Aluminum and silica intake in drinking water and the risk of Alzheimer's disease or cognitive decline: findings of the 15-year follow-up PAQUID cohort.

Rondeau Virginie[1,2], Jacqmin-Gadda Hélène[1,2], Commenges Daniel[1,2], Helmer Catherine[2,3], Jean-François Dartigues[2,3].

Abbreviations: Al, Aluminum; AD, Alzheimer's Disease; MMSE, Mini Mental State Examination; Si, Silica

Running head: Aluminum, silica in water and Alzheimer's disease

ABSTRACT

The authors examined associations between exposure to aluminum or silica from drinking water and risk of cognitive decline, dementia and Alzheimer's disease. Subjects were followed-up for 15 years with an active search for incident cases of dementia, aged 65 years and over living in 91 civil drinking water areas in Southern France. Two measures of exposure to aluminum were assessed: a geographical exposure and an individual exposure taking into account the daily consumption of tap and bottled water. A total of 1,925 subjects free from dementia at baseline and with reliable water assessment were analyzed.

Using random effects models, cognitive decline with time was greater in subjects with a higher daily aluminum intake from drinking water (≥ 0.1 mg/day, $p = 0.005$) or a higher geographical 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 RR = 0.89, $p = 0.036$). However, the geographical 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.

Key Words

Aluminum; Alzheimer's disease; cognitive functions; dementia; drinking water; silica;

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

The hypothesis that aluminum (Al) exposure is aetiologically 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, two histological lesions that are characteristic of the disease (1). Several studies report 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. Ecological 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 risk or odds ratio ranging from 1.35 to 2.67 (4-8). All the epidemiological studies thus far, except one (9), however, have ignored the individual daily intake of drinking water.

Some, but not all, epidemiological and experimental studies suggest silica species can reduce aluminum oral absorption and/or enhance aluminum excretion and protect against aluminum-induced adverse effects (5, 9, 10). The silica (Si) content of tap water can vary according to the geographical region, with typically high Si levels in hard water areas and low levels in soft water areas. In two studies carried out in Egypt (11) or UK (12), bottled water of all brands (spring or mineral waters) contained higher levels of Si than tap water. This may well be because tap water treatment (i.e. by Al flocculation) decreases the Si content. We previously reported a geographical association between aluminum and silica and the cognitive decline or dementia on the data of the PAQUID (Personnes âgées Quid) cohort (4, 5) for subjects followed

during 8 years and with a low number of exposed subject. Our aim in the present work was to analyse the associations with more precise daily Al or silica intake on a larger cohort followed-up to 15 years, with additional exposed subjects and with a majority of new events occurring after the 8-year of follow-up.

MATERIALS AND METHODS

Participants/recruitment

Figure 1 illustrates the study flow chart. Briefly, PAQUID is an ongoing prospective-cohort population-based study of the epidemiology of dementia and Alzheimer's disease in the elderly population in France (13). The study beginning in 1988, initially included a community-based cohort of 3,777 elderly people, aged 65 and older, and living at home in one of 75 randomized rural or urban drinking water areas of the administrative areas of Gironde or 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 the data of the ALMA+ cohort (for aluminum – maladie d'Alzheimer). 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 aged 75 years and over at entry lived at home in one of the 14 drinking water areas of the administrative area of Dordogne in south-western France with five drinking water areas with mean levels of Al between 0.050 and 0.100 mg/l and nine areas with Al ≥ 0.100 mg/l. These subjects,first seen in 1999 then in 2003, were expected to be comparable with the subjects seen at the 10-year follow-up of the PAQUID cohort. The cognitive decline was analyzed on the PAQUID cohort and the ALMA+ cohort. Dementia and AD were investigated only on the

PAQUID cohort because of the non-symmetrical screening process in the two cohorts and because of the two different follow-up.

Assessment of cognitive functions, dementia and AD

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

Measure of exposure and water consumption

On the basis of information given by the sanitary administration, we respectively divided the PAQUID sample and the ALMA+ sample into 77 and 14 drinking water areas. For each area, we computed a weighted mean of all measures of aluminum and silica by using the results of chemical analyses of drinking water carried out by the sanitary administration between 1991 and 1994. In order to evaluate the past exposure of subjects, the history of the water distribution network over the previous ten years (1981-1991) was evaluated into the PAQUID cohort.

The 8-year follow-up questionnaire in the PAQUID cohort and the three following ones as well as the first and second in the ALMA+ cohort included a dietary investigation that contained specific questions relating to the daily consumption of tap water (including water used in making tea, coffee, soup or alcoholic drink) and bottled water (spring or mineral) and their brand most frequently consumed. The first non-missing information collected was used for each individual exposure, assuming a stable daily water consumption over the period of observation. The composition of the various bottled waters was provided by the respective distributing companies. On the contrary to the mineral water, the composition of bottled spring water may change over time; even so we used an average over several measurements across time (mean number of values 1.9). For each subject, a daily mean intake of aluminum or silica from tap water and/or bottled water was computed. The statistical analyses are then based on two kinds of drinking water indicators for aluminum or silica: a geographical exposure (in mg/liter) previously used in the PAQUID cohort (5) and an individual indicator, more precise (in mg/day) 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 subject-specific random intercept and slope to take into account the intra-subject correlation. A random intercept specific for each geographical area controlled for the potential intra-area correlation. Since the distribution of the MMSE scores was not normal, we analyzed the square root of the number of errors according to time (5). Besides the variable *time* representing the number of years after the initial visit, a binary indicator for the initial visit was

introduced to account for the first-passing effect, possibly due to stress. Aluminum was considered as a quantitative variable, or as a binary variable with the threshold of 0.1 mg/liter already used in previous ecological studies (6, 7), or 0.1 mg/day for individual exposure, or in four classes according to the three terciles (on subjects) under 0.1 mg/day and the category above 0.1 mg/day. Silica was considered as a quantitative variable or as a binary variable with 11.25 mg/liter for the geographical exposure (the median in our sample) or with 10.55 mg/day as the cut-off for the individual exposure (the median of daily intake in our sample) or into 4 classes according to the four quartiles. We adjusted for potential confounders: educational level (18), wine consumption (19), place of residence (rural versus urban) and the cohort (PAQUID or ALMA+).

To examine the robustness of the results in the main analysis on cognitive decline we assessed influence diagnostics, using the 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 AD were performed using a Cox proportional hazard model with delayed entry (21) to estimate relative risks (RR) and to adjust for covariates. Age was taken as the basic time scale in the analysis, so that the risks of dementia or AD were adjusted non-parametrically for age. A stratified analysis for gender was performed (21).

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

RESULTS

Among the 4,177 subjects (3,777 from PAQUID and 400 from ALMA+) who initially agreed to participate, 207 with prevalent dementia were excluded. The current study is restricted to the 1,925 subjects (among the 3,970 non-demented at their first visit) in 91 geographical areas, who have non-missing values for daily consumption of Al or Silica from drinking water and for adjustment covariates. Subjects from PAQUID lost to follow-up or died before the 8-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 age = 82.52 and 82.31, p = 0.51; MMSE scores = 24.91 and 25.93, p<0.0001; percentage of women = 61.66% and 59.27%, p = 0.47; percentage of high educated patients = 70.66 and 66.53, p = 0.18). The ALMA+ patients had a higher consumption of Al from drinking water (mean = 0.136 mg/day) than in the PAQUID cohort (mean = 0.009 mg/day), p<0.0001.

The mean consumption of drinking water was 0.94 (SD = 0.49) liters/day. Tap water was the sole source of water intake for 43.7 percent of the subjects; 40.3 percent drank only bottled water. The compositions of Al in tap water varied greatly from one parish to another from 0.001 to 0.514 mg/liter, with a mean value of 0.043 mg/liter (median = 0.009 mg/liter) depending largely on the method of water treatment used (i.e. by Al flocculation or not). In bottled water, when available or detectable, the concentrations of Al are very small with a maximum value of 0.032 mg/liter and with a mean value of 0.002 mg/liter (median = 0). Silica levels in tap 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 (Pearson correlation coefficient = –0.18, *p*

= 0.13). In bottled water, the concentrations of Si ranged from 2 mg/liter to 77.6 mg/liter. The daily mean intake of Al and Si from drinking water is described in Table 2. The correlation between geographical exposures and individual exposure was 0.71 (p<0.001) for aluminum and 0.13 (p<0.001) for silica. Among subjects studied, 112 were exposed to more than 0.1mg/day of aluminum essentially due to a high consumption of tap water with high levels of Al.

Relation between cognitive functions and water composition into the PAQUID and ALMA+ cohort

Aluminum intake interacted significantly with time (Table 3). Cognitive decline was greater in subjects with a high daily Al intake (greater than 0.1 mg/day or an increase of 0.1 mg/day). However, Al had no significant association with the values of the MMSE scores at inception in the cohort. As an example, a woman without a diploma aged 75 years at inception, with a low daily silica intake (<10.55mg/day) and a low daily Al intake (<0.1 mg/day) would in 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 Al intake (≥ 0.1mg/day), she would lose 5.0 points. In these models, even after adjustment for different factors, significant but very low intra-parish correlation was obtained (in model 1 from Table 3, the variance of the intra-parish random effect = 0.008, p = 0.019). This may mean that other geographical factors may also influence cognitive decline.

The same tendencies were obtained using the geographical tap water exposure: 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 geographical exposure was significantly associated with cognitive functions.

The interaction between Al and time was no longer significant (p = 0.78) when excluding the demented subjects. This suggests that cognitive decline with time is related to daily Al intake only when associated with a dementia process.

Among the 20 most influential subjects (about 1% of the sample) 7 had a high consumption of aluminum (> 0.100 mg/day). The parameter estimate for aluminum by time after deleting the 20 most influential patients was unchanged but had a larger p-value (β = 0.045, p = 0.01) than on the full dataset.

When repeating the cognitive decline analysis using only the PAQUID sample we observed very similar interactions aluminum or silica with time (model 2 in Table 3, β = 0.020, p = 0.004 for Al; β = -0.003, p = 0.10 for silica).

The principal lifetime occupation with an eight-class variable was also added. The effects of aluminium by time and silica by time (not shown in the tables) were unchanged, respectively β = 0.046 (p = 0.009) and β = -0.004 (p = 0.35) in model 1.

Relation between dementia or Alzheimer's disease and water composition into 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 follow-up duration was 11.3 years. Only 13 subjects had high daily consumption of Al from drinking water (≥ 0.1mg/day), among them 6 (46.2%) were demented. There were 364 subjects (78.9 percent) classified as having Alzheimer's disease (probable or possible). 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 Al intake (adjusted relative risk (RR) = 2.26 for Al≥0.1 mg/day, *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 for a dose-response effect for aluminum was apparent (likelihood ratio statistic = 3.52, 3 df, *p* = 0.32, model 7, table 4) even though a significant linear relation between aluminum and dementia was obtained in model 6 (adjusted RR for aluminum = 1.28 for an increase of 0.1 mg/day, *p* = 0.017). The model 6 with aluminum as a continuous variable was slightly better than that (model 5) in which aluminum was in two classes (Akaike difference = 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 intakes 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 geographical tap water exposure, the concentrations of Al or Silica were no more associated with the risk of dementia or AD, although the tendencies were similar (results not shown here).

DISCUSSION

We found that the cognitive decline and the risk of dementia were higher for high consumption of Al from drinking water. Even if almost the same tendencies as previously published on Paquid (5) were obtained on the effect of geographical exposure to aluminum, this exposure was no more significantly associated with dementia. This result being based on a small number of exposed subjects in this sample (n = 46 with Al ≥0.100mg/l), it may be explained by a lack of power in the analysis. This strengthens the importance of using an individual rather than a

geographical exposure. The analysis did not show any evidence for silica intake to be associated with the evolution of cognitive functions; however it showed an inverse association between silica intake from drinking water and the risk of dementia, or more specifically of AD.

Biases and limitations

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

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

Subjects drinking only bottled water may have a particular exposure 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 excluding those persons. In the dementia analysis on the Paquid sample (749 subjects excluded over 1,677), the effect of aluminum remained equivalent (for instance the model 5 in Table 4 became, RR = 2.31, p = 0.045), but silica was no more significant (RR = 1.04, p = 0.13).

The bottled water consumption may also change with time and may be different for demented patients compared to non-demented patients. We studied this evolution on the subsample of 476 subjects from the PAQUID cohort seen at each follow-up time since the assessment of daily water consumption (T8, T10, T13, T15). The intraclass correlation coefficient based on a random effect linear regression for the daily intake of bottled water was equal to 0.54. This indicates that the daily bottled intake was rather stable between T8 and T15. The same tendencies were observed for the 402

non-demented patients (ρ = 0.55), and for the 74 demented patients (ρ = 0.47). It seems that the disease does not change that much the consumption habits of bottled drinking water. Furthermore the water consumption information was mainly collected on non-demented patients (1406/1677 = 83.8%). All these comments strengthen the validity of our results even if the information for the bottled water consumption was only available after the 8-year follow-up.

We may think that the social or educational level may influence the bottled water consumption and so the daily intake of Al or Si. A high consumption of bottled water leads to a lower Al intake and most of the time to a greater silica intake. The mean daily bottled consumption was not significantly different in our sample for high educated patients (0.48 liter/day) compared to low educated patients (0.47 liter/day).

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

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

Strengths

A great advantage of our study was that we had an estimate of the daily individual intakes of Al and silica supplied by the drinking water, and not merely the geographical concentrations of these elements, as in most epidemiologic studies previously published (4, 5, 7, 24). This individual intake of drinking water is more precise and leads to more accurate findings.

Only one recent French cohort (EPIDOS) analyzed also the individual daily consumption of aluminum or silica from drinking water (9). At baseline, low silica concentration was associated with low cognitive performance and with more AD patients. No significant changes were observed with aluminum intakes. These results corroborate our results for silica only. The EPIDOS study was however a selected population of volunteers not representative of the general population and with much lower levels of aluminum (maximum = 0,063 mg/liter).

The study of cognitive functions in addition to the risk of dementia has two main methodological interests. First, the evolution of the MMSE score is not sensitive to diagnostic errors that may be present in the detection of AD cases. Secondly, cognitive decline precedes by three to five years the occurrence of dementia and is less subject to competitive morbidity or mortality.

The survey design incorporates a grouping of the participants into drinking water areas, this has the advantage to give heterogeneity in the drinking water exposures or other environmental factors but this may induce a correlation of the observations. In a random effect survival model (5, 25) no significant intra-group correlation was observed ($p = 0.31$). The effects of aluminum (RR = 2.22, SE = 0.43 for model5 in Table 4) and silica (RR = 0.90, SE = 0.05) were unchanged. It is thus unlikely that

some unmeasured environmental factor shared by the members of the same parish could play a confounding role on dementia.

Further studies are needed to settle the debate over the link between aluminum or silica in drinking water and neurological disorders and cognitive impairment. Ideally, in such studies individual data on drinking water exposure as well as other relevant risk factors is needed to assess this potential risk.

Acknowledgements

author affiliations

[1] *INSERM, U897 (Biostatistic), Bordeaux, F-33076, FRANCE;*

[2] *Université Victor Segalen Bordeaux 2, Bordeaux, F-33076, FRANCE.*

[3] *INSERM, U897 (Epidemiology, Public Health and Development), Bordeaux, F-33076, FRANCE.*

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Conflict of interest: none

TABLE LEGEND

Table 1: Distribution of potential confounding variables across levels of aluminum concentrations, PAQUID study, France, 1988-2003.

Table 2: Daily intakes of aluminum and silica supplied by drinking water (n = 1,925).

Table 3: Daily consumption of aluminum and silica (mg/day) or geographical exposure to aluminum and silica from drinking water and cognitive decline for the square root of the number of errors in the Mini-Mental State Examination, the PAQUID and ALMA+ cohorts, France, 1988-2003.

Table 4: Daily aluminum or silica consumption from drinking water and risk of dementia or Alzheimer's disease, the PAQUID cohort, France, 1988-2003.

Table 1: Distribution of potential confounding variables across levels of aluminum concentrations, the PAQUID and ALMA+ cohorts, France, 1988-2003.

	Aluminum from tap water (n = 1,883*)		Daily consumption of aluminum (from tap water and/or bottled water) (n = 1,925)		
	Geographical exposure		Individual exposure		
Characteristics at baseline	≥ 0.100 mg/liter (n = 216)	< 0.100 mg/liter (n = 1,667)	≥ 0.100 mg/day (n = 112)	< 0.100 mg/day (n = 1,813)	Total (n = 1,925)
Silica from tap water (geographical exposure)					
≥ 11.25 mg/liter	131 (60.7%)	1,033 (62.2%)	73 (65.2%)	1,091 (61.8%)	1,164 (62.1%)
< 11.25 mg/liter	85 (39.3%)	627 (37.8%)	39 (34.8%)	673 (38.2%)	712 (37.9%)
Daily intake of silica (from tap water and/or bottled water)					
≥ 10.55 mg/day	141 (65.3%)	860 (51.6%)	87 (77.7%)	935 (51.6%)	1,022 (53.1%)
< 10.55 mg/day	75 (34.7%)	807 (48.4%)	25 (22.3%)	878 (48.4%)	903 (4.9%))
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 (62.4%)
Education					
No education or primary school (ages 6 through 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					
Non-drinkers or mild drinkers	104 (48.2%)	1,372 (82.3%)	47 (41.9%)	1,466 (80.9%)	1,513 (78.6%)
Moderate or heavy drinkers	112 (51.8%)	295 (17.7%)	65 (58.1%)	347 (19.1%)	412 (21.4 %)

* Tap water aluminum concentrations were not available for each geographical area, thus among the 1,925 subjects analyzed, only 1,883 had no missing values for tap water aluminum concentration

Table 2: Daily intakes of aluminum and silica supplied by drinking water (n = 1925)

Element	Intake in mg / day mean ± SD* (min-max)	Amount supplied by tap water	Amount supplied by bottled water	Pearson correlati coefficient
Aluminum	0.025 ± 0.08 (0-1.03)	95.9 %	4.1 %	P = 0.17 (p<*0.0001)*
Silica	13.37 ± 10.76 (0-108)	41.0 %	59.0 %	

* SD, standard deviation

Table 3: Daily consumption of aluminum and silica (mg/day) or geographical exposure to aluminum and silica from drinking water and cognitive decline for the square root of the number of errors in the Mini-Mental State Examination, the PAQUID and ALMA+ cohorts, France, 1988-2003.

	Cognitive decline*	
Daily consumption (mg/day)	β (SD[†])	*p-values*
Model 1		
Aluminum (≥ 0.1 vs < 0.1)	-0.15 (0.098)	0.08
Time (years) by aluminum	0.049 (0.018)	**0.005**
Silica (≥10.55 vs < 10.55)	-0.022 (0.029)	0.46
Time (years) by silica	-0.005 (0.004)	0.24
Model 2		
Aluminum (continuous[‡])	-0.031 (0.023)	0.19
Time (years) by aluminum	0.017 (0.005)	**0.001**
Silica (continuous[§])	-0.020 (0.014)	0.15
Time (years) by silica	-0.003 (0.002)	0.11
Geographical exposure (mg/liter)		
Model 3		
Aluminum (≥ 0.1 vs < 0.1)	-0.12 (0.070)	0.09
Time (years) by aluminum	0.038 (0.011)	**<0.001**
Silica (≥11.25 vs < 11.25)	-0.018 (0.034)	0.60
Time (years) by silica	-0.003 (0.004)	0.45
Model 4		
Aluminum (continuous[‡])	-0.023 (0.024)	0.35
Time (years) by aluminum	0.014 (0.004)	**<0.001**
Silica (continuous[§])	-0.032 (0.053)	0.55
Time (years) by silica	-0.0004 (0.007)	0.99

[*] adjusted for *time*, an indicator for the first follow-up (*indicT0*), *age*, *time* by *age*, *gender*, *time* by *gender*, *indicT0* by *gender*, *educational level*, *time* by *educational level*, *indicT0* by *educational level, cohort.*

[†] SD, standard deviation

[‡] aluminum given for an increase of 0.1 mg/day

[§] silica given for an increase of 10 mg/day

Table 4: Daily aluminum or silica consumption from drinking water and risk of dementia or Alzheimer's disease, the PAQUID cohort, France, 1988-2003.

Variable in mg/day	Dementia (461 cases) RR*	95% CI*	*p-value*	Alzheimer (364 cases) RR*	95% CI*	*p-value*
Model 1[†]						
Al* ≥0.1 vs <0.1	2.59	1.15, 5.80	**0.021**	3.35	1.49, 7.52	**0.003**
Model 2[†]						
Al (continuous) [§]	1.29	1.05, 1.58	**0.014**	1.36	1.11, 1.67	**<0.001**
Model 3[†]						
Si* ≥10.55 vs <10.55	0.91	0.76, 1.10	0.330	0.91	0.74, 1.12	0.360
Model 4[†]						
Si (continuous) [#]	0.89	0.80, 0.98	**0.002**	0.88	0.79, 0.99	**0.030**
Model 5[‡]						
Al ≥0.1 vs <0.1	2.26	1.00, 5.07	**0.049**	2.80	1.24, 6.32	**0.013**
Si (continuous) [#]	0.89	0.81, 0.99	**0.036**	0.89	0.79, 1.00	**0.045**
Model 6[‡]						
Al (continuous) [§]	1.28	1.05, 1.58	**0.017**	1.34	1.09, 1.65	**<0.006**
Si (continuous) [#]	0.89	0.81, 0.99	**0.028**	0.88	0.79, 0.99	**0.035**
Model 7[‡]						
Al						
<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**
Si (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

* CI, confidence interval; RR, relative risk; Al, aluminum; Si, silica

[†] Nonparametrically adjusted for age and gender

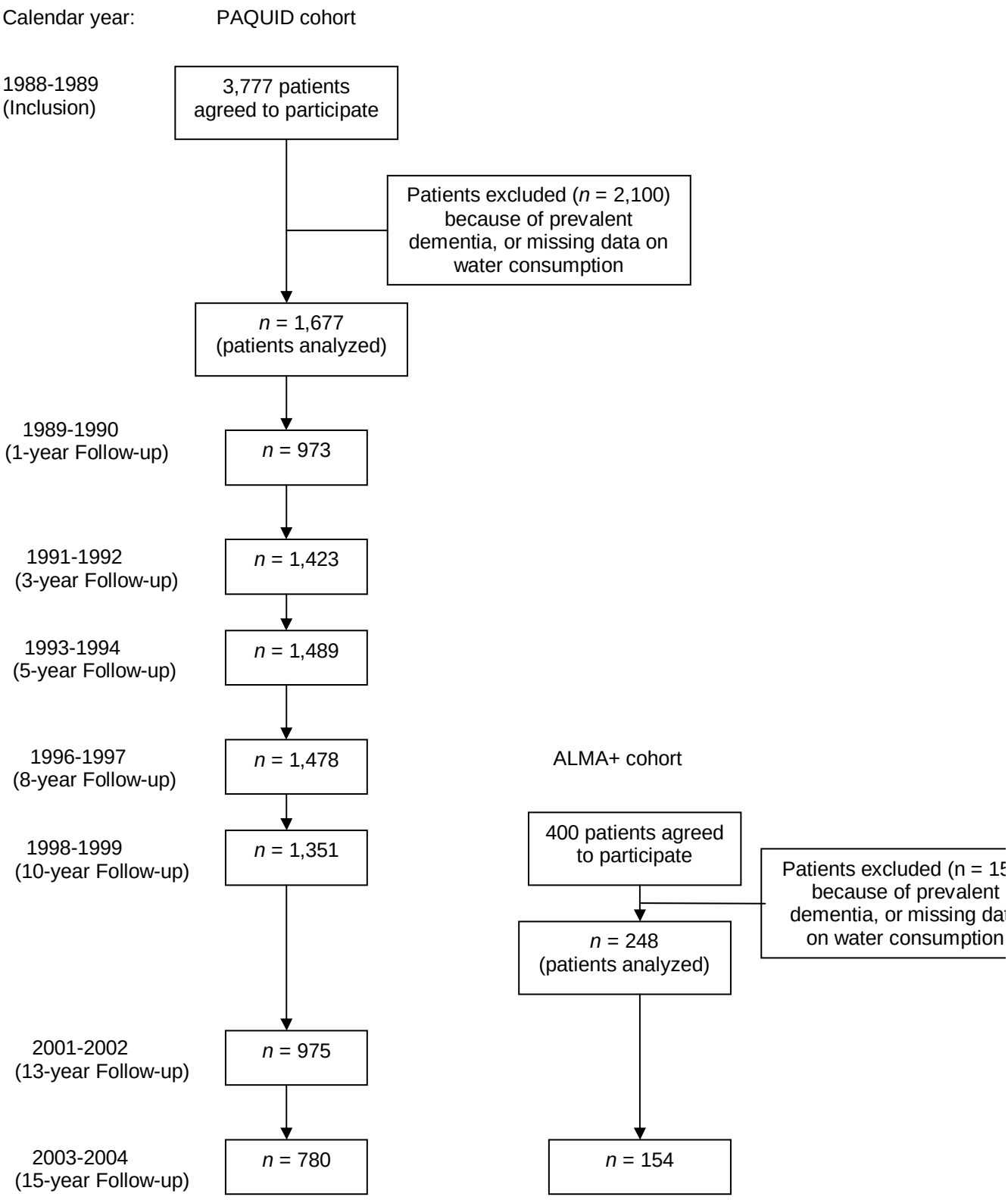
[‡] Nonparametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption and place of residence

[§] RR given for an increase of 0.1 mg/day of aluminum

[#] RR given for an increase of 10 mg/day of silica

FIGURE LEGEND

Figure 1: Diagram of the analysed population from the PAQUID (Personnes âgées Quid) and the ALMA+ (Aluminum Maladie d'Alzheimer) cohorts and its follow-up.


Calendar year:
PAQUID cohort
1988-1989
(Inclusion)
3,777 patients
agreed to participate
Patients excluded (n = 2,100)
because of prevalent
dementia, or missing data on
water consumption
n = 1,677
(patients analyzed)
1989-1990
(1-year Follow-up)
n = 973
1991-1992
(3-year Follow-up)
n = 1,423
1993-1994
(5-year Follow-up)
n = 1,489
1996-1997
(8-year Follow-up)
n = 1,478
1998-1999
(10-year Follow-up)
n = 1,351
2001-2002
(13-year Follow-up)
n = 975
2003-2004
(15-year Follow-up)
n = 780
ALMA+ cohort
400 patients agreed
to participate
Patients excluded (n = 15
because of prevalent
dementia, or missing da
on water consumption
n = 248
(patients analyzed)
n = 154

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