Neurotoxicology 83 (2021) 157–165

Contents lists available at ScienceDirect

Neurotoxicology

journal homepage: www.elsevier.com/locate/neuro

Full Length Article

Association between aluminum in drinking water and incident Alzheimer's disease in the Canadian Study of Health and Aging cohort

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ARTICLE INFO

Keywords:
Aluminum
Alzheimer's disease
Dementia
Fluoride
Silica
Drinking water

ABSTRACT

Epidemiological evidence linking aluminum in drinking water and Alzheimer's disease (AD) has been inconsistent, with previous studies often limited by small sample sizes. The present study addresses this issue using data from the Canadian Study of Health and Aging (CSHA), a prospective cohort of 10,263 subjects followed-up from 1991-1992 through 2001–2002. Participants' residential histories were linked to municipal drinking water sources in 35 Canadian municipalities to obtain ecologic pH, aluminum, fluoride, iron and silica concentrations in drinking water. Cox proportional hazards models were used to examine associations between aluminum and incident AD [Hazard Ratios (HRs), 95% confidence intervals (CIs)], adjusting for age, gender, history of stroke, education, and high blood pressure.

A total of 240 incident AD cases were identified during follow-up of 3, 638 subjects derived from the CSHA cohort with complete data on all covariates. With categorical aluminum measurements, there was an increasing, but not statistically significant, exposure-response relationship (HR = 1.34, 95% CI 0.88−2.04, in the highest aluminum exposure category; $p = 0.13$ for linear trend). Similar results were observed using continuous aluminum measurements (HR=1.21, 95% CI 0.97−1.52, at the interquartile range of 333.8 μg/L; $p = 0.09$ for linear trend). In a subsample genotyped for ApoE-ε4, there was some evidence of an association between aluminum and AD ($p = 0.03$ for linear trend).

Although a clear association between aluminum in drinking water and AD was not found, the linear trend observed in ApoE-ε4 subsample warrants further examination.

1. Introduction

Alzheimer's disease (AD) presents with progressive memory loss, confusion and disorientation. In Canada, AD and other dementias are common with a prevalence rate of 2130 per 100,000 population aged over 65 years during 2010 and 2011 (Gaskin et al., 2017). A variety of socio-demographic and genetic characteristics are associated with increased risk of AD (Heininger, 2000; Hersi et al., 2017; Krewski et al., 2017; Little et al., 2017); however, the known risk factors do not account for the full burden of AD, suggesting that other environmental factors may play a role in the development of AD (Gauthier et al., 2000; Frisardi et al., 2010). Aluminum has been shown to be neurotoxic in toxicological studies (Krewski et al., 2007; Willhite et al., 2014). Since aluminum is found in natural waters and is used in municipal water treatment (Willhite et al., 2012), examining drinking water aluminum intake as a risk factor has been pursued in epidemiological studies (Tomljenovic,

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https://doi.org/10.1016/j.neuro.2020.04.002
Received 26 April 2019; Received in revised form 3 March 2020; Accepted 15 April 2020
Available online 29 April 2020

2011; Walton, 2013).

The epidemiologic evidence regarding aluminum in drinking water and the risk of AD remains conflicted in that several studies reported positive relationships between aluminum in drinking water and increased risk for AD (Gauthier et al., 2000; Rondeau et al., 2000, 2009; Martyn et al., 1989; Forbes and McLachlan, 1996; Jacqmin-Gadda et al., 1996; McLachlan et al., 1996); but others failed to confirm those observations (Frecker, 1991; Neri and Hewitt, 1991; Wood et al., 1988; Wettstein et al., 1991; Forster et al., 1995; Sohn et al., 1996; Gillette--Guyonnet et al., 2005; Flaten, 1990, 2001).

The present study examines the association between aluminum concentration in drinking water and incident AD risk through analyses of the Canadian Study of Health and Aging (CSHA) cohort. Some of the limitations of previous studies pertaining to sample size and case definition have been addressed in our study by using a relatively large analytical cohort with well-defined disease outcomes. In addition, detailed residence histories provided by members of the cohort were obtained and were linked with drinking water sources. The baseline interview provided information on possible confounders and effect modifiers. Since water pH influences gastrointestinal bioavailability of aluminum (Krewski et al., 2007; Willhite et al., 2014), and ingested silica, fluoride and iron can alter aluminum uptake or modify aluminum-induced neurotoxicity (Flaten, 2001), the present study also included those drinking water parameters in the analysis. As lifetime AD risk increases with the ApoE-ε4 allele (Seshadri et al., 1995; Henderson et al., 1995; Bartzokis et al., 2006), a separate analysis was performed to assess the relationship between aluminum exposure and AD risk in a subsample genotyped for ApoE-ε4.

2. Methods

The present study was an analysis of the CSHA cohort, which had been linked to water quality data provided by provincial and/or municipal sources.

2.1. Population

The CSHA is a national longitudinal study of people aged 65 years and over, designed to investigate the prevalence and incidence of dementia, along with associated risk factors (CSHA Working Group, 1994; 2000). The study began in 1991–1992 (CSHA-1) with follow-ups in 1996–1997 (CSHA-2) and in 2001–2002 (CSHA-3). The cohort was formed from two groups: a random sample from the community (n = 9008) and a non-random sample from long-term care institutions (n = 1255), yielding a total of 10,263 individuals. All subjects participated in a baseline interview and consented to follow-up. We excluded subjects that were diagnosed with AD at baseline, those with no information on risk factor questionnaire data, and those who did not have residential history data for at least 7 years during the exposure window of interest (1980–1991). This exposure window was selected after considering the biologically plausible time frame of 10–20 years for aluminum exposure to contribute to development of Alzheimer's disease (Ohyagi and Miyoshi, 2013; Weiner et al., 2012) and difficulty in procuring drinking water quality data prior to 1980 from local and national authorities in Canada. Although life-time exposure data are preferable, lack of historical exposure information was expected. Therefore, a minimum of 7 year data were deemed essential for exposure assessment (by experts) as this period would capture more than 50% of the information within exposure window of 12 years.

2.2. Ascertainment of AD

AD was diagnosed using standardized neuropsychological testing. Community participants were administered the Modified Mini-Mental State Examination (3MS) screening test for cognitive impairment (Teng and Chui, 1987; Hebert et al., 1992) at their baseline interview. Individuals who screened positive (a 3MS score below 78) were invited to participate in clinical evaluations. Apolipoprotein E (ApoE) allele status was determined in a sub-sample (n = 764) of the subjects who voluntarily donated a blood sample for genotyping during clinical examination (Lindsay et al., 2002; McLeod et al., 1998; CSHA Working Group, 1994; 2000). A physician conducted a standardized physical and neurological examination for all these subjects. A psychometrist administered 15 neuropsychological tests to all subjects who had a 3MS score between 50 and 78. Institutional participants were evaluated using similar protocol, but they were not pre-screened using the 3MS.

The results from these examinations were used to make a preliminary diagnosis of AD using criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (APA, 1987). The independent diagnoses made by the two clinicians were later combined, and the subjects were classified as no AD, possible AD or probable AD. They also sub-classified the subjects according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Subjects were also assigned a diagnosis according to DSM-IV criteria for AD (APA, 1994) and the National Institute of Neurological Disorders and Stroke Association – Association internationale pour la recherche et l'enseignement en neurosciences (NINDS-AIREN) criteria for vascular dementia during follow-up (Roman et al., 1993).

We defined AD cases as subjects diagnosed with either possible or probable AD according to DSM-III-R and NINCDS-ADRDA criteria.

2.3. Exposure assignment

The residential history and source of drinking water at each residence lived in by each participant was obtained at the baseline interview. The residence location was linked to their local water treatment or distribution facility. We obtained drinking water pH and the mean concentrations of aluminum, fluoride, silica and iron for the period 1980–2000 from all Canadian provincial and municipal sources for each treatment plant and for private wells, where available. The corresponding drinking water data, obtained directly from various municipalities, were used to create annualized exposure records for the 12 year exposure window (1980–1991) for each subject. Finally, the exposure level for each subject was obtained by computing an average of the annualized exposure, weighted by the length of time lived at each residence for the period 1980–1991. As water quality data could not be obtained for all these years for some subjects, we relied on partial histories to estimate mean water concentration of exposure; but only when sufficient information was available. A requirement of at least seven years of complete residential history with corresponding municipal water data for the period 1980–1991 was imposed as the minimum information needed to assign a subject an exposure estimate. Subjects who lacked matching water data for at least 7 years of residence during exposure window received no exposure estimate.

Water quality data for early 80s were not available for several water treatment or distribution facilities in various municipalities. Therefore, we had to rely on extrapolation of data for these missing years based on years for which annual water data were available between 1980 and 2000. However, this extrapolation of data to missing years within exposure window was implemented only if no significant changes to the source and water treatment procedures were implemented in a municipality throughout 1980–2000 to avoid erroneous approximation of recent data.

2.4. Questionnaire

The study questionnaire collected data on sociodemographic characteristics, such as age, gender, residence and education of study participants at baseline. Lifestyle factors such as smoking, wine consumption, consumption of coffee or tea, and regular physical

exercise were also collected. Participants also provided information on use of non-steroidal anti-inflammatory drugs (NSAIDS), and their health conditions, including history of stroke, high blood pressure and head injury, diabetes, cancer, epilepsy and Parkinson's disease.

2.5. Statistical analyses

Cox proportional hazards regression models were used to study the association between aluminum concentrations in drinking water and AD incidence using two models: a minimally adjusted model that included only age as a covariate, and a fully adjusted model that included education, stroke and high blood pressure in addition to age. This selection of covariates was based on a review of the current scientific literature, as none of the covariates demonstrated strong evidence of confounding in our analyses (Rondeau et al., 2000; Gabin et al., 2017; Honig et al., 2003; Wu et al., 2003). A stratified Cox model was used to control for a possible non-proportionality effects related to sex (Rondeau et al., 2000), and hazard ratios (HRs) and 95% confidence intervals (95% CI) were computed. The proportional hazards assumption for aluminum was checked using a time-varying covariate. A subject was considered at risk from the day of the first screening interview to the date of AD diagnosis or the date of loss to follow-up or death. Subjects surviving to the last visit without a diagnosis of AD were censored at the date of that interview.

Separate analyses were conducted including aluminum intake as either a continuous or a categorical variable. These analyses would allow comparisons with previous literature and also with random effects models that used aluminum intake as a continuous variable. For our main categorical analyses, aluminum drinking water concentrations were divided into quartiles as determined from the distribution of levels among non-diseased subjects. As the 4th quartile spanned a wide range of concentrations (121.6–749.9 μg/L), this quartile was further divided into two groups at the median level (443.3 μg/L). The continuous aluminum variable was rescaled using the interquartile range (IQR = 333.8 μg/L) to produce HR estimates of relevance that quantify the risk of high exposure. Aluminum concentrations were also dichotomized into high (≥100 μg/L) or low (<100 μg/L) categories to explore a possible threshold effect (Rondeau et al., 2009).

Silica, pH, fluoride, and iron were categorized based on exposure quartiles among non-diseased subjects. Each of these parameters was included in the fully adjusted model to investigate potential confounding.

A separate analysis adjusting for the influence of ApoE-ε4 in relation to aluminum exposure and AD risk was performed by comparing subjects with at least one ApoE-ε4 allele (haploid or diploid) to those with two ApoE-ε3 alleles in the genotyped sub-sample.

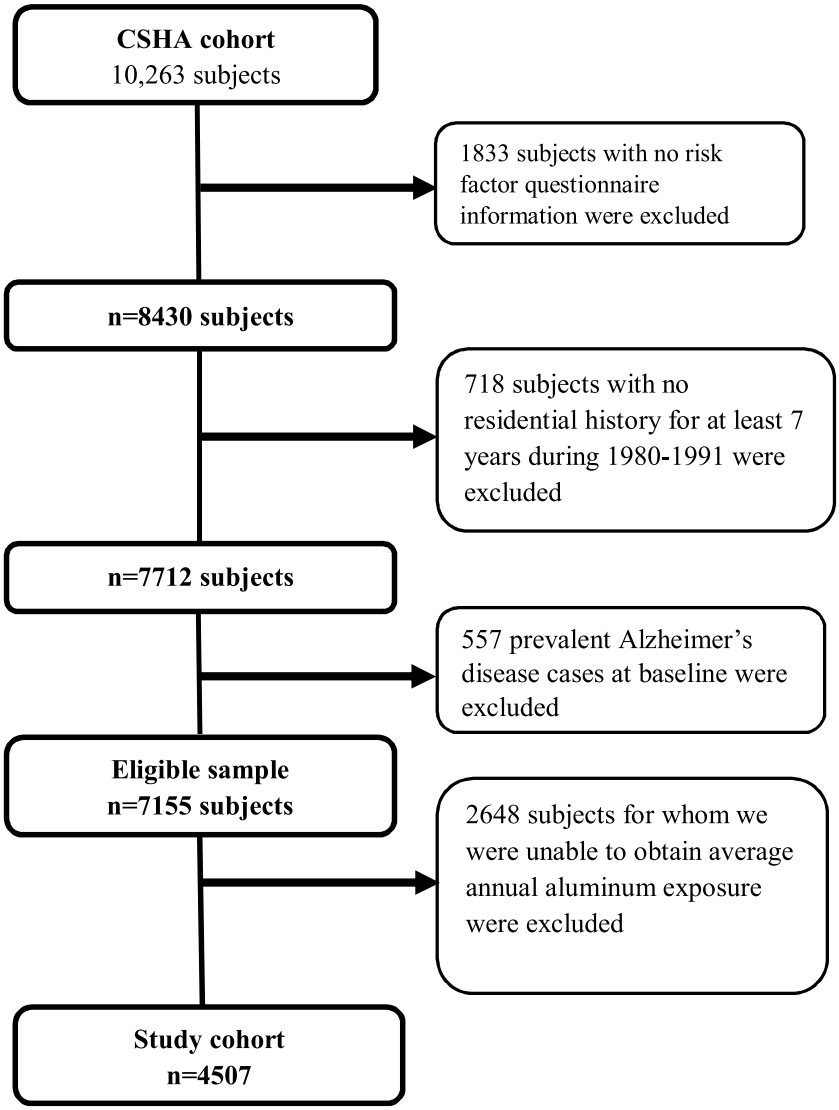

Fig. 1. Participants in the current study derived from Canadian Study of Health and Aging (CSHA) cohort, 1991–1992.

A random-effects Cox regression model was used to assess unobserved ecological effects as a result of the clustering of patients by municipality (Krewski et al., 2009). Individuals were assigned to 35 municipalities based on the longest duration of residence between 1980 and 1991.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, NC); random-effects models were also explored using R version 2.15.

3. Results

3.1. Main results

The final cohort consisted of 4507 subjects. Of the initial pool of 10,263 total subjects who participated in the baseline CSHA interview, we excluded 3108 ineligible subjects. A further 2648 subjects were excluded because we were unable to obtain estimates of aluminum exposure. Fig. 1 illustrates derivation of our study cohort from the participants of CSHA. The average follow-up was 6.49 years with a standard deviation (SD) of 3.27 years. The total person-years of follow-up was approximately 23,832 person-years. AD was diagnosed in 315 subjects; 240 of these cases had sufficient information to be included in the fully adjusted final model comprising of 3638 subjects.

Baseline characteristics of our study cohort were shown in Table 1 by categories of aluminum exposure. The mean age of the cohort at baseline was 75.5 years (SD 7.1). Majority of study participants were females, smokers, and had 9–13 years of formal education. About 12% and 33% of the subjects in highest exposure category suffered from stroke and high blood pressure, respectively. Significant differences were observed among exposure categories with respect to consumption of wine, coffee and tea.

Table 2 reports descriptive statistics for all water parameters. The mean aluminum concentration was 134.1 μg/L (SD 152.5 μg/L). Drinking water was slightly basic with an average pH of 7.4.

Table 3 provides associations between aluminum in drinking water and AD. There was no significant association between the highest aluminum exposure category and AD (HR = 1.34, 95% CI 0.88−2.04) in the fully adjusted model. In addition, no linear trend in AD risk was observed across aluminum categories ($p = 0.13$). The risk of AD at aluminum concentrations above 100 μg/L was not different from the risk below this cut-point (HR = 1.07, 95% CI 0.83−1.40). Similar results were observed using continuous aluminum measurements (HR = 1.21, 95% CI 0.97−1.52, at the interquartile-range of 333.8 μg/L; $p = 0.09$ for linear trend).

There was no evidence of non-proportionality of the hazard function in the Cox regression model.

The effect of other drinking water factors (drinking water pH, fluoride, silica and iron) was explored by adding each factor in turn to the fully adjusted model (Table 4). None of these models was statistically significant. Adjustment for drinking water pH, fluoride, and iron reversed the apparent relationship of Aluminum and AD, although the effect was not statistically significant.

3.2. Apolipoprotein E

There was no evidence of an interaction between ApoE-ε4 status and aluminum exposure in the sub-cohort genotyped for ApoE ($p > 0.05$, data not shown). A positive linear trend ($p = 0.03$) was observed for the association between aluminum in drinking water and AD after adjusting for ApoE-ε4 status (Table 5). In the continuous model, the risk of AD was slightly lower following ApoE adjustment (HR = 1.31 at the IQR of 333.8 μg/L, 95% CI 0.98–1.74), compared to the model without ApoE adjustment (HR = 1.37 at the IQR, 95% CI 1.03–1.81). Supplemental data on aluminum exposure by ApoE-ε4 status and related AD risk was provided in supplementary material (Supplementary Material).

3.3. Residential history

Results from models adjusting for municipality of residence using random-effects Cox regression were consistent with our main analyses. HRs were slightly attenuated relative to the standard Cox regression model and the uncertainty was greater (HR = 1.19 at the IQR of 333.8 μg/L, 95% CI 0.93–1.53, for the random-effects model compared to 1.21 at the IQR, 95% CI 0.97–1.52, for the standard Cox model).

4. Discussion

The present study represents the largest prospective evaluation of aluminum in drinking water and AD conducted to date. Higher aluminum concentrations in residential drinking water were not associated with increased risk of AD, although HRs greater than the null value of unity were observed for the highest levels of aluminum intake when measured as a categorical and as a continuous variable at the IQR.

Subjects in this study were grouped by municipality, which may have induced a degree of clustering in the data (HEI, 2000). Adjusting for this ecological correlation using a random-effects model reduced the magnitude of aluminum effect on AD, when compared to the standard Cox model.

Estimation of aluminum intake based on tap water, in our study, will under-estimate total intake, since they do not account for intake from other sources (Krewski et al., 2007; Willhite et al., 2014), including beverages and cooking. We expect the misclassification to be non-differential, possibly resulting in attenuated risk estimates. A substantial loss of the eligible sample could potentially bias the findings of our study; however, a supplementary analysis performed by imputing all missing exposure data yielded similar results, rendering credence to our findings (Supplementary Material).

The form of aluminum present in the drinking water - specifically hydroxides, oxides, fluorides, silicates and sulfates of aluminum, colloidal aluminum, and organic aluminum (Driscoll and Letterman, 1995; Rieber et al., 1995; Schintu et al., 2000; Frankowski et al., 2011) - may be of etiologic relevance. Aluminum speciation would be a desirable aspect of exposure ascertainment in future studies of the association between aluminum and AD. Our results contrast with those from a case-control study ($n = 68$ AD cases) that assigned aluminum exposure based on residential history and aluminum speciation data, and adjusted for ApoE-ε4 allele status (Gauthier et al., 2000). In that study, only organic aluminum was associated with AD (Odds ratio = 2.67, 95% CI 1.04–6.90). The present study and literary evidence (Rondeau et al., 2006) does not support the interaction effect of ApoE-ε4 polymorphism and aluminum exposure on AD risk. However, the attenuation and borderline significance of the relationship between high Al exposure and AD observed after adjusting for ApoE-ε4 allele status, in our sub-group of genotyped subjects, warrant further study of this association in ApoE-ε4 polymorphism.

A number of previous studies have investigated associations between aluminum in drinking water and AD (Rondeau et al., 2000, 2009; Martyn et al., 1989; Forbes and McLachlan, 1996; Jacqmin-Gadda et al., 1996; McLachlan et al., 1996; Frecker, 1991; Neri and Hewitt, 1991; Wood et al., 1988; Wettstein et al., 1991; Forster et al., 1995; Sohn et al., 1996; Gillette-Guyonnet et al., 2005; Flaten, 1990, 2001). Davenward et al. (2013) found that administration of silicon-rich water for 12 weeks reduced the aluminum body burden in 3 of 15 AD patients, and that these patients had clinically relevant improvements in cognition, suggesting a possible role of aluminum in AD. Two large prospective studies (Rondeau et al., 2000, 2009) included relevant socio-demographic and water quality covariates: the most recent examined a 15 year follow-up of the PAQUID cohort where individual intakes of aluminum and silica based on daily consumption of tap and bottled water were assessed (Rondeau et al., 2009). These authors reported that elevated daily aluminum intake from water (≥100 μg/day) was associated with increased risk of AD (relative risk (RR) = 3.35, $p = 0.003$) and that there

Table 1
Baseline characteristics of study subjects by five categories of aluminum concentrations in drinking water, Canadian Study of Health and Aging (CSHA), 1991–1992.

Characteristic	Number of subjects (%)						*P* value[a]
	Total (n = 4507)	Aluminum in drinking water categories (μg/L)					
		<46.5 (n = 1043)	46.5–104 (n = 1325)	104–121.6 (n = 1220)	121 .6–443.3 (n = 438)	≥ 443.3 (n = 481)	
Gender							
Female	2689 (59.7)	661 (63.4)	780 (58.9)	695 (57.0)	272 (62.1)	281 (58.4)	0.0225
Male	1818 (40.3)	382 (36.6)	545 (41.1)	525 (43.0)	166 (37.9)	200 (41.6)	
Education							
0–9 years	1139 (25.3)	343 (32.9)	262 (19.8)	248 (20.3)	126 (28.8)	160 (33.3)	<0.0001
9–13 years	2030 (45.0)	484 (46.4)	602 (45.4)	558 (45.7)	185 (42.2)	201 (41.8)	
≥ 13 years	1294 (28.7)	204 (19.6)	442 (33.4)	409 (33.5)	124 (28.3)	115 (23.9)	
Unknown	44 (1.0)	12 (1.2)	19 (1.4)	5 (0.4)	3 (0.7)	5 (1.0)	
Regular wine consumption							
Yes	705 (15.6)	138 (13.2)	260 (19.6)	207 (17.0)	67 (15.3)	33 (6.9)	<0.0001
No	3701 (82.1)	875 (83.9)	1038 (78.3)	988 (81.0)	361 (82.4)	439 (91.3)	
Unknown	101 (2.2)	30 (2.9)	27 (2.0)	25 (2.0)	10 (2.3)	9 (1.9)	
Regular exercise							
Yes	2805 (62.2)	589 (56.5)	862 (65.1)	793 (65.0)	267 (61.0)	294 (61.1)	<0.0001
No	1599 (35.5)	433 (41.5)	432 (32.6)	404 (33.1)	163 (37.2)	167 (34.7)	
Unknown	103 (2.3)	21 (2.0)	31 (2.3)	23 (1.9)	8 (1.8)	20 (4.2)	
Regular smoker							
Yes	2289 (50.8)	488 (46.8)	687 (51.8)	646 (53.0)	238 (54.3)	230 (47.8)	0.0079
No	2143 (47.5)	532 (51.0)	617 (46.6)	554 (45.4)	191 (43.6)	249 (51.8)	
Unknown	75 (1.7)	23 (2.2)	21 (1.6)	20 (1.6)	9 (2.1)	2 (0.4)	
Regular NSAID[b] use							
Yes	675 (15.0)	149 (14.3)	168 (12.7)	199 (16.3)	75 (17.1)	84 (17.5)	0.0214
No	3832 (85.0)	894 (85.7)	1157 (87.3)	1021 (83.7)	363 (82.9)	397 (82.5)	
Previous head injury							
Yes	732 (16.2)	138 (13.2)	229 (17.3)	218 (17.9)	72 (16.4)	75 (15.6)	0.0383
No	3403 (75.5)	820 (78.6)	982 (74.1)	918 (75.2)	328 (74.9)	355 (73.8)	
Unknown	372 (8.3)	85 (8.1)	114 (8.6)	84 (6.9)	38 (8.7)	51 (10.6)	
Regular coffee consumption							
Yes	3156 (70.0)	659 (63.2)	954 (72.0)	883 (72.4)	287 (65.5)	373 (77.5)	<0.0001
No	1274 (28.3)	361 (34.6)	354 (26.7)	315 (25.8)	142 (32.4)	102 (21.2)	
Unknown	77 (1.7)	23 (2.2)	17 (1.3)	22 (1.8)	9 (2.1)	6 (1.2)	
Regular tea consumption							
Yes	3160 (70.1)	769 (73.7)	952 (71.8)	838 (68.7)	320 (73.1)	281 (58.4)	<0.0001
No	1271 (28.2)	252 (24.2)	357 (26.9)	358 (29.3)	113 (25.8)	191 (39.7)	
Unknown	76 (1.7)	22 (2.1)	16 (1.2)	24 (2.0)	5 (1.1)	9 (1.9)	
Previous stroke							
Yes	392 (8.7)	79 (7.6)	110 (8.3)	107 (8.8)	39 (8.9)	57 (11.9)	0.1833
No	3412 (75.7)	778 (74.6)	983 (74.2)	950 (77.9)	340 (77.6)	361 (75.1)	
Unknown	703 (15.6)	186 (17.8)	232 (17.5)	163 (13.4)	59 (13.5)	63 (13.1)	
High blood pressure							
Yes	1538 (34.1)	362 (34.7)	436 (32.9)	416 (34.1)	165 (37.7)	159 (33.1)	0.6017
No	2415 (53.6)	535 (51.3)	709 (53.5)	681 (55.8)	233 (53.2)	257 (53.4)	
Unknown	554 (12.3)	146 (14.0)	180 (13.6)	123 (10.1)	40 (9.1)	65 (13.5)	
Diabetes							
Yes	454 (10.1)	102 (9.8)	118 (8.9)	133 (10.9)	49 (11.2)	52 (10.8)	0.7225
No	3375 (74.9)	756 (72.5)	979 (73.9)	941 (77.1)	330 (75.3)	369 (76.7)	
Unknown	678 (15.0)	185 (17.7)	228 (17.2)	146 (12.0)	59 (13.5)	60 (12.5)	
Cancer							
Yes	645 (14.3)	124 (11.9)	201 (15.2)	198 (16.2)	56 (12.8)	66 (13.7)	0.1539
No	3091 (68.6)	701 (67.2)	881 (66.5)	863 (70.7)	292 (66.7)	354 (73.6)	
Unknown	771 (17.1)	218 (20.9)	243 (18.3)	159 (13.0)	90 (20.5)	61 (12.7)	
Epilepsy							
Yes	34 (0.8)	5 (0.5)	8 (0.6)	11 (0.9)	6 (1.4)	4 (0.8)	0.4821
No	3740 (83.0)	842 (80.7)	1069 (80.7)	1050 (86.1)	371 (84.7)	408 (84.8)	
Unknown	733 (16.3)	196 (18.8)	248 (18.7)	159 (13.0)	61 (13.9)	69 (14.3)	
Parkinson's disease							
Yes	59 (1.3)	14 (1.3)	16 (1.2)	12 (1.0)	10 (2.3)	7 (1.5)	0.3487
No	3709 (82.3)	839 (80.4)	1065 (80.4)	1041 (85.3)	361 (82.4)	403 (83.8)	
Unknown	739 (16.4)	190 (18.2)	244 (18.4)	167 (13.7)	67 (15.3)	71 (14.8)	
At least 1 ApoE ε4 allele[c]							
Yes	199 (4.4)	46 (4.4)	57 (4.3)	44 (3.6)	20 (4.6)	32 (6.7)	0.0331
No	565 (12.5)	152 (14.6)	156 (11.8)	144 (11.8)	66 (15.1)	47 (9.8)	
Not genotyped	3743 (83.0)	845 (81.0)	1112 (83.9)	1032 (84.6)	352 (80.4)	402 (83.6)	
Questionnaire respondents							
Proxies	636 (14.1)	146 (14.0)	184 (13.9)	147 (12.1)	80 (18.3)	79 (16.4)	0.0128
Self	3871 (85.9)	897 (86.0)	1141 (86.1)	1073 (87.9)	358 (81.7)	402 (83.6)	
Source for recruitment							
Long-term care institutions	324 (7.2)	64 (6.1)	111 (8.4)	67 (5.5)	33 (7.5)	49 (10.2)	0.0026
Community	4183 (92.8)	979 (93.9)	1214 (91.6)	1153 (94.5)	405 (92.5)	432 (89.8)	

[a] *p* values for differences between five aluminum categories based on chi-square test for proportions.
[b] NSAID denotes Non-steroidal anti-inflammatory drug.
[c] ApoE denotes apolipoprotein E.

Table 2
Distribution of water parameters ($n = 4507$), Canadian Study of Health and Aging (CSHA), 1991–2002.

Statistics	Aluminum (μg/L)	pH	Fluoride(mg/L)	Silica (mg/L)	Iron (μg/L)
All subjects					
N[a]	4507	4507	4356	3362	4507
Mean[b]	134.07	7.4	0.55	2.69	48.9
Standard deviation	152.47	0.8	0.45	2.04	48.6
Median	103.91	7.7	0.84	3.07	46.3
Range	4.49–749.85	5.7–8.9	0.02–1.16	0.29–12.51	0.01–384.29

[a] N denotes number of subjects.
[b] Mean computed based on average annualized exposure concentration for each individual, weighted by the length of time lived at each residence.

Table 3
Hazard ratios (HRs) and 95% confidence intervals (CIs) for Alzheimer's disease (AD) risk in relation to aluminum (Al) concentrations in drinking water, Canadian Study of Health and Aging (CSHA), 1991–2002.

Aluminum exposure	No. of incident AD cases	No. of subjects	Minimally adjusted model[a]		Fully adjusted model[b]	
			HR[c] (95% CI)	*p*-value[d]	HR[c] (95% CI)	*p* value[d]
Categorical Al exposure (μg/L)	240	3638		0.08[e]		0.13[e]
0 to <46.5	53	823	1.00[f]		1.00[f]	
46.5 to <104	64	1033	0.92 (0.63–1.32)	0.64	1.01 (0.70–1.46)	0.96
104 to <121.6	66	1025	0.95 (0.66–1.37)	0.79	1.02 (0.71–1.48)	0.90
121.6 to <443.3	19	364	0.84 (0.49–1.42)	0.51	0.88 (0.52–1.49)	0.64
≥443.3	38	393	1.35 (0.88–2.04)	0.17	1.34 (0.88–2.04)	0.18
Continuous Al exposure (HR at IQR = 333.8 μg/L of Al exposure)	240	3638	1.25 (1.00–1.57)	0.05	1.21 (0.97–1.52)	0.09
Threshold Al exposure (≥100 μg/L versus <100 μg/L)	240	3638	1.08 (0.83–1.40)	0.60	1.07 (0.83–1.40)	0.60

[a] Minimally adjusted model (adjusted only for age, and stratified by gender).
[b] Fully adjusted model (adjusted for age, education, previous history of stroke, and blood pressure, and stratified by gender).
[c] HR calculated relative to the reference category for categorical aluminum exposures, and for an increase of 333.8 μg/L aluminum (the interquartile range of aluminum exposures) in drinking water for continuous exposure.
[d] Two-sided *p*-value for HR from Cox regression model being different from that in the reference category.
[e] Two-sided *p*-value for increasing or decreasing linear trend in HR based on Cox regression model.
[f] Reference category based on lowest aluminum exposure levels.

Table 4
Hazard ratios (HRs) and 95% confidence intervals (CIs) for Alzheimer's disease (AD) in relation to aluminum drinking water levels adjusted for other water parameters using fully adjusted model, Canadian Study of Health and Aging (CSHA), 1991–2002.

Water parameter adjusted	Incident AD cases	No. of subjects	Al exposure categories (μg/L)	HR[a]	95% CI	*p* value[b]	*p* trend[c]
pH	240	3638					
	53	823	0–46.5	1.00[d]			0.70
	64	1033	46.5–104	0.86	(0.57–1.30)	0.48	
	66	1025	104–121.6	0.76	(0.48–1.21)	0.25	
	19	364	121.6–443.3	0.81	(0.46–1.42)	0.46	
	38	393	≥443.3	0.79	(0.44–1.41)	0.42	
Fl	227	3497					
	42	698	0–46.5	1.00[d]			0.73
	64	1032	46.5–104	0.81	(0.49–1.33)	0.41	
	66	1024	104–121.6	0.93	(0.58–1.50)	0.76	
	17	350	121.6–443.3	0.65	(0.34–1.24)	0.20	
	38	393	≥443.3	0.84	(0.44–1.59)	0.59	
Fe	240	3638					
	53	823	0–46.5	1.00[d]			0.60
	64	1033	46.5–104	0.98	(0.66–1.46)	0.92	
	66	1025	104–121.6	0.91	(0.56-1.47)	0.69	
	19	364	121.6–443.3	0.85	(0.48–1.52)	0.59	
	38	393	≥443.3	1.08	(0.67–1.75)	0.76	
Si	184	2661					
	24	371	0–46.5	1.00[d]			0.67
	43	621	46.5–104	1.07	(0.64–1.80)	0.79	
	64	983	104–121.6	1.22	(0.72–2.08)	0.46	
	15	295	121.6–443.3	0.89	(0.45–1.75)	0.73	
	38	391	≥443.3	1.14	(0.66–1.97)	0.65	

[a] HRs adjusted for age, education, previous history of stroke, and blood pressure, and stratified by gender.
[b] Two-sided *p*-value for HR from Cox regression model being different from that in the reference category.
[c] Two-sided *p*-value for increasing or decreasing linear trend in HR based on Cox regression model.
[d] Reference group.

Table 5
Hazard ratios (HRs) and 95% confidence intervals (CIs) for Alzheimer's disease (AD) in relation to aluminum drinking water levels adjusted for ApoE ε4 status, Canadian Study of Health and Aging (CSHA), 1991–2002.

Aluminum exposure categories (μg/L)	Incident cases	N	HR[a]	95% CI	*p* value[b]	*p* trend[c]
0–46.5	28	159	1.00[d]			
46.5–104	23	165	0.90	(0.51–1.58)	0.71	
104–121.6	29	166	1.09	(0.64–1.85)	0.75	0.03
121.6–443.3	11	67	0.94	(0.46–1.91)	0.85	
≥443.3	23	72	1.70	(0.97–3.01)	0.06	
Total	114	629				

[a] HRs adjusted for ApoE ε4 Status, age, education, previous history of stroke and blood pressure, and stratified by gender.
[b] Two-sided *p*-value relative to reference category based on based Cox regression model.
[c] Two-sided *p*-value for increasing or decreasing linear trend in HR based on Cox regression model.
[d] Reference group.

was a linear relationship between aluminum consumption and AD (RR = 1.36 over 100 μg/day, $p < 0.001$). Despite the strengths of this study, these results must be interpreted with caution, as only 13 subjects were exposed to an intake of more than 100 μg aluminum/day (Rondeau et al., 2009). Our analysis of 2618 subjects with residential drinking water aluminum at the same cut-point did not find a statistically significant association between aluminum in drinking water and AD.

A recent systematic review of risk factors for Alzheimer's disease did not document sufficient evidence to conclude that aluminum plays a role in either the onset or progression of this disease (Hersi et al., 2017). Other individual reports also support the conclusion that aluminum accumulation alone does not cause AD (Willhite et al., 2012). Our results are consistent with observations on 1462 French women over 75 years of age followed for up to 7 years that found no difference in aluminum intakes by women with and without diagnosed AD (Gillette-Guyonnet et al., 2005). A small ($n = 38$) randomized, double-blind placebo-controlled, crossover trial with oral aluminum hydroxide and citrate (for 3 days and washout period of 3 weeks) sufficient to maintain serum aluminum between 50 and 150 μg/L found no differences in cognitive abilities of normal volunteers or in demented (including AD) patients (Molloy et al., 2007). Moreover, there was no association between ApoE-ε4 genotype and aluminum absorption and neither were there any changes in cognitive function in AD patients after acute aluminum doses (Molloy et al., 2007). AD is a multifactorial neurodegenerative disease related to age (Jorm and Jolley, 1998), genetics (Little et al., 2017; Seshadri et al., 1995; Henderson et al., 1995; Bartzokis et al., 2006; Cruts et al., 1995; Perez-Tur et al., 1995; Religa et al., 2003; Lambert and Amouyel, 2011; Lambert et al., 2013a,b; Harold et al., 2009; Hollingworth et al., 2011; Rosenthal and Kamboh, 2014,) and environmental (Lane and Farlow, 2005; Grant, 1997; Mayeux et al., 1999; Levitt and Karlinsky, 1992; Clarke et al., 1998; Snowdon et al., 1996; Huang et al., 2005; Afzal et al., 2014; Littlejohns et al., 2014; Lopes da Silva et al., 2014; Cooper, 2003) factors. The characteristic progressive cognitive decline in AD is due to neuronal death after accumulation of senile plaques with β-amyloid (Aβ) aggregation and neurofibrillary tangles comprised of hyperphosphorylated tau (Spires-Jones and Hyman, 2014). It was suggested that aluminum selectively binds to the hyperphosphorylated forms of the paired helical elements tau in AD neurofibrillary tangles, thereby retarding PHFtau proteolysis (Shin, 1997; Shin et al., 1994, 1995). Increased Aβ reduces synaptic function in the neocortex and microglia as a consequence of oxidized synaptosomal membranes due to superoxide free radicals (Christen, 2000). While the available data suggest that aluminum accumulation in the brain is not sufficient in and of itself to cause AD, aluminum-induced generation of superoxide semi-reduced $[AlO_2^{\bullet}]^{+2}$ radicals and increased intracellular H_2O_2, $O_2^{\bullet-}$ and $OH^{\bullet}$– leads to apoptosis (Krewski et al., 2007). These reactions along with aluminum enhancement of Aβ oligomerization (Bolognin et al., 2011, 2013; Kawahara and Kato-Negishi, 2011) suggest aluminum may play a contributory role in AD, but how aluminum-induced oxidative damage might relate to established genetic and environmental AD risk factors is not known.

The present analysis has a number of methodological strengths, including the size and prospective nature of the study, along with well-defined disease diagnoses. Detailed information about individual socio-demographic characteristics, as well data on other important drinking water parameters, allowed for an evaluation of possible confounding of these covariates on the association between aluminum and AD. The impact of residual confounding on our findings would be minimal because our sensitivity analysis that adjusted for all the available covariates yielded results consistent with our main findings. Finally, the use of a random-effects Cox regression model allowed for the possibility of clustering by municipality.

5. Conclusion

In conclusion, the present study found no overall association between aluminum concentrations in drinking water and risk of AD in the CSHA cohort. Nonetheless, the hazard ratios greater than null value of unity seen in the present analysis, and positive linear trend observed in the sub-cohort genotyped for ApoE, warrant further investigation. As aluminum in drinking water represents 0.008–0.8% of total daily aluminum exposure (Krewski et al., 2007; Willhite et al., 2014), accounting for all aluminum sources of exposure is necessary when considering AD risk. Ideally, future studies will include data on individual drinking water and other aluminum sources. Given the diverse forms of aluminum in drinking water (Driscoll and Letterman, 1995; Rieber et al., 1995; Schintu et al., 2000; Frankowski et al., 2011) and their varying gastrointestinal bioavailability (Krewski et al., 2007; Willhite et al., 2014), future studies should measure individual aluminum species present in drinking water, as the form of aluminum to which people may be exposed could be an important factor in further evaluating potential aluminum health risks.

Funding

Partial financial support was provided by the Natural Sciences and Engineering Research Council of Canada (NSERC) to D Krewski, who holds the NSERC Industrial Research Chair in Risk Science at the University of Ottawa (http://www.nserc-crsng.gc.ca) a peer-reviewed university-industry research partnership program. D Krewski, C Willhite, and N Yenugadhati are affiliated with Risk Sciences International (www.risksciences.com), a Canadian company established in 2006 in partnership with the University of Ottawa that has conducted work on aluminum and health for public and private sector clients. The scientific opinions and conclusions expressed in the paper are exclusively those of the authors, and are independent of sources of financial support.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

This work was conducted as part of Nicole Van Dyke's M.Sc. thesis (authored as Nicole Boom) at the University of Ottawa. We thank the Federal-Provincial-Territorial Committee on Drinking Water (CDW),

provincial and territorial municipal authorities in Canada for providing water quality data. The authors also acknowledge Dr Yuanli Shi's assistance in conducting analyses with random-effects models.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neuro.2020.04.002.

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