American Journal of Epidemiology
Vol. 152, No. 1
Printed in U.S.A.
Copyright © 2000 by The Johns Hopkins University School of Hygiene and Public Health
All rights reserved

Relation between Aluminum Concentrations in Drinking Water and Alzheimer's Disease: An 8-year Follow-up Study

Virginie Rondeau, Daniel Commenges, Hélène Jacqmin-Gadda, and Jean-François Dartigues

To investigate the effect of aluminum and silica in drinking water on the risk of dementia and Alzheimer's disease, the authors analyzed data from a large prospective cohort (Paquid), including 3,777 subjects aged 65 years and over living at home in 75 civil parishes in Gironde and Dordogne in southwestern France in 1988–1989. The subjects were followed for up for 8 years with an active search for incident cases of dementia or Alzheimer's disease. Mean exposure to aluminum and silica in drinking water was estimated in each area. The sample studied included 2,698 nondemented subjects at baseline, for whom components of drinking water and covariates were available. A total of 253 incident cases of dementia (with 17 exposed to high levels of aluminum), including 182 Alzheimer's disease (with 13 exposed to high aluminum levels), were identified. The relative risk of dementia adjusted for age, gender, educational level, place of residence, and wine consumption was 1.99 (95 percent CI: 1.20, 3.28) for subjects exposed to an aluminum concentration greater than 0.1 mg/liter. This result was confirmed for Alzheimer's disease (adjusted relative risk = 2.14, 95 percent CI: 1.21, 3.80). However, no dose-response relation was found. Inversely, the adjusted relative risk of dementia for subjects exposed to silica (≥11.25 mg/liter) was 0.74 (95 percent CI: 0.58, 0.96). These findings support the hypothesis that a high concentration of aluminum in drinking water may be a risk factor for Alzheimer's disease. *Am J Epidemiol* 2000;152:59–66.

aluminum; Alzheimer's disease; dementia; drinking water; silica

Although much effort has been devoted to identifying the genetic determinants of Alzheimer's disease (1), it is likely that certain environmental factors play a role in this disease. Because of its proven neurotoxicity, aluminum may be one such factor. Although the hypothesis of a link between aluminum and Alzheimer's disease has been supported by several biological findings (2–5), uncertainty still prevails. Dialysis encephalopathy (6) is one of the main observations in favor of the neurotoxicity of aluminum because it proves that aluminum is able to reach the brain and induce neurofibrillary degeneration and neuronal death. Some previous epidemiologic studies have suggested an association between aluminum from drinking water and dementia (7–9). However, there is much controversy regarding these findings and their interpretation, in particular owing to recently published epidemiologic studies that failed to find an association (10, 11). Other sources of exposure to aluminum have been examined: Rifat et al. (12) showed a relation between exposure to aluminum powder and cognitive impairment, but, more recently, Graves et al. (13) failed to find a relation between occupational exposures to aluminum and Alzheimer's disease. Studies on the role of aluminum-containing products (antacids and antiperspirants) and Alzheimer's disease have reported both positive and negative results (14, 15). On the other hand, Birchall and Chappell (16) and Exley et al. (17) have put forward the hypothesis that silicon in water could be a protective factor against aluminum toxicity.

In previous papers (18, 19), we showed that baseline cognitive impairment of subjects in the Paquid cohort seemed to be associated with levels of aluminum and silica in drinking water. Here we present results for incident dementia and Alzheimer's disease based on 8 years of follow-up.

MATERIALS AND METHODS

Sample

The Paquid cohort was designed to prospectively study a representative random sample of 3,777 people aged 65 years or older at baseline and living at home in one of 75 randomized rural or urban parishes of the administrative areas of Gironde or Dordogne in southwestern France. Subjects were randomly selected from electoral rolls, and baseline data were collected in 1988–1989. The general methodology of Paquid has been fully described elsewhere (20, 21).

Assessment of dementia and Alzheimer's disease

Subjects who agreed to participate underwent a 1-hour home interview with a specially trained psychologist.

Received for publication April 8, 1999, and accepted for publication November 17, 1999.

Abbreviations: MMSE, Mini-Mental State Examination; n.f. deaths, no follow-up because the patients died; n.f. refusals, no follow-up because the patients refused; RR, relative risk.

From the INSERM Unité 330, Université Victor Segalen Bordeaux II, 33076 Bordeaux, France. (Reprint requests to Dr. Virginie Rondeau at this address.)

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011

Prevalent and incident cases of dementia were detected by a two-step procedure. First, after the psychometric evaluation, the psychologist systematically completed a standardized questionnaire designed to obtain the A (memory impairment), B (impairment of at least one other cognitive function), and C (interference with social and professional life) criteria for dementia according to the DSM-III-R (22). Second, subjects who were positive for these criteria were examined by a senior neurologist, who confirmed the diagnosis and applied the NINCDS-ADRDA (23) criteria for Alzheimer's disease and the Hachinski score for vascular dementia (24) to document the diagnosis of dementia and its etiology: probable or possible Alzheimer's disease or other type of dementia.

Follow up

Subjects were then reevaluated with the same procedure as for the baseline screening 1, 3, 5, and 8 years after the initial visit in Gironde and 3, 5, and 8 years after the initial visit in Dordogne to diagnose incident cases of dementia. To improve the sensitivity of the detection of incident cases, another criterion was added for the selection of subjects for the second stage (neurologic examination): Subjects were selected for this stage if they met the criteria for DSM-III-R dementia or if they had experienced a cognitive decline of more than two points at the Mini-Mental State Examination (MMSE) score.

Measure of exposure

A specific study (Aluminum Maladie d'Alzheimer (ALMA)) was started in 1991 to examine the relation between aluminum in drinking water and Alzheimer's disease for the Paquid subjects. After investigation of the water distribution network, the sample was divided into 77 drinking water areas (with the largest parish of the study, Bordeaux, divided into three areas). Two surveys were carried out in 1991 to measure pH and concentrations of aluminum, calcium, and fluorine in each water supply and to study the variability of the measurements. These data were described in detail by Jacqmin-Gadda et al. (18). Then all the results of the chemical analyses of drinking water (including silica) carried out by the sanitary administration between 1991 and 1994 were collected. To evaluate the past exposure of the subjects, we retraced the history of the water distribution network over the previous 10 years (1981–1991). During this period, any parish for which there was not full information for sources constituting at least 20 percent of the water supply was excluded from the study. Therefore, for each drinking water area, we computed a weighted mean of all the measures of each drinking water component. The weighting took into account the length of the period of use of each water supply over the previous 10 years (1981–1991) and the relative contribution of each water supply. Our study is based on 70 areas for which measurements were available.

Statistical analysis

A Cox proportional hazard model with delayed entry (25) was performed to estimate relative risks and adjust for covariates. Age was chosen as the basic time scale in the analysis, so the risk of dementia or Alzheimer's disease were adjusted nonparametrically for age. This has two implications: first, it enables inferences on the effects of risk factors to be made without making parametric assumptions about the effect of age, and second, the hazard functions are the age-specific incidence of the disease (25, 26). For the analyses, we excluded the subjects with prevalent dementia at baseline. A subject was considered at risk from his age at entry into the cohort to his age of censorship or age of outcome. Subjects still unaffected at the last visit were right-censored at that time. Deceased subjects who were unaffected at the last visit were right-censored at that date, i.e., the last time their disease status was assessed. For a demented subject, we considered half of the time between the last visit at which the subject was seen nondemented and the first visit at which he was diagnosed as demented. This midpoint imputation is a reasonable procedure to estimate relative risks when interval widths are not too large (26).

In a previous analysis (26), we observed that the proportional hazards assumption was violated for gender, so we chose to perform a stratified analysis for gender (27). We tried three different ways of coding aluminum: as a quantitative variable, as a binary variable with the threshold of 0.1 mg/liter already used in previous studies (7, 9), and in four classes according to the three tertiles (on parishes) under 0.1 and the category above 0.1 mg/liter; silica was coded as a binary variable with 11.25 mg/liter (the median in our sample) as the cutoff. We adjusted for potential confounders: educational level with five classes coded by four binary variables (no education, did not graduate from primary school, graduated from primary school, high school level, and university level (28)); wine consumption (nondrinkers or mild drinkers vs. moderate or heavy drinkers) (29), and place of residence (rural vs. urban). Adjustment for baseline cognitive status measured by the MMSE (30) scores was performed in a complementary analysis (MMSE was available for 2,658 subjects).

We then examined separately the effect of bottled mineral water consumption (daily consumption of mineral water vs. no or occasional consumption). This information was collected only at the 3-year follow-up visit. Thereafter, we examined the subsample of nondemented subjects who were visited at that follow-up and used incident cases of dementia between the 3- and 8-year follow-up visits.

We performed a sensitivity analysis to assess how the subjects who had no follow-up because they refused (n.f. refusals) and those who had no follow-up because they died before any follow-up visit (n.f. deaths) may have affected our estimates. Four extreme possibilities were considered. The first assumed that none of the n.f. refusals had developed dementia. The second assumed that all of those subjects had developed dementia. The third supposed that none of the n.f. deaths had developed dementia. The last extreme possibility assumed that all n.f. deaths had developed dementia. New ages of outcome or censorship were attributed to these subjects (refusals or deaths). For demented subjects, the age of dementia was evaluated by the age at entry in the cohort plus the mean duration until dementia in

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011

the study (3.6 years). For nondemented subjects, the age of censoring was evaluated by the age at entry into the cohort plus the mean follow-up evaluation (5.9 years).

The main analyses were performed with EGRET software (EGRET Statistics and Epidemiology Research Corporation, Seattle, Washington).

RESULTS

Among the 3,777 subjects who initially agreed to participate, 102 with prevalent dementia were excluded and 3,675 were nondemented at the first visit. Measurements of water and adjustment covariates were available for 3,401 subjects unaffected at the initial visit. Among the 3,401 subjects, 703 (20.6 percent) did not participate in the follow-up because they had died before any dementia evaluation ($n = 383$, 11.3 percent) or had refused the follow-up procedure ($n = 320$, 9.4 percent); the percentages were not significantly different between those exposed and nonexposed to aluminum (deaths, $p = 0.42$; refusals, $p = 0.27$) (table 1). At least one complete follow-up evaluation was performed on 2,698 subjects (79.3 percent). During the 8-year follow-up of these subjects, 253 subjects were diagnosed with dementia; among these, 17 had been exposed to high levels of aluminum (≥0.1 mg/liter). There were 182 (72.0 percent) who were classified as having Alzheimer's disease (probable or possible); among these, 13 had been exposed to high levels of aluminum. The incidence rates for all causes of dementia and for Alzheimer's disease were estimated as 1.69 per 100 person-years and 1.22 per 100 person-years, respectively.

TABLE 1. Numbers and percentages of subjects followed in the cohort and subjects who had no follow-up because they died (n.f. deaths) or refused (n.f. refusals) for 3,401 subjects eligible at baseline, Paquid study, France, 1988–1989

Aluminum (mg/liter)	Followed at least once (%)	n.f deaths		n.f. refusals		Total	
		No.	%	No.	%	No.	%
≥0.1	63 (73.3)	12	13.9	11	12.8	86	100
<0.1	2,635 (79.5)	371	11.2	309	9.3	3,315	100
Total	2,698 (79.3)	383	11.3	320	9.4	3,401	

The mean follow-up duration was 5.9 years. Table 2 shows the follow-up of the cohort, with the number and percentages of surviving subjects who were followed at 1, 3, 5, and 8 years.

Aluminum levels in water supplies ranged from 0.001 to 0.459 mg/liter, with a median value of 0.009 mg/liter. Among subjects followed up at least once, 63 living in four parishes were exposed to more than 0.1 mg/liter of aluminum. Silica levels in water ranged from 4.2 to 22.4 mg/liter and were inversely related to aluminum concentrations, but this negative correlation was weak in our study (Spearman rank correlation coefficient = –0.18, $p = 0.13$). At baseline, 91 percent of the individuals had lived more than 10 years in the same parish, and the mean length of residence in the same parish was 41 years. Baseline characteristics of the cohort at risk, according to level of aluminum, are shown in table 3.

The results of the analyses (table 4) suggest that the risk of dementia was higher for subjects living in parishes where the mean aluminum concentrations exceeded 0.1 mg/liter than for those living in areas where concentrations were less than 0.1 mg/liter (relative risk (RR) nonparametrically adjusted for age and gender = 2.33, $p < 0.001$, model 1). Conversely, higher silica concentrations (≥11.25 mg/liter) were associated with a reduced risk of dementia (RR nonparametrically adjusted for age and gender = 0.71, $p = 0.007$, model 3). After additional adjustment for educational level, wine consumption, and place of residence, aluminum and silica concentrations remained associated with dementia (RR for aluminum = 1.99, $p = 0.007$; RR for silica = 0.74, $p = 0.021$, model 5). We also performed a model equivalent to model 5, in which we added the principal lifetime occupation with an eight-class variable, coded by seven binary variables: The RR for aluminum and silica (not shown in the tables) were unchanged, and occupation was not significant (likelihood ratio test = 10.6, 7 df, $p = 0.16$). It did not seem necessary to adjust for occupation after having adjusted for education level. When aluminum concentrations were separated into four classes, no tendency for a dose-response effect for aluminum was apparent (table 4, model 4, likelihood ratio statistic = 6.12, 3 df, $p = 0.11$), even though a significant linear relation between aluminum and dementia was obtained in model 6 (adjusted RR for aluminum = 1.25 for an increase of 0.1 mg/liter, $p = 0.015$). However, the model with aluminum in two classes was slightly better than

TABLE 2. Follow-up of the cohort with numbers and percentages of surviving subjects who completed the follow-up evaluation 1, 3, 5, and 8 years after the initial visit, according to aluminum exposure in the 3,401 subjects eligible at baseline, Paquid study, France, 1988–1989

Aluminum exposure (mg/liter)	No. of subjects (%)*				
	1 year†	3 years	5 years	8 years	Eligible at baseline
≥0.1	0 (0)	57 (77.0)	53 (75.7)	46 (73.0)	86
<0.1	1,693 (68.8)	2,046 (69.6)	1,867 (71.2)	1,403 (62.4)	3,315
Total	1,693 (68.3)	2,103 (69.8)	1,920 (71.3)	1,449 (62.5)	3,401

* Percentages were calculated on the number of surviving subjects at follow-up times.
† Only subjects living in one of the parishes of the administrative area of Gironde were seen.

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011

TABLE 3. Distribution of potential confounding variables across levels of aluminum exposure concentrations, Paquid study, France, 1988–1997

	Aluminum ≥0.1 mg/liter (n = 63)		Aluminum <0.1 mg/liter (n = 2,635)		Total (n = 2,698)	
	No.	%	No.	%	No.	%
Silica (mg/liter)						
≥11.25	16	25.4	1,613	61.2	1,629	60.4
<11.25	47	74.6	1,022	38.8	1,069	39.6
Education						
No education	21	33.3	816	31.0	837	31.0
Did not graduate from elementary school	31	49.2	1,194	45.3	1,225	45.4
Graduated from elementary school	9	14.3	322	12.2	331	12.3
High school level	2	3.2	156	5.9	158	5.9
University level	0	0.0	147	5.6	147	5.4
Place of residence						
Rural	16	25.4	817	31.0	833	30.9
Urban	47	74.6	1,818	69.0	1,865	69.1
Wine consumption						
Nondrinkers or light drinkers	54	85.7	2,208	83.8	2,262	83.8
Moderate or heavy drinkers	9	14.3	427	16.2	436	16.2

that in which aluminum was a continuous variable (Akaike criterion: 2,722.0 vs. 2,723.1) (table 4, models 5 and 6). There was no significant interaction between aluminum and silica concentrations (likelihood ratio test = 0.72, $p = 0.48$). The results of model 5 were not significantly changed after adjustment for baseline MMSE (RR for aluminum = 2.08, $p = 0.005$; RR for silica = 0.74, $p = 0.017$). The pH level was not associated with dementia, and the interaction between aluminum and pH was not significant.

Analyses restricted to cases classified as Alzheimer's disease (182 cases) also suggested a deleterious effect of high aluminum concentrations and a protective effect of high silica concentrations on the risk of Alzheimer's disease (table 5). These effects were not significant for other types of dementia (71 cases), although the relative risks were of the same order. This may be explained by a lack of power in the latter analysis.

The observations are summarized in table 6. Among the exposed subjects, the expected number of demented cases, using the Cox model adjusted for covariates (27), was computed to be 8.71 while 17 cases were observed, and the expected number of Alzheimer's cases was computed to be 5.65 while 13 cases were observed.

Information about mineral water consumption was collected for 1,638 nondemented subjects seen at the 3-year follow-up for whom covariates were available; 105 subjects developed dementia (including 88 Alzheimer's disease cases) between the 3- and the 8-year follow-up. In this subsample, 48 percent of the subjects were classified as daily drinkers of mineral water. The analysis of this subsample, adjusted for age, gender, educational level, wine consumption, place of residence, and silica yielded a relative risk of 2.89 (95 percent CI: 1.51, 5.52, $p < 0.001$) for aluminum ≥0.1 mg/liter. This relative risk reached 3.36 (95 percent CI: 1.74, 6.49, $p < 0.001$) after adjustment for mineral water consumption. There was no evidence of a significant interaction between aluminum and mineral water consumption. In this subanalysis, after adjustment for educational level, wine consumption, place of residence, and aluminum, the relative risk for silica was estimated to be 0.61 (95 percent CI: 0.41, 0.91, $p = 0.016$). The effect of silica was not changed after adjustment for mineral water consumption (RR = 0.61, 95 percent CI: 0.41, 0.91, $p = 0.016$). In the analyses, we considered as exposed all the subjects living in parishes with high levels of aluminum. An alternative was to consider subjects who drank daily mineral water as nonexposed; in this case, the effect of aluminum still remained unchanged and was still significantly associated with dementia.

The results of the sensitivity analyses on the 320 n.f. refusals and the 383 n.f. deaths are presented in tables 7 and 8, respectively. The sensitivity analyses on n.f. refusals and n.f. deaths showed a decrease in the effect of aluminum on dementia compared with results in the study, but the effect of aluminum on the risk of dementia remained significant. The effect of silica was also changed slightly in these sensitivity analyses, and it was no longer significant in the fourth assumption, i.e., that all n.f. deaths had developed dementia.

DISCUSSION

In this study, high aluminum levels in drinking water (≥0.1 mg/liter) were associated with an elevated risk of dementia and Alzheimer's disease. This result is highly significant despite the small number of subjects exposed to such levels. No dose-response relation was apparent in the analyses. Although this weakens the plausibility that aluminum has a causal effect on Alzheimer's disease, the interpretation may also be that there is a threshold effect around 0.1 mg/liter. Inversely, high silica levels (≥11.25 mg/liter)

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011

TABLE 4. Relative risks and 95% confidence intervals for 253 cases of dementia according to aluminum and silica concentrations in the water, Paquid study*, France, 1988–1997

Variable	RR†	95% CI†	*p* value
Model 1‡			
Aluminum ≥0.1 vs. <0.1 mg/liter	2.33	1.42, 3.82	<0.001
Model 2‡			
Aluminum (continuous)§	1.36	1.15, 1.61	<0.001
Model 3‡			
Silica ≥11.25 vs. <11.25 mg/liter	0.71	0.56, 0.91	0.007
Model 4¶			
Aluminum concentration (mg/liter)			
<0.0038	1		
≥0.0038–<0.0110	1.03	0.74, 1.43	0.850
≥0.0110–<0.1000	0.98	0.69, 1.40	0.920
≥0.1000	2.00	1.15, 3.50	0.015
Silica ≥11.25 vs. <11.25 mg/liter	0.74	0.58, 0.96	0.026
Model 5¶			
Aluminum ≥0.1 vs. <0.1 mg/liter	1.99	1.20, 3.28	0.007
Silica ≥11.25 vs. <11.25 mg/liter	0.74	0.58, 0.96	0.021
Model 6¶			
Aluminum (continuous)§	1.25	1.05, 1.50	0.015
Silica ≥11.25 vs. <11.25 mg/liter	0.76	0.59, 0.98	0.037

* Analyses performed on the sample of 2,698 nondemented subjects at baseline for whom components of drinking water and covariates were available.
† RR, relative risk; CI, confidence interval.
‡ Nonparametrically adjusted for age and gender.
§ Concentrations of aluminum (RR given for an increase of 0.1 mg/liter).
¶ Nonparametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption, and place of residence.

TABLE 5. Relative risks and 95% confidence intervals for 182 cases of Alzheimer's disease according to aluminum and silica concentrations in the water, Paquid study*, France, 1988–1997

Variable	RR†	95% CI†	*p* value
Model 1‡			
Aluminum ≥0.1 vs. <0.1 mg/liter	2.20	1.24, 3.84	0.007
Model 2‡			
Aluminum (continuous)§	1.46	1.23, 1.74	<0.001
Model 3‡			
Silica ≥11.25 vs. <11.25 mg/liter	0.69	0.52, 0.94	0.016
Model 4¶			
Aluminum concentration (mg/liter)			
<0.0038	1		
≥0.0038–<0.0110	1.16	0.78, 1.72	0.460
≥0.0110–<0.1000	0.97	0.63, 1.49	0.880
≥0.1000	2.27	1.19, 4.34	0.013
Silica ≥11.25 vs. <11.25 mg/liter	0.74	0.54, 1.00	0.052
Model 5¶			
Aluminum ≥0.1 vs. <0.1 mg/liter	2.14	1.21, 3.80	0.007
Silica ≥11.25 vs. <11.25 mg/liter	0.73	0.55, 0.99	0.040
Model 6¶			
Aluminum (continuous)§	1.35	1.11, 1.62	0.003
Silica ≥11.25 vs. <11.25 mg/liter	0.77	0.57, 1.04	0.087

* Analyses performed on the sample of 2,698 nondemented subjects at baseline, for whom components of drinking water and covariates were available.
† RR, relative risk; CI, confidence interval.
‡ Nonparametrically adjusted for age and gender.
§ Concentrations of aluminum (RR given for an increase of 0.1 mg/liter).
¶ Nonparametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption, and place of residence.

were associated with a lower risk of dementia and Alzheimer's disease.

Subjects who refused to participate in the follow-up (31) or who died are probably more likely to be demented. If the participation of these subjects were different in the exposed and the nonexposed groups, this could produce an "attrition" bias. In our study, the percentages of deaths before any follow-up visit and refusals before any follow-up visit were slightly higher for subjects exposed to aluminum, but this difference was not significant, which makes such a bias unlikely. The effect of aluminum estimated in the sensitivity analyses appeared to be somewhat lower than that calculated from the study (table 4, model 5). Nonetheless, all these sensitivity analyses suggest that the main result is robust.

Since the number of demented subjects exposed to high levels of aluminum was low, our results could be sensitive to a misdiagnosis of demented subjects. Therefore, in an additional analysis, we chose to define as demented the subjects who screened positive in the first stage of the diagnostic procedure. The prevalent who "screened positive" were removed, so we analyzed 2,670 subjects. Among these, 359 (of whom 21 exposed to aluminum) were considered as demented by the new definition. The results remained unchanged; high levels of aluminum were still significantly associated with an elevated risk of dementia (adjusted RR = 1.95, $p = 0.004$). Therefore, it is unlikely that the apparent effect of aluminum comes from a misclassification of the subjects.

In our analyses, Alzheimer's subjects were classified as those with probable or possible Alzheimer's disease. To

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011

TABLE 6. Expected and observed numbers of cases of dementia or Alzheimer's disease according to aluminum exposure after an 8-year follow-up of 2,698 subjects, Paquid study*, France, 1988–1997

	Aluminum <0.1 mg/liter (*n* = 2,635)	Aluminum ≥0.1 mg/liter (*n* = 63)
Dementia subjects		
Observed no.	236	17
Expected no.	244.29	8.71
Alzheimer's disease subjects		
Observed no.	169	13
Expected no.	176.35	5.65

* Expected number calculated with Martingale residuals, nonparametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption, and place of residence.

TABLE 7. Results of the sensitivity analyses on dementia for subjects who refused to participate in the follow-up procedure comparing two extreme possibilities, Paquid study*, France, 1988–1997

	None†		All‡	
	RR	95% CI	RR	95% CI
Aluminum ≥0.1 vs. <0.1 mg/liter§	1.90	1.15, 3.14	1.53	1.04, 2.26
Silica ≥11.25 vs. <11.25 mg/liter§	0.76	0.59, 0.97	0.85	0.72, 1.00

* Analyses performed on 3,018 subjects: 2,698 were followed effectively at least once, and 320 subjects refused the follow-up procedure.

† Relative risk (RR) and 95% confidence interval (CI) under the assumption that none of the subjects who refused the follow-up procedure had developed dementia.

‡ RR and 95% CI under the assumption that all of the subjects who refused the follow-up procedure had developed dementia.

§ Nonparametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption, and place of residence.

TABLE 8. Results of the sensitivity analyses on dementia for subjects who died before any follow-up evaluation comparing two extreme possibilities, Paquid study*, France, 1988–1997

	None†		All‡	
	RR	95% CI	RR	95% CI
Aluminum ≥0.1 vs. <0.1 mg/liter§	1.98	1.20, 3.27	1.52	1.04, 2.22
Silica ≥11.25 vs. <11.25 mg/liter§	0.69	0.54, 0.89	1.06	0.89, 1.24

* Analyses performed on 3,081 subjects: 2,698 were followed effectively at least once and 383 subjects died before any follow-up evaluation.

† Relative risk (RR) and 95% confidence interval (CI) under the assumption that none of the subjects died before any follow-up evaluation.

‡ RR and 95% CI under the assumption that all of the subjects died before any follow-up evaluation had developed dementia.

§ Nonparametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption, and place of residence.

increase the specificity of the analyses, another analysis was performed that considered only the 89 probable Alzheimer's disease cases, including six exposed subjects. A higher risk of Alzheimer's disease was still associated with a higher concentration of aluminum (adjusted RR = 1.77), although the association was not significant ($p = 0.19$), probably due to a lack of power of the analysis.

Of course, when studying the effects of risk factors in an old population, it must be remembered that the subjects are highly selected because they are still alive and have not developed the disease. Selection in a heterogeneous population may produce apparent effects that are different from true effects, as shown by Aalen (32). One way of partially coping with this problem is to adjust on explanatory variables that may explain part of the heterogeneity. This is why, in an additional analysis, we adjusted for baseline cognitive status, which is a good predictor of dementia and Alzheimer's disease. Controlling this baseline heterogeneity did not modify the relative risks for aluminum and silica.

The Paquid survey design incorporates a grouping of the participants into parishes, and this may induce a correlation of the observations. It is thus not to be excluded that some unmeasured environmental factor shared by the members of the same parish could play a confounding role. Analysis of dependent survival data by the classical Cox proportional hazard model using conventional partial likelihood methods may underestimate the variance of regression coefficients specific to each group, leading to incorrect inferences. We thus considered a "frailty model" (27) to take into account the grouping of the subjects in the different parishes. In the frailty model, the hazard function depends partly on an unobservable random variable (a random effect) thought to act multiplicatively on the hazard. A large value of the variance of the random effects means closer positive relation between the subjects of the same parish and a greater heterogeneity between the groups. The Statistical Analysis System (version 6.12) was used for these analyses (SAS Institute, Inc., Cary, North Carolina). An SAS macro (World Wide Web site: http://biostat.mcw.edu/Software.html) was used to implement the frailty model. The macro did not allow left truncated data, so we analyzed the delay between the time of entry into the cohort and the time of censorship or the time of outcome and then adjusted for age at entry. The estimated variance of the frailty parameter was not significantly different from zero ($p = 0.21$). This means we may admit that there is no intragroup correlation in our sample or that such a correlation is weak. The relative risks for aluminum and silica were unchanged, but the standard errors of these regression coefficients were slightly increased. However, aluminum and silica concentrations were still significantly associated with dementia ($p = 0.004$ and 0.042, respectively).

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011

Several investigators have described how the pH of drinking water may affect the solubility of aluminum components (33). It is plausible that the biological availability of aluminum is higher for low pH than for high pH, which would lead to an interaction between pH and aluminum. These results were not confirmed in our study; nevertheless, 98.7 percent of the pH values were higher than 7 (range, 6.31–8.44).

Surface waters (lakes or rivers) are often treated with aluminum sulphate to induce flocculation and remove organic and other contaminants. Indeed, in the parishes in this study, the median aluminum concentration was higher in surface waters compared with underground waters (0.023 vs. 0.006 mg/liter). However, no elevated incidence of dementia was found for subjects living in areas supplied by surface waters.

Significant amounts of aluminum may also be supplied from aluminum cooking utensils. We therefore performed an additional analysis including the use of aluminum cookware as an explanatory variable; no influence on the risk of dementia was observed (RR = 1.04, $p = 0.86$, results based on 1,586 participants who had answered this question at the 3-year follow-up).

Our results confirm the significant association of Alzheimer's disease with exposure to aluminum in drinking water previously reported in some epidemiologic studies (7, 9). Nevertheless, two recent studies failed to find a relation with aluminum in drinking water (10, 11). The study by Forster et al. (10) had a modest statistical power with a small number of subjects (109 cases and 109 controls). Furthermore, the inconsistency of our results with those of Forster et al. (10) and Martyn et al. (11) might be explained by the fact that their studies examined younger subjects (aged 43–75 years) than in the Paquid cohort, so they examined presenile rather than senile dementia of the Alzheimer type. As suggested by Taylor et al. (34), it is plausible that there is an increase in aluminum absorption with age, so the effect of aluminum may be larger after age 75 years than before. Moreover, genetic factors are more influential in the etiology of presenile dementia.

Using theoretical chemistry and biological examples, Birchall (35) and Belles et al. (36) argued that the major role of silica is to interact with aluminum in such a way as to reduce the biological availability of all sources of dietary aluminum and not only of aluminum from drinking water. Our results are concordant with this hypothesis, since we found an inverse relation between silica concentration and risk of dementia, and this is independent of the aluminum concentration in drinking water. If the assumption of Birchall is true, the exact risk attributable to aluminum is probably underestimated in our study, which does not consider total daily aluminum intake (which is difficult to measure). However, many authors have postulated that aluminum in drinking water may be more bioavailable than aluminum from other sources.

In conclusion, our study suggests that a concentration of aluminum in drinking water above 0.1 mg/liter may be a risk factor of dementia and, especially, Alzheimer's disease. This result needs to be confirmed using a higher number of exposed subjects.

ACKNOWLEDGMENTS

Supported by Agence de Bassin Seine-Normandie, Aluminum Péchiney, ARMA (Institut du Cerveau), Association Recherche et Partage, AXA-AGIPI, Groupe Danone, Caisse Nationale d'Assurance Maladie des Travailleurs Salariés, Caisse Primaire d'Assurance Maladie de la Dordogne, CAPIMMEC, Conseil Général de la Dordogne, Conseil Général de la Gironde, Conseil Régional d'Aquitaine, Caisse de Retraite Interentreprises, Direction Régionale des Affaires Sanitaires et Sociales d'Aquitaine, 2010 Média, Fondation de France, INSERM, M.G.E.N., Ministère de la Recherche et de la Technologie, Ministère de l'Aménagement du Territoire et de l'Environnement, M.S.A. de la Dordogne, M.S.A. de la Gironde, Novartis Pharma.

The authors thank Luc Letenneur and the Paquid staff for their collaboration in the study and the DDASS Dordogne and DDASS Gironde who took part in the study by supplying data on drinking water components.

REFERENCES

1. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–5.
2. McLachlan DRC. Aluminum and the risk for Alzheimer's disease. Environmetrics 1995;6:233–75.
3. Huang Y, Herman MM, Liu J, et al. Neurofibrillary lesions in experimental aluminum-induced encephalopathy and Alzheimer's disease share immunoreactivity for amyloid precursor protein, A beta, alpha 1-antichymotrypsin and ubiquity-protein conjugates. Brain Res 1997;771:213–20.
4. Cucarella C, Montoliu C, Hermenegildo C, et al. Chronic exposure to aluminum impairs neuronal glutamate-nitric oxide-cyclic GMP pathway. J Neurochem 1998;70:1609–14.
5. Roberts NB, Clough A, Bellia JP, et al. Increased absorption of aluminium from a normal dietary intake in dementia. J Inorg Biochem 1998;69:171–6.
6. Alfrey AC, Legendre GR, Kaehny WD. The dialysis encephalopathy syndrome: possible aluminum intoxication. N Engl J Med 1976;294:184–8.
7. Martyn CN, Barker DJP, Osmond C, et al. Geographical relation between Alzheimer's disease and aluminum in drinking water. Lancet 1989;1:59–62.
8. Flaten TP. Geographical associations between aluminium in drinking water and death rates with dementia (including Alzheimer's disease), Parkinson's disease and amyotrophic lateral sclerosis in Norway. Environ Geochem Health 1990; 12:152–67.
9. McLachlan DRC, Bergeron C, Smith JE, et al. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. Neurology 1996;46:401–5.
10. Forster DP, Newens AJ, Kay DWK, et al. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England. J Epidemiol Community Health 1995;49:253–8.
11. Martyn CN, Coggon DN, Lacey RF, et al. Aluminum concentrations in drinking water and risk of Alzheimer's disease. Epidemiology 1997;8:281–6.
12. Rifat SL, Eastwood MR, McLachlan DRC, et al. Effect of exposure of miners to aluminium powder. Lancet 1990;336: 1162–5.
13. Graves AB, Rosner D, Echeverria D, et al. Occupational expo-

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011

sures to solvents and aluminium and estimated risk of Alzheimer's disease. Occup Environ Med 1998;55:627–33.
14. Graves AB, White E, Koepsell TD, et al. The association between aluminum-containing products and Alzheimer's disease. J Clin Epidemiol 1990;43:35–44.
15. Colin-Jones D, Langman MJS, Lawson DH, et al. Alzheimer's disease in antacid users. (Letter). Lancet 1989;1:1453.
16. Birchall JD, Chappell JS. Aluminium, water chemistry, and Alzheimer's disease (Letter). Lancet 1989;1:953.
17. Exley C, Pinnegar JK, Taylor H. Hydroxyaluminosilicates and acute aluminium toxicity in fish. J Theor Biol 1997;189: 133–9.
18. Jacqmin-Gadda H, Commenges D, Letenneur L, et al. Components of drinking water and risk of cognitive impairment in the elderly. Am J Epidemiol 1994;139:48–57.
19. Jacqmin-Gadda H, Commenges D, Letenneur L, et al. Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 1996;7:281–5.
20. Letenneur L, Commenges D, Dartigues JF, et al. Incidence of dementia and Alzheimer's disease in elderly community residents of south-western France. Int J Epidemiol 1994;23: 1256–61.
21. Barberger-Gateau P, Commenges D, Gagnon M, et al. Instrumental activities of daily living as a screening tool for cognitive impairment in elderly community dwellers. J Am Geriatr Soc 1992;40:1229–34.
22. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Edition III revised (DSM-III-R). Washington DC: American Psychiatric Association, 1987.
23. Mc Khann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ARDA work group under the auspices of the department of health and human services task force on Alzheimer's disease. Neurology 1984;34:939–44.
24. Hachinski V, Lliff L, Zilhka F, et al. Cerebral blood flow in dementia. Arch Neurol 1975;32:632–7.
25. Commenges D, Letenneur L, Joly P. Re: "Serum transferrin saturation, stroke incidence, and mortality in women and men. The NHANES I Epidemiologic Followup Study." (Letter). Am J Epidemiol 1997;146:683–4.
26. Commenges D, Letenneur L, Joly P, et al. Modelling age-specific risk: application to dementia. Stat Med 1998;17:1973–88.
27. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York, NY: Springer-Verlag, 1997.
28. Letenneur L, Gilleron V, Commenges D, et al. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the Paquid project. J Neurol Neurosurg Psychiat 1999;66:177–83.
29. Orgogozo JM, Dartigues JF, Lafont S, et al. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. Rev Neurol 1997;153:185–92.
30. Folstein MF, Folstein SE, McHugh PR. ''Mini-Mental State'': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–90.
31. Jacqmin-Gadda H, Fabrigoule C, Commenges D, et al. A 5-year longitudinal study of the Mini- Mental State Examination in normal aging. Am J Epidemiol 1997;145;498–506.
32. Aalen OO. Effects of frailty in survival analysis. Stat Methods Med Res 1994;3:227–43.
33. Forbes WF, McAiney LM, Agwani N. Geochemical risk factors for mental functioning based on the Ontario Longitudinal Study of Aging (LSA) II. The role of pH. Can J Aging 1994; 13:249–67.
34. Taylor GA, Ferrier IN, McLoughlin IJ, et al. Gastrointestinal absorption of aluminium in Alzheimer's disease: response to aluminium citrate. Age Ageing 1992;21:81–90.
35. Birchall JD. The interrelationship between silicon and aluminium in the biological effects of aluminium. (Ciba Found Symp 169). Chichester, England: John Wiley & Sons, 1992;50–68.
36. Belles M, Sanchez DJ, Gomez M, et al. Silicon reduces aluminum accumulation in rats: relevance to the aluminium hypothesis of Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:83–7.

Downloaded from aje.oxfordjournals.org by guest on July 24, 2011