European Journal of Epidemiology **18**: 305–309, 2003.

CARDIOVASCULAR DISEASES

Cardiovascular mortality and calcium and magnesium in drinking water: An ecological study in elderly people

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Accepted in revised form 30 October 2002

Abstract. *Background*: Previous studies found relations between cardiovascular mortality and minerals in drinking water, but the major works considered water hardness or neglected the differences between adults and elderly. Drinking water is an important source of calcium in the elderly particularly because of increased needs and decreased consumption of dairy products. *Methods*: We collected informations about all deaths (14,311) occurring in 69 parishes of the South–West of France during 7 years (1990–1996). We obtained the causes of deaths from a special service of INSERM for each death, with age at death and sex. The exposure value was supplied by administrative source (DDASS) and by measurement surveys. We use an extra-Poisson variation model to take into account the heterogeneity of the population of these parishes. *Results*: A significant relationship was observed between calcium and cardiovascular mortality with a RR: 0.90 for non-cerebrovascular causes and RR: 0.86 for cerebrovascular (when calcium is higher than the second tercile: 94 mg/l). We found a protective effect of magnesium concentrations between 4 and 11 mg/l with a RR: 0.92 for non-cerebrovascular and RR: 0.77 for cerebrovascular mortality, as compared to concentrations lower than 4 mg/l. *Conclusions*: These findings strongly suggest a potential protective dose-effect relation between calcium in drinking water and cardiovascular causes. For magnesium, a U-shape effect is possible, especially for cerebrovascular mortality.

Key words: Calcium, Cardiovascular mortality, Drinking water, Elderly, Magnesium, Poisson regression

Introduction

Cardiovascular mortality represents the main cause of mortality in people over 65 years of age, with an incidence of 1.9 per 1000 person-years among men and 1.3 per 1000 among women [1] in 1990 in France. Previous epidemiologic studies have suggested an inverse relationship between the number of deaths by cardiovascular pathologies and water hardness [2], mainly determined by concentrations of calcium and magnesium.

Calcium and magnesium are antagonistic enzymatic activators. Calcium is essential to coagulation, nerve impulse and muscular contraction, in particular for the cardiac muscle. Magnesium is involved in the transfer and the release of energy and takes part in cardiac physiology. The results of epidemiologic studies have suggested a potential hypotensive action for calcium and an effect against thrombosis for magnesium [3–5].

In developed countries, dairy products represent the most significant source of calcium. However, it is recognized that the intestinal absorption of calcium decreases with aging [6], and particularly among women [7]. Moreover, elderly are sometimes confronted with a problem of lactose intolerance; for these subjects drinking water becomes the major source of calcium [8, 9]. The daily intake of magnesium in the developed countries is insufficient compared to recommended values [10]. Moreover, since the magnesium in drinking water is in ionized form, it might be more bioavailable than that provided by solid foods [11, 12]. This may also be the case for calcium which seems to be at least as bioavailable in water as in milk [13].

The various studies about the role of calcium and magnesium have often shown a protective effect of these two elements on cardiovascular mortality. However these works are essentially based on studies of correlations between the concentrations of these minerals in water and the death rates in the various geographical areas [14, 15]. Moreover, some of these studies have considered the hardness of water as a global factor rather than the separate effect of calcium and magnesium [16].

Recently, Rylander et al. [17] found that deaths by ischaemic cardiopathies were inversely associated with the concentrations of calcium and magnesium in drinking water. According to the same authors, calcium may have a protective effect on cerebrovascular mortality in men. However, this relation was not found by Yang et al. [18, 19] who suggested that magnesium in drinking water may have a protective effect. This protective effect of magnesium was also found in other studies on cardiovascular mortality [20]. Nevertheless, some doubts persist regarding these possible relationships because of contradictory [21] or non-significant [22, 23] results. Finally, the relationship between cardiovascular mortality and the mineral elements of drinking water has rarely been studied in elderly [24].

The major aim of this study was to assess the relationship between cardiovascular mortality in the elderly and the concentration of calcium and magnesium in drinking water. In effect, the few number of studies among elderly encourage us to investigate more precisely this relationship [6, 7]. The study was based on the population of the 75 parishes from which the PAQUID sample was drawn. We have also studied separately cerebrovascular and other cardiovascular mortality. The water distribution network had already been studied for these parishes and mean concentrations of calcium and magnesium were already available. Deaths certificates were collected for a 7-years period and the analysis beared on 14,331 deaths and 777,493 persons-years.

Methods

Populations

Our sample was composed by the population living in the 75 parishes included in PAQUID, which is a prospective cohort in the South–West of France. These parishes were drawn at random among all parishes of Gironde and Dordogne according to a design in five strata based on the size of the parish. We considered the population between 1st January 1990 and 31st December 1996, aged over 65 years and we collected all deaths occurring in this population. The number of person-years was calculated using the average of the population between the two dates, for sex and age (5-years classes). We obtained the distribution of the population of the parishes by age and sex from the 'Institut National de la Statistique et des Etudes Economiques' (INSEE). The causes of deaths were provided by the SC8 (a specialized department of the 'Institut Nationale de la Santé Et de la Recherche Médicale') from the death certificates. For each death, we recorded sex, age at death (1-year precision), parish of residence and main cause of death (coding on four numbers accorded to ICD-9). We observed 14,311 deaths and the total number of person-years was 777,493.

Measure of exposure

We divided each parish into distribution zones, supplied by one particular water source, on the basis ofinformation given by the sanitary administration. Two measurement surveys were carried out in 1991 to measure pH and concentrations of calcium and magnesium in each zone. For each water supply, the mean of the determinations for the two surveys and of the routine measurements, collected by the sanitary administration between 1991 and 1994, were computed. For each distribution zone, we computed average values for calcium and magnesium concentration using the hourly flow or the relative contribution of each water source in the composition of drinking water in the zone. The details of the measures of the concentrations of the elements were described in previous publications [25]. Six parishes were excluded from the study because of recent changes in the distribution network. Finally, our sample considered 69 parishes for which data were available.

Statistical analysis

We used a model of extra-Poisson variation regression in order to study the relationship between cardiovascular mortality and calcium and magnesium on the grouped data: the variable to be explained was the number of cardiovascular deaths in the parishes [26]. The heterogeneity within the parishes was taken into account by the introduction of an over-dispersion parameter. Indeed, this heterogeneity could introduce an underestimation of the variance and thus lead to anti-conservative tests. The extra-Poisson variation model was performed using the GENMOD procedure of the SAS software with the 'dscale' option. This parameter was used in order to correct the estimators of variances without modify estimation of the parameters themselves. So, the scale option changes only the confidence interval limits. All these models were adjusted on the sex and age (by 5-years classes) of the subjects and on the rurality of the parishes.

Calcium and magnesium concentrations were regarded categorized in three classes in order to allow for a possible 'U-shape' or for a dose-effect relation. The cut-off points were fixed at the tertiles values. The rural status of a parish was based on the five categories of the INSEE definition and we re-coded this variable into a dichotomic variable taking urban status as the reference class.

Results

When we considered global cardiovascular mortality (See Table 1), we observed a protective effect of higher calcium concentration (RR: 0.90 – Confidence Interval of 95% (CI95) [0.84; 0.96] – for concentration >94 mg/l). We also found a protective effect of magnesium between 4 and 11 mg/l with estimated relative risk between 0.88 and 0.92 (respectively among women and men with , CI95 [0.81; 0.96] and, CI95 [0.84; 1.00]).

Table 1. Poisson models on global cardiovascular mortality, adjusted on age (France, 1990–1997)

	Men		Women		Both sexes	
	RR	95% CI	RR	95% CI	RR	95% CI
Calcium (mg/l)						
[9; 53]	1.00	–	1.00	–	1.00	–
[53; 94]	0.96	0.89; 1.05	0.95	0.88; 1.03	0.95	0.90; 1.01
[94; 146]	0.91[a]	0.83; 0.99	0.90[b]	0.83; 0.97	0.90[b]	0.84; 0.96
Magnesium (mg/l)						
[1; 4]	1.00	–	1.00	–	1.00	–
[4; 11]	0.92[a]	0.84; 1.00	0.88[b]	0.81; 0.96	0.90[b]	0.85; 0.96
[11; 34]	0.98	0.88; 1.10	0.89	0.80; 0.99	0.93	0.86; 1.01
Urban[d]	1.00	0.99; 1.03	1.02	0.99; 1.05	1.01	0.99; 1.04
Scale[e]	1.00		1.14		1.15	

[a] $p \leqslant 0.05$; [b] $p \leqslant 0.01$; [c] $p \leqslant 0.001$; [d] vs. rural; [e] Allows overdispersion relatively to a regular Poisson model.

Table 2. Poisson models on cardiovascular but non-cerebrovascular mortality, adjusted on age (France, 1990–1997)

	Men		Women		Both sexes	
	RR	95% CI	RR	95% CI	RR	95% CI
Calcium (mg/l)						
[9; 53]	1.00	–	1.00	–	1.00	–
[53; 94]	0.94	0.86; 1.03	0.96	0.88; 1.05	0.95	0.88; 1.01
[94; 146]	0.90[a]	0.81; 0.99	0.91[a]	0.83; 0.99	0.90[b]	0.84; 0.97
Magnesium (mg/l)						
[1; 4]	1.00	–	1.00	–	1.00	–
[4; 11]	0.94	0.85; 1.04	0.90[a]	0.82; 0.99	0.92[a]	0.86; 0.99
[11; 34]	1.02	0.90; 1.15	0.90	0.79; 1.02	0.96	0.87;1.05
Urban[d]	1.02	0.99; 1.05	1.02	0.99; 1.06	1.02	1.00; 1.05
Scale[e]	0.98		1.10		1.11	

[a] $p \leqslant 0.05$; [b] $p \leqslant 0.01$; [c] $p \leqslant 0.001$; [d] vs. rural; [e] allows overdispersion relatively to a regular Poisson model.

We then analysed separately non-cerebrovascular (cardiovascular) mortality (10,492 deaths) and cerebrovascular mortality (3819 deaths). Table 2 shows the results of the extra-variation Poisson models for cardiovascular mortality, excluding cerebrovascular origin. These models suggested a protective effect of a high concentration of calcium on cardiovascular mortality with a dose–response effect. This effect seemed to be similar in both sexes, with a significant relative risk in the parishes having a water with a content higher than 94 mg/l (RR: 0.90, CI95 [0.84; 0.97]). Concentration of magnesium between 4 and 11 mg/l seemed to be slightly protective on cardiovascular mortality (RR: 0.92, CI95 [0.86; 0.99]).

Table 3 shows the results of the extra-variation Poisson models for cerebrovascular mortality. About calcium, we found roughly similar results on cerebrovascular mortality than on cardiovascular mortality. We observed a protective relationship for concentration >94 mg/l. This effect seemed slightly clearer among women (RR: 0.84 vs. 0.89, with CI95 respectively [0.74; 0.97] and [0.74; 1.07]). However, we observed a more significant protective effect for magnesium for concentration between 4 and 11 mg/l. This effect seemed similar on both sexes and highly significant (RR: 0.77, $p \leqslant 0.001$).

The rural status of parishes did not seem to be associated with cardiovascular mortality, and we found this result in all models we performed.

Discussion

These findings suggest a protective effect of calcium in drinking water with a dose-effect relationship. This effect is similar in both sexes with a RR: 0.90 in cardiovascular mortality and RR: 0.86 in cerebrovascular mortality.

Magnesium seems to be protective on cardiovascular mortality for concentrations between 4 and 11 mg/l (RR: 0.90). The effect of magnesium seems to be higher on cerebrovascular mortality (RR: 0.77).

Considering two different causes in CV mortality among the elderly was the major originality of this analysis. Few analysis were performed among this population and all of them considered only cardiovascular cause, without distinction between the subcauses. Furthermore, we could estimate independently

Table 3. Poisson models on cerebrovascular mortality, adjusted on age (France, 1990–1997)

	Men		Women		Both sexes	
	RR	95% CI	RR	95% CI	RR	95% CI
Calcium (mg/l)						
[9; 53]	1.00	–	1.00	–	1.00	–
[53; 94]	0.94	0.79; 1.11	0.90	0.79; 1.03	0.91	0.82; 1.01
[94; 146]	0.89	0.74; 1.07	0.84[a]	0.74; 0.97	0.86[b]	0.77; 0.96
Magnesium (mg/)						
[1; 4]	1.00	–	1.00	–	1.00	–
[4; 11]	0.74[c]	0.63; 0.88	0.79[b]	0.69; 0.91	0.77[c]	0.69; 0.86
[11; 34]	0.91	0.72; 1.14	0.93	0.78; 1.11	0.92	0.80; 1.06
Urban[d]	1.07	1.00; 1.14	1.10	1.05; 1.15	1.09	1.05; 1.13
Scale	0.99		1.01		1.00	

[a] $p \leqslant 0.05$; [b] $p \leqslant 0.01$; [c] $p \leqslant 0.001$; [d] vs. rural; [e] allows overdispersion relatively to a regular Poisson model.

the effect of calcium and magnesium on CVD, which has never been investigated among the elderly.

A weakness of our study may come from the exposure measurement. We measured concentration of these two minerals on several public taps in each parish to compare the reliability. This reliability of the measurement of calcium concentration is >90% [25].[1] Moreover, we used the average of several values to reduce the variability of these mineral concentrations. However the concentrations of the minerals were collected only at community level: we supposed that all persons living in a given parish had the same exposure, while in fact concentrations could be different between households. There are also other sources of calcium, e.g. nutrition and medication. Indeed, the main calcium intake comes from food, although its bioavailability may be lower than in drinking water. This hypothesis was made in a recent study by Bostick et al. [27] who found a significant relation between ischemic mortality and calcium, but not with milk products (or vitamin D). Furthermore, the mineral composition of food (especially potatoes and vegetables) can be modified when they are cooked in water, and these changes depend on water hardness [28]. The concentration of minerals in the drinking water of a parish may be a good indicator of exposure to these minerals for subjects who live a long time in these parishes. At the beginning of the Paquid study, the average stay of subject in the same parish was about 40 years.

Causes of deaths were collected from death certificates, which are completed by general practitioners. They are certainly some misclassifications but it is very likely that misclassification did not depend on calcium concentration. Such non-differential misclassification can only make the RRs closer to one.

Calcium and magnesium were introduced as categorized variables with three levels given by the tertiles. This had the advantage of providing a certain flexibility (possibility of observing U-shape or dose-effect relation) and avoiding multiplicity of tests (as compared to trying several different codings or using a variable with a larger number of categories).

We also adjusted on rural place of residence which may be considered as a good indicator of several confounders such as dietary habits (wine or water consumption for example) or economical level of household. Furthermore, rural place of residence might be a confounding factor, if both classification error and cardiovascular mortality depend on it; However this variable was not significant.

As in the review by Sharett [29], our work supports the hypothesis of a protective effect of calcium in drinking water. Sharett reported the results of many epidemiologic studies of the 70's in Great-Britain which found strong correlations between calcium and cardiovascular mortality, but without any effect of magnesium. A possible protective effect of calcium on cardiovascular diseases has already been described in nutritional studies: diets rich in calcium and magnesium are associated with lower blood pressure [4], especially among women.

In conclusion, the present study has found a dose-effect relationship between calcium contained in drinking water and cardiovascular mortality and a U-shape effect of magnesium more pronounced for cerebrovascular mortality. These findings meet several criteria that suggest an interpretation in terms of causal effect. The statistical tests are highly significant; there is a consistency between men and women; people have been exposed to drinking water before developing the cardiovascular disease and dying, and there is no doubt about the direction of causal relationship if it exists: we cannot imagine that the calcium concentration is influenced by the rate of cardiovascular mortality. There is a biological plausibility and a biological gradient (monotone dose-effect relationship) for calcium. In view of this, we think that more precise studies should now be undertaken, in particular cohort or intervention studies. Cohort design would permit us to control the other sources of calcium intake and to investigate more

[1] Unpublished technical report INSERM U330, April 1993.

precisely the cardiovascular causes of death. An intervention study of Calcium supplementation would have the advantage of randomization, leading to more secure interpretation in term of causality.

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