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Original Contribution

Aluminum and Silica in Drinking Water and the Risk of Alzheimer's Disease or Cognitive Decline: Findings From 15-Year Follow-up of the PAQUID Cohort

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The authors examined associations between exposure to aluminum or silica from drinking water and risk of cognitive decline, dementia, and Alzheimer's disease among elderly subjects followed for 15 years (1988–2003). They actively searched for incident cases of dementia among persons aged 65 years or over living in 91 civil drinking-water areas in southern France. Two measures of exposure to aluminum were assessed: geographic exposure and individual exposure, taking into account daily consumption of tap water and bottled water. A total of 1,925 subjects who were free of dementia at baseline and had reliable water assessment data were analyzed. Using random-effects models, the authors found that cognitive decline with time was greater in subjects with a higher daily intake of aluminum from drinking water ($\geq$0.1 mg/day, $P = 0.005$) or higher geographic exposure to aluminum. Using a Cox model, a high daily intake of aluminum was significantly associated with increased risk of dementia. Conversely, an increase of 10 mg/day in silica intake was associated with a reduced risk of dementia (adjusted relative risk = 0.89, $P = 0.036$). However, geographic exposure to aluminum or silica from tap water was not associated with dementia. High consumption of aluminum from drinking water may be a risk factor for Alzheimer's disease.

aluminum; Alzheimer disease; cognition; dementia; silicon dioxide; water; water supply

Abbreviations: ALMA+, Aluminum–Maladie d'Alzheimer; EPIDOS, Epidémiologie de l'Ostéoporose; MMSE, Mini-Mental State Examination; PAQUID, Personnes âgées Quid; RR, relative risk.

Alzheimer's disease is a neurodegenerative cerebral disorder defined as a progressive deterioration of cognitive function and loss of autonomy. Although knowledge of the pathophysiology of Alzheimer's disease has greatly progressed over the past several decades, its causal mechanisms are far from clear.

The hypothesis that aluminum exposure is etiologically related to Alzheimer's disease has led to much debate. The possibility of such a relation was suggested by the presence of aluminum in senile plaques and neurofibrillary degeneration, 2 histologic lesions that are characteristic of the disease (1). Several studies have found that intake of aluminum (2, 3) increases expression of amyloid protein in rodent tissues, a step that may be critical to the development of Alzheimer's disease. Ecologic studies have suggested that concentrations of aluminum in drinking water of 0.1–0.2 mg/L may increase the risk of Alzheimer's disease, with relative risks or odds ratios ranging from 1.35 to 2.67 (4–8). However, of the epidemiologic studies conducted thus far, all but 1 (9) have ignored individual daily intake of drinking water.

Some epidemiologic and experimental studies, but not all, suggest that silica can reduce oral absorption of aluminum and/or enhance aluminum excretion and protect against aluminum-induced adverse effects (5, 9, 10). The silica content of tap water can vary according to geographic region, with typically high silica levels in hard-water areas and low levels in soft-water areas. In 2 studies carried out in Egypt (11) and the United Kingdom (12), bottled water of all brands (spring or mineral water) contained higher levels of silica than tap water, perhaps because treatment of tap water (i.e., by aluminum flocculation) decreases its silica content. We previously reported a geographic association between aluminum and silica and cognitive decline or dementia in data from the Personnes âgées Quid (PAQUID) cohort (4, 5). Subjects

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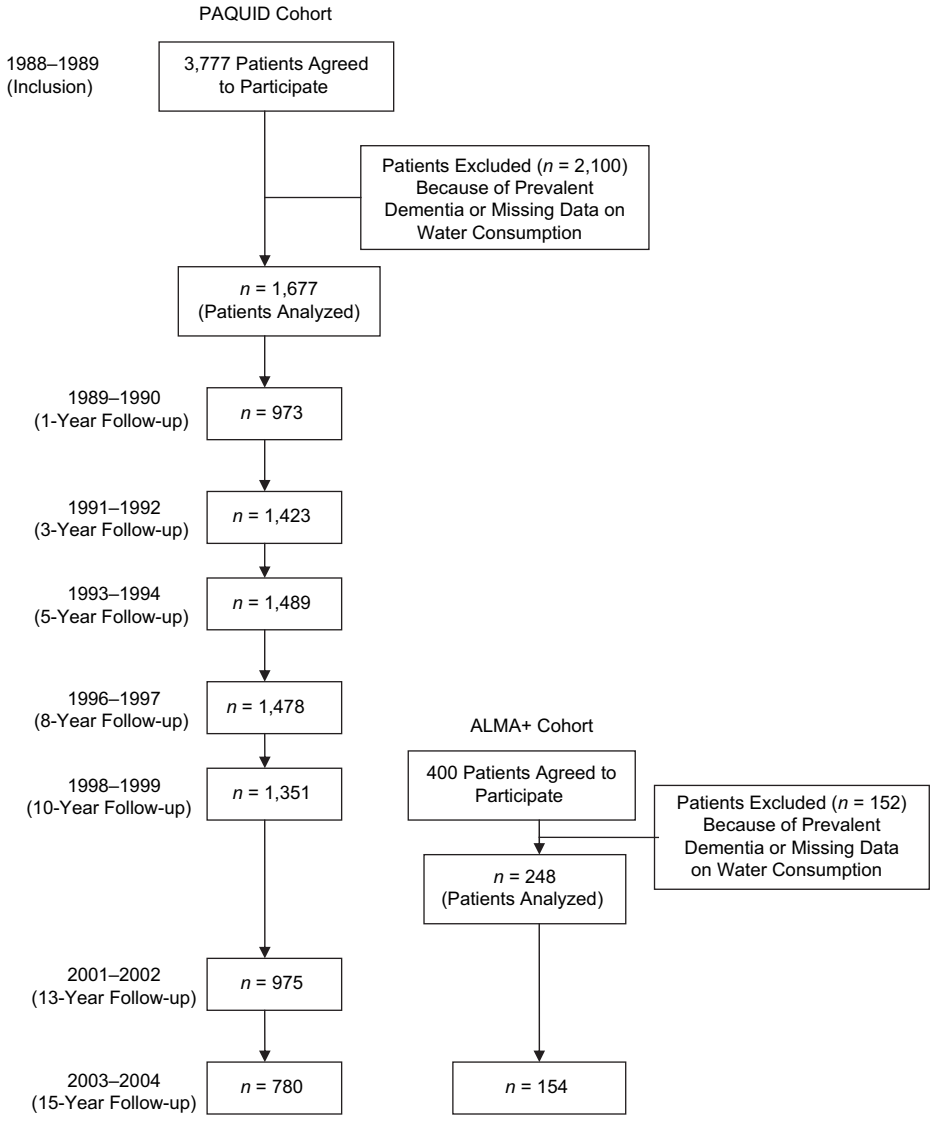

Figure 1. Follow-up of participants from the Personnes âgées Quid (PAQUID) and Aluminum–Maladie d'Alzheimer (ALMA+) cohorts for analysis of the relation between drinking water aluminum and silica and risk of Alzheimer's disease, France, 1988–2003.

were followed for 8 years, and there were few exposed subjects. Our aim in the present work was to analyze the associations with more precise data on daily aluminum and silica intake in a larger cohort followed for 15 years, with additional numbers of exposed subjects and with a majority of new events occurring after the eighth year of follow-up.

MATERIALS AND METHODS

Participants and recruitment

Figure 1 illustrates the course of the study. Briefly, the PAQUID Study is an ongoing prospective, population-based cohort study of the epidemiology of dementia and Alzheimer's disease in the elderly population of France (13). The study, beginning in 1988, initially included a community-based cohort of 3,777 elderly people aged 65 years or older who were living at home in one of 75 randomized rural or urban drinking-water areas in the administrative regions of Gironde and Dordogne in southwestern France. Subjects were randomly selected from electoral rolls and were followed up regularly between 1988 and 2004. The PAQUID Study was approved by an ethical review committee.

To increase the number of exposed subjects, we added subjects from the Aluminum–Maladie d'Alzheimer (ALMA+) cohort. This cohort of 400 subjects was randomly selected from electoral rolls at the same time as the 10-year follow-up of the PAQUID cohort. These subjects, who were aged 75 years or over at study entry, lived at home in one of the 14 drinking-water areas in the administrative region of Dordogne in southwestern France. There were 5 drinking-water areas with mean aluminum levels of

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0.050–0.100 mg/L and 9 areas with aluminum levels greater than or equal to 0.100 mg/L. These subjects, who were first seen in 1999 and then again in 2003, were expected to be comparable with subjects seen at the 10-year follow-up of the PAQUID cohort.

Cognitive decline was analyzed in both the PAQUID cohort and the ALMA+ cohort. Dementia and Alzheimer's disease were investigated only in the PAQUID cohort, because of the nonsymmetrical screening process in the 2 cohorts and because of the 2 different follow-up periods.

Assessment of cognitive function, dementia, and Alzheimer's disease

At baseline, a psychologist who gathered data on sociodemographic factors, medical antecedents, and functional disability saw subjects at home. Assessment of intellectual functioning included an evaluation of global mental status (the Mini-Mental State Examination (MMSE)) (14) and a battery of other tests. At the end of the visit, the psychologist systematically completed a standardized questionnaire designed to obtain information on *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (15) criteria for dementia. A senior neurologist subsequently saw subjects who met these criteria at home to confirm and complete the diagnosis of dementia, to apply the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease (16), and to calculate the Hachinski score (17) for vascular dementia.

Measure of exposure and water consumption

On the basis of information provided by the sanitary administration, we divided the PAQUID and ALMA+ samples into 77 and 14 drinking-water areas, respectively. For each area, we computed a weighted mean of all measures of aluminum and silica using the results of chemical analyses of drinking water carried out by the sanitary administration between 1991 and 1994 (unpublished data). For evaluation of subjects' past exposure, the history of the water distribution network over the previous 10 years (1981–1991) was evaluated in the PAQUID cohort.

The 8-year follow-up questionnaire given to the PAQUID cohort and the 3 following questionnaires, as well as the first and second questionnaires given to the ALMA+ cohort, included a dietary investigation that contained specific questions relating to daily consumption of tap water (including water used in making tea, coffee, soup, or alcoholic drinks) and bottled water (spring or mineral water) and the brand of bottled water most frequently consumed. The first nonmissing information collected was used for each individual exposure, assuming stable daily water consumption throughout the period of observation. The composition of the various bottled waters was provided by the respective distributing companies. Contrary to the case with mineral water, the composition of bottled spring water may change over time; even so, we used an average of several measurements taken across time (mean number of values = 1.9). For each subject, daily mean intake of aluminum or silica from tap water and/or bottled water was computed. The statistical analyses were then based on 2 kinds of drinking water indicators for aluminum or silica: a geographic exposure measure (in mg/L) previously used in the PAQUID cohort (5) and an individual indicator (in mg/day) that was more precise, taking daily bottled and tap water consumption into account.

Statistical analysis

Analyses of cognitive decline were performed using a random-effects linear regression model, including a subject-specific random intercept and slope to account for intrasubject correlation. A random intercept that was specific for each geographic area controlled for potential intra-area correlation. Since the distribution of MMSE scores was not normal, we analyzed the square root of the number of errors according to time (5). Besides the time variable representing the number of years after the initial visit, a binary indicator for the initial visit was introduced to account for a first-pass effect, possibly due to stress. Aluminum was considered as a quantitative variable or as a categorical variable. A binary variable was chosen with the threshold of 0.1 mg/L already used in previous ecologic studies (6, 7), or 0.1 mg/day for individual exposure. Four classes were also used according to the 3 tertiles (on subjects) under 0.1 mg/day and the category at or above 0.1 mg/day. Silica was considered as a quantitative variable or as a binary variable with 11.25 mg/L as the cutoff for geographic exposure (the median in our sample) and 10.55 mg/day as the cutoff for individual exposure (the median daily intake in our sample), or in 4 quartiles. We adjusted for the following potential confounders: educational level (18), wine consumption (19), place of residence (rural vs. urban), and cohort (PAQUID or ALMA+).

To examine the robustness of results from the main analysis on cognitive decline, we assessed influence diagnostics, using Cook's D statistic (20) in the final adjusted model. The 20 most globally influential subjects were removed, and updated estimates of model parameters were computed.

Analyses of the risk of dementia or Alzheimer's disease were performed using a Cox proportional hazards model with delayed entry (21) to estimate relative risks and to adjust for covariates. Age was used as the basic time scale in the analysis, so the risks of dementia or Alzheimer's disease were adjusted nonparametrically for age. A stratified analysis for gender was performed (21).

All analyses were conducted using MIXED and PHREG in SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Among the 4,177 subjects (3,777 from the PAQUID cohort and 400 from the ALMA+ cohort) who initially agreed to participate, 207 with prevalent dementia were excluded. The current study was restricted to the 1,925 subjects (among the 3,970 who were nondemented at their first visit) in 91 geographic areas who had nonmissing values for daily consumption of aluminum or silica in drinking water and for adjustment covariates. Subjects from the PAQUID cohort

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Table 1. Distribution of Potentially Confounding Variables Across Levels of Drinking Water Aluminum and Silica Concentration, PAQUID and ALMA+ Cohorts, France, 1988–2003

Baseline Characteristic	Aluminum From Tap Water (n = 1,883[a])—Geographic Exposure				Aluminum From Tap Water and/or Bottled Water (n = 1,925)—Individual Exposure					
	≥0.100 mg/L (n = 216)		<0.100 mg/L (n = 1,667)		≥0.100 mg/day (n = 112)		<0.100 mg/day (n = 1,813)		Total (n = 1,925)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Silica from tap water (geographic exposure), mg/L										
≥11.25	131	60.7	1,033	62.2	73	65.2	1,091	61.8	1,164	62.1
<11.25	85	39.3	627	37.8	39	34.8	673	38.2	712	37.9
Silica from tap water and/or bottled water, mg/day										
≥10.55	141	65.3	860	51.6	87	77.7	935	51.6	1,022	53.1
<10.55	75	34.7	807	48.4	25	22.3	878	48.4	903	46.9
Gender										
Male	89	41.2	640	38.4	48	42.9	696	38.4	744	38.6
Female	127	58.8	1,027	61.6	64	57.1	1,117	61.6	1,181	61.4
Education										
No education or primary school (ages 6–12 years) without diploma	77	35.7	481	28.9	36	32.1	539	29.7	575	29.9
At least primary school with diploma	139	64.3	1,186	71.1	76	67.9	1,274	70.3	1,350	70.1
Place of residence										
Rural	182	84.3	604	36.2	100	89.3	721	39.8	821	42.7
Urban	34	15.7	1,063	63.8	12	10.7	1,092	60.2	1,104	57.3
Wine consumption										
Nondrinker or light drinker	104	48.2	1,372	82.3	47	41.9	1,466	80.9	1,513	78.6
Moderate or heavy drinker	112	51.8	295	17.7	65	58.1	347	19.1	412	21.4

Abbreviations: ALMA+, Aluminum–Maladie d'Alzheimer; PAQUID, Personnes âgées Quid.

[a] Tap water aluminum concentrations were not available for all geographic areas; thus, among the 1,925 subjects analyzed, only 1,883 had no missing values for tap water aluminum concentration.

who were lost to follow-up or died before the eighth year of follow-up had no measure of water consumption and were excluded from the study. Baseline characteristics of the study sample are shown in Table 1.

The PAQUID sample at the 10-year follow-up and the ALMA+ sample at entrance were, as expected, very similar: Mean ages were 82.52 years and 82.31 years, respectively ($P = 0.51$); MMSE scores were 24.91 and 25.93, respectively ($P < 0.0001$); percentages of women were 61.66 and 59.27 ($P = 0.47$); and percentages of highly educated patients were 70.66 and 66.53 ($P = 0.18$). The ALMA+ patients had higher consumption of aluminum from drinking water (mean = 0.136 mg/day) than patients in the PAQUID cohort (mean = 0.009 mg/day) ($P < 0.0001$).

Mean consumption of drinking water was 0.94 L/day (standard deviation, 0.49). Tap water was the sole source of water intake for 43.7% of the subjects; 40.3% drank only bottled water. The composition of aluminum in tap water varied greatly from one parish to another—from 0.001 mg/L to 0.514 mg/L, with a mean value of 0.043 mg/L (median, 0.009 mg/L), depending largely on the method of water treatment used (i.e., aluminum flocculation or no aluminum flocculation). Concentrations of aluminum in bottled water, when available or detectable, were very low, with a maximum of 0.032 mg/L and a mean of 0.002 mg/L (median, 0 mg/L). Silica levels in tap water ranged from 4.2 mg/L to 22.4 mg/L and were inversely related to aluminum concentrations, but this negative correlation was weak in our study (Pearson correlation coefficient = −0.18; $P = 0.13$). In bottled water, concentrations of silica ranged from 2 mg/L to 77.6 mg/L. Table 2 shows the daily mean intake of aluminum and silica from drinking water in the study subjects. The correlation between geographic exposures and individual exposure was 0.71 ($P < 0.001$) for aluminum and 0.13 ($P < 0.001$) for silica. Among the subjects studied, 112 were exposed to at least 0.1 mg/day of aluminum, essentially because of high consumption of tap water with high levels of aluminum.

Relation between cognitive function and water composition in the PAQUID and ALMA+ cohorts

Aluminum intake interacted significantly with time (Table 3). Cognitive decline was greater in subjects with a high daily aluminum intake (≥0.1 mg/day or an increase of 0.1 mg/day). However, aluminum had no significant

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Table 2. Daily Intakes of Aluminum and Silica in Drinking Water ($n = 1{,}925$), PAQUID and ALMA+ Cohorts, France, 1988–2003[a]

Element	Mean Intake, mg/day	Range of Intakes, mg/day	Amount Supplied by Tap Water, %	Amount Supplied by Bottled Water, %
Aluminum	0.025 (0.08)[b]	0–1.03	95.9	4.1
Silica	13.37 (10.76)	0–108	41.0	59.0

Abbreviations: ALMA+, Aluminum–Maladie d'Alzheimer; PAQUID, Personnes âgées Quid.

* $P < 0.0001$.

[a] Pearson correlation coefficient = 0.17*.

[b] Numbers in parentheses, standard deviation.

association with the MMSE scores at inception. For example, a woman without a primary school diploma who was aged 75 years at inception with low daily silica (<10.55 mg/day) and aluminum (<0.1 mg/day) intakes would, on average, lose 1.5 points on the MMSE score between the first follow-up and the 15-year follow-up; but with a high daily aluminum intake (≥0.1 mg/day), she would lose 5.0 points. In these models, even after adjustment for different factors, significant but very low intraparish correlation was obtained (in model 1 from Table 3, the variance of the intraparish random effect was 0.008 ($P = 0.019$)). This may mean that other geographic factors may also influence cognitive decline.

The same tendencies were obtained using the geographic tap water exposure measure: Cognitive decline with time was greater in subjects exposed to high levels of aluminum (models 3 and 4, Table 3). Neither individual intake of silica nor geographic exposure was significantly associated with cognitive function.

The interaction between aluminum and time was no longer significant ($P = 0.78$) when the demented subjects were excluded. This suggests that cognitive decline with time is related to daily aluminum intake only when it is associated with a dementia process.

Among the 20 most influential subjects (approximately 1% of the sample), 7 had a high consumption of aluminum (>0.100 mg/day). After deletion of the 20 most influential patients, the parameter estimate for aluminum × time was unchanged, but it had a larger P value ($\beta = 0.045$, $P = 0.01$) than it did in the full data set.

When we repeated the cognitive decline analysis using only the PAQUID sample, we observed very similar interactions of aluminum or silica with time (comparison with model 2 in Table 3: for aluminum, $\beta = 0.020$, $P = 0.004$; for silica, $\beta = -0.003$, $P = 0.10$).

An 8-class variable for principal lifetime occupation was also added. The effects of aluminum and silica according to time (not shown in the tables) were unchanged (in model 1, $\beta = 0.046$ ($P = 0.009$) and $\beta = -0.004$ ($P = 0.35$), respectively).

Relation between dementia or Alzheimer's disease and water composition in the PAQUID cohort

Over the 15 years of follow-up of the PAQUID cohort, 1,677 subjects were analyzed and 461 subjects were diagnosed with dementia. The mean duration of follow-up was 11.3 years. Only 13 subjects had high daily consumption of aluminum from drinking water (≥0.1 mg/day); among them, 6 (46.2%) were demented. There were 364 subjects (78.9%) classified as having probable or possible Alzheimer's disease. The incidence rates for all causes of dementia and for Alzheimer's disease were estimated as 2.44 per 100 person-years and 1.92 per 100 person-years, respectively.

The risk of dementia was higher for subjects with a high daily aluminum intake (for intake ≥ 0.1 mg/day, adjusted relative risk (RR) = 2.26, $P = 0.049$; model 5, Table 4). Conversely, an increase of 10 mg/day in silica intake was associated with a reduced risk of dementia (adjusted RR = 0.89, $P = 0.036$; model 5). No tendency toward a dose-response effect for aluminum was apparent (likelihood ratio statistic = 3.52 (3 df), $P = 0.32$; model 7, Table 4), even

Table 3. Relation Between Daily Consumption of Aluminum and Silica From Drinking Water or Geographic Exposure From Drinking Water and Cognitive Decline, PAQUID and ALMA+ Cohorts, France, 1988–2003

Measure of Aluminum or Silica Exposure	Cognitive Decline[a]		*P* Value
	β[b]	Standard Deviation	
Daily consumption, mg/day			
Model 1			
Aluminum (≥0.1 vs. <0.1)	−0.15	0.098	0.08
Time (years) × aluminum	0.049	0.018	0.005
Silica (≥10.55 vs. <10.55)	−0.022	0.029	0.46
Time (years) × silica	−0.005	0.004	0.24
Model 2			
Aluminum (continuous)[c]	−0.031	0.023	0.19
Time (years) × aluminum	0.017	0.005	0.001
Silica (continuous)[d]	−0.020	0.014	0.15
Time (years) × silica	−0.003	0.002	0.11
Geographic exposure, mg/L			
Model 3			
Aluminum (≥0.1 vs. <0.1)	−0.12	0.070	0.09
Time (years) × aluminum	0.038	0.011	<0.001
Silica (≥11.25 vs. <11.25)	−0.018	0.034	0.60
Time (years) × silica	−0.003	0.004	0.45
Model 4			
Aluminum (continuous)[c]	−0.023	0.024	0.35
Time (years) × aluminum	0.014	0.004	<0.001
Silica (continuous)[d]	−0.032	0.053	0.55
Time (years) × silica	−0.0004	0.007	0.99

Abbreviations: ALMA+, Aluminum–Maladie d'Alzheimer; PAQUID, Personnes âgées Quid; SD, standard deviation.

[a] Adjusted for time, an indicator for the first follow-up (indicT0), age, time × age, gender, time × gender, indicT0 × gender, educational level, time × educational level, indicT0 × educational level, and cohort.

[b] Square root of the number of errors on the Mini-Mental State Examination (14).

[c] Increase of 0.1 mg/day.

[d] Increase of 10 mg/day.

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Table 4. Daily Aluminum or Silica Consumption From Drinking Water and Risk of Dementia or Alzheimer's Disease, PAQUID Cohort, France, 1988–2003

Daily Consumption, mg/day	Dementia (461 Cases)			Alzheimer's Disease (364 Cases)		
	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Model 1[a]						
Aluminum (≥0.1 vs. <0.1)	2.59	1.15, 5.80	0.021	3.35	1.49, 7.52	0.003
Model 2[a]						
Aluminum (continuous)[b]	1.29	1.05, 1.58	0.014	1.36	1.11, 1.67	<0.001
Model 3[a]						
Silica (≥10.55 vs. <10.55)	0.91	0.76, 1.10	0.330	0.91	0.74, 1.12	0.360
Model 4[a]						
Silica (continuous)[c]	0.89	0.80, 0.98	0.002	0.88	0.79, 0.99	0.030
Model 5[d]						
Aluminum (≥0.1 vs. <0.1)	2.26	1.00, 5.07	0.049	2.80	1.24, 6.32	0.013
Silica (continuous)[c]	0.89	0.81, 0.99	0.036	0.89	0.79, 1.00	0.045
Model 6[d]						
Aluminum (continuous)[b]	1.28	1.05, 1.58	0.017	1.34	1.09, 1.65	<0.006
Silica (continuous)[c]	0.89	0.81, 0.99	0.028	0.88	0.79, 0.99	0.035
Model 7[d]						
Aluminum						
<0.0012	1			1		
0.0012–<0.0045	0.96	0.76, 1.21	0.727	0.99	0.76, 1.28	0.910
0.0045–<0.1000	0.98	0.78, 1.24	0.860	1.05	0.81, 1.37	0.698
≥0.1000	2.34	1.03, 5.32	0.044	3.04	1.32, 6.97	0.009
Silica (quartiles)						
>15.45	1			1		
>10.55–15.45	1.14	0.87, 1.49	0.354	1.14	0.84, 1.55	0.403
>5.86–10.55	1.34	1.03, 1.75	0.029	1.38	1.03, 1.86	0.034
≤5.86	1.33	1.01, 1.74	0.041	1.33	0.98, 1.80	0.071

Abbreviations: CI, confidence interval; PAQUID, Personnes âgées Quid; RR, relative risk.
[a] Nonparametrically adjusted for age and gender.
[b] Increase of 0.1 mg/day.
[c] Increase of 10 mg/day.
[d] Nonparametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption, and place of residence.

though a significant linear relation between aluminum and dementia was obtained in model 6 (for an increase of 0.1 mg/day, adjusted RR for aluminum = 1.28; $P = 0.017$). Model 6, with aluminum entered as a continuous variable, was slightly better than model 5, in which aluminum was divided into 2 classes (difference in Akaike's Information Criterion = 1.1). There was no significant interaction between aluminum and silica concentrations.

Analyses restricted to cases classified as Alzheimer's disease (364 cases) also suggested a deleterious effect of high aluminum intake and a protective effect of high silica intake. These effects were not significant for other types of dementia (97 cases; data not shown).

Using the geographic measure of tap-water exposure, concentrations of aluminum or silica were no more associated with the risk of dementia or Alzheimer's disease, although the tendencies were similar (results not shown).

DISCUSSION

We found that the risks of cognitive decline and dementia were higher for high consumption of aluminum from drinking water. Even though we observed almost the same tendencies regarding the effect of geographic exposure to aluminum as in the previous PAQUID cohort (5), geographic exposure was no more significantly associated with dementia. Because it was based on a small number of exposed subjects in this sample (46 subjects with aluminum intakes ≥ 0.100 mg/L), this result may be explained by a lack of statistical power in the analysis. This strengthens the importance of using an individual measure of exposure rather than a geographic measure of exposure. The analysis did not show any evidence of silica intake's being associated with the evolution of cognitive function; however, it showed an inverse association between silica intake from

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drinking water and the risk of dementia, or more specifically Alzheimer's disease.

Biases and limitations

The findings of our study warrant caution in interpretation, owing to some limitations.

Although we adjusted for several potentially confounding factors, the possibility of residual confounding cannot be completely excluded. We thus adjusted for several individual factors, such as age, gender, wine consumption, educational level, and place of residence (which is potentially associated with bottled water consumption).

Subjects drinking only bottled water may have different exposures, since they are not exposed to aluminum from drinking water and can be more exposed to silica (if the bottled water contains high levels of silica). We repeated the main analyses after excluding those persons. In the dementia analysis in the PAQUID sample (749 subjects excluded out of 1,677), the effect of aluminum remained equivalent (for instance, for model 5 in Table 4, RR = 2.31 and $P = 0.045$), but the effect of silica was no longer significant (RR = 1.04, $P = 0.13$).

Consumption of bottled water may change over time and may differ for demented patients and nondemented patients. We studied this evolution in the subsample of 476 PAQUID subjects who had been seen at each follow-up since the assessment of daily water consumption (the 8-, 10-, 13-, and 15-year follow-ups). The intraclass correlation coefficient, based on a random-effect linear regression for daily intake of bottled water, was 0.54. This indicates that daily bottled intake was rather stable between the 8-year follow-up and the 15-year follow-up. The same tendencies were observed for the 402 nondemented patients ($\rho = 0.55$) and the 74 demented patients ($\rho = 0.47$). It seems that dementia does not much change the consumption of bottled drinking water. Furthermore, the information on water consumption was mainly collected in nondemented patients (1,406/1,677 = 83.8%). This strengthens the validity of our results, even though the information on bottled water consumption was available only after the 8-year follow-up.

One may think that social status or educational level might influence bottled water consumption and thus daily intake of aluminum or silica. A high consumption of bottled water leads to a lower aluminum intake and most of the time to a greater silica intake. However, mean daily bottled water consumption was not significantly different for highly educated patients (0.48 L/day) and less-educated patients (0.47 L/day) in our sample.

In the analyses of dementia in the PAQUID cohort, only 13 subjects were exposed to at least 0.1 mg/day of aluminum, essentially because of a high consumption of tap water with high levels of aluminum. These subjects were distributed in 5 drinking-water areas with aluminum levels of more than 0.05 mg/L. Even though the number of subjects with a high daily aluminum intake was low, almost half of them (6/13) developed dementia over the 15 years of follow-up.

Food contributes approximately 95% and drinking water 1%–2% of the typical human's daily aluminum intake. However, the limited data available (22) suggest that the bioavailability of oral aluminum (namely, the fraction that is actually taken up into the bloodstream) from food (~0.1%) is less than that from water (~0.3%). Yokel et al. (22) recently suggested that food provides approximately 25-fold more aluminum to systemic circulation (and potential aluminum body burden) than does drinking water. Evidence surrounding the relation between aluminum in food and the risk of Alzheimer's disease is minimal (23), probably because of the difficulty of obtaining accurate exposure information in dietary studies.

Strengths

A great advantage of our study was that we had estimates of daily individual intakes of aluminum and silica supplied by drinking water, not merely the geographic concentrations of these elements as in most previously published epidemiologic studies (4, 5, 7, 24). These individual data on intakes from drinking water are more precise and lead to more accurate findings.

In only 1 recent French cohort study (the Epidémiologie de l'Ostéoporose (EPIDOS) Study) did investigators also analyze individual daily consumption of aluminum or silica from drinking water (9). At baseline, a low silica concentration was associated with low cognitive performance and with more Alzheimer's disease. No significant changes were observed with aluminum intake. These results corroborate our results for silica only. However, the EPIDOS Study comprised a selected population of volunteers who were not representative of the general population and had much lower levels of aluminum intake (maximum = 0.063 mg/L).

The study of cognitive function in addition to the risk of dementia has 2 main methodological purposes. First, the evolution of the MMSE score is not sensitive to diagnostic errors that may be present in the detection of Alzheimer's disease. Second, cognitive decline precedes the occurrence of dementia by 3–5 years and is less subject to competitive morbidity or mortality.

The survey design incorporated grouping of the participants into drinking-water areas. This had the advantage of producing heterogeneity in drinking water exposures or other environmental factors, but it may have induced correlation of the observations. In a random-effect survival model (5, 25), no significant intragroup correlation was observed ($P = 0.31$). The effects of aluminum (for model 5 in Table 4, RR = 2.22; standard error, 0.43) and silica (RR = 0.90; standard error, 0.05) were unchanged. It is thus unlikely that some unmeasured environmental factor shared by the members of the same parish could have played a confounding role in the analysis of dementia.

Further studies are needed to settle the debate over the link between aluminum or silica in drinking water and neurologic disorders and cognitive impairment. Ideally, in such studies individual data on drinking water exposure and other relevant risk factors would be collected for assessment of this potential risk.

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