Cognitive impairment and composition of drinking water in women: findings of the EPIDOS Study[1–3]

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ABSTRACT

Background: The concentration of aluminum or silica in drinking water may be a potential environmental risk factor for Alzheimer disease (AD).

Objectives: The objective was to investigate at baseline the potential association between the composition of drinking water and the level of cognitive function in women taking part in the Epidemiology of Osteoporosis (EPIDOS) Study and to determine during follow-up the effects of the composition of drinking water on the risk of AD.

Design: Women aged ≥75 y (n = 7598) were recruited between 1992 and 1994 in 5 geographic areas of France. The participants from one center (n = 1462) were followed for ≤7 y; during this time, an active search for incident cases of AD was conducted. The initial questionnaire comprised a food consumption survey with specific questions about the daily consumption of tap and mineral water. The evaluation of cognitive function was based on the Short Portable Mental Status Questionnaire. During follow-up, the diagnosis of dementia was made by a geriatrician and a neurologist.

Results: A low silica concentration was associated with low cognitive performance at baseline. Compared with the nondemented subjects, the women with a diagnosis of AD during follow-up were older at inclusion, had a lower financial status and educational level, had a poorer perception of their own health, and had a more difficult time performing activities of daily living. A multivariate analysis including potential confounding factors showed that women with AD appeared to have been exposed to lower amounts of silica at baseline.

Conclusions: Silica in drinking water may reduce the risk of developing AD in elderly women. The results corroborate those of another epidemiologic study carried out in France. The potential effect of silica needs to be confirmed in additional investigations. *Am J Clin Nutr* 2005;81:897–902.

KEY WORDS Alzheimer disease, drinking water, silica, aluminum, elderly

INTRODUCTION

Alzheimer disease (AD) is a neurodegenerative cerebral disorder defined as progressive deterioration of cognitive function and loss of independence. With the aging of the population, AD has become a major public health problem because of its considerable consequences in terms of dependence and cost. In France the prevalence of the disease is currently estimated at >400 000 cases and its incidence at 100 000 new cases per year according to data from the Paquid Study (1, 2). New therapies have resulted in undeniable progress in the treatment of the disease (3). However, AD is still chronic and incurable. Although knowledge of the pathophysiology of AD has greatly progressed over the past 10 y, its causal mechanisms are far from clear. AD appears to involve a combination of factors that are both individual (probably including genetic predisposition) and environmental. The concentration of aluminum in drinking water may be one of the environmental risk factors for AD. The possibility of such a relation, suggested by the presence of aluminum in senile plaques (SP) and neurofibrillary degeneration, 2 histologic lesions that are characteristic of the disease, was initially put forward by Vogt (4) and then by Martyn et al (5). Since then, the various epidemiologic studies available have yielded conflicting results and are therefore inconclusive (6–10). Other elements present in drinking water, such as calcium, cadmium, and zinc could also have an effect on cognitive aging (6, 11, 12). Results from the Paquid Study suggest that the relation between aluminum and the risk of cognitive decline is influenced by the pH and the silica concentration of the water; a high aluminum concentration may be associated with an increased risk of cognitive impairment when the silica concentration and pH are low. Conversely, when the pH and silica concentration are high, a high concentration of aluminum may be associated with a lower risk of AD (6, 11). On the other hand, a high calcium concentration could have a effect. In a more recent study, Rondeau et al (13) examined the relation between the quality of drinking water and the development of AD during the 8-y follow-up of the Paquid cohort. It was found that the risk of developing AD was twice as high in subjects exposed to an aluminum concentration in their drinking water ≥0.1 mg/L. The findings also showed an effect of silica: subjects exposed to a

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high silica concentration (≥11.25 mg/L) appeared to have a lower risk of developing AD than did those exposed to a low silica concentration (relative risk = 0.73, $P = 0.042$). Further studies still seem necessary to confirm these results and to exclude causes of error related to certain methodologic biases. If such associations do indeed exist, measures could be taken to reduce the incidence of AD.

The Epidemiology of Osteoporosis (EPIDOS) Study is a French cohort of >7500 women aged >75 y. As part of this study, daily water consumption was accurately recorded during the initial evaluation and again in a subpopulation of women who were reassessed after 7 y. The primary aim of our study was to study the relation between drinking water composition and cognitive function assessed at the initial visit, based on the overall data of the EPIDOS Study. At a later stage, we studied the relation between drinking water composition and incident AD observed during follow-up in a subpopulation of the EPIDOS Study cohort.

SUBJECTS AND METHODS

The EPIDOS Study cohort

EPIDOS is a French prospective multicenter study that began in 1992–1994, the initial aim of which was to study risk factors for fracture of the femoral neck. This study recruited 7598 women aged >75 y in 5 French cities (Amiens, Lyon, Montpellier, Paris, and Toulouse). The methodology of this study was precisely described elsewhere (14). The study was approved by the Advisory Committee for the Protection of Persons participating in Biomedical Research, and all women taking part gave their informed consent. Data were initially collected in each investigating center by specially trained nursing staff.

Cognitive performance

Cognitive impairment was assessed with the use of the Short Portable Mental Status Questionnaire (SPMSQ) (15). The SPMSQ, a 10-item questionnaire, was developed to detect the presence of intellectual impairment in older adults living in the community and residing in institutions. It focuses on orientation but includes 2 items on memory (telephone number and street address, mother's maiden name) and 1 item on concentration (serial subtraction of 3 from 20). Scores range from 0 to 10 (10 being the normal value). Pfeiffer initially classified subjects who made ≤2 errors as intact, those who made 3 or 4 errors as mildly impaired, those who made 5-7 errors as moderately impaired, and those who made 8-10 errors as severely impaired (15). The methodologic qualities of this test make it suitable for use in epidemiologic studies (16–20). For the purposes of our study, we considered women with a Pfeiffer score ≥8 to have normal cognitive function, whereas those with a score of <8 were considered to have cognitive impairment.

Water consumption

The initial questionnaire included a dietary investigation that contained specific questions relating to the daily consumption of tap water (including water used in making tea or coffee) and mineral water and the brand of mineral water most frequently consumed [Badoit, Evian, and Volvic (Danone Group, Bourg la Reine, France); Contrex, Perrier, Vittel Grande Source, and Vittel Hepar (Nestle Waters, Issy les Moulineaux, France); Vichy Célestin and Vichy Grande Source (Castel Group, Thiais, France); and "others"] (*see* **Appendix A**). We obtained standard water composition data for the tap water supply in each city, during the period of inclusion (1992–1994), from the local water companies. From these data we extracted the contents of calcium, silica, and aluminum. The composition of the various mineral waters was provided by the respective distributing companies.

Other characteristics

The sociodemographic characteristics of the women were recorded with their age, marital status, monthly income, and educational level. Perceived state of health was noted, as were the diseases declared at the time of inclusion in the study (arterial hypertension, history of cerebrovascular accident and ischemic heart disease, thyroid dysfunction, impairment of sight and hearing, Parkinson disease, diabetes, depression). Tobacco consumption was also noted, whether past or current. Functional status was assessed on the basis of 3 items relating to basic activities of daily living (dressing, toileting, mobility) and by Lawton's Instrumental Activity of Daily Living scale (IADL), which comprises 8 items: ability to use the telephone, do the shopping, prepare meals, do housework, do the washing, use transport, manage medication, and manage finance (21).

Every 4 mo for 5 y, all participants were questioned about intercurrent disorders. Any withdrawals and the reasons for such were recorded. Information on the various medications consumed was collected yearly on a full questionnaire.

Follow-up of the EPIDOS Study cohort in Toulouse

Those women in the EPIDOS Study cohort in Toulouse who wished to volunteer were included in a prospective study of AD risk factors in 1999–2000. In this new investigation, data were collected at the home of the elderly person during an interview carried out by specially trained investigators, after the participant had been informed of the aims of the study and had given her written consent. During this visit, independence in instrumental activities of daily living was reassessed. Current diseases and treatments were noted according to the model previously used in the EPIDOS Study cohort.

A questionnaire on water consumption, identical to that used for the initial assessment, was completed by each participant. We obtained from the water companies of this area the composition of the water supply during the period concerned.

Cognitive function was assessed with the SPMSQ (15), the Mini Mental State Examination (22), and the Grober and Buschke test (23). After the interview, the data collected were analyzed in a double-blind manner by a geriatrician and a neurologist from the Departments of Internal Medicine and Clinical Gerontology to establish a diagnosis. Clinical suspicion of dementia was diagnosed by using the Diagnostic and Statistical Manual of Mental Disorders (4th ed) criteria and probable or possible AD with the National Institute of Neurological and Communicative Disorders/Alzheimer's Disease and Related Disorders Association (24). If the 2 investigators did not agree, they examined the records conjointly, and, if necessary, further information was sought from the treating physician by telephone. Computed tomography reports or the scans themselves were reviewed to specify the etiology of dementia (differentiation between neurodegenerative and vascular dementia). The subjects were then classified into 4 groups: normal cognitive function, mild cognitive impairment (MCI) according to the criteria of Petersen et al

(25), AD, and other types of dementia. Retroactive application of MCI criteria to the data collected during the study was performed as it was previously for other studies (26). The Petersen amnestic MCI criteria were operationalized as follows: *1*) impaired memory (Grober ad Buschke procedure: Word List Delayed Recall score of <1 SD below the mean), *2*) normal mental status (Mini-Mental State Examination score ≥26), *3*) normal daily functioning (no instrumental impairments), and *4*) absence of dementia.

In Toulouse, 1462 women were initially recruited in the EPIDOS Study cohort. Data on cognitive status were available for 714 women (48.8% of the initial cohort). During the first 5 y of follow-up, AD was diagnosed in 72 women. Six hundred forty-two women were reassessed in the prospective study of AD risk factors (follow-up at 7 y). Of these women, 450 were normal, 58 had mild cognitive impairment, 38 had AD, and 96 had another type of dementia including mixed dementia. Overall, 206 women in the EPIDOS Study cohort in Toulouse developed dementia during the 7 y of follow-up, of whom 110 (53.4%) received a diagnosis of AD. Of the other 748 women, whose cognitive status remained undetermined, 25.8% ($n = 193$) died during follow-up at 7 y, 54.7% ($n = 414$) were lost to follow-up, and 18.9% ($n = 141$) withdrew from the follow-up study.

Statistical analysis

Data were analyzed with SAS software (version 8.02; SAS Institute Inc, Cary, NC). Bivariate analysis was based on conventional means comparison tests for quantitative variables (Student's *t* test or Kruskall-Wallis test) and frequency distribution comparison for qualitative variables (chi-square test or Fisher's exact test according to the size of the series). Multivariate analysis was based on logistic regression with a Pfeiffer score ≥8 as a dependent variable (cross-sectional analysis) or an AD diagnosis (longitudinal analysis). The variables included in the initial model were those related to the 25% threshold after bivariate analysis. Analysis was carried out by using stepwise regression, and goodness of fit was assessed by the Hosmer-Lemeshow test (27).

Women consuming "other" mineral waters or Vichy Grande Source were excluded from the analysis because we did not know the exact composition of these waters. To study the relation between water composition and development of AD during follow-up, we excluded those women who initially had what we considered to be an abnormal Pfeiffer score (<8).

RESULTS

The composition of the city water supply and the various mineral waters is given in **Table 1**. The compositions varied greatly from one city to another and depended largely on the method of water treatment used. The highest aluminum concentrations were found in Toulouse (0.063 mg/L). Silica and calcium were mainly supplied by mineral water, with concentrations ranging from 8.6 to 36.4 mg/L for silica and from 11 to 563 mg/L for calcium. However, the water in Paris, Montpellier, and Amiens had a relatively high calcium concentration. The mean daily water consumption of women at the time of inclusion in the study was 0.94 ± 0.47 L. Tap water was the sole source of water intake for 48.1% of the women; 31.3% of the women drank only mineral water, and 20% of the women drank both tap water and mineral water. We found geographic differences in mineral water consumption; the highest consumption was in Amiens, and the lowest consumption was in Toulouse. The women's daily intakes of aluminum, silica, and calcium are shown in **Table 2**. The mean daily intake of aluminum ranged from 0 to 0.189 mg/L, of silica from 0.04 to 89.2 mg/L, and of calcium from 0.6 to 1593.3 mg/L.

TABLE 1
Aluminum, silica, and calcium concentrations of mineral waters and city water supplies

	Aluminum	Silica	Calcium
Mineral water[1]		*mg/L*	
Badoit	Undetectable	33.4	187
Contrex	<0.003	8.6	480
Evian	Undetectable	15.2	82
Perrier	0.013	10	152
Vichy Célestin	0.032	36.4	98
Vittel Grande Source	<0.003	9.5	204
Vittel Hépar	<0.003	8.8	563
Volvic	0.005	35.7	11
City water supply, 1992–1994[2]			
Paris (Orly-Vanne, Loing)	0.013	5.2	93.6
Boulogne Billancourt	0.061	5.1	86
Toulouse	0.063	4.6	41.7
Toulouse, 1999–2000[3]	0.060	4	39
Montpellier	0.052	6.4	118.6
Amiens	0.01	11.2	110
Lyon	0.04	4	60

[1] *See* text for manufacturers.
[2] Time of enrollment in the Epidemiology of Osteoporosis (EPIDOS) Study.
[3] Time period of the prospective study of Alzheimer disease risk factors and diagnosis.

Relation between cognitive function and water composition

Women with a Pfeiffer score ≥8 at the first assessment had a higher daily water consumption and a higher daily silica intake (10.34 ± 10.25 compared with 9.07 ± 8.18 mg/d; $P = 0.0104$). The Pfeiffer score was independent of the type of water consumed. No difference in daily aluminum or calcium intakes was observed between the normal women and those with cognitive impairment. Daily silica intake was positively correlated with the Pfeiffer score over time (Pearson's coefficient = 0.0328, $P = 0.0133$); a higher score is better. After adjustment for confounding factors (age, center, income, educational level, history of cerebrovascular accident), we found a significant association between daily silica intake and cognitive performance (**Table 3**). The risk of a low Pfeiffer score (<8) decreased by 1% when silica intake increased by 1 mg/d.

TABLE 2
Daily intakes of aluminum, silica, and calcium supplied by drinking water[1]

Element	Intake	Amount supplied by mineral water
	mg/d	*%*
Aluminum	0.0231 ± 0.025[2]	5.6
Silica	10.17 ± 10.01	72.2
Calcium	134.8 ± 154.1	69.1

[1] $n = 6135$.
[2] $\bar{x}$ ± SD (all such values).

TABLE 3
Factors associated with a low Pfeiffer score (<8): cross-sectional analysis of data at baseline in the Epidemiology of Osteoporosis (EPIDOS) Study of 5691 women aged ≥75 y

	Model[2]		
Variable to be explained[1]	Odds ratio	95% CI	P^3
Age (y)	1.11	1.09, 1.13	<0.001
Educational level (reference: general certificate of education or more)	—	—	<0.001[4]
Certificates of education for vocational training	1.34	0.90, 2.01	0.15
Secondary education certificate	2.21	1.51, 3.24	<0.001
Education to school-leaving age	4.57	3.10, 6.74	<0.001
No schooling	9.19	5.40, 15.65	<0.001
Monthly income (reference: >€915)	—	—	<0.001[4]
€547–915	1.66	1.30, 2.11	<0.001
<€547	2.50	1.84, 3.39	<0.001
Unknown	3.11	2.31, 4.20	<0.001
History of cerebrovascular stroke	1.57	1.11, 2.24	0.011
Silica (mg/d)	0.99	0.98, 0.99	0.036

[1] Multivariate analysis based on logistic regression. Cognitive impairment with a low Short Portable Mental Status Questionnaire (SPMSQ) score (<8; $n = 629$) compared with cognitively intact (SPMSQ score ≥ 8; $n = 5069$).
[2] $P = 0.5991$ (Hosmer and Lemeshow test).
[3] After adjustment for confounding factors (age, center, income, educational level, and history of cerebrovascular accident).
[4] Overall *P*.

TABLE 5
Factors associated with Alzheimer disease (AD) in 383 women aged ≥75 y in the Toulouse cohort of the Epidemiology of Osteoporosis (EPIDOS) Study[1]

	Model[3]		
Variable to be explained[2]	Odds ratio	95% CI	P^4
Pfeiffer test	0.52	0.35, 0.79	0.0019
Age (y)	1.15	1.06, 1.24	0.0004
Monthly income (reference: >€915)			0.0036[5]
€547–915	3.72	1.73, 8.00	0.0008
<€547	4.46	1.02, 19.52	0.0470
Unknown	3.19	1.47, 6.95	0.0035
Silica (reference: > 12 mg/d)			0.1887[5]
9–12 mg/d	2.00	0.56, 7.07	0.2829
5–8 mg/d	1.81	0.73, 4.48	0.1986
≤4 mg/d	2.74	1.09, 6.86	0.0316
Trend test	1.36	1.02, 1.83	0.0378

[1] Women who consumed "other" mineral waters or Vichy Grande Source were excluded from the analysis because the composition of these waters was unknown. To study the relation between water composition and development of AD during follow-up, we excluded those women who initially had what we considered to be an abnormal Pfeiffer score (<8).
[2] Multivariate analysis based on logistic regression. Dementia of AD type ($n = 60$) was compared with normal cognitive function ($n = 323$).
[3] $P = 0.41$ (Hosmer and Lemeshow test).
[4] After adjustment for confounding factors (age, Pfeiffer score, and income).
[5] Overall *P*.

Relation between AD and water composition

The women who developed AD during follow-up were significantly older at inclusion than were those with normal cognitive function (81.1 ± 4.3 compared with 79.2 ± 3.3 y; $P = 0.02$). They also had a lower monthly income and educational level and had greater difficulty with IADL (**Table 4**).

TABLE 4
Comparison of characteristics observed on inclusion in the study of women who developed Alzheimer disease (AD) during follow-up and of women who maintained normal cognitive function[1]

Characteristic on inclusion	Women with AD ($n = 60$)	Women with normal cognitive function ($n = 323$)	P^2
Age (y)	81.1 ± 4.3	79.2 ± 3.3	0.002
Education to school-leaving age (%)	83.3	91.1	0.068
Monthly income >€915 (%)	21.7	49.8	0.0008
Abnormal IADL (%)	18.3	6	0.022

[1] Women who consumed "other" mineral waters or Vichy Grande Source were excluded from the analysis because the composition of these waters was unknown. To study the relation between water composition and development of AD during follow-up, we excluded those women who initially had what we considered to be an abnormal Pfeiffer score (<8). IADL, Instrumental Activity of Daily Living.
[2] Bivariate analysis was based on conventional means comparison tests for quantitative variables (Student's *t* test or Kruskall-Wallis test) and frequency distribution comparison for qualitative variables (chi-square test or Fisher's exact test).

We found no change in total daily water consumption during follow-up in any of the women who were reassessed. However, after their inclusion in the EPIDOS Study, the daily silica and calcium intakes of the women who developed AD during follow-up decreased significantly: 3.364 ± 7.54 mg/d ($P = 0.0193$) and 56.66 ± 104.99 mg/d ($P = 0.04$), respectively. We found no significant changes in aluminum intakes. On inclusion in the study, these women had a significantly lower silica intake than did those who maintained normal cognitive function (6.575 ± 6.312 compared with 9.665 ± 11.567 mg/d; $P = 0.0277$).

Logistic regression was performed, and the following variables were initially included (educational level, previous history of ischemic heart disease, daily water consumption). After adjustment for confounding factors (age, Pfeiffer score, income), we found a significant association between daily silica intake and AD (*P* for trend = 0.0378; odds ratio: 1.36; 95% CI: 1.02, 1.83) (**Table 5**). Women with AD were 2.7 times as likely to have a low daily silica intake (≤4 mg/d) than were the others. These results are consistent with the relation found in cross-sectional analysis of the data initially collected in the EPIDOS Study cohort.

DISCUSSION

Our preliminary aim was to study the relation between water composition and cognitive function on the basis of the data initially collected in the EPIDOS Study, which recruited 7598 women aged ≥75 y in 5 French cities (Amiens, Lyon, Montpellier, Paris, and Toulouse). This cross-sectional analysis showed a significant association between silica concentration in the daily drinking water and the level of cognitive performance. No relation was found between cognitive function and daily intake of

aluminum or calcium in drinking water. However, the cross-sectional design of the study limited the scope of our results. Nevertheless, some of the women in the EPIDOS Study cohort in Toulouse were followed for 7 y, and their cognitive function was assessed. On the basis of this population, we therefore studied the relation between drinking water composition and the presence of AD. This analysis showed an inverse association between silica intake from drinking water and the presence of AD and confirmed the results concerning silica previously obtained in the Paquid cohort (11, 13). However, it did not show any evidence for aluminum as a risk factor for AD nor a role for calcium.

In interpreting these results, a certain number of limitations must be taken into account. First, the participants were volunteers and therefore were not representative of the general population. Moreover, only 48.8% of the women in the initial cohort in Toulouse were reexamined and had their cognitive state assessed, which probably limited the number of women who received a diagnosis and may have led to selection bias during follow-up. Thus, we could not study the relative risk of AD associated with water composition. However, our study was prospective and could precisely determine the cognitive status of women (normal cognitive function or AD). Therefore, a case-control study nested in the cohort was possible. One of the strong points of the study was the performance of cognitive assessments at the outset of the study with the SPMSQ, and only those with scores $\geq$8 were included. (According to Pfeiffer's classification, women who initially had an abnormal SPMSQ score, ie, $<$8, were classified as cognitively impaired and were excluded from statistical analysis when we studied the relation between AD and water composition.) Another great advantage of our study was that we knew the daily individual intakes of aluminum, silica, and calcium supplied by the drinking water, and not merely the concentrations of these elements in the region concerned, as in most epidemiologic studies previously published.

Aluminum is an abundant and common element that makes up $\approx$8% of the earth's crust. Its presence in water is due to components that are used as coagulating factors in water distribution systems. Several modes of exposure contribute to the total intake of aluminum in humans. Aluminum from drinking water represents $\leq$10% of total intake, but the aluminum in water may have greater biological availability than that in solid foods. In the general population, numerous epidemiologic studies have examined the possible link between the presence of aluminum in drinking water and AD. The 1994 World Health Organization (WHO) guidelines on drinking water state that "the epidemiologic and physiologic data which are available at the present time do not make it possible to attribute to aluminum a causal role in AD." In 1997, the report of the International Programme on Chemical Safety confirmed this analysis of the risk. Taking into account current knowledge of aluminum toxicity, the WHO recommends a concentration of 0.2 mg Al/L in drinking water, a concentration that is founded not on health considerations but on concerns about the color of the water treated. In our study we found no relation between aluminum and cognitive function, as was previously suggested. The aluminum concentrations that we noted were very low compared with those presented in previous epidemiologic studies. In particular, Martyn et al (5) showed an increased risk of AD in regions where the aluminum concentration was $>$0.11 mg/L. In the Paquid cohort, an increased risk of AD was also found in subjects exposed to an aluminum concentration in drinking water $\geq$0.1 mg/L (13). In our study, concentrations of aluminum in city water supplies ranged from 0.01 mg/L (Amiens) to 0.063 mg/L (Toulouse) and were lower than the thresholds used in the other studies (11, 13). Probably few or none of our subjects were exposed to doses of aluminum high enough to be considered toxic.

Silicon is the most commonly found substance on earth after oxygen. It is the second most abundant element in the earth's crust. Silica is the hydrosoluble, oxidated form of silicon. In water and in foods, silica is dissolved in the form of silicic acid and is then absorbed through the gastrointestinal wall and excreted in urine. In the body, it has long been known that silica is involved in bone formation and increases bone mineral density. Our work suggests that the silica in drinking water may have a effect against impairment of cognitive function and the presence of AD, as was shown in the Paquid cohort (13). It would appear that women with AD were less often exposed to lower daily intakes of silica. It would appear that women with AD were more likely to have had low daily intakes of silica. According to some investigators (28–30), silica may be the natural antidote to aluminum. Aluminum is mainly found in the form of aluminosilicate and insoluble oxides. It may also be found in a soluble form (aluminum hydroxide and aluminum hydrates) with an acid pH.

The toxic effect of aluminum on biological systems is observed with an acid pH: Al^{3+} ions may replace the ions generally present at the binding sites of enzymes and proteins, leading to slower cell metabolism and cell replication. Silicon, in the form of silicic acid, may influence the biological availability of aluminum. With an alkaline pH, binding of aluminum to silicic acid could lead to the formation of stable complexes of hydroxyaluminosilicates, which may decrease aluminum availability by reducing its gastrointestinal absorption and increasing the rate of renal excretion. There is considerable experimental evidence in support of the role of aluminum in the formation of senile plaques. Soluble β-amyloid peptides adopt an α-helix conformation: the presence of aluminum in physiologic concentrations may alter the conformation of these peptides into β-pleated sheets and induce aggregation of β-amyloid protein (31–33). Induction of the formation of hydroxyaluminosilicate complexes, by the addition of silicic acid, could prevent the harmful effects of aluminum that have been observed in AD lesions (34) and could therefore open an interesting new therapeutic pathway.

In conclusion, the results of our study suggest that high silica concentrations in drinking water may protect against impairment of cognitive function. However, further studies are necessary to not only confirm these results but to also clarify the causal role of aluminum in AD.

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SG-G, SA, FN, and HG collected the data. SA and HG were responsible for the statistical analysis and the analysis and interpretation of the data. SG-G and FN were responsible for the acquisition of data and subjects. SG-G prepared the manuscript. SG-G, SA, FN, HG, VdlG, and BV contributed to the concept and study design. SG-G, SA, FN, BV, and HG had no conflicts of interest. VdlG held a salaried position with the Danone Group at the time of the study.

REFERENCES

1. Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurology 2000;54(suppl):S10–5.
2. Letenneur L, Commenges D, Dartigues JF, Barberger-Gateau P. Incidence of dementia and Alzheimer's disease in elderly community residents of south-western France. Int J Epidemiol 1994;23:1256–61.
3. Mayeux R, Sano M. Treatment of Alzheimer's disease. N Engl J Med 1999;341:1670–9.
4. Vogt T. Water quality and health study of a possible relationship between aluminium in drinking water and dementia. Oslo, Norway: Central Bureau of Statistics of Norway, 1986. (Sociale og Okonomiske Studier, 61:1-99.)
5. Martyn CN, Barker DJ, Osmond C, Harris EC, Edwardson JA, Laey RF. Geographical relation between Alzheimer's disease and aluminium in drinking water. Lancet 1989;1:59–62.
6. 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.
7. Forster DP, Newens AJ, Kay DW, 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.
8. McLachlan DR, Bergeron C, Smith JE, Boomer D, Rifat SL. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminium in municipal drinking water employing weighted residential histories. Neurology 1996;46:2:401–5.
9. Martyn CN, Coggon DN, Inskip H, et al. Aluminum concentrations in drinking water and risk of Alzheimer's disease. Epidemiology 1997;8: 281–6.
10. Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gaurreau D. Aluminium forms in drinking water and risk of Alzheimer's disease. Environ Res 2000;84:234–46.
11. Jacqmin-Gadda H, Commenges D, Letenneur L, et al. Silica and aluminium in drinking water and cognitive impairment in the elderly. Epidemiology 1996;7:281–5.
12. Emsley CL, Gao S, Li Y, et al. Trace element levels in drinking water and cognitive function among elderly Chinese. Am J Epidemiol 2000;151: 913–20.
13. Rondeau V, Commenges D, Jacqmin-Gadda H, Dartigues JF. Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study. Am J Epidemiol 2000;152:59–66.
14. Dargent-Molina P, Favier F, Grandjean H, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 1996;348: 145–9.
15. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. J Am Geriatr Soc 1975; 23:433–41.
16. Fillenbaum G, Heyman A, Williams K, et al. Sensitivity and specificity of standardized screens of cognitive impairment and dementia among elderly black and white community residents. J Clin Epidemiol 1990; 43:651–60.
17. Erkinjuntti T, Sulkava R, Wikstrom J, et al. Short portable mental status questionnaire as a screening test for dementia and delirium among the elderly. J Am Geriatr Soc 1987;35:412–6.
18. Foreman M. Reliability and validity of mental status questionnaires in elderly hospitalised patients. Nurs Res 1987;37:216–20.
19. Wolber G, Romaniuk M, Esatman E, et al. Validity of the short portable mental status questionnaire with elderly psychiatric patients. J Consult Clin Psychol 1984;52:712–3.
20. Davis PB, Morris JC, Grant E. Brief screening tests versus clinical staging in senile dementia of the Alzheimer type. J Am Geriatr Soc 1990;38:129–35.
21. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86.
22. Folstein M, Folstein S, McHugh P. Mini Mental State. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
23. Grober E, Buschke H, Crystal H, et al. Screening for dementia by memory testing. Neurology 1988;38:900–3.
24. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.
25. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.
26. Ganguli M, Dodge HH, Shen C, Dekosky ST. Mild cognitive impairment amnestic type. Neurology 2004;63:115–21.
27. Hosmer D, Lemeshow S. Applied logistic regression. New York, NY: John Wiley & Sons, 1989.
28. Birchall JD, Chappell JS. Aluminium, water chemistry and Alzheimer's disease. Lancet 1989;1:1453 (letter).
29. Birchall JD, Chappell S. The chemistry of aluminium and silicon in relation to Alzheimer's disease. Clin Chem 1988;34:265–7.
30. Doll R. Review: Alzheimer's disease and environmental aluminium. Age Ageing 1993;22:138–45.
31. Exley C, Price NC, Kelly SM, et al. An interaction of beta-amyloid with aluminium in vitro. FEBS Lett 1993;324:293–5.
32. Kawahara M, Moramoto K, Kobayashi K, et al. Aluminum promotes the aggregation of Alzheimer's amyloid beta-protein in vitro. Biochem Biophys Res Comm 1994;198:531–5.
33. Exley C, Pinnegar JK, Taylor H. Hydroxyaluminosilicates and acute aluminium toxicity in fish. J Theor Biol 1997;189:133–9.
34. Fasman GD, Perczel A, Moore CD. Solubilisation of beta-amyloïd (1–42) peptide: reversing the beta-sheet conformation induced by aluminium with silicates. Proc Natl Acad Sci U S A 1995;92:369–71.

Appendix A Questionnaire on water consumption[1]

*Do you drink mineral water:
☐ no
☐ yes
If so, how much do you drink per day?
number of glasses: _____
or number of liters: _____
which do you generally drink?
☐ Badoit
☐ Contrex
☐ Evian
☐ Perrier
☐ Vichy Célestin
☐ Vichy Grande Source
☐ Vittel Grande Source
☐ Vittel Hépar
☐ Volvic
☐ Other
*How much tap water do you drink per day?
number of glasses; _____
or number of liters: _____

[1] See text for water manufacturers.