects of genes and environment factors. Thus, other genetic and environment variables, as well as their possible interaction, may well be potential contributors to the heterogeneity observed.

The strength of this meta-analysis is including a large sample size of 77623 cases and large participants. To our best knowledge, this is the first meta-analysis to assess the association between the levels of calcium in drinking water and CHD mortality risk. Furthermore, there is no significant publication bias was found, indicating that our results are stable. However, some limitations in this meta-analysis should be concerned. First, as a meta-analysis of observational studies, some recall or selection bias may be inherent in the original studies, especially in case-control studies. The information on exposures for prospective study is collected before the diagnosis of the disease, so that the prospective study is less susceptible to bias than case-control studies. The results of the meta-regression showed no evidence of significant heterogeneity between subgroups, but the summary RR was different in subgroup analyses by study design. In our meta-analysis, the significant association was only found in the case-control studies, but not in the prospective studies, while only 2 studies included were prospective design. Therefore, more original studies with prospective design are wanted in the future studies. Second, for the subgroups of geographic locations, the association was only significant in the Europe. There is only one study come from China. So, we did not combine the results for other contries. Due to this limitation, the results are applicable to the Europe population, but cannot be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between the levels of calcium in drinking water and CHD mortality risk. Finally, evidence of high between-study heterogeneity was found in the pooled analysis, but the between-study heterogeneity was successfully explained by the meta-regression.

In summary, results from this meta-analysis suggested that the higher levels of calcium in drinking water could reduce the risk of CHD mortality, especially in Europe population. Since potential bias was existed in this meta-analysis, further studies are needed to confirm the results.

Disclosure conflict of interest

None.

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